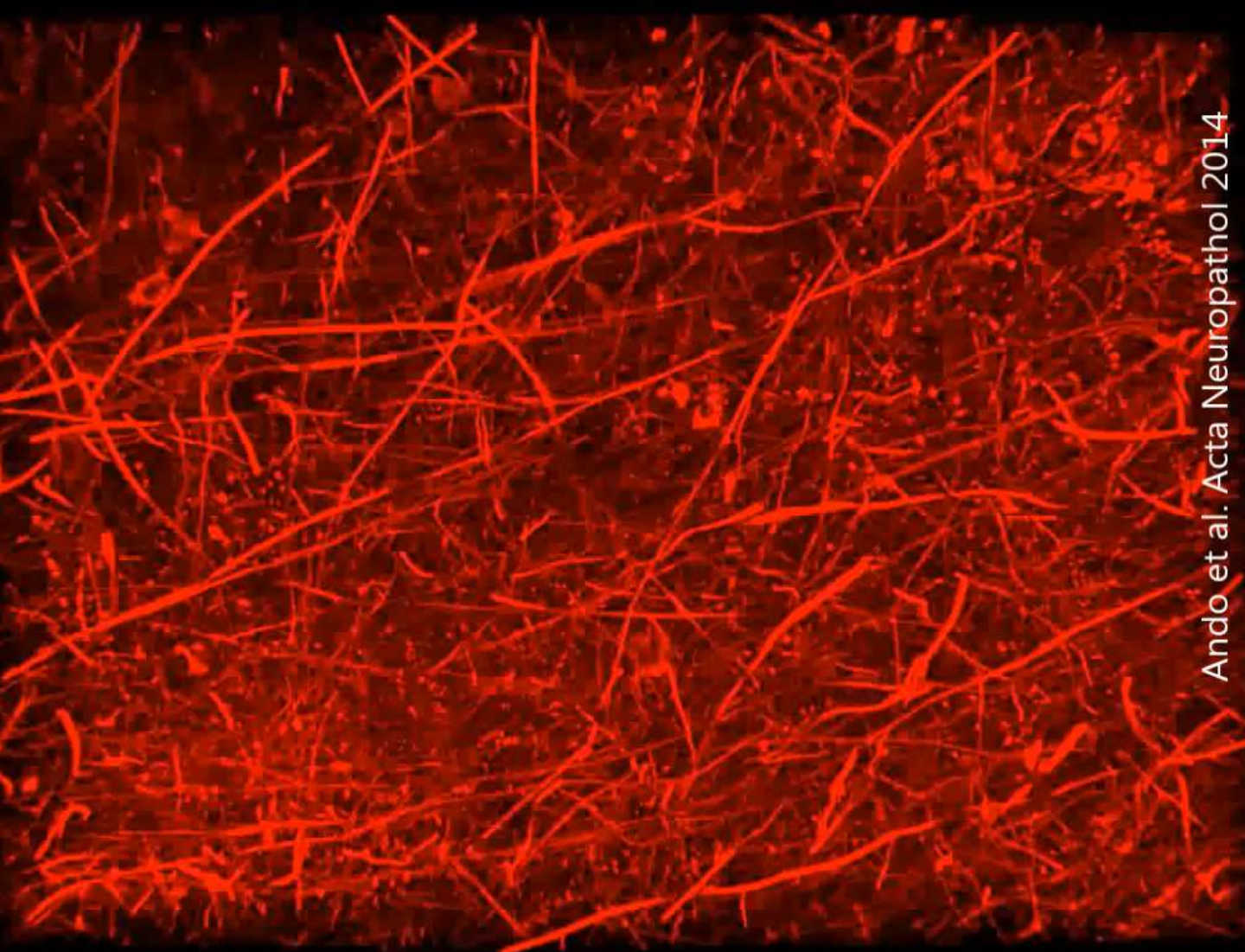
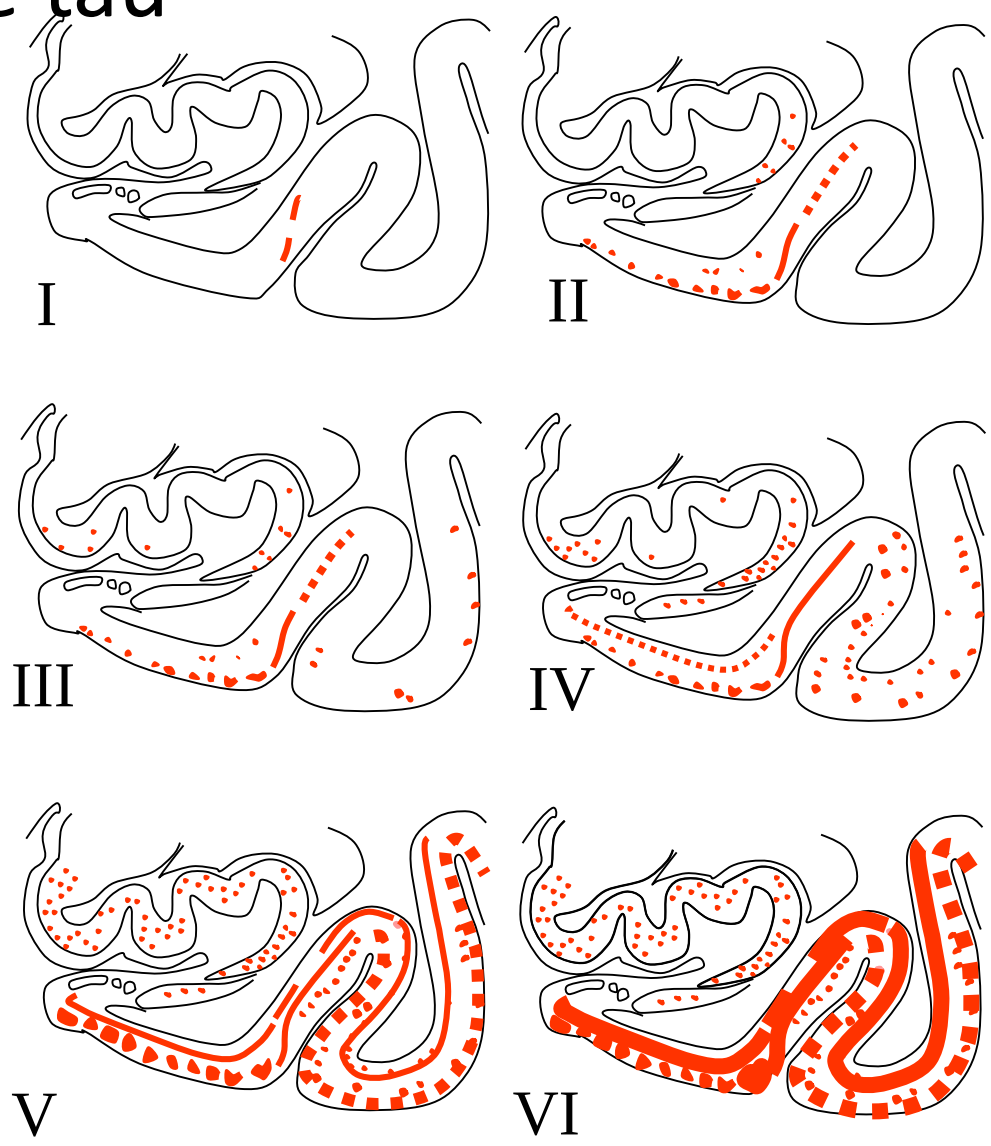
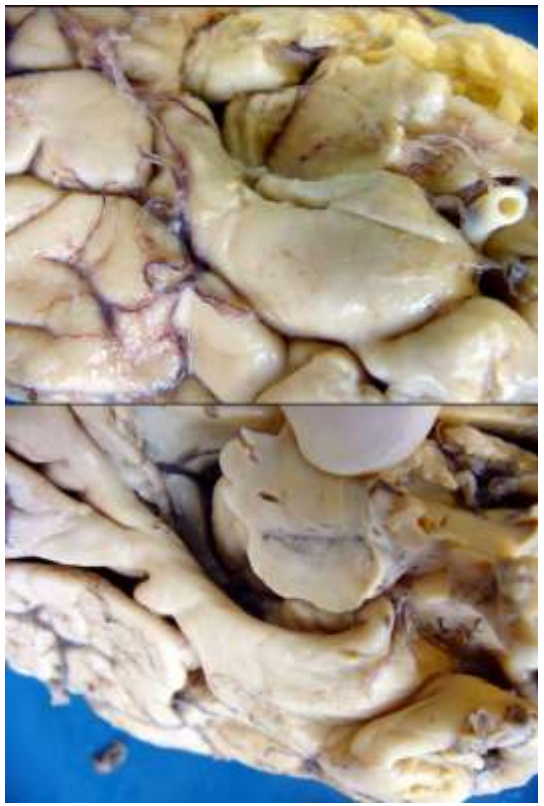
Synergy of Aβ and Tau pathology: Neuropathological Data

Ando K, Laborde Q, Lazar A, Godefroy D, Youssef I, Amar M, Pooler A, Potier MC, Delatour B, Duyckaerts C. Inside Alzheimer brain with CLARITY: senile plaques, neurofibrillary tangles and axons in 3-D. Acta Neuropathol. 2014 Sep;128(3):457-9.



Pathologie tau



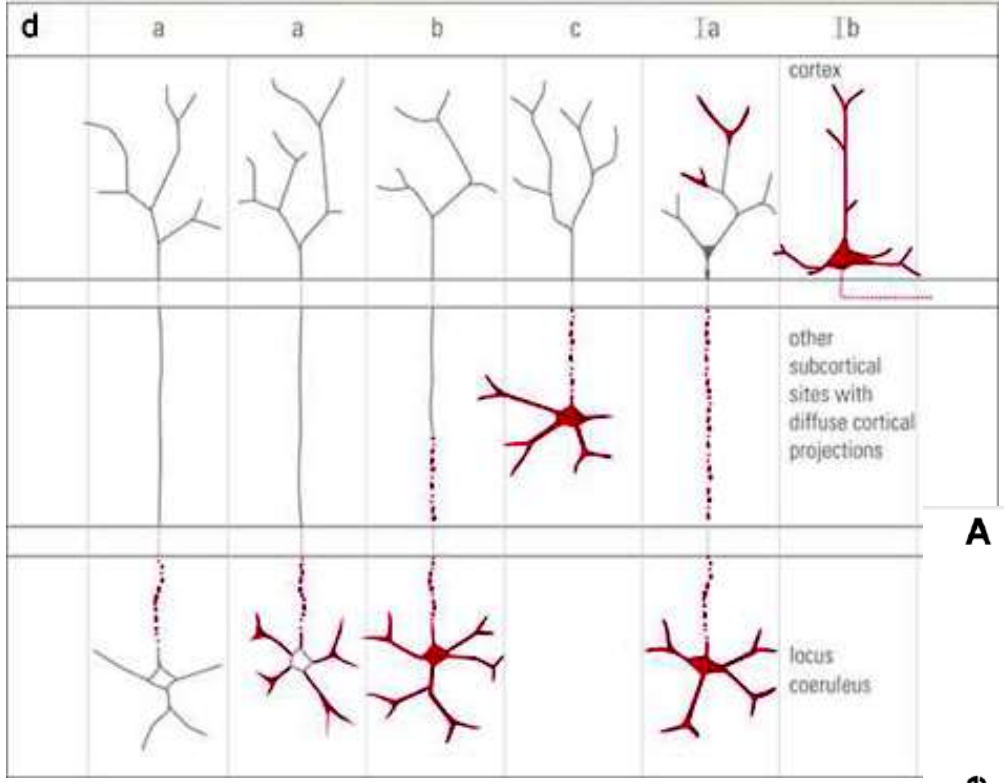


Neuropathological stageing of Alzheimer-related changes

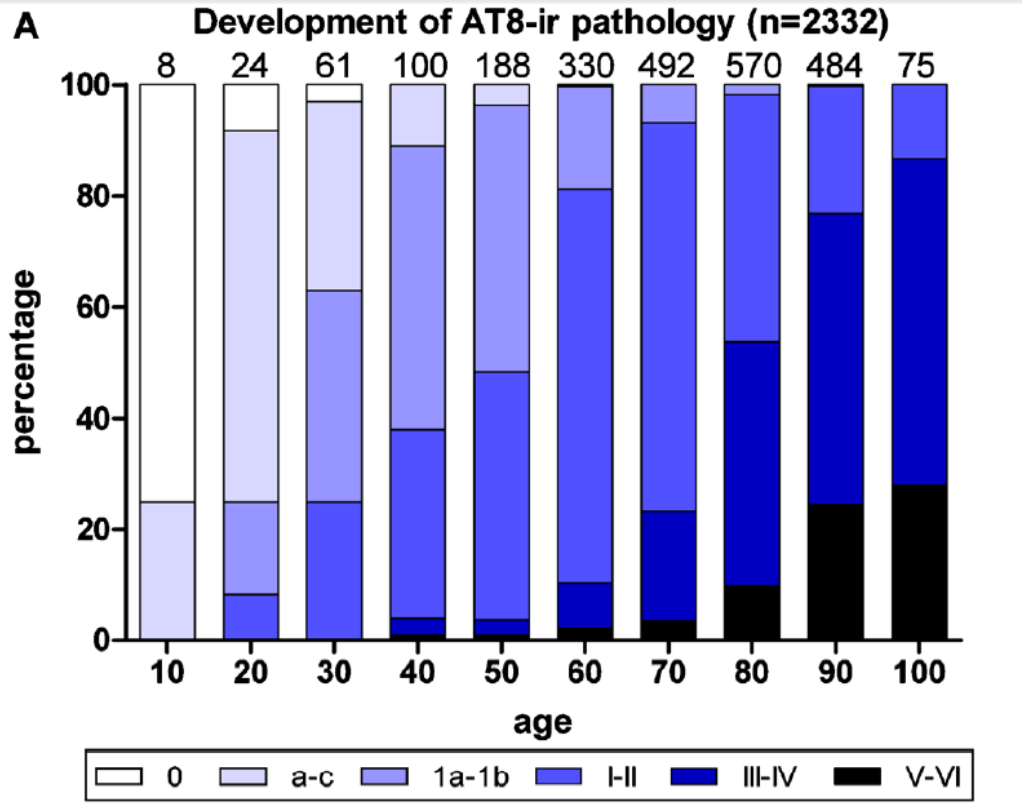
H. Braak and E. Braak*

Acta Neuropathol (1991) 82: 239 – 259

Zentrum der Morphologie, Theodor-Stern-Kai 7, W-6000 Frankfurt/Main 70, Federal Republic of Germany



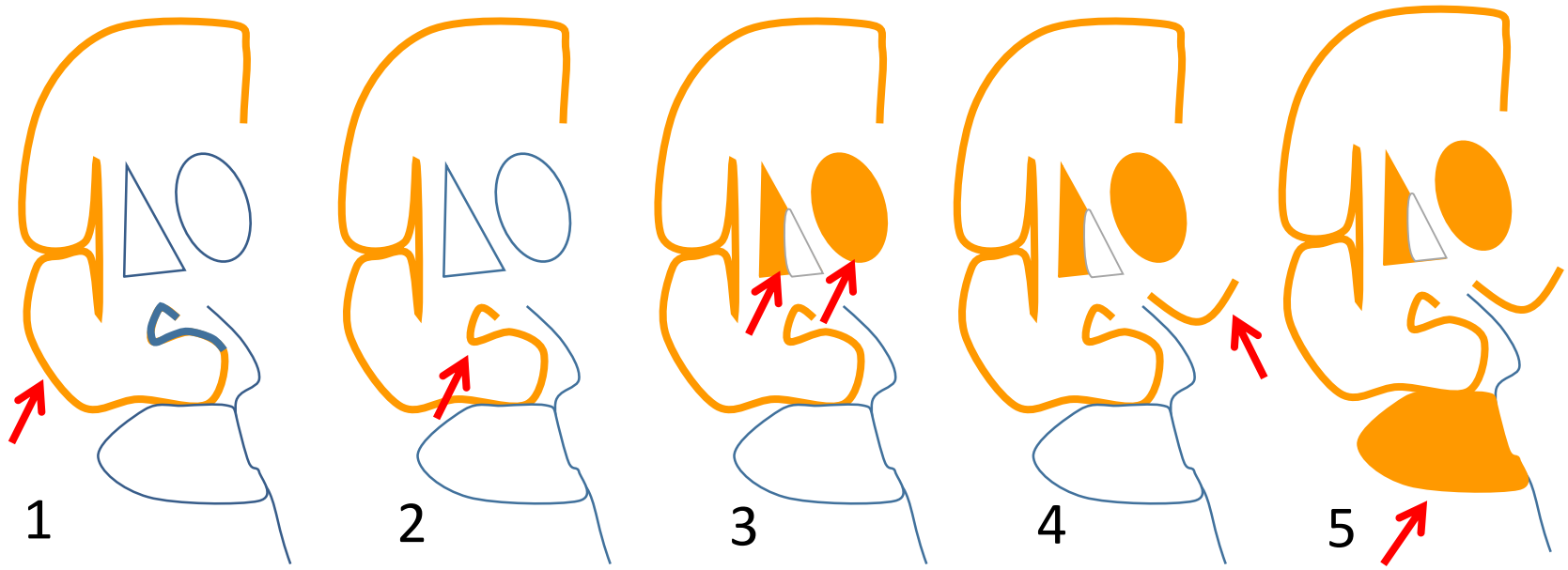
Braak & Del Tredici, Acta Neuropathol 2011



Braak et al. J Neuropath Exp Neurol 2011

Duyckaerts C (2011) Tau pathology in children and young adults: can you still be unconditionally baptist? Acta Neuropathol 121 (2):145-147.

Aβ deposits



Phases of Aβ-deposition in the human brain and its relevance for the development of AD

Dietmar R. Thal, MD; Udo Rüb, MD; Mario Orantes, MD; and Heiko Braak, MD

NEUROLOGY 2002;58:1791–1800

letters to nature

Nature **353**, 844 - 846 (31 October 1991); doi:10.1038/353844a0

Early-onset Alzheimer's disease caused by mutations at codon 717 of the β-amyloid precursor protein gene

MARIE-CHRISTINE CHARTIER-HARLIN, FIONA CRAWFORD, HENRY HOULDEN, ANDREW WARREN*, DAVID HUGHES, LIANA FIDANI, ALISON GOATE, MARTIN ROSSOR, PENELOPE ROQUES, JOHN HARDY & MIKE MULLAN†

Alzheimer's Disease Research Group, Departments of Biochemistry and Neurology, St Mary's Hospital Medical School, Imperial College, London W2 1PG, UK
*Departments of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA
†To whom correspondence should be addressed

A MUTATION at codon 717 of the β-amyloid precursor protein gene has been found to cosegregate with familial Alzheimer's disease in a single family[1]. This mutation has been reported in a further five out of ~ 100 families multiply affected by Alzheimer's disease[1–4]. We have identified another family, F19, in which we have detected linkage between the β-amyloid precursor protein gene and Alzheimer's disease. Direct sequencing of exon 17 (ref. 5) in affected individuals from this family has revealed a base change producing a Val → Gly substitution, also at codon 717. The occurrence of a second allelic variant at codon 717 linked to the Alzheimer's phenotype supports the hypothesis that they are pathogenic mutations.

APP

ARTICLES

Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease

R. Sherrington*, E. I. Rogaev*, Y. Liang*, E. A. Rogaeva*, G. Levesque*, M. Ikeda*, H. Chi*, C. Lin*, G. Li*, K. Holman*, T. Tsuda*, L. Mar†, J.-F. Foncin§, A. C. Bruni‖, M. P. Montesi‖, S. Sorbi‖, I. Rainero¶, L. Pinessi¶, L. Nee☆, I. Chumakov, D. Pollen††, A. Brookes†, P. Sanseau**, R. J. Polinsky‡‡, W. Wasco‡‡, H. A. R. Da Silva§§, J. L. Haines‡‡, M. A. Pericak-Vance§§, R. E. Tanzi‡‡, A. D. Roses§§, P. E. Fraser*, J. M. Rommens† & P. H. St George-Hyslop*¶‖**

* Centre for Research into Neurodegenerative Diseases, Departments of Medicine (Neurology) and Medical Biophysics, University of Toronto, Toronto, and Department of Medicine, Division of Neurology, The Toronto Hospital, Toronto, Ontario, M5S 1A8, Canada
† Research Institute, The Hospital for Sick Children, and Department of Molecular and Medical Genetics, University of Toronto, Toronto, Ontario, M5S 1A8, Canada
§ Laboratoire de Neurohistologie, Ecole Pratique des Hautes Etudes and U106, INSERM La Salpetriere, 75651 Paris Cedex 13, France
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¶ Department of Neurology and Psychiatry, University of Florence, viale Morgagni 85, Florence, Italy
# Department of Neurology, University of Turin, via Cherasco 15, 10126 Turin, Italy
☆ Clinical Neuropharmacology Section, NINDS, 9000 Rockville Pike, Bethesda, Maryland 20892, USA
** Centre d'Etude Polymorphisme Humaine, 27 Rue Juliette Dodu, 75010, Paris, France
†† Department of Neurology, University of Massachusetts Medical Center, 55 Lake Avenue, Worcester, Massachusetts 01655, USA
‡‡ Molecular Neurogenetics Laboratory and Laboratory of Genetics and Aging, Massachusetts General Hospital, Departments of Neurology and Genetics, Harvard Medical School, Boston, Massachusetts 02114, USA
§§ Bryan Alzheimer's Disease Research Center, Duke University Medical Center, Durham, North Carolina 27710, USA
¶¶ Molecular Pathology, Glaxo Research and Development, Greenford Road, Greenford, Middlesex UB6 0HE, UK
Sandoz Research Institute, Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey 07936, USA
† MRC Human Genetics Unit, Western General Hospital, Crewe Road, Edinburgh, UK

PS1

Candidate Gene for the Chromosome 1 Familial Alzheimer's Disease Locus

Ephrat Levy-Lahad,* Wilma Wasco,* Parvoneh Poorkaj, Donna M. Romano, Junko Oshima, Warren H. Pettingell, Chang-en Yu, Paul D. Jondro, Stephen D. Schmidt, Kai Wang, Annette C. Crowley, Ying-Hui Fu, Suzanne Y. Guenette, David Galas, Ellen Nemens, Ellen M. Wijsman, Thomas D. Bird, Gerard D. Schellenberg,† Rudolph E. Tanzi

A candidate gene for the chromosome 1 Alzheimer's disease (AD) locus was identified (*STM2*). The predicted amino acid sequence for *STM2* is homologous to that of the recently cloned chromosome 14 AD gene (S182). A point mutation in *STM2*, resulting in the substitution of an isoleucine for an asparagine (N141I), was identified in affected people from Volga German AD kindreds. This N141I mutation occurs at an amino acid residue that is conserved in human S182 and in the mouse S182 homolog. The presence of missense mutations in AD subjects in two highly similar genes strongly supports the hypothesis that mutations in both are pathogenic.

PS2

Alzheimer's Disease: The Amyloid Cascade Hypothesis

John A. Hardy and Gerald A. Higgins

The mutations in APP so far described are responsible only for a small proportion of cases of Alzheimer's disease (*23*). Indeed, most cases of Alzheimer's seem to occur in a sporadic fashion, suggesting that there must be other causes of the disease. The cascade hypothesis suggests that other causes of Alzheimer's act by initially triggering AβP deposition. For example, there is an association between head trauma and Alzheimer's (*24*). Dementia pugilistica, exhibited by boxers, may be thought of as a variant of Alzheimer's disease because these individuals exhibit both AβP deposits and neurofibrillary tangles (*25*). Furthermore, amyloid deposition occurs as an acute response to neuronal injury in both man and animals (*26*). This deposition could be

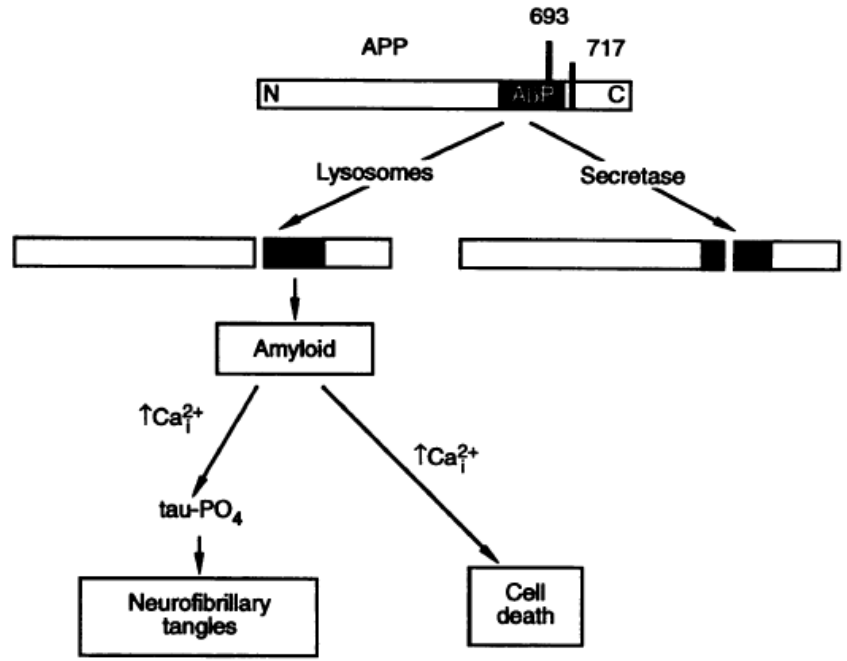
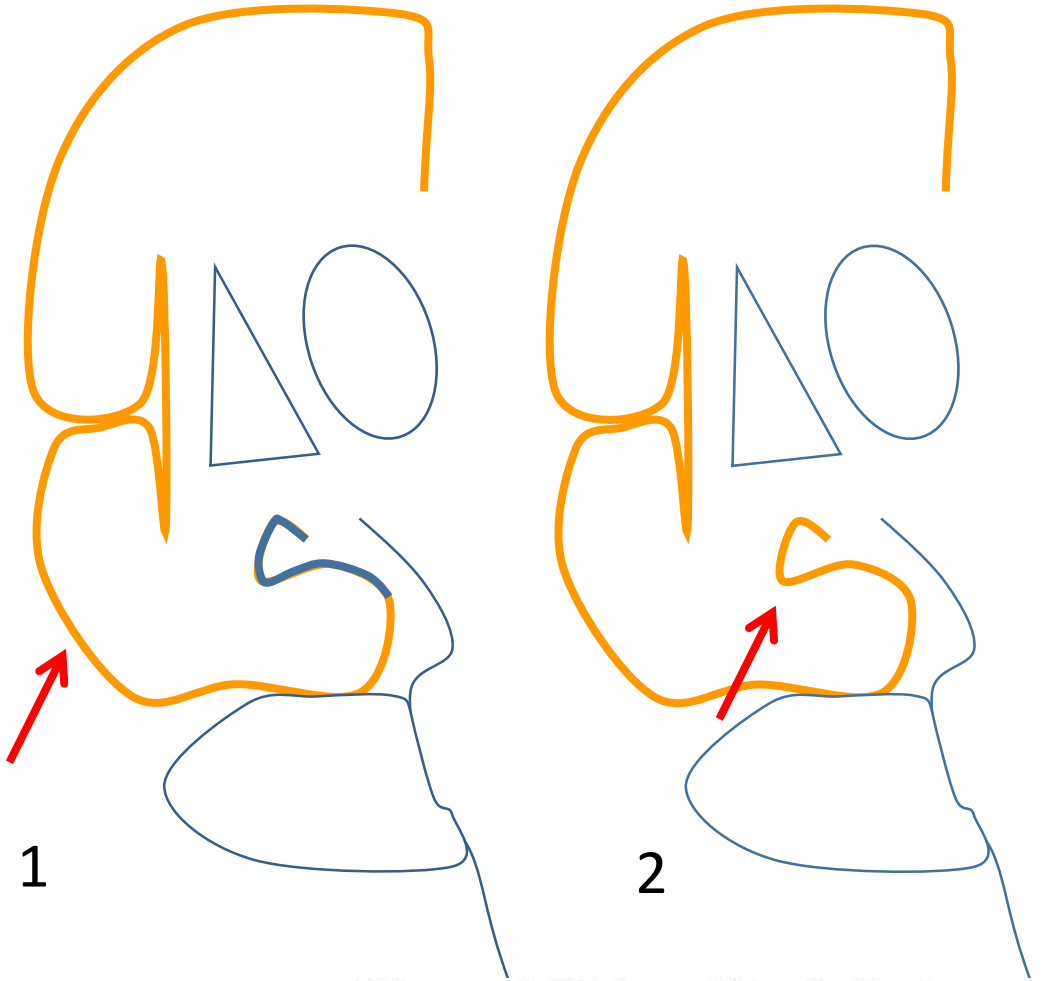


Fig. 1. The amyloid cascade hypothesis. Processing of APP can occur via two pathways: (i) Cleavage within AβP by the secretase, which generates peptide products that do not precipitate to form amyloid and (ii) cleavage in the endosomal-lysosomal compartment, resulting in intact AβP that precipitates to form amyloid and, in turn, causes neurofibrillary tangles and cell death, the hallmarks of Alzheimer's disease.

Aβ is not directly responsible for the symptoms

Aβ pathology

If Aβ was directly toxic, patients should be aphasic, apractic, agnostic very early (Thal phase 1). They should be amnestic secondarily.



Phases of Aβ-deposition in the human brain and its relevance for the development of AD

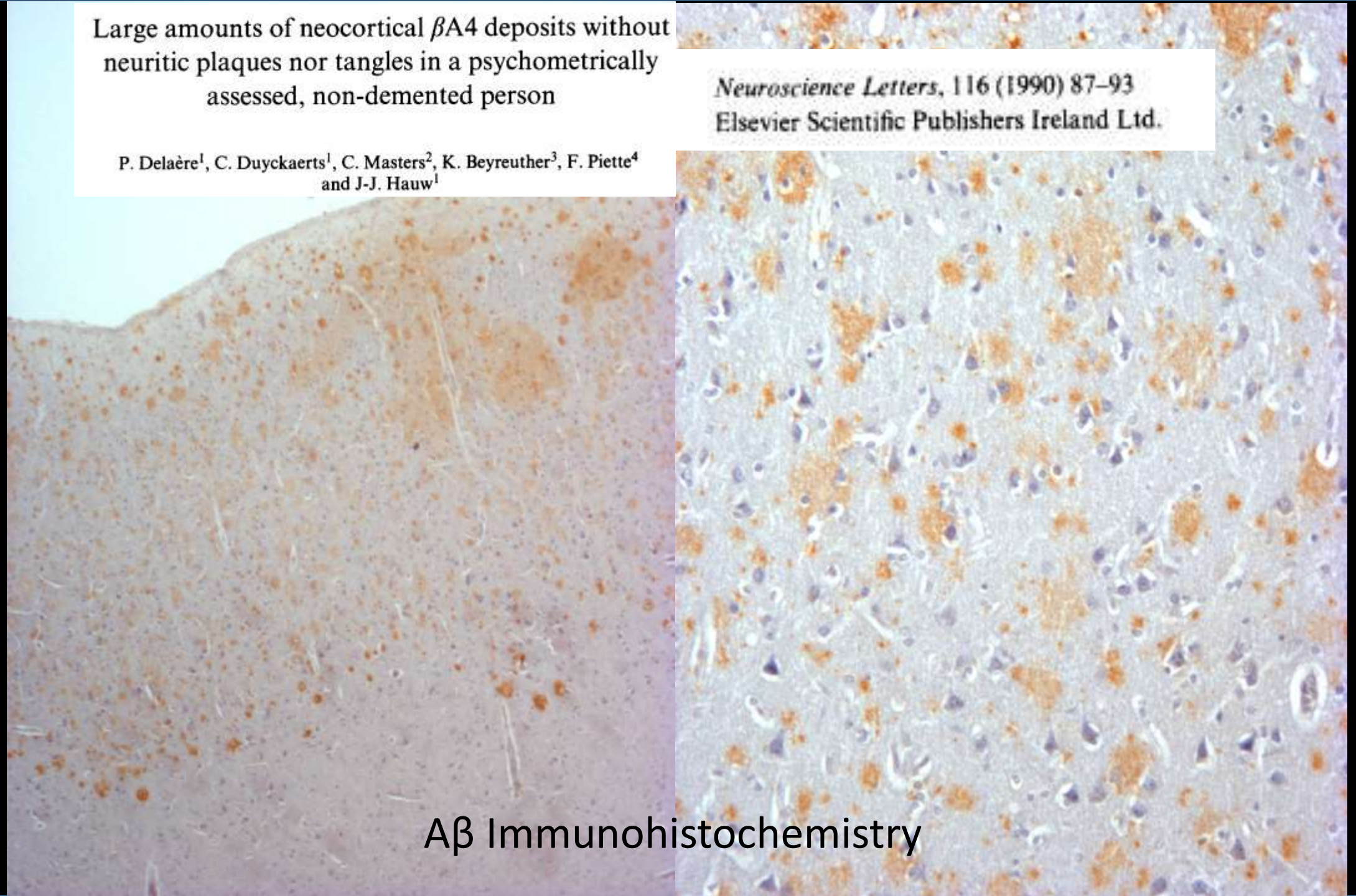
Dietmar R. Thal, MD; Udo Rüb, MD; Mario Orantes, MD; and Heiko Braak, MD

NEUROLOGY 2002;58:1791–1800

Large amounts of neocortical βA4 deposits without neuritic plaques nor tangles in a psychometrically assessed, non-demented person

P. Delaère[1], C. Duyckaerts[1], C. Masters[2], K. Beyreuther[3], F. Piette[4] and J-J. Hauw[1]

Neuroscience Letters, 116 (1990) 87–93
Elsevier Scientific Publishers Ireland Ltd.



Aβ Immunohistochemistry

If Aβ has to be the initiator of the pathology, how does it synchronize with tau pathology ?

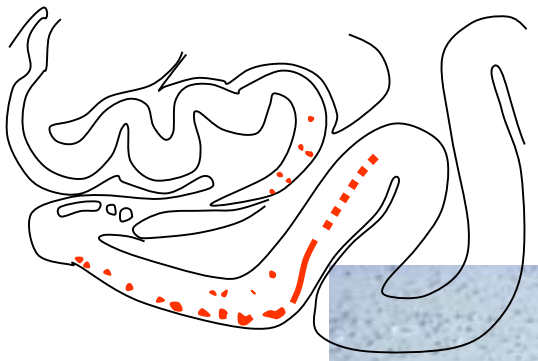
Three examples with three systems of connections:

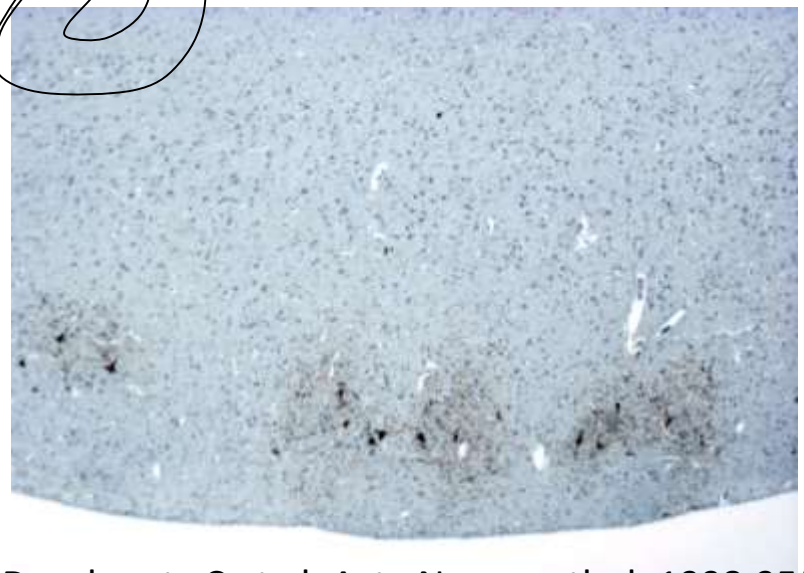
1) Entorhino-dentate
2) Subiculo-fornico-mammillary
3) Subcortico-cortical

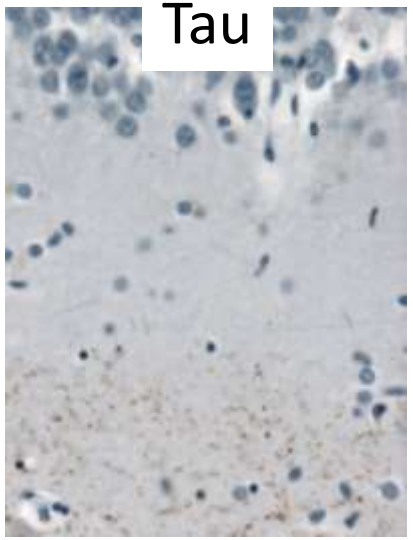
Entorhinal cortex

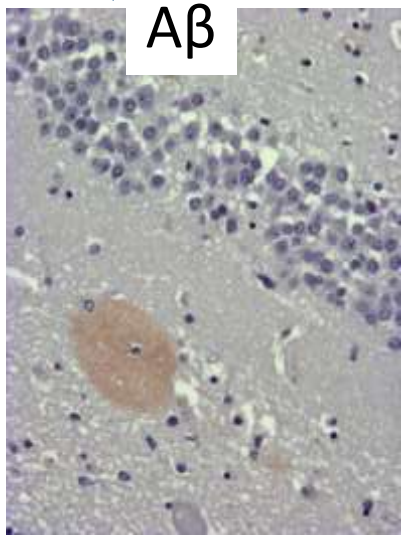
Perforant path

Dentate gyrus

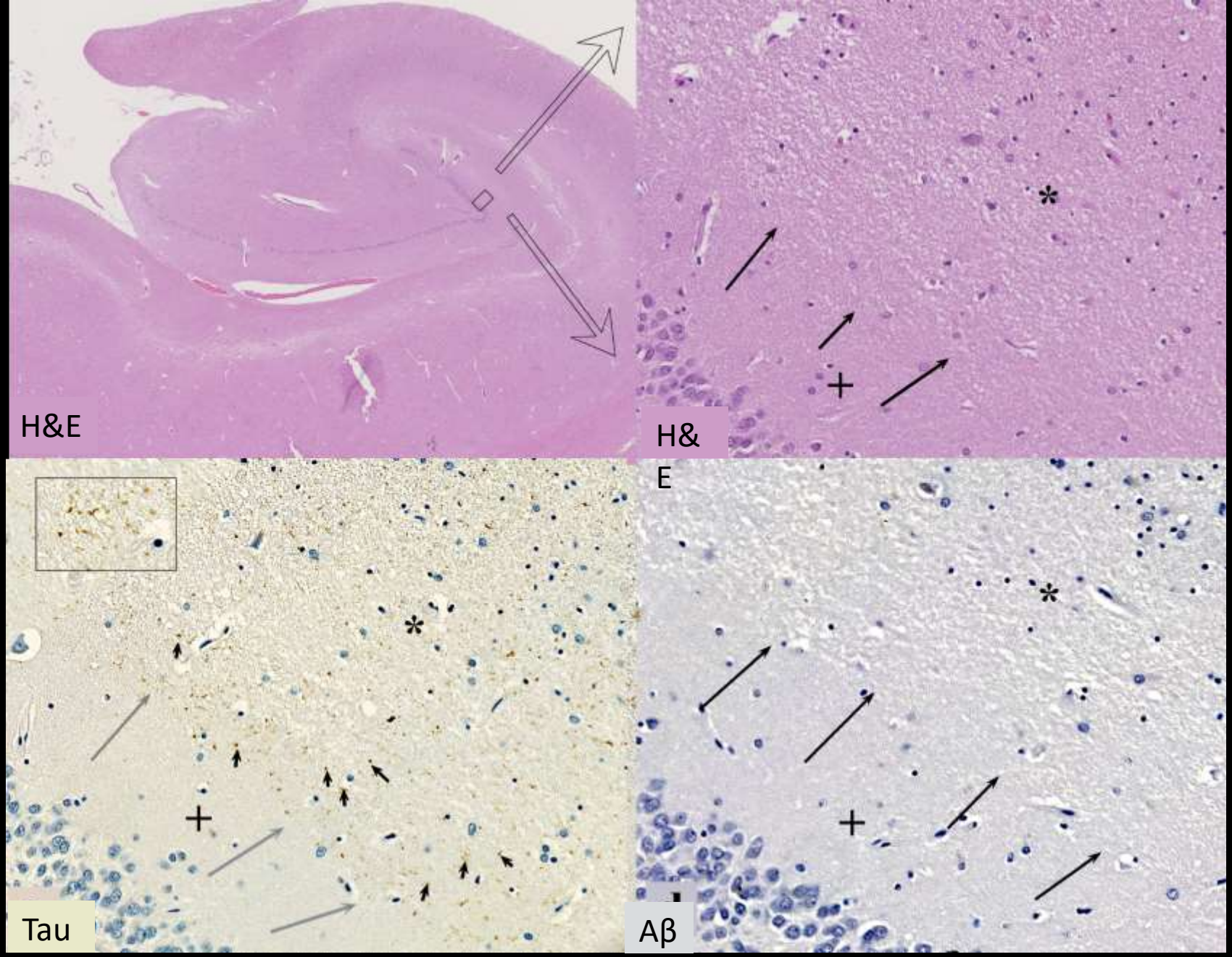








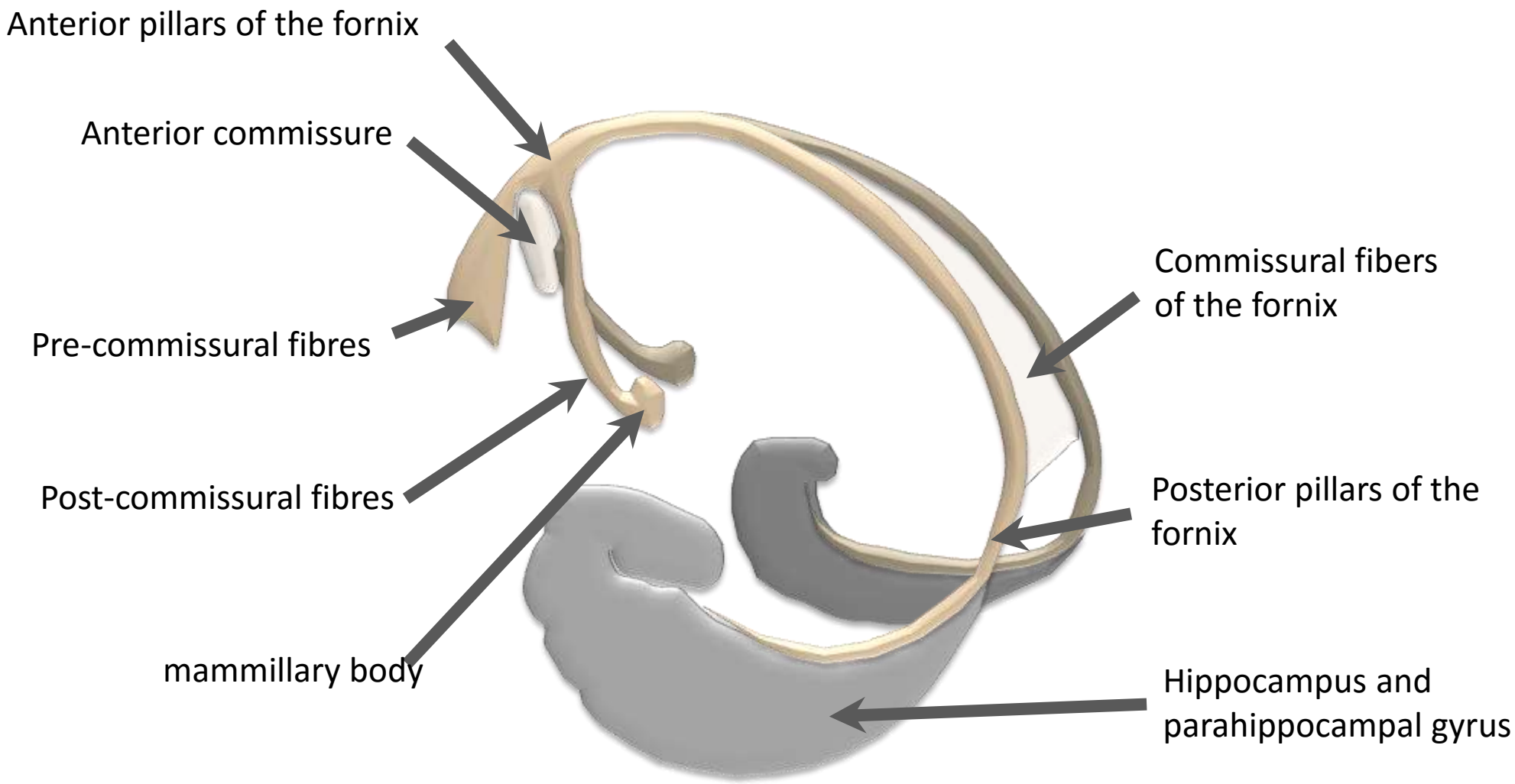
Duyckaerts C et al. Acta Neuropathol. 1998;95(4):413-20.

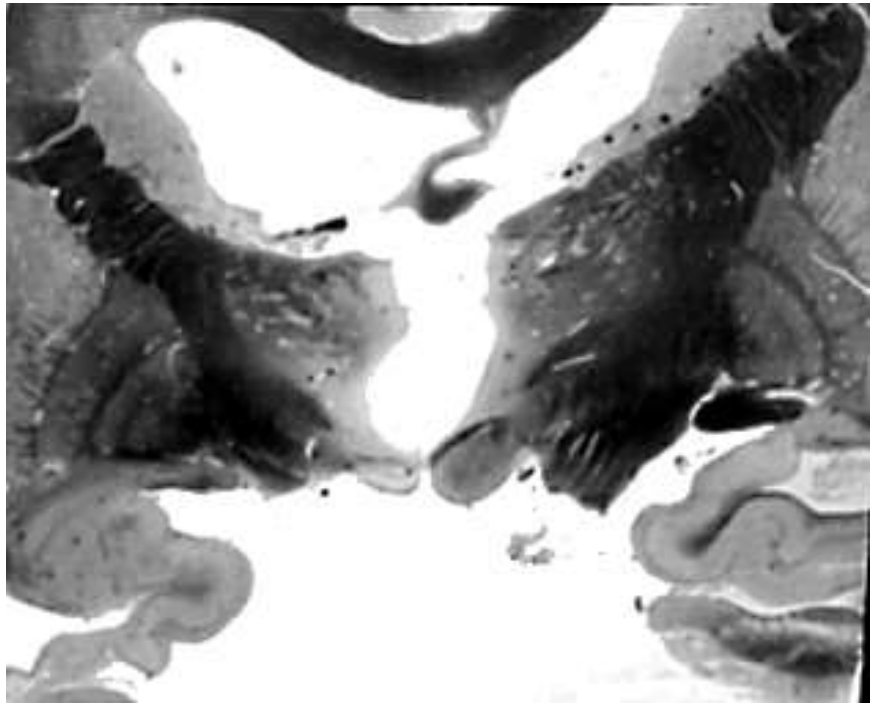


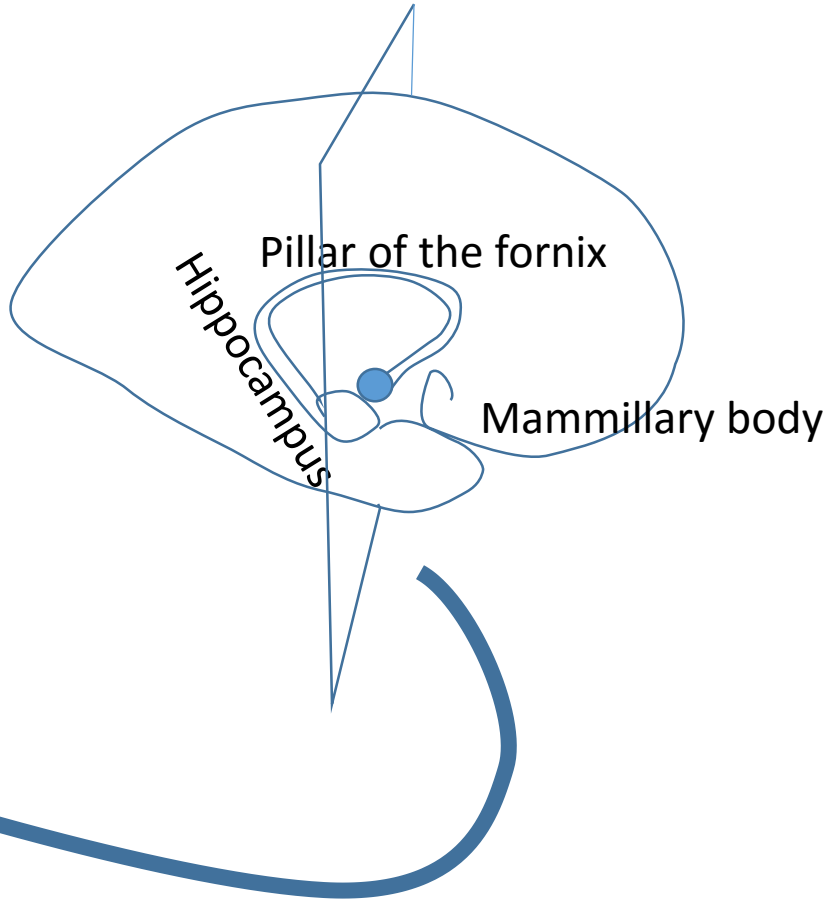
Eisele YS, Duyckaerts C. Propagation of Aß pathology: hypotheses, discoveries, and yet unresolved questions from experimental and human brain studies. Acta Neuropathol. 2015 Dec 29. [Epub ahead of print]

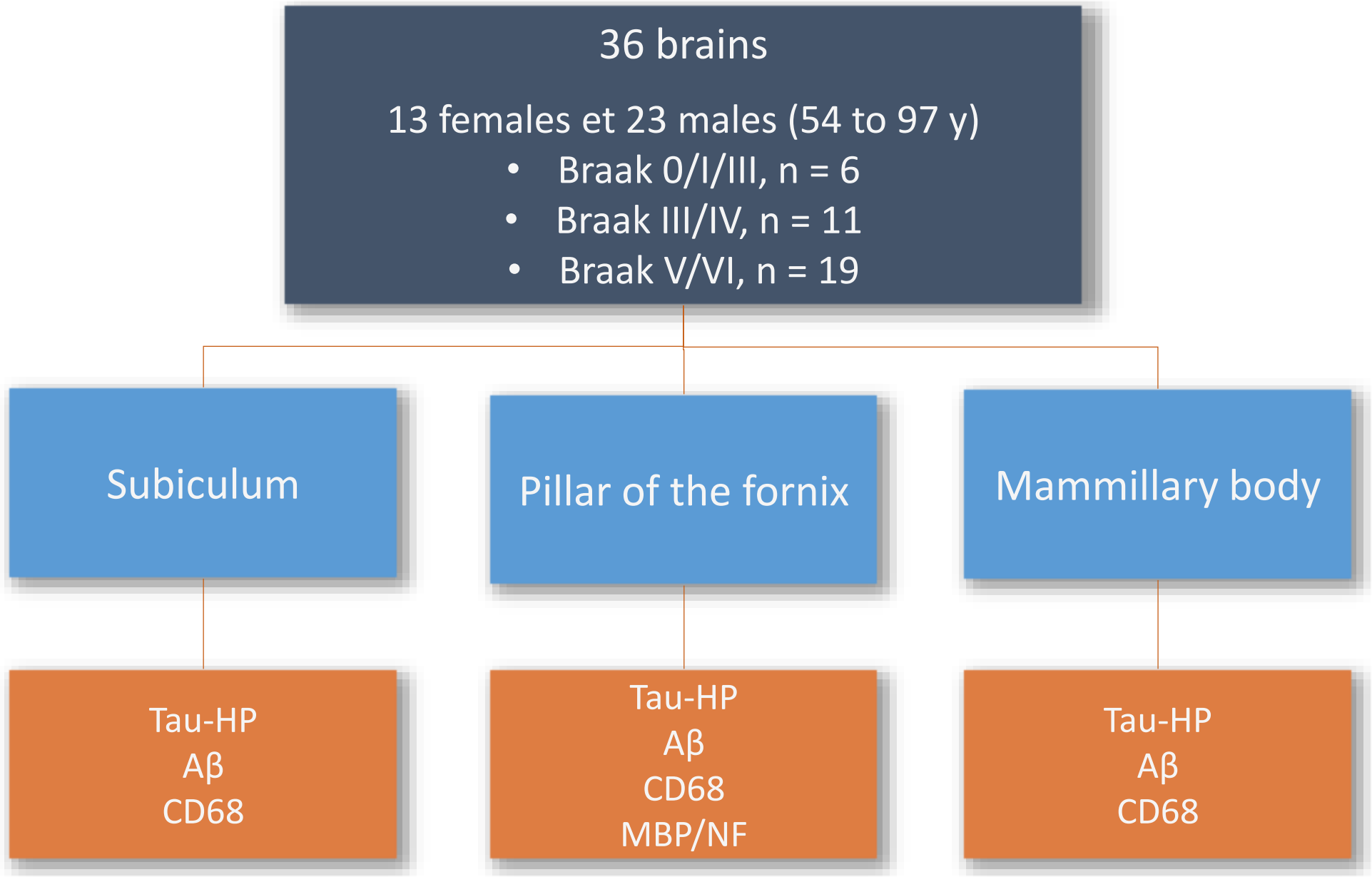
- Tau pathology is apparent ***before*** Aβ accumulation is visible

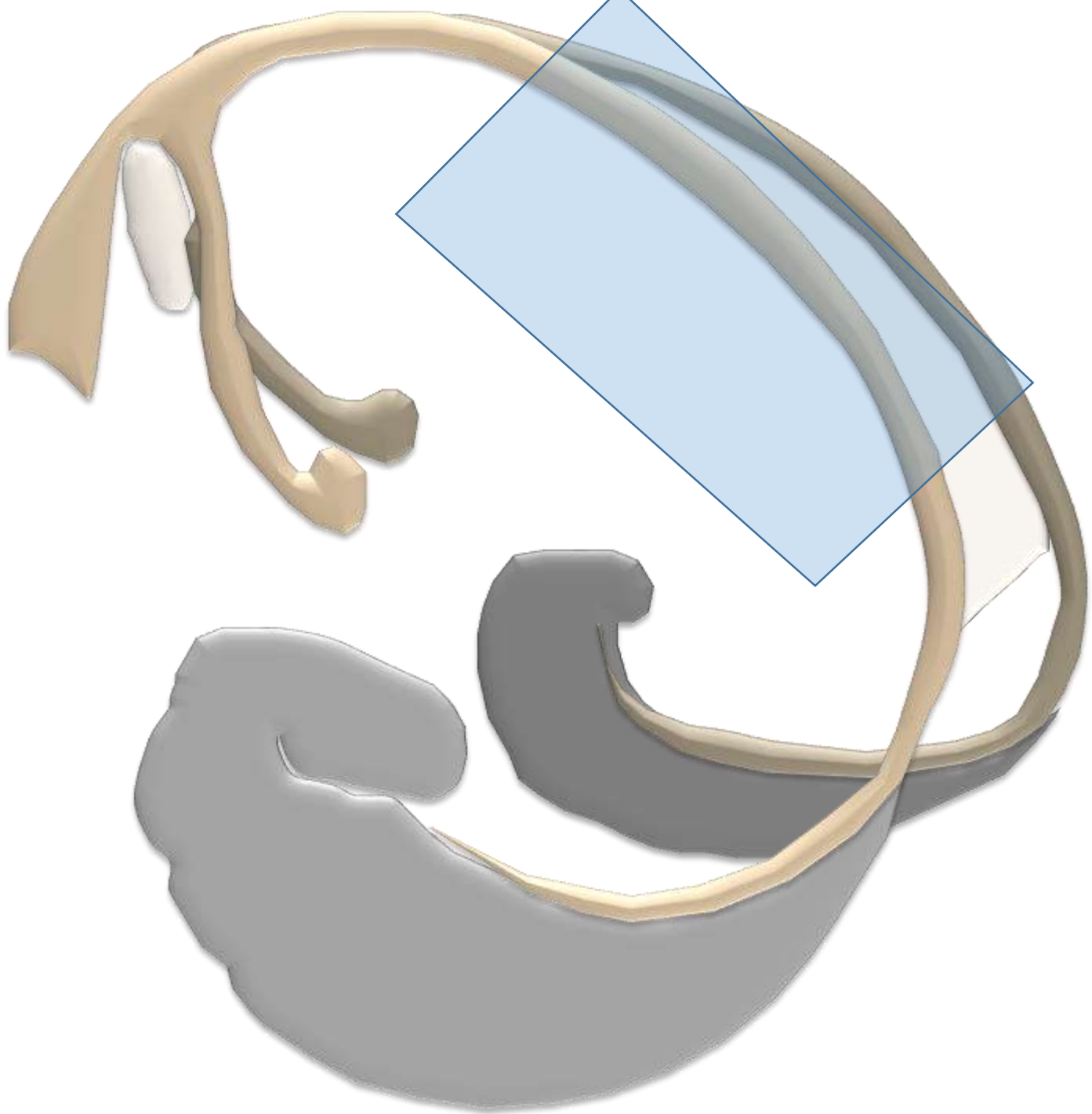
The subiculo-fornico-mammillary system





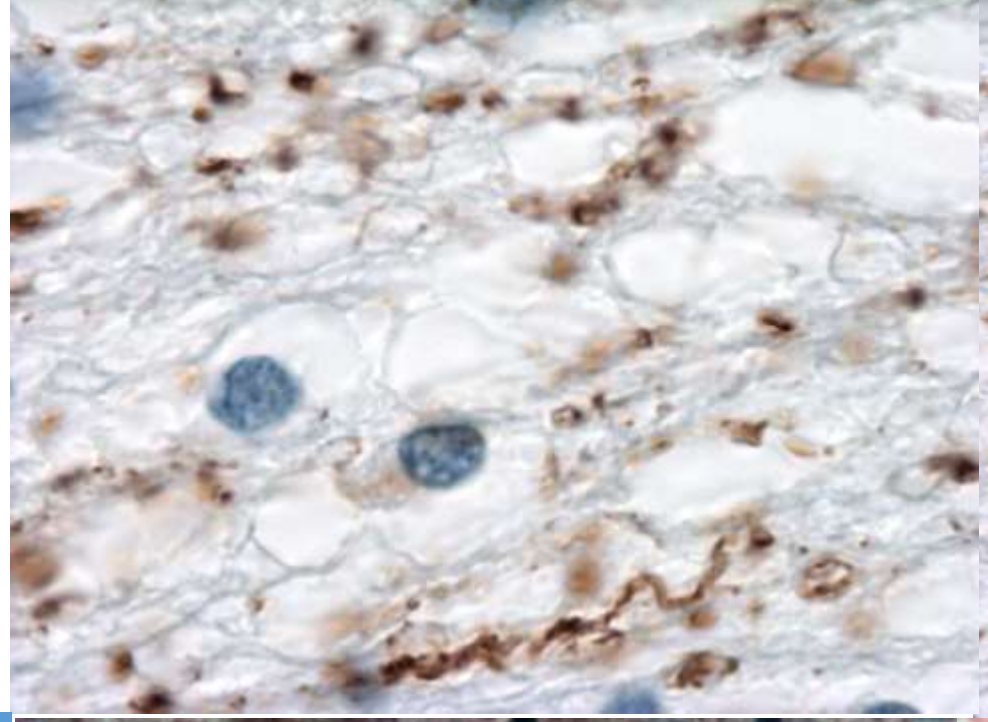

Pillar of the fornix
Hippocampus
Mammillary body

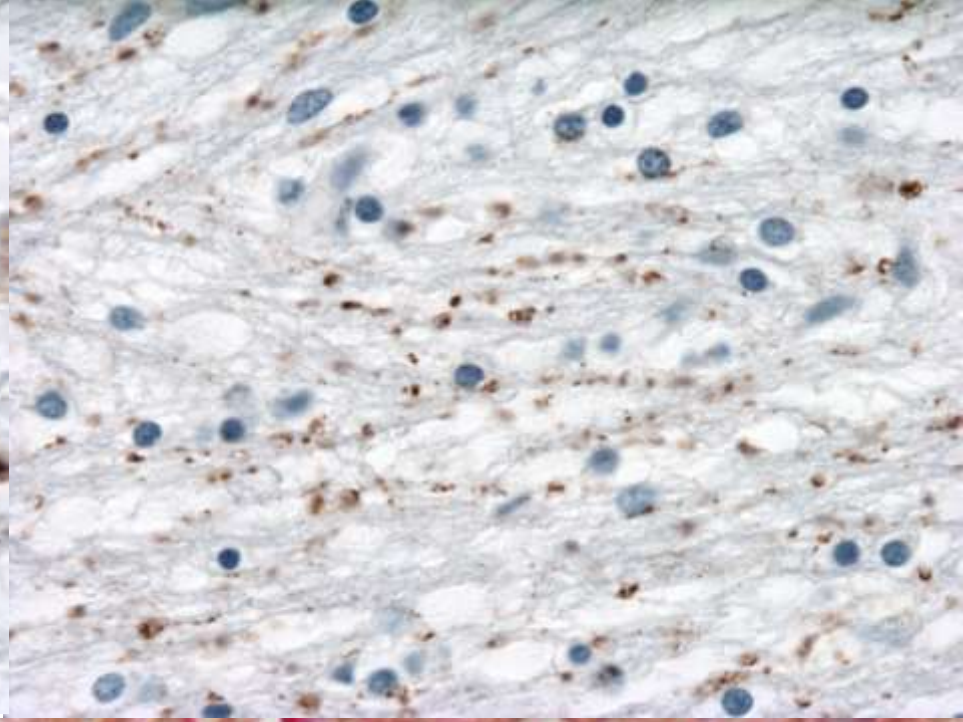

36 brains
13 females et 23 males (54 to 97 y)
• Braak 0/I/III, n = 6
• Braak III/IV, n = 11
• Braak V/VI, n = 19
Subiculum
Pillar of the fornix
Mammillary body
Tau-HP
Aβ
CD68
Tau-HP
Aβ
CD68
MBP/NF
Tau-HP
Aβ
CD68



Pillar of the fornix

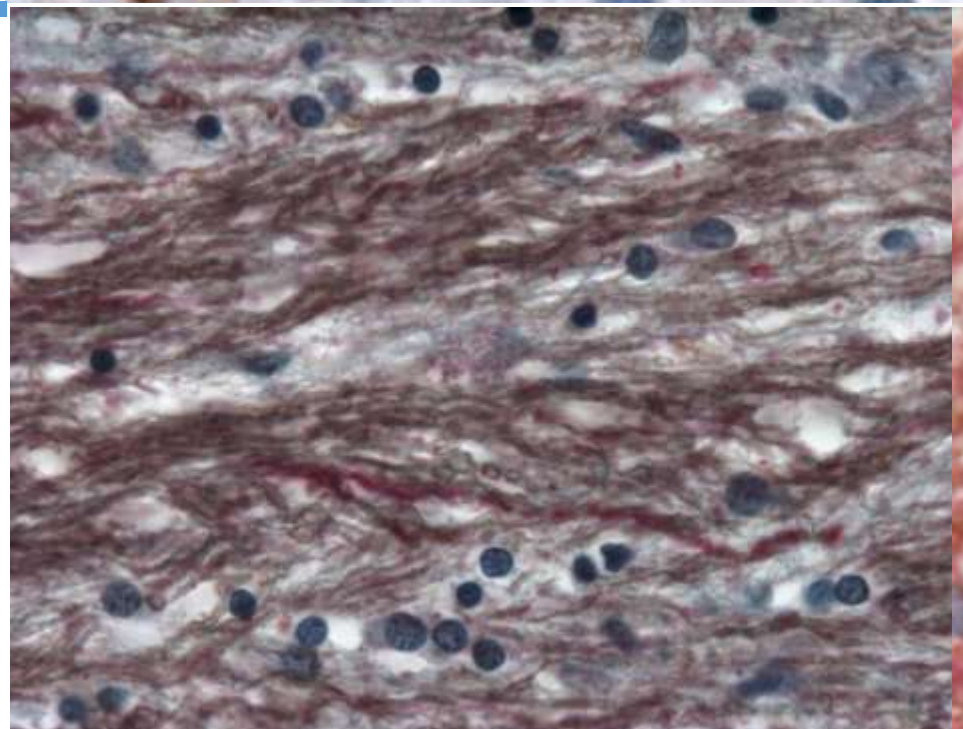
Tau

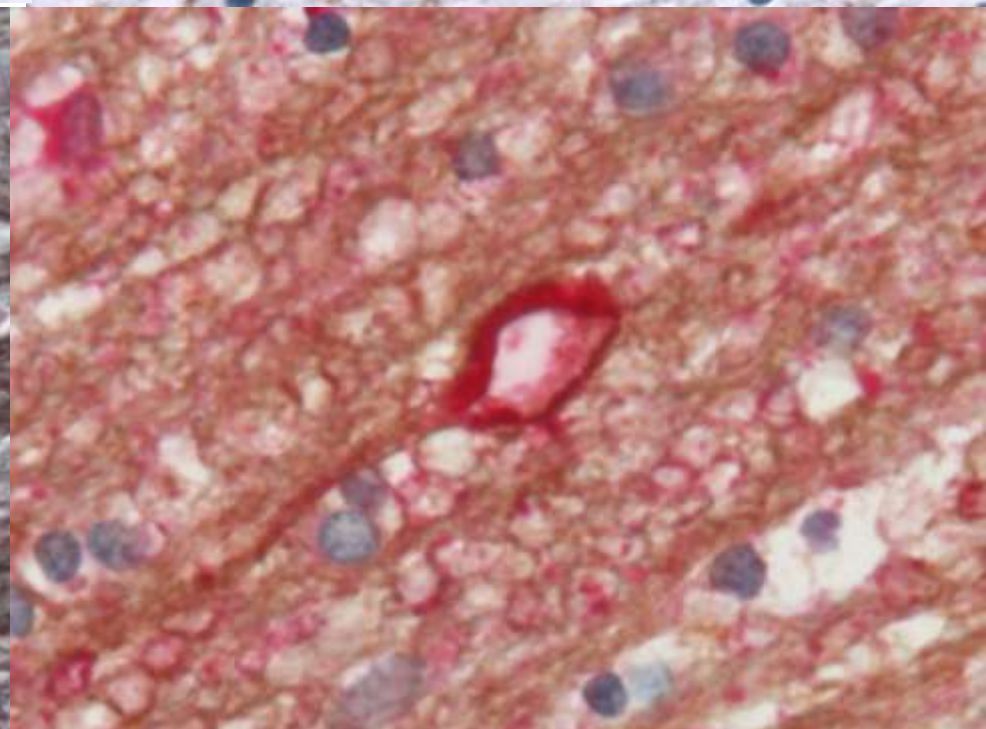


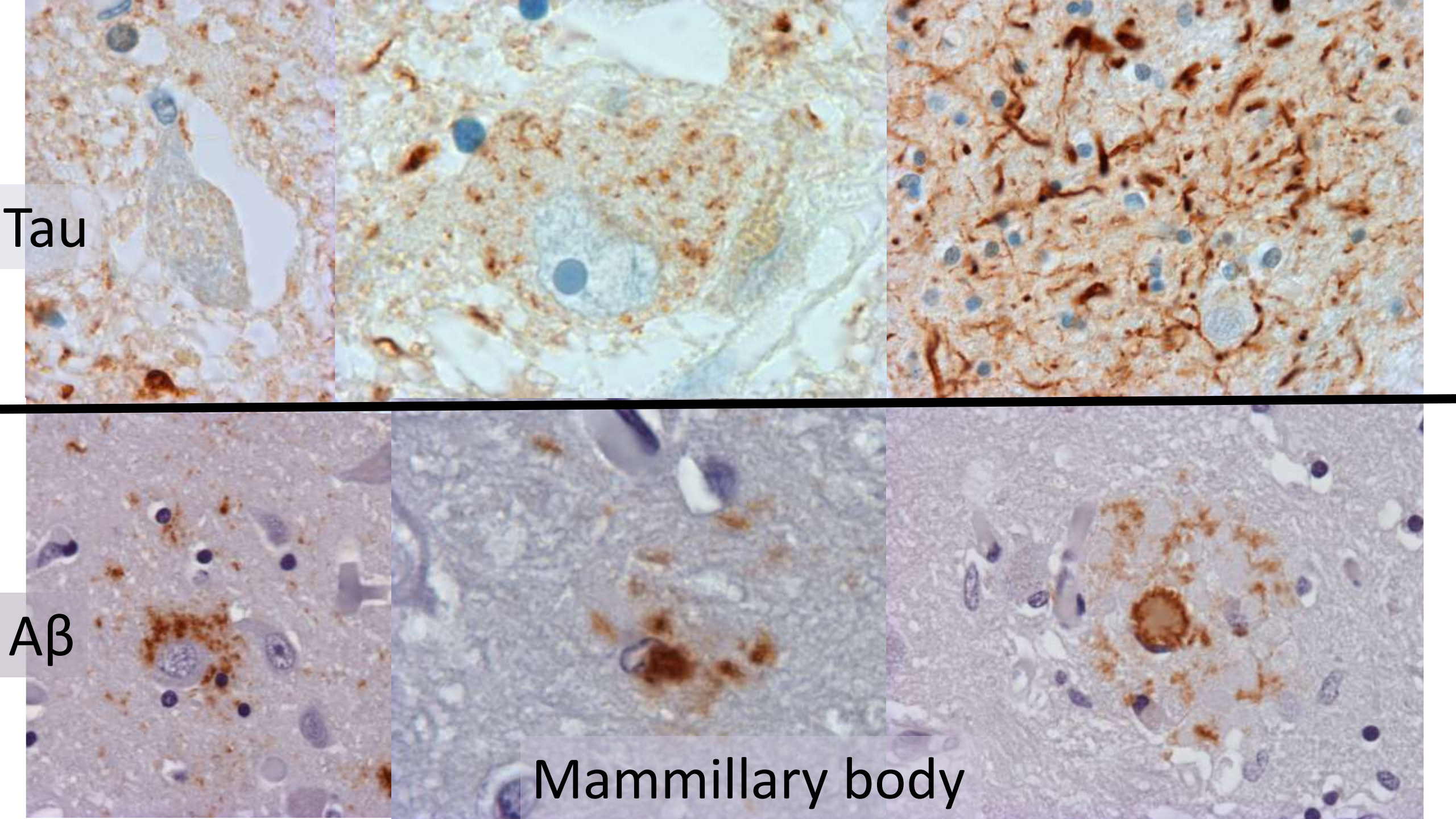


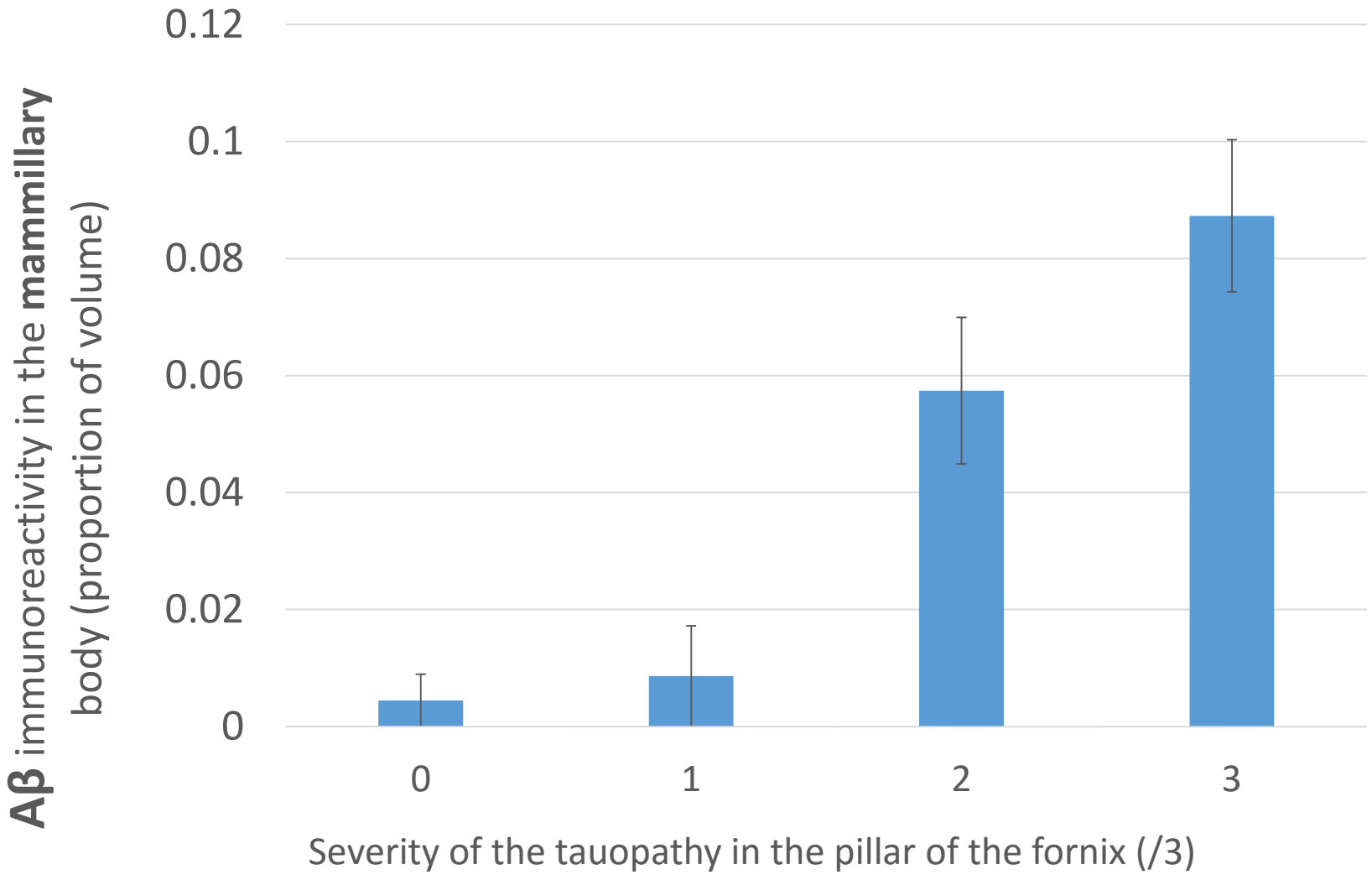
Myelin basic protein: brown

Neurofilament: red



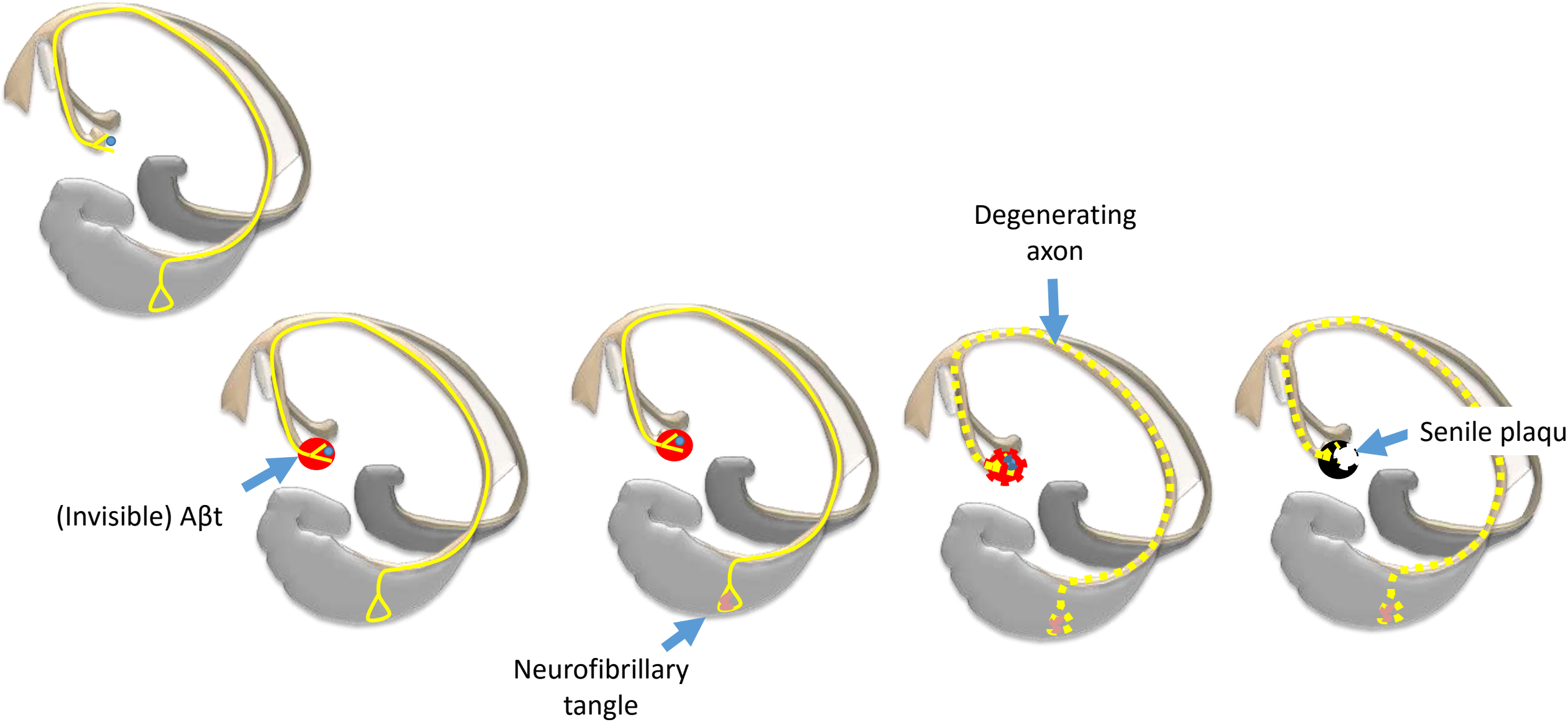


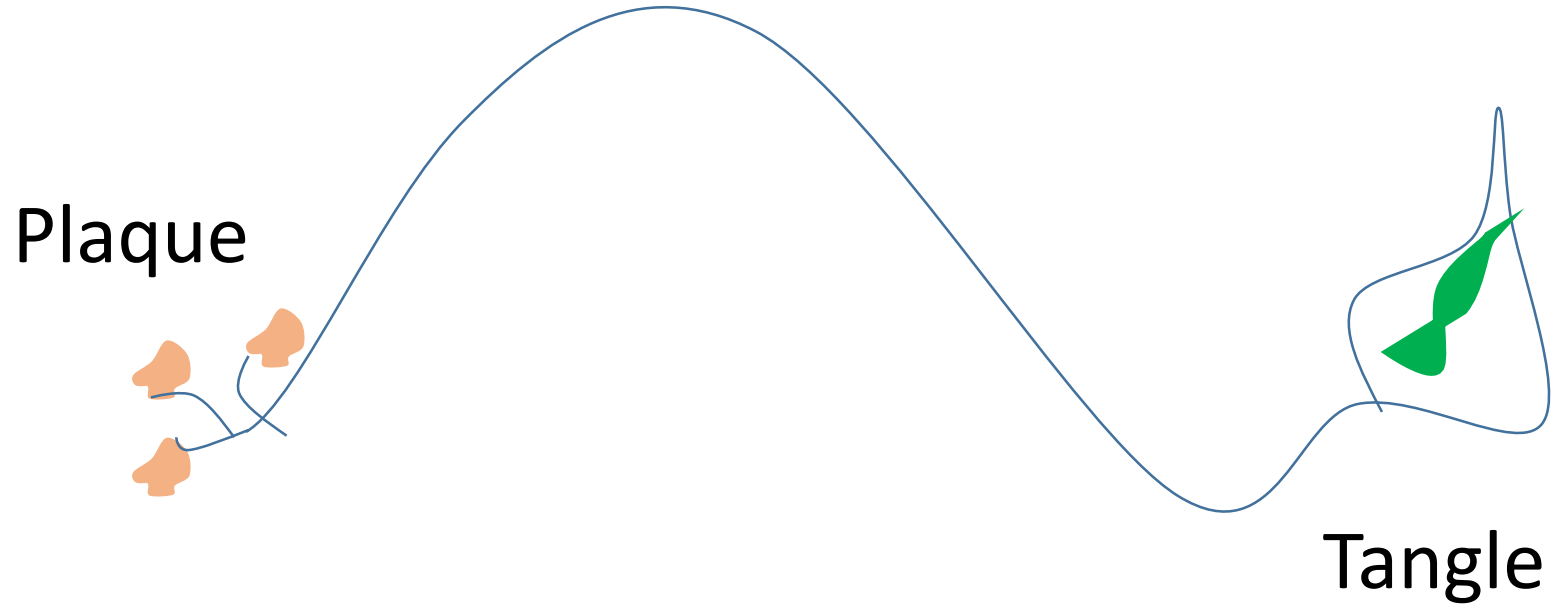

Tau
Aβ
Mammillary body


0.12
0.1
0.08
0.06
0.04
0.02
0
Aβ immunoreactivity in the mammillary body (proportion of volume)
0
1
2
3
Severity of the tauopathy in the pillar of the fornix (/3)

Relationship between axons of the pillar of the fornix and Ab accumulation in the mammillary body

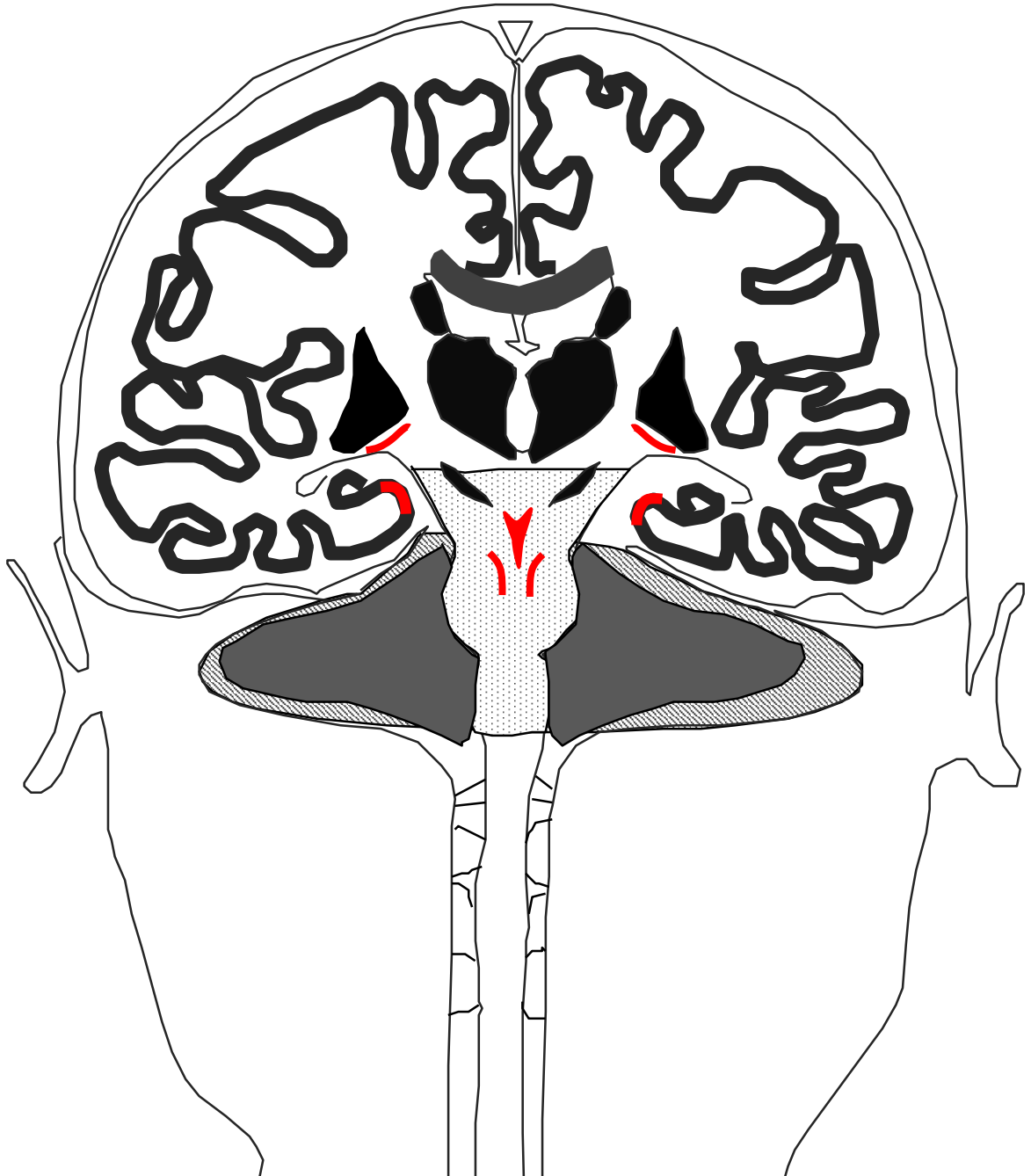
	Aβ – (Mam body)	Aβ + (Mam body)
Tau – (Fornix)	7	1
Tau + (Fornix)	4	21


(Invisible) Aβt
Neurofibrillary tangle
Degenerating axon
Senile plaqu

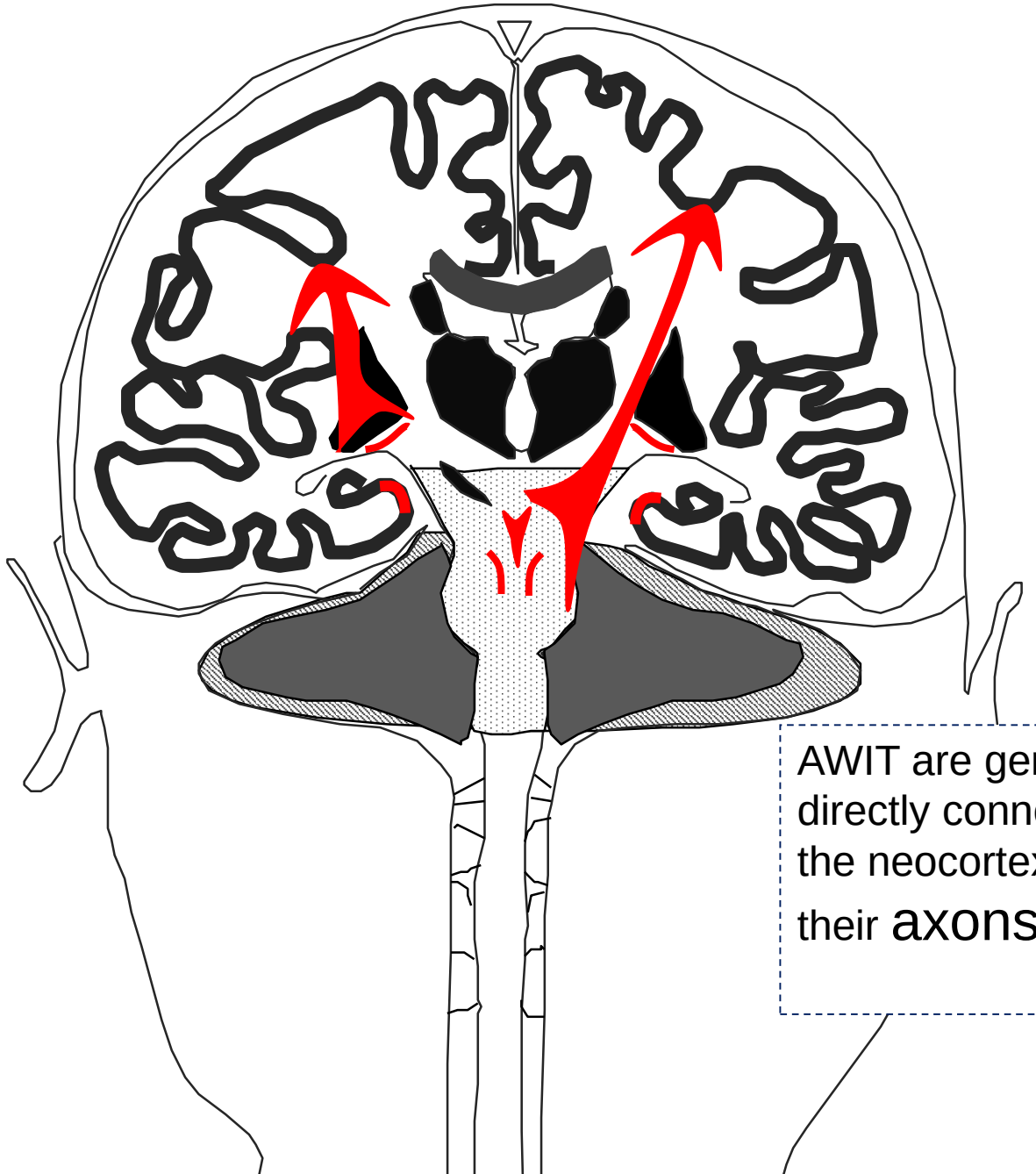


Aβ accumulates at the ***synapses*** located at the extremity of the axon whose cell body contains tangles

Areas with initial tau pathology (AWIT)

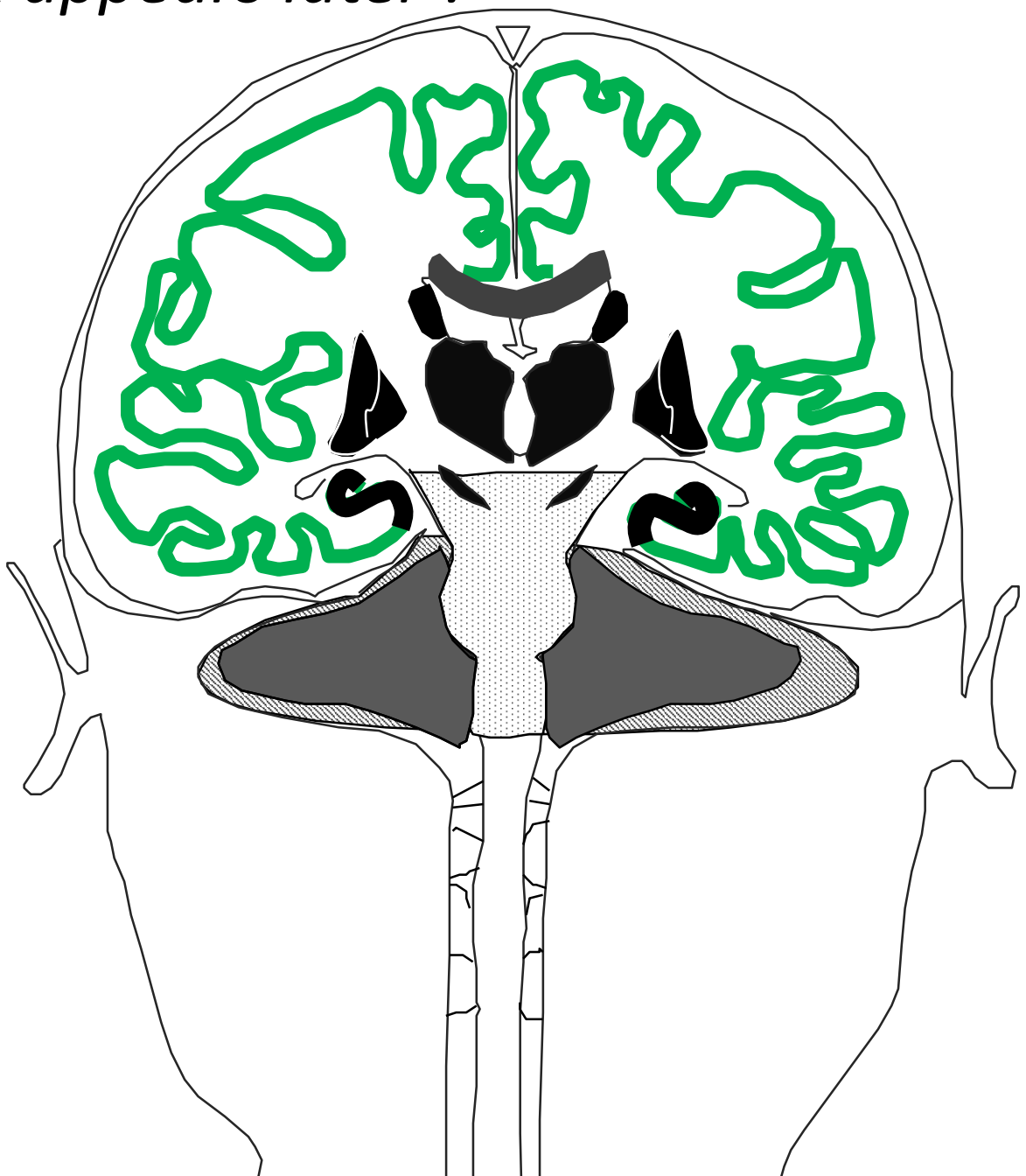


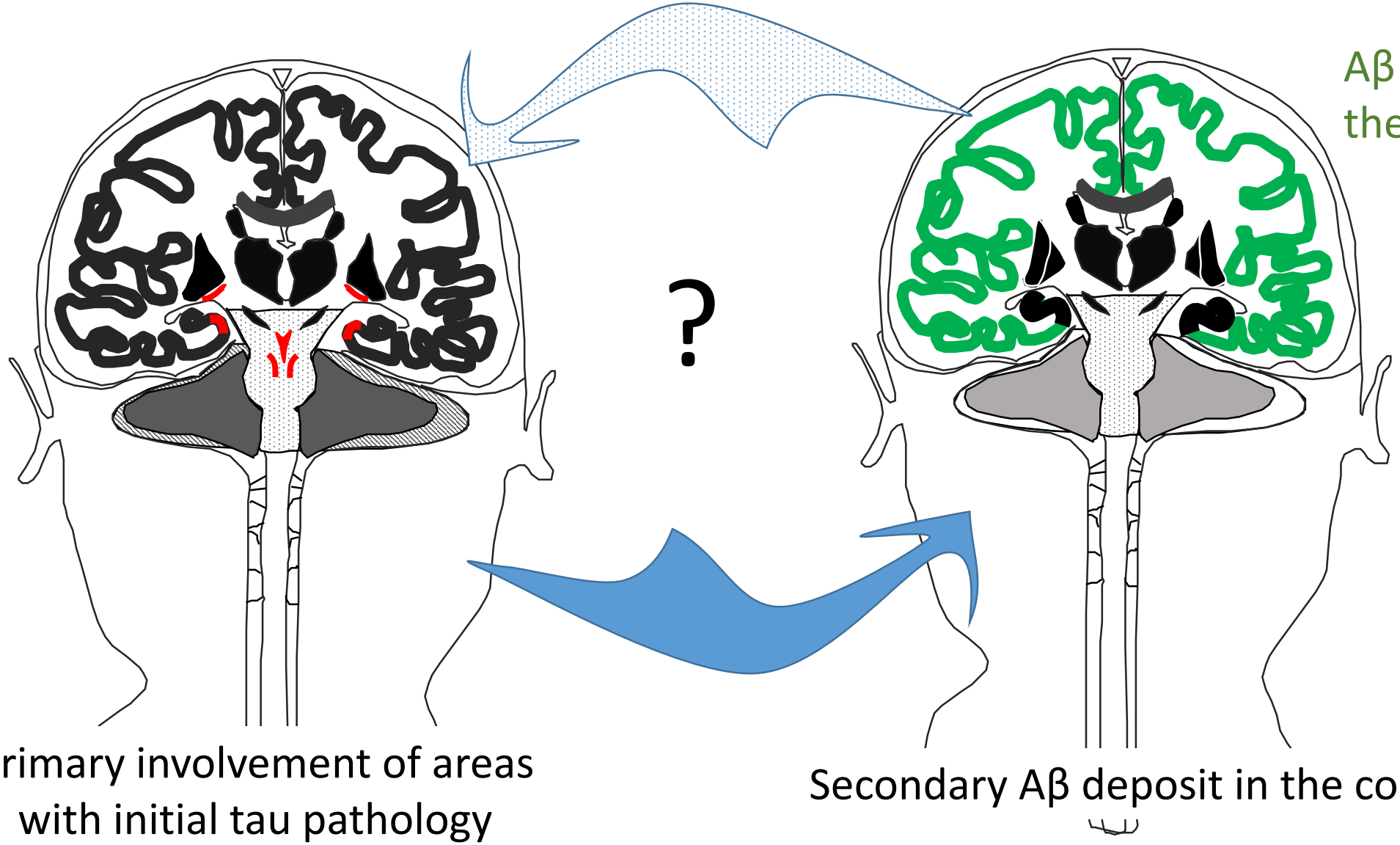
Areas with initial tau pathology (AWIT)



AWIT are generally directly connected with the neocortex through their axons

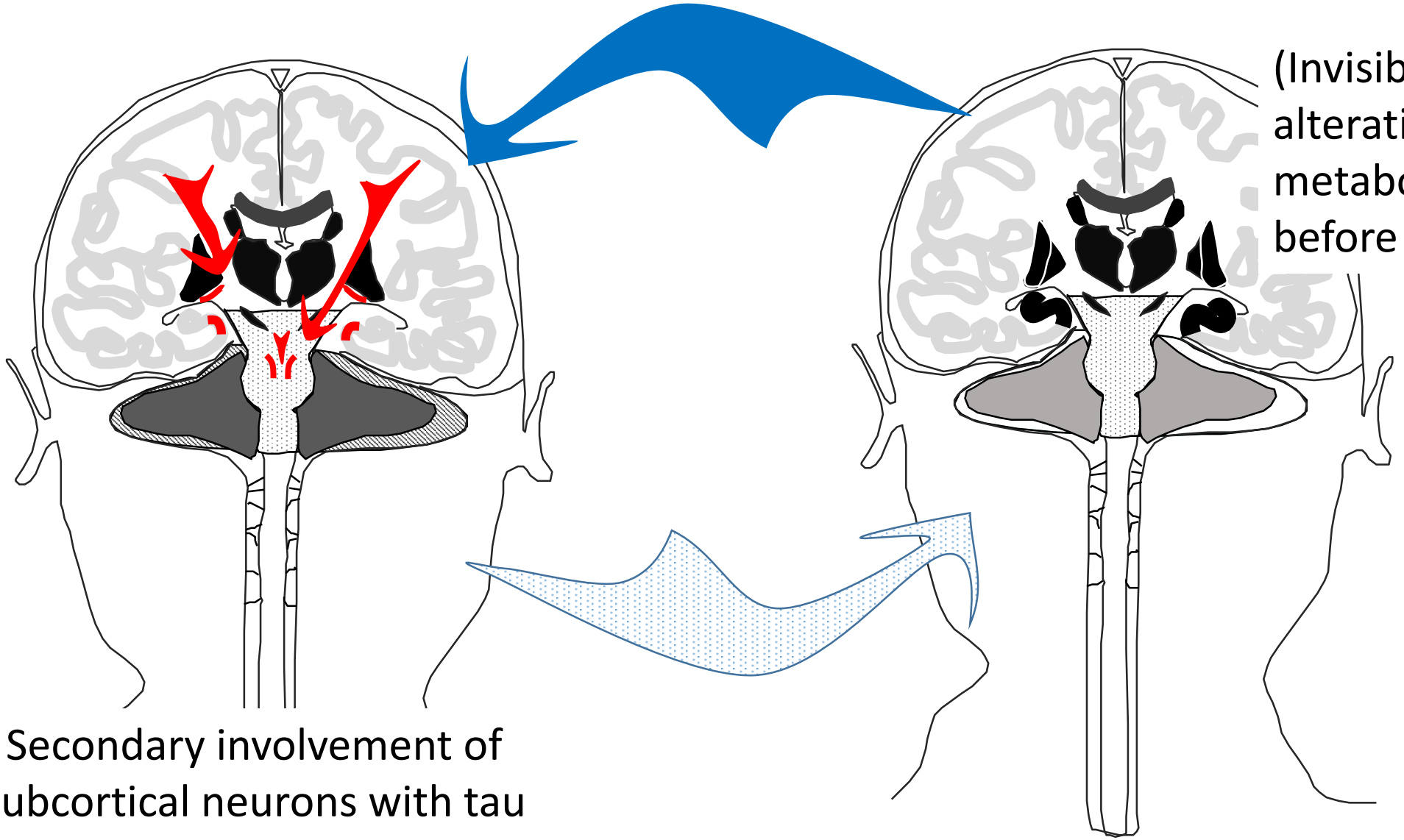
But Aβ in the cortex appears later !





"Extracellular and aggregated amyloid-Aβ may only be produced under pathological conditions by nerve cells that contain abnormal tau" Del Braak & Del Tredici Brain 138:2814–2833

But if we consider the cascade hypothesis as solidly established because of the genetic data, then there is an alternative hypothesis…



(Invisible) alterations of Aβ metabolism before deposits

Secondary involvement of subcortical neurons with tau pathology

Conclusions may be inadequate if the ***visible*** **Aβ** ***deposits*** are considered as the primary alteration.

PART as an example.

Tau pathology with (almost) no visible Aβ deposits

Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff · Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha · Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah · Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H. Neltner · Ismael Santa-Maria · William W. Seeley · Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masaki Takao · Dietmar R. Thal · Jonathan B. Toledo · Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer · Masahito Yamada · Peter T. Nelson

Received: 24 July 2014 / Revised: 26 September 2014 / Accepted: 28 September 2014

Table 2 Primary age-related tauopathy (PART): working classification

1. Requires

   NFTs present with Braak stage ≤IV (usually III or lower)

2. Then subclassify as follows

Category	Thal Aβ Phase[a]	Other disease associated with NFT[b]
Definite	0	Absent
Possible	1–2	Absent

Examples

Primary age-related tauopathy (PART), Definite, Braak stage II

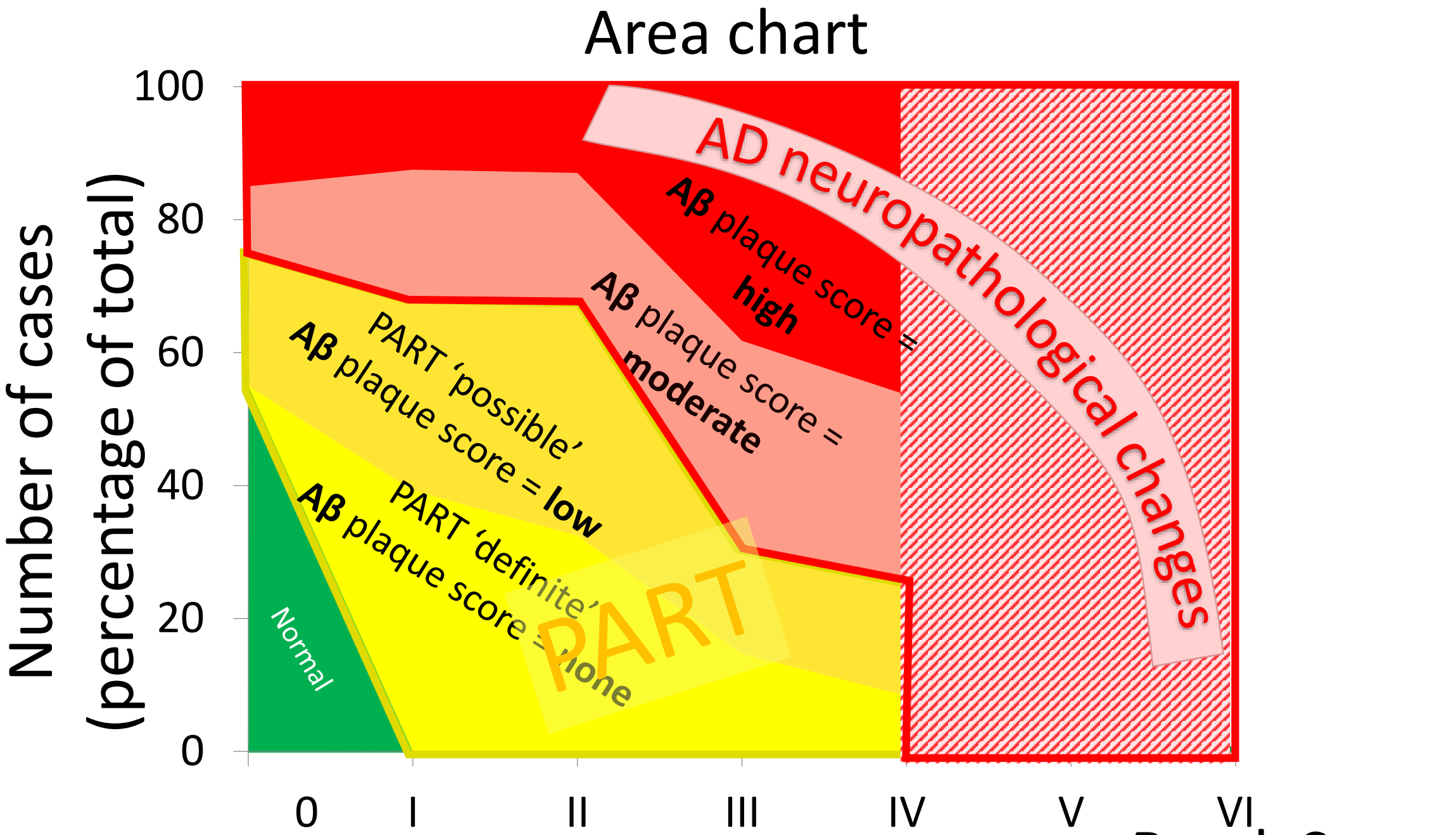
Primary age-related tauopathy (PART), Possible, Braak stage III, Thal Aβ phase 2

3. Ancillary studies (not required)

Immunohistochemistry: 3R and 4R tau-positive

Electron microscopy: paired helical filaments present

Genetics: absence of pathogenic FTLD-tau mutation



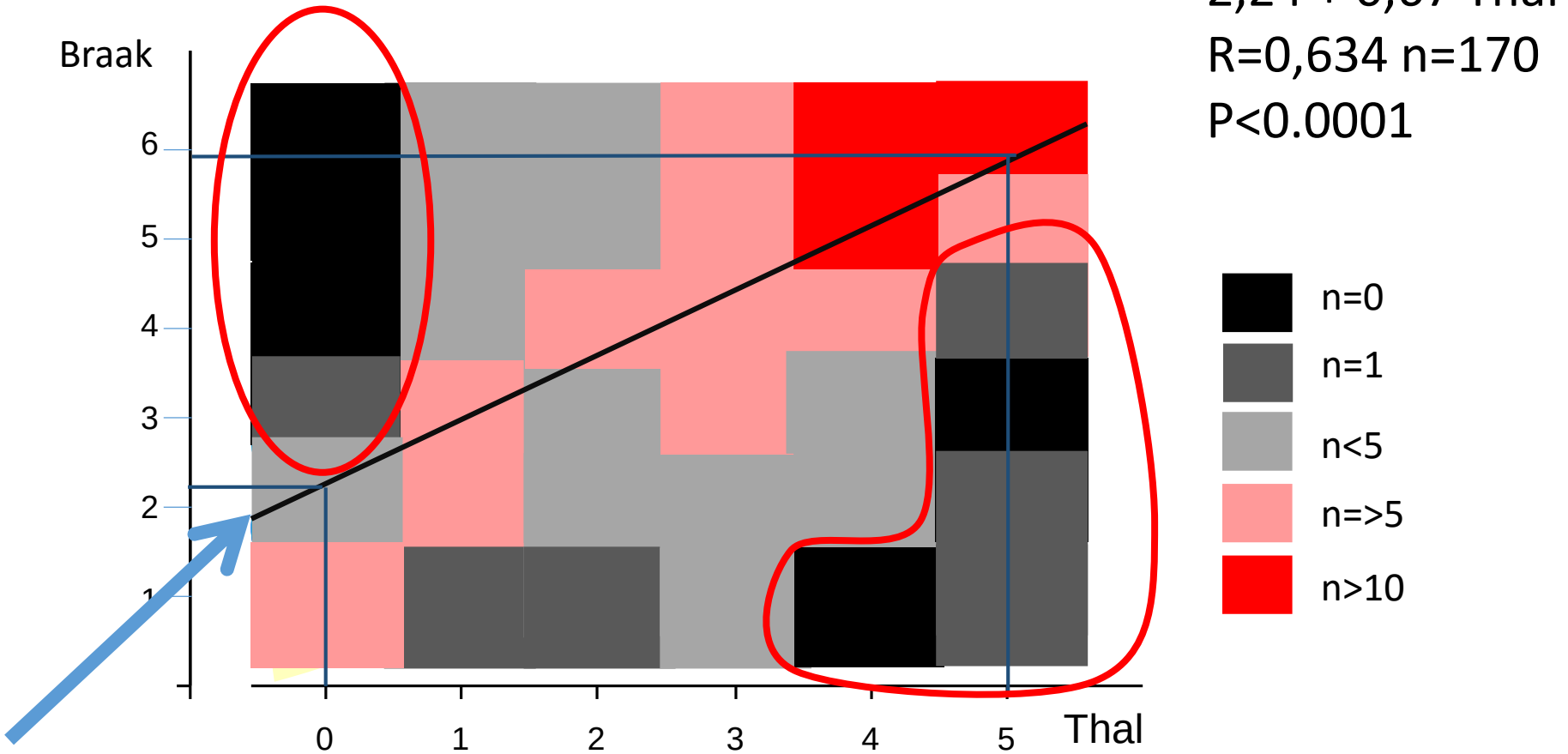
Duyckaerts et al. (2015) Part is part of Alzheimer disease Acta Neuropathol 129:749–756
Data from Braak H, Del Tredici K (2014) Acta Neuropathol 128:767–772.

Number of cases

Sum of columns	9	21	17	34	39	50	**170**
6	0	2	3	6	16	41	68
5	0	3	2	9	13	6	33
4	0	3	6	6	5	1	21
3	1	6	2	7	3	0	19
2	3	6	3	3	2	1	18
1	5	1	1	3	0	1	11
	0	1	2	3	4	5	Sum of rows

Braak Tau

Thal Aβ

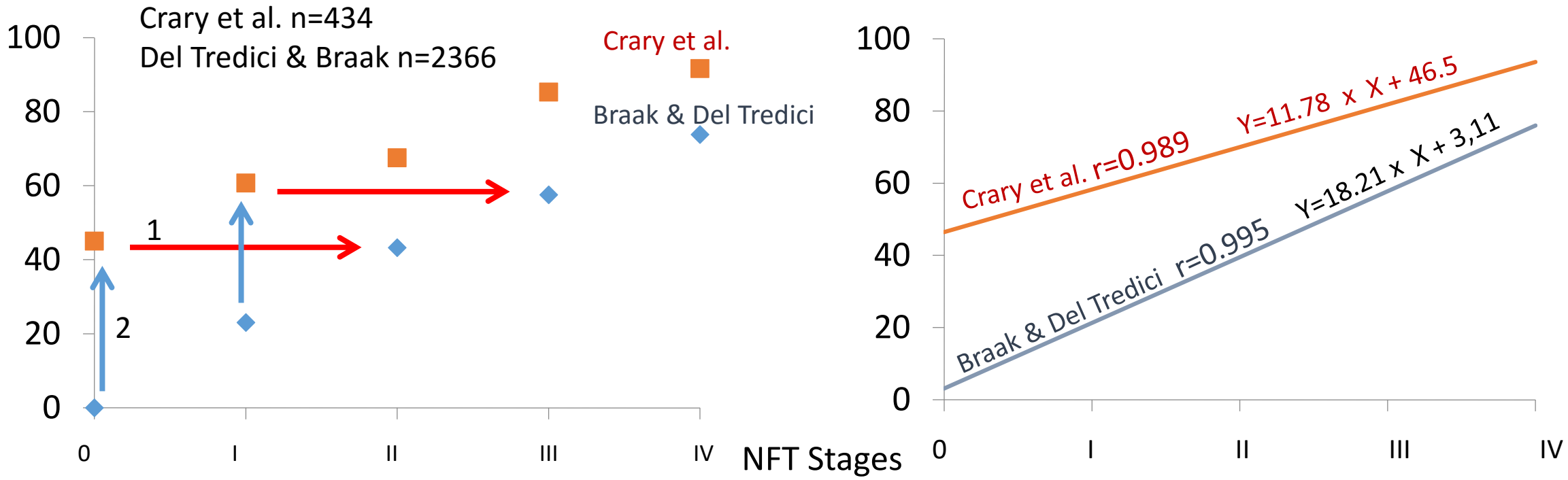


The profile is not altered by associated pathologies

Within the group of PART cases, proportion of cases with Aβ deposits

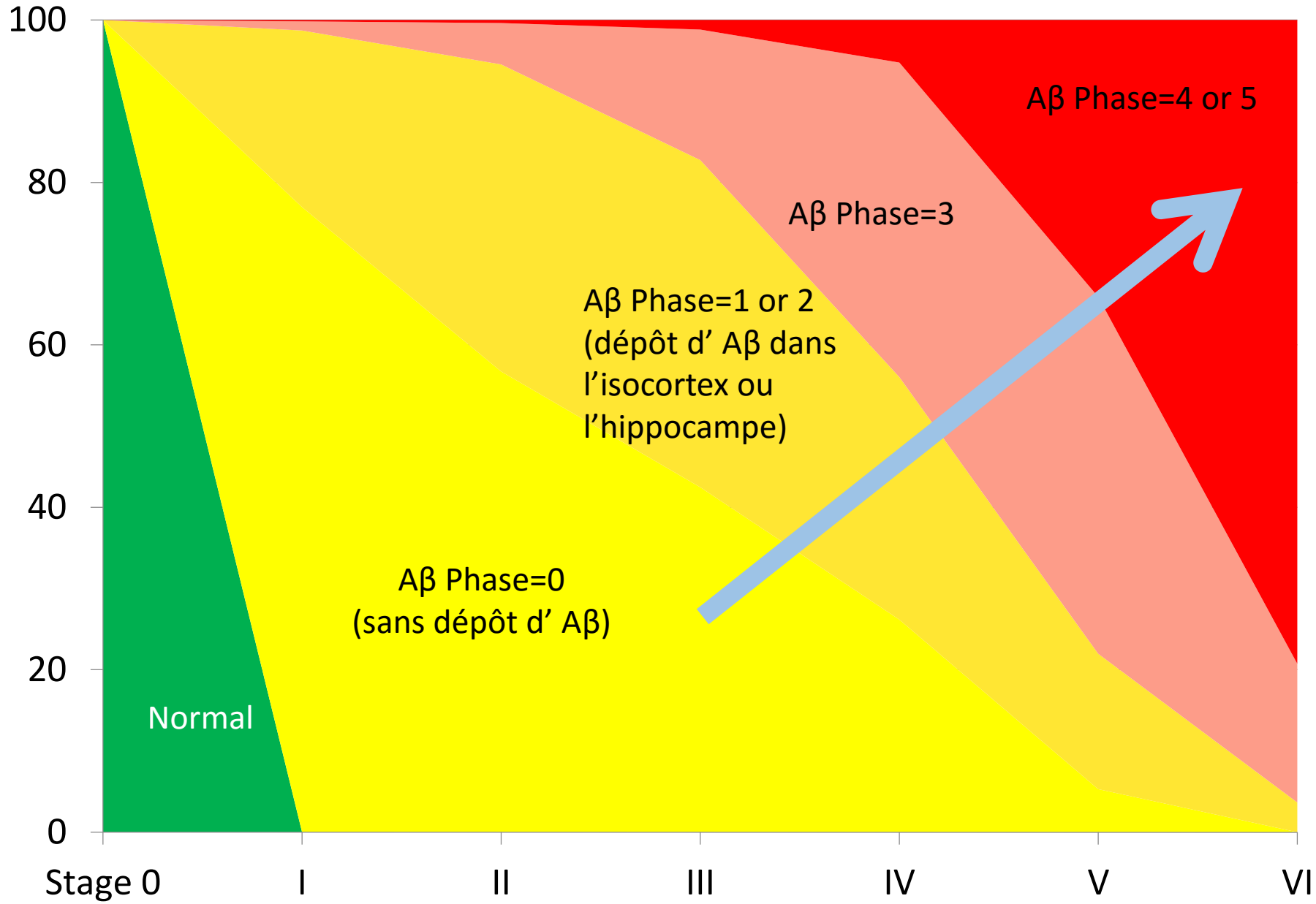
« low density of amyloid plaques »

« Aβ phase >0 »



Among PART cases, the proportion of subjects with Aβ deposits increases linearily with Braak stages.

<u>Unlikely</u> if tau and Aβ were independent.

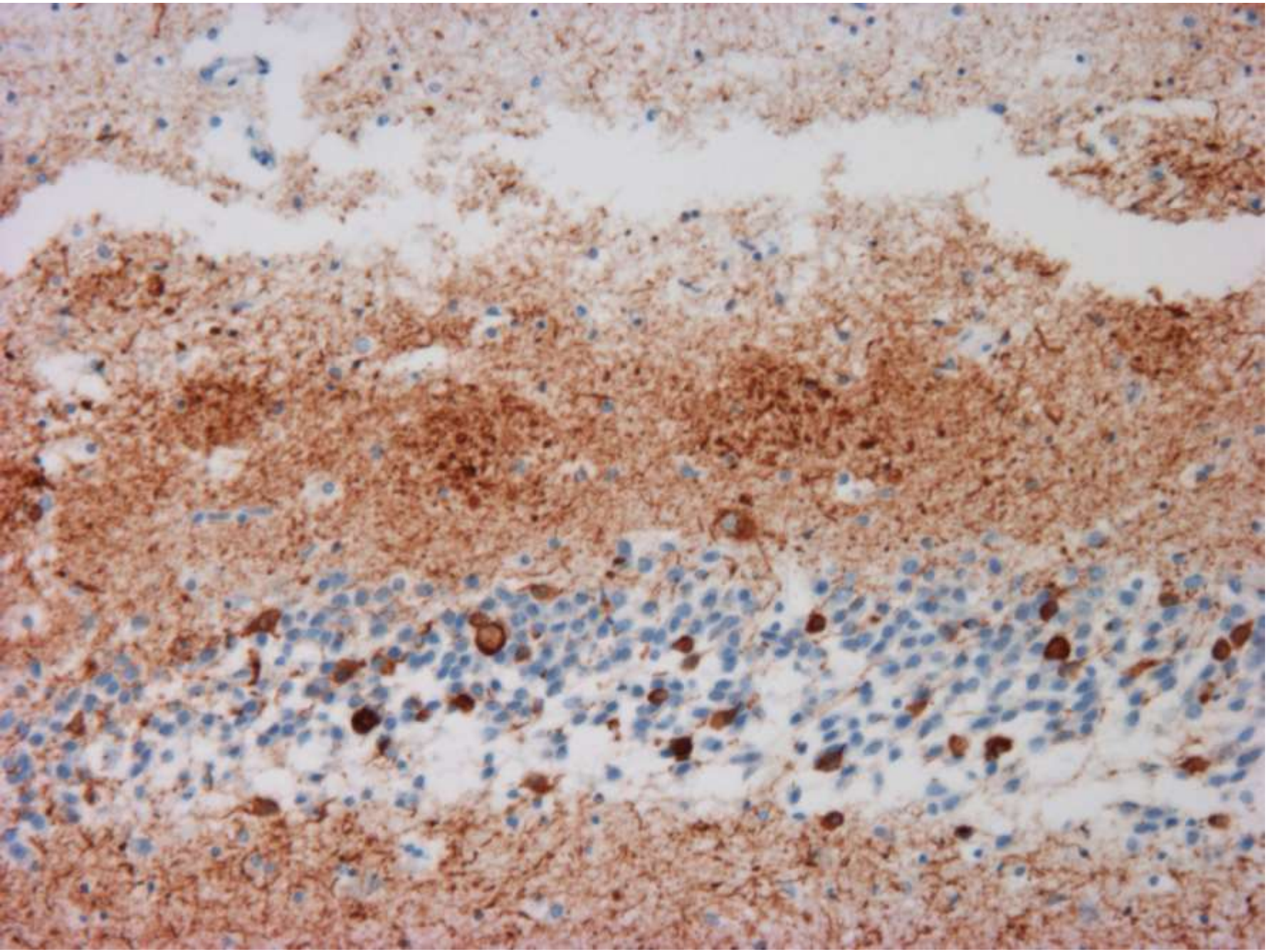


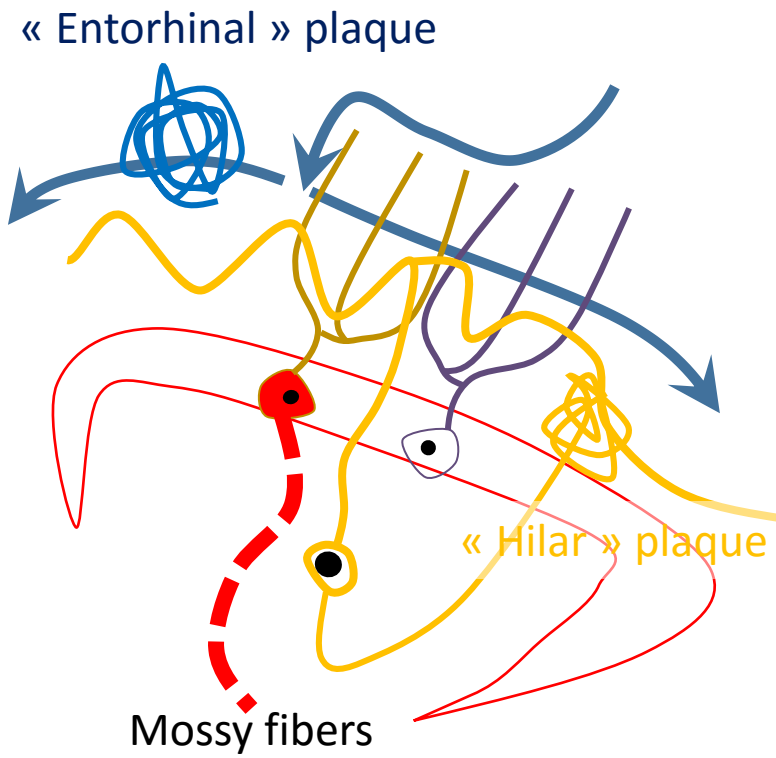
PART is part of Alzheimer disease. Acta Neuropathol (2015) 129:749–756

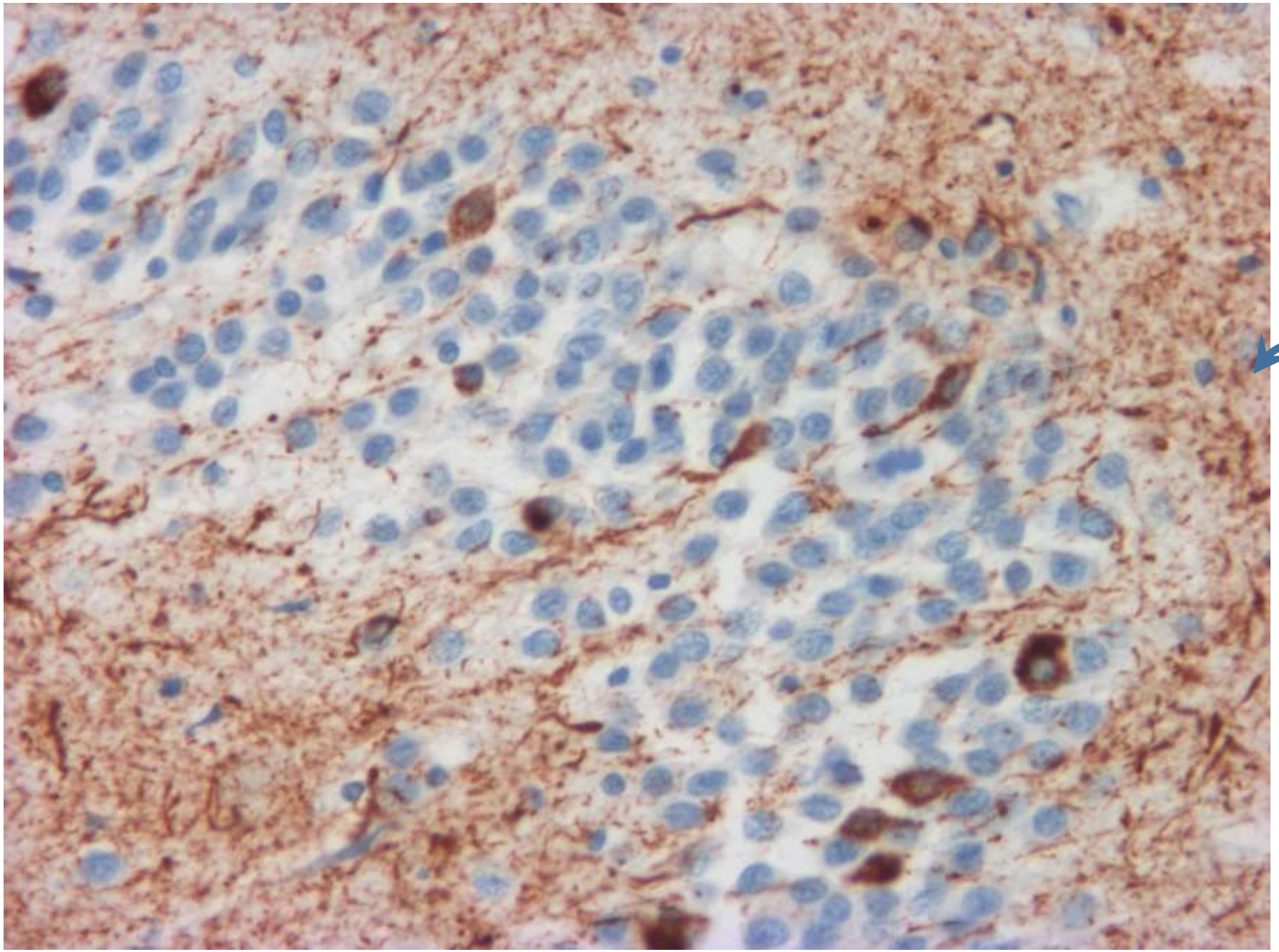
Charles Duyckaerts,[1] Heiko Braak,[2] Jean-Pierre Brion,[3] Luc Buée,[4] Kelly Del Tredici,[2] Michel Goedert,[5] Glenda Halliday,[6]Manuela Neumann,[7,8] Maria Grazia Spillantini,[9] Markus Tolnay,[10] Toshiki Uchihara[11]

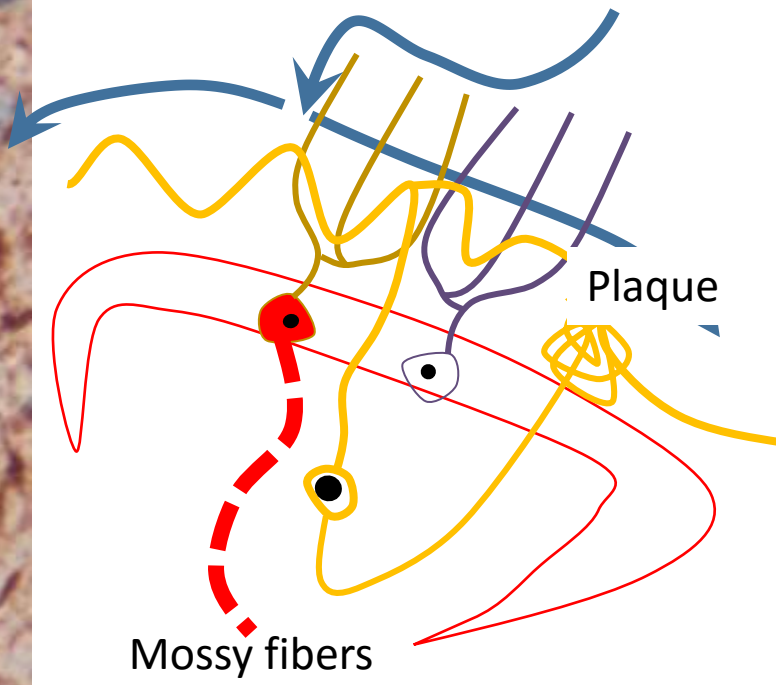
It could well be inaccurate to consider plaques and in general Aβ deposits as the initial step of Aβ pathogenesis and as the toxic species

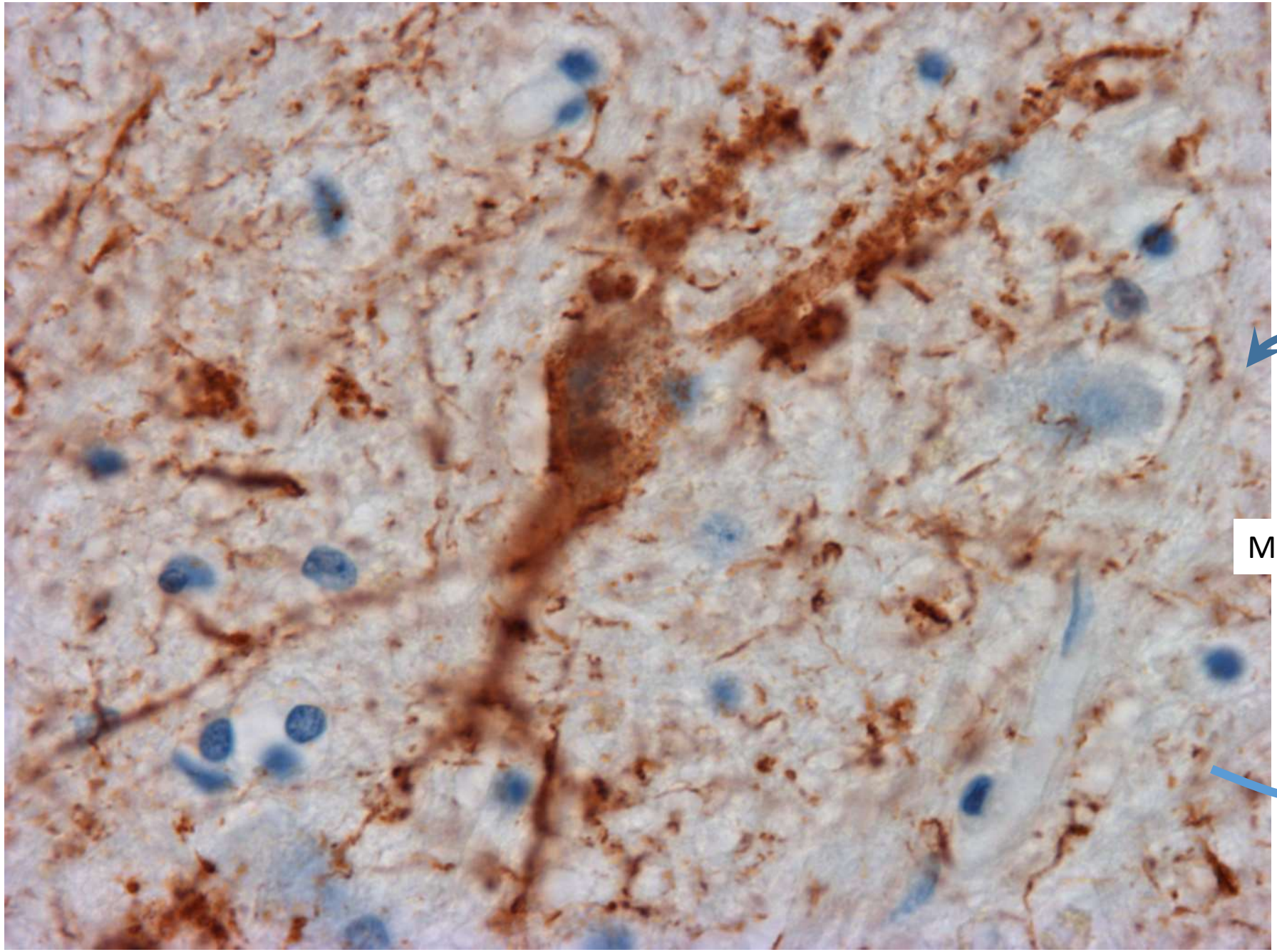
Once started how do the lesions propagate ?

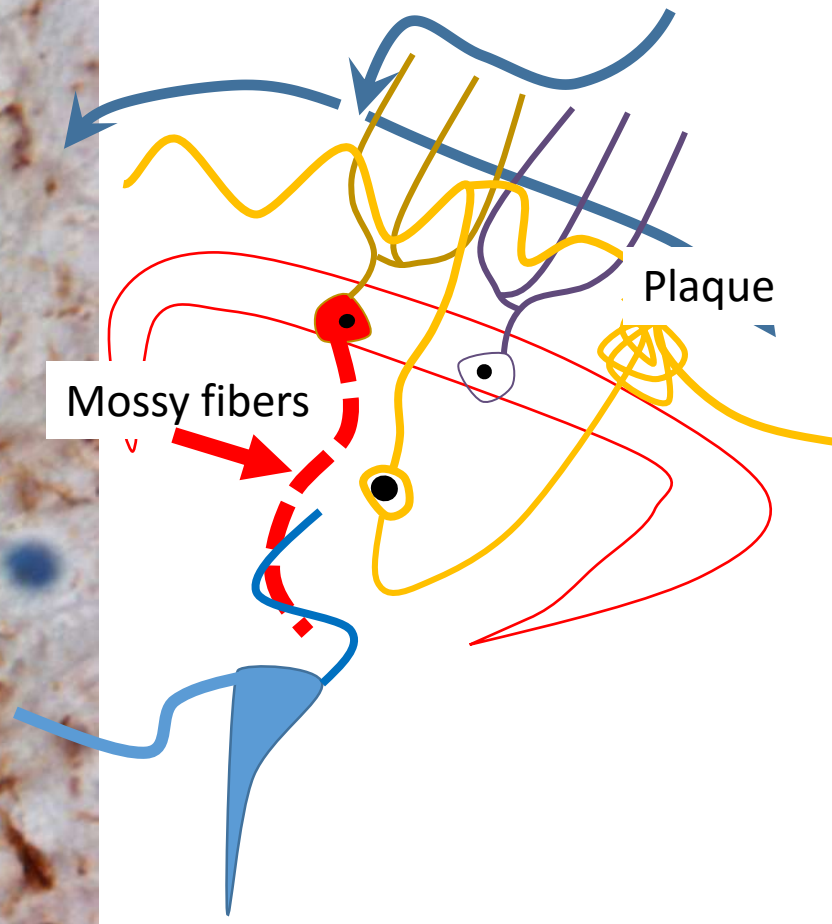



« Entorhinal » plaque
« Hilar » plaque
Mossy fibers

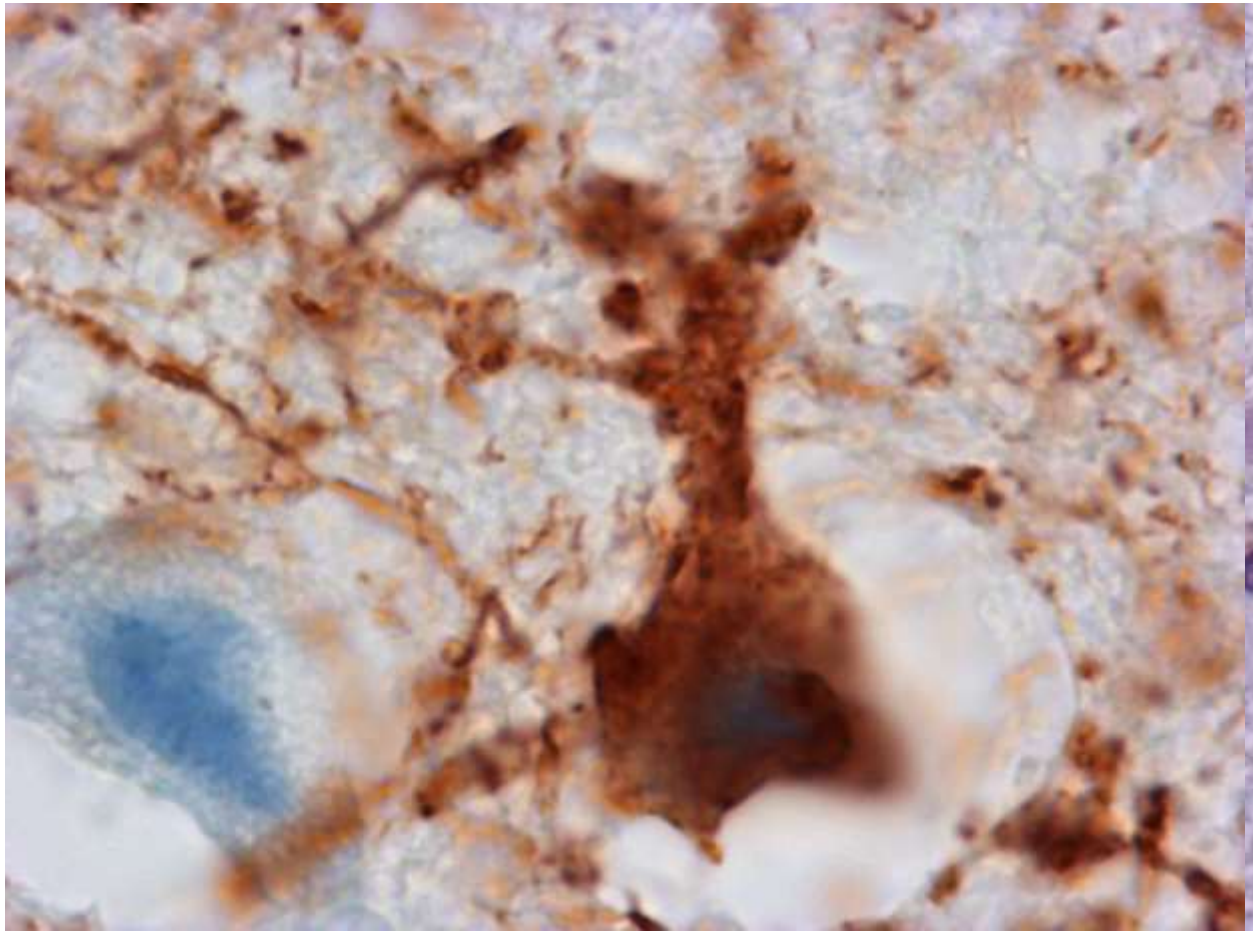



Plaque
Mossy fibers

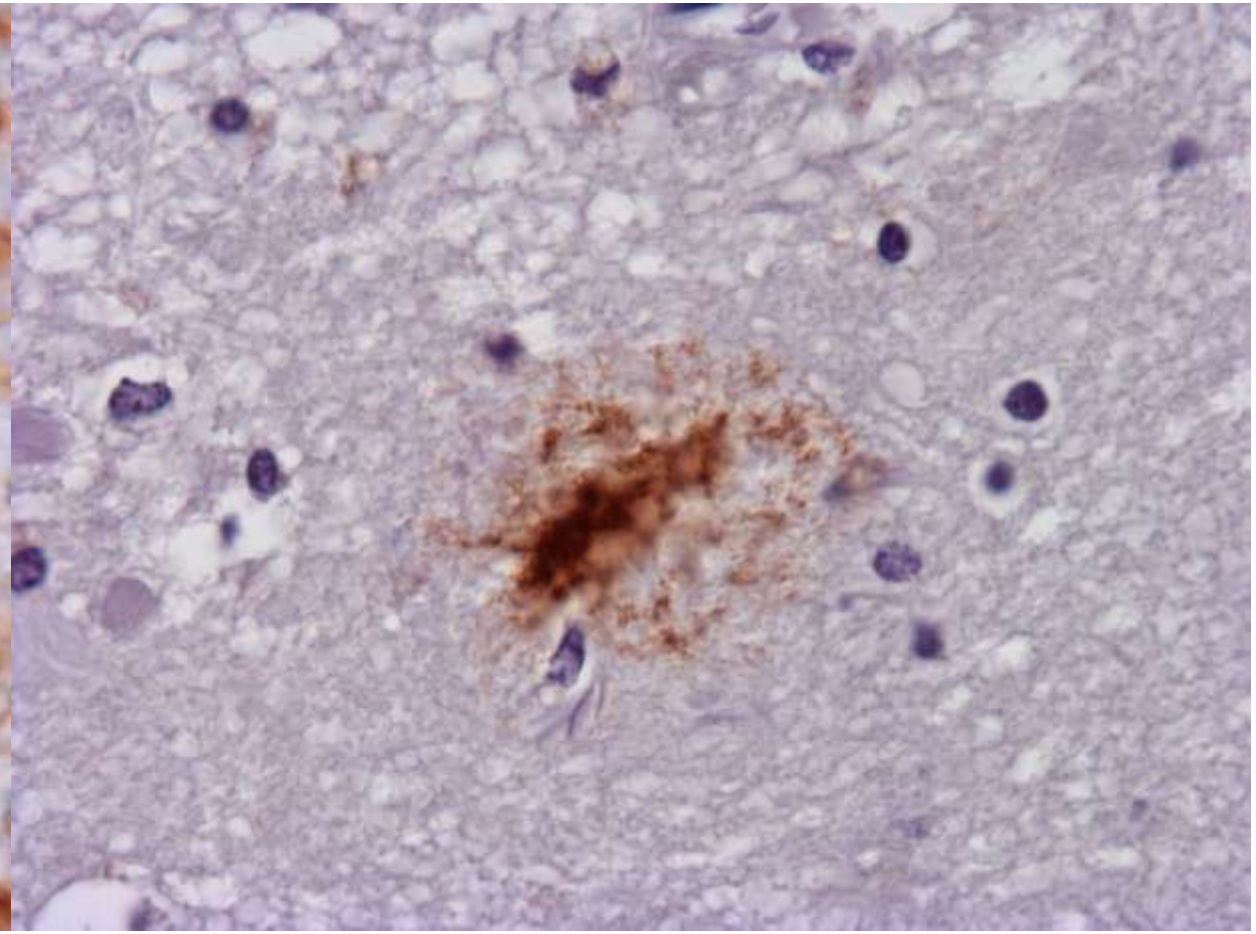



Plaque
Mossy fibers

Only in regions with plaques ?



Tau



Aβ

Conclusions

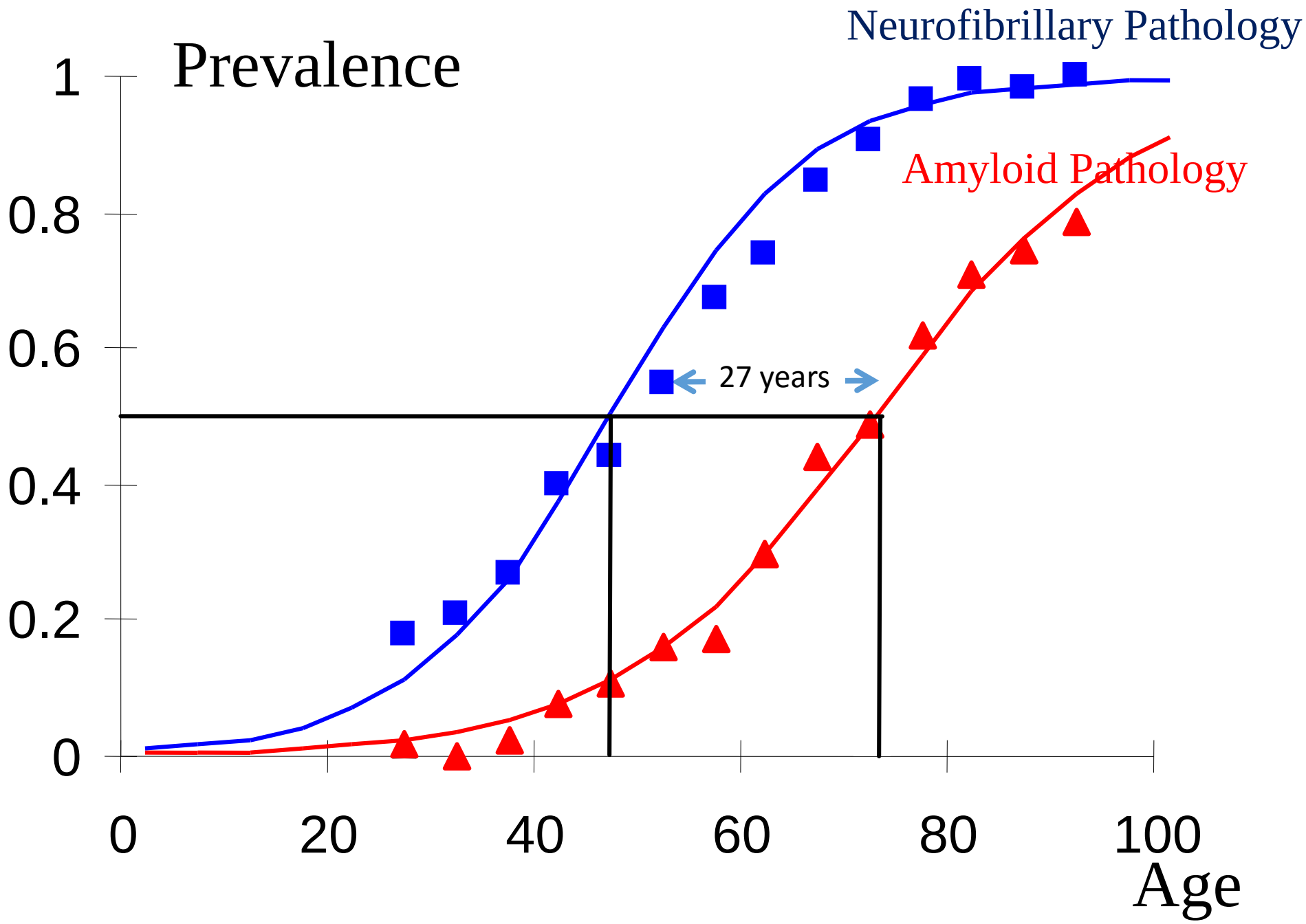
- Alzheimer disease is essentially a tauopathy
- This tauopathy is related to a change in Aβ metabolism
- The initial alteration in Aβ metabolism may not be visible
- (Visible) Aβ accumulation is a late event in the cascade
- The propagation of tau pathology through synapses occurs only in region with Aβ accumulation

Many thanks to…

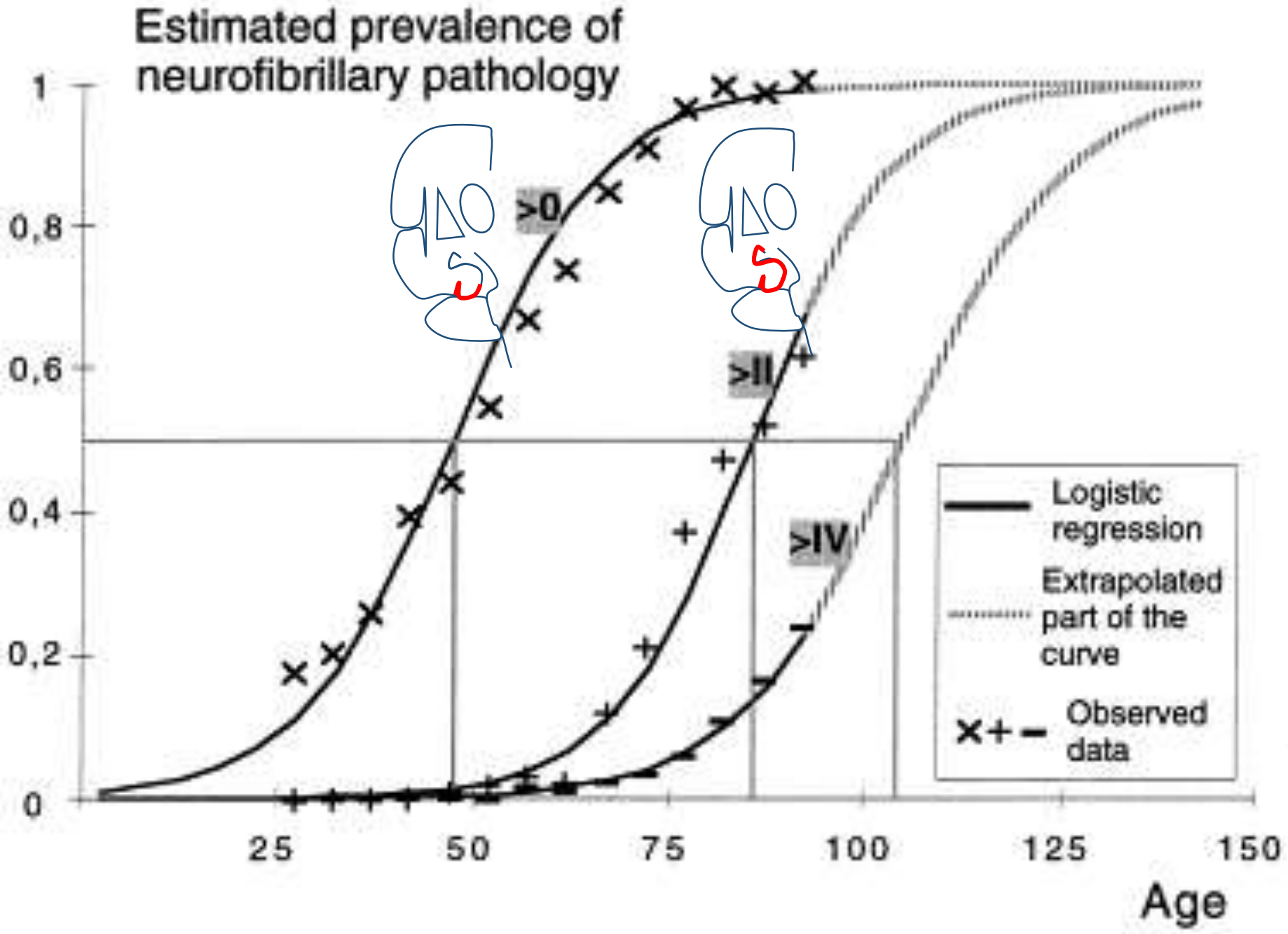
The patients and their family

Brain Bank GIE NeuroCEB
(France Alzheimer, France Parkinson, ARSEP, CSC)

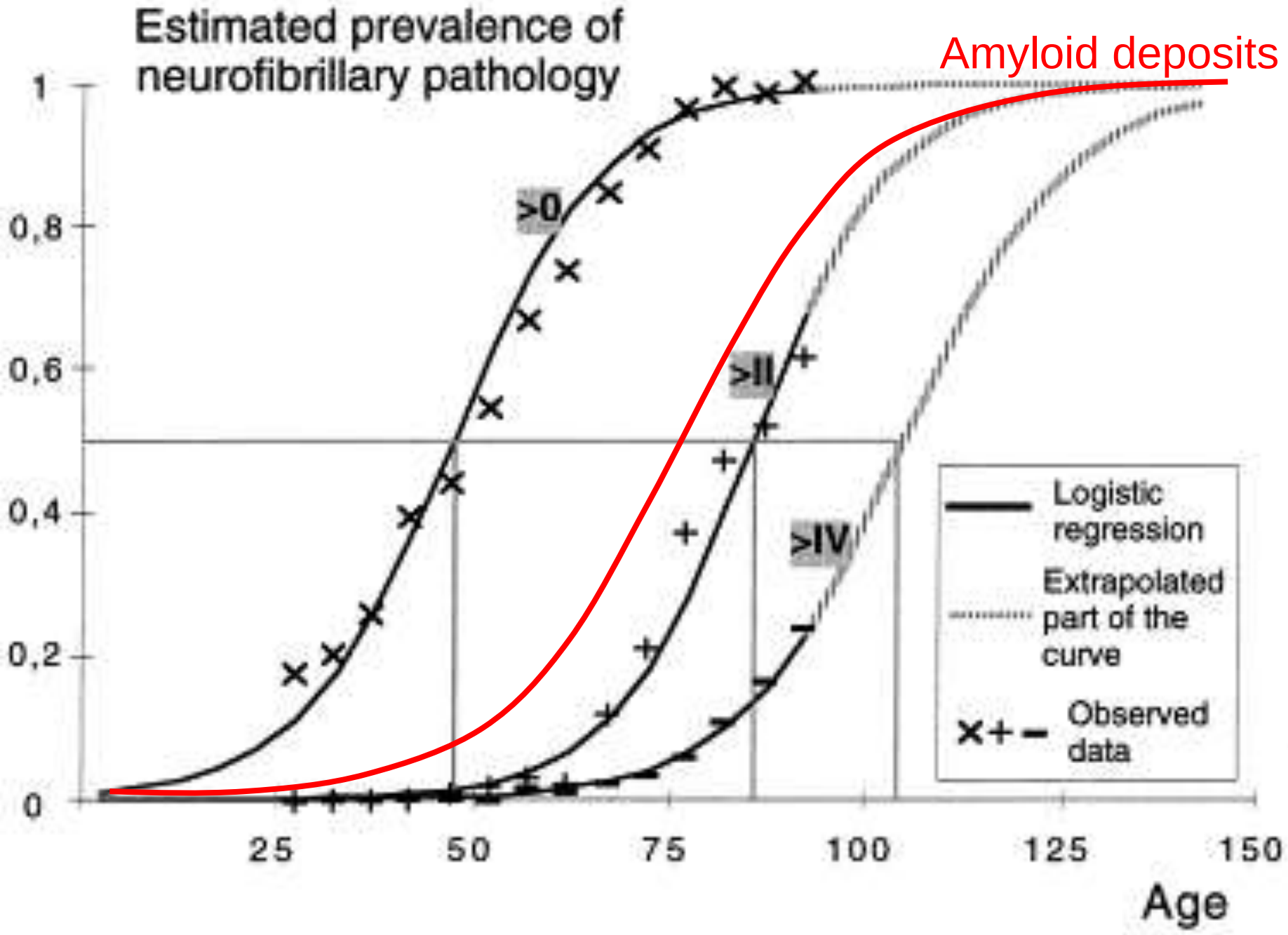
Manon Thierry



From Duyckaerts & Hauw, Neurobiol Aging 1997; Data of Braak & Braak, Neurobiol Aging 1997



Duyckaerts & Hauw Neurobiol Aging 1997, 18: 362-369



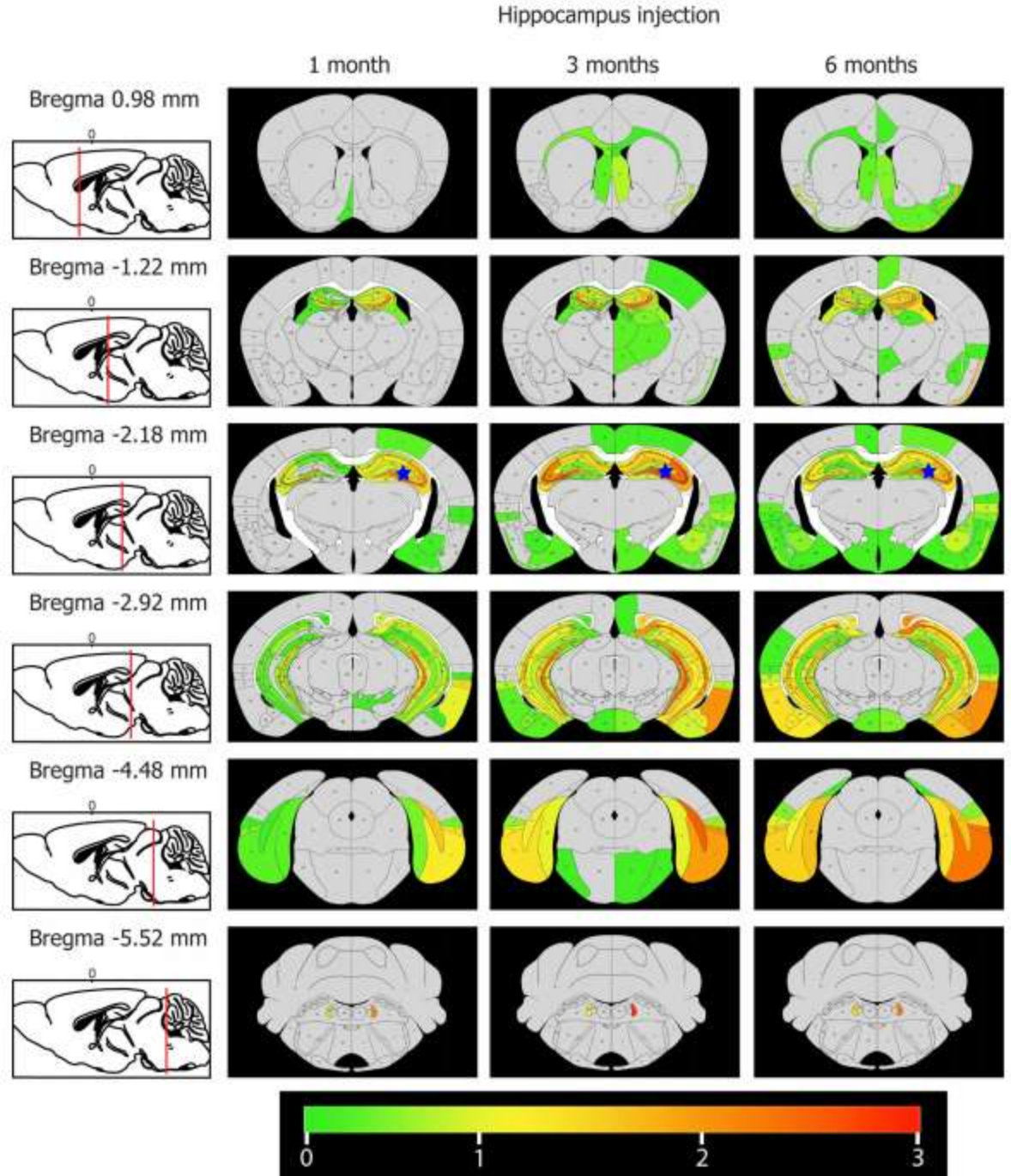
Duyckaerts & Hauw Neurobiol Aging 1997, 18: 362-369

1024 • The Journal of Neuroscience, January 16, 2013 • 33(3):1024–1037

Neurobiology of Disease

Synthetic Tau Fibrils Mediate Transmission of Neurofibrillary Tangles in a Transgenic Mouse Model of Alzheimer's-Like Tauopathy

Michiyo Iba, Jing L. Guo, Jennifer D. McBride, Bin Zhang, John Q. Trojanowski, and Virginia M.-Y. Lee
Center for Neurodegenerative Disease Research, Institute on Aging, Department of Pathology and Laboratory, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104



Neurobiology of Aging 36 (2015) 2043–2052

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Acute amnestic encephalopathy in amyloid-β oligomer–injected mice is due to their widespread diffusion in vivo

Stéphane Epelbaum [a,b,*], Ihsen Youssef [a], Pascale N. Lacor [c], Pierre Chaurand [d], Eric Duplus [e], Bernard Brugg [e], Charles Duyckaerts [a,f], Benoît Delatour [a]

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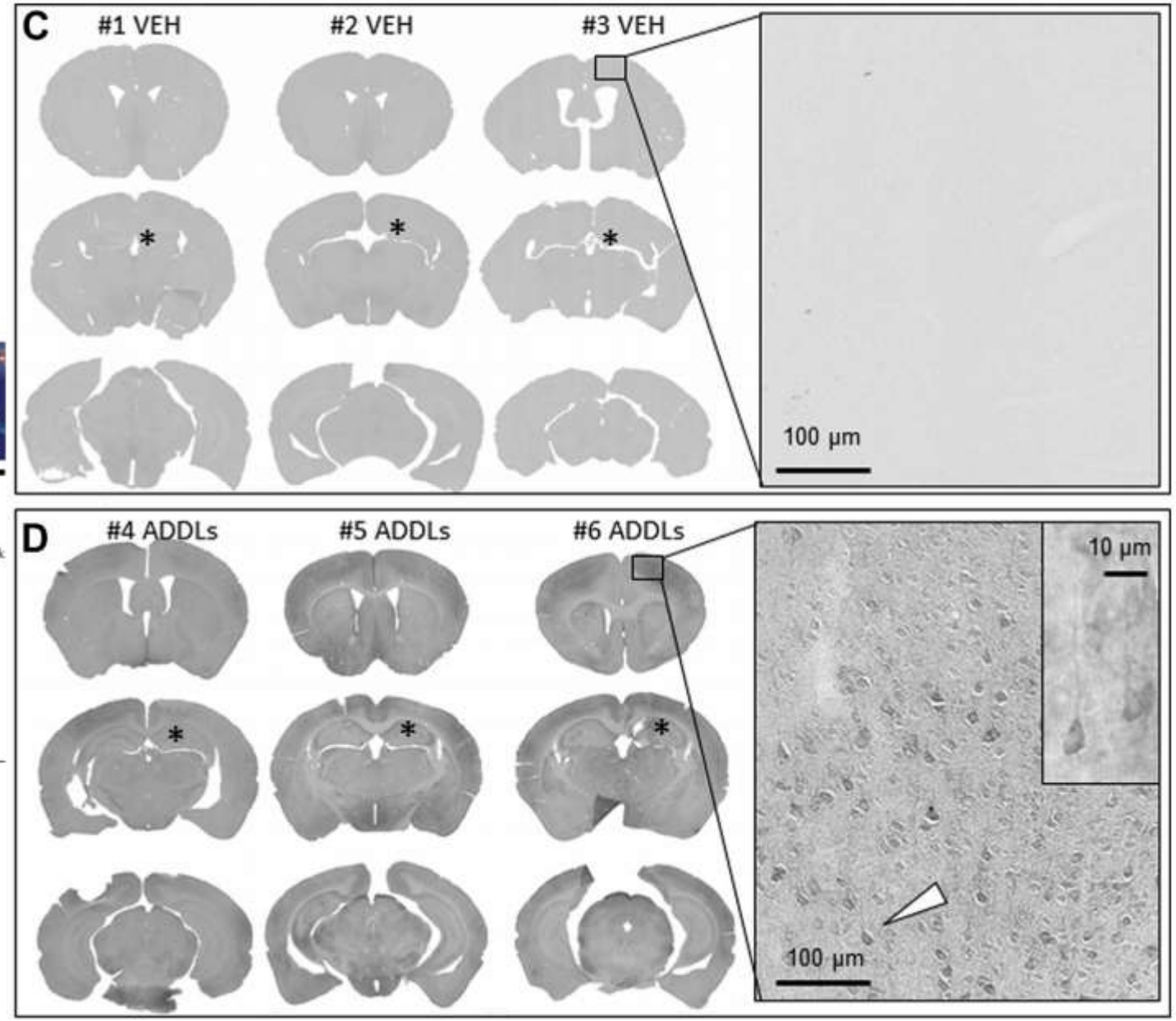
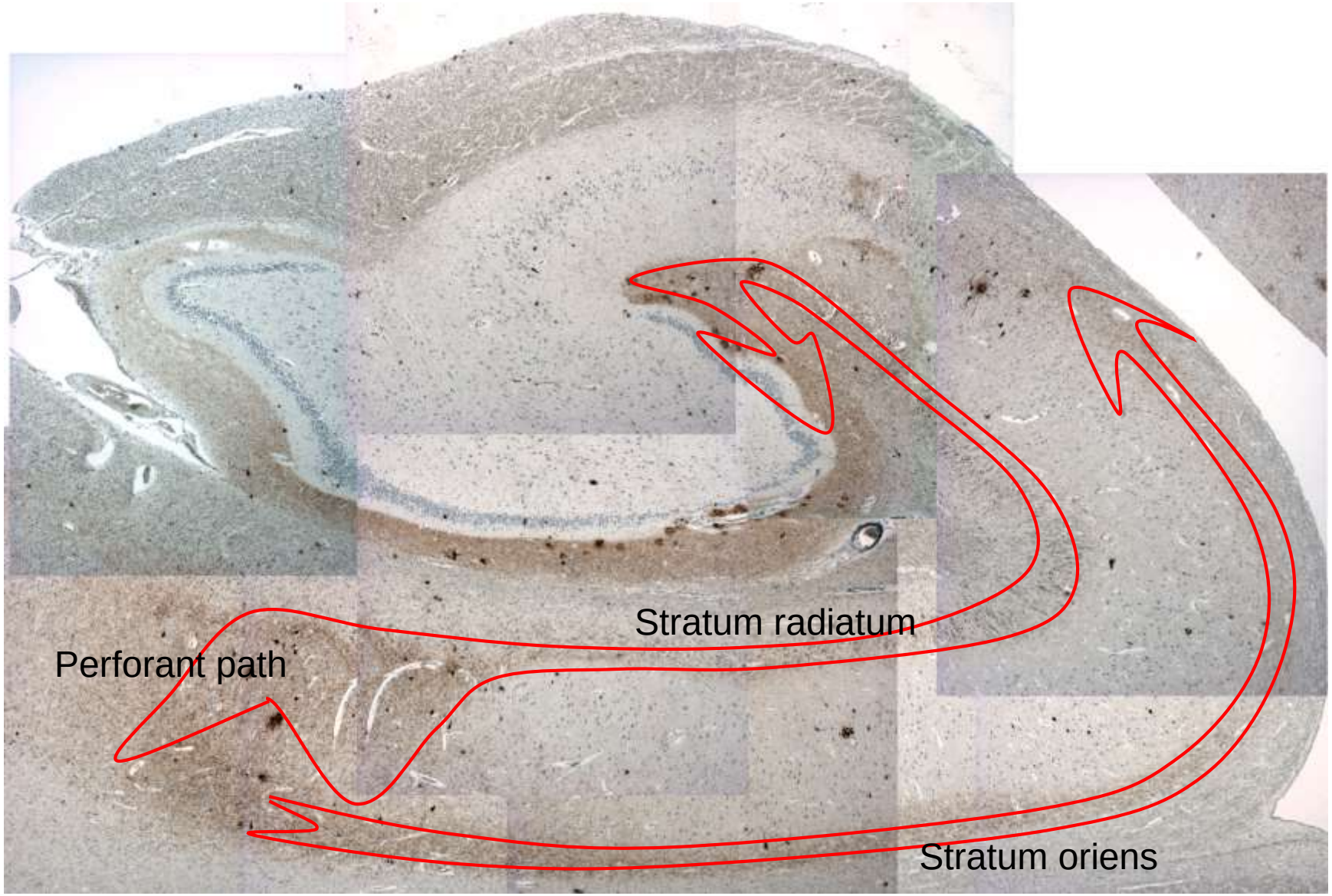
[c] Department of Neurobiology, Northwestern University, Evanston, IL, USA
[d] Department of Chemistry, Université de Montréal, Montreal, Canada
[e] CNRS-UPMC UMR 8256, Biological Adaptation and Ageing (B2A), Université P. et M.Curie, Team: Degenerative Processes in Neurons and Networks (DP2N), Paris, France
[f] Laboratoire de neuropathologie Escourolle, Hôpital de la Pitié Salpêtrière, Paris, France

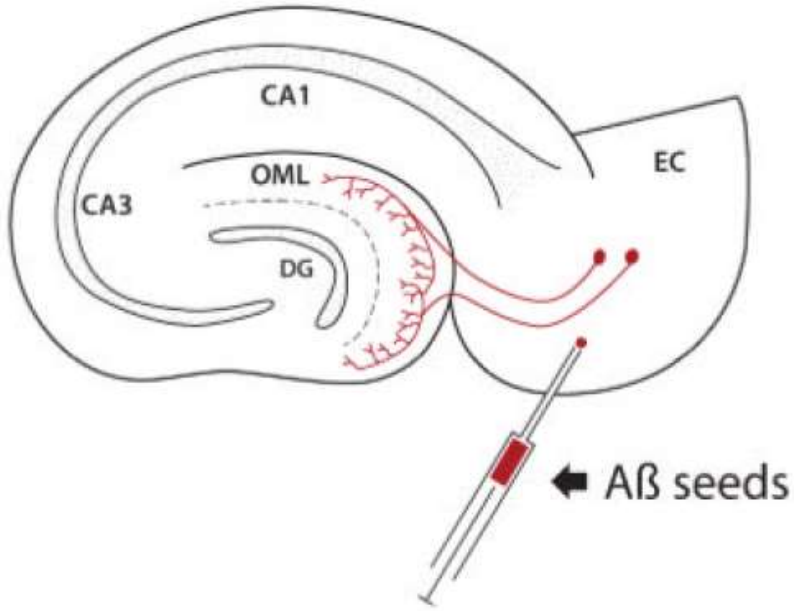


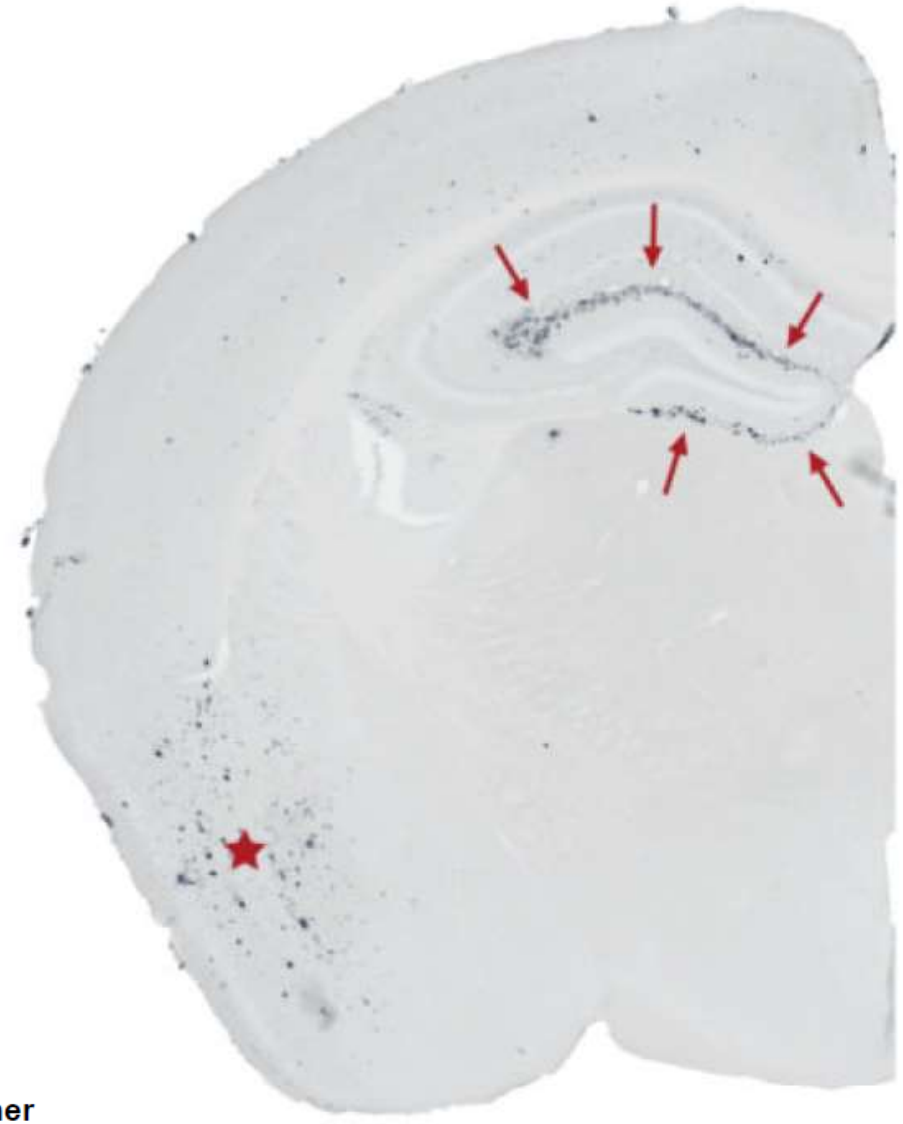
Hybrid models : synergy of tau and Aβ pathology



Tau (AT8) IHC

APP23 mouse





Ann Neurol. 2011 October ; 70(4): 532–540. doi:10.1002/ana.22615.

Pathogenic Protein Seeding in Alzheimer's Disease and Other Neurodegenerative Disorders

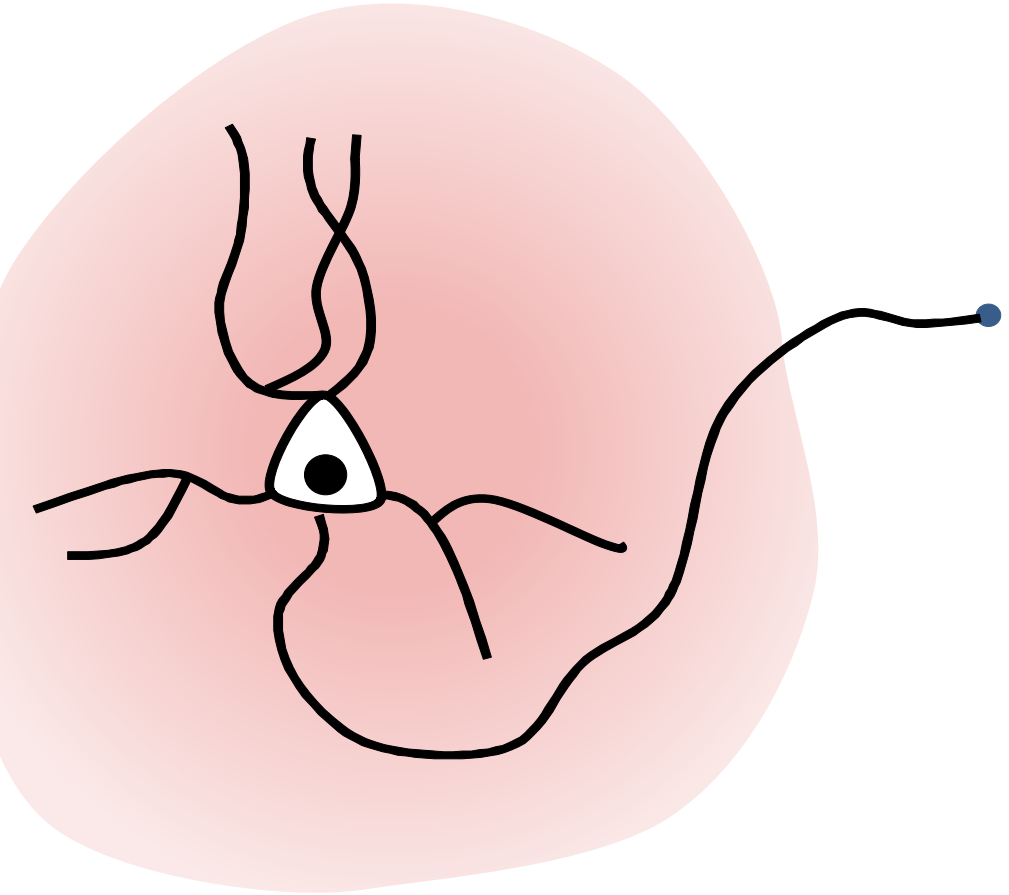
Mathias Jucker[1,2] and **Lary C. Walker**[3]

[1]Department of Cellular Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, D-72076 Tübingen, Germany

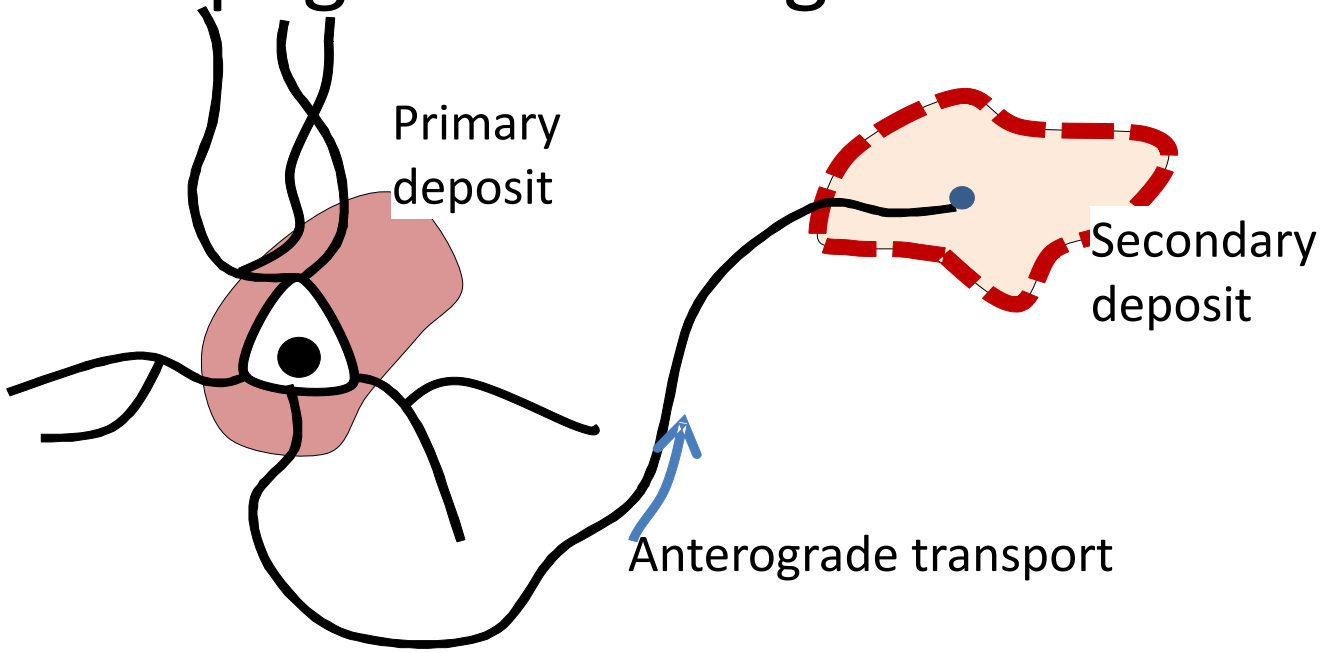
[2]DZNE - German Center for Neurodegenerative Diseases, D-72076 Tübingen, Germany

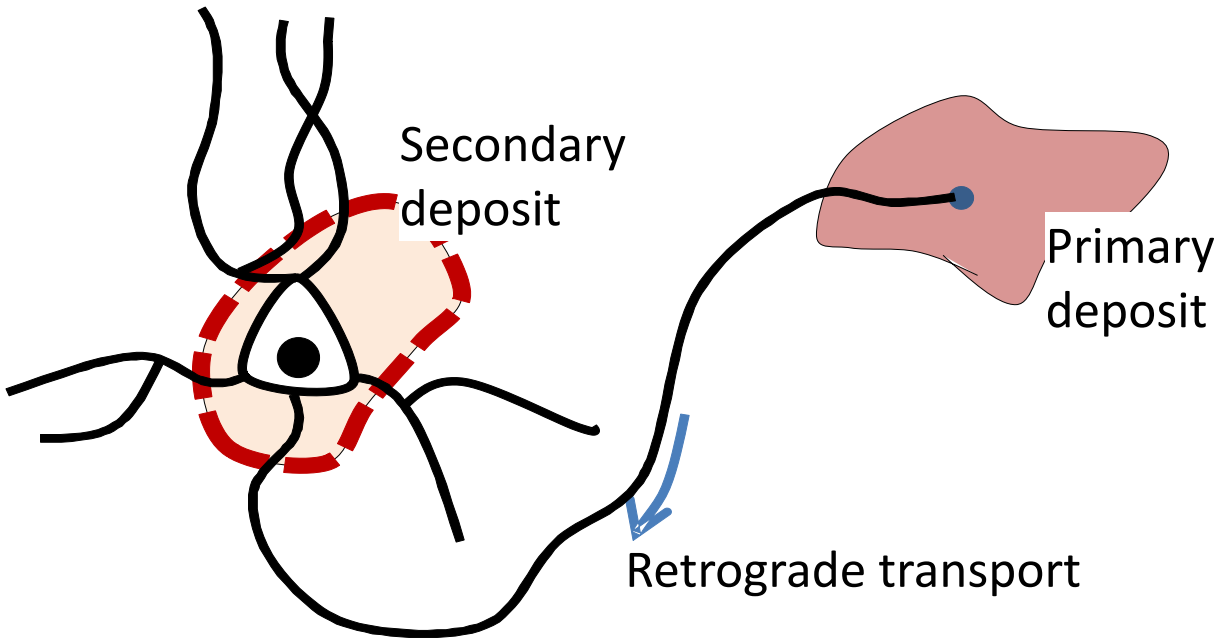
[3]Yerkes National Primate Research Center and Department of Neurology, Emory University, Atlanta, GA, 30329 USA

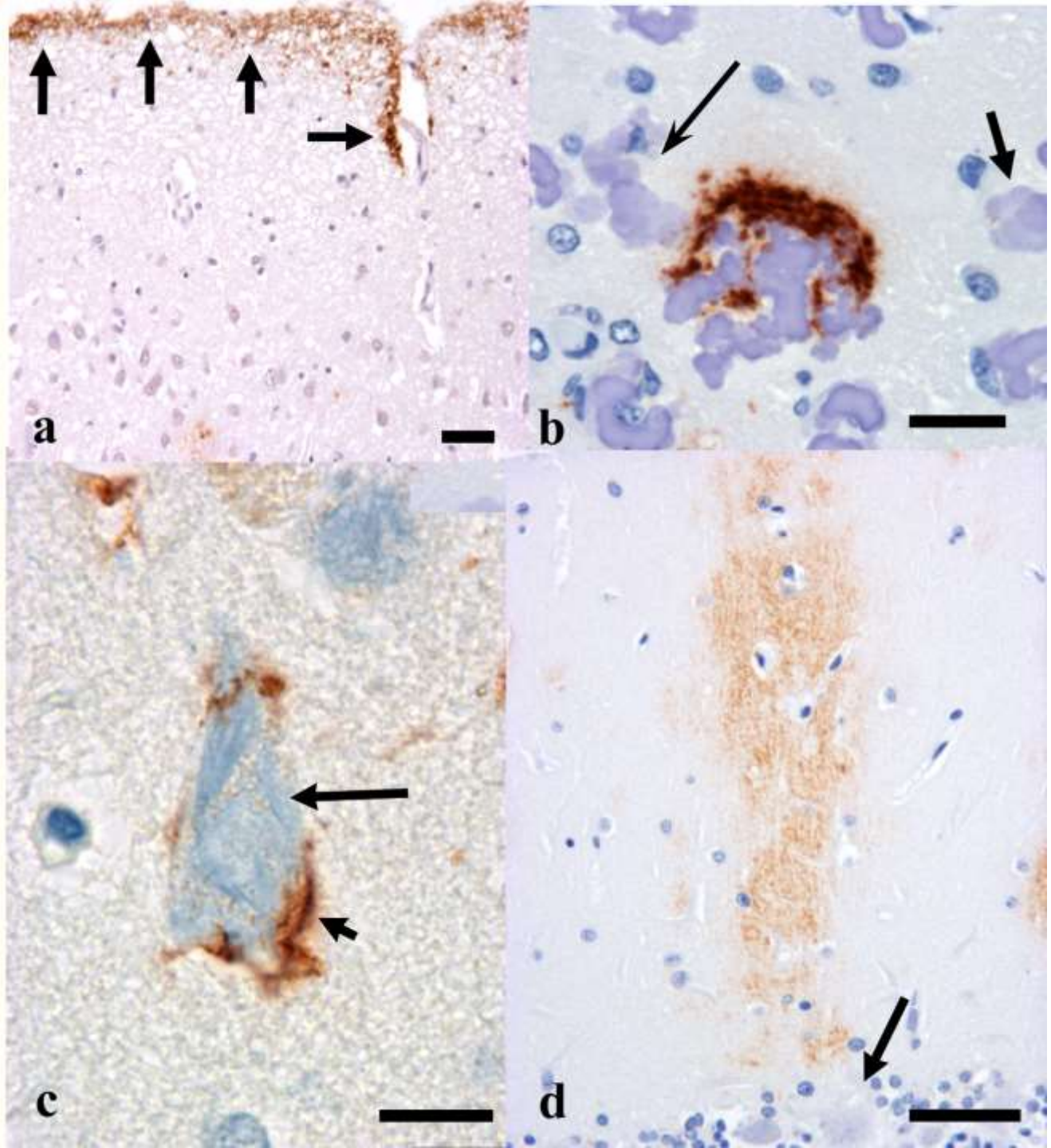
Diffusion

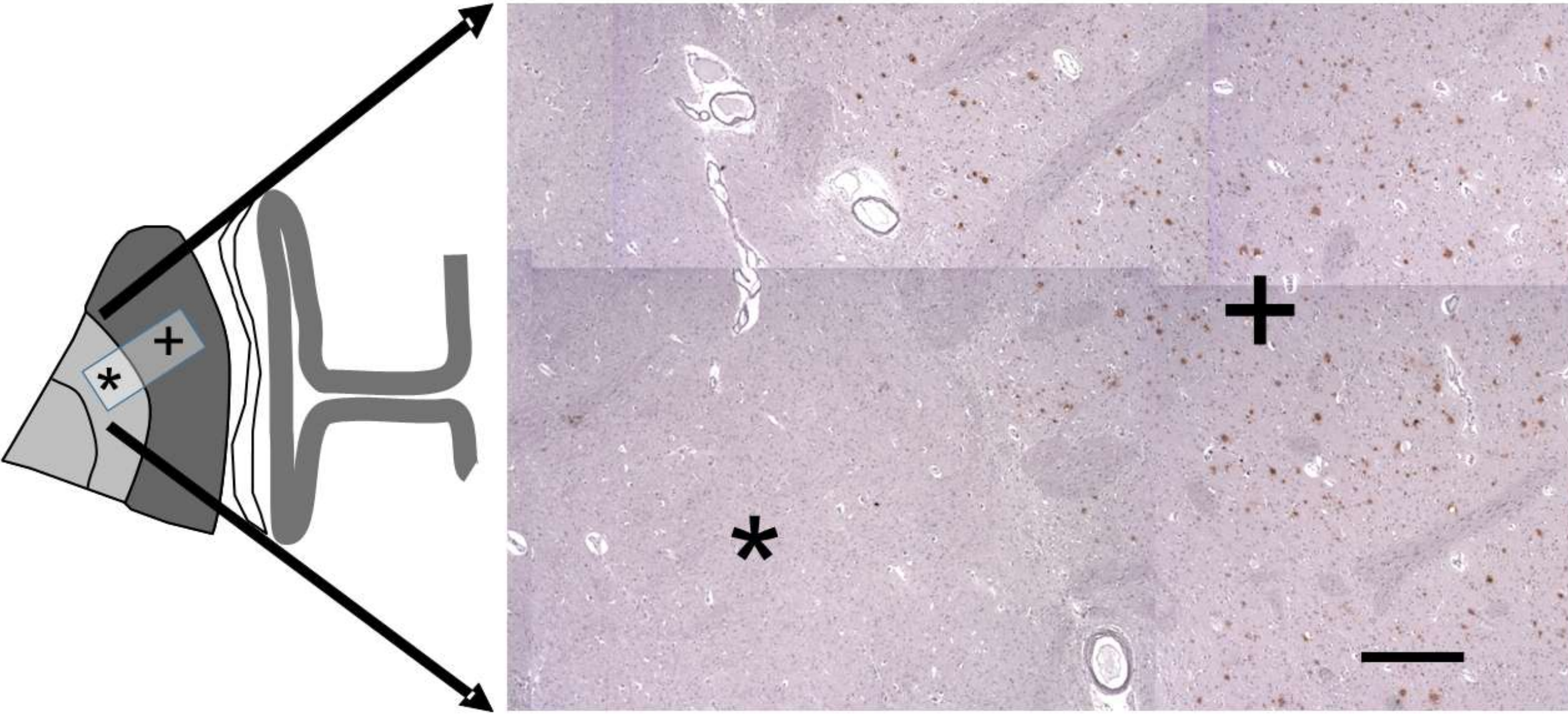


Propagation through connections

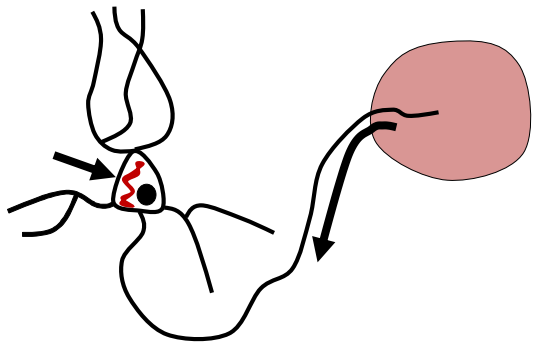





a
b
c
d



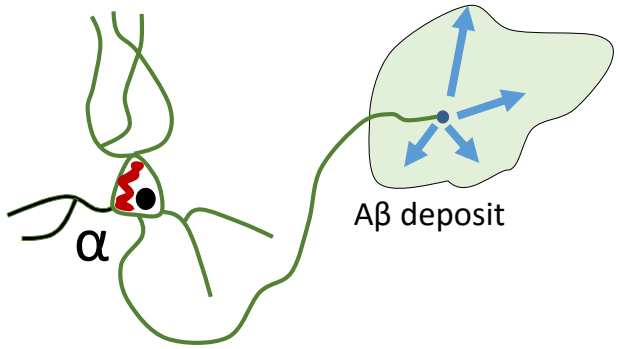
Aβ deposits induce tau aggregation



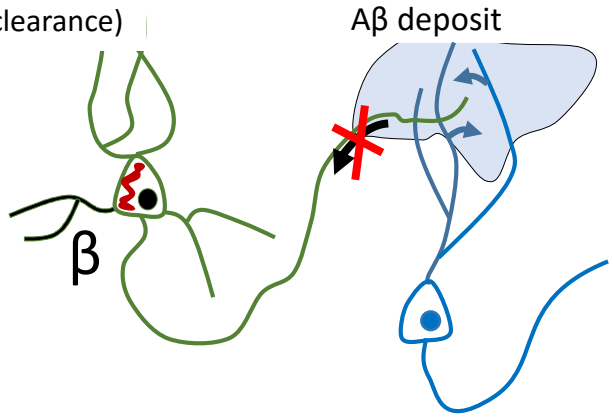
Mann DMA, Hardy J (2013) Amyloid or tau: the chicken or the egg? Acta Neuropathol 126:609–13

Tau aggregates induce Aβ deposition

Presynaptic
(increased secretion)



Postsynaptic
(defect of clearance)



Braak H, Del Tredici K (2013) Amyloid-β may be released from non-junctional varicosities of axons generated from abnormal tau-containing brainstem nuclei in sporadic Alzheimer's disease: a hypothesis. Acta Neuropathol 126:303–6.