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Mechanisms of Cell-to-Cell Transmission of Pathological Tau:

A Review

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Abstract

IMPORTANCE—Intracellular tau protein aggregates are a pathological hallmark of neurodegenerative tauopathies, including Alzheimer disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick disease. Emerging evidence supports a model of cell-to-cell transmission of proteinaceous pathological tau seeds, which leads to recruitment and templated fibrillization of endogenous cellular tau followed by the spread of abnormal tau throughout the brain. These findings lead to the strain hypothesis, which predicts that distinct conformational strains or polymorphs of tau may underlie the clinical and neuropathological heterogeneity and cell-type specificity of tauopathies. In this review, we describe the evidence for propagation of distinct tau strains in cell culture and animal models of AD and mechanistic insights into cell-to-cell transmission of pathological tau.

OBSERVATIONS—Intracranial injections of synthetic tau-preformed fibrils and human brain-derived pathological tau into nontransgenic wild-type mice and transgenic mouse models of AD expressing β -amyloid and tau-amyloid deposits yield widespread pathological tau aggregates observed in neuroanatomically connected brain regions distant from the site of injection. Furthermore, when human brain-derived pathological tau obtained from distinct tauopathies (ie, brains with AD, PSP, and CBD) were injected into the brains of wild-type mice, they seeded tau pathology and faithfully recapitulated cell-type specific tau inclusions characteristic of each

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tauopathy in a time-dependent, dose-dependent, and injection site-dependent spread reflective of the connectome of the injection site.

CONCLUSIONS AND RELEVANCE—These findings provide compelling evidence that misfolded or pathological conformers of tau undergo cell-to-cell spread in a tauopathy strain-specific manner. Importantly, evidence to date supports that pathological tau strains do not behave like infectious agents, despite growing evidence that these tau strains undergo templated propagation and spread linked to the neuroanatomical connectome of the injection site.

Tau is a natively unstructured protein expressed as 6 isoforms in the adult human brain that result from alternative splicing of the *MAPT* gene.¹ Tau has a number of functions, the most well studied of which is the ability to stabilize microtubules within axons of neurons; however, tau is expressed in glial cells in low quantities.² Tau isoforms are composed of either 3 or 4 microtubule-binding repeats (MTBRs; 3R or 4R), which mediate binding of tau to microtubules.³ Additionally, tau consists of 0 to 2 acidic domains (0–2N) in the N-terminal portion of the molecule and an internal proline-rich domain between the N-terminal inserts and MTBRs (Figure 1).⁴

Aberrant misfolding of tau protein leads to formation of beta-sheet fibrils that accumulate within cells of the central nervous system (CNS), resulting in neurodegenerative diseases, collectively termed *tauopathies*.⁵ Neurodegenerative proteinopathies are characterized by accumulations of misfolded proteins within the CNS, such as tau in Alzheimer diseases (AD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and Pick disease, and α -synuclein in Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.^{6,7} A distinct subset of these diseases that are characterized by their infectious nature were termed *prions* and are epitomized by Creutzfeldt-Jakob disease.⁸ Stably propagated conformations of prion proteins are referred to as strains; by analogy, mounting evidence suggests that unique pathological strains of tau protein are responsible for the clinical heterogeneity and cell-type specificity of tauopathies. Despite the similarities to prions, there is no epidemiological or other evidence that pathological tau is infectious.⁹

Tau strains derived from distinct tauopathies are propagated in vivo on intracranial injection into wild-type mice and transgenic mouse models of AD composed of β -amyloid or tau amyloid; these pathologies closely recapitulate distinct features of human AD and its associated tauopathies. In this review, we describe the properties of tau as a prion-like pathogen and examine the literature on the transmission of proteopathic tau seeds between cells, the mechanisms of uptake and processing, and recruitment of cellular tau in the process of templated fibrillization and spread of tau pathology.

Tau Fibrillization and *MAPT* Gene Mutations in Neurodegenerative Diseases

Aberrant misfolding of tau leads to fibrillization and the formation of paired helical filaments with all 6 tau isoforms that constitute neurofibrillary tangles (NFTs) in AD,¹⁰ whereas tau tangles in PSP and CBD include predominantly 4R isoforms, and tangles in Pick disease consist predominantly of 3R isoforms.⁷ While regulated phosphorylation of tau is implicated in normal development, the tau that makes up NFTs is hyperphosphorylated compared with tau in normal adult postmortem brains¹¹; however, rapidly processed

surgically excised tissue samples from normal adult brains show a similar phosphorylation pattern to NFTs in the brains of individuals with AD.¹² While some *MAPT* genetic mutations that are pathogenic for familial frontotemporal dementia have been shown to promote tau fibrillization,¹³ the sporadic initiation of tau fibrillization is not fully understood. It has been suggested to result from hyperphosphorylation of tau that reduces microtubule-binding affinity and leads to an increased concentration of free tau that more readily fibrillizes, as previously reviewed.¹⁴ Recent publications implicate a liquid-liquid phase separation that forms droplets of tau induced by electrostatic interactions that provide a molecular crowding environment to promote fibril formation.¹⁵ The formation of higher-order aggregates of tau, whether in oligomers or fibrils, leads to neuron death through gain-of-function toxicity and/or the loss of function of microtubule stabilization.¹⁴ Tau is also implicated as a mediator of β -amyloid-induced neurodegeneration, in that tau reduction rescued β -amyloid-induced axonal transport defects in primary neurons, and crossing mice that express both human amyloid protein precursor and β -amyloid with tau knockout mice resulted in the rescue of the dendritic hyperexcitability phenotype and restored network synchronicity.¹⁶ Regardless of the mechanisms, it is clear that mutations in the *MAPT* gene result in neurodegenerative diseases, as demonstrated by mutations leading to familial frontotemporal dementia (a condition formerly known as *frontotemporal dementia with parkinsonism-17*).¹⁷

AD Pathological Hallmarks and Spatiotemporal Spread

Tau aggregates form NFTs, neuropil threads, and plaque-associated tau neurites composed of both 3R and 4R tau isoforms. These constitute the 3 major AD tau pathologies (Figure 2) in addition to extra-cellular amyloid plaques formed by β -amyloid peptides.¹⁸ In AD, tau pathology is thought to initiate in the locus ceruleus and transentorhinal region of the brain and follow a stereotypical spatiotemporal progression through the hippocampus and then to other cortical regions.¹⁹ The stereotypical pattern of pathological tau deposition in AD is predictable and correlates with disease severity, resulting in 6 defined stages of AD tau pathology (Braak stages) that allow for reproducible classification of the disease process.²⁰ Building on these findings from postmortem autopsy studies of tau neuropathology, newly developed molecular tau imaging techniques have confirmed the spatiotemporal spread of pathological tau using tau-specific ligands in positron emission tomography and functional magnetic resonance imaging and have demonstrated that strongly connected nodes developed more tau pathology in AD and have supported the notion of transneuronal spread of pathological tau.²¹

Though most well characterized in AD, pathological aggregation of tau is responsible for a heterogeneous class of neurodegenerative diseases (Table). Alzheimer disease-like tau pathology consisting of 3R and 4R tau isoforms are observed in the absence of β -amyloid plaques or very few plaques in elderly individuals with absent or mild cognitive deficits; this condition is referred to as *primary age-related tauopathy*.²² However, it remains controversial whether primary age-related tauopathy represents a distinct entity or an early stage of AD with low β -amyloid plaque burden that will eventually progress.²³ Furthermore, 4R tau accumulations in neuronal processes manifest as argyrophilic grains, resulting in argyrophilic grain disease.²⁴ Yet, in other tauopathies, glia are affected as well as neurons,

and these glial and neuronal tau inclusions demonstrate distinct morphological and biochemical differences.² In CBD, ballooned neurons harboring tau inclusions are observed in the neocortex, while neuropil threads, astrocytic plaques, and oligodendrocyte coiled bodies are observed in gray and white matter. In contrast, PSP presents with cortical gray and white matter tau pathology as well as changes in brainstem and other subcortical regions consisting of neuronal aggregates and tufted astrocytes. In Pick disease, neurons and glia are affected, but the morphology of pathological aggregates in neurons are very distinct, forming dense, spherical Pick bodies.⁷ Last, astrocytic tau aggregates that are characterized as aging-related tau astrogliopathy are observed in the aging brain, but the clinical significance of this is an area of active investigation.²⁵

Novel conformation-selective antitau antibodies have been identified that selectively bind to AD-tau but not to pathological tau present in 4R-tauopathies and 3R-tauopathies.²⁶ This suggests that conformational differences of pathological tau aggregates constitute distinct strains in the various tauopathies. While several studies have attempted to address the interactions of coincident neurodegenerative proteinopathies, it is unclear how the presence of coincident tauopathies may influence the spread and severity of clinical dementia.²⁷ While the spread of tau pathology was initially thought to reflect selective vulnerability of neuronal populations, increasing evidence supports a model of cell-to-cell transmission that could account for progression of clinical phenotypes, although both concepts are not mutually exclusive.²⁸

Cell Culture Models of Seeded Tau Aggregation

Synthetic tau preformed fibrils (PFFs) can act as seeds in a templated fibrillization reaction in which misfolded tau recruits and corrupts normal, soluble tau into a fibrillar conformation. This process has been demonstrated in vitro and in vivo with recombinant tau proteins assembled into PFFs under different conditions and shown to propagate misfolded conformations that are capable of further seeding tau fibrillization in cell-culture models.²⁹ These studies provide proof of concept for the principle that misfolded tau released by a cell could propagate misfolded tau conformation by direct uptake into recipient cells and act as a template for tau fibrillization by direct protein-protein interactions between a pathological tau seed and naive cellular tau.³⁰

Consistent with synthetic tau PFFs, disease-relevant proteopathic tau seeds derived from human brains and mouse model of AD are capable of seeding aggregation of various forms of tau. Importantly, tau derived from the brains of humans with AD seeds the fibrillization of full-length recombinant tau protein in vitro and in primary neurons from wild-type mice, recruiting endogenous mouse tau into insoluble fibrillar aggregates.³¹ A sensitive cellular assay consisting of mutant tau fragments tagged with cyan fluorescent protein or yellow fluorescent protein has been used to demonstrate the seeding of tau aggregates by paired helical filaments derived from the brains of humans with AD and to detect proteopathic human tau seeds derived from mouse brains of transgenic P301S mice that overexpress tau with a *MAPT* missense mutation used as a tauopathy model.³² Furthermore, tau seeds derived from various sources of recombinant tau, human brains, and mouse brains have seeded cellular tau aggregation in a HEK293T cell-culture model that expresses a mutant

human tau fragment that results in stable propagation of putatively distinct tau strains,³³ although tau seeds generated from P301S-recombinant tau fibrils do not seed endogenous mouse tau in wild-type neurons.³⁴

Mouse Model Evidence of Pathological Tau Transmission

The stable propagation of pathological tau conformations derived from the brains of humans with AD (referred to as *AD-tau*) in cell culture and mouse models has prompted the use of the term *strains* to describe pathological conformers of proteopathic tau seeds with distinct biological and biochemical properties.^{31,33,35} The transmission of tau strains in vivo is based mainly on intracranial injections of AD-tau or synthetic tau PFFs into the CNS of transgenic or nontransgenic animals, but transmission to the CNS after peripheral injections also has been reported.³⁶ Indeed, in AD mouse models of β -amyloid amyloidosis, injections of AD-tau seeded all 3 forms of AD tau pathology (ie, NFTs, neuropil threads, and plaque-associated tau-positive neurites) that recapitulated all of the hallmark tau and β -amyloid pathologies of AD.³⁵ Importantly, intracerebral injections of pathological tau derived from different tauopathies (eg, CBD-tau and PSP-tau) demonstrated cell-type selectivity, inducing astroglial and oligodendroglial tau pathology and recapitulating aspects of human disease.^{31,37–39} These studies provide supporting evidence for the notion that distinct tauopathies may result from conformational strains of tau that convey cell-type specificity. These data also suggest that transmission of tau pathology may not be exclusively transsynaptic and that any form of release of tau from neurons or glial cells, whether in solution or extracellular vesicles not mediated by synaptic activity, may be sufficient to enable transmission of pathological tau.

Despite the evidence that tau is transmitted between cells within an individual, there is to our knowledge no evidence of infectious or prionlike transmission between animals. Studies of the serial propagation of strains in vivo are at early stages.³⁵ However, it should be noted that in a small cohort of individuals with iatrogenic Creutzfeldt-Jakob disease who had received human cadaveric pituitary-derived human growth factor hormone contaminated with prions, moderate to severe β -amyloid pathology was observed in gray matter and vasculature at autopsy, which prompted concerns of prionlike transmission of β -amyloid.⁴⁰ A follow-up study also observed potential transmission of β -amyloid pathology from dural grafts; yet, in both studies, tau pathology was absent. Researchers therefore concluded that β -amyloid seeding did not represent infectious AD.⁴¹ Moreover, since traumatic brain injury induces or accelerates β -amyloid pathology and neurosurgery is a form of traumatic brain injury, all studies of β -amyloid deposition in the brains of patients who underwent brain surgery will be subject to the confound associated with trauma-induced β -amyloid deposition.^{42,43} Last, procedures to remove or inactivate prions have been shown to be ineffective at removing or inactivating α -synuclein fibrils, prompting consideration to treat tau and α -synuclein fibrils with sodium dodecyl sulfate, 1%, for laboratory decontamination.⁴⁴

Determining the intracellular localization and mechanism of pathological tau seeding of endogenous tau can be pursued using in vivo animal models,^{37–39,45–48} and recent studies have examined the interactions of pathological tau with other disease proteins, including β -amyloid. For example, recent studies of tau-seeded aggregation induced by intracerebral

injections of human AD-tau into mice carrying 5 mutations associated with familial Alzheimer disease ($5 \times \text{FAD}$) that rapidly develop abundant β -amyloid plaques have provided the most complete mouse model of human AD tau pathology and β -amyloid pathology to date.³⁵ Studies using this system have provided new evidence that tau is disrupted at axon terminals in dystrophic neurites surrounding β -amyloid plaques preceding the induction of tau tangles after intracerebral AD-tau injections. On introduction of fibrillary AD-tau seeds, intracellular tau in axons surrounding plaques is thought to be primed for aggregation and is rapidly induced to form plaque-associated neuritic tau pathology that becomes hyperphosphorylated, and when plaques with neuritic tau are abundant, only rare tangles form; when they are less abundant, AD-like NFTs form.³⁵ Because tau-positive neuropil threads also form in this model, this is to our knowledge the first mouse model that develops β -amyloid plaques and all 3 forms of tau pathology found in the human AD brain (ie, NFTs, neuropil threads, and plaque-associated tau-positive neurites).

Mechanisms of Release, Uptake, and Cellular Processing

While these data provide strong evidence for the cell-to-cell transmission of tau pathology, the mechanisms of cellular release, up-take, processing, and subsequent seeding of naive cellular tau remain incompletely understood (Figure 3). Although it was initially conceived of as a strictly intracellular molecule, there is now evidence indicating that tau is present extracellularly in the CNS. Tau can be detected in normal cerebrospinal fluid and hyperphosphorylated tau is detected in patients with AD.^{49,50} Because this corresponds with neuron loss, it is speculated that this increase is the result of dying neurons releasing cellular contents.^{48,51,52} Recent emerging evidence^{53–55} suggests that normal endogenous tau is also released from living neurons in an activity-dependent manner. The exact mechanism of tau release is unclear, and there are data^{56–58} supporting the view that both vesicle-bound and soluble free extracellular populations of tau exist. These findings have prompted drug discovery efforts to develop tau antibodies as immunotherapies to block the cell-to-cell transmission of pathological tau. Binding of extracellular tau protein with antibodies could inhibit the transmission of pathological tau through several possible mechanisms. A few examples include blocking the uptake of pathological seeds into adjacent cells through steric bulk or interfering with receptor-mediated processes, prompting microglia-mediated degradation of seeds or blocking templated fibrillization by sterically hindering recruitment of monomers onto growing fibrils. Multiple groups^{59–64} have demonstrated that tau antibodies block the transmission of pathological tau spread throughout the brain in transgenic AD mouse models, leading to several clinical trials of tau immunotherapy.

Once released from neurons, proteopathic tau seeds are taken up by interconnected neurons or adjacent glial cells.^{30,65,66} The mechanisms of cellular uptake are plausibly similar for both potential pools of either vesicle-bound or free tau, including clathrin-mediated endocytosis, micropinocytosis, or direct membrane fusion.^{67–69} For instance, expression of the negative regulator of clathrin-mediated endocytosis, bridging integrator-1 (*BIN1*) gene, is inversely correlated with tau pathology, demonstrating that *BIN1* overexpression reduces endocytosis and inhibits transmission of tau in cell-culture models.⁶⁹ In addition, tau species also have been shown to undergo fluid-phase bulk endocytosis or receptor-mediated uptake,

specifically interruption of tau binding to cell-surface heparin-sulfate proteoglycans (HSPG) with small molecules or genetic knockdown of HSPG-synthesizing enzyme Ext1 and inhibits fibril uptake and transcellular propagation.^{29,66,70} Studies focused on characterizing the nature of pathological tau taken up by neurons^{29,65,71} have suggested that the high-molecular-weight, soluble phosphorylated tau identified in the brain extracts of humans with AD are readily internalized,⁷² as well as tau oligomers and PFFs.^{29,65,71} Our laboratory has demonstrated that fluorophore-labeled tau fibrils are taken up into wild-type²⁹ and tau-green fluorescent protein-expressing⁴⁷ primary hippocampal neurons in vitro. In these models, synthetic tau fibrils or human brain-derived pathological tau seeds are taken up broadly across the neuron and coalesce into concentrated aggregates within the perikarya; however, the fibrillization of endogenous mouse tau primarily occurs within axons with rare cell-body pathology, raising questions of how tau is processed once internalized and whether it encounters normal cellular tau free in the cytosol or bound to microtubules to initiate the templated fibrillization process.

Tracking the fate of the internalized proteopathic seeds has proven challenging, although progress is being made using pH-sensitive fluorophore-labeled tau. Experiments using labeled α -synuclein PFFs have demonstrated that these synthetic PFFs do transit through acidified compartments in late endosomes and lysosomes.^{47,73} Furthermore, enhanced cellular seeding of tau and α -synuclein is evident on inhibition of lysosomal processing of tau seeds using the small molecule inhibitor chloroquine.^{47,73} However, it remains unclear whether this process is mediated by disruption of lysosomal integrity, which allows these proteopathic seeds to escape degradation in lysosomes and encounter cellular substrates for templated fibrillization or whether there are other mechanisms to account for this, including mechanisms linked to decreased clearance of these seeds. Recent evidence supports the idea that tau aggregates physically damage endosomal membranes by detection of luminal sugars that become exposed to the cytosol on vesicle damage with galectin-3 and galectin-8.^{69,74} Treatment of primary neurons with tau seeds induces binding of galectin-8 to endosomal vesicles, supporting the notion that, at uptake and entry into the endolysosomal pathway, tau aggregates damage vesicles and allow exposure of internalized seeds to the cytosolic compartment, providing access to naive tau fibrillization substrates.⁷⁴

Conclusions

In summary, pathological tau is clearly a transmissible pathogen, but unlike prions, there is no evidence of infectivity of tau aggregates. Transmission of stable, disease-specific species of pathological tau in animal models of tau-seeded aggregation by intracerebral injection provides strong evidence supporting unique pathological tau strains. Cell-to-cell transmission of proteopathic tau seeds in cell culture and animal models supports the propagation of tau seeds between cells and throughout the brain. Provocative recent data from animal model studies suggest that pools of tau in dystrophic neurites surrounding β -amyloid plaques may be primed for aggregation, which means they may be the initial site of tau aggregate seeding in AD. Emerging data from a number of laboratories are beginning to unravel the mechanisms of cellular release of normal and pathological tau in both vesicle-bound and soluble pools; uptake into neurons, primarily via bulk fluid-phase endocytosis and partially through receptor-mediated events; and the release of these diverse species of

tau from damaged membrane-bound cellular compartments to permit recruitment of normal cellular tau via templated fibrillization by pathological tau seeds.

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Figure 1.
Schematic of Tau Isoforms
Six human tau isoforms, consisting of 0 to 2 N-terminal inserts encoded by exons 2 and 3, the proline-rich internal domain, and the microtubule-binding repeat (MTBR) domains encoded by exons 9 through 12; 3R tau contains 3 MTBR and excludes exon 10 as a result of alternative splicing.

Figure 2.**Tau Morphology in Various Tauopathies**

Immunohistochemistry staining with phosphotau antibody PHF1 demonstrates distinct morphology and cell-type specificity of various tau pathologies. Asterisks indicate neuritic plaques and arrowheads indicate neuropil threads in Alzheimer disease (B); arrowheads indicate balloon neurons in the pons (C) and asterisks indicate astrocytic plaques in the hippocampus (D) of an individual with corticobasal degeneration; arrowheads indicate thorny astrocytes in the amygdala of an individual with aging-related tau astroglipathy (H). NFTs indicates neurofibrillary tangles.

Figure 3.
Schematic Representation of Cell-to-Cell Transmission of Tau Pathology and Cortical Spread of Alzheimer Disease–Associated Tau

The foreground image depicts the following steps in cell-to-cell transmission of pathological tau: a, tau seeds are released from neurons as free tau and tau in vesicle-bound pools; b, the released tau is taken up into interconnected neurons by a variety of mechanisms, including bulk fluid-phase endocytosis, receptor-mediated uptake, and direct membrane fusion; c, tau seeds taken up by a recipient neuron are processed in late endosomes and lysosomes, where they induce vesicle damage and escape into the cytoplasm; d, tau seeds that encounter endogenous cellular tau initiate templated fibrillization and recruit native monomeric tau into new tau fibrils. The background image of a human brain with Alzheimer disease shows the spread of tau pathology from the medial temporal lobe (darker green) to other cortical areas (lighter green), while largely sparing primary sensory and motor regions (negligible green shading, as in the primary motor cortex).

Table.

Summary Describing Neuropathological and Clinical Phenotypes of the Most Common Tauopathies

Tauopathy	Phenotypes			Neuropathological	Clinical
	Tau Isoforms	Gross			
Alzheimer disease	3R and 4R	Reduced brain weight, cortical atrophy, enlarged ventricles		Tau NFTs, neuropil threads, and plaque-associated neurites with β -amyloid disease progression from locus ceruleus and transentorhinal cortex to entorhinal cortex, CA1 and CA2 hippocampal regions, CA3 hippocampal region and fusiform and lingual gyri, and neocortical regions.	Memory loss, executive dysfunction, language difficulties, and visual/spatial problems that ultimately impair ability to function independently
Corticobasal degeneration	4R	Asymmetrical atrophy in posterior frontal and parietal lobes and substantia nigra pallor		Ballooned neurons in neocortex, intraneuronal basophilic inclusions, astrocytic plaques, and oligodendrocyte coiled bodies in cortical and subcortical regions with neuron loss; NFTs in basal ganglia and brainstem; severe neuron loss in substantia nigra with astrogliosis.	Corticobasal syndrome: asymmetric limb rigidity, akinesia, or dystonia, plus progressive nonfluent aphasia and behavioral variant frontotemporal dementia
Progressive supranuclear palsy	4R	Substantia nigra and locus ceruleus pallor		Tufted astrocytes, NFTs, and globose tangles in cortical and subcortical regions with neuron loss; NFTs in substantia nigra, globus pallidus, and subthalamic nucleus.	Ocular motor dysfunction, postural instability, akinesia, and speech or language disorders, such as progressive nonfluent aphasia
Pick disease	3R	Severe atrophy of frontotemporal neocortex creating a so-called knife-edge appearance		Dense spherical Pick bodies, especially in the dentate gyrus, and ballooned neurons in cortical and subcortical regions with neuron loss and glial inclusions in gray and white matter.	Behavioral variant frontotemporal dementia and executive function impairments or primary progressive aphasia
Argyrophilic grain disease	4R	None		Argyrophilic grains in neuronal processes, pretangle neurons with perinuclear tau in transentorhinal cortex, entorhinal cortex, presubiculum, CA1 of hippocampus, and temporal cortex. Ballooned neurons in limbic regions and oligodendrocyte coiled bodies.	Cognitive decline, behavioral abnormalities, and episodic memory loss
Primary age-related tauopathy	3R and 4R	None		NFTs restricted largely to hippocampus and entorhinal cortex, with infrequent 3-amyloid plaques.	Absent to mild cognitive impairment

Abbreviations: NFTs, neurofibrillary tangles; 3R, 3 microtubule binding repeat; 4R, 4 microtubule binding repeats.