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Alzheimer's Disease and Common Co-Morbidities

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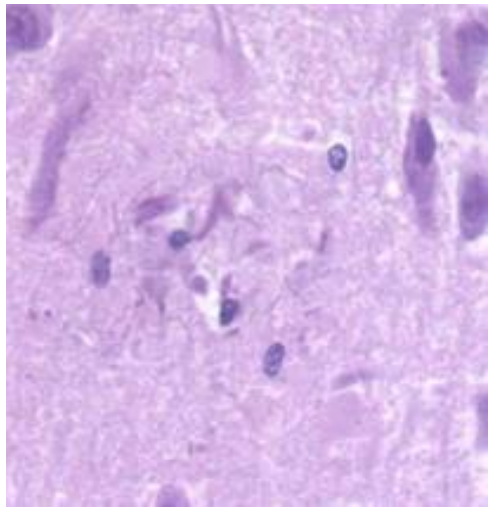
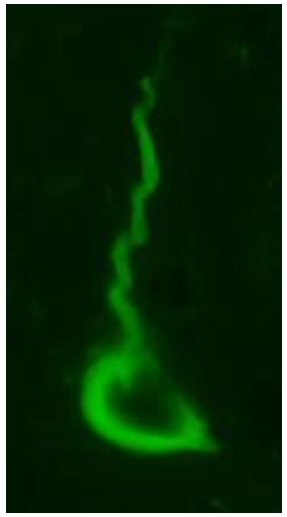
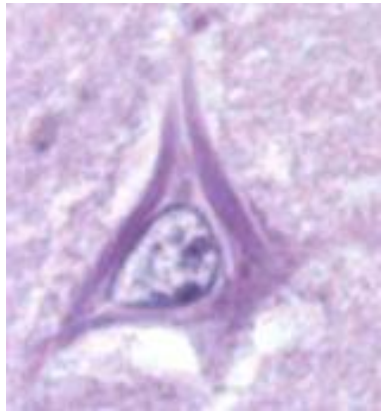
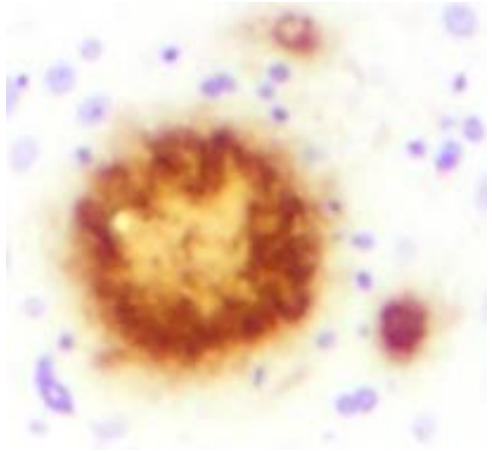
Session Learning Objectives

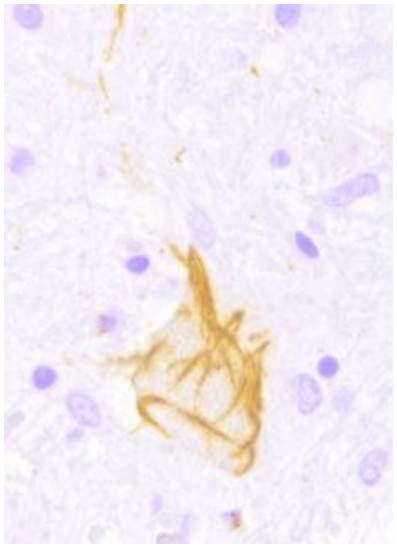
- Determine the distribution and severity of Alzheimer's disease neuropathologic change
- Name the major co-morbid neuropathologic changes that are associated with dementia
- Describe how to coalesce neuropathologic and other data into a comprehensive autopsy report

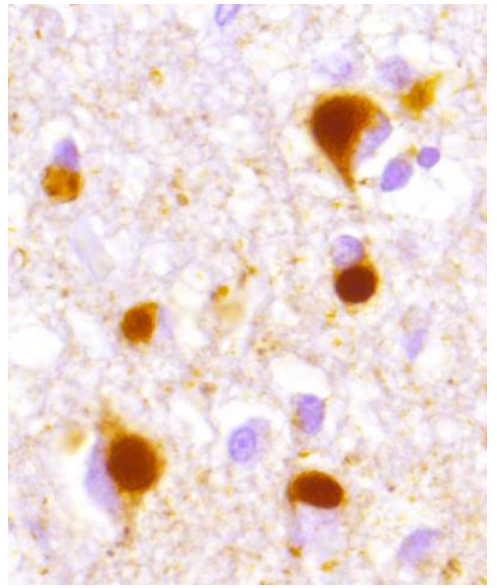


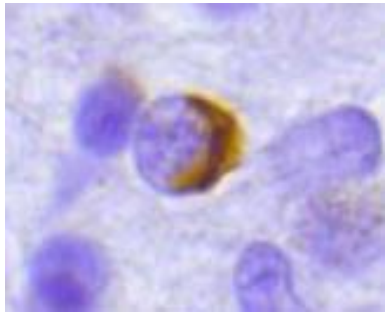


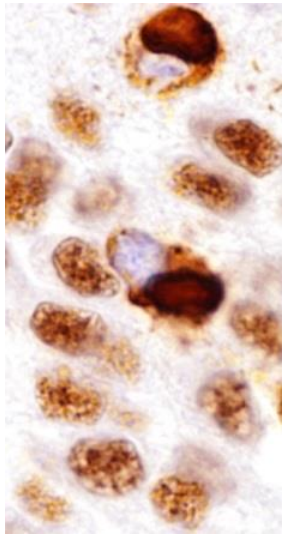


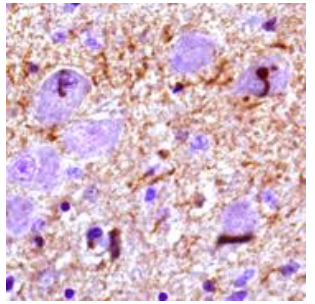


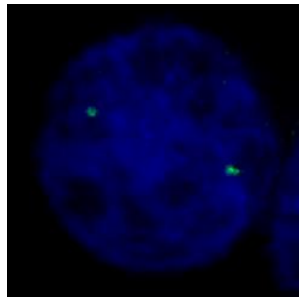








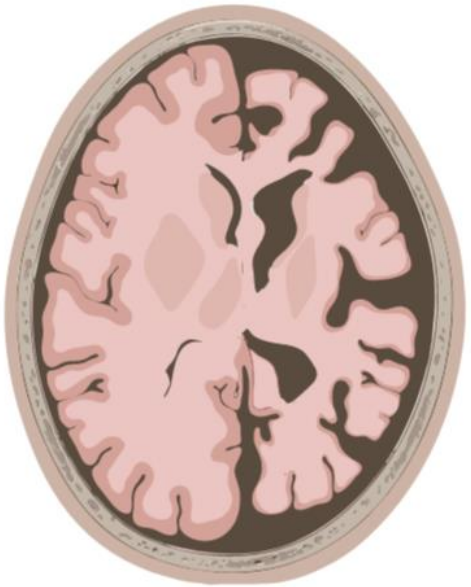




Neurodegenerative Disease Overview

Disease	Lesions	Components
Alzheimer's Disease	Senile plaques Neurofibrillary tangles	Amyloid β Tau
Amyotrophic Lateral Sclerosis	Cytoplasmic inclusions	TDP-43
Parkinson's Disease Dementia with Lewy Bodies	Lewy bodies	α-synuclein
Tauopathies (i.e. Pick's Disease, Progressive Supranuclear Palsy)	Neuronal and glial inclusions	Tau
Frontotemporal Degeneration	Cytoplasmic and nuclear inclusions	TDP-43/Tau
Multiple System Atrophy	Glial cytoplasmic inclusions	α-synuclein
Prion Disease	Spongiform degeneration Prion plaques	Prion protein
Trinucleotide Repeat Diseases (i.e. Huntington's Disease)	Nuclear and cytoplasmic inclusions	Polyglutamine expansion
Chronic Traumatic Encephalopathy	Neuronal and glial inclusions	Tau

Part I:
Alzheimer's Disease Neuropathologic Change (ADNC)



Dementia

Progressive and irreversible syndrome characterized by cognitive dysfunction typically over multiple cognitive domains resulting in impairment in activities of daily living.

Progressive memory dysfunction

Stepwise neurologic decline

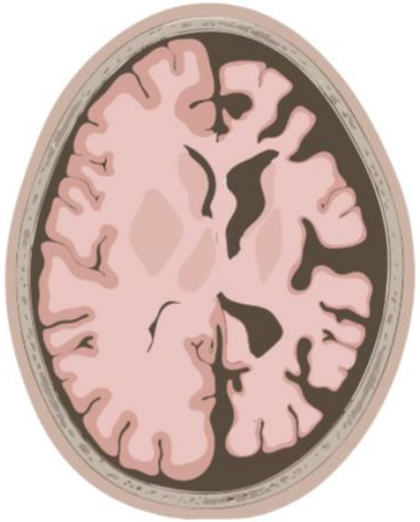
Behavioral/ Personality changes

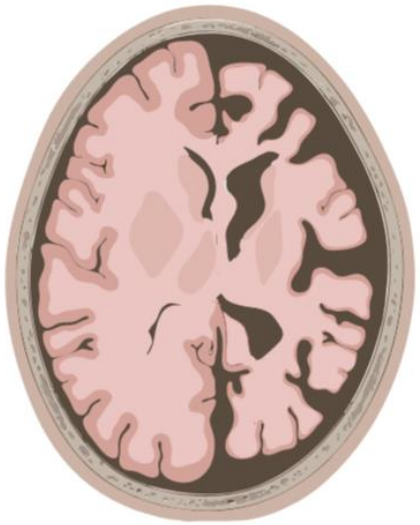
Language dysfunction

Weakness, spasticity

Movement disorder

Dementia





Progressive memory dysfunction

Amyloid plaques
Neurofibrillary tangles

Cerebrovascular disease

Stepwise neurologic decline

Dementia

Lewy Bodies

Behavioral/ Personality changes

TDP-43
Tau

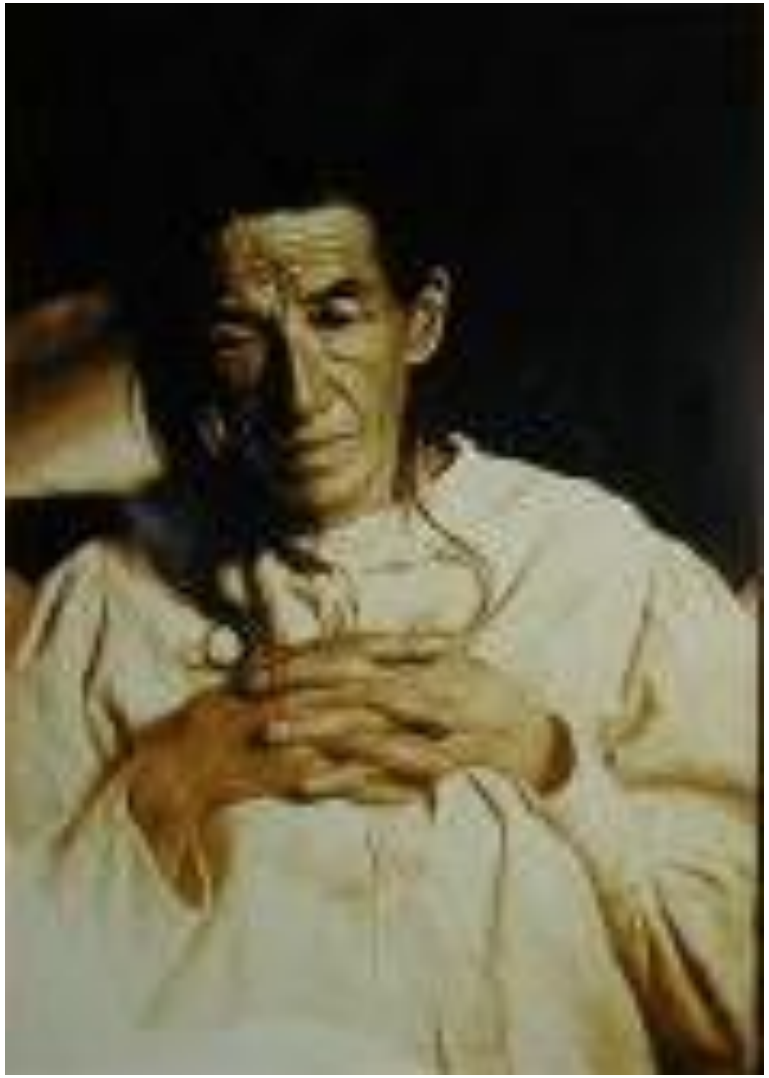
Language dysfunction

TDP-43

Movement disorder

Weakness, spasticity

Alzheimer's Disease

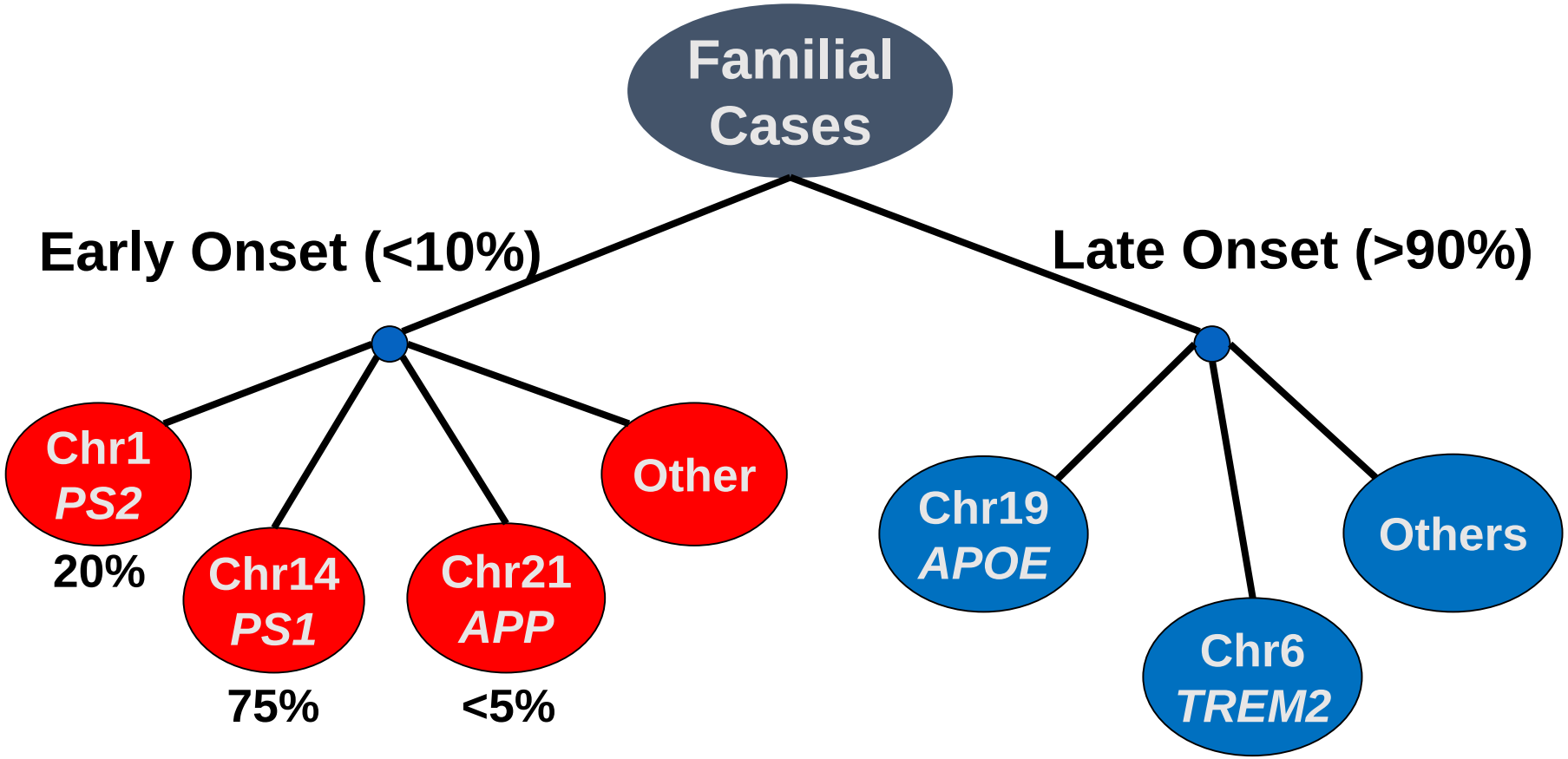


- Auguste Deter

- Severe memory deficits
- Cognitive impairments
- Speech difficulties
- Perceptual abnormalities including hallucinations and delusions

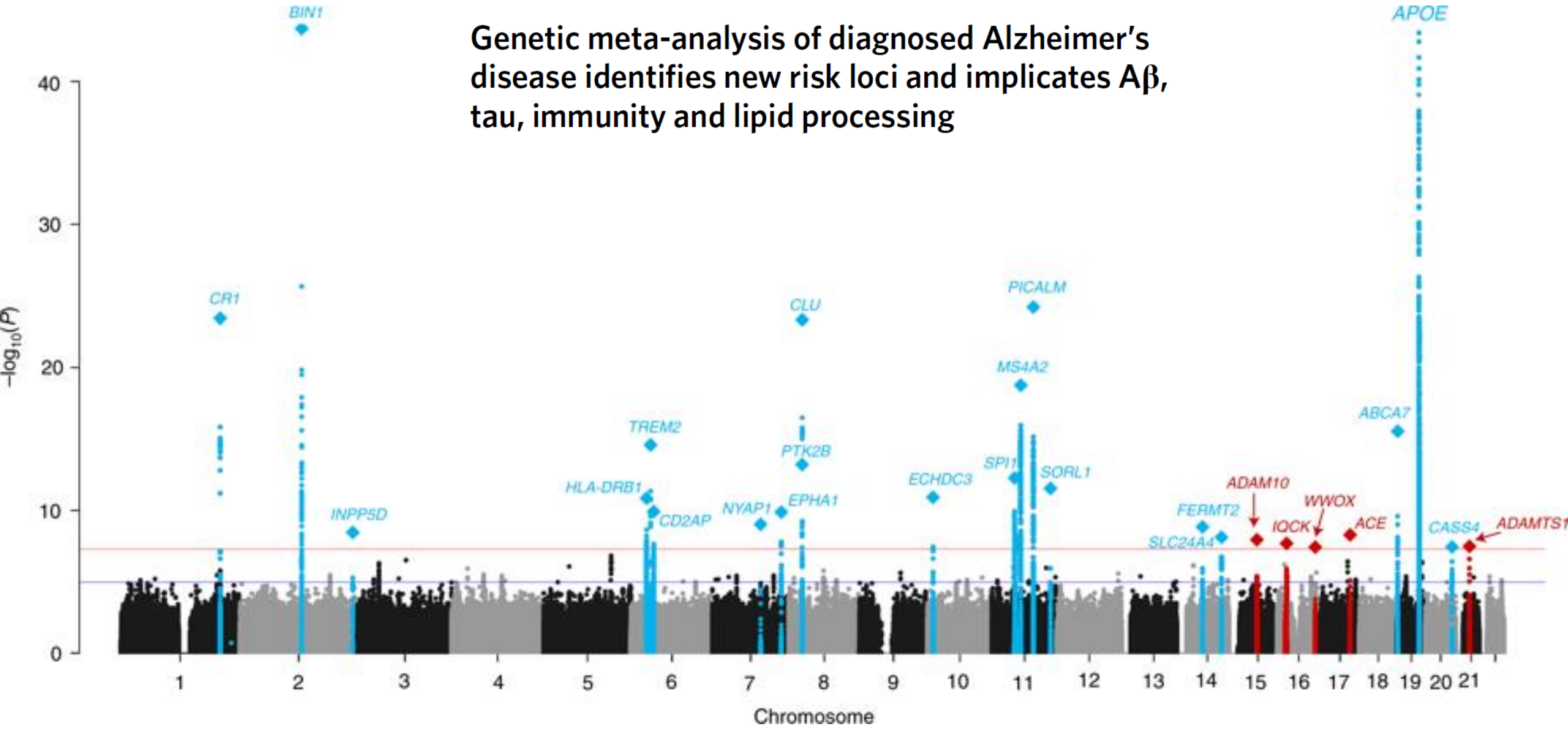
- Died on April 8, 1906 (51 years old) due to complications from a decubitus ulcer

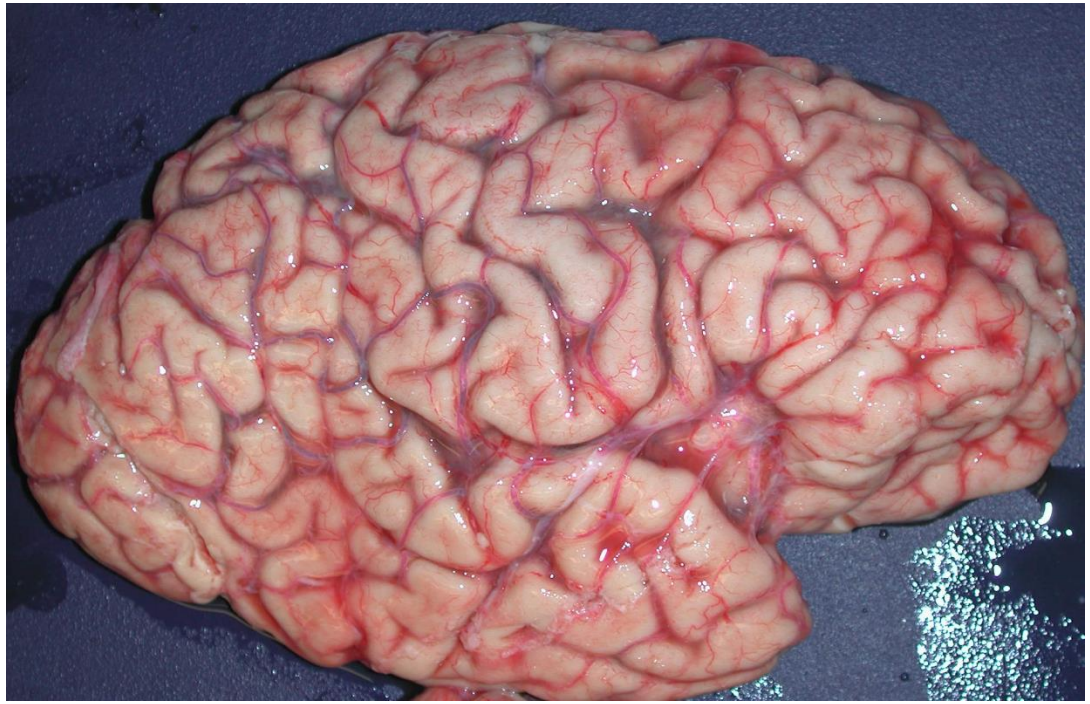
Genetics of Alzheimer's Disease



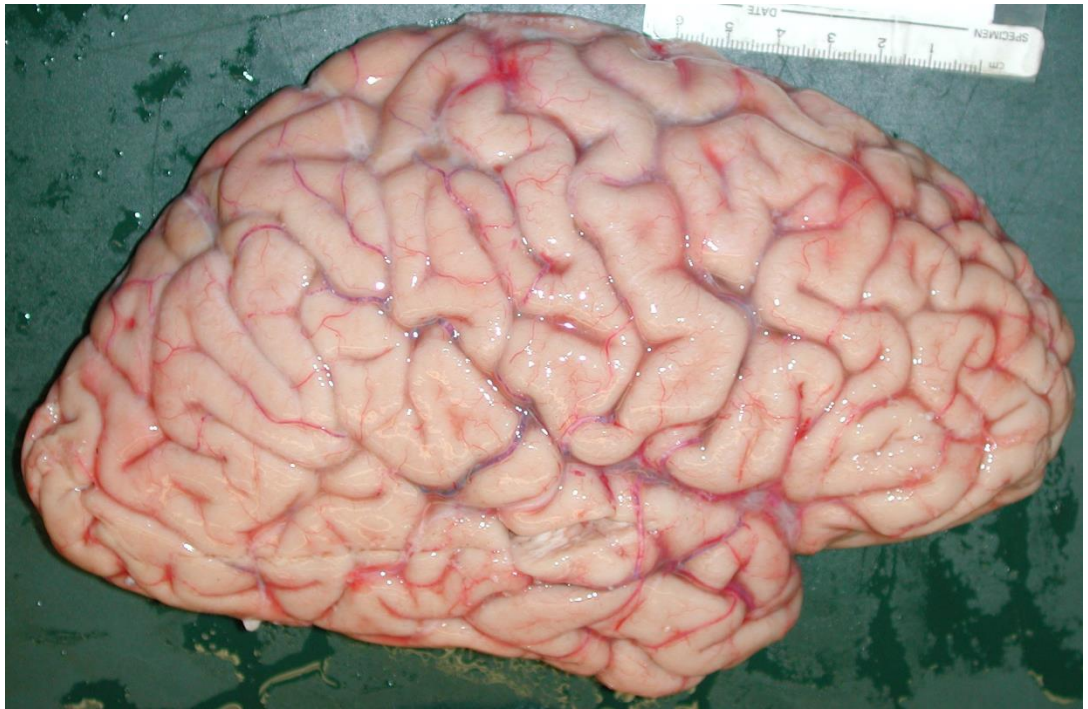
ARTICLES
https://doi.org/10.1038/s41588-019-0358-2
nature genetics

Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing





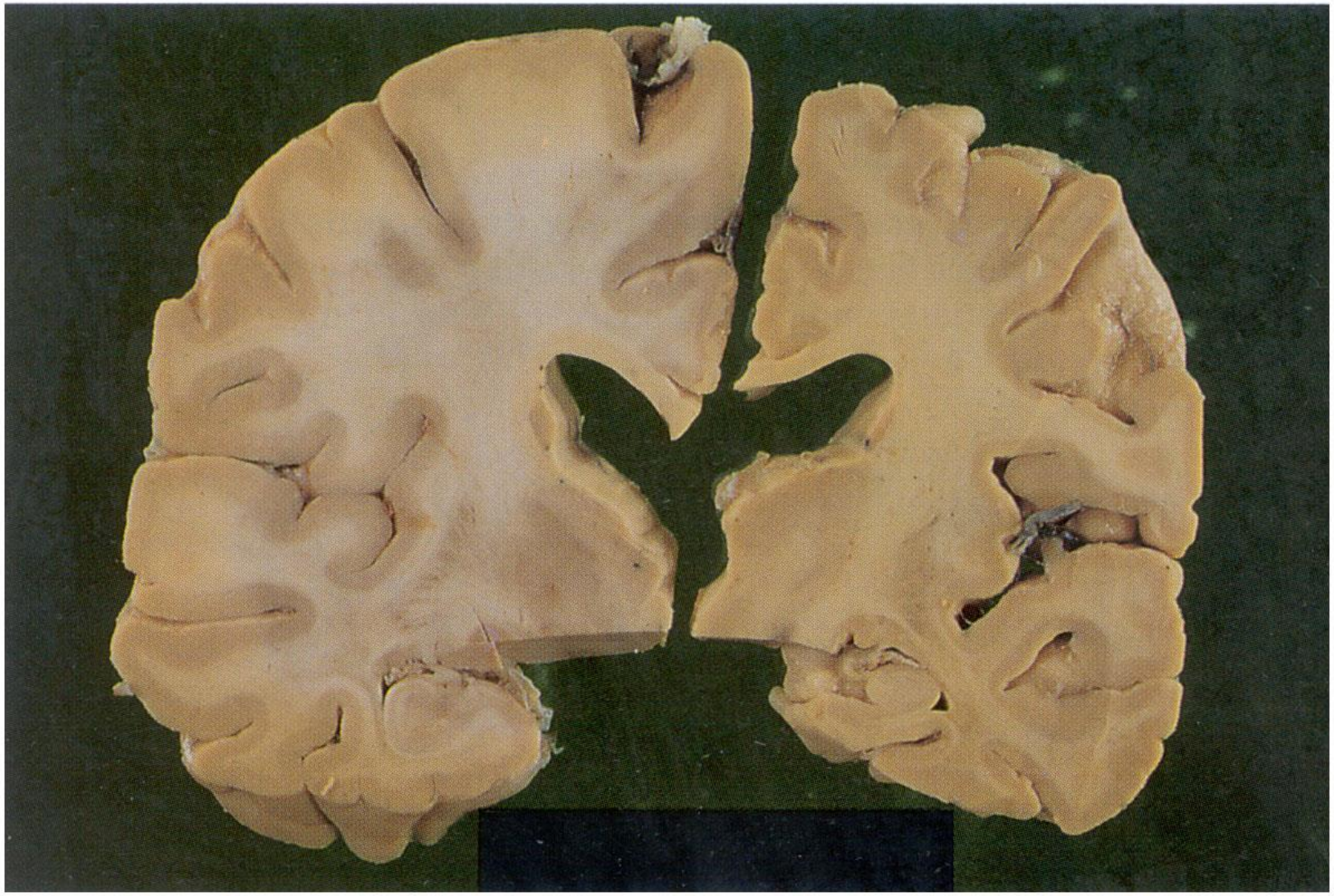
Alzheimer’s disease brain



Normal brain

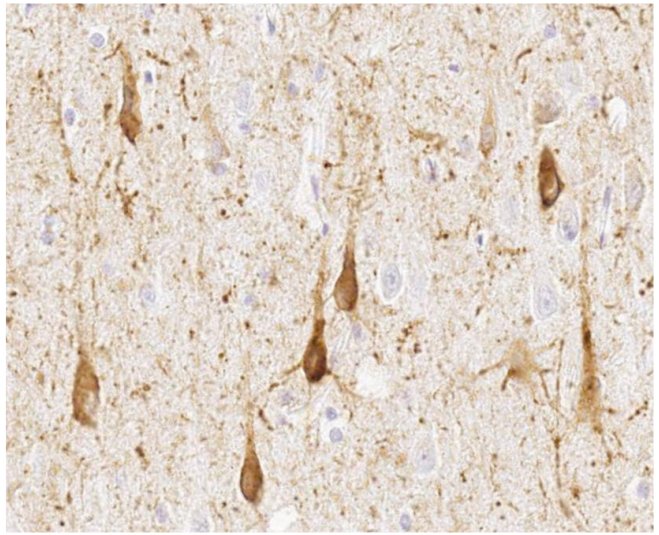
Alzheimer's Disease, Gross Pathology

Diffuse cerebral atrophy

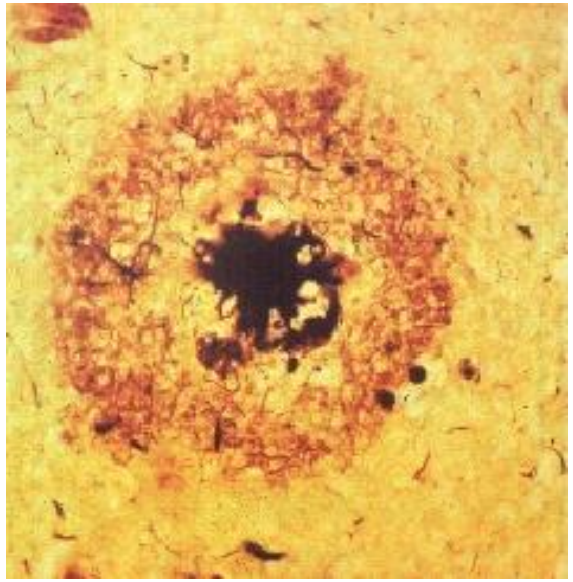


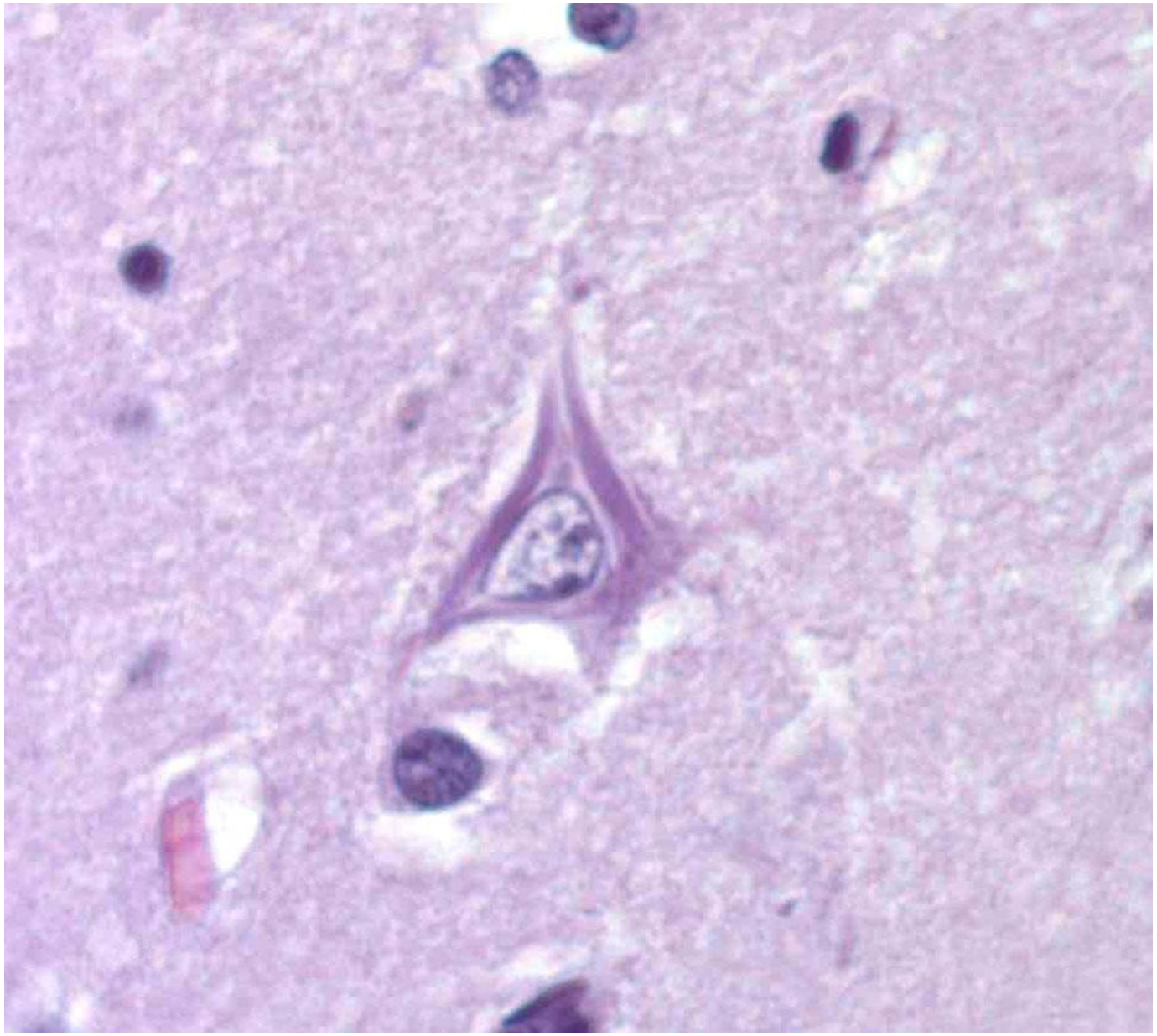
Molecular Composition of the Hallmark Lesions of Alzheimer's Disease

- **Neurofibrillary tangles**
  - **Intracellular (neurons)**
  - **Contain paired helical filaments comprised of the microtubule associated protein tau which is abnormally phosphorylated**
  - **Biochemically insoluble**

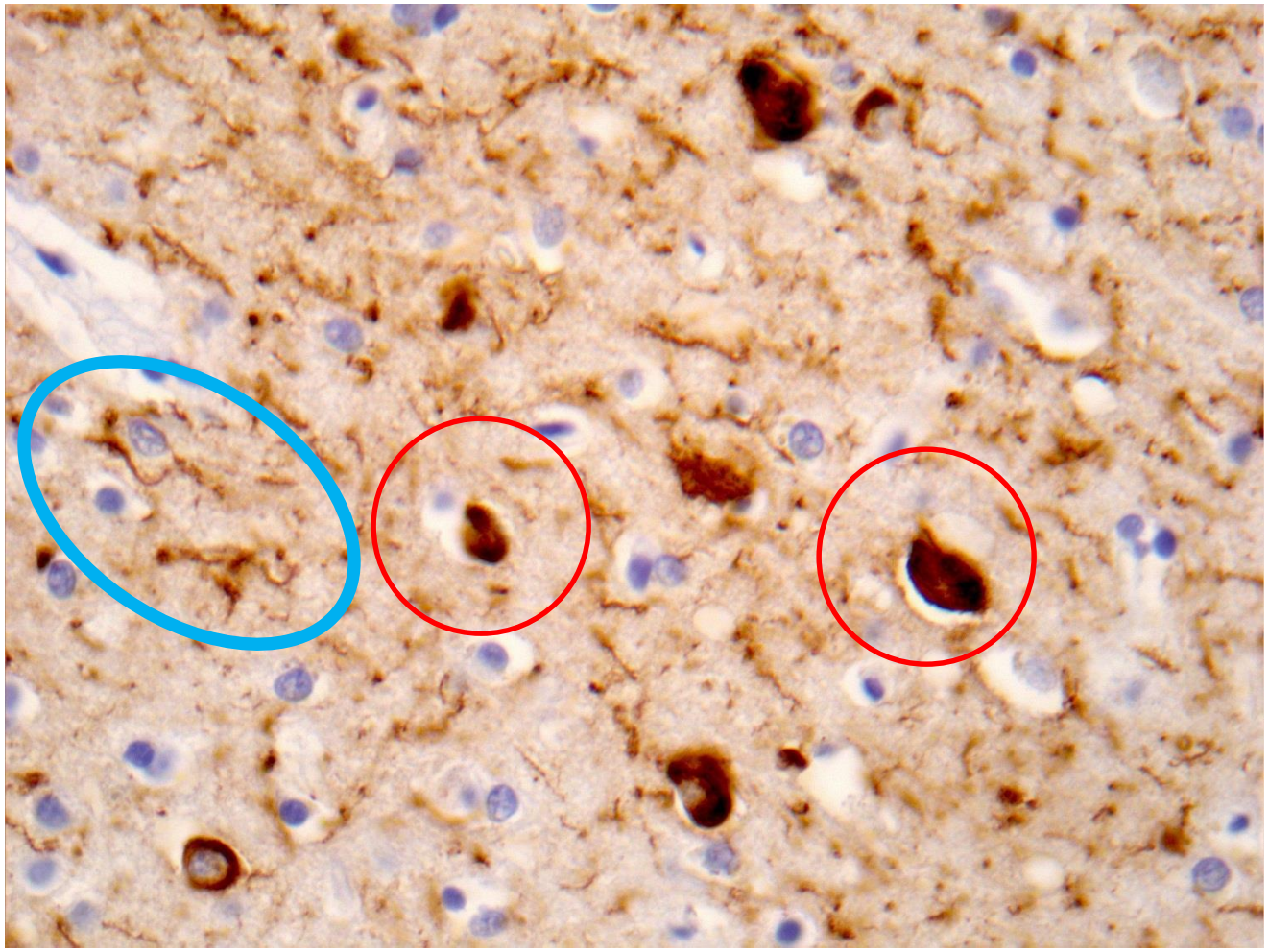


- **Amyloid plaques**
  - **Extracellular**
  - **Contain straight fibrils comprised of Aβ**
    - **i.e. 39-42 amino acid long peptides which is cleaved from the β-amyloid precursor proteins (APPs)**
  - **Biochemically insoluble**





Neurofibrillary tangle



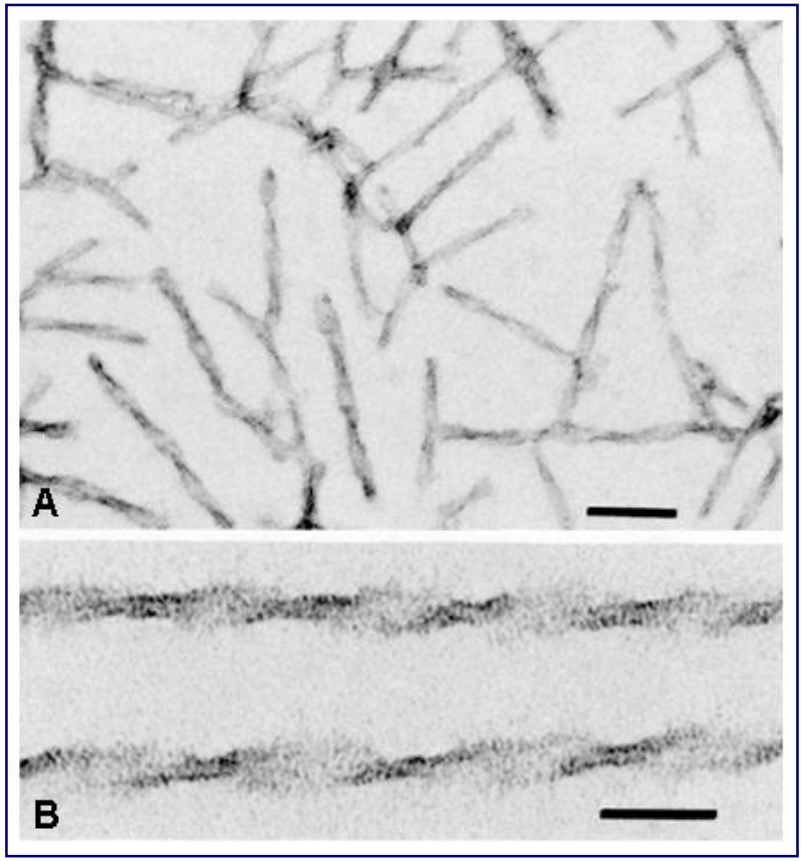
Neurofibrillary tangles

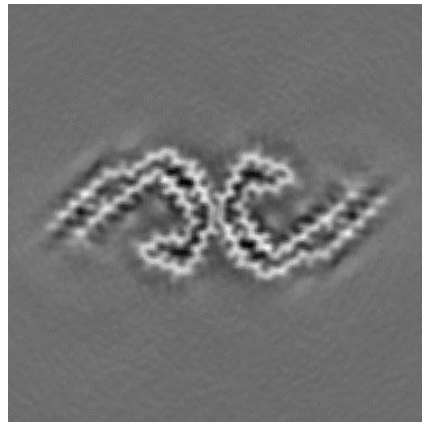
Neuritic threads

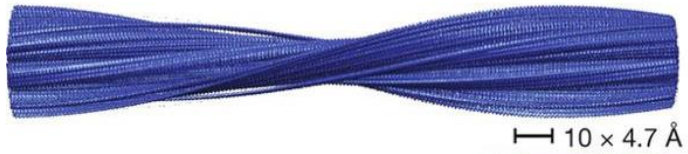
Immunohistochemical stain for phosphorylated tau

Paired helical filament-Tau

- ***MAPT* (Chr 17q21): normal tau protein binds to and stabilizes microtubules**
- **Insoluble**
- **Mainly found in neuronal cell bodies and dendrites**
- **Aberrantly hyperphosphorylated at many serine and threonine residues**
- **Pathologic tau is unable to bind to microtubules unless it is dephosphorylated *in vitro***



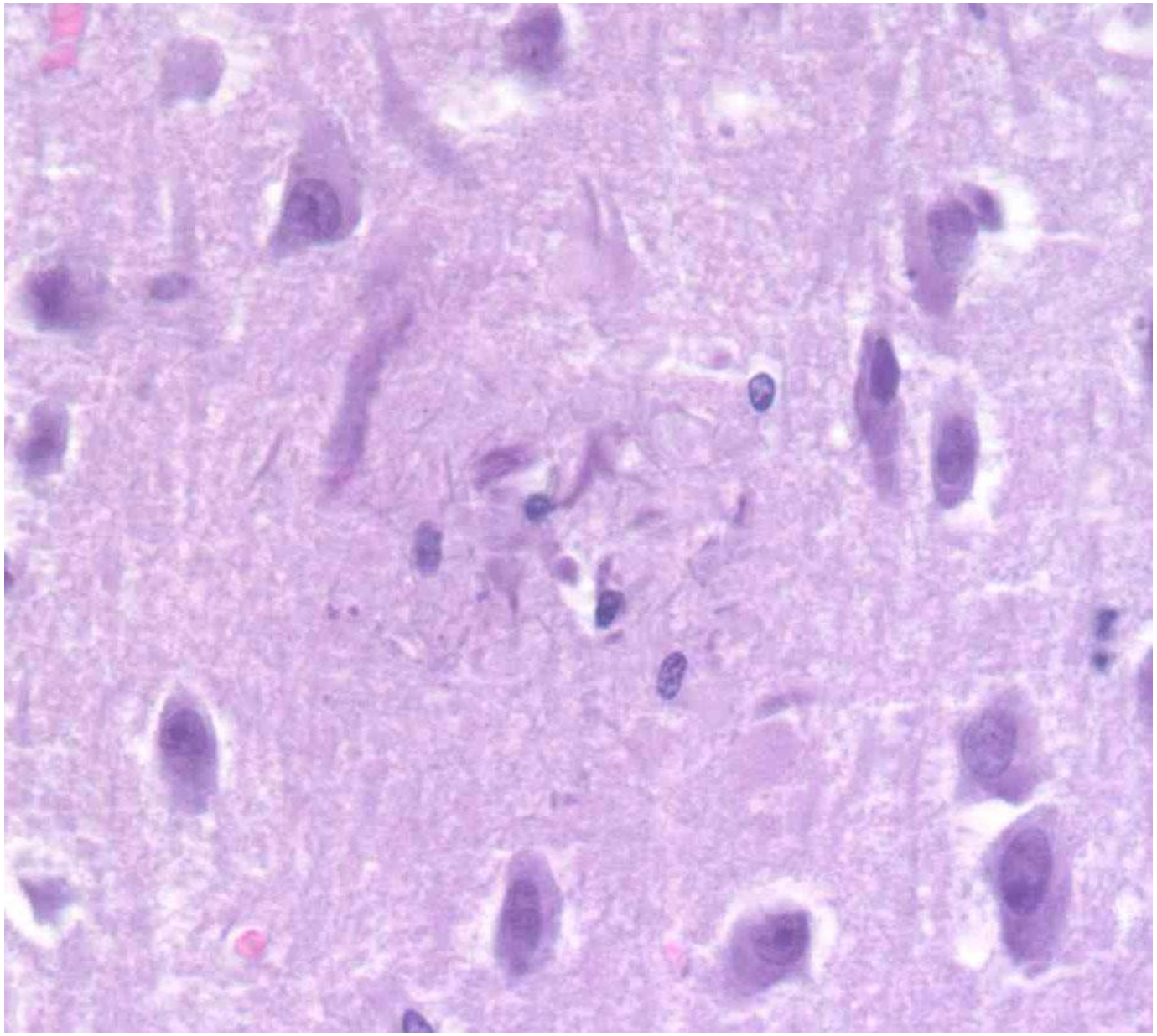




Fitzpatrick et al., Nature, 2017
Falcon et al., Acta NP, 2018

A68: A Major Subunit of Paired Helical Filaments and Derivatized Forms of Normal Tau

VIRGINIA M.-Y. LEE,* BRIAN J. BALIN, LASZLO OTVOS, JR., JOHN Q. TROJANOWSKI



Amyloid plaque

Alzheimer's Disease Plaques

- "Plaques are not made of tau. The 50,000 or so people working on the amyloid cascade hypothesis would consider this statement highly incompetent. To say that Alzheimer saw plaques and tangles where neurons had once been is equally incompetent."

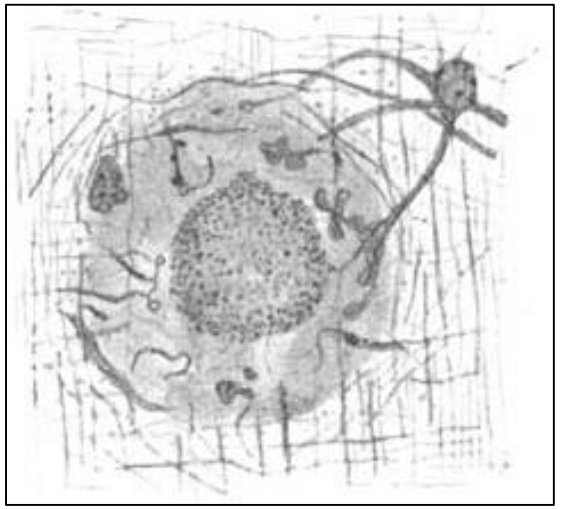
Über eigenartige Krankheitsfälle des späteren Alters.

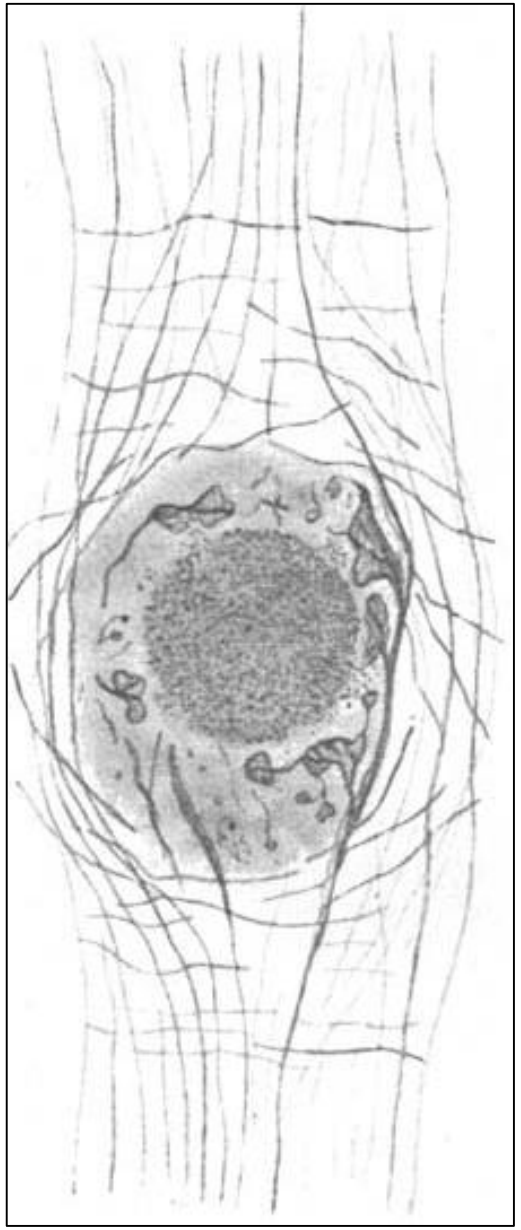
Von

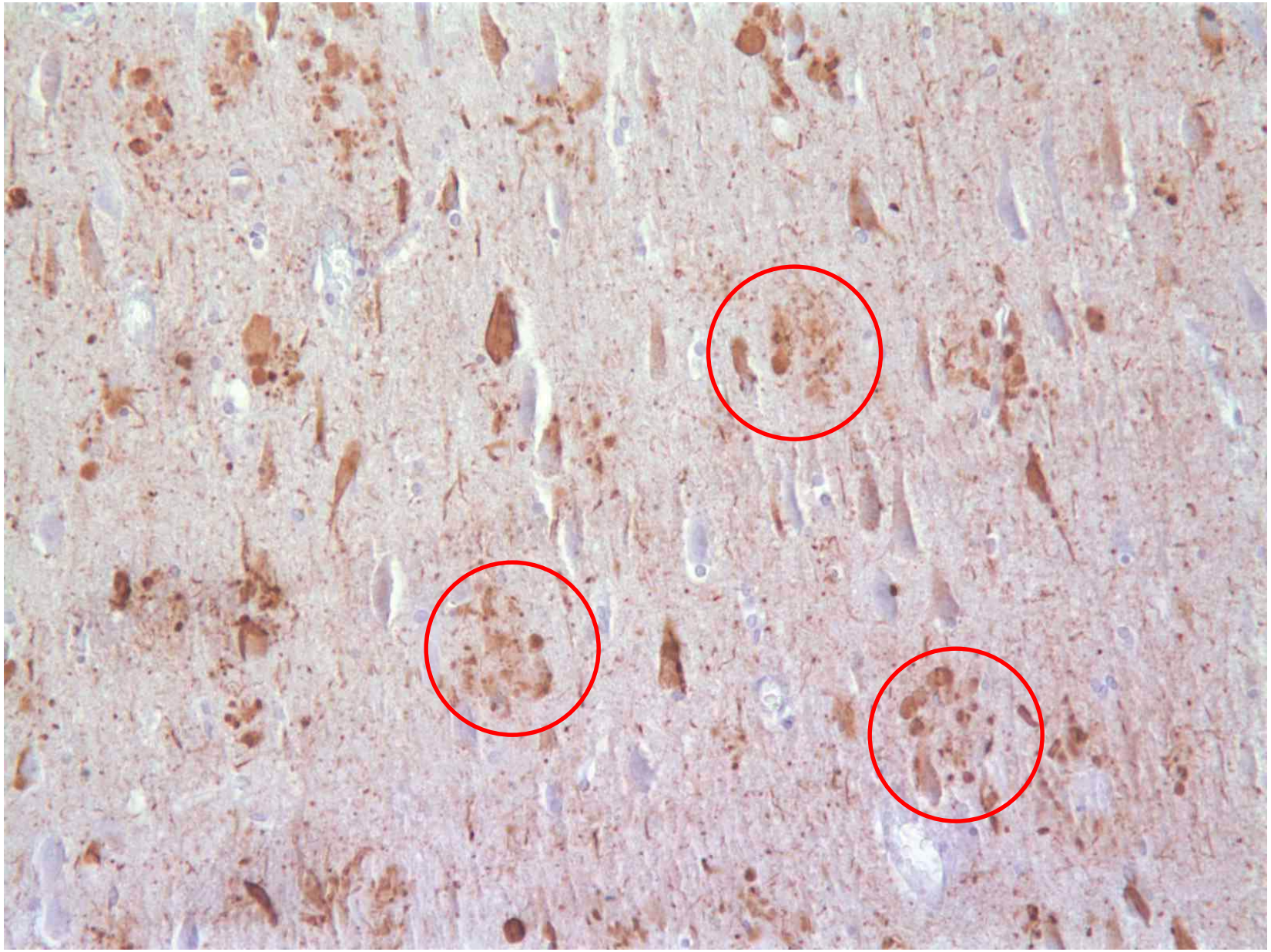
A. Alzheimer.

Mit 10 Textfiguren und 2 Tafeln.

(Eingegangen am 11. Januar 1911.)



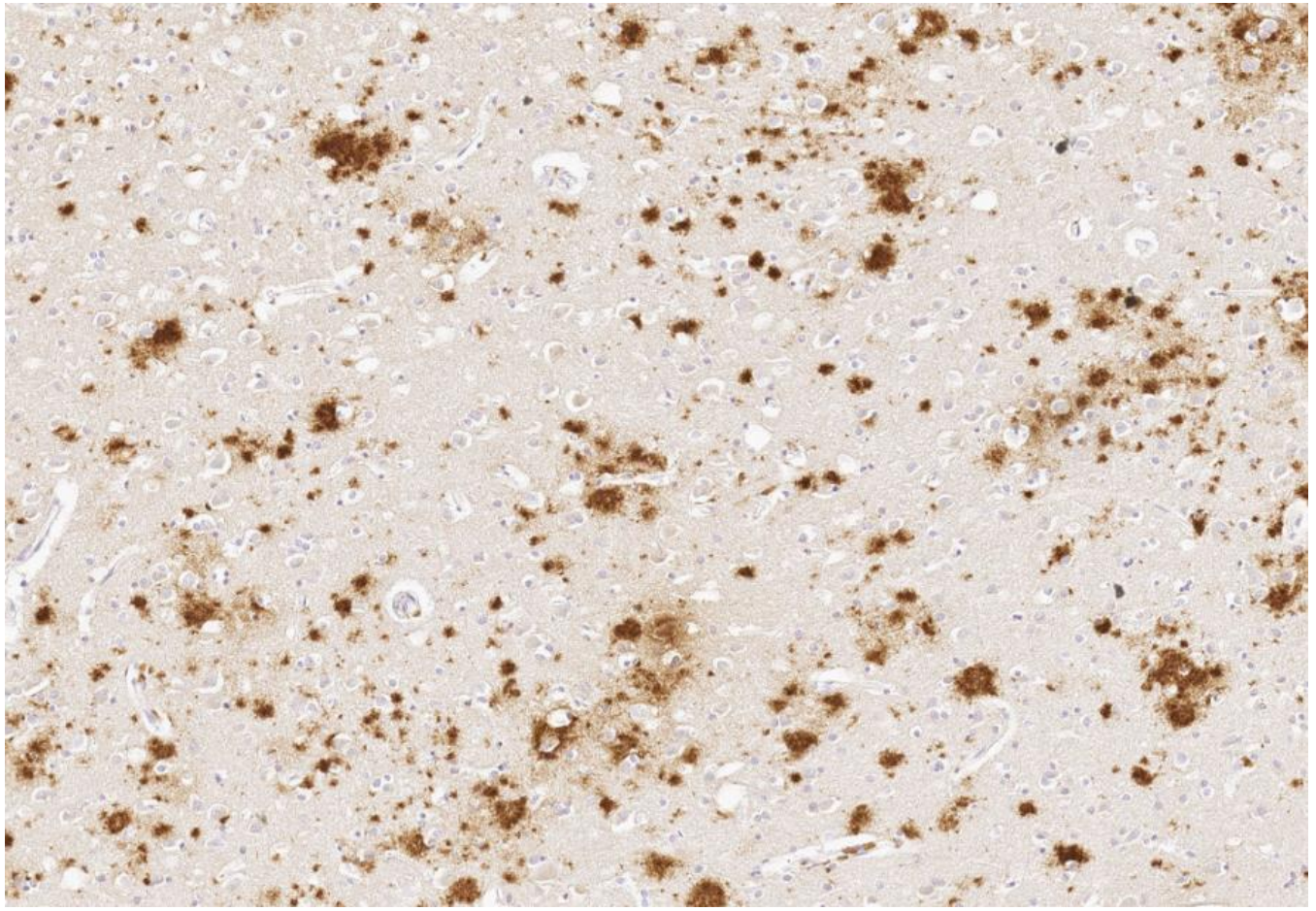




Neuritic plaques

Alzheimer's Disease

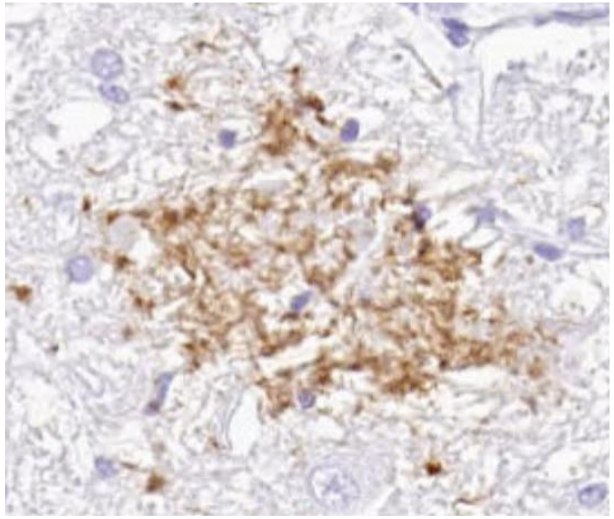
Amyloid Plaques

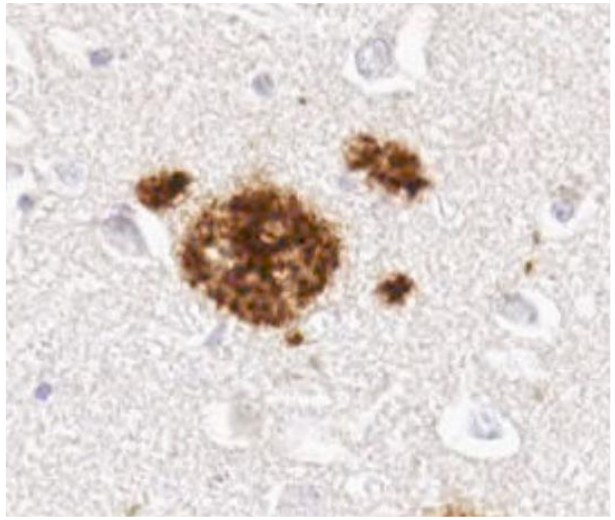


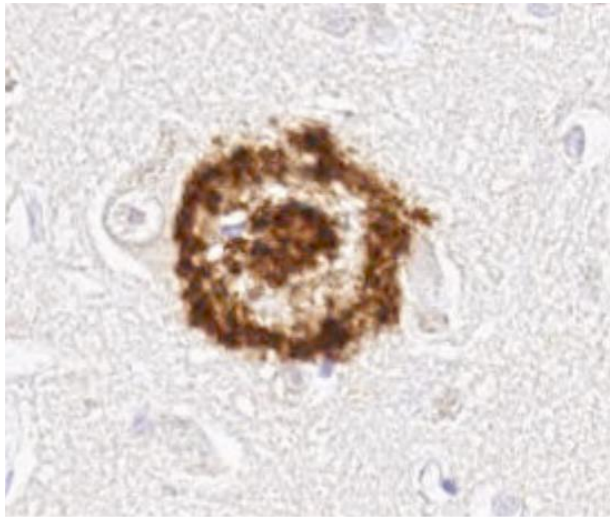
- **Extracellular deposition of aggregated straight fibrils**
- **Comprised of 39-42 amino acid long Aβ peptides cleaved from amyloid precursor protein (APP)**

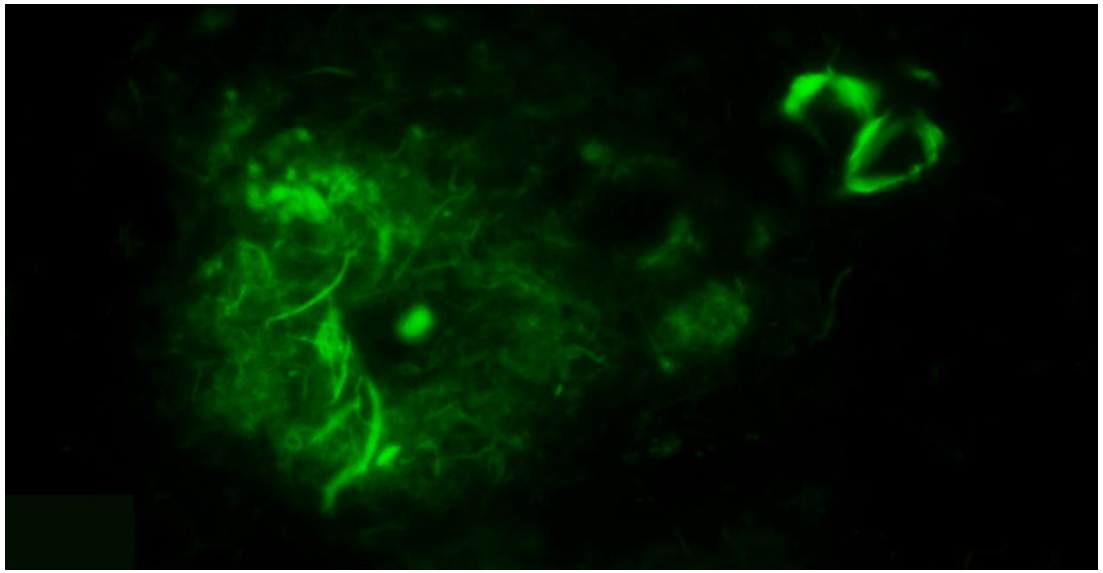
Alzheimer's Disease

Diverse Morphology of Amyloid Plaques

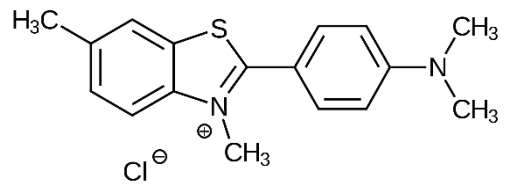




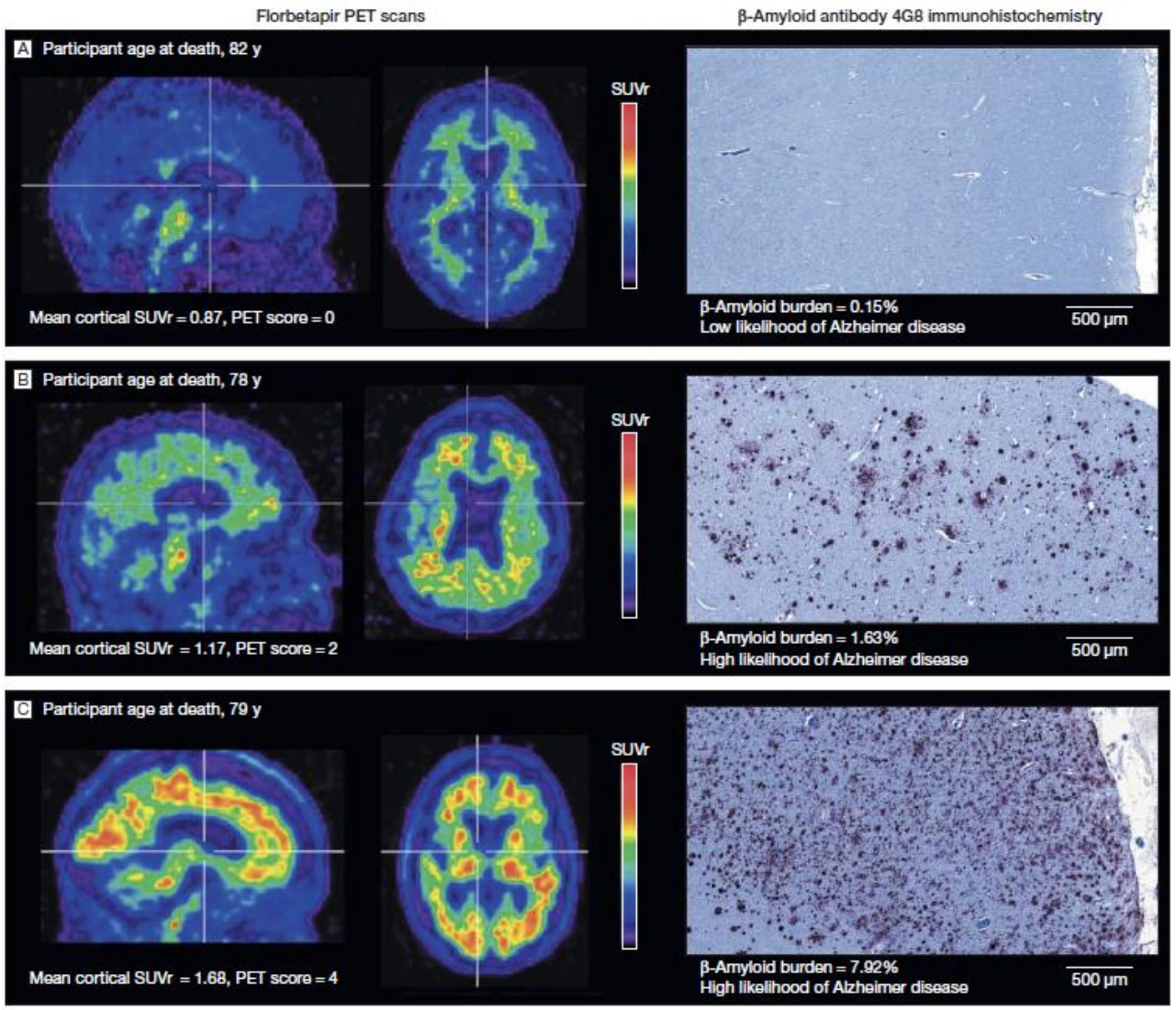




Thioflavin



Neuroimaging: Amyloid PET



JAMA, January 19, 2011—Vol 305, No. 3 275

Use of Florbetapir-PET for Imaging β-Amyloid Pathology

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Adam S. Fleisher, MD, MAS
Marwan N. Sabbagh, MD
Carl H. Sadowsky, MD
Eric M. Reiman, MD
Simone P. Zehntner, PhD
Daniel M. Skovronsky, MD, PhD
for the AV45-A07 Study Group

Thank you!

j/k

Part II:
NIA-AA Alzheimer's Disease Neuropathology Criteria

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

Bradley T. Hyman[a], Creighton H. Phelps[b], Thomas G. Beach[c], Eileen H. Bigio[d], Nigel J. Cairns[e,f], Maria C. Carrillo[g], Dennis W. Dickson[h], Charles Duyckaerts[i], Matthew P. Frosch[j], Eliezer Masliah[k,l], Suzanne S. Mirra[m], Peter T. Nelson[n], Julie A. Schneider[o,p,q], Dietmar Rudolf Thal[r], Bill Thies[g], John Q. Trojanowski[s], Harry V. Vinters[t,u], Thomas J. Montine[v,*]

Alzheimer's & Dementia 8 (2012) 1–13

NIA-Reagan Criteria (1997)

CERAD (1991)

Khachaturian Criteria (1984)

NIA-AA Criteria: Conceptual Change

- Prior NIA-Reagan criteria resulted in a probability statement about how likely the observed neuropathologic change was associated with clinical AD (low, intermediate, high *probability*)
- Current NIA-AA criteria reports the amount of AD neuropathologic change (ADNC) irrespective of clinical data (low, intermediate high *level of ADNC*)
- Presence of atherosclerosis defines cardiovascular disease, does not require symptoms such as angina, myocardial infarction
- Presence of ADNC defines Alzheimer's disease irrespective of clinical syndrome

“ABC” Score

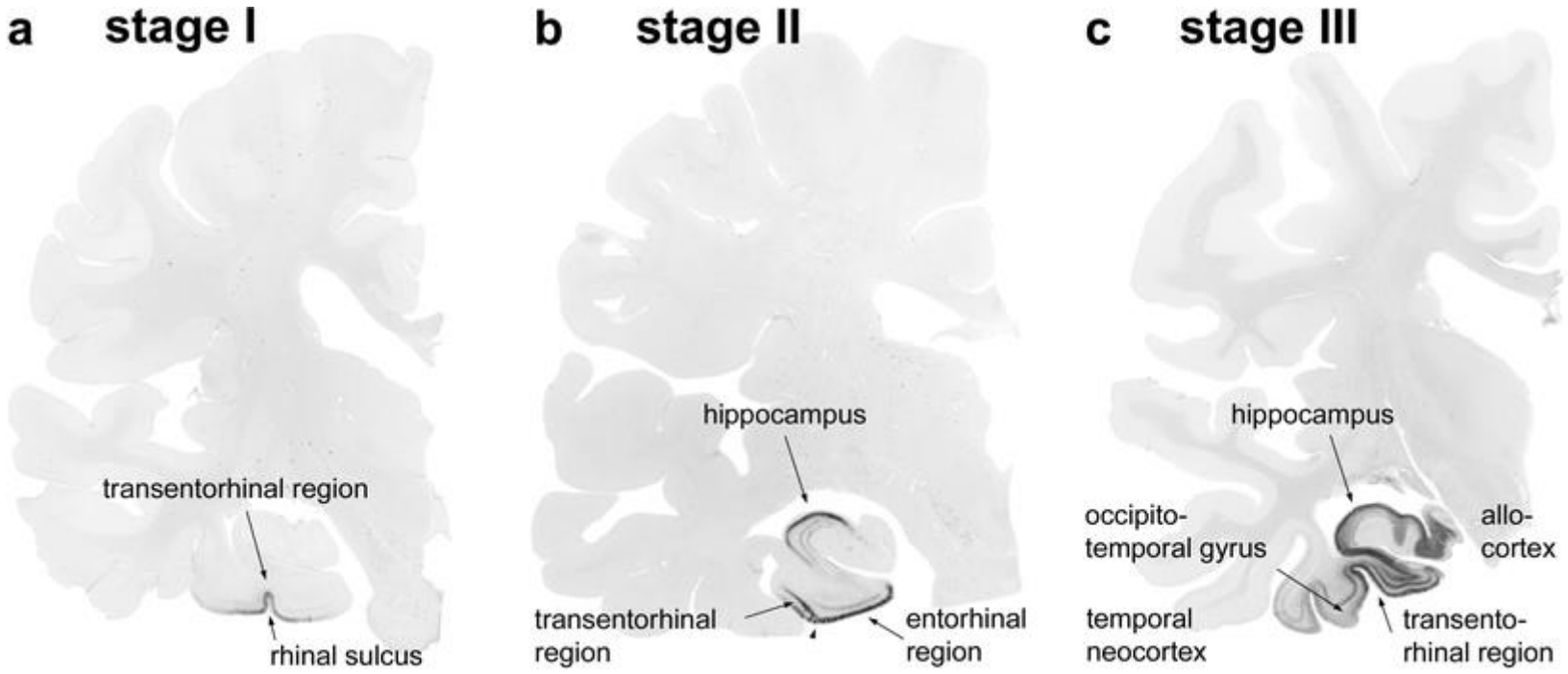
AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer’s disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

Acta Neuropathol (2012) 123:1–11

Braak Stages of Neurofibrillary Degeneration

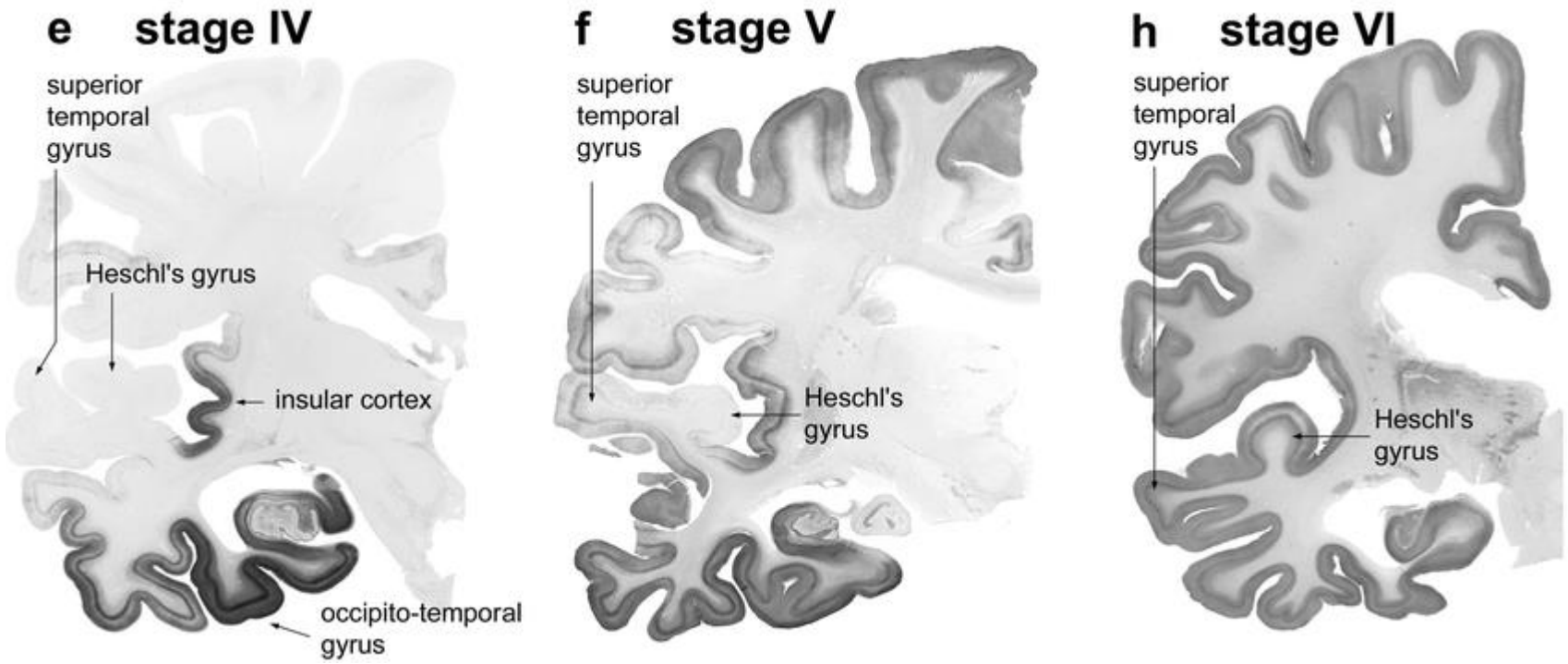


Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry

Heiko Braak · Irina Alafuzoff · Thomas Arzberger · Hans Kretzschmar · Kelly Del Tredici

Acta Neuropathol (2006) 112:389–404

Braak Stages of Neurofibrillary Degeneration



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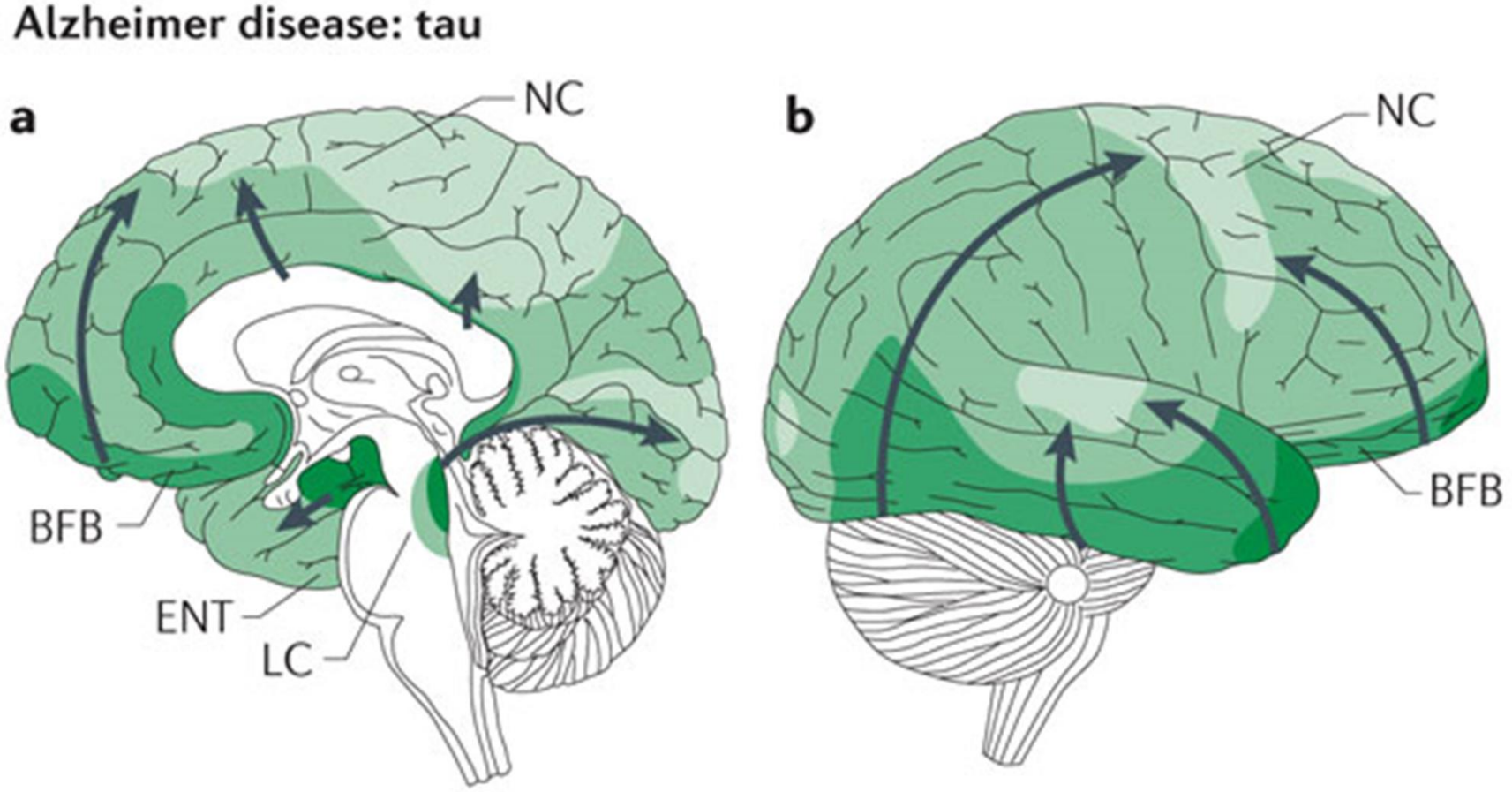
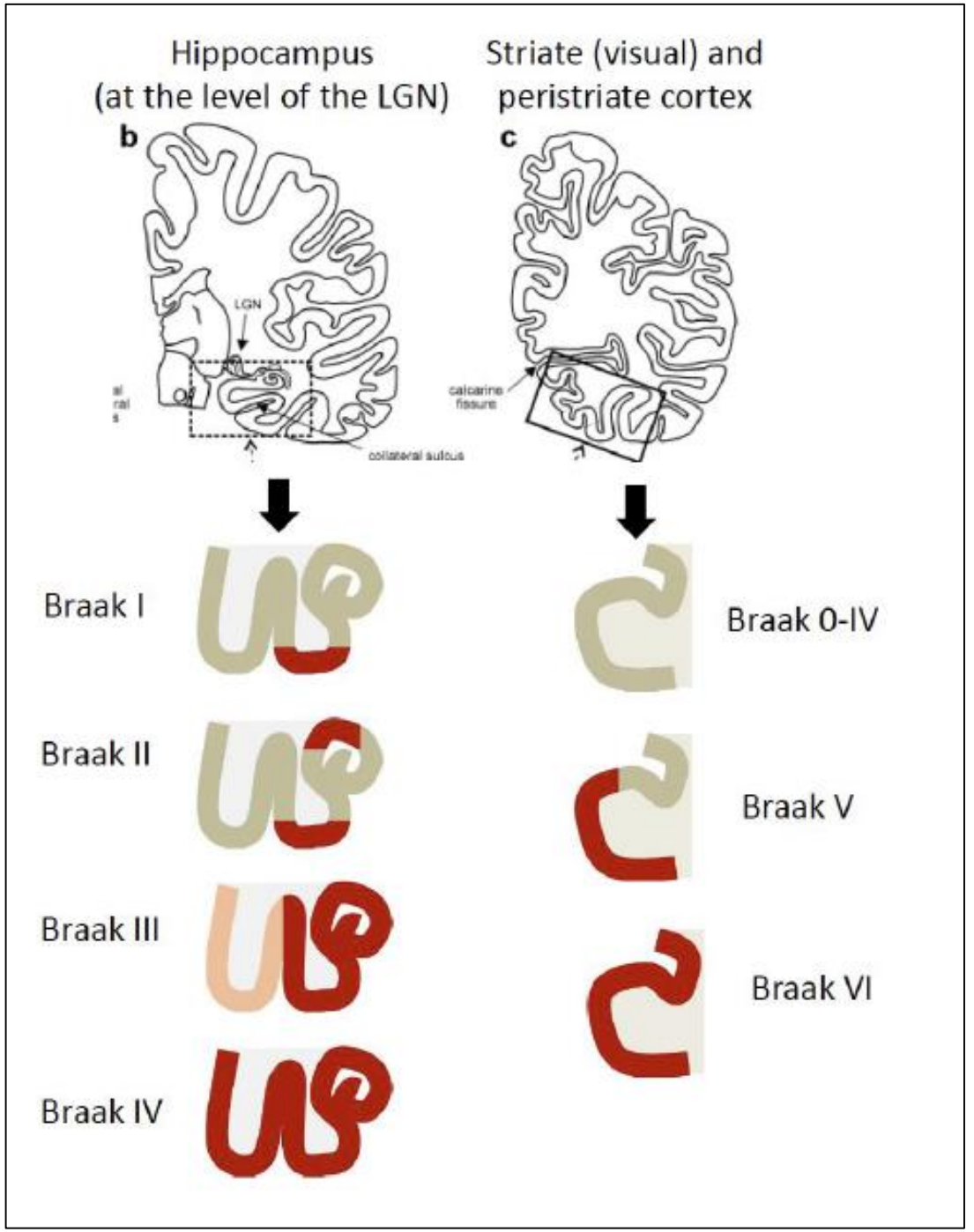
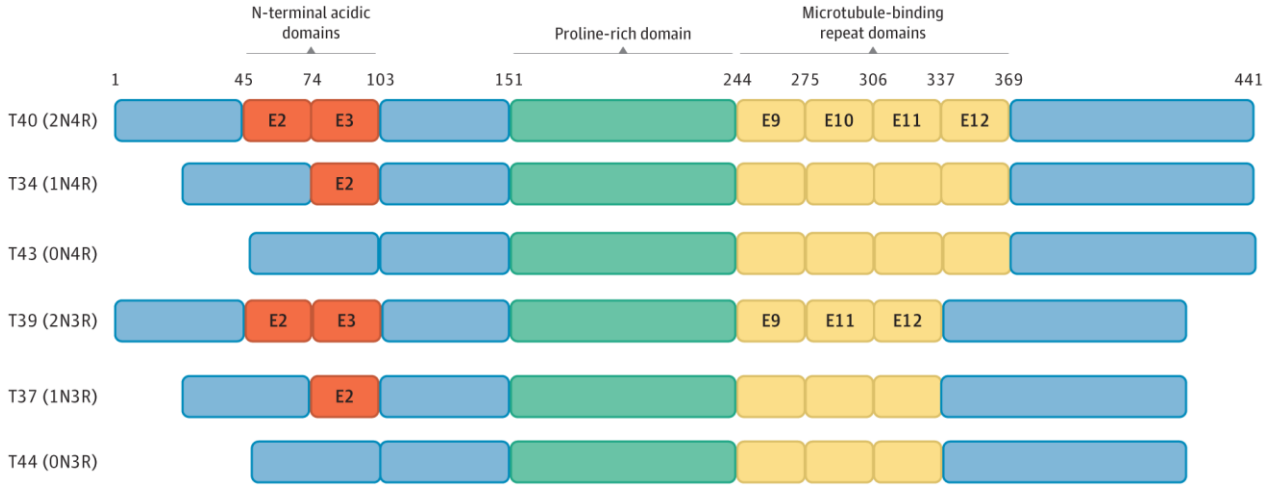


Spreading of pathology in neurodegenerative diseases: a focus on human studies.
Johannes Brettschneider, Kelly Del Tredici, Virginia M.-Y. Lee & John Q. Trojanowski.
Nature Reviews Neuroscience 16, 109–120 (2015)

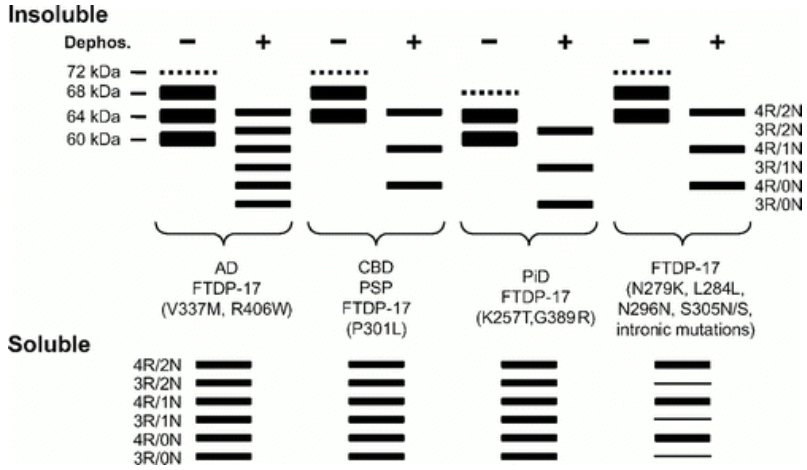
Braak Staging



Biochemical Classification of Tauopathies



Gibbons et al., 2019



Trojanowski and Lee, 2001

A: Thal Phase (Amyloid)

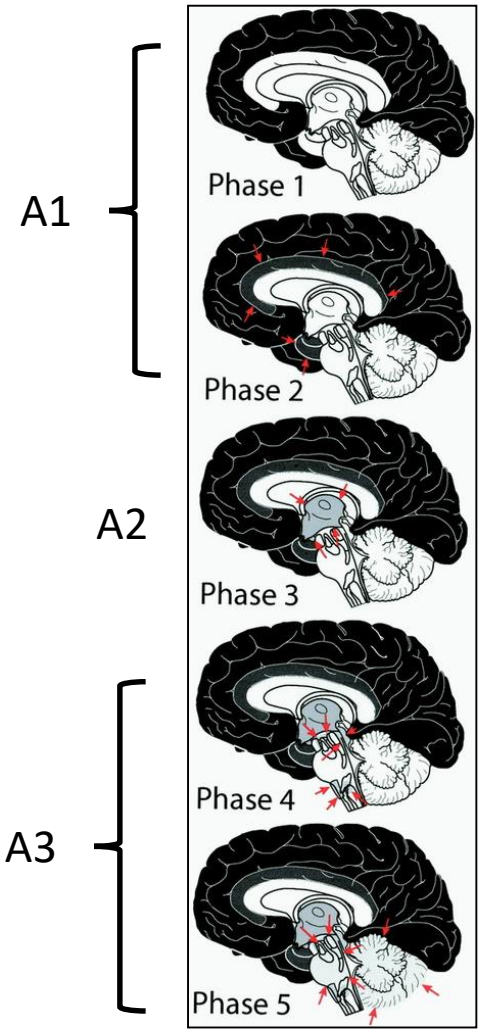
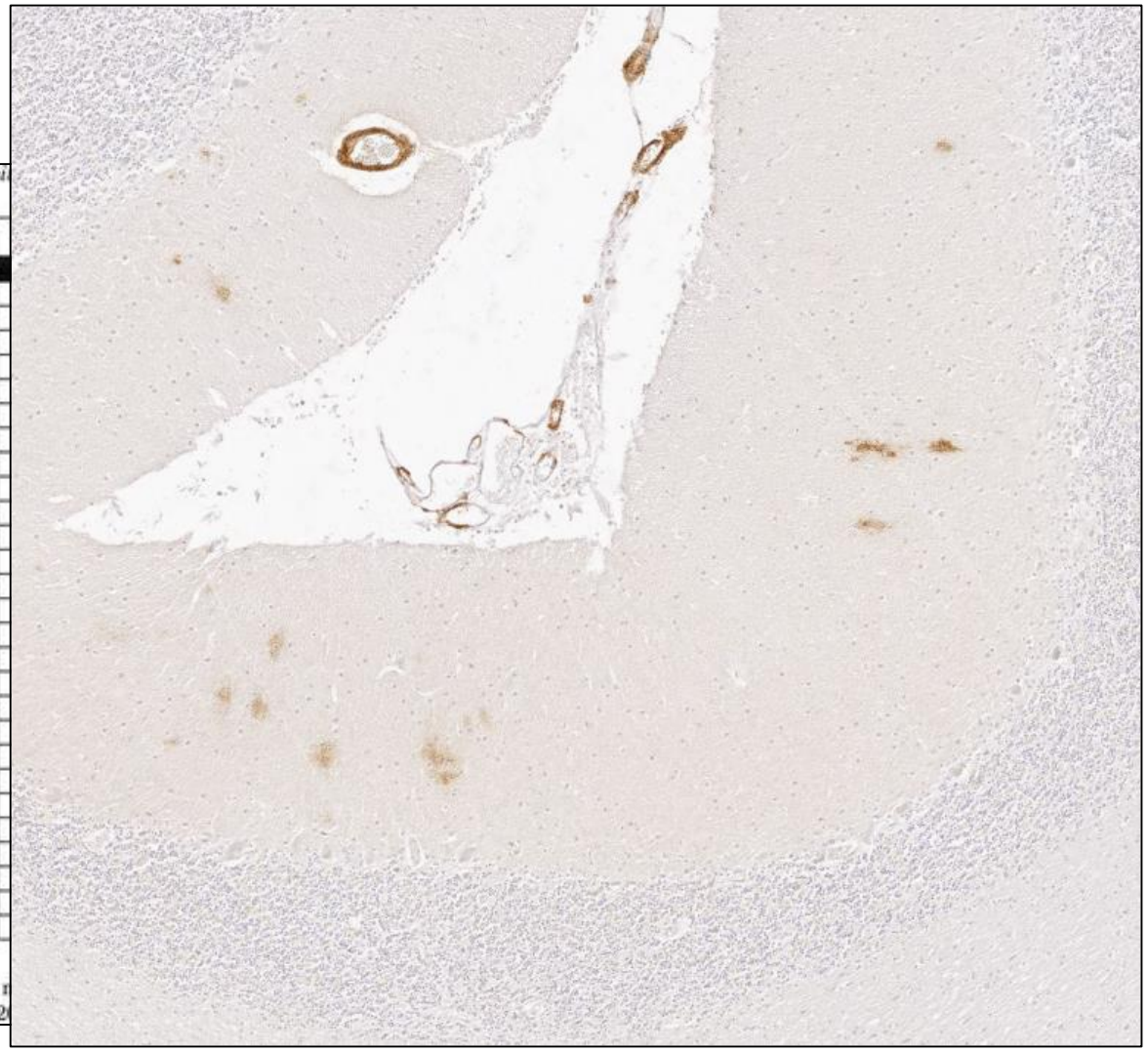


Table *Percentage of cases exhibiting Aβ-deposi*

Neocortex
CA1
Entorhinal Region
Gyrus cinguli
Amygdala
Fascia Dentata
Presubiculum
Thalamus
Striatum
Hypothalamus
Basal Forebrain Nuclei (Meynert)
CA4
Central Gray
Superior Collicle
Red Nucleus
Inferior Olivary Nucleus
Substantia Nigra
Reticular Formation of the Medulla Oblongata
Cerebellar Molecular Layer
Reticular Formation of the Pons
Anterior and Central Raphe nuclei
Locus coeruleus
Parabrachial Nuclei
Reticulo Tegmental Nucleus (Bechterew)
Dorsal Tegmental Nucleus (Gudden)
Nuclei Pontis
Cerebellar Granule Cell Layer
Dentate Nucleus

Regions exhibiting Aβ deposits in phase 1 are r
phase 4 in 40% gray, and those in phase 5 in 2



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

C: CERAD (Neuritic Plaques)

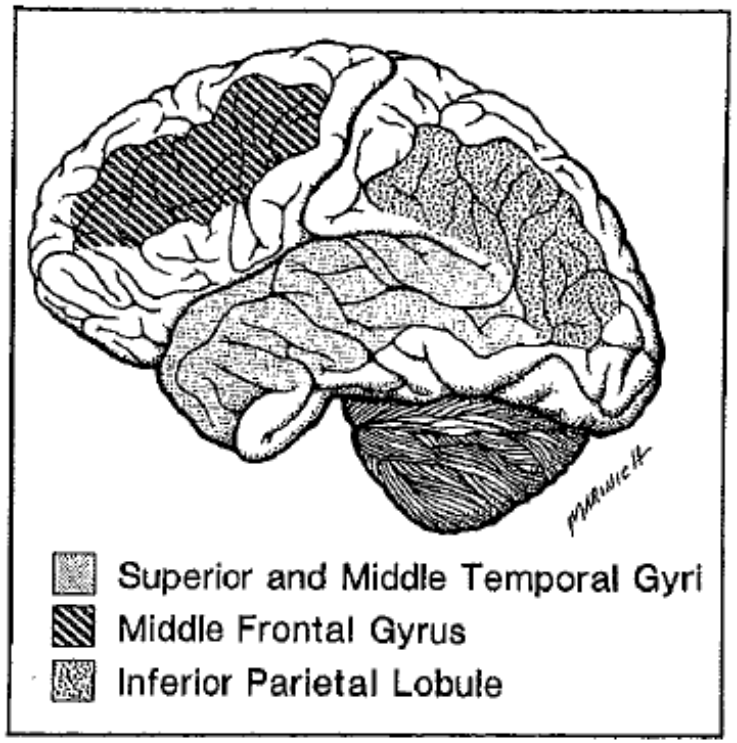


Figure 1. This diagram of the lateral surface of the brain illustrates the areas of neocortex from which recommended neocortical sections are taken.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD).
Part II. Standardization of the neuropathologic assessment of Alzheimer's disease

S.S. Mirra, MD; A. Heyman, MD; D. McKeel, MD; S.M. Sumi, MD; B.J. Crain, MD, PhD; L.M. Brownlee, BChE, MD; F.S. Vogel, MD; J.P. Hughes, MS; G. van Belle, PhD; L. Berg, MD; and participating CERAD neuropathologists*

NEUROLOGY 1991;41:479-486

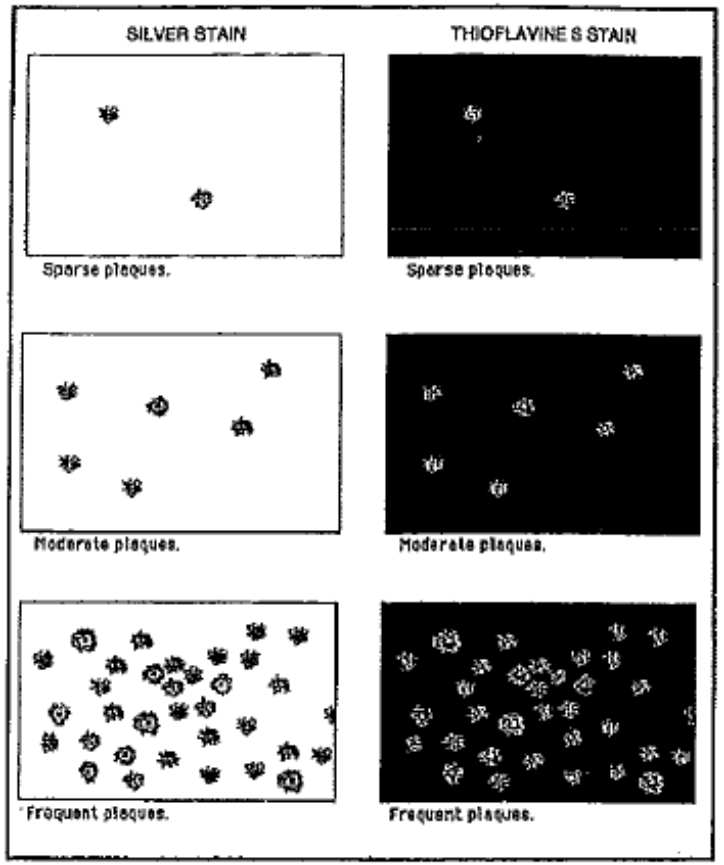
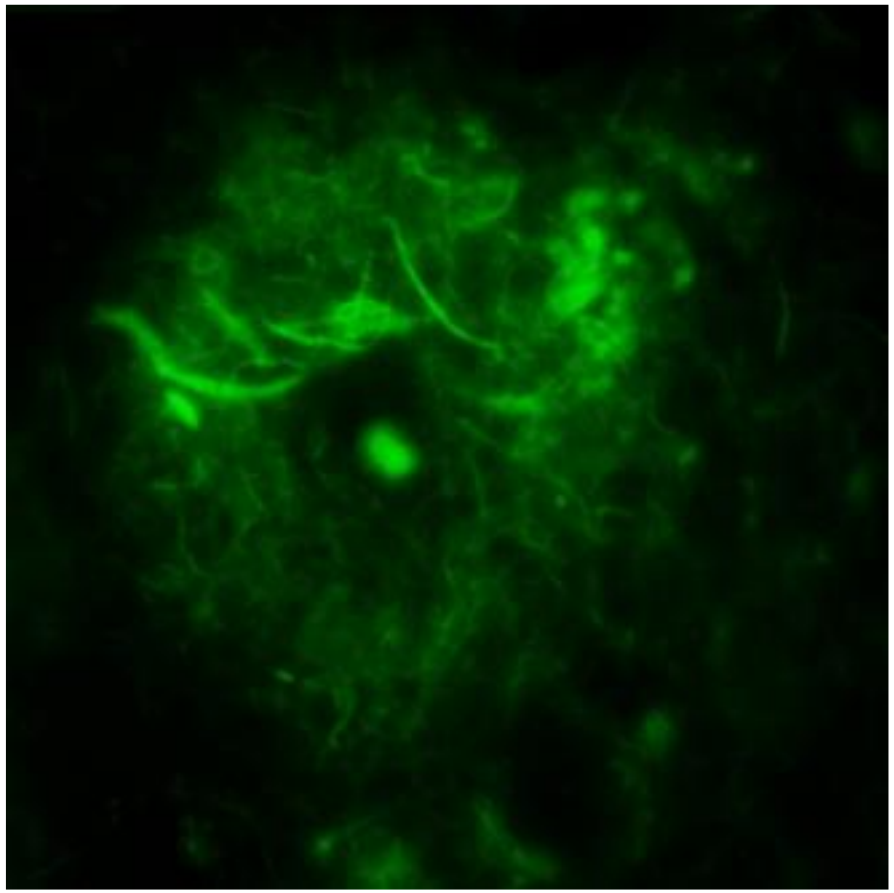


Figure 2. Senile plaques (neuritic) per 100× microscopic field. This cartoon provides a guide to semiquantitative assessment of plaque density per square millimeter.



“ABC” Score

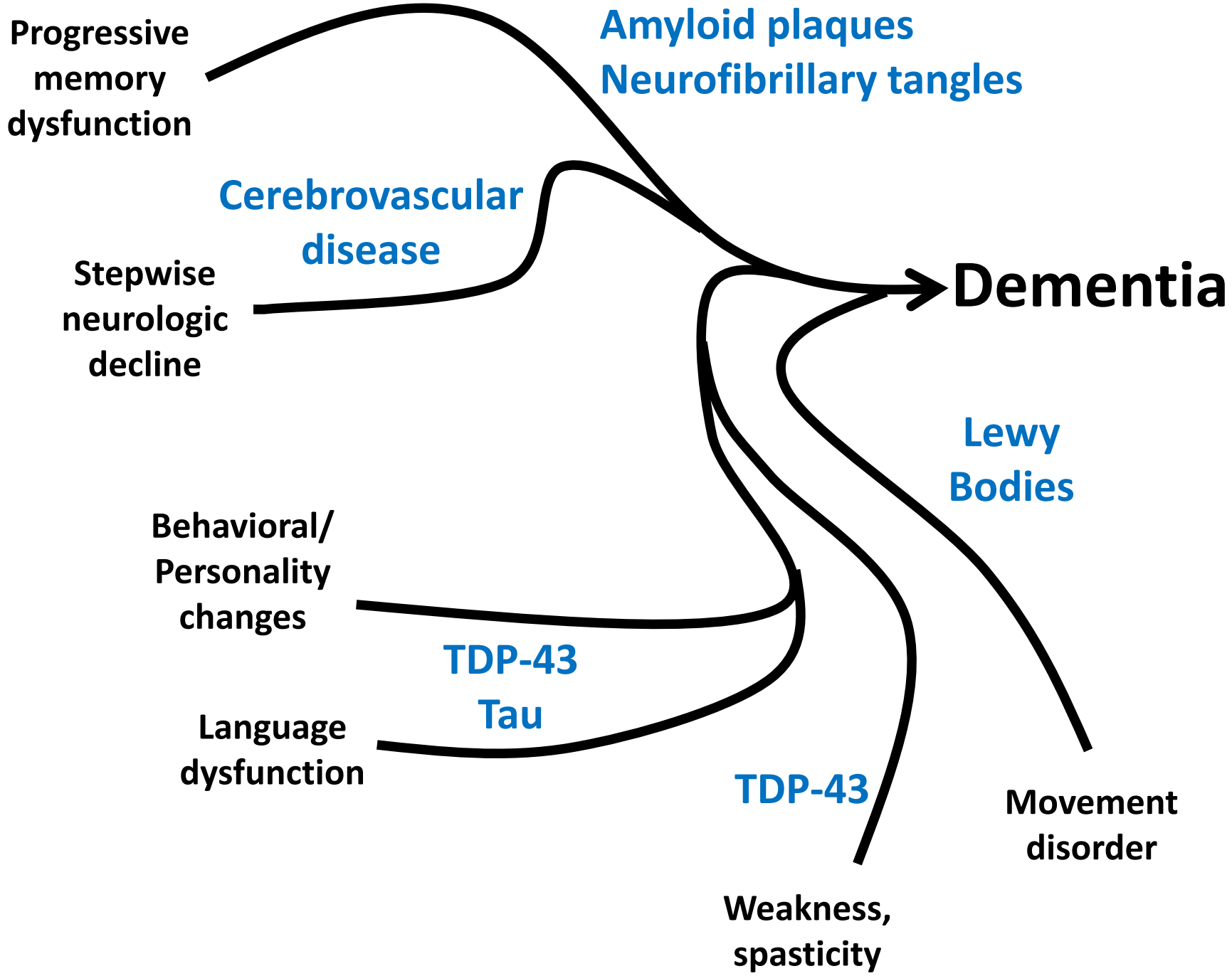
AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer’s disease: a practical approach

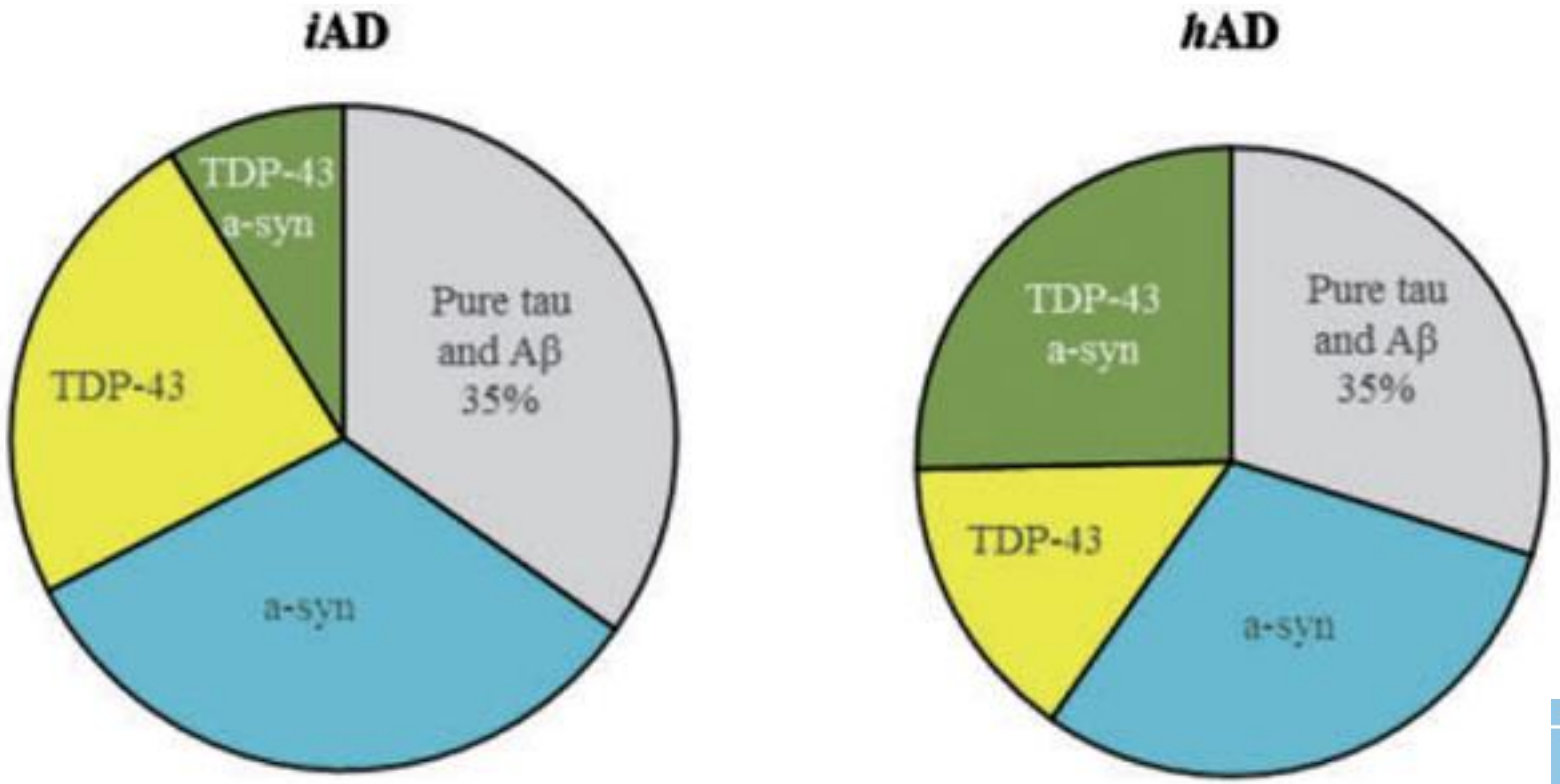
Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

Acta Neuropathol (2012) 123:1–11

II. “Alzheimer’s Disease” Heterogeneity


Progressive memory dysfunction
Amyloid plaques
Neurofibrillary tangles
Cerebrovascular disease
Stepwise neurologic decline
Dementia
Lewy Bodies
Behavioral/ Personality changes
TDP-43
Tau
Language dysfunction
TDP-43
Movement disorder
Weakness, spasticity

Co-morbid Neurodegenerative Disease Pathologic Change

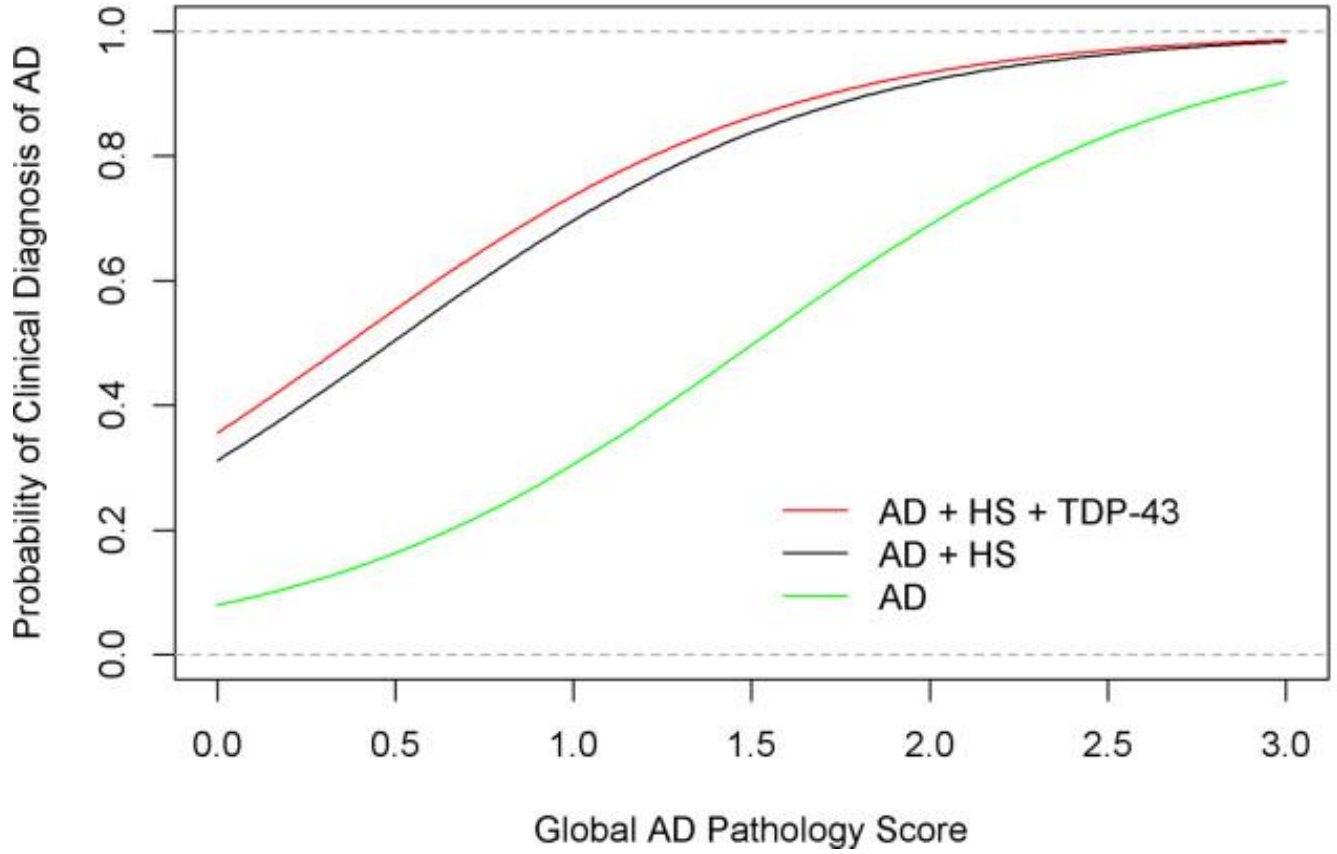


doi:10.1093/brain/awy146 BRAIN 2018: 141; 2181–2193 | 2181
BRAIN
A JOURNAL OF NEUROLOGY

Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated

Robinson JL, et al., Brain 141: 2181-2193, 2018

TDP-43 & Hippocampal Sclerosis and Risk for AD Dementia



Nag S., et al., Annals of Neurology 77(6): 942-52, 2015

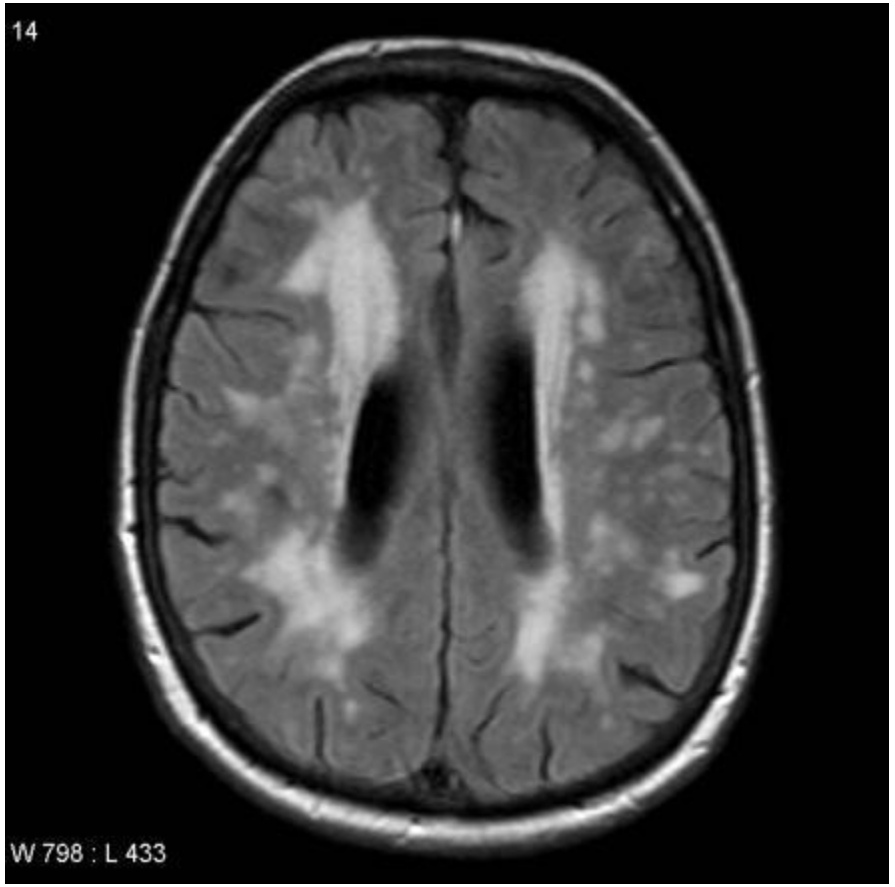
Attributable Risk for AD Dementia

Neuropathological indices	Fraction attributable % (95% CI)[a]
Alzheimer's disease (ADNC)	39.4 (31.5–47.4)
Vascular disease pathology[b]	24.8 (17.3–32.1)
LATE-NC	**17.3** (13.1–22.0)
α-Synucleinopathy/Lewy body pathology	11.9 (8.4–15.6)

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Brain, 2019

Vascular Dementia



From www.radiopaedia.org

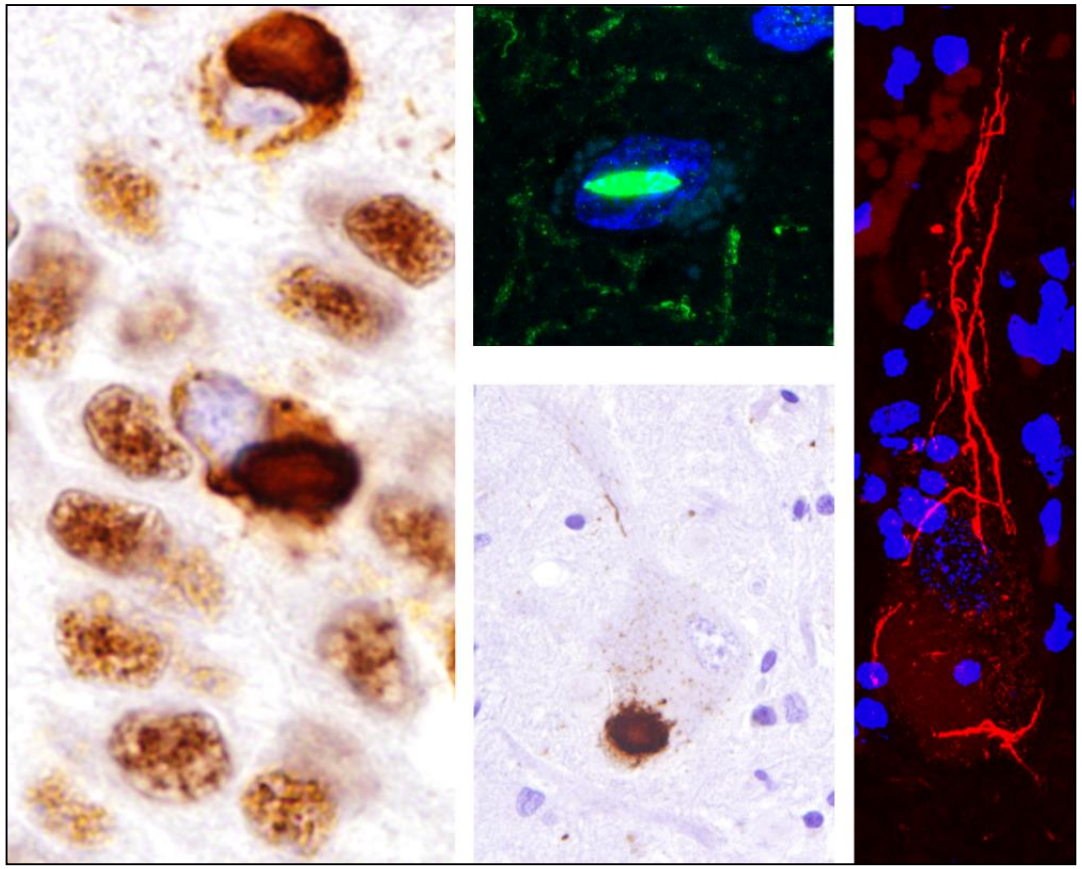
- Multi-infarct dementia
- Subcortical vascular dementia
- Strategic infarct dementia
- Step-wise decline with clinical phenotype depending on vascular territory that is affected

BRAIN
A JOURNAL OF NEUROLOGY

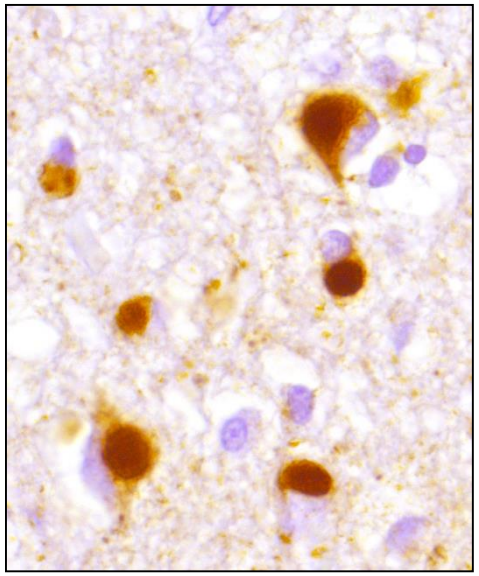
Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment

Olivia A. Skrobot,[1] Johannes Attems,[2] Margaret Esiri,[3] Tibor Hortobágyi,[4,5] James W. Ironside,[6] Rajesh N. Kalaria,[2] Andrew King,[7] George A. Lammie,[8] David Mann,[9] James Neal,[10] Yoav Ben-Shlomo,[11] Patrick G. Kehoe[1] and Seth Love[1]

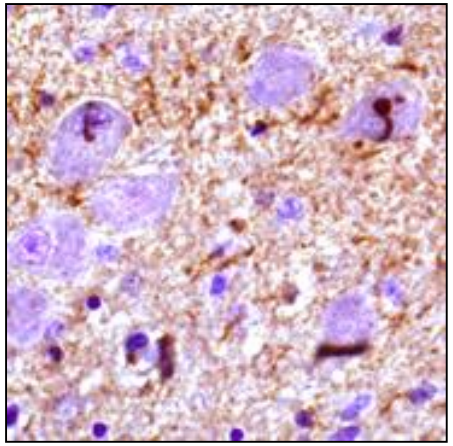
Microscopic Neuropathology of Frontotemporal Lobar Degeneration



TDP-43
(TAR DNA Binding protein of 43 kDa)

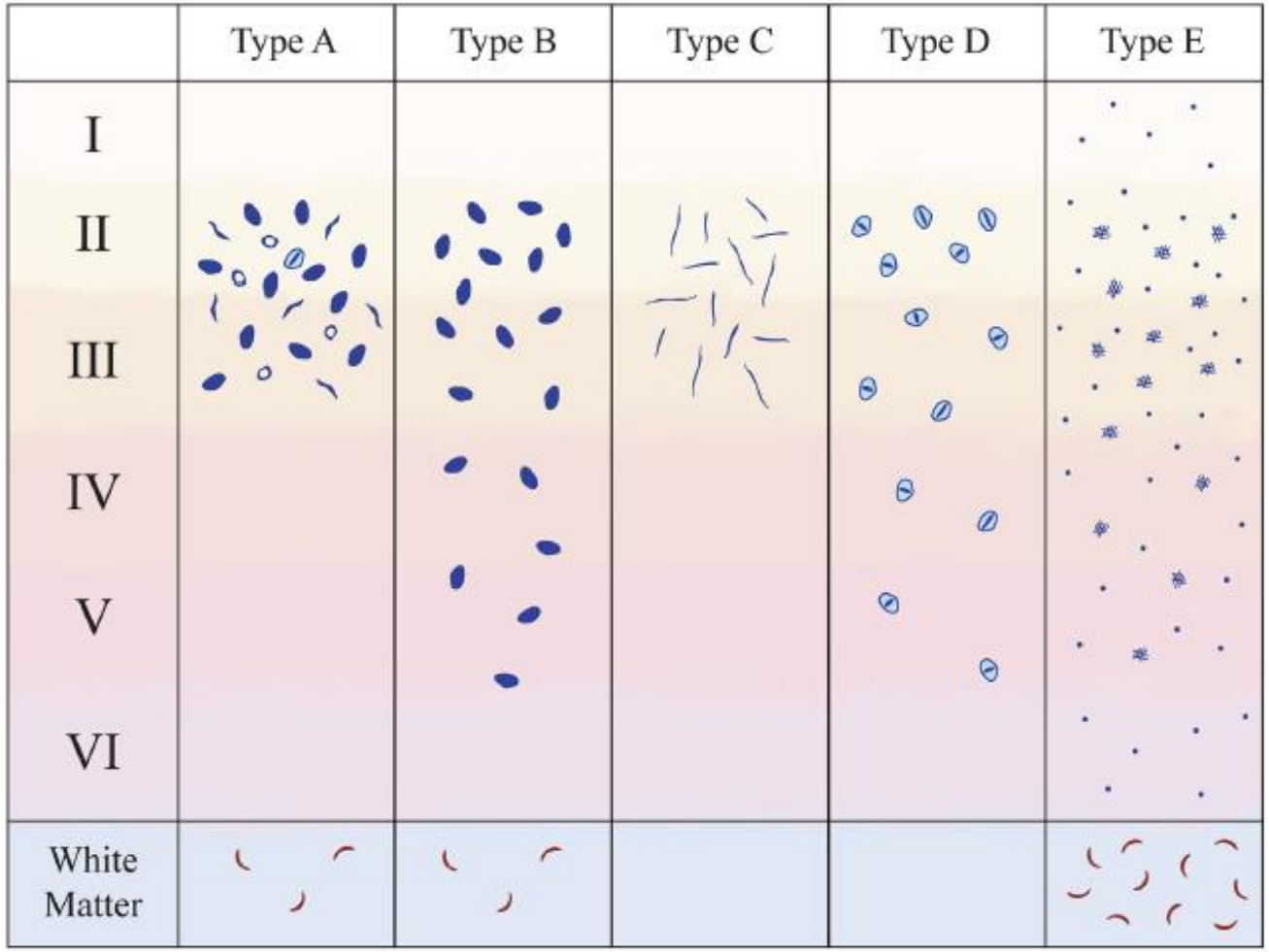


Tau



(FUS)
Fused-In-Sarcoma

FTLD-TDP Subtypes



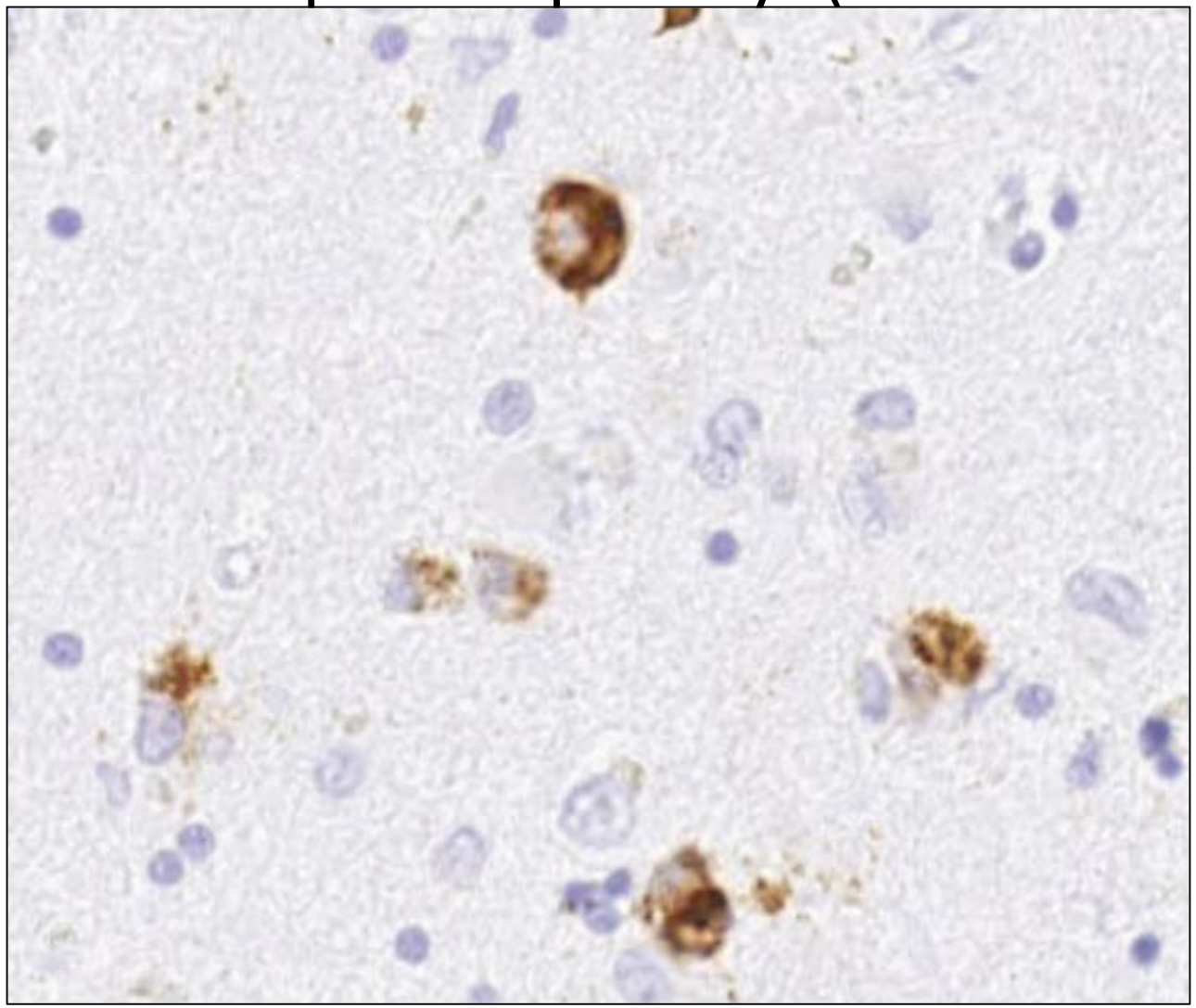
Expansion of the classification of FTLD-TDP: distinct pathology associated with rapidly progressive frontotemporal degeneration

Edward B. Lee[1,2,3] · Sílvia Porta[2,3] · G. Michael Baer[4] · Yan Xu[2,3] · EunRan Suh[2,3] · Linda K. Kwong[2,3] · Lauren Elman[4] · Murray Grossman[4] · Virginia M.-Y. Lee[2,3] · David J. Irwin[4] · Vivianna M. Van Deerlin[2,3] · John Q. Trojanowski[2,3]

Diseases with TDP-43 Pathology

- Frontotemporal lobar degeneration with TDP-43 inclusions
- Amyotrophic lateral sclerosis
- Limbic-predominant Age-related TDP-43 Encephalopathy
- Corticobasal degeneration
- Trauma RElated NeuroDegeneration
- Parkinsonism-dementia complex of Guam
- Perry syndrome
- Alexander’s disease

Limbic-predominant Age-related TDP-43 Encephalopathy (LATE-NC)

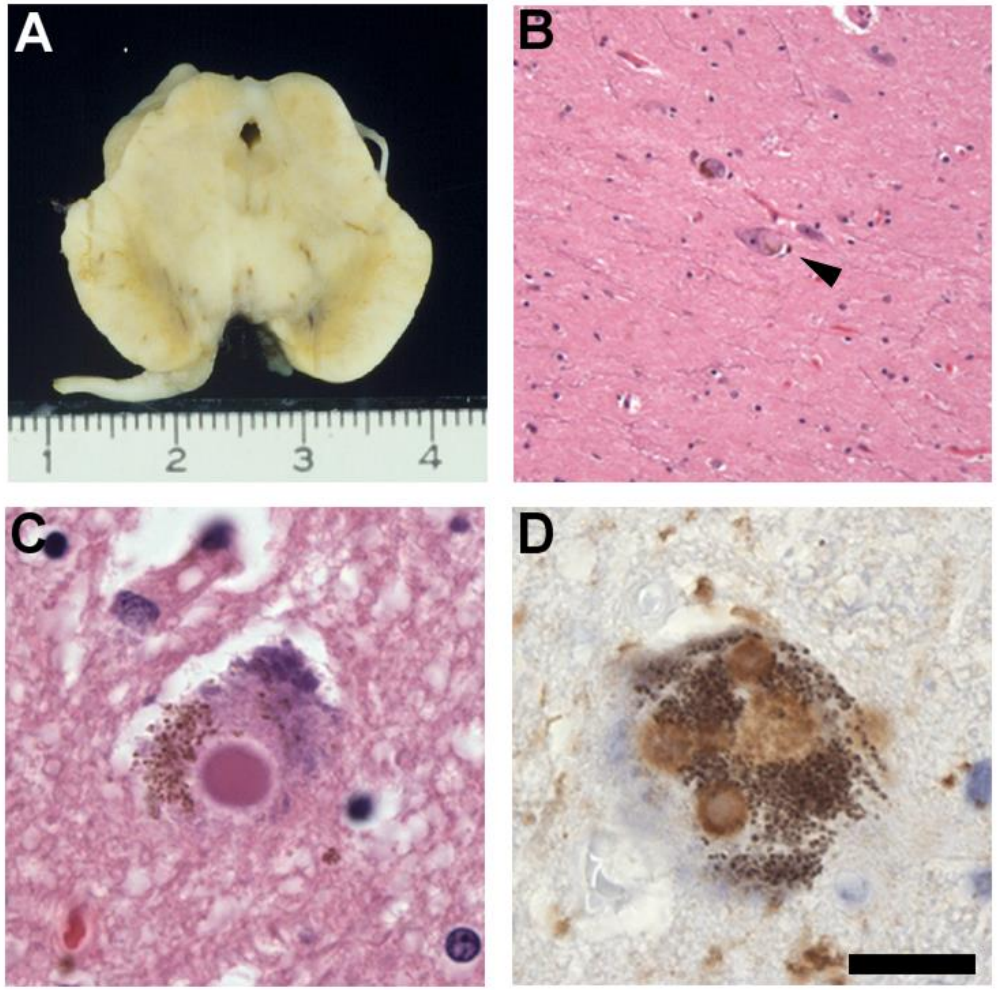


Simplified staging of TDP-43 proteinopathy* for routine LATE-NC diagnosis (consensus recommendation)	
0	None
1	Amygdala
2	Hippocampus
3	Middle frontal gyrus (MFG)

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Brain, 2019

Lewy Body Disease (PD, PDD, DLB): α-synuclein



- **8-30μm neuronal cytoplasmic Inclusions with a hyaline eosinophilic core and a pale halo**
- **Small, soluble protein of 140 amino acids**
- **Member of a diverse family of synaptic proteins**
- **Enriched in presynaptic terminals of neurons may function in synaptic transmission**

Diseases with α-Synuclein Pathology

- Parkinson's disease
- Parkinson's disease dementia
- Dementia with Lewy bodies
- "Lewy body variant of Alzheimer's disease"
  - Combined AD and DLB pathology
- Multiple System Atrophy
- Neurodegeneration with brain iron accumulation 1 (formerly HS-disease)
- Diseases with variable α-synuclein pathology
  - Down's syndrome
  - Sporadic and familial Alzheimer's disease
  - Guam parkinsonism-dementia complex

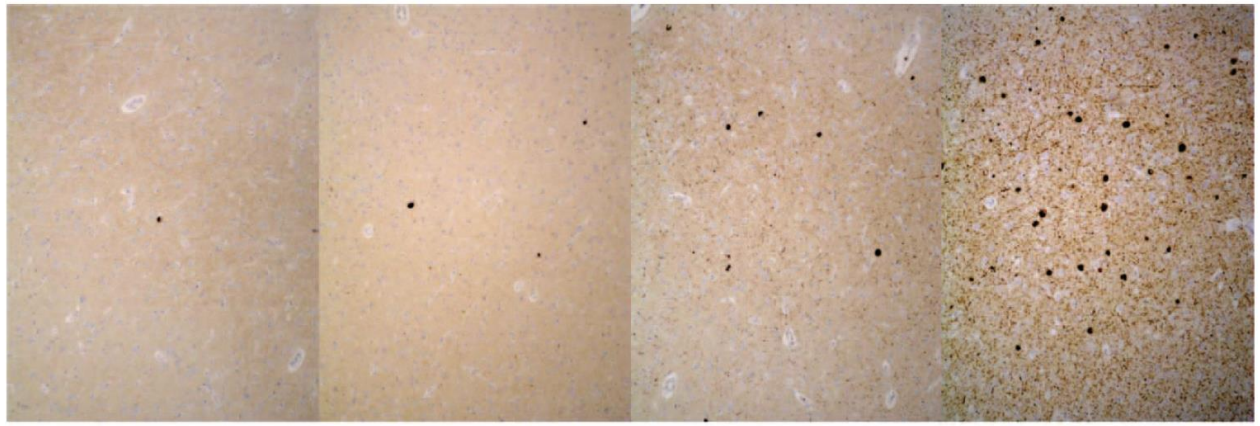
Lewy Body Disease Patterns

Diagnosis and management of dementia with Lewy bodies

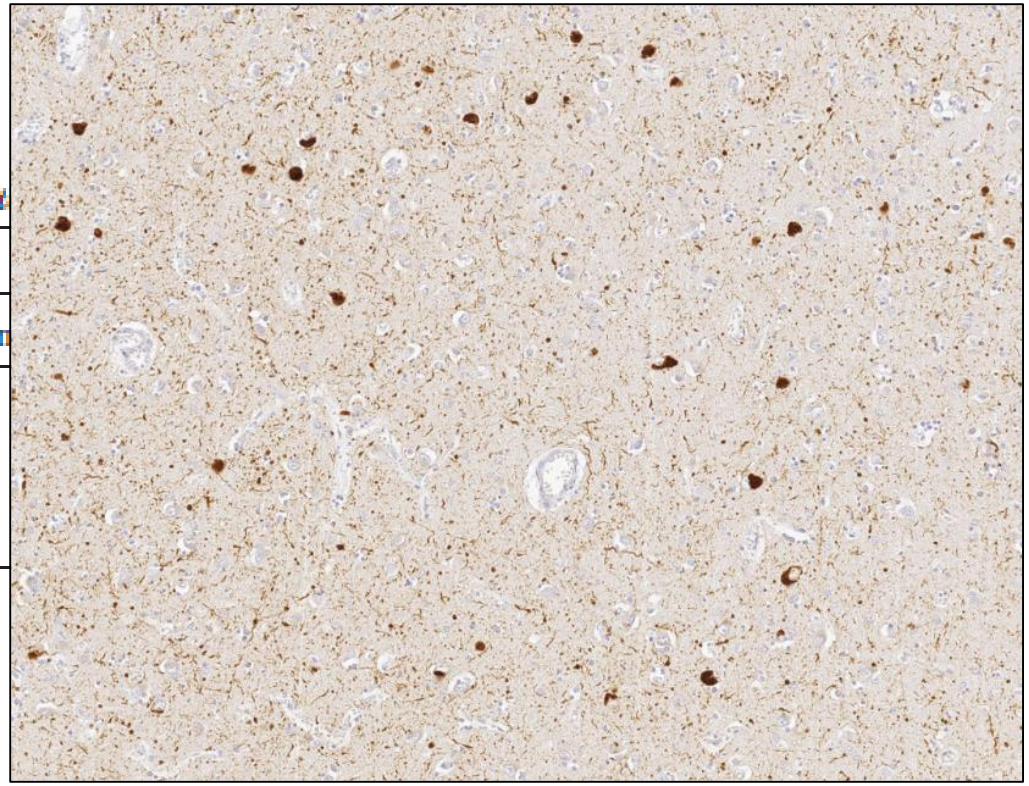
Third report of the DLB consortium

***Table 2** Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainst*

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions			
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cin
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	

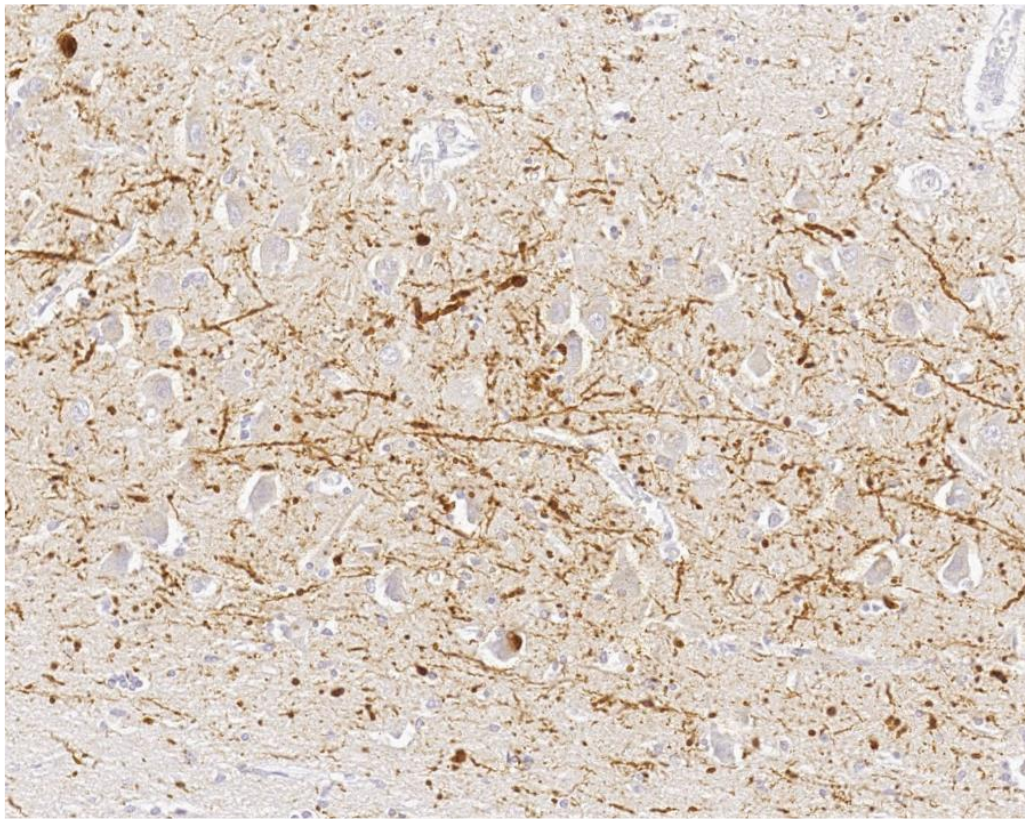


1 (mild) 2 (moderate) 3 (severe) 4 (very severe)



Amygdala-predominant

Lewy Body Disease: Unique CA2 Prediliction



III. The Ultimate Diagnosis: Reporting Autopsy Results

Integrated Neurodegenerative Disease Autopsy Report

1. Macroscopic (gross) description
2. Microscopic description

   "We stained XYZ and we saw ABC, etc."

3. Pathologic diagnosis

   High level of Alzheimer's disease neuropathologic change (A3, B3, C3)

   Lewy body disease, transitional pattern

   Limbic-predominant age-related TDP-43 encephalopathy (LATE), Stage 3

4. Clinicopathologic correlation

   "This x year old male had a clinical history of dementia with Lewy bodies. We saw xyz which correlates well with the history of dementia, etc.

5. Final integrated diagnosis

Integrated neurodegenerative disease autopsy diagnosis

Edward B. Lee[1]

Acta Neuropathologica (2018) 135:643–646

Let’s look at a few cases…

Integrated Neurodegenerative Disease Autopsy Report

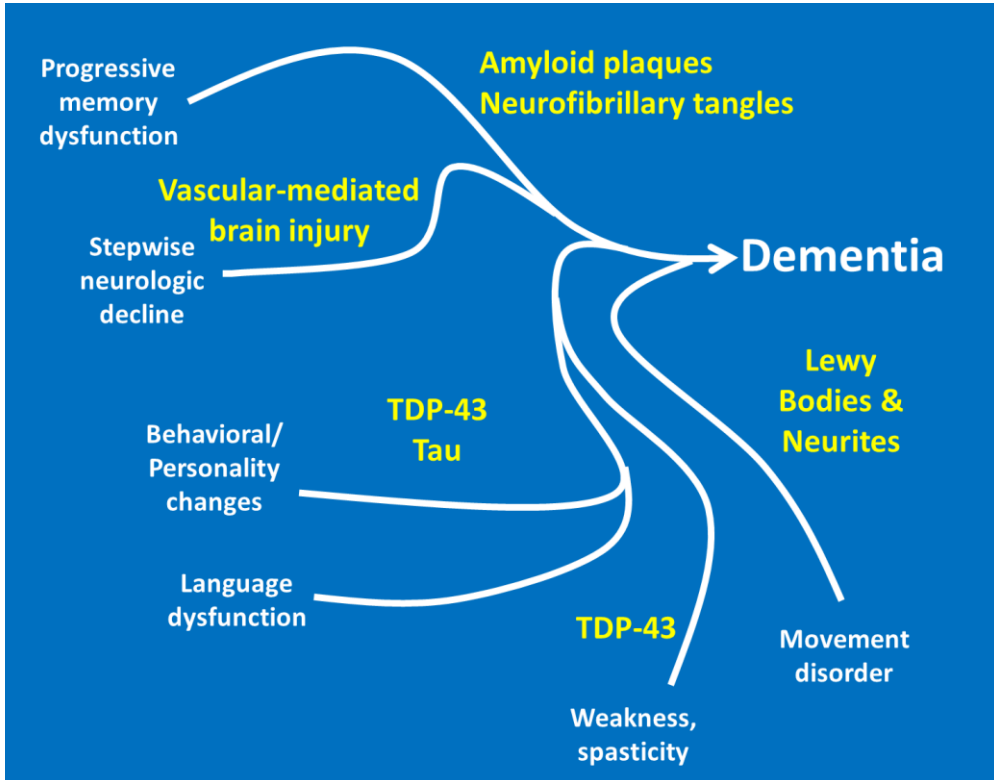
- Alzheimer's disease, posterior cortical atrophy variant
  - Histologic diagnosis: High level of Alzheimer's Disease neuropathologic change (A3, B3, C3)
  - Co-morbid pathology: LATE-NC (Stage 2)
  - Clinical classification: Posterior cortical atrophy
  - Biochemical data: 3R+4R tauopathy
  - Molecular data: *APOE* E3/E4, *TREM2* p.R47H

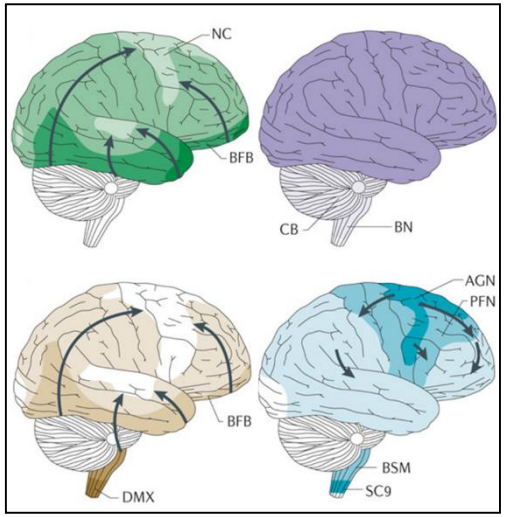
Integrated neurodegenerative disease autopsy diagnosis

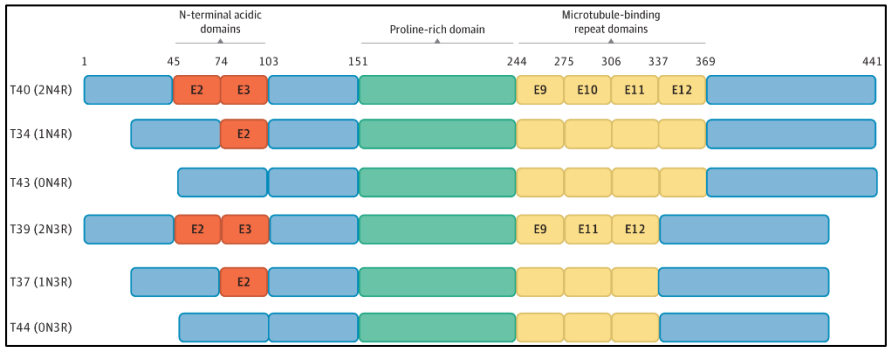
Edward B. Lee[1]

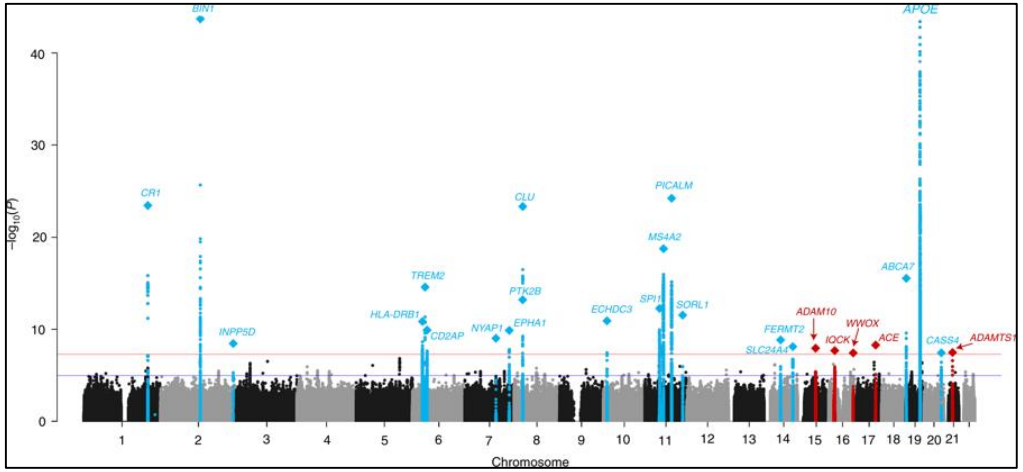
Acta Neuropathologica (2018) 135:643–646

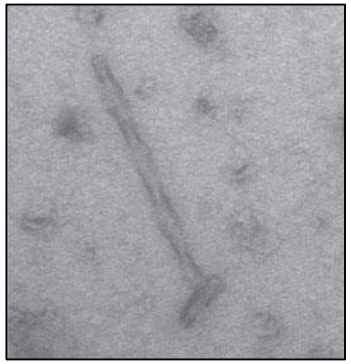
Autopsy: Final Comprehensive Disease Classification











Thank you!

Q&A