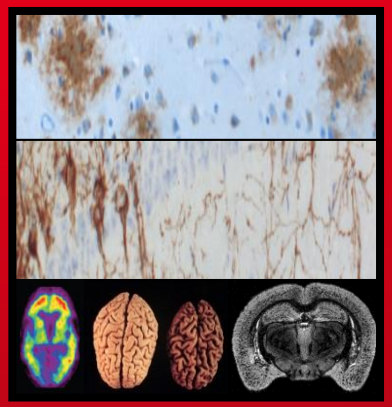
Alzheimer's disease



Marc Dhenain

Multimodal Imaging of
Neurodegenerative Diseases
and Therapies

MIRCen, CEA-CNRS UMR 9199
Fontenay-aux-Roses

ALZHEIMER'S DISEASE
Clinical symptoms

Progressive and irreversible decline of cognitive functions

- Memory loss/amnesia
- Langage deterioration
- Spatio-temporal disorientation
- Loss of recognition (including faces)
- → Loss of autonomy

Age of onset: average 65-70 years, duration: 10 years

Prevalance increase with age: 1% at 65 years, 20-35 % at 85 years

~ 50 Millions individuals affected in the world (~1 million in France)

→ Huge social cost, huge economic cost

ALZHEIMER'S DISEASE
CURRENT STATE OF AD DRUG DEVELOPMENT

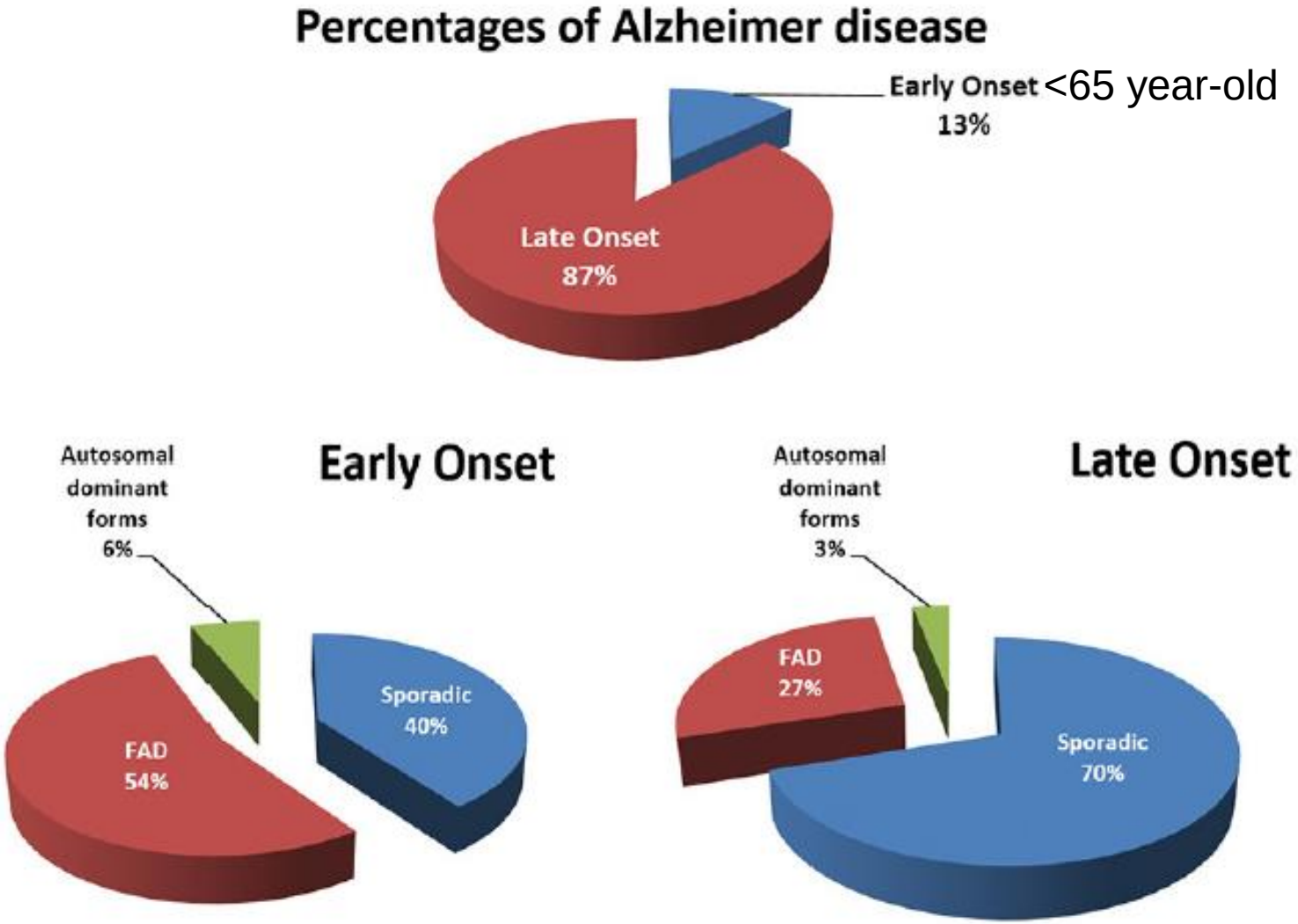
- Only five approved drugs (four cholinesterase inhibitors, one NMDA antagonist)

- 413 trials
  124 in Phase 1
  206 in Phase 2
  83 in Phase 3

- **Attrition rate of 99.6%!**

Data from clinicaltrials.gov looking at period 2002-2012
Analysed by Cummings et al. 2014

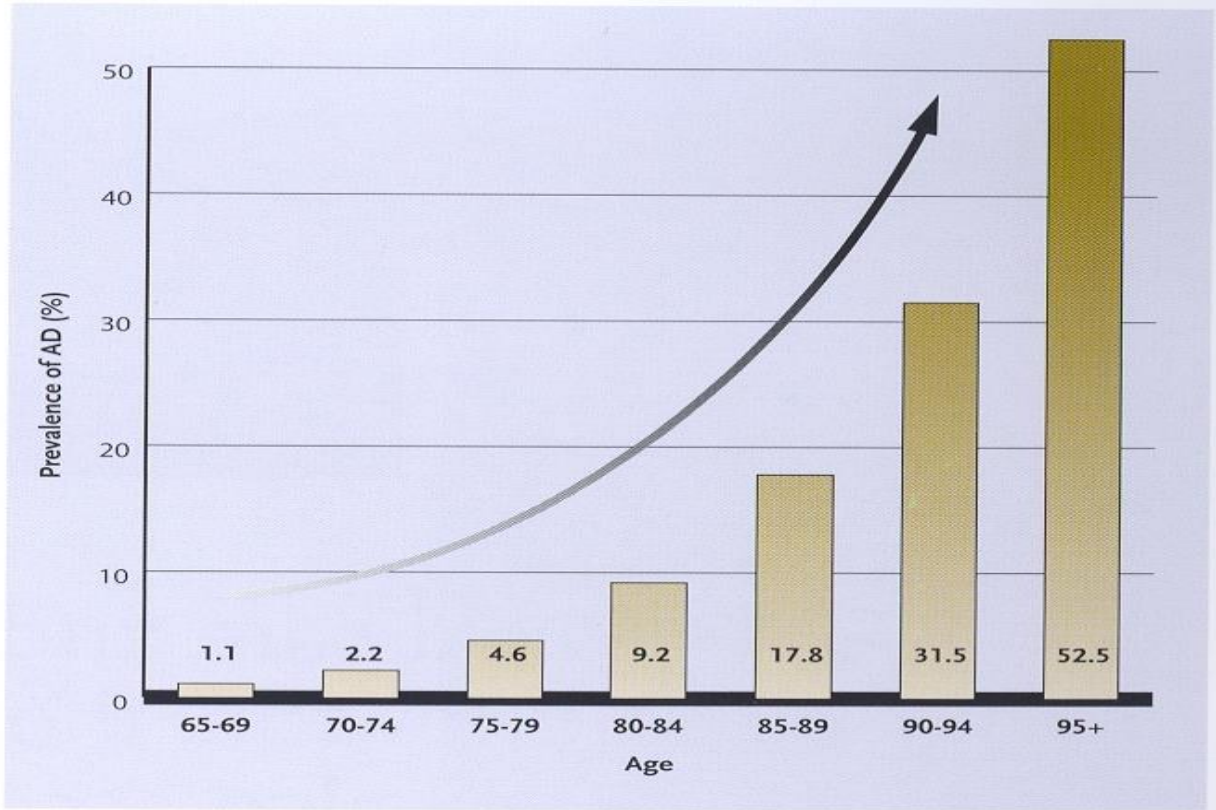
ALZHEIMER'S DISEASE
Autosomal dominant / familial / sporadic forms



Gentier & Van Leeuwen, Frontiers Mol Neurosc, 2015 (10.3389/fnmol.2015.00047)

ALZHEIMER'S DISEASE

Aging is the first risk factor



Increased prevalence of Alzheimer's disease with age among US population.

Adapted from: U.S. General Accounting Office/Health and Human Services (98-16). Alzheimer's Disease. Estimates of Prevalence in the United States.

RISK FACTORS (ALZHEIMER)

Age

Education level

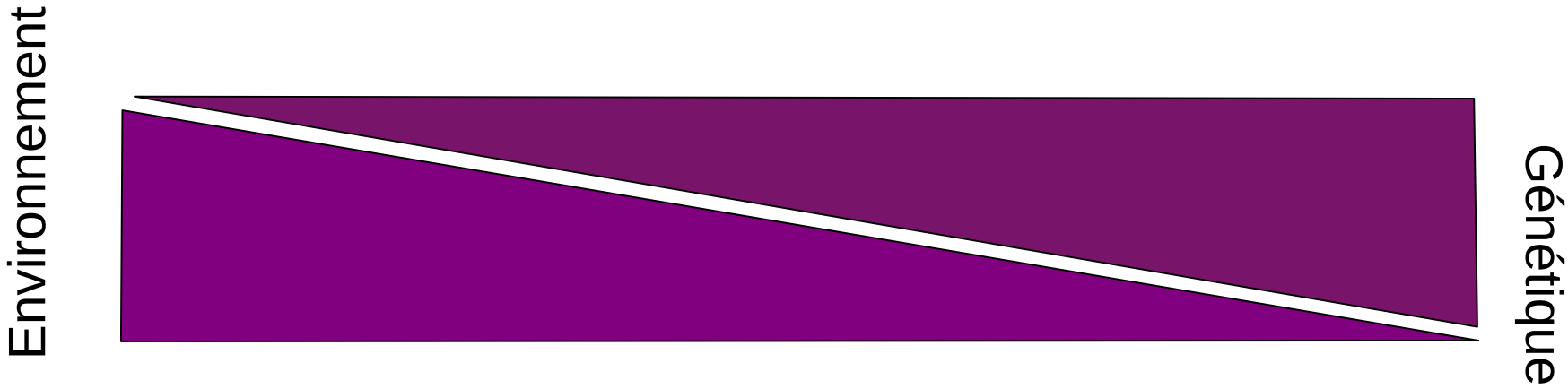
Familial History

Positive genotype Apolipoprotein E 4/4

Arterial hypertension

Hyperinsulinemia

FACTEURS DE RISQUES: CONCEPTS



Maladies environnementales	Maladies multifactorielles	Maladies génétiques
Ex. Cancer du fumeur Amiante…		Ex. Chorée de huntington

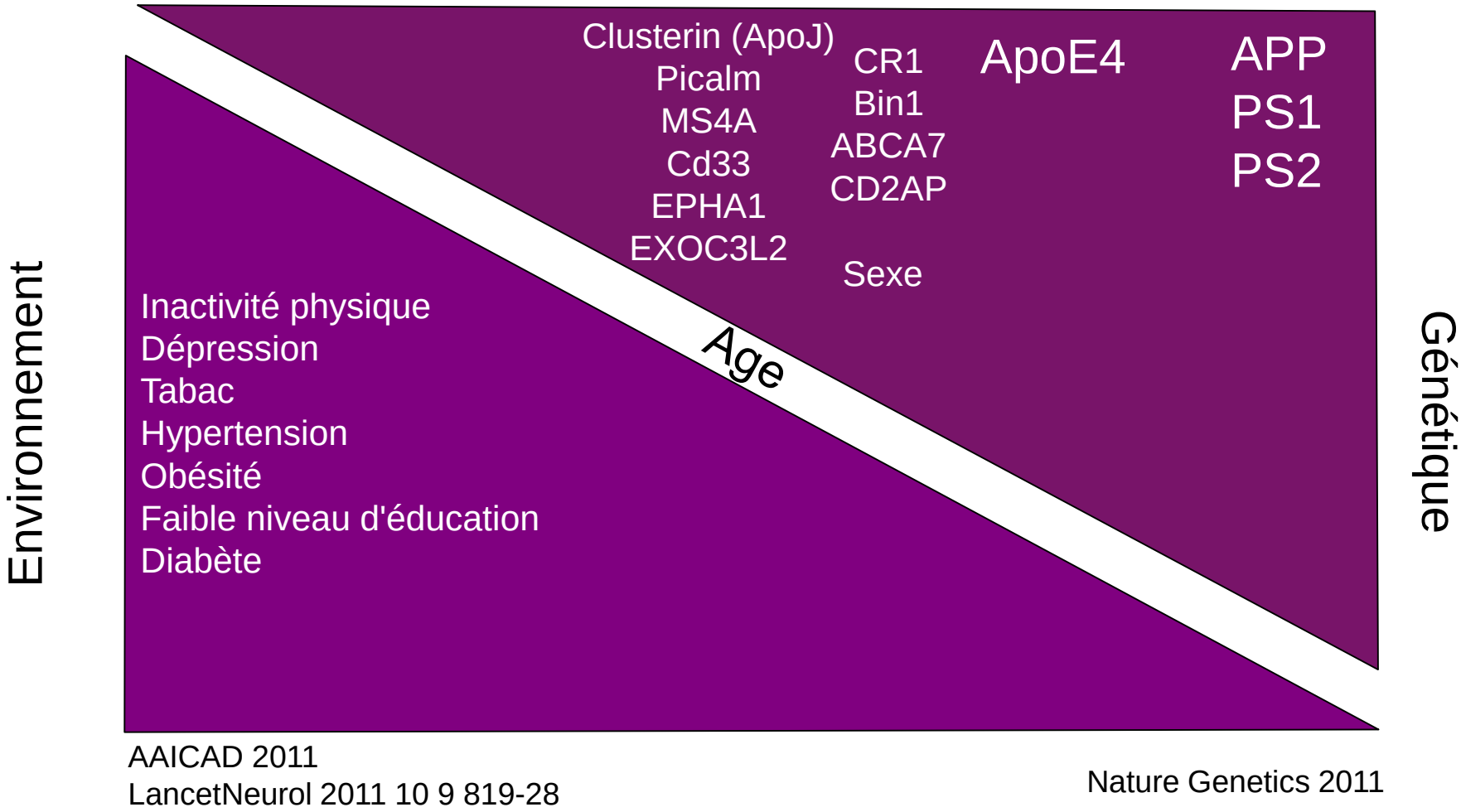
FACTEURS DE RISQUES ET DE SUSCEPTIBILITÉ

Maladies environnementales

Maladies multifactorielles

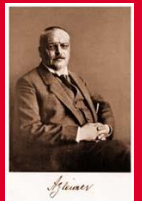
Maladies génétiques

Facteurs susceptibilité



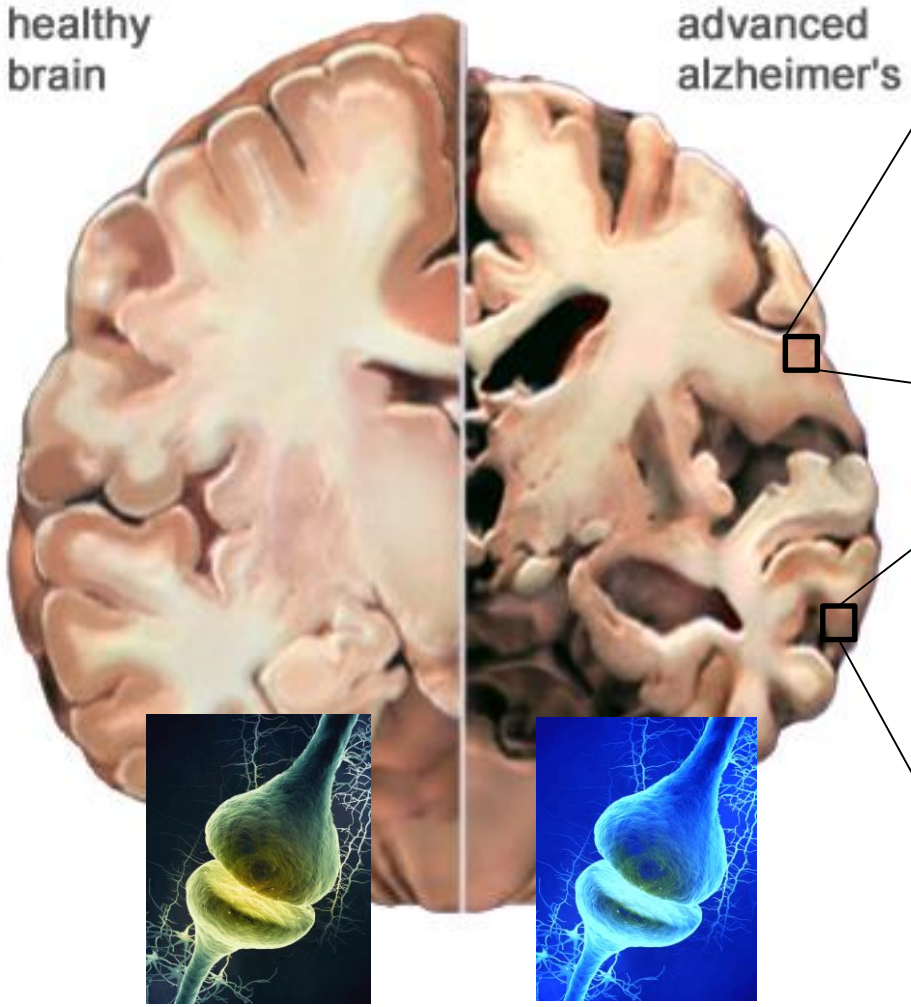
AAICAD 2011
LancetNeurol 2011 10 9 819-28

Nature Genetics 2011



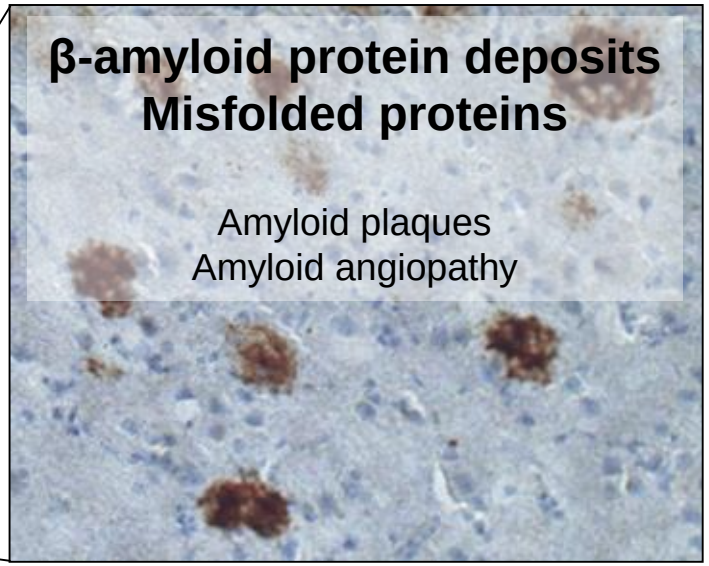
ALZHEIMER'S DISEASE
Neuropathology

Cerebral atrophy



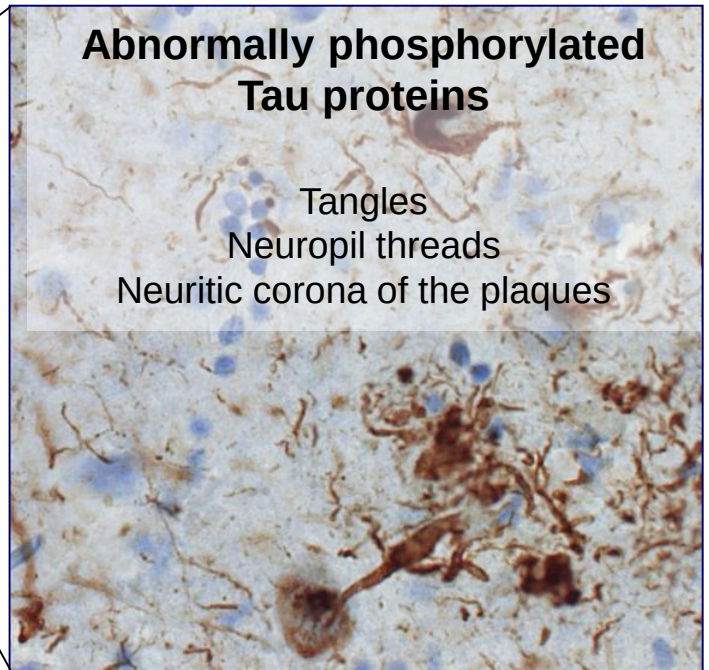
β-amyloid protein deposits
Misfolded proteins

Amyloid plaques
Amyloid angiopathy



Abnormally phosphorylated
Tau proteins

Tangles
Neuropil threads
Neuritic corona of the plaques



Duyckaerts C et al. Acta Neuropathol. 2009

ALZHEIMER'S DISEASE
IMAGING

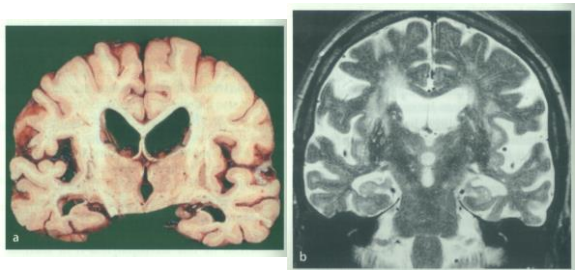
β amyloid protein deposits
Misfolded proteins

Amyloid plaques
Amyloid angiopathy

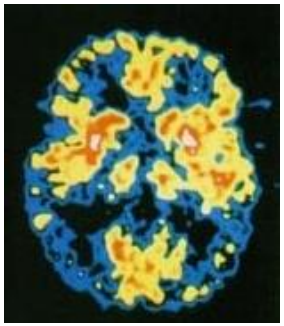
Abnormally phosphorylated
Tau proteins

Tangles
Neuropil threads
Neuritic corona of the plaques

Cerebral atrophy



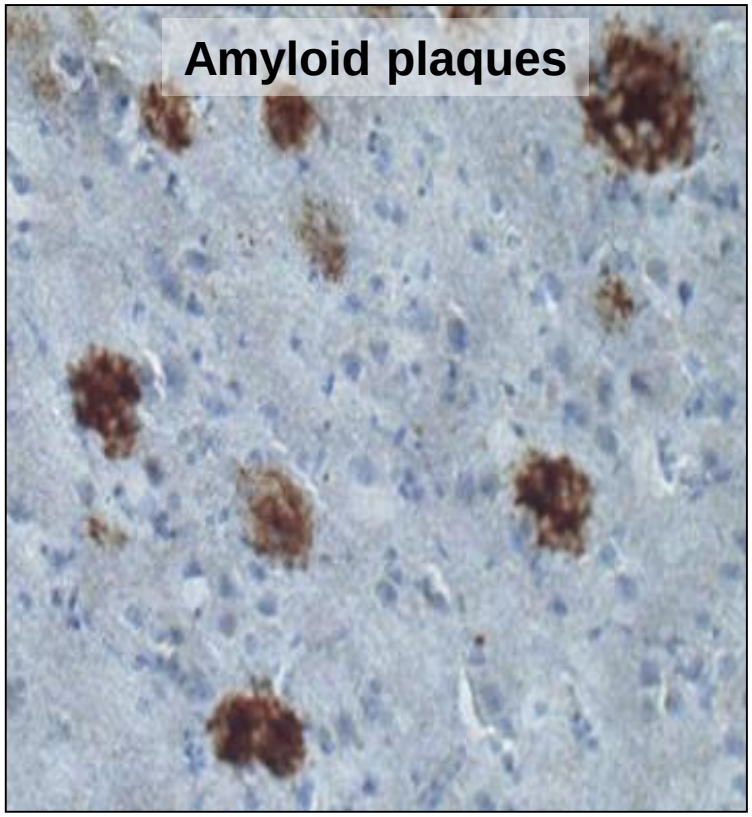
Functional alterations

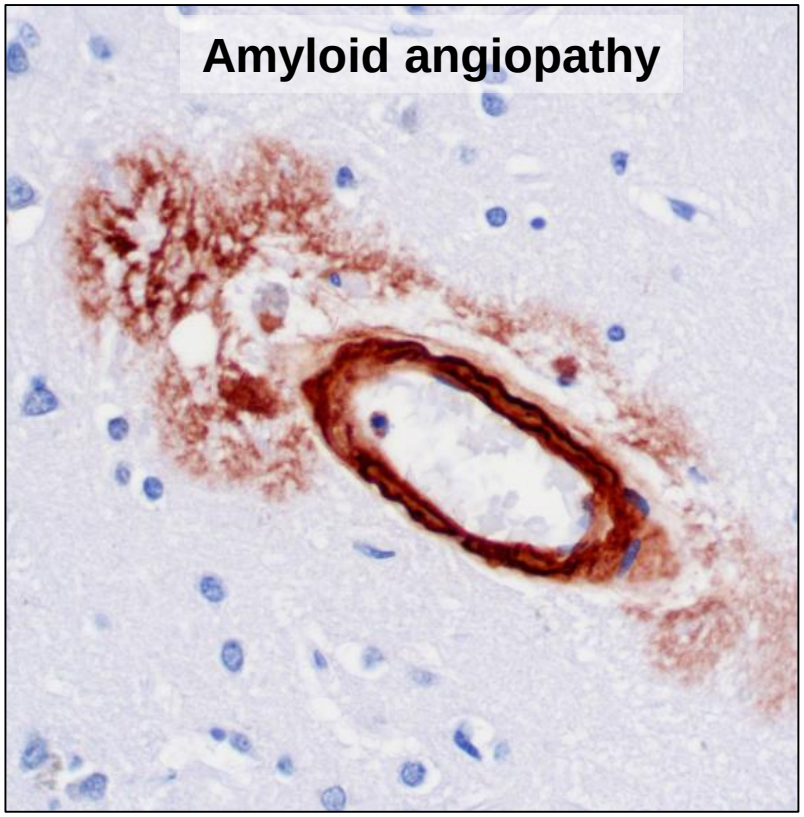


Cognitive alterations

ALZHEIMER'S DISEASE PATHOLOGY
β-amyloid

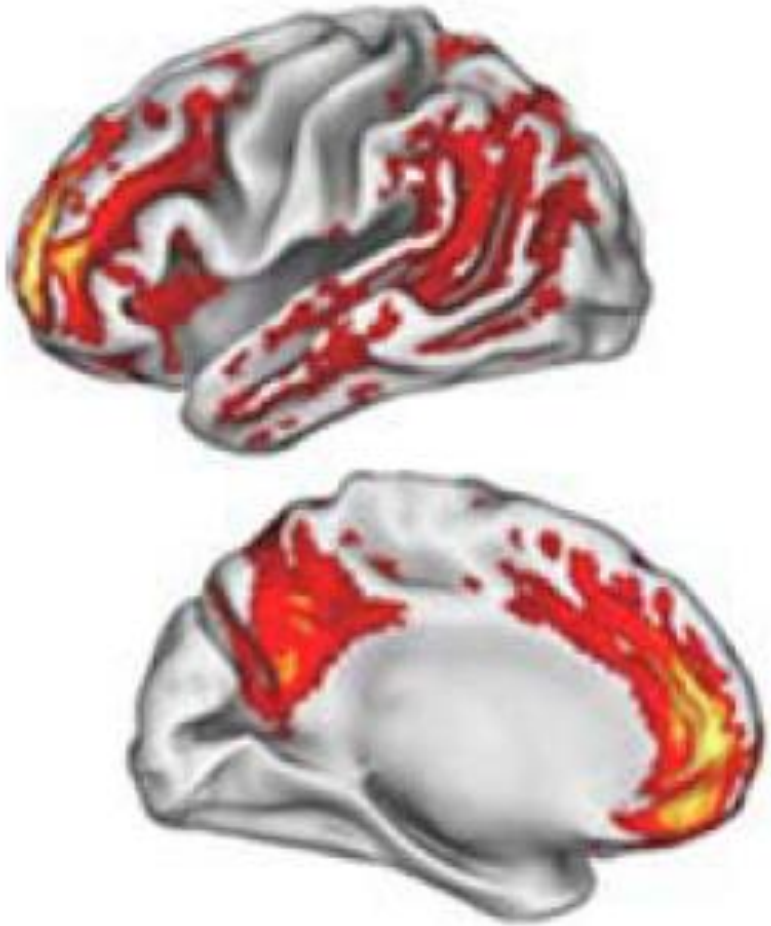
Extracellular deposition of misfolded β-amyloid (Aβ) proteins





Poorly correlated with cognitive scores

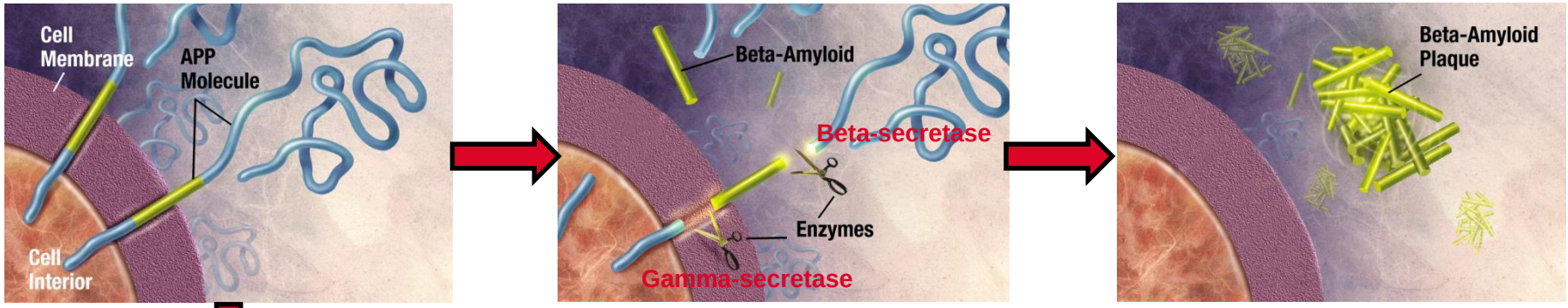
LOCATION OF β-AMYLOID IN THE BRAIN
Cortical regions first



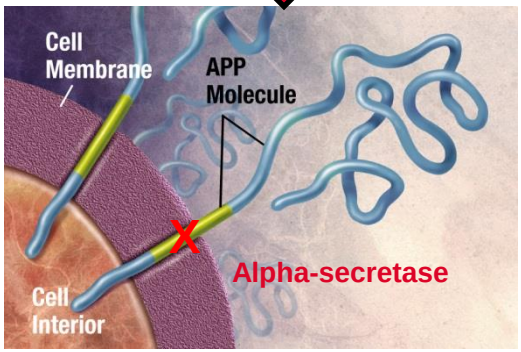
Thal D.R., 2002. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 58, 1791-1800.
Buckner et al. J Neurosci. 2005 Aug 24;25(34):7709-17.

ORIGIN OF β-AMYLOID
Proteolytic cleavage of amyloid precursor protein (APP)

Amyloidogenic pathway



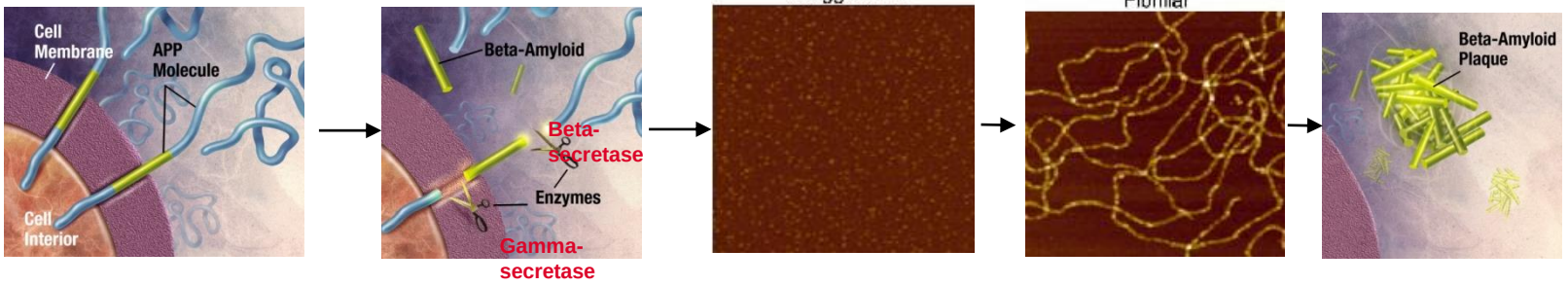
Non amyloidogenic pathway



APP : Amyloid Precursor Protein

Mutations of APP or gamma-secretase components lead to Alzheimer's disease

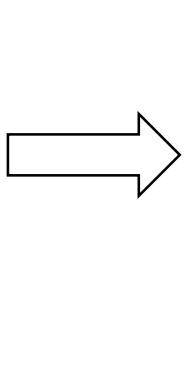
EX. OF AMYLOID PLAQUES
FROM APP TO AGGREGATED FORMS OF AMYLOID



APP : Amyloid Protein Precursor

Protein structures

Alpha helix and beta pleated sheet



α-helix

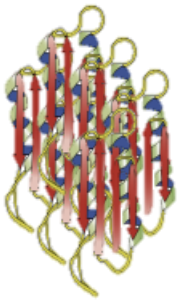
β-pleated sheets

Native protein

Misfolded protein

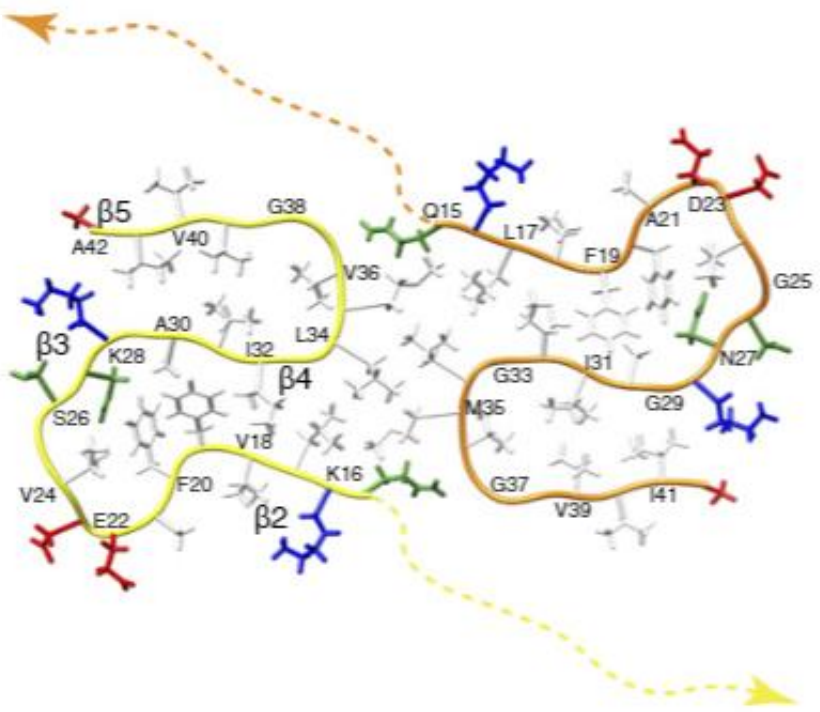
SOLUBLE

AGREGATES

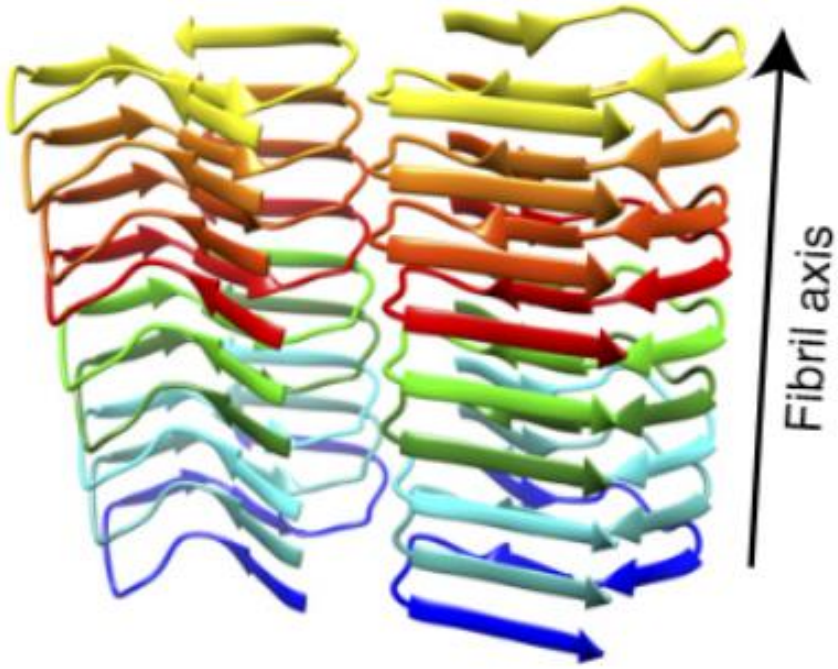


β-AMYLOID FIBRILS/AGREGATES ARE MADE OF MISFOLDED β-AMYLOID PROTEINS

Two Aβ
→ Double-horseshoe–like cross–β-sheet



Series of two Aβ form fibrils
→ β-sheet structures

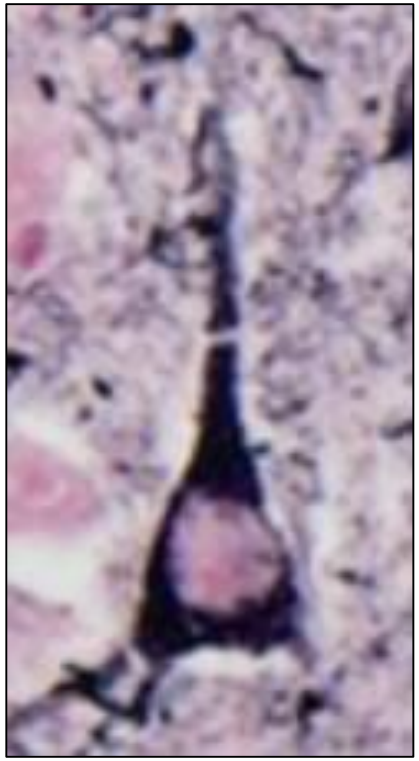


Walti, M. A. *et al. (2016). "Atomic-resolution structure of a disease-relevant Abeta(1-42) amyloid fibril."* Proc Natl Acad Sci U S A ***113(34): E4976-4984.***

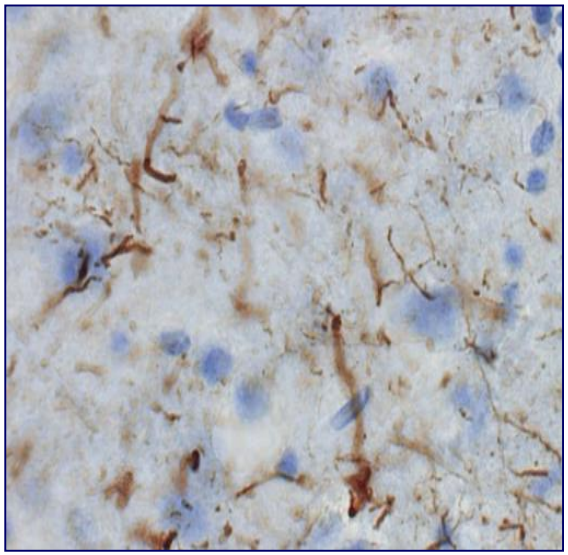
ALZHEIMER'S DISEASE PATHOLOGY

Tau (tubulin-associated unit) lesions

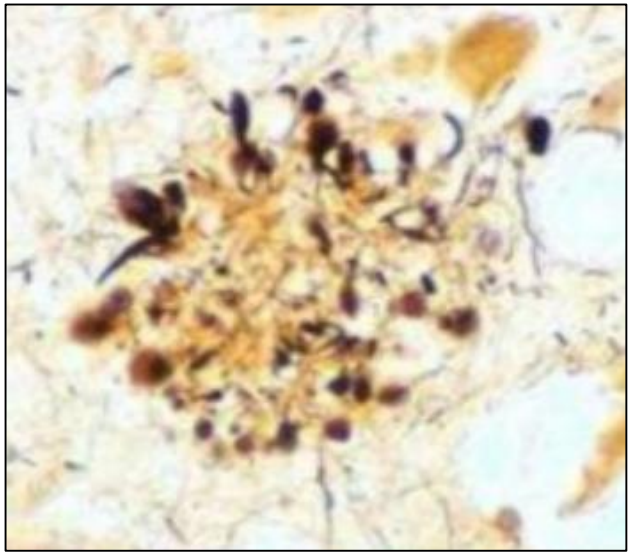
Intracellular deposition of abnormally phosphorylated tau proteins



Neurofibrillary tangles
(within cell soma)



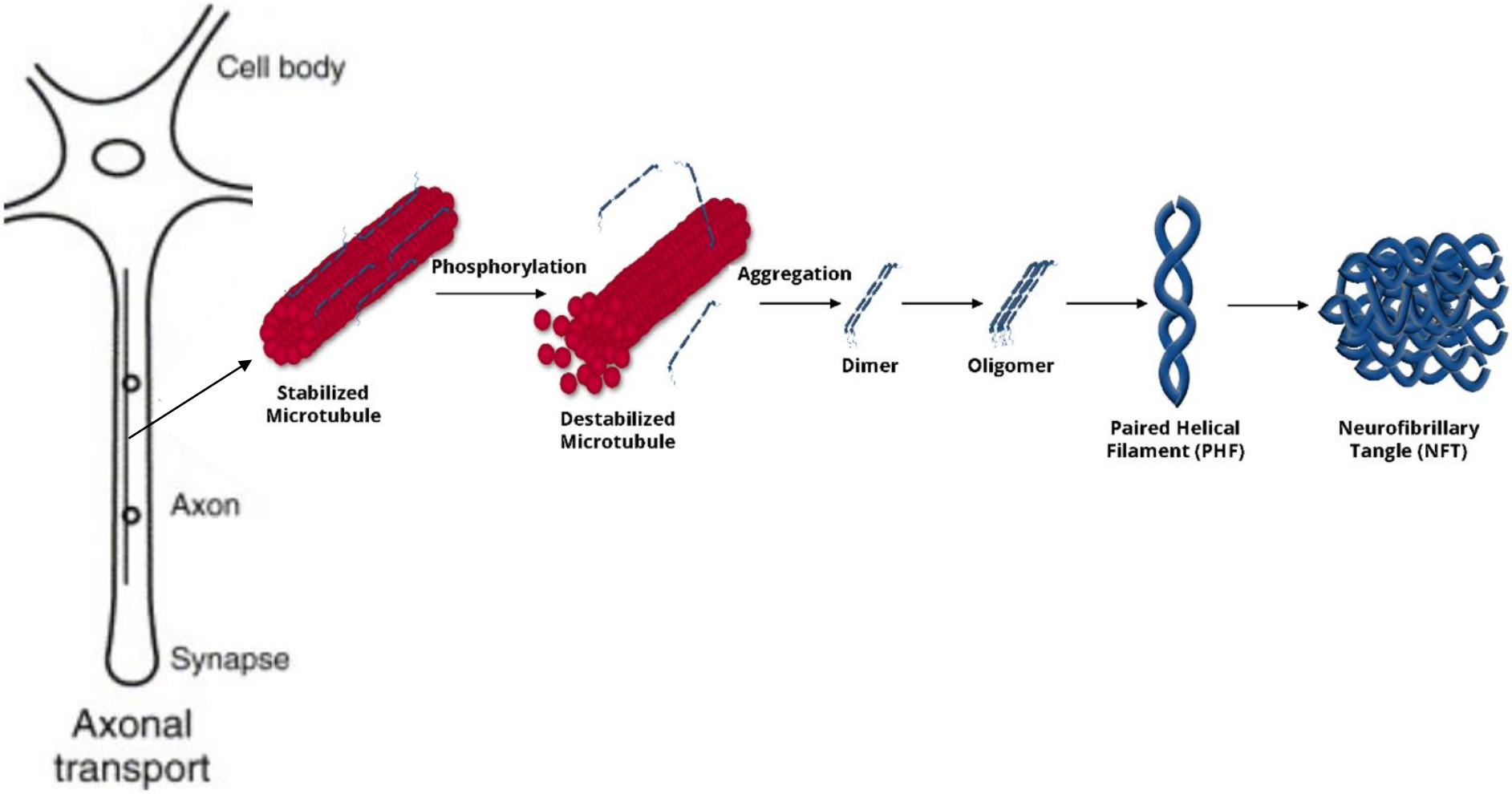
Neuropil threads*
(within neurites)



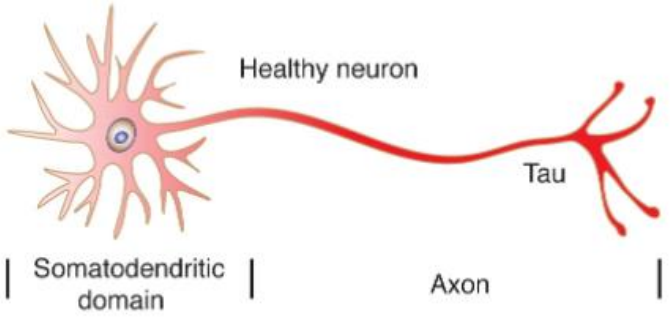
Neuritic plaques**
(amyloid + tau)

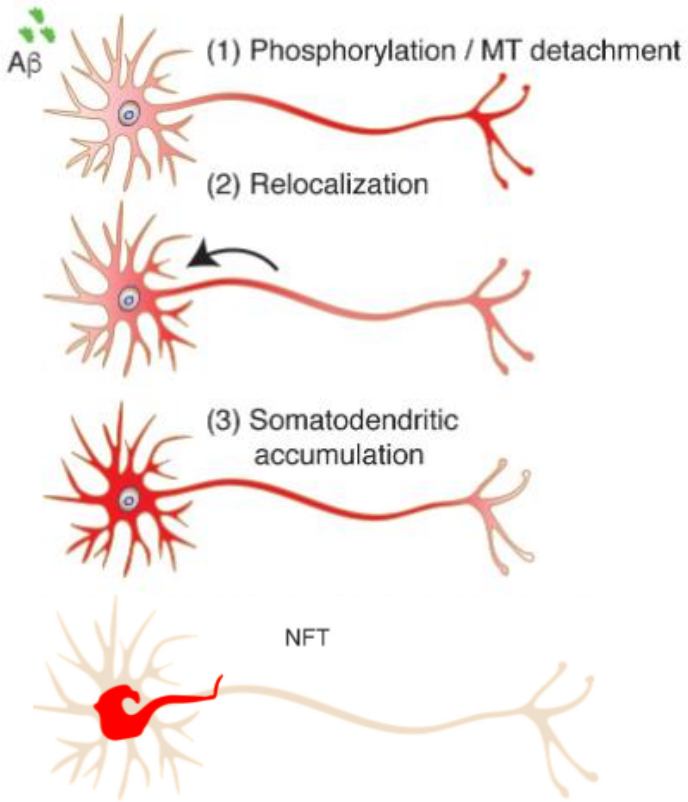
* Neuropil = Unmyelinated axons, dendrites and glial cell processes
** Neurite = Axon or dendrite

ORIGIN OF TAU LESIONS
Abnormal phosphorylation of tubulin-associated unit



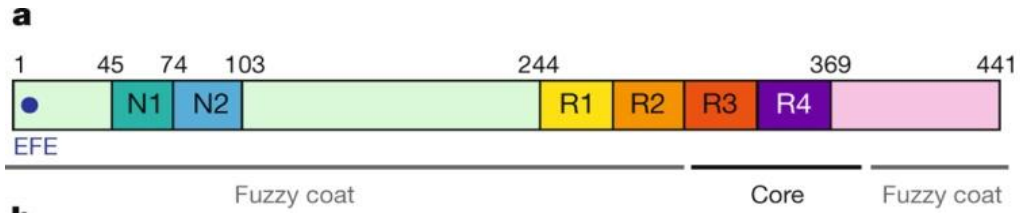
ALZHEIMER'S DISEASE
RELOCATION OF TAU TO THE SOMA

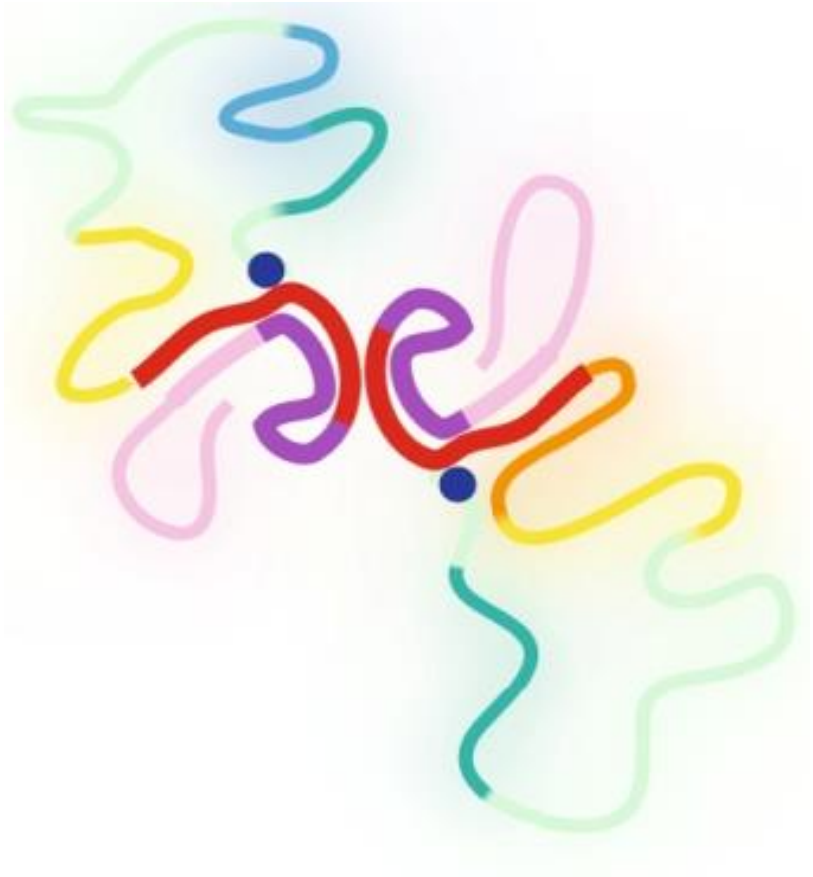




https://doi.org/10.15252/embj.201797724

TAU FIBRILS/AGREGATES ARE MADE OF MISFOLDED TAU PROTEINS



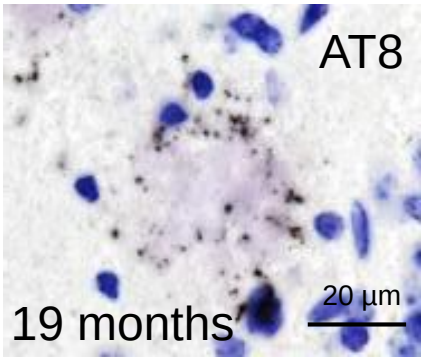


Fitzpatrick AWP et al. Cryo-EM structures of tau filaments from Alzheimer's disease. Nature. 2017 Jul 13;547(7662):185-+.

AMYLOID-β INDUCES TAU PATHOLOGY
Example in amyloid-β bearing mice

APP/PS1dE9

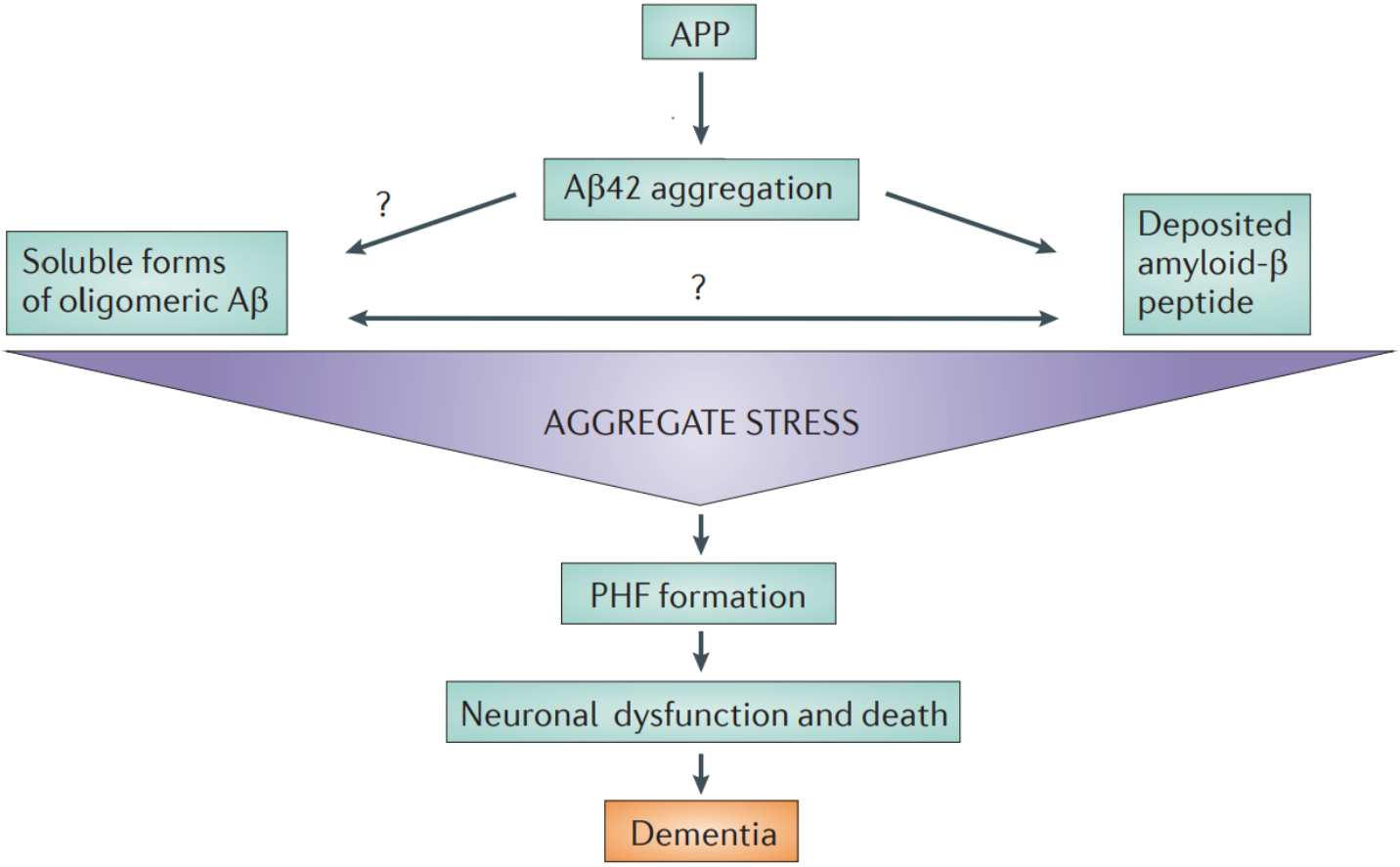
Neuritic plaques



Lam, BioRxiv, 2021; Metaxas, Scientific Reports, 2019; Radde, Embo Reports, 2006

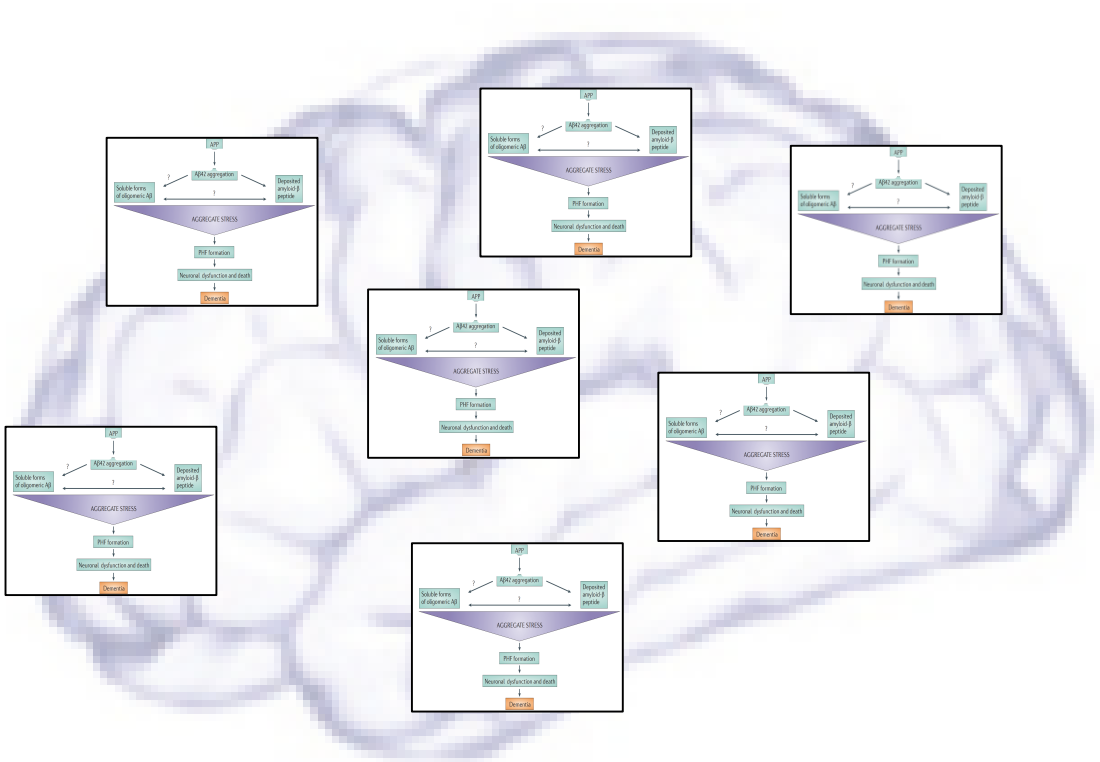
INTEGRATION WITHIN A THEORICAL FRAMEWORK
The amyloid cascade hypothesis

Hardy, J.A., Higgins, G.A., 1992.
Alzheimer's disease: the amyloid cascade hypothesis. Science 256, 184-185.



Karran, E., Mercken, M., De Strooper, B., 2011.
Nature Reviews Drug Discovery 10, 698-U1600. https://doi.org/10.1038/nrd3505.

THE AMYLOID CASCADE HYPOTHESIS
A region automomous view? (pop-corn model)

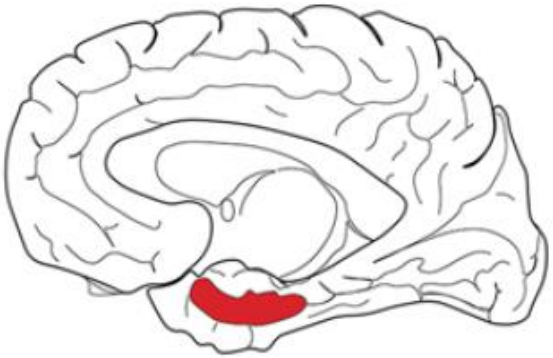


Processes occuring simultaneously in different brain regions

possibly depending on regional susceptibility (activity dependant?, other local factors?)

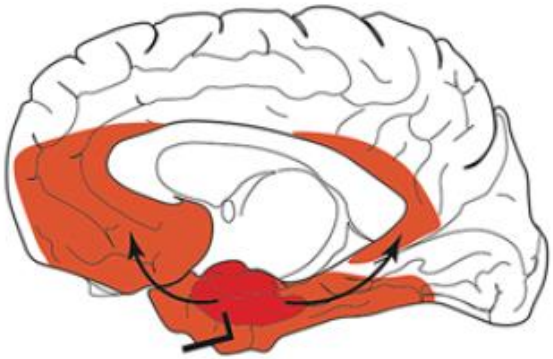
https://www.alzforum.org/news/research-news/popcorn-plaque-alzheimer-disease-slow-yet-plaque-growth-fast

TAU LESIONS
PROGRESSIVE COLONISATION OF THE BRAIN



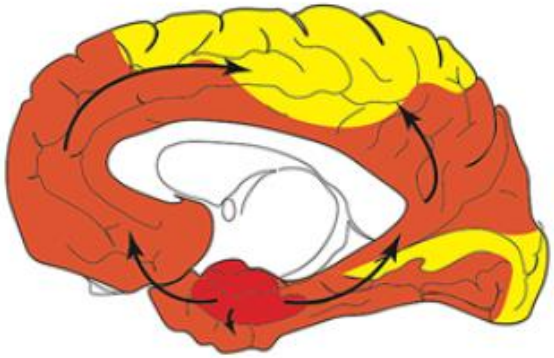
Stages I-II

Transentorhinal



Stages III-IV

Limbic



Stages V-VI

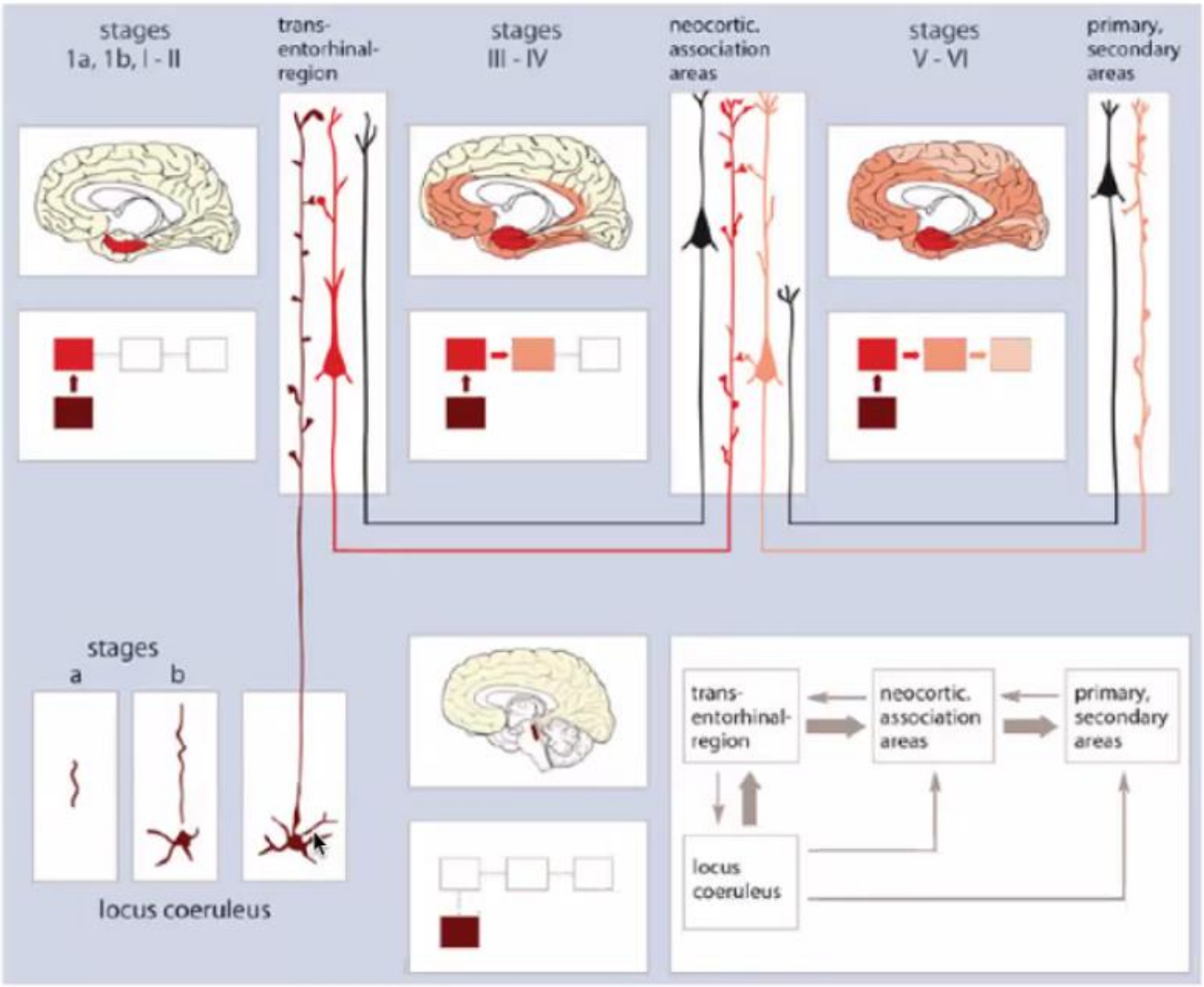
Isocortical

Braak, H. and E. Braak (1991). Acta Neuropathologica **82: 239-259.**

Strong correlation with cognitive scores

Mutation of tau does not lead to Alzheimer's disease

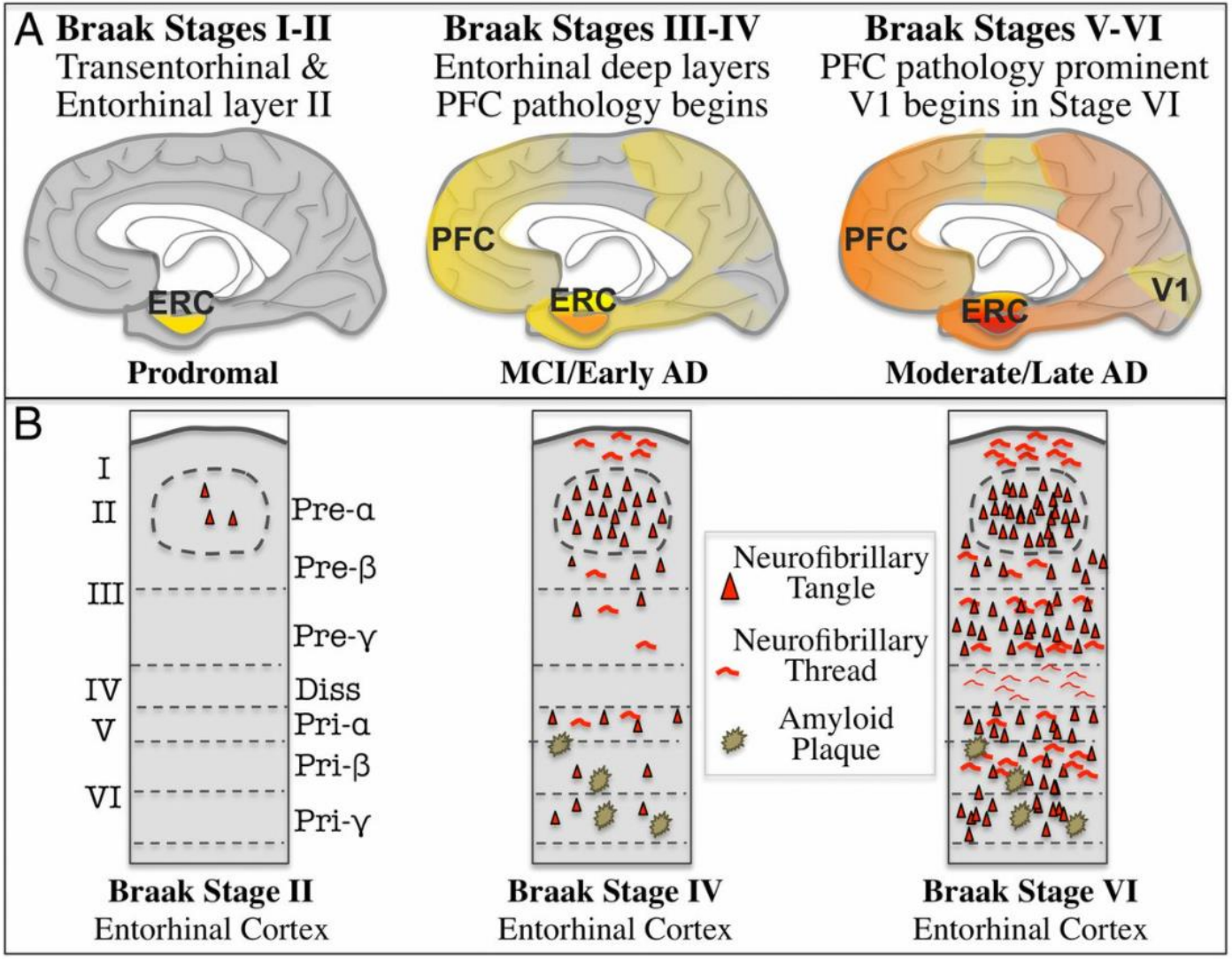
TAU LESIONS
PROGRESSIVE COLONISATION OF THE BRAIN



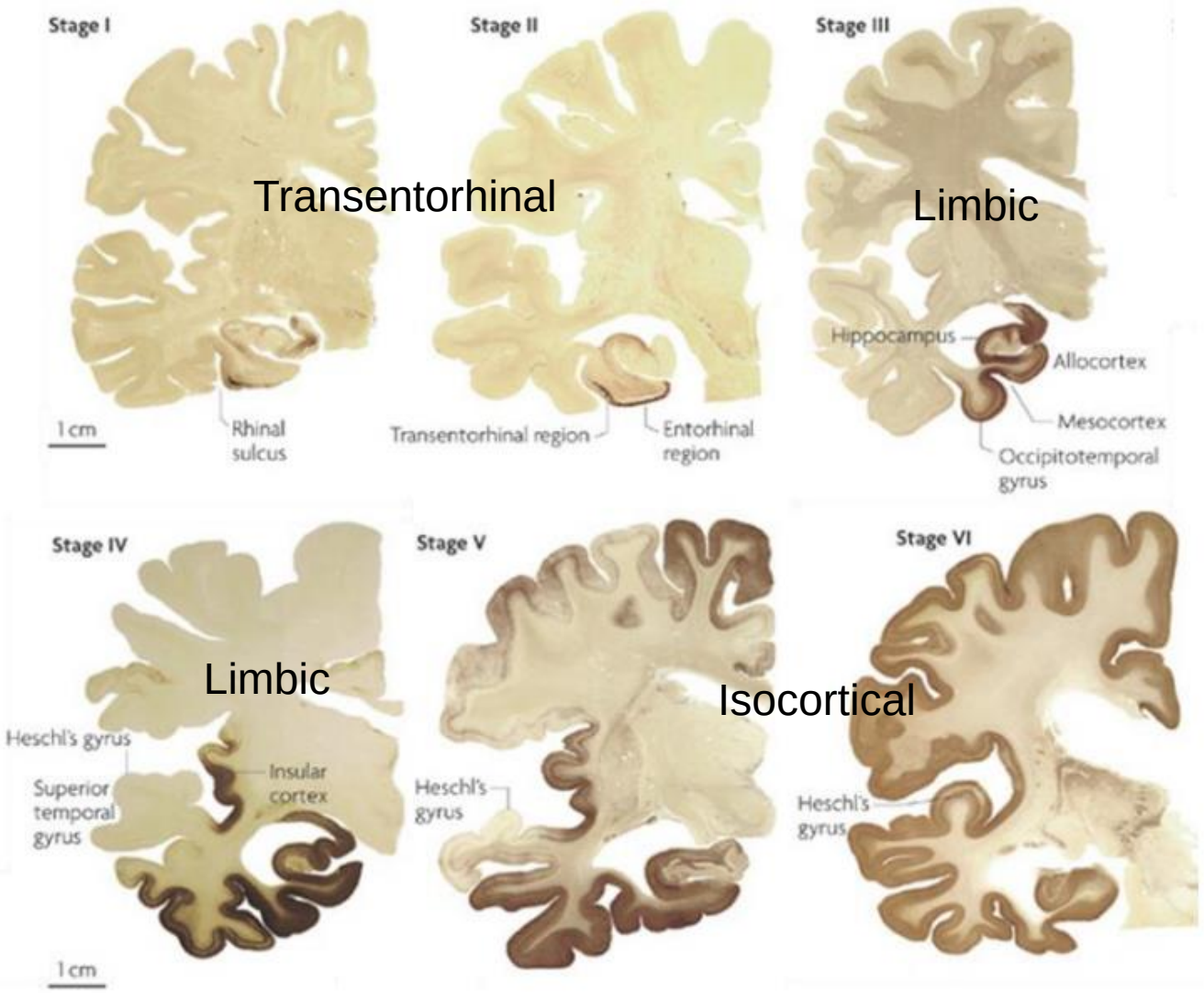
Anterograde progression (from cell soma to periphery through axon) ?

TAU LESIONS

PROGRESSIVE COLONISATION OF THE BRAIN



TAU LESIONS
PROGRESSIVE COLONISATION OF THE BRAIN



Transentorhinal

Limbic

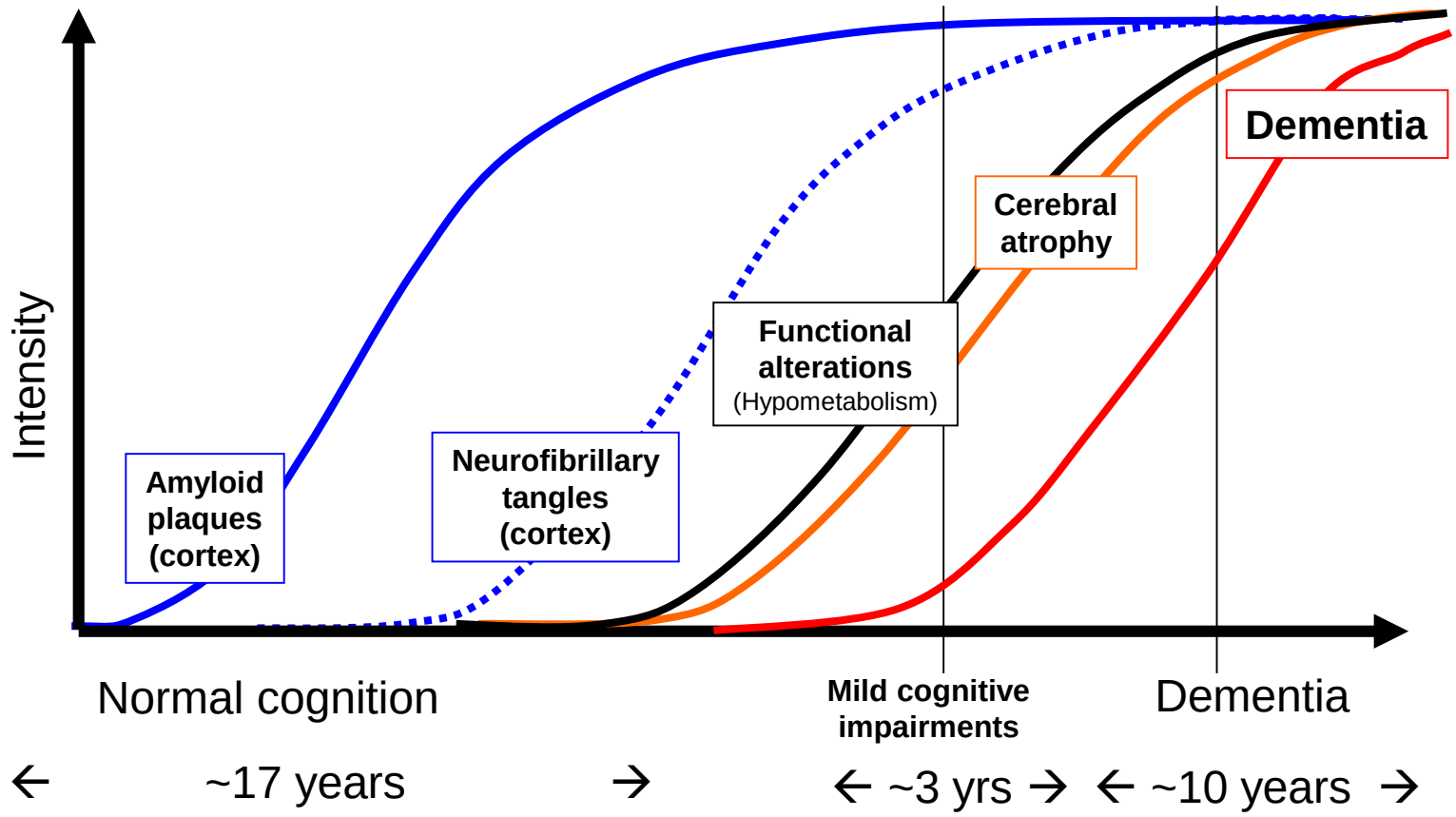
Limbic

Isocortical

Kretzschmar, 2009

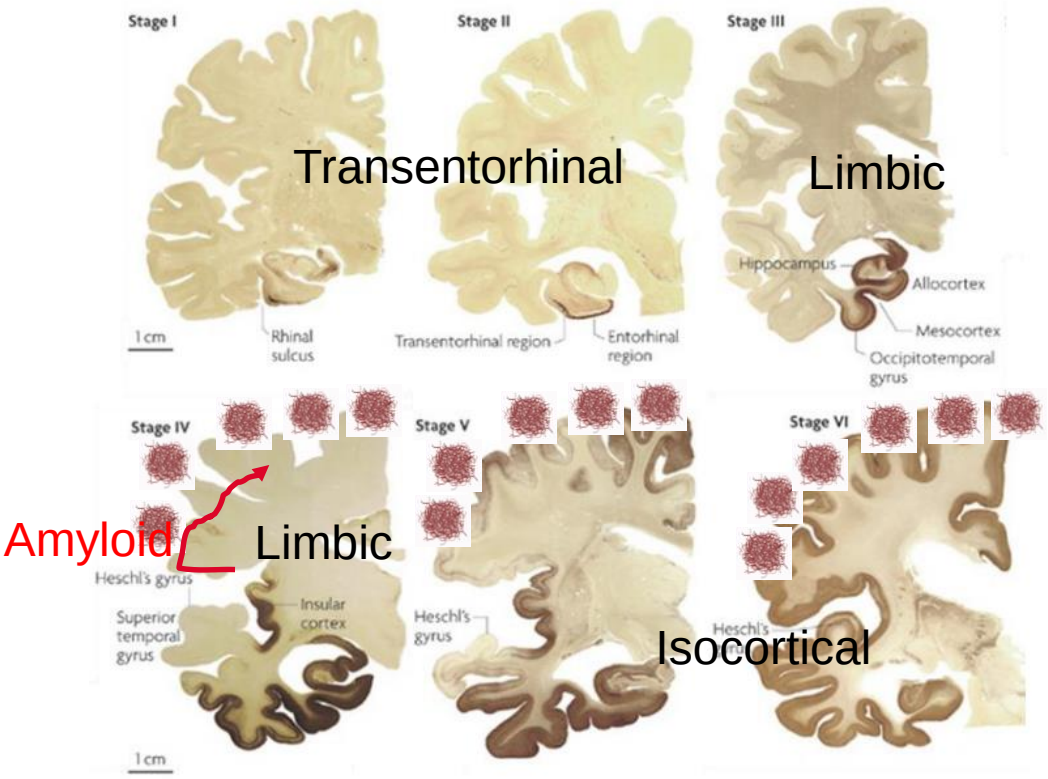
NATURAL HISTORY OF ALZHEIMER'S DISEASE
Does it recapitulates the amyloid cascade ?

Jack et al, Lancet Neurol. 2013



Probably partly innacurate: This scheme reflect Cortical Braak stages IV-V

β-AMYLOID AND TAU LESIONS ARE NOT IN THE SAME REGIONS



Two possible hypothesis

Amyloid → Induce Tau

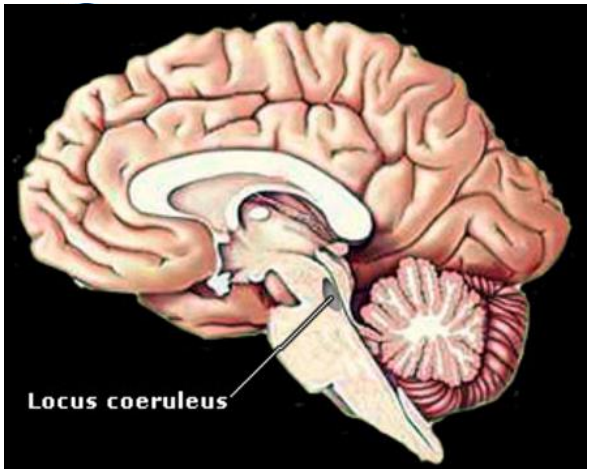
Tau postive neurons → Induce amyloid

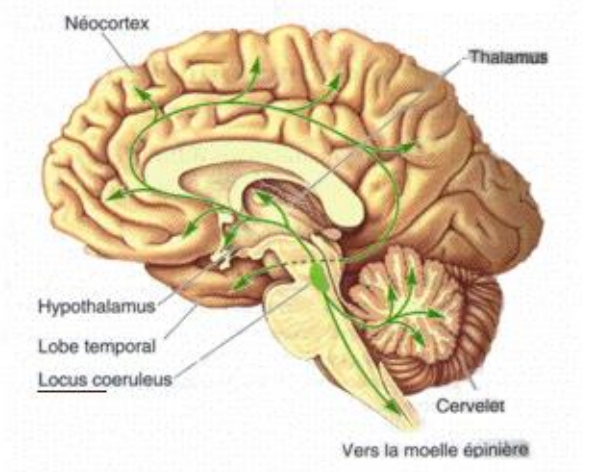
Not fully consistant with the "amyloid hypothesis / pop-corn model"

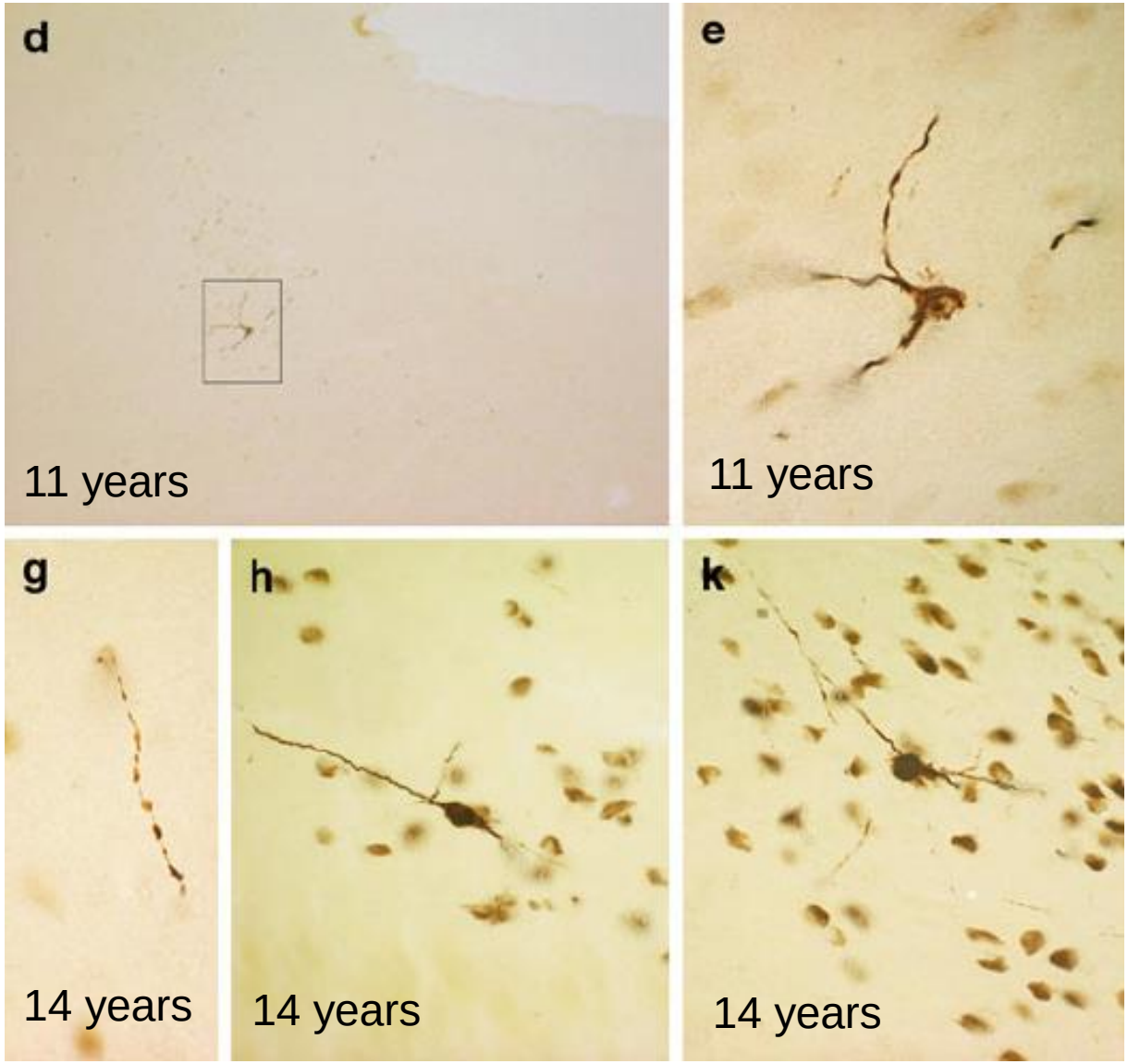
Duyckaerts, C. (2015). Acta Neuropathol **129(5): 749-756.**

TAU LESIONS START IN LOCUS COERULEUS IN CHILDHOOD

PROGRESSIVE COLONISATION OF THE BRAIN

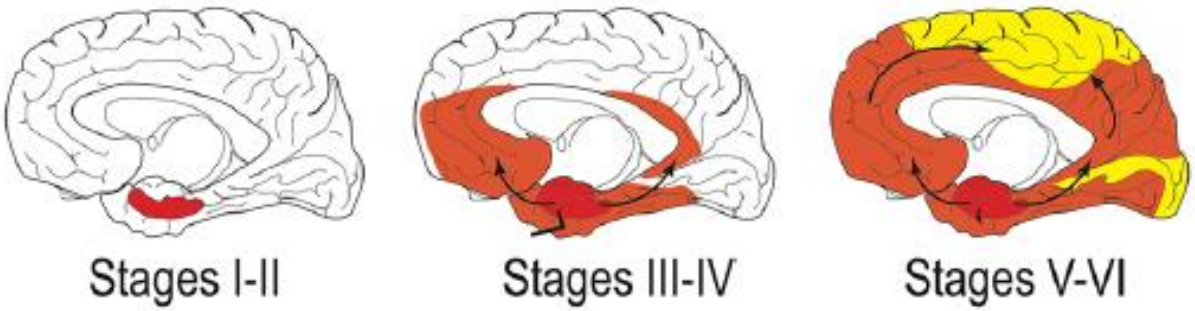


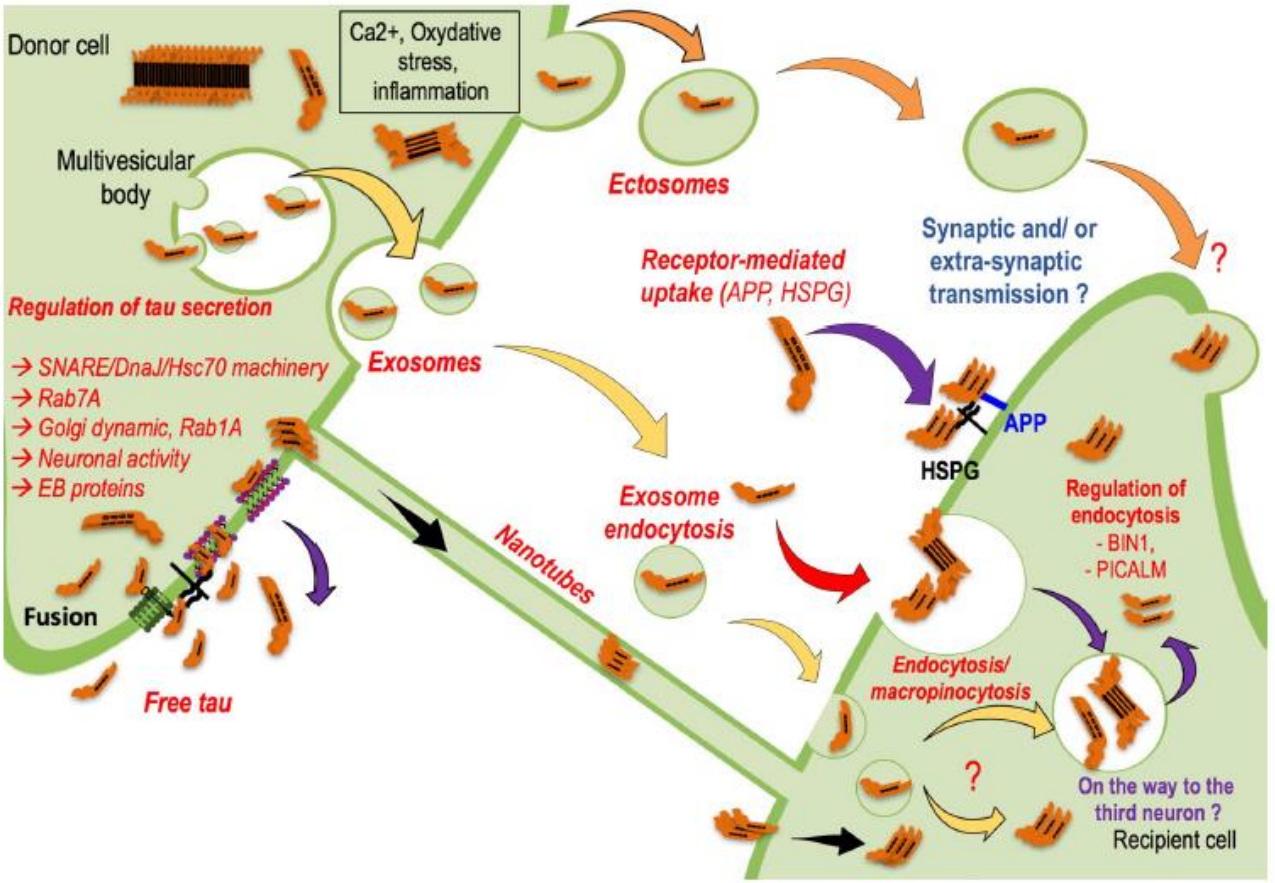




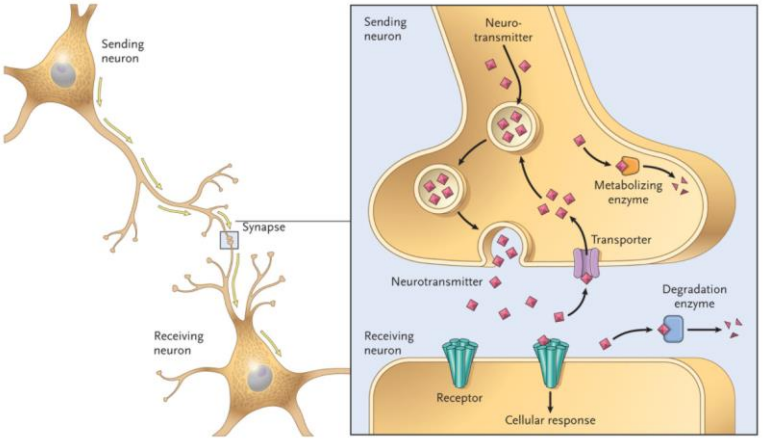
Braak, Acta Neuropathol, 2011

TAU PROTEINS SPREADING



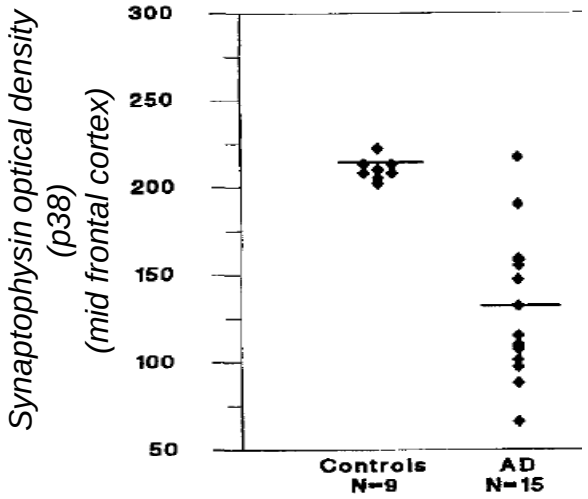


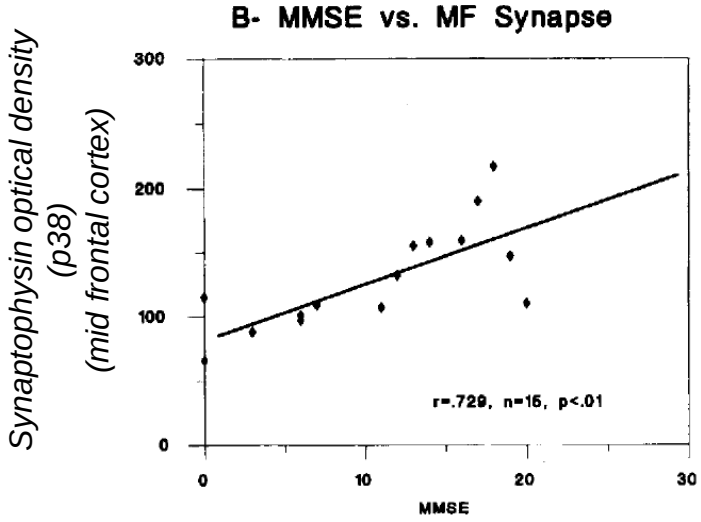
SYNAPTIC IMPAIRMENTS
Critical lesions but measures are challenging in humans



Pre-synaptic
Synaptophysin

Post-synaptic
PSD95



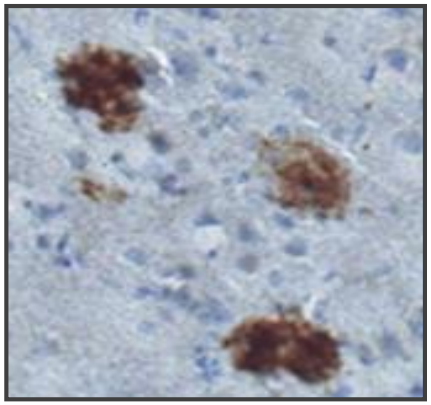


Terry, R.D., 1991. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann. Neurol. 30, 572-580. https://doi.org/10.1002/ana.410300410.

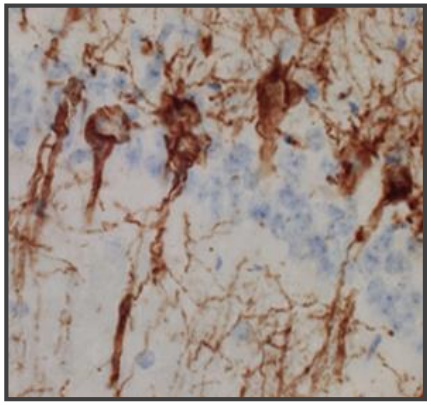
Autopsy was performed within 8 hours (range, 2-8 hours)

INTEGRATION OF THE INFLAMMATION WITHIN AD PATHOPHYSIOLOGY

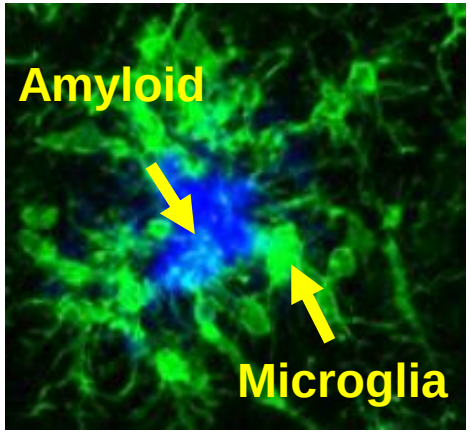
Neuropathology



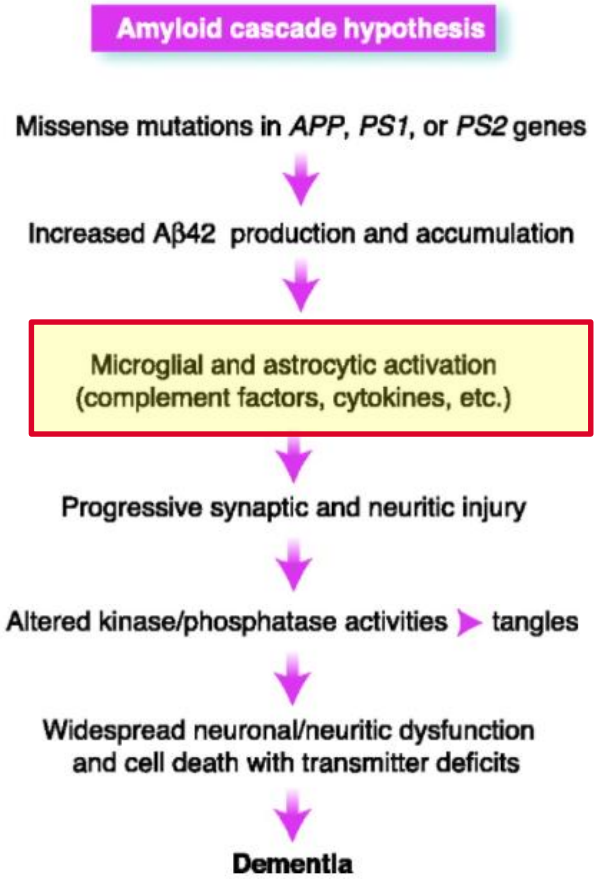
Amyloid (Aβ)



Tau



Inflammation



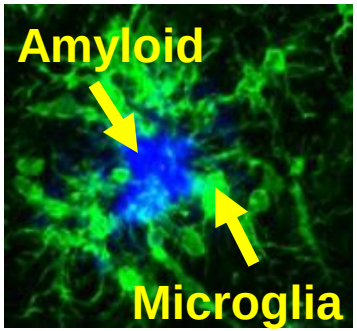
Hardy, J., Selkoe, D.J., 2002. Science 297, 353-356.

IS INFLAMMATION REALLY BAD ?

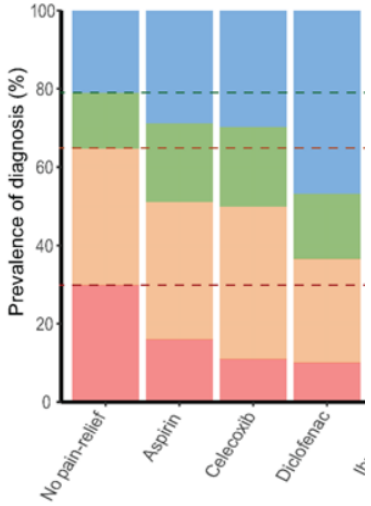
New era since ~ 2015

INFLAMMATION - MICROGLIA

Microglia close to amyloid plaques
- ROS ; Cytokines
→ Toxics ?

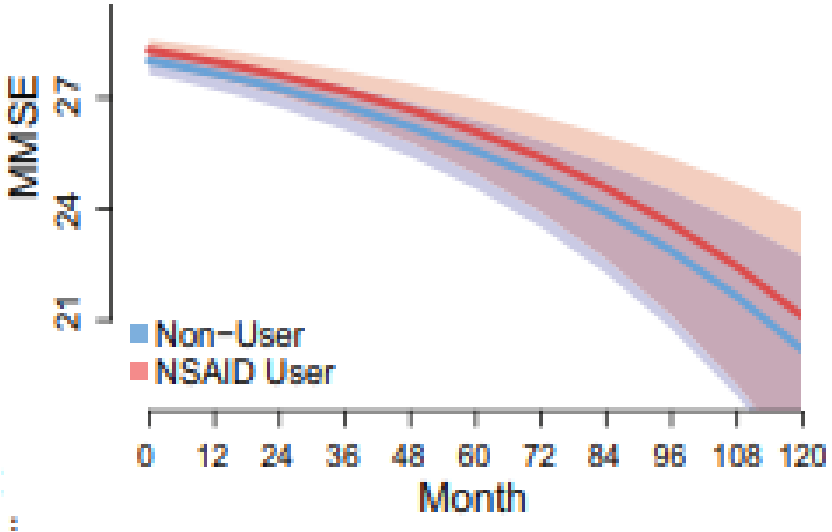


Non steroidal anti-inflammatory drugs prevent AD occurence



1619 individuals classified as
- Cognitively normal
- Early mild cognitive impairment
- Late mild cognitive impairment
- Alzheimer

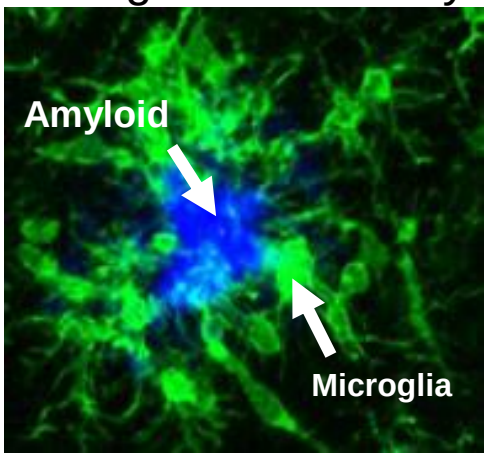
But non-steroidal anti-inflammatory drugs are innefficient during therapies (except diclofenac)

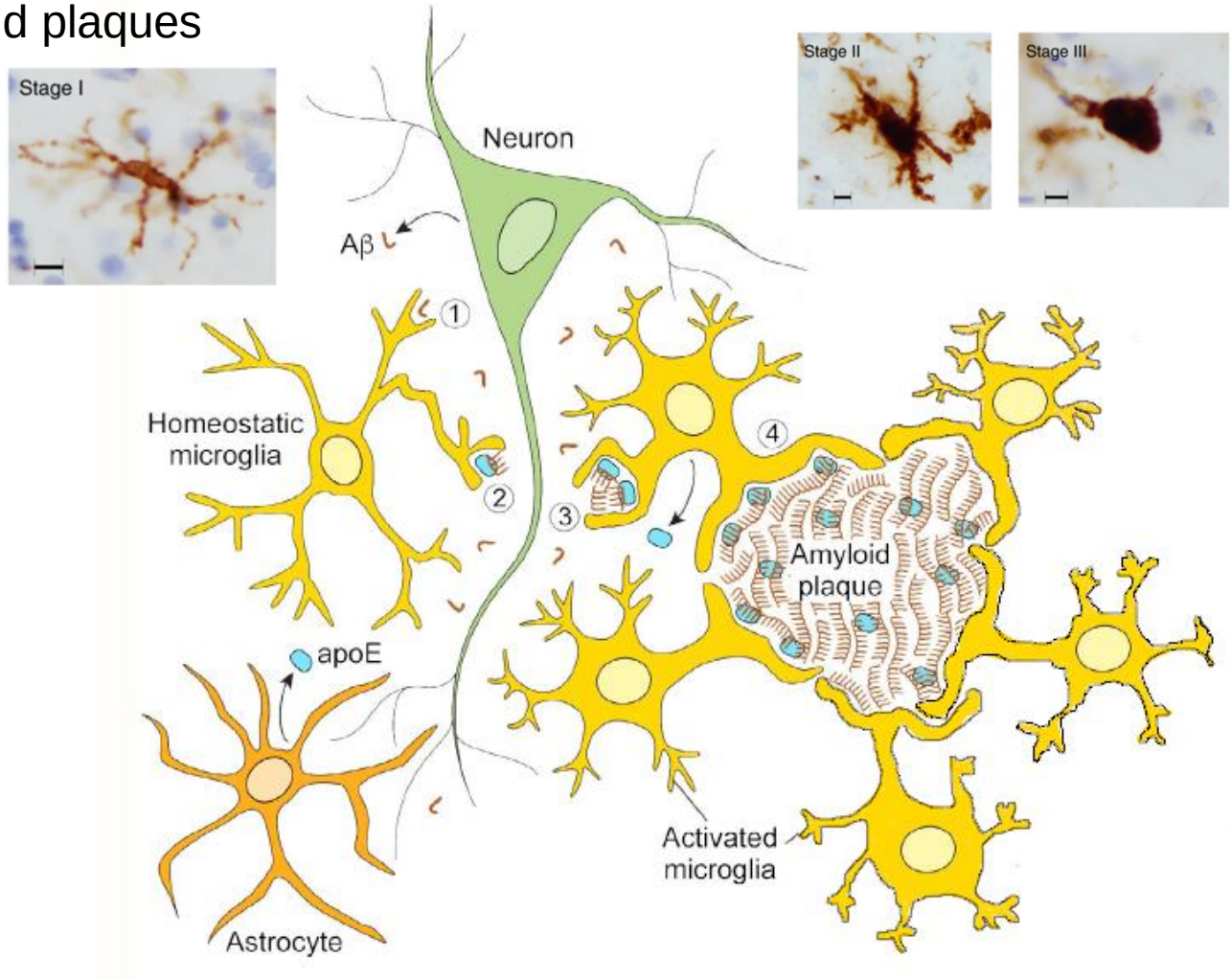


Rivers-Auty, 2020.
Brain Commun 2 https://doi.org/ARTN 109 10.1093/braincomms/fcaa109.

EARLY PHASES OF AMYLOIDOSIS
Microglia is protective by removing or shielding amyloid

Microglia phogocyte amyloid
Microglia shields amyloid plaques

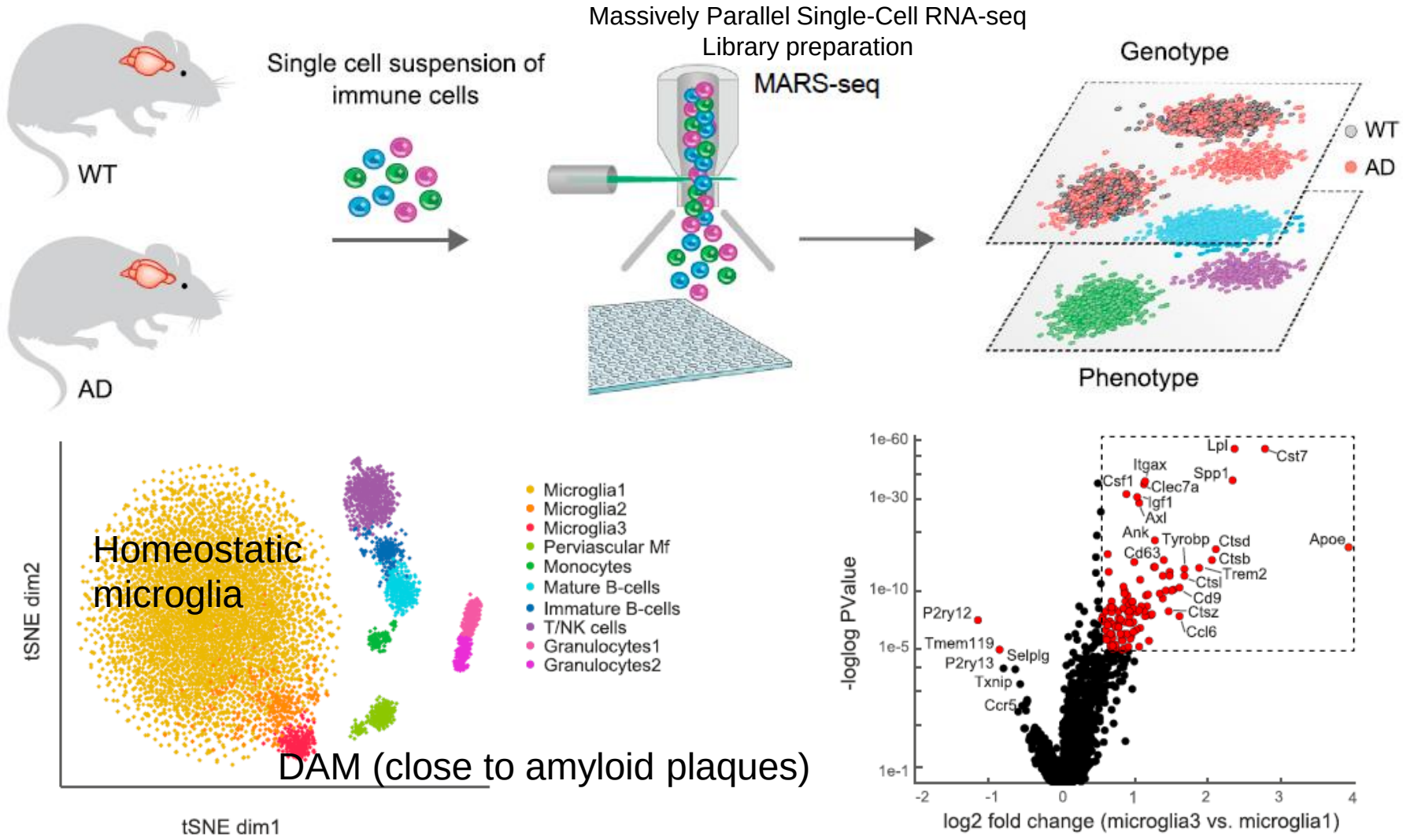




Stage 1 → Stage 2

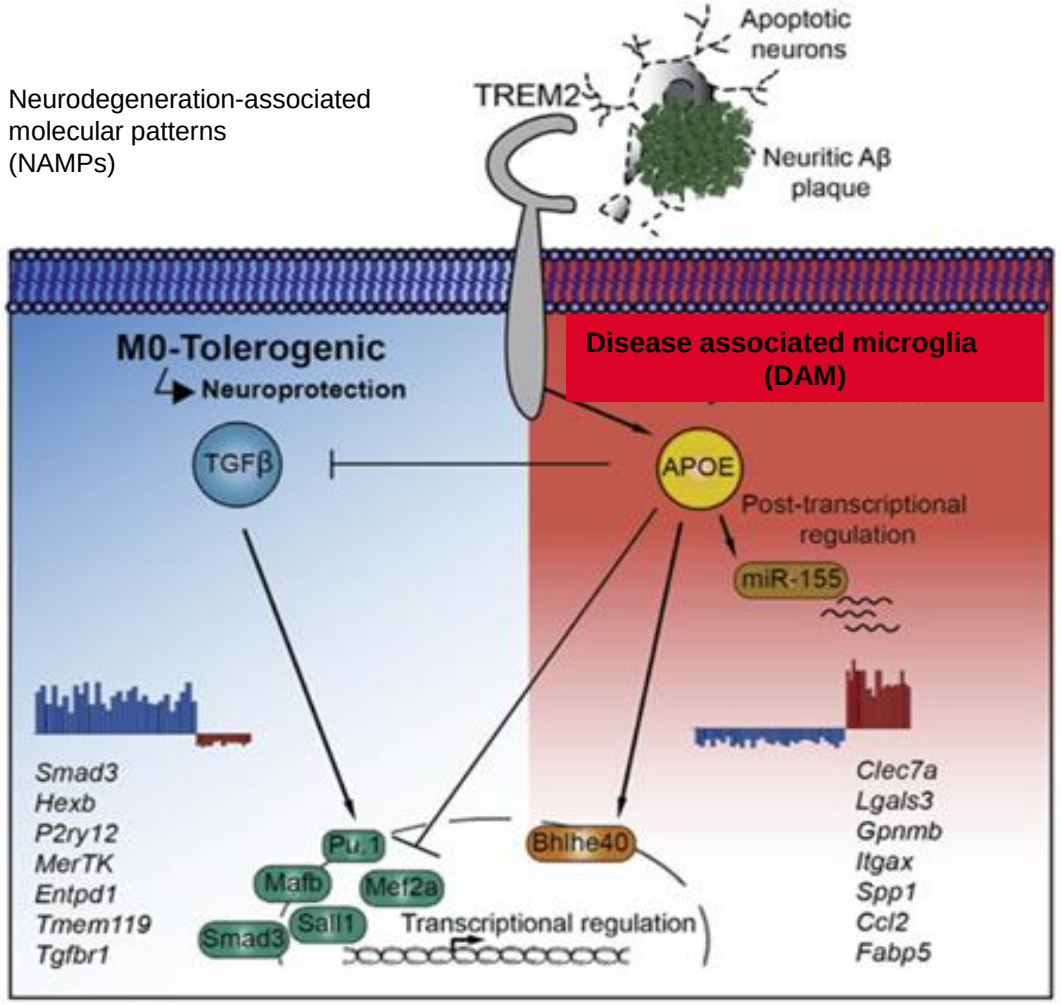
Adapted from Hansen. J Cell Biol. 2018

TRANSCRIPTOMIC CHANGES OF MICROGLIA
Disease associated microglia (DAM)



Keren-Shaul, 2017. A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. Cell 169, 1276-+. https://doi.org/10.1016/j.cell.2017.05.018.

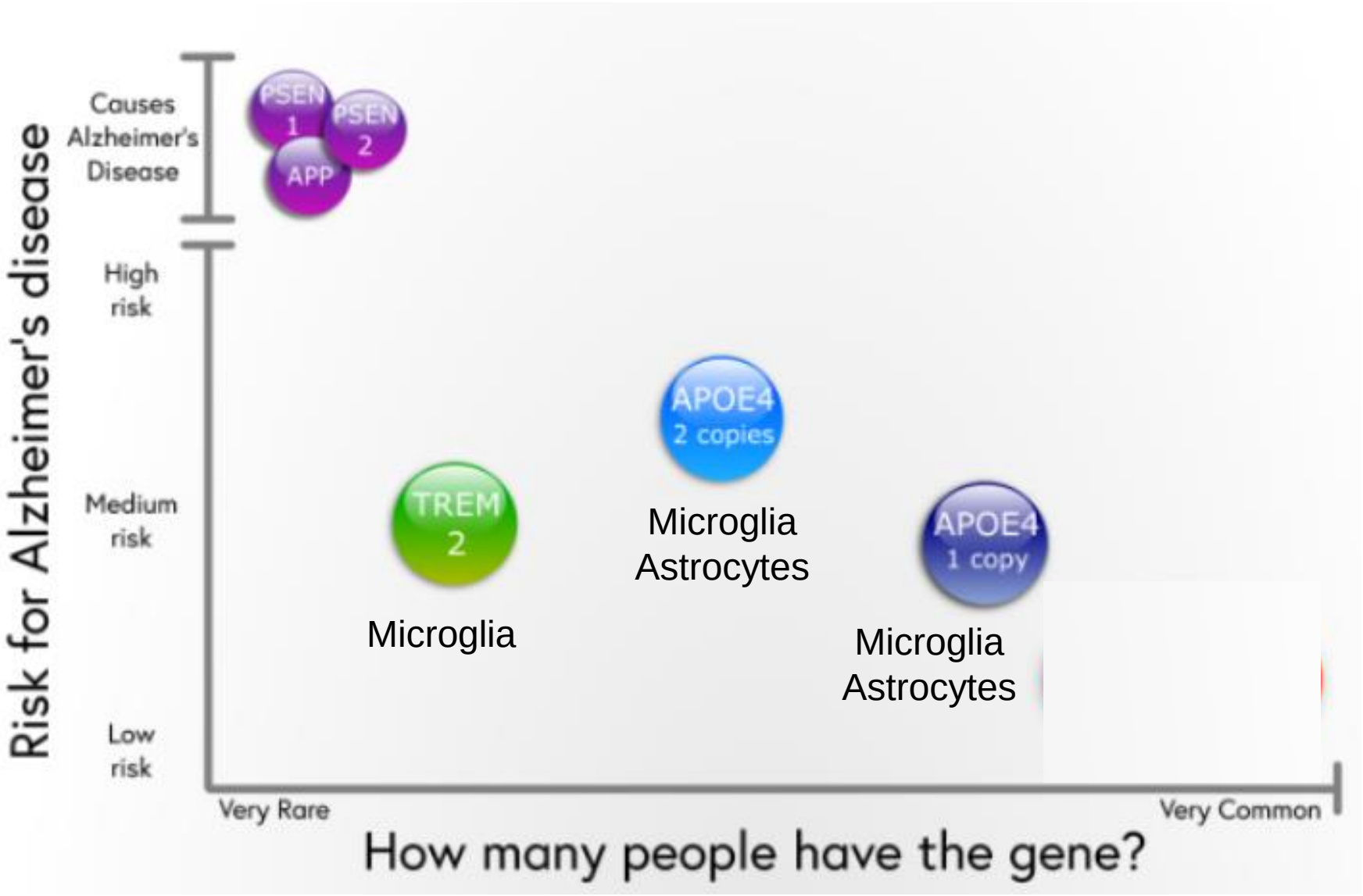
TRANSCRIPTOMIC CHANGES OF MICROGLIA
Disease associated microglia (DAM)



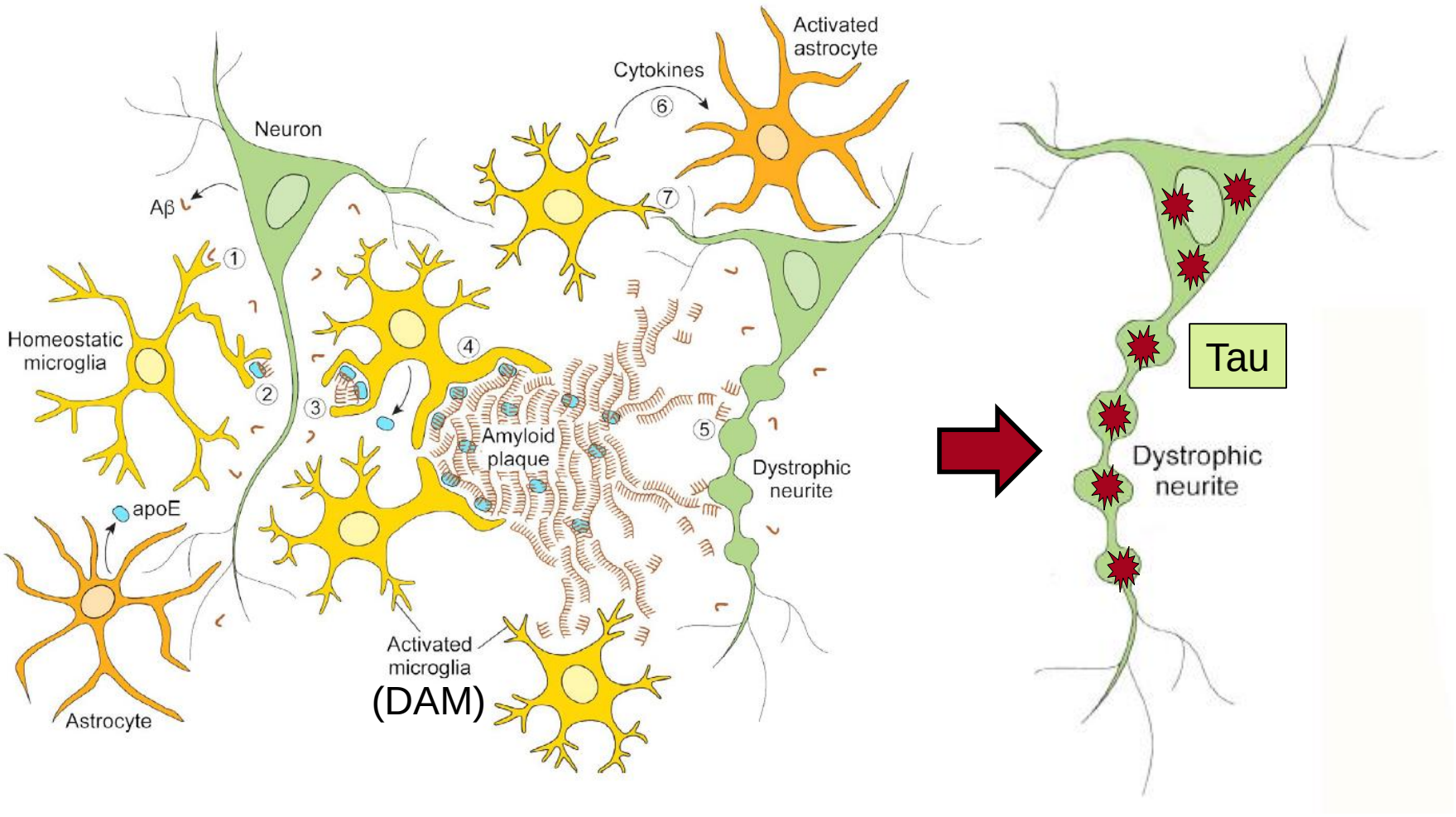
Krasemann S et al.. [The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases]. *Immunity*. 2017 Sep 19;47(3):566-581.e9.

https://www.alzforum.org/news/research-news/apoe-and-trem2-flip-microglial-switch-neurodegenerative-disease

GENETIC FACTORS LINKED TO MICROGLIA…



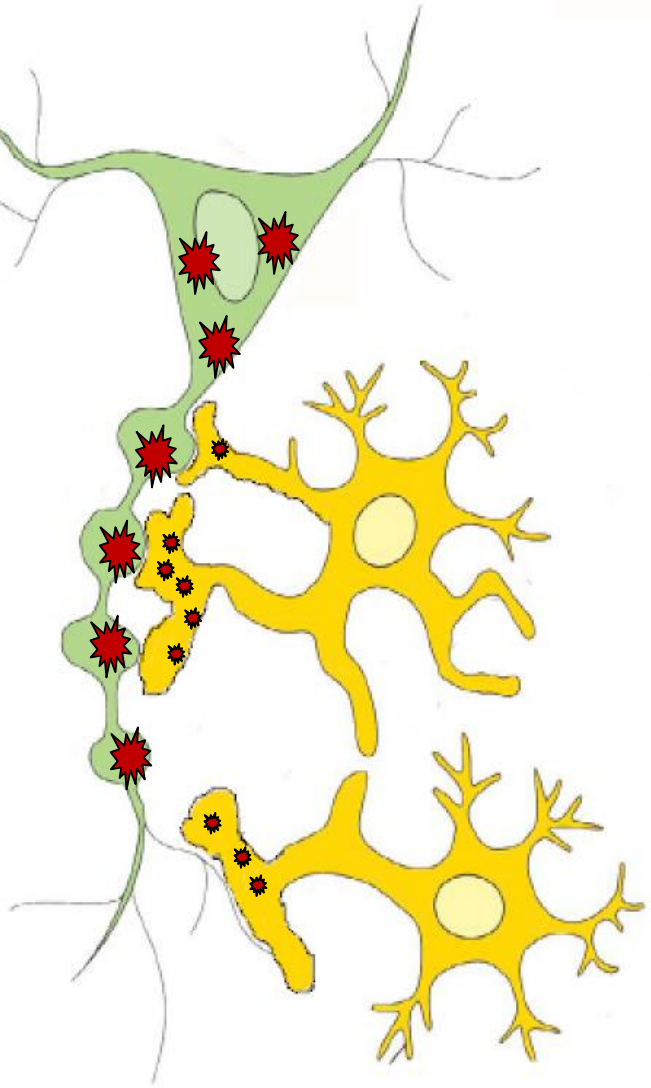
EARLY PHASES OF AMYLOIDOSIS
Shielding amyloid plaques prevents tau pathology



Stage 1 → Stage 2

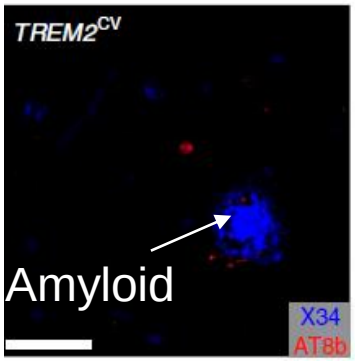
Adapted from Hansen. J Cell Biol. 2018

LATE STAGES OF AMYLOIDOSIS / TAUOPATIES
Microglia eliminate tau lesions ?

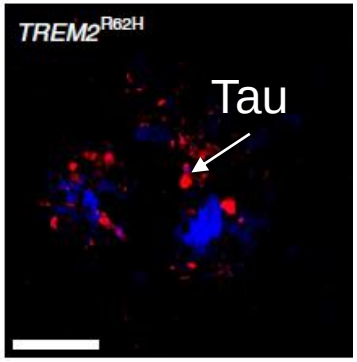


(DAM)

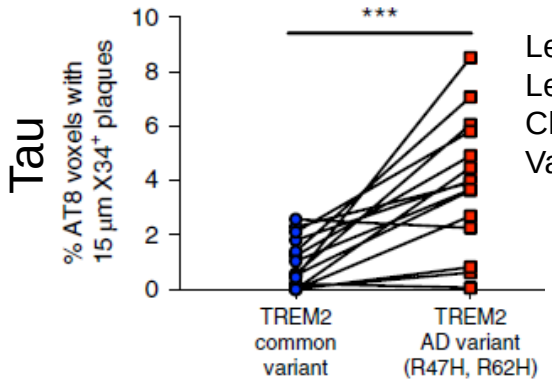
Reduction of Trem2-microglia
→ increases tau lesions



Active microglia



Inactive microglia

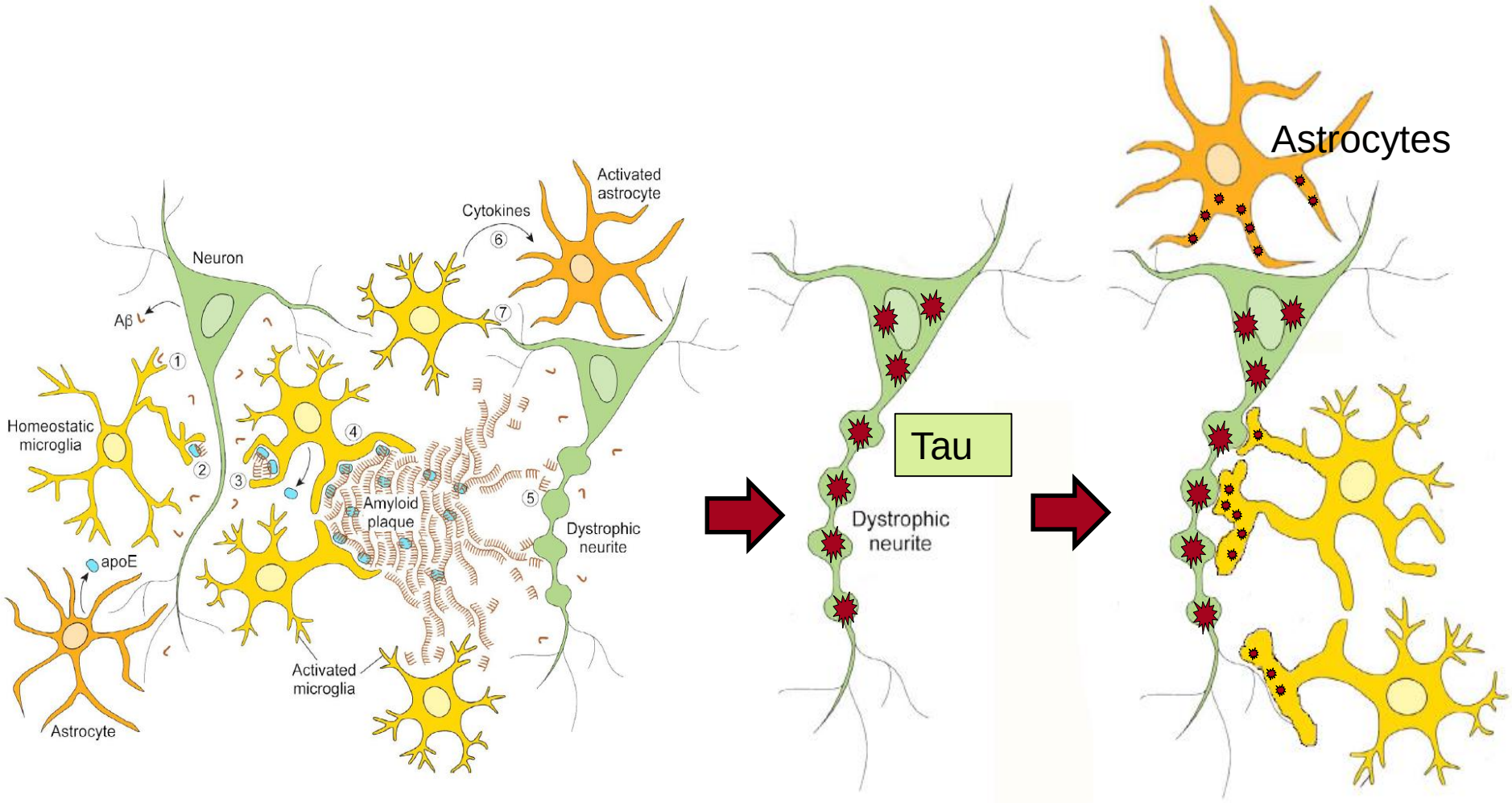


Leyns, Nat Neurosci. 2019
Lee, Neuron. 2021
Clayton, Mol Neurodeg, 2021
Vautheny, Neur Dis, 2021

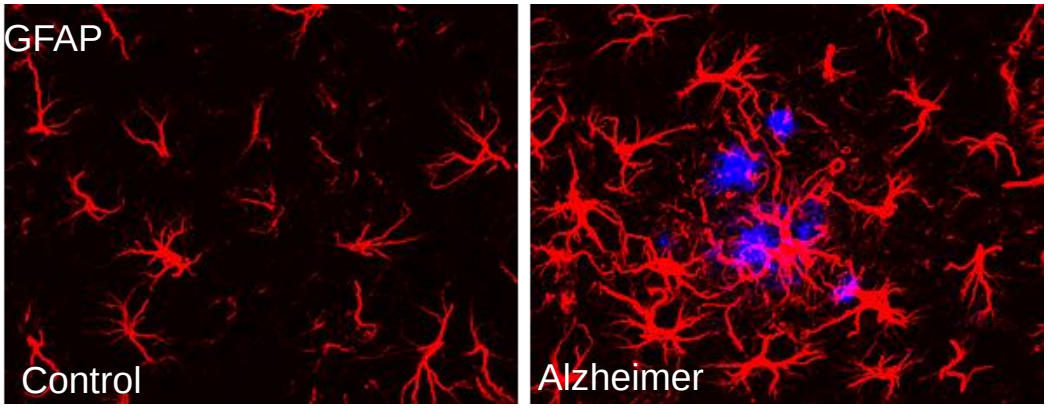
Phagocytosis of tau-positive synapses
- Role of C1q

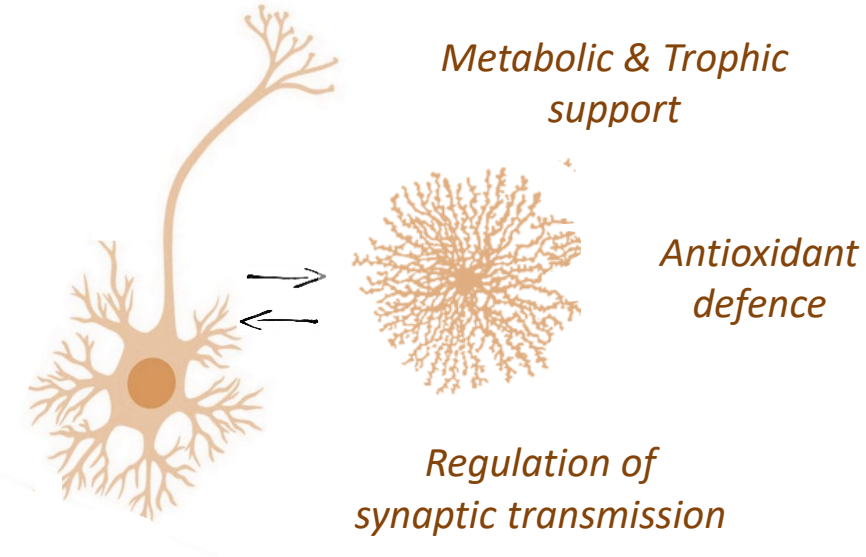
Dejanovic, Neuron. 2018
Lee, Neuron. 2021

DO NOT FORGET THE ASTROCYTES…



ASTROCYTE REACTIVITY IN ALZHEIMER



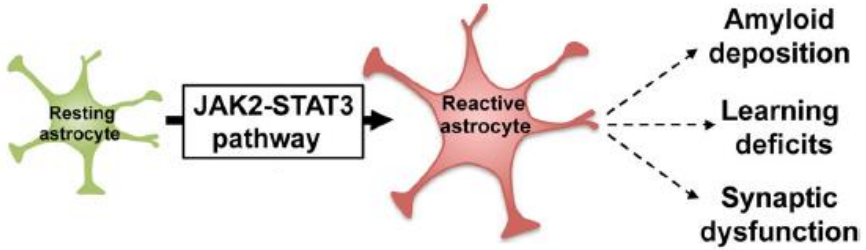


Metabolic & Trophic support

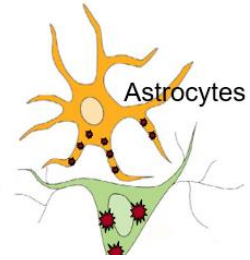
Antioxidant defence

Regulation of synaptic transmission

Ben Haim et al. Front. Cell Neuro, 2015
Spanos et al. Cells 2020



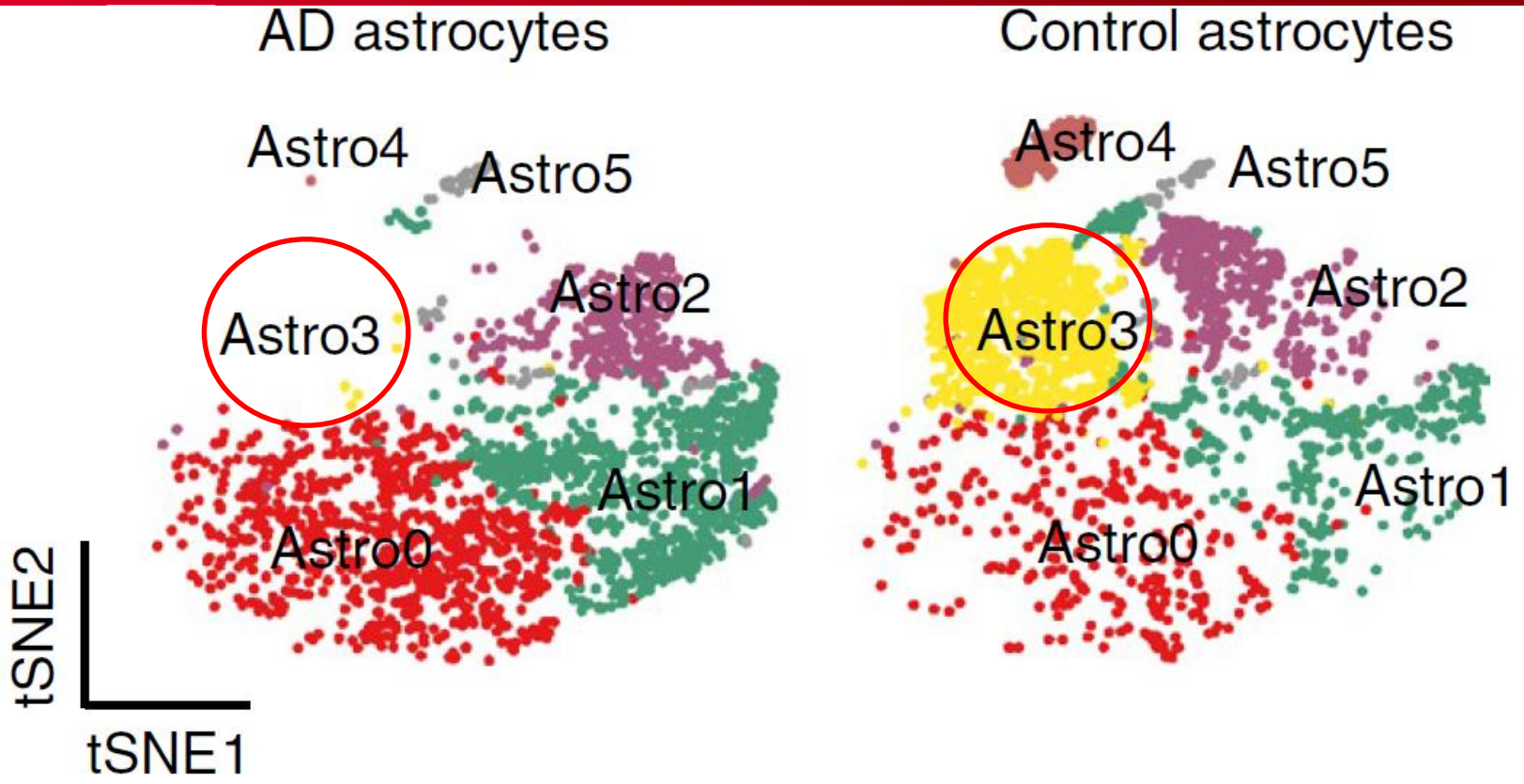
Ceyzériat et al.
Acta Neuropathologica Communications (2018) 6:104



Tau is toxic on astrocytes

Maté de Gérando et al. Brain, 2021

TRANSCRIPTIONAL CHANGES IN ASTROCYTES
Weakened metabolic coordination with neurons ?



Astro 3: Genes involved in coordination of lipid and oxidative metabolism between neurons and astrocytes.

snRNAseq, Alzheimer's disease patients

Zhou, Y.Y., 2020.
Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. Nature Medicine 26, 131-+. https://doi.org/10.1038/s41591-019-0695-9.