TC 41

Searching for non-amyloid related causes in AD

Tau

WCN 2013 Vienna

Sept 25, 2013, 11:00-12:30

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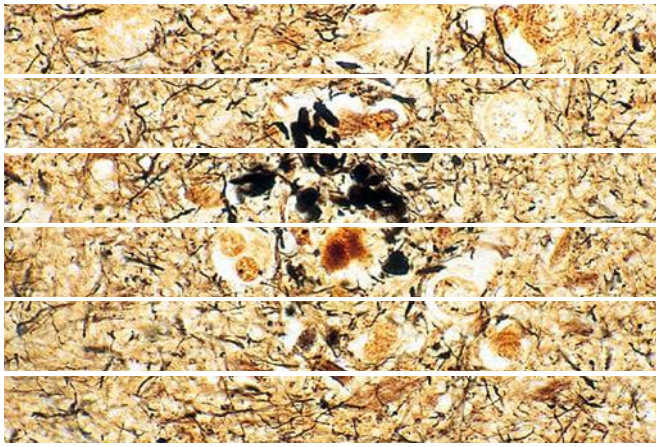
Disclosures

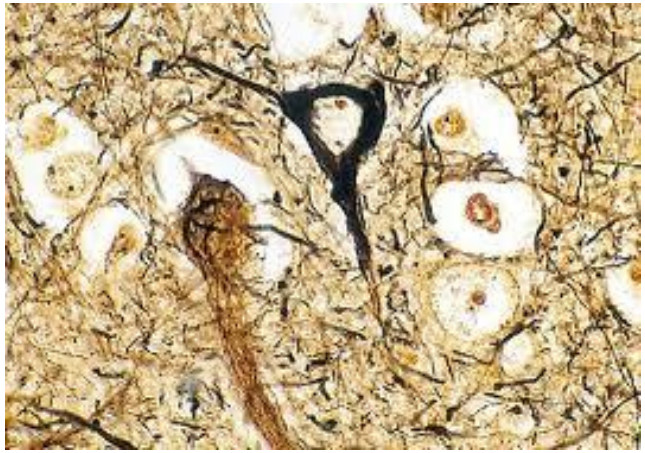
- I received honoraria from Novartis, Merz and Lundbeck for lectures and consultations

- I have been investigator in studies sponsored by Novartis, Ever Pharma, Servier, GSK

Neuritic plaque (Bielschowsky)

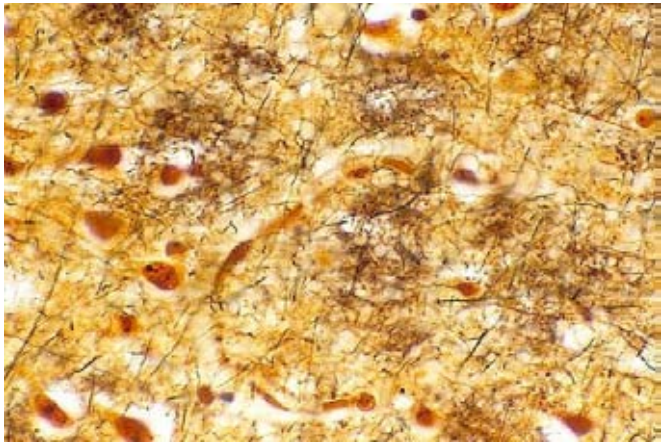


Neurofibrill. Tangle

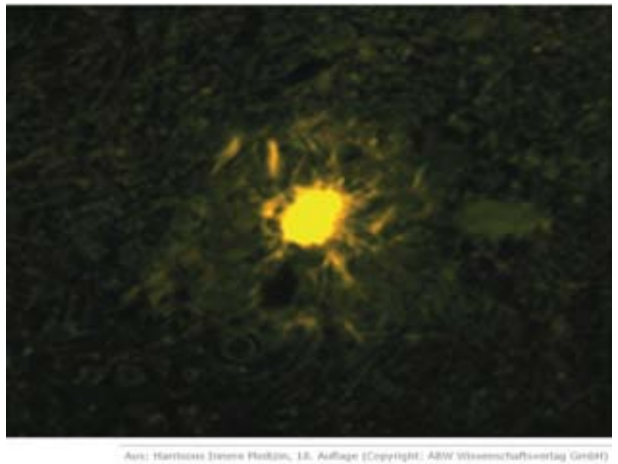


NF Deg.

Diffuse plaque



Amyloid Plaque (Thioflavin S)



Amy loid

W. Rosenblum, VCU Harrison Internal Medicine Thieme

Neuropathological criteria/classifications of AD

History

Khachaturian Diagnosis of Alzheimer's disease
Arch Neurol 1985; 42:1097

Tierney M et al. The NINCDS-ADRDA Work Group
Neurology 1988; 38:359

Mirra et al. (CERAD)
Neurology 1991;41:479

Braak & Braak
Acta Neuropathol 1991;82:239

The National Institute on Aging and Reagan Inst. Working Gr.
Neurobiol Aging 1997; 18 (Suppl 1) S1

Geddes et al, Review

Neurobiology of Aging 1997;S418:S99

NEUROPATHOLOGIC CRITERIA OF ALZHEIMER'S DISEASE

Neuropathologic Criteria	Age/Stage	SP	NP	NFT		
				NeoCtx	Hippo	EntCtx
Khachaturian (18)	< 50	> 2–5/mm^2		> 2–5/mm^2		
	50–65	> 8		some		
	66–75	> 10		some		
	> 75	> 15				
CERAD for age > 75 (22)	Uncertain		Sparse			
	Suggest		Moderate			
	Indicate		Frequent			
Braak (8)	I-II (Entorhinal)			Sparse	Sparse	Present
	III-IV (Limbic)			Sparse	Occasional	Abundant
	V-VI (Neocortical)			Abundant	Abundant	Abundant
NIA-RI AD Research (25)	Low Likelihood		Sparse	Sparse	Sparse	Present
	Intermediate		Moderate	Sparse	Occasional	Abundant
	High Likelihood		Frequent	Abundant	Abundant	Abundant
NIA-RI Routine* (25)	Low Likelihood		Sparse	Absent	Absent	Present
	Intermediate		Moderate	Absent	Present	Present
	High Likelihood		Frequent	Present	Present	Present
Tierney A1 (31)			Present in Hippo		Present	
Tierney A2			Hippo and NeoCtx	Present	Present	
Tierney A3			Present in NeoCtx	Present		
Nun Study (29)		> 15/mm^2		Present		
Neocortical NFT				Present		

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease

Hymen et al. *Alzheimer's & Dementia 2012;8:1*

A0: no Aβ or amyloid plaques
A1: Thal phase 1 or 2
A2: Thal phase 3
A3: Thal phase 4 or 5

B. NFT stage (modified from Braak for silver-based histochemistry [20] or phospho-tau

B0: no NFTs
B1: Braak stage I or II
B2: Braak stage III or IV
B3: Braak stage V or VI

IHC

C. Neuritic plaque score (modified from CERAD [21])

C0: no neuritic plaques
C1: CERAD score sparse
C2: CERAD score moderate
C3: CERAD score frequent

A_x,B_y,C_z

No, low, intermediate, high AD „neuropathologic change“

Neuropath. diagnosis of Alzheimer‘s disease

does not necessarily mean

Alzheimer dementia

but may occur in

Normal cognition

Subjective memory impairment

Mild cognitive impairment-(mnestic domaine)

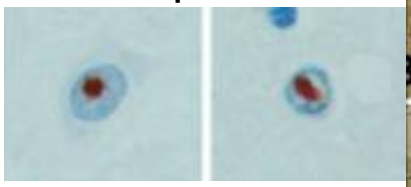
Co-morbidities occur – utilization of other than AD (immuno) histochem. markers

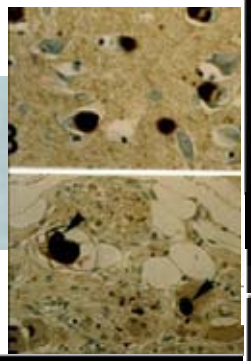
Infarcts, lacunes (vascular cognitive impairment)

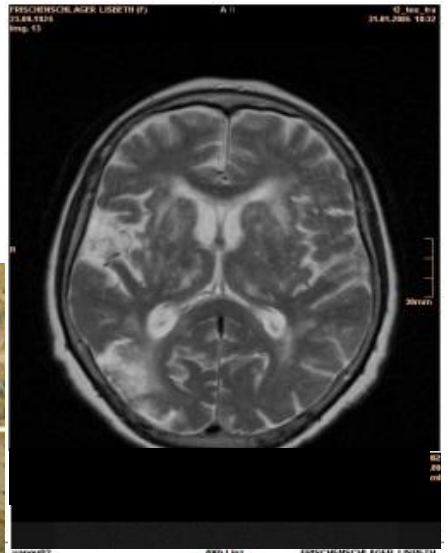
Lewy-body-pathology (Parkinson dementia)

TDP-43, Hipp.Sclerosis

Josephs





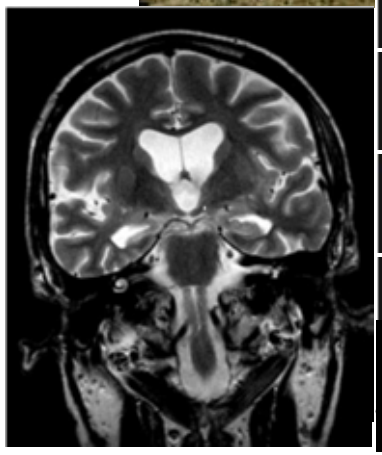


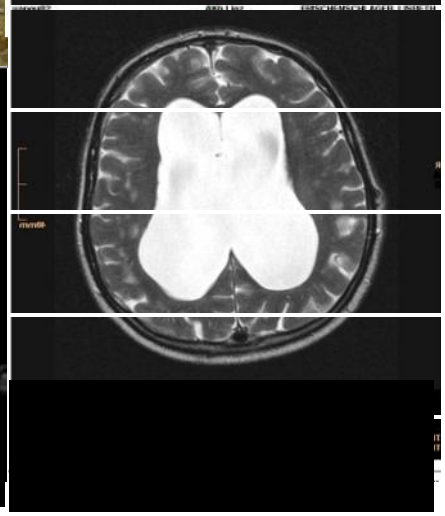
Normal pressure hydrocephalus

Metabolic/toxic lesions

Schizophrenia, depression

Medication





Schneider *Neurology 2007;69:2197*

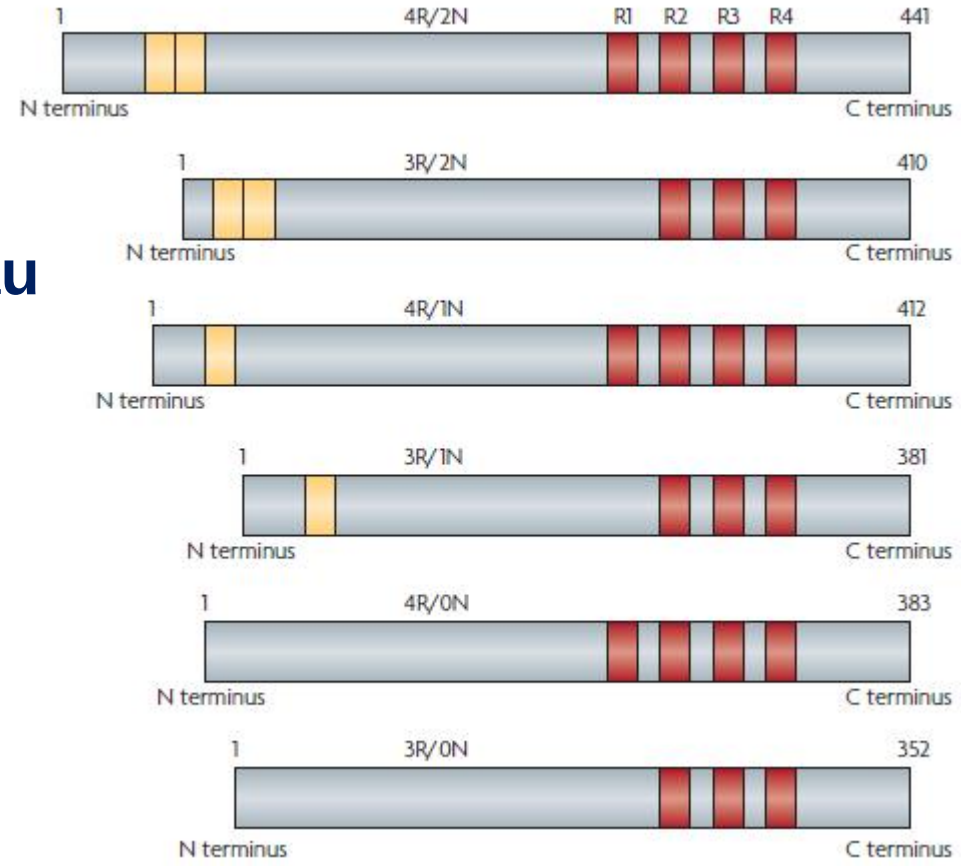
Tau

Projection domaine **Tubulin binding domaine**

Exons 2,3 10

6 Tau isoforms

3 and 4 repeat Tau



In AD no Tau mutation

in contrast to FTD

Reversible phosphorylation of tau binding - microtubuli

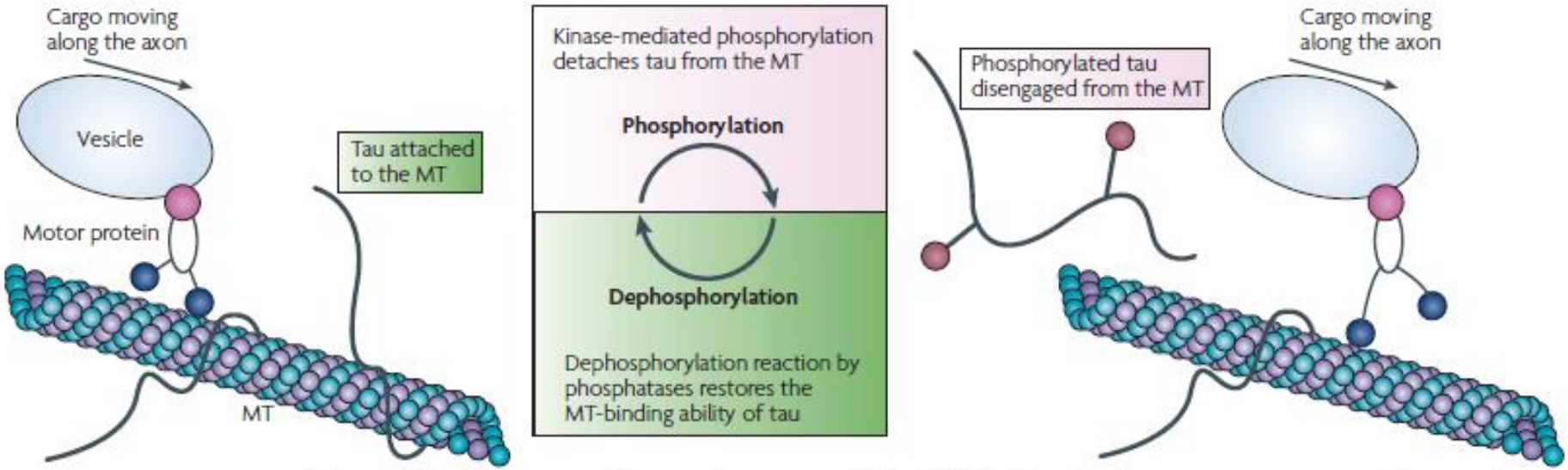
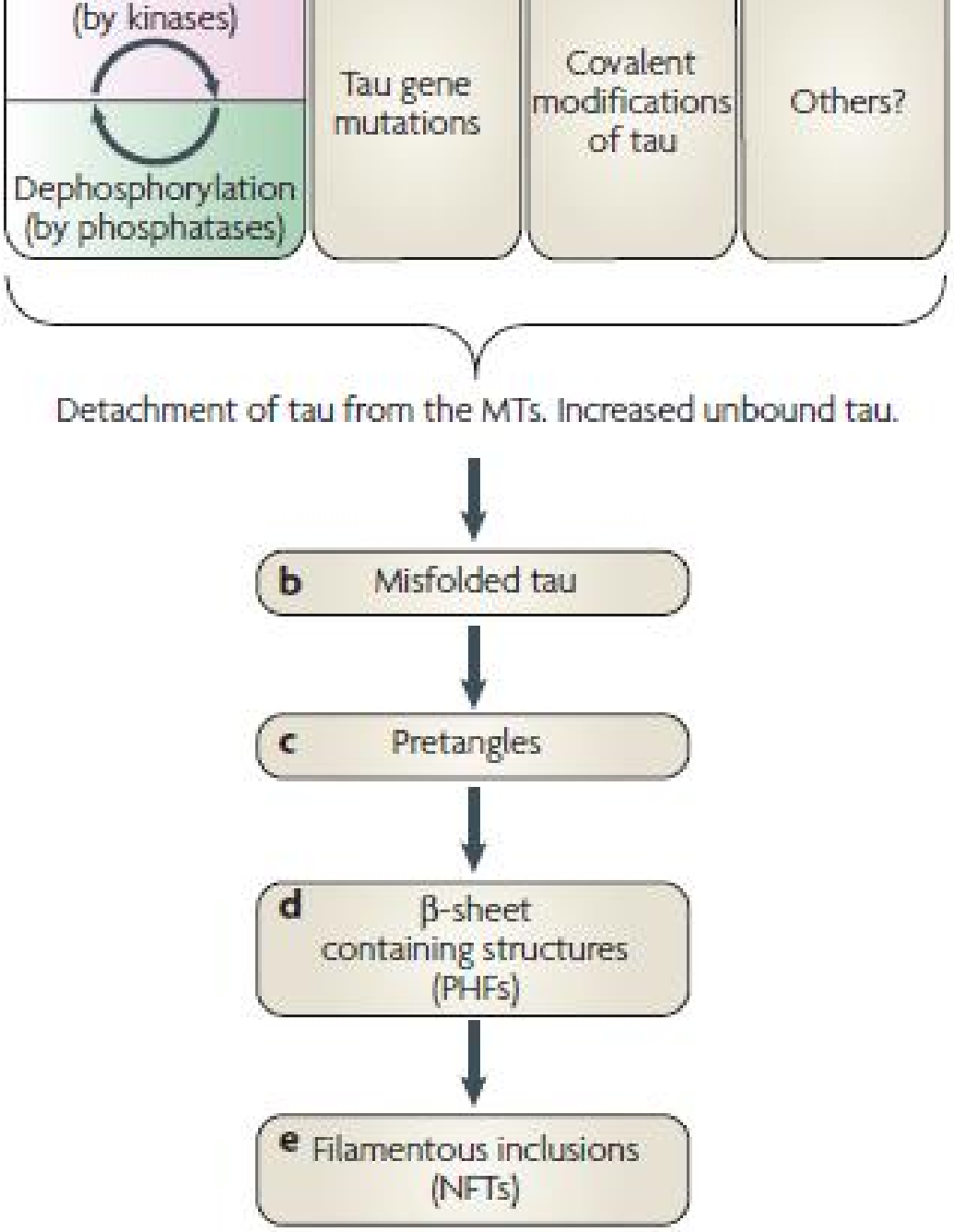


Figure 3 | **The dynamic equilibrium of tau microtubule (MT) binding.** A schematic representation of the normal dynamic equilibrium of tau, on and off the MTs, which is primarily determined by the phosphorylation state of tau. Although the presence of tau on the MTs presents a physical obstacle for vesicles and other cargoes that are moving along the axon, MT-bound tau is essential to MT integrity. Thus, relatively frequent cycles of tau–MT binding (promoted by dephosphorylation of tau) and detachment of tau from the MT (promoted by phosphorylation of tau) are needed in order to maintain effective axonal transport.

Ballatore, Lee, Trojanowski *Nature Review Neuroscience 2007;8:663*



Ballatore, Lee, Trojanowski *Nature Review Neuroscience 2007;8:663*

Tau conformation and paired helical filaments

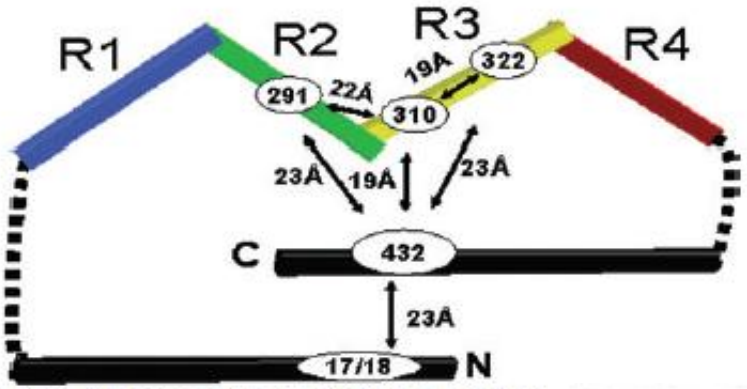


Figure 3. Model of the conformation of tau in solution deduced by f transfer. The molecule shows a paperclip-like fold which brings the N- vicinity of the repeat domain. Similar folded conformations are recognize for abnormal tau from Alzheimer's disease brain (eg, Alz-50, MC1, TG3). A labeled residues are indicated.

Mandelkow

Brain Pathol 2007;11:83

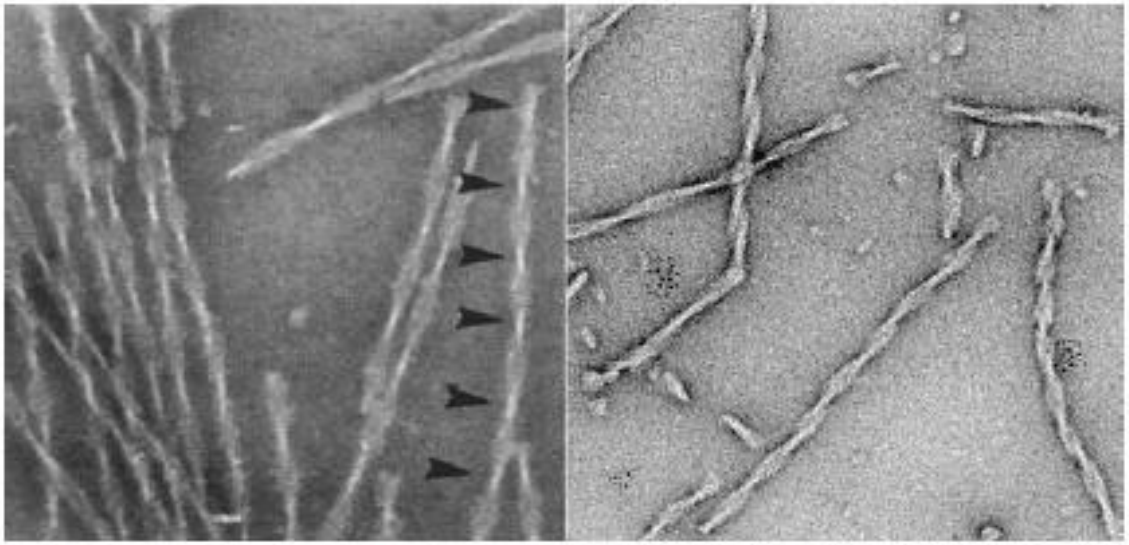
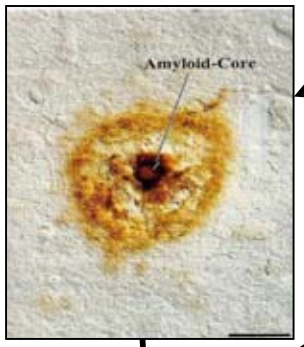


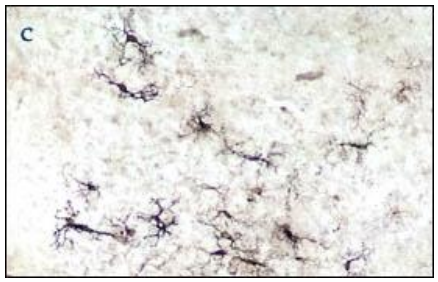
Figure 4. Electron micrographs of paired helical filaments isolated from Alzheimer's disease brain (left) or assembled *in vitro* from recombinant tau (repeat domain with pro-aggregation mutation ΔK280). Note the typical twisted appearance with crossover repeats of ~80 nm (arrowheads).

Amyloid



APP-Mutation
ß-u.?-Secretase
Presenilin-1

activ. microglia/degen.



+ IL-1ß,IL-6,TNF-?,IL-8

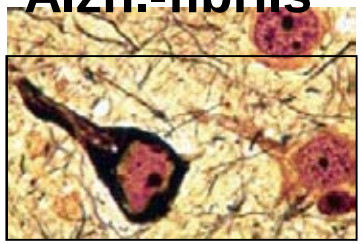
Wnt

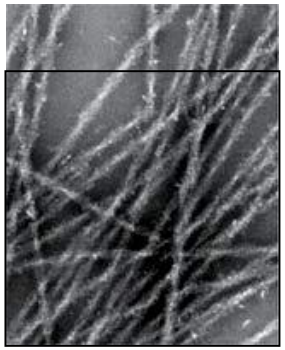
dvl

GSK3ß, CDK5, ERK2,
MARK4, AMPK, SAPK/JNK,
SRPK2 ***KINASES***

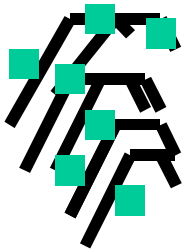
Hyperphos.-?Oligomers

Alzh.-fibrils

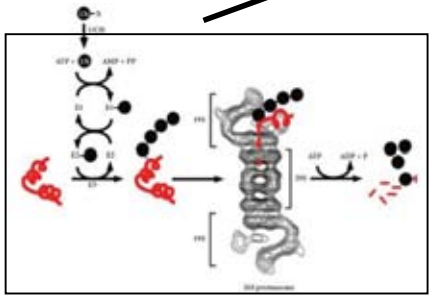




?Aggregation



Blockade



Microtubuli
MAP-?z

Ubiquitin-Proteasome-Syst.

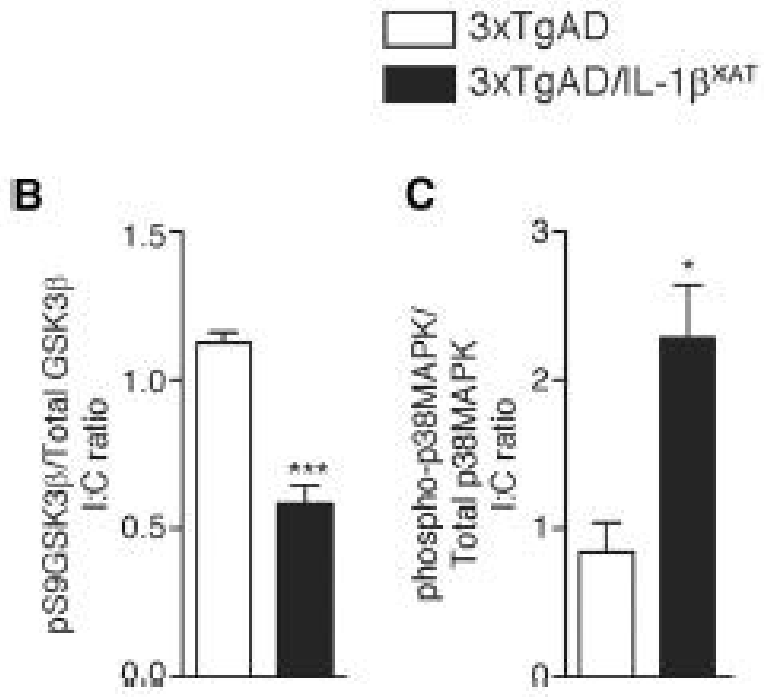
Blurton-Jones, La Ferla *Curr Alz Res 2006*

Kinases/Tau hyperphosphorylation are induced by

- Aß oligomers
- Prion Protein Complex
- Inflammatory mechanisms (IL-1ß etc.)
- Oxidative Stress
- Mitochondrial fission protein Drp1
- 5-Lipooxygenase
- Stress, ß adrenergic pathway
- Ca++ etc.

Inflammat. cytokines induce kinases and P-Tau formation
Glia-Tau interaction

Gosh J et al. *J Neurosci 2013;33:5053*



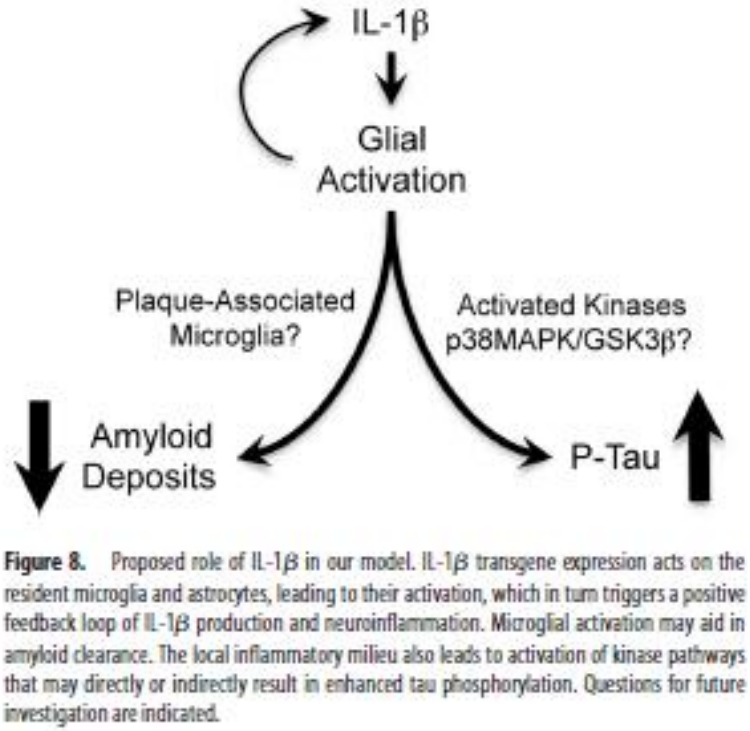


Figure 8. Proposed role of IL-1β in our model. IL-1β transgene expression acts on the resident microglia and astrocytes, leading to their activation, which in turn triggers a positive feedback loop of IL-1β production and neuroinflammation. Microglial activation may aid in amyloid clearance. The local inflammatory milieu also leads to activation of kinase pathways that may directly or indirectly result in enhanced tau phosphorylation. Questions for future investigation are indicated.

Mutant APP, PS1, Tau ±IL-1ß overexpression

amyloid down
GSK3ß and MAPK up
P-tau up

There is early increase of Tau and P-Tau in the CSF in preclinical AD

Suggesting an early pathogenetic role of Tau in AD

Visser et al. (DESCRIPTA study) *Lancet Neurol 2009;8:619*

Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study

	Controls (n=89)	Subjective cognitive impairment (n=60)	Non-amnestic MCI (n=37)	Amnestic MCI (n=71)
Age (years)	67·1 (6·4)	66·0 (7·9)	70·0 (7·7)§,¶	70·0 (7·7)*¶
Years in education	..	11·8 (4·1)	10·7 (3·7)	10·4 (3·3)
Women	48 (54%)	29 (48%)	17 (46%)	34 (48%)
MMSE score	29·3 (0·9)	28·8 (1·2)	27·6 (2·2)‡	25·9 (2·8)‡**‡‡
CDR-SOB	..	0·7 (0·7)	1·3 (0·9)¶	1·7 (1·2)**
Depression	..	7 (13%)	2 (6%)	2 (3%)
Delayed recall (z score)	..	0·46 (0·94)	−0·49 (0·77)**	−1·97 (0·74)**§§
Carrier of APOE ε4	..	29 (53%)	11 (36%)	37 (53%)§§
$A\beta_{42}$ (pg/mL)¶¶	703 (194)	653 (268)	583 (272)	493 (254)‡‖‡‡
T-tau (pg/mL)¶¶	329 (133)	360 (200)	401 (278)	539 (375)‡††
P-tau (pg/mL)	53 (20)	62 (27)§	67 (33)	84 (54)‡
CSF AD profile	28 (31%)	31 (52%)†	25 (68%)†	56 (79%)‡‖

NFTs

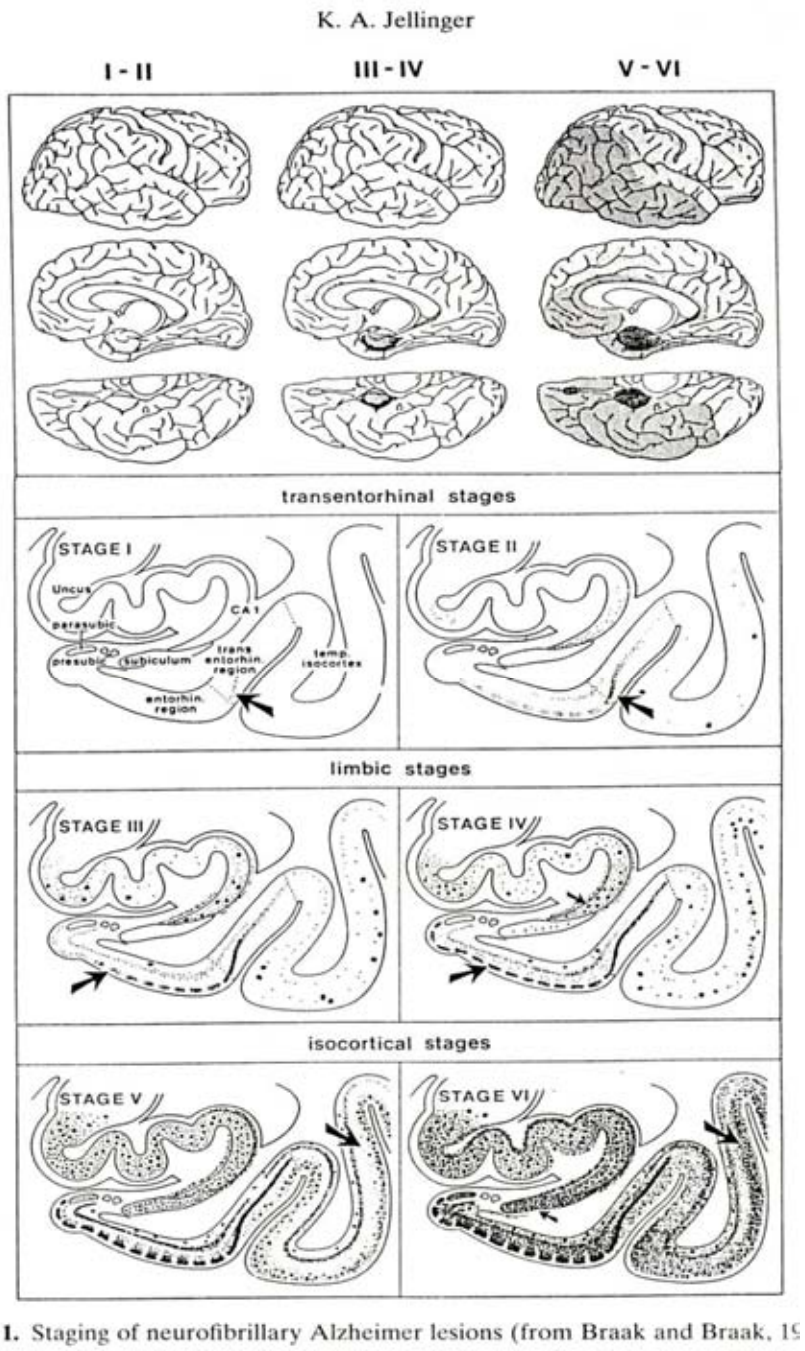
Braak & Braak

Acta Neuropathol 1991;82:23

I,II

III,IV

V,VI

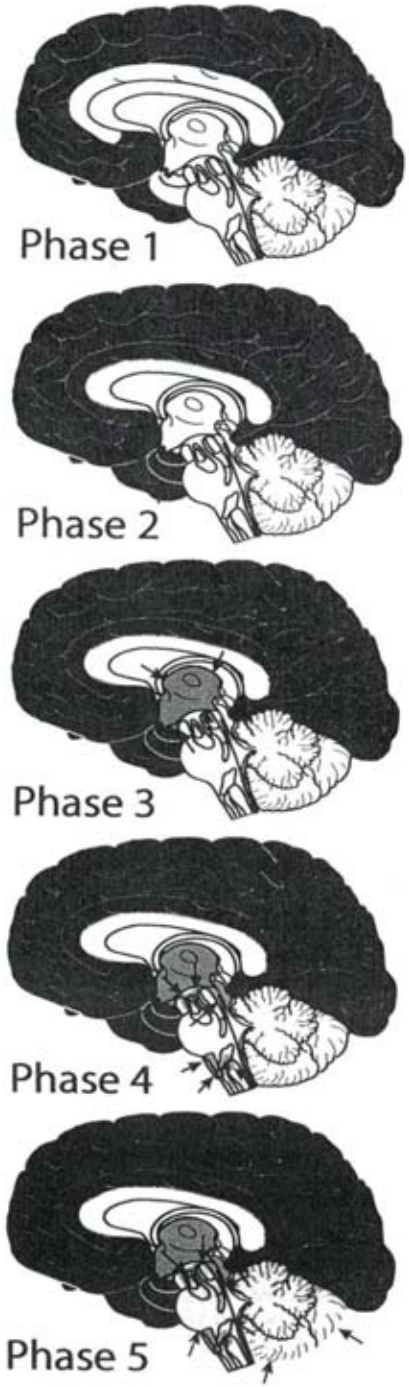


g. 1. Staging of neurofibrillary Alzheimer lesions (from Braak and Braak, 19

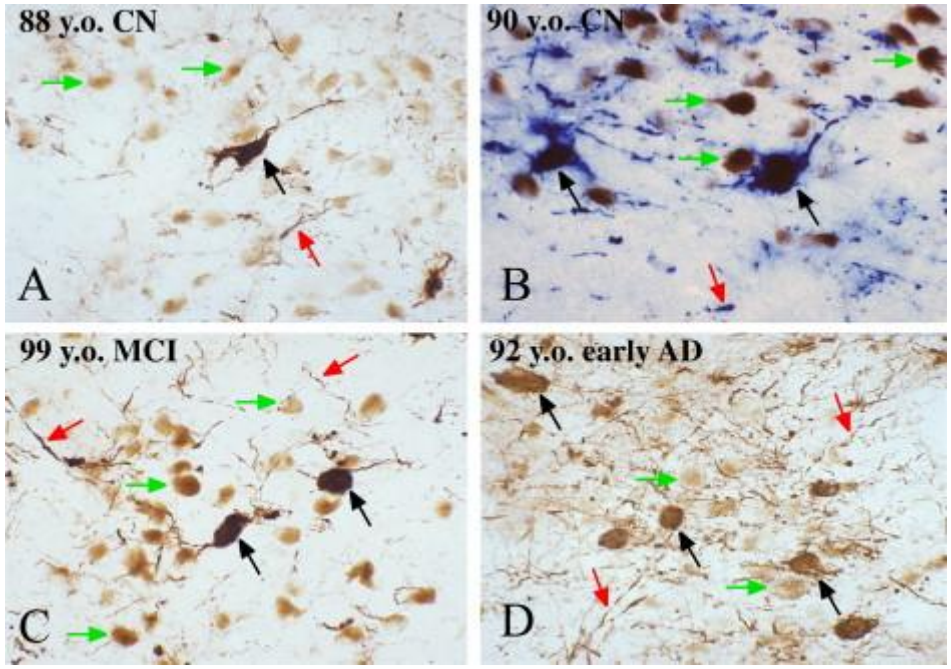
Plaques

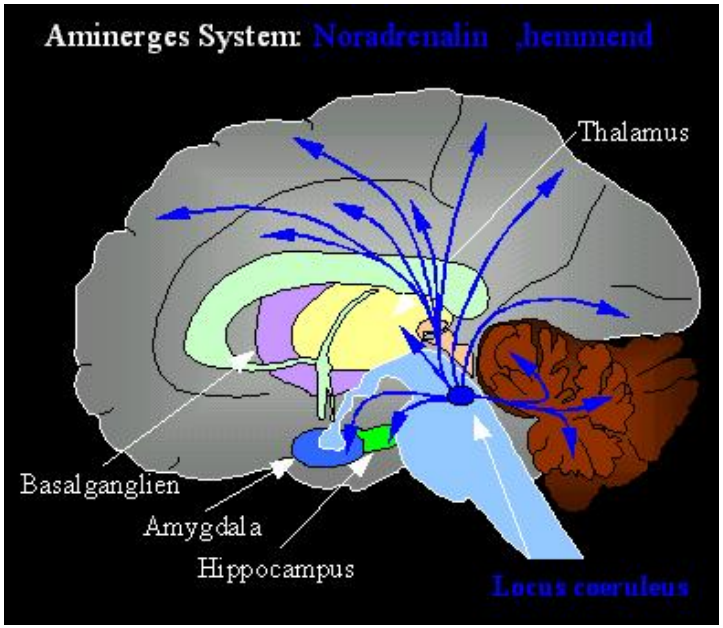
Thal et al

Neurology. 2002;58:1791



Tangles occur in the loc. coeruleus in the 1.-2nd decade





http://brain.exp.univie.ac.at

Grudzien et al *Neurobiol Aging 2007; 28:327*

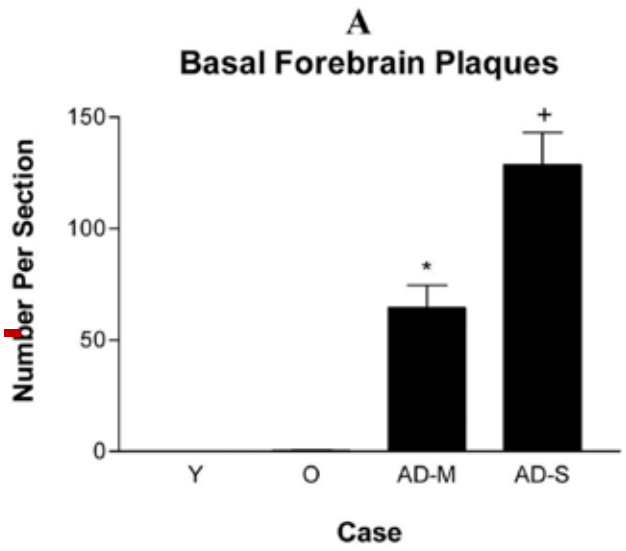
C. Geula et al.

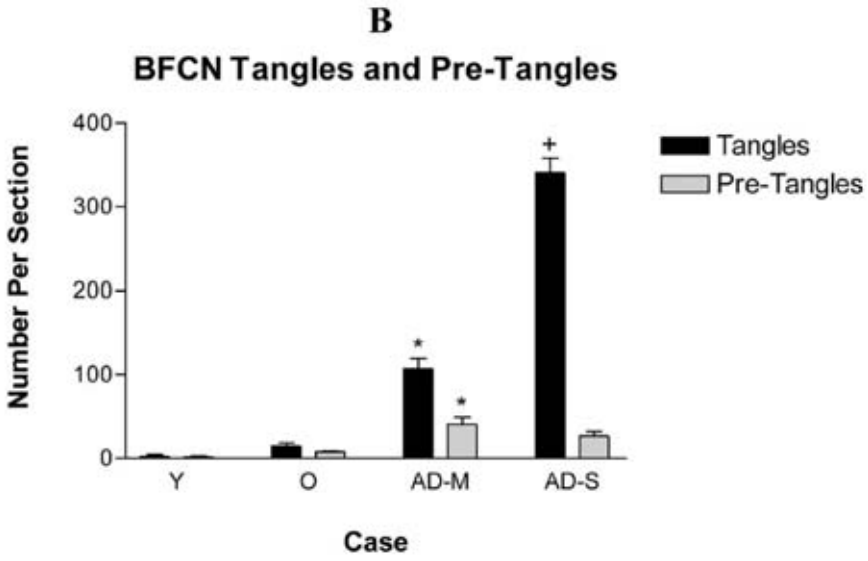
Early cholinergic neuronal and axonal pathology in young persons, aging and AD- Basal forebrain and cortex

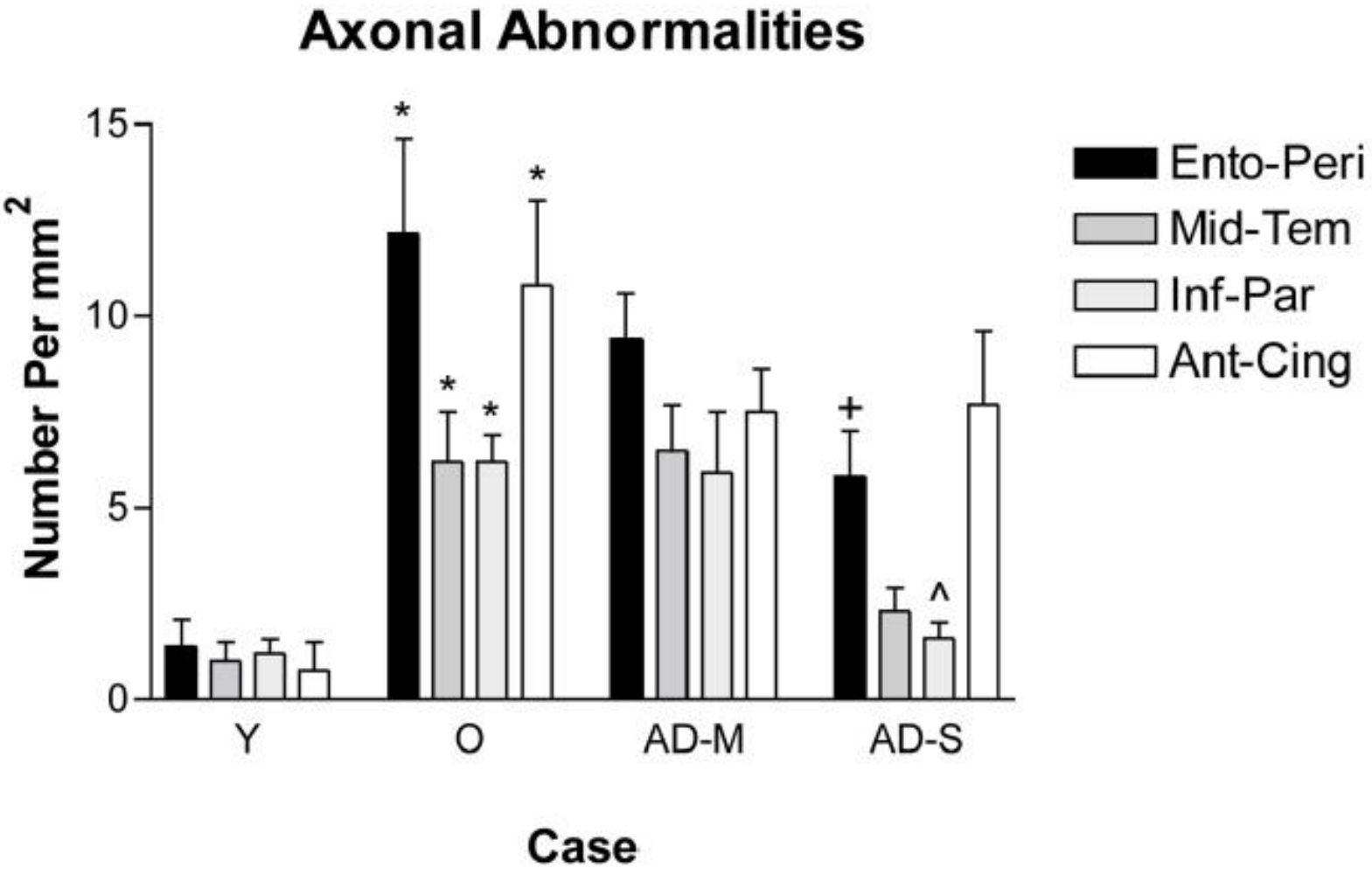
J Neuropathol Exp Neurol
2008; 67(4): 309

Normal controls
(N=13; 26-93 yrs;
Y< 65, O ≥ 65 yrs)

AD patients
(N=10; mild, M; severe, S)







C. Geula et al. 2008

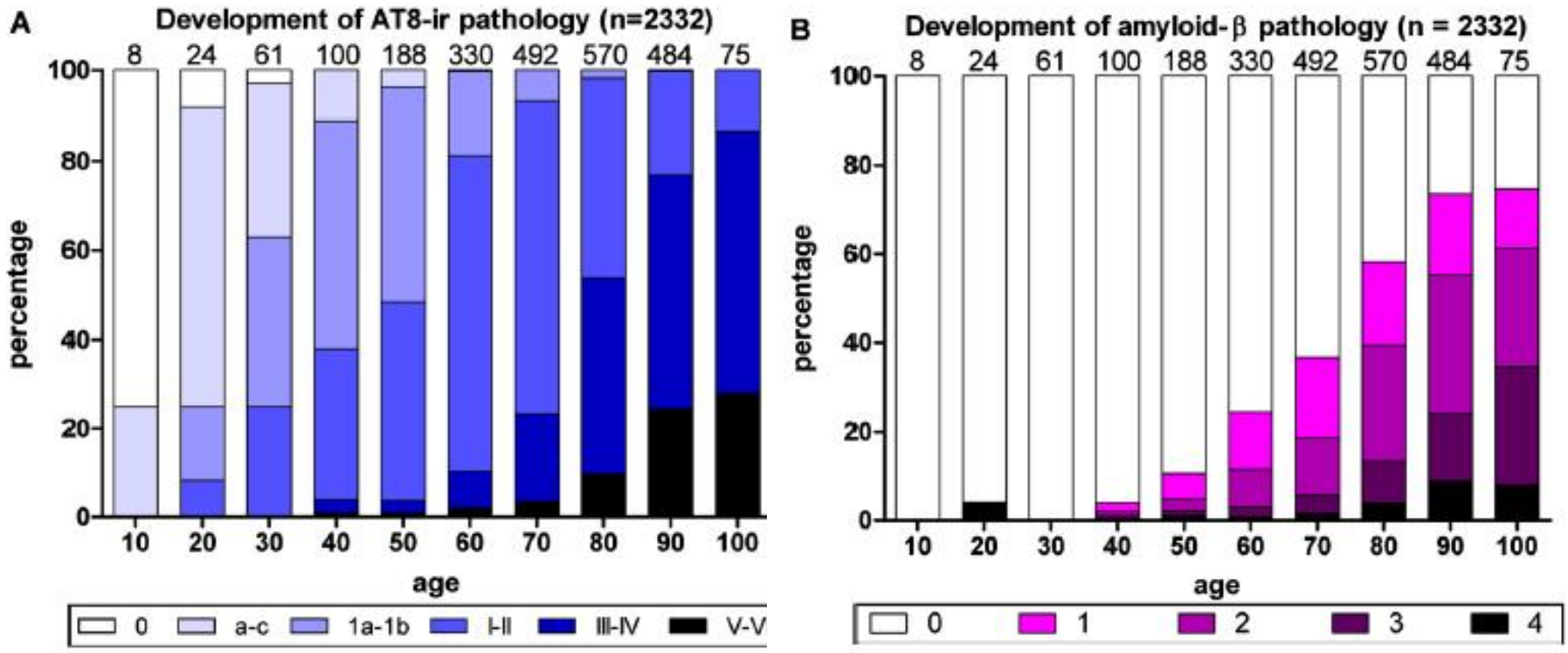
Attems, Thomas, Jellinger

Neuropathol Appl Neurobiol 2012;38:582

Subcort. pre-tangle formation starts early and correlates with cortical tangles

N=239; age 55-102, diagnostically unselected

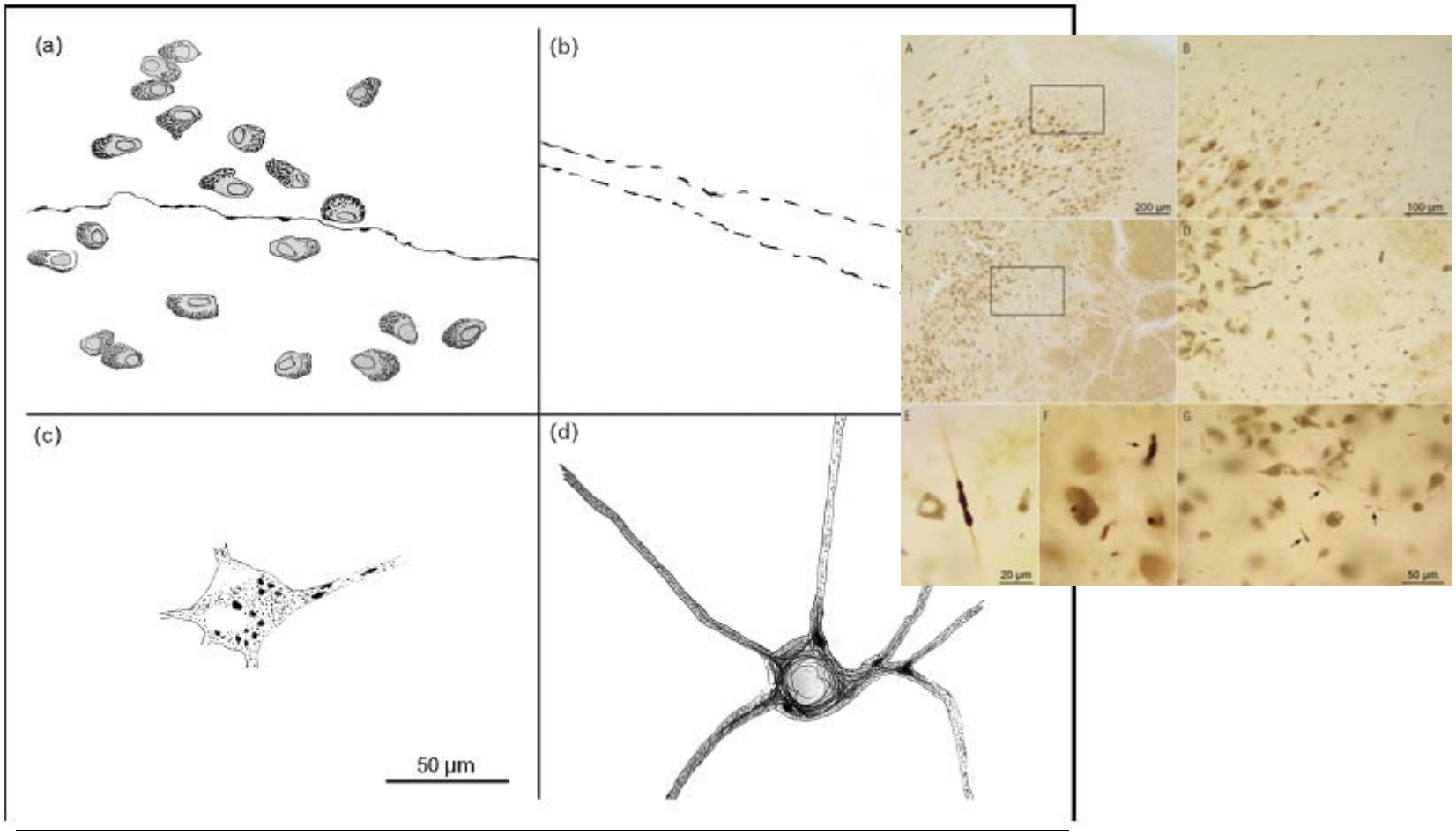
	Olfact. Bulb	Subst. nigra	Lc	N. dors. motor X
Braak 0	53	44	44%	
↓				
Braak VI	100	100	100	95%



a	locus coeruleus area
b	midbrain tegmentum, super. cerebell. peduncle, dorsal motor X
c	raphe, nucl. basalis magnocellularis
1a-b +	cortical involvement
I-VI	**Classical Braak&Braak stages**

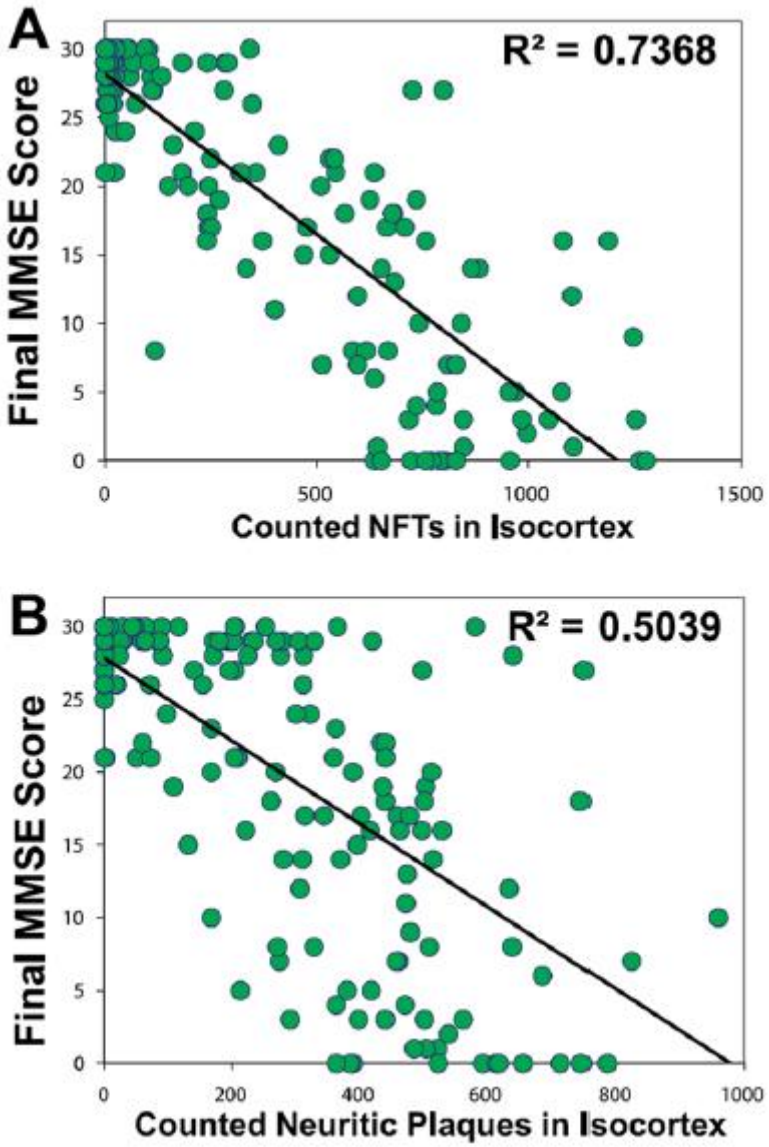
Braak et al *J Neuropathol Exp Neurol 2011;70, 960*

Neurofibrillary degeneration in the L.coer. early in life



Braak & Del Tredici *Curr Opin Neurol 2008;12:708*

Neuritic pathology correlates best with cognitive decline



Nelson *J NPathExpNeurol 2012;71:263*

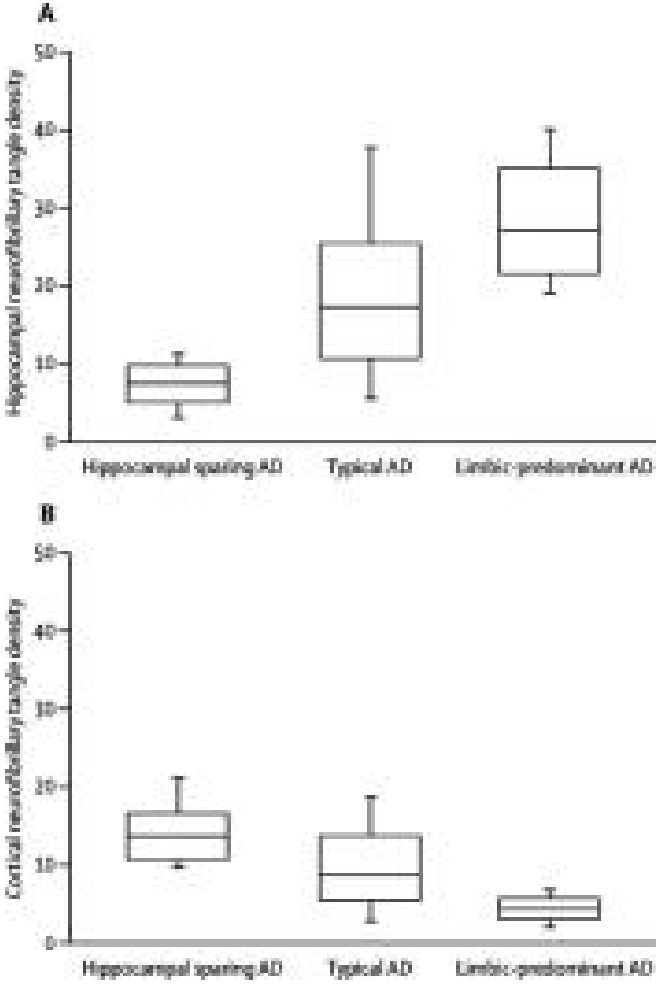
Lancet Neurol. 2011 September ; 10(9): 785–796. doi:10.1016/S1474-4422(11)70156-9.

Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study

Melissa E. Murray, PhD[1], **Neill R. Graff-Radford, MBBCh, FRCP (London)**[3], **Owen A. Ross, PhD**[1], **Ronald C. Petersen, MD**[4], **Ranjan Duara, MD**[5], and **Dennis W. Dickson, MD**[1]

Hipp NFT

Cort NFT

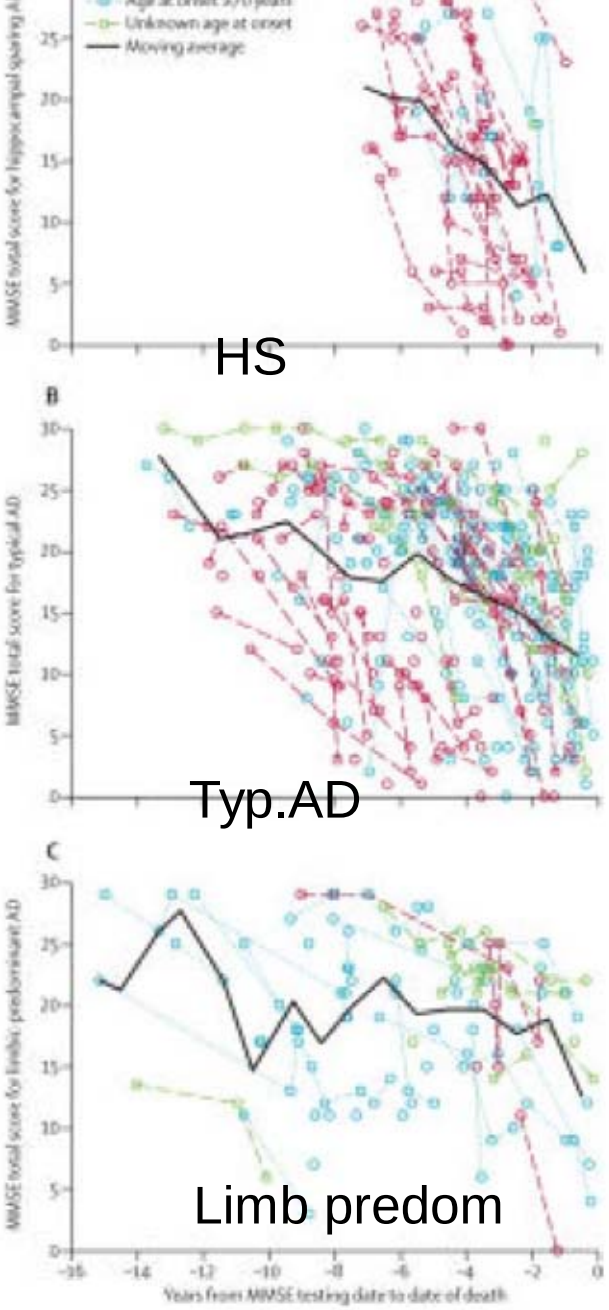


Hippoc. Sparing AD

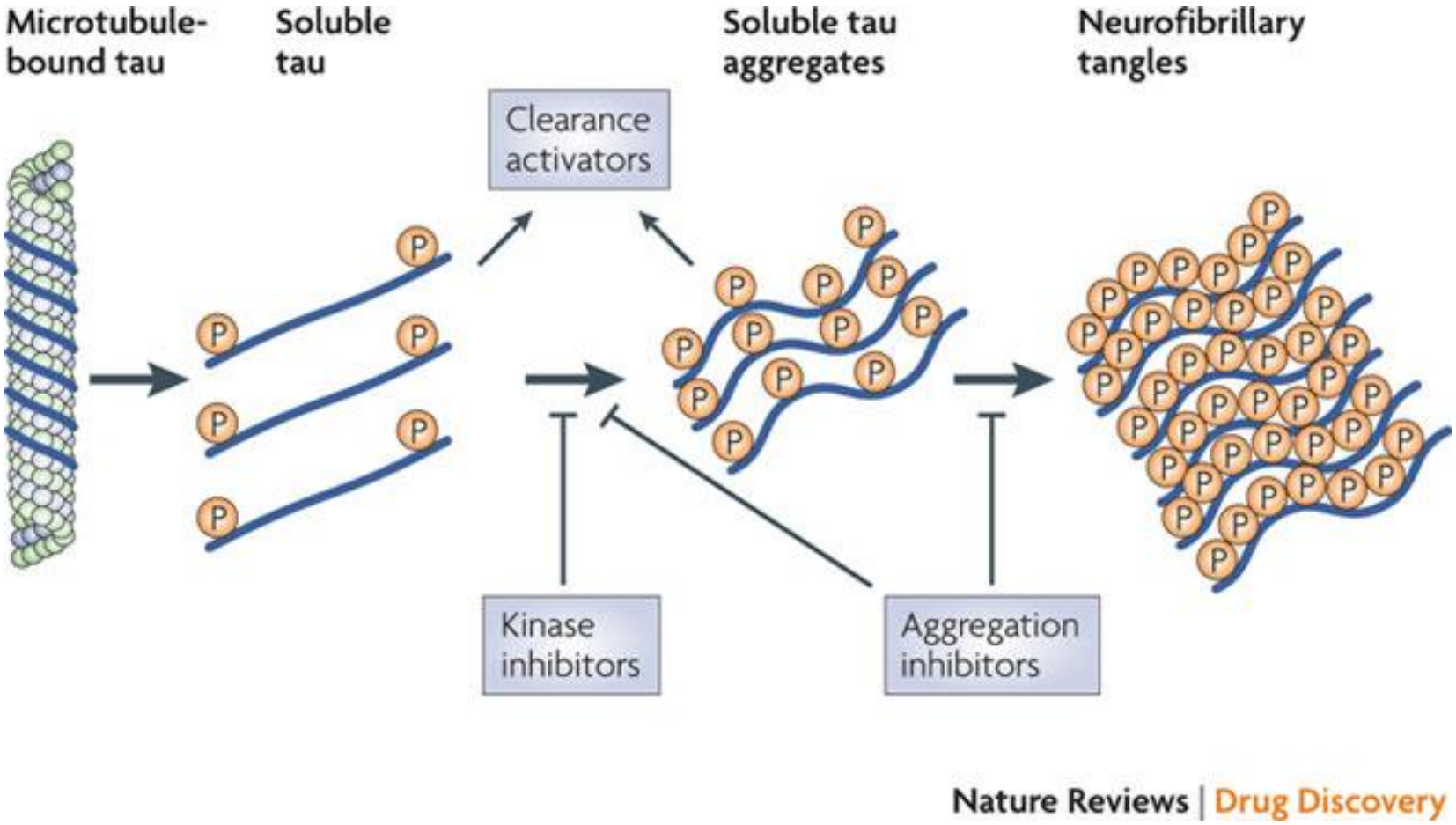
Typical AD

Limbic predominant AD

MMSE



Years MMSE until death



Citron

Nature Reviews 2010;9:387

Experimental therapies targeting Tau

Kinase inhibitors

Inhibition of Tau fibril formation,
and their co-factors *(small molecules, anti-lipids, heparine, N744, PTH)*
Fibril assembly inhibitors and dissolution of aggregates

Clearing of misfolded tau (chaperones)

Stabilisation of microtubuli (palcitaxel et al.)

Aß oligomers directed therapies

Anti-inflammatory therapies

Ballatore, Lee, Trojanowski *Nature Review Neuroscience 2007;8:663*
Brunden *Exp Neurology 2010;223:304*

Summary

- Tau pathology is found early in live both subcortically and in the cortex
- Early subcortical tau pathology is found in AD-before amyloid changes
- These findings lead to a revision of the Braak&Braak classification-
  Inclusion of early subcortical pathology
- Tau pathology is mandatory for the neuropathological diagnosis of AD
- CSF Tau and P-Tau are increased and Aß reduced in prodromal AD
- There is an interaction of Aß and Tau
- Neurofibrillary degeneration correlates best with cognitive decline
- There are tau-pathology related clinical subtypes of AD
- Drugs are developed to prevent/treat tau pathology formation
  and progression

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