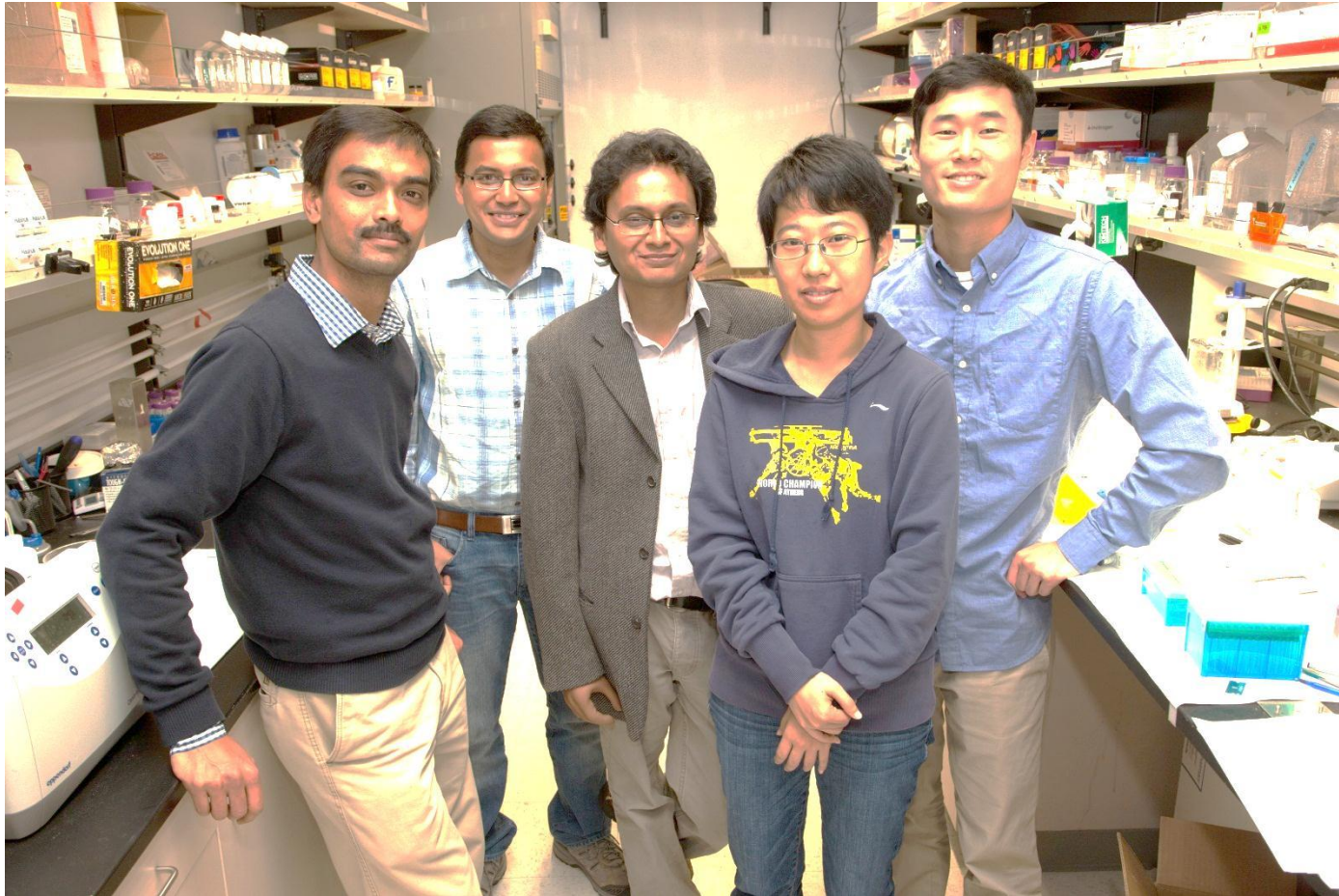


INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Pennsylvania, Philadelphia	Post-doc	7/05- 12/07	Neuronal cell-biology, neuropathology
University of Pennsylvania hospital, Philadelphia	Residency/ Fellowship	7/01-6/06	Anatomic/Neuro-pathology (clinical)
Temple University school of medicine, Philadelphia	PhD	7/97-6/01	Cell Biology/Neuroscience
R.G. Kar Medical College, Calcutta, India	MD	9/89-6/96	Medicine

Subhojit Roy, MD, PhD, Assistant professor, UCSD

UTPAL ARCHAN

LINA YONG



AXONAL TRANSPORT/
NEURONAL
TRAFFICKING

NEURODEGENERATION

www.roylab.org

2ND LIFE...

<http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers>

<http://adrc.ucsd.edu/>

Human neurodegenerative neuropathology: the template for asking the right questions

- Look at the diseased brain to ask what's *really* happening?
- Do experiments in simple model-systems and test/validate hypotheses in human brain tissue

Brain banking

- System of NIH-funded brain banks in the US
- Why neuropathology?
- Different neurodegenerative pathologies

Alzheimer's Disease Centers

- Clinical core – patient follow-up
- Administrative/education core
- Neuropathology core – neuropathologist..

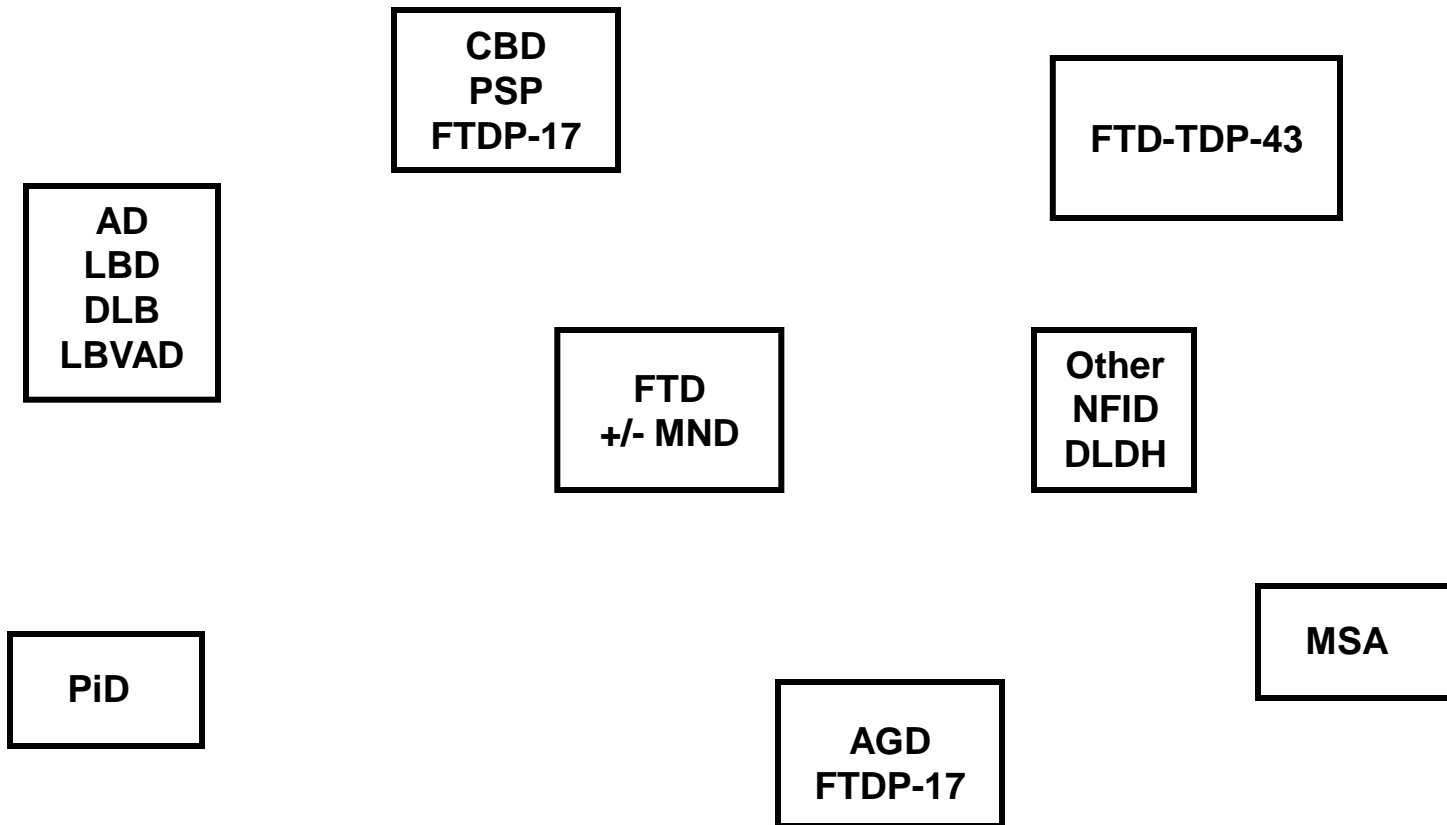
Brain → Dissected, ½ fixed, half stored in formalin → Tissue sections from fixed brains → Slides H&E and immunostains (tau, amyloid beta, synuclein) → Final diagnosis to patient family

- Tissue exchange between centers
- Numerous research projects supported within and outside institution

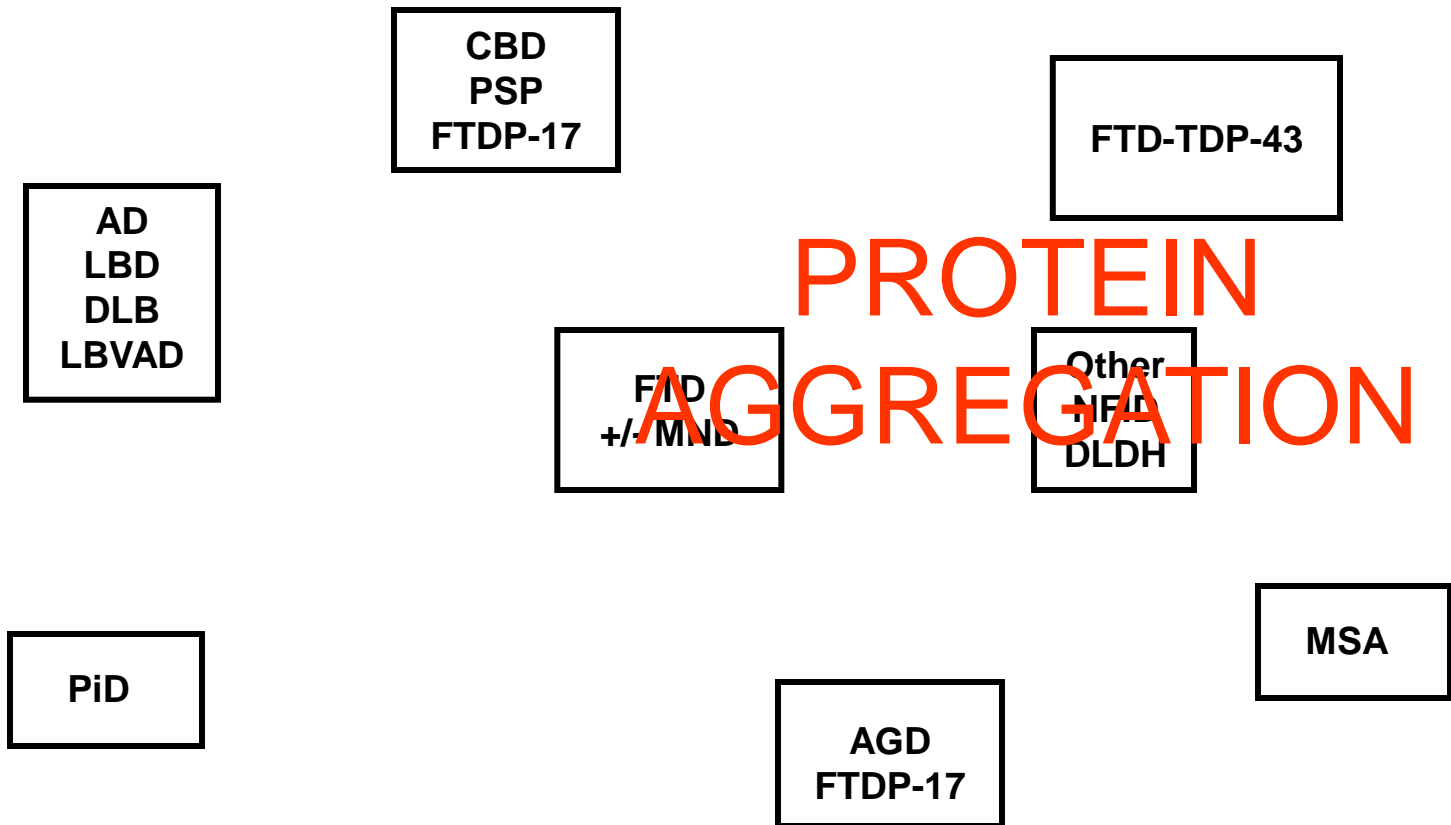
5604 Diagnosis						
		MF	HP	ST	AM	
Tau	AD (Br. 5/6) + ?CBD	3+ (WM path)	3+	3+		
Abeta		3+ (vasc+)	3+	3+		
a-syn						Rare
5605						
Tau	(Br. 2/3) + ? Unknown	Neg	2+	1+		
Abeta		2+	None (?)	1+		
a-syn						Neg
5608						
Tau	?LBD (extra stains needed)	Neg	1+			Neg
Abeta		Neg	Neg (?)			Neg
a-syn				3+		
5609						
	?LBD (extra stains needed)					
Tau		Neg	1+ (only EC)	Neg		
Abeta		Neg	Neg	1+		
a-syn						2+

"Sorting through the
nomenclature quagmire of
neurodegenerative diseases using
neuropathology"

Neuropathology of Dementias



Neuropathology of Dementias



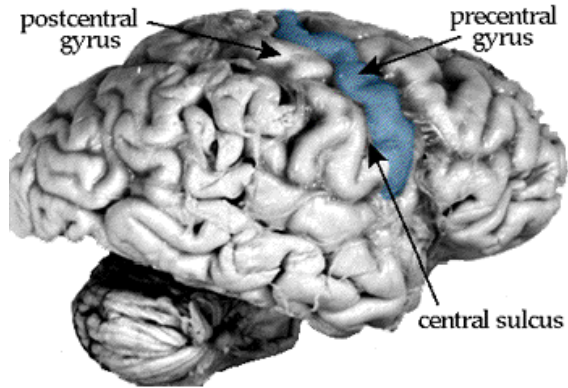
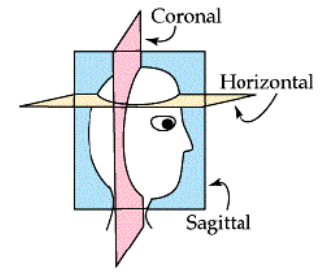
Concept of protein aggregation

- Proteins that are normally soluble, become insoluble and fibrillize intra-cellularly (tau, alpha-synuclein) or extra-cellularly (amyloid-beta)
- Aggregates into similar fibrillar forms “amyloid” that appear structurally and biophysically similar
- Dogma: Proteinaceous aggregates drives neuropathology

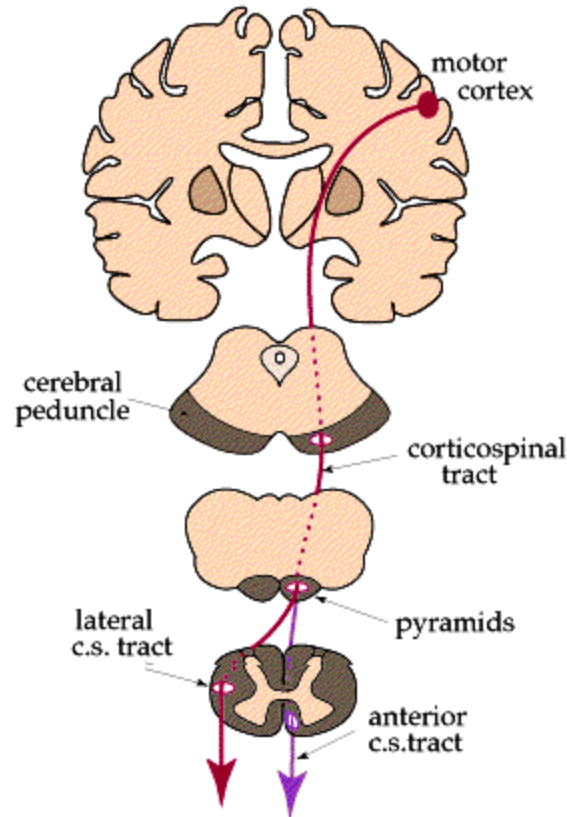
Brief discussion of:

- Simple algorithm for neuropathologic diagnosis using two immunostains
- Story of TDP-43: recent example of neuropathology-driven research

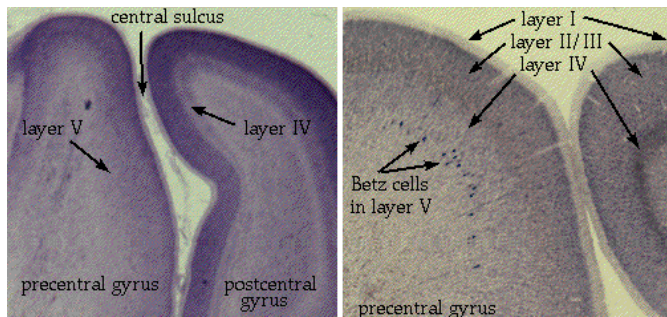
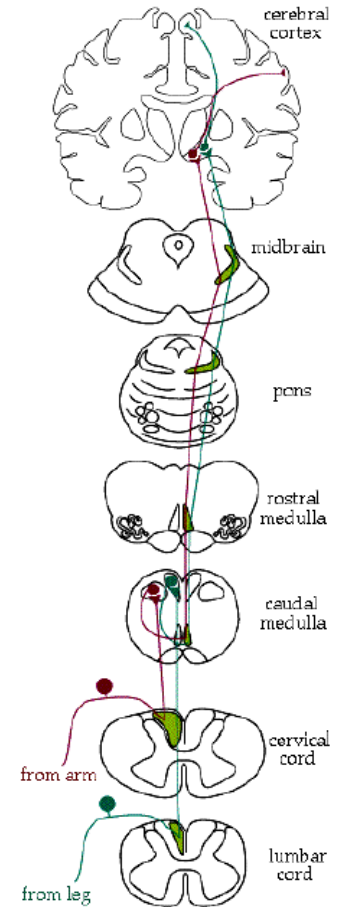
Basic neuroanatomy



Basic motor pathway



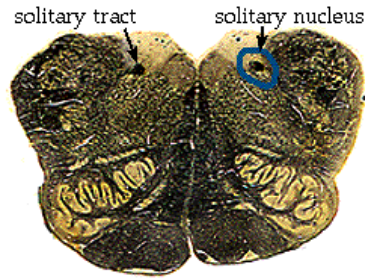
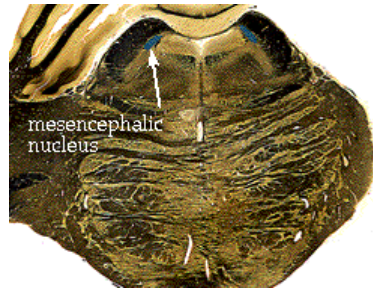
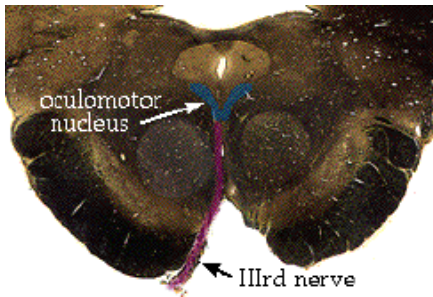
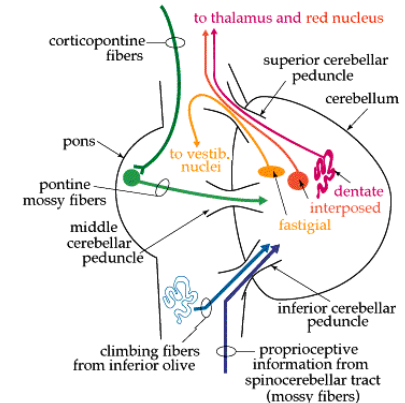
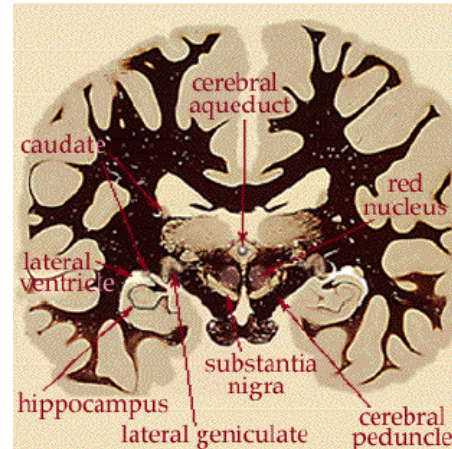
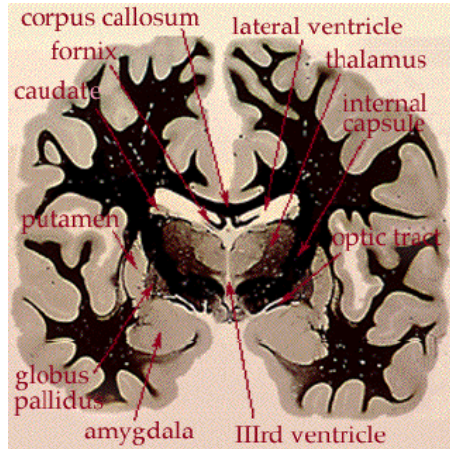
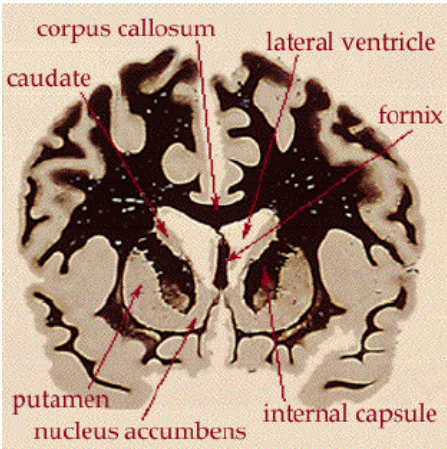
Basic sensory pathway (touch)



Neocortex/isocortex= 6 layered cortex

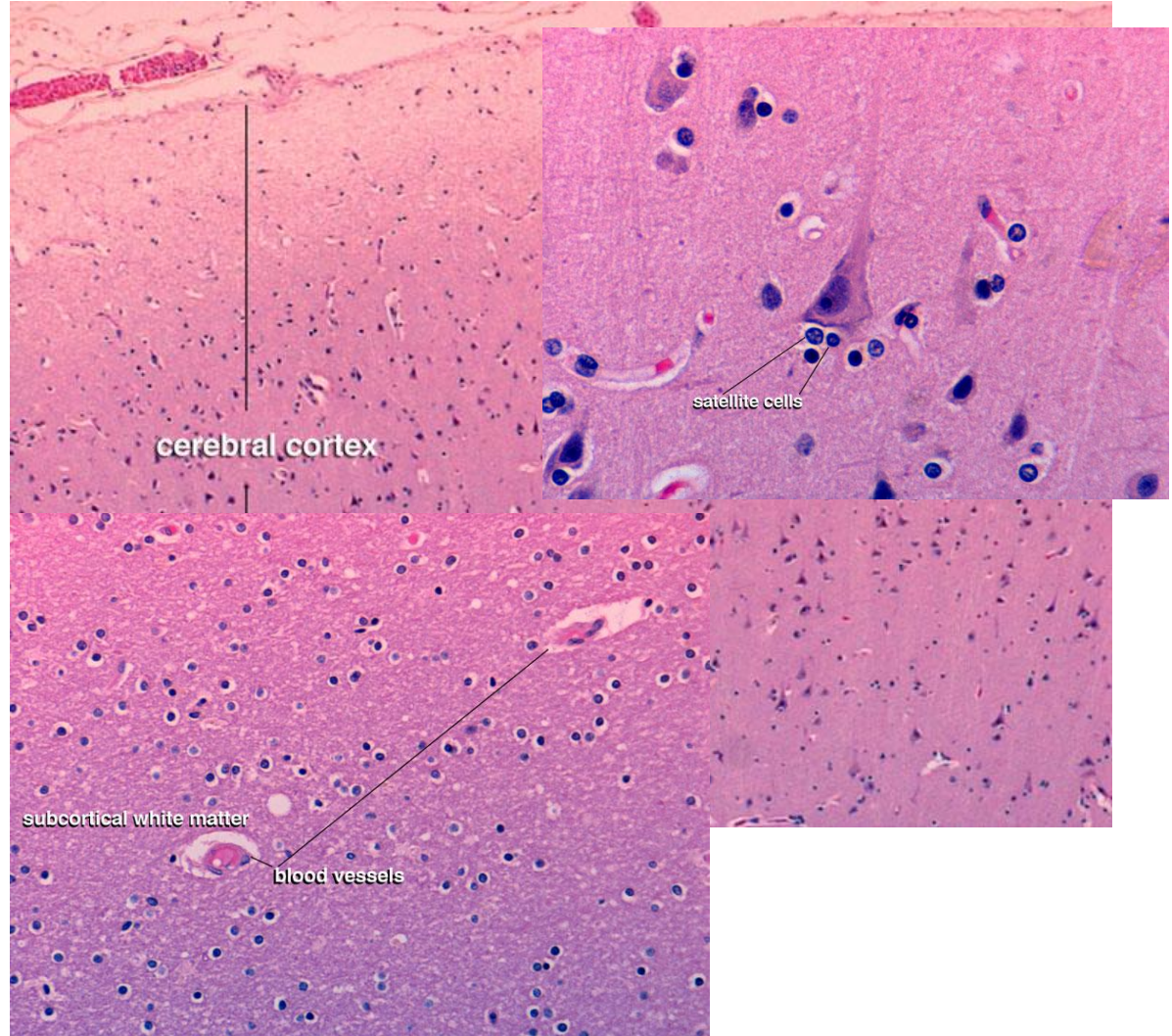
Archi/paleocortex= limbic system

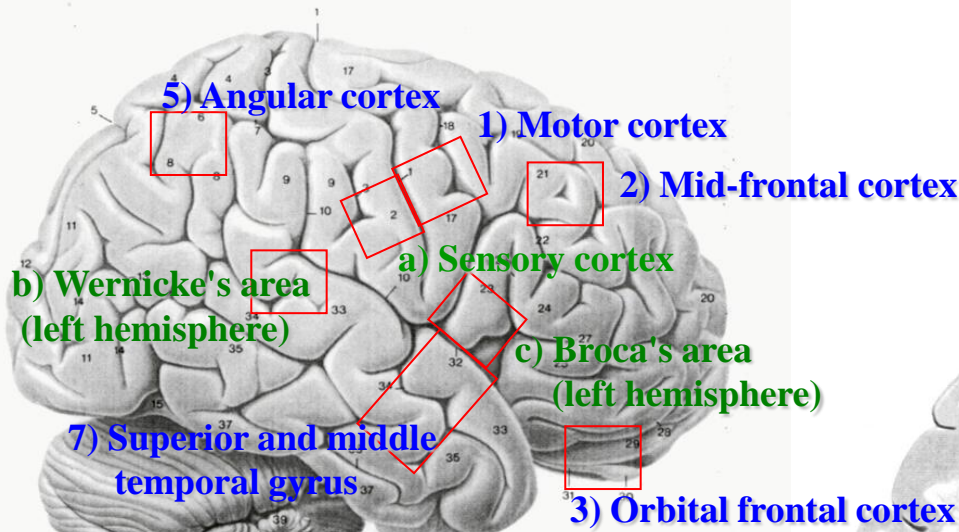
Basic neuroanatomy



Principal cell types of the nervous system

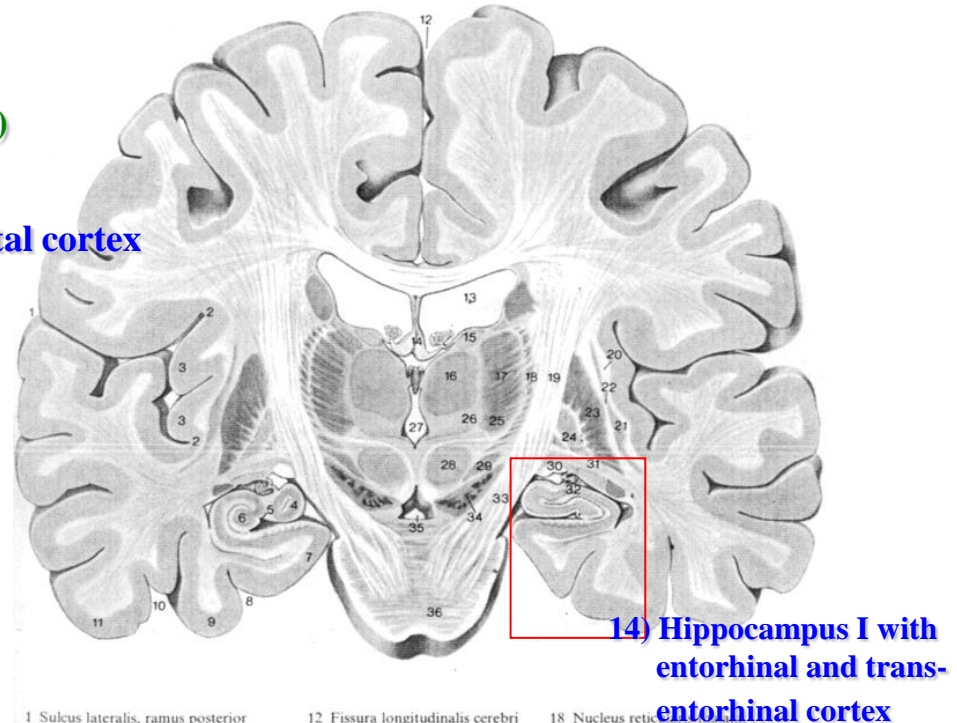
- CNS:
 - Neuron
 - Astrocyte
 - Oligodendrocyte
 - Microglia
- PNS
 - Neuron
 - Schwann cell





- 1 Sulcus centralis
- 2 Gyrus postcentralis
- 3 Sulcus postcentralis
- 4 Lobulus parietalis superior
- 5 Sulcus parieto-occipitalis
- 6 Lobulus parietalis inferior
- 7 Sulcus intraparietalis
- 8 Gyrus angularis
- 9 Gyrus supramarginalis
- 10 Sulcus lateralis, ramus posterior
- 11 Gyri occipitales
- 12 Sulcus lunatus
- 13 Sulcus occipitalis anterior
- 14 Suli occipitales
- 15 Incisura preoccipitalis
- 16 Hemispherium cerebelli
- 17 Gyrus precentralis
- 18 Sulcus precentralis
- 19 Sulcus frontalis superior
- 20 Gyrus frontalis superior
- 21 Gyrus frontalis medius
- 22 Sulcus frontalis inferior
- 23 Pars opercularis
- 24 Pars triangularis } Gyrus frontalis inferior
- 25 Pars orbitalis
- 26 Sulcus lateralis, ramus ascendens
- 27 Sulcus lateralis, ramus anterior
- 28 Sulci orbitales
- 29 Gyri orbitales
- 30 Bulbus olfactorius
- 31 Tractus olfactorius
- 32 Sulcus lateralis
- 33 Gyrus temporalis superior
- 34 Sulcus temporalis superior
- 35 Gyrus temporalis medius
- 36 Sulcus temporalis inferior
- 37 Gyrus temporalis inferior
- 38 Pons
- 39 Flocculus
- 40 Medulla oblongata

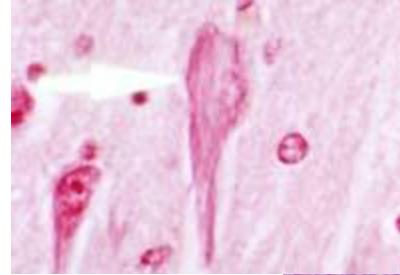
Fig. 7. Lateral view of the brain (1/1 ×)



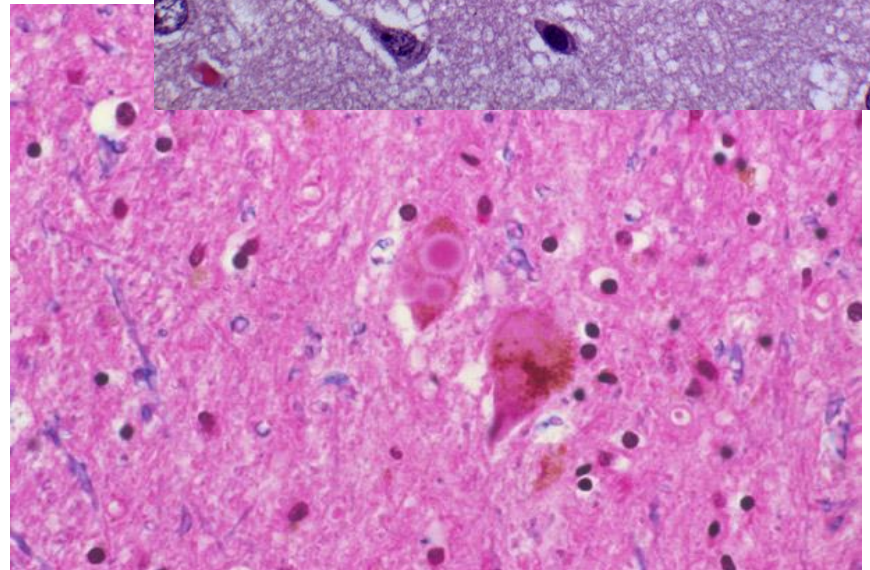
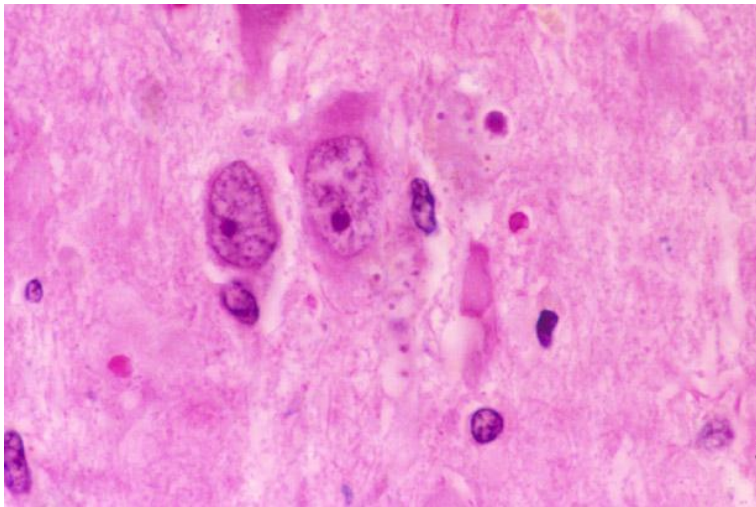
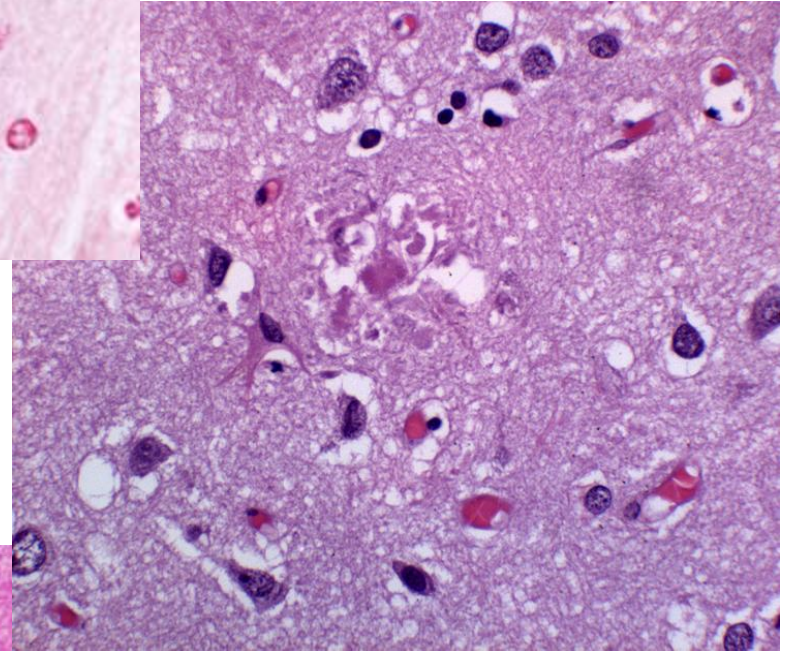
- 1 Sulcus lateralis, ramus posterior
- 2 Sulcus circularis insulae
- 3 Gyrus longus insulae
- 4 Gyrus intralimbicus
- 5 Sulcus hippocampi
- 6 Gyrus dentatus
- 7 Gyrus parahippocampalis
- 8 Sulcus collateralis
- 9 Gyrus occipitotemporalis lateralis
- 10 Sulcus occipitotemporalis
- 11 Gyrus temporalis inferior
- 12 Fissura longitudinalis cerebri
- 13 Ventriculus lateralis, pars centralis
- 14 Corpus fornicis
- 15 Nucleus lateralis dorsalis
- 16 Nucleus medialis thalami
- 17 Nucleus ventralis lateralis
- 18 Nucleus reticularis
- 19 Capsula interna, crus posterius
- 20 Capsula extrema
- 21 Claustrum
- 22 Capsula externa
- 23 Putamen
- 24 Globus pallidus
- 25 Nucleus ventralis posterolateralis
- 26 Nucleus centromedianus
- 27 Ventriculus tertius
- 28 Nucleus ruber
- 29 Nucleus subthalamicus
- 30 Tractus opticus
- 31 Capsula interna, pars sublentiformis
- 32 Plexus choroideus ventriculi lateralis
- 33 Pedunculus cerebri
- 34 Substantia nigra
- 35 Fossa interpeduncularis
- 36 Pons

Fig. 67. Section through the thalamus, the cerebral peduncle and the pons (6/5 ×)

What can we see on H&E stains?



- Some tangles, neuritic dystrophy
- Granulovacuolar degeneration
- Some Lewy bodies
- Pick bodies



Neuropathologic Diagnosis of Dementias

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composed predominantly of:

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3R/4R-tau

Pick bodies
3R-tau

Neuronal/glia
inclusions
4R-tau

Ubiquitinated
Inclusions
TDP43+

α -synuclein
inclusions

Other
NFID, DLBD

+ senile plaques

No senile plaques

AD
AD+LBD

AGD*
FTDP-17

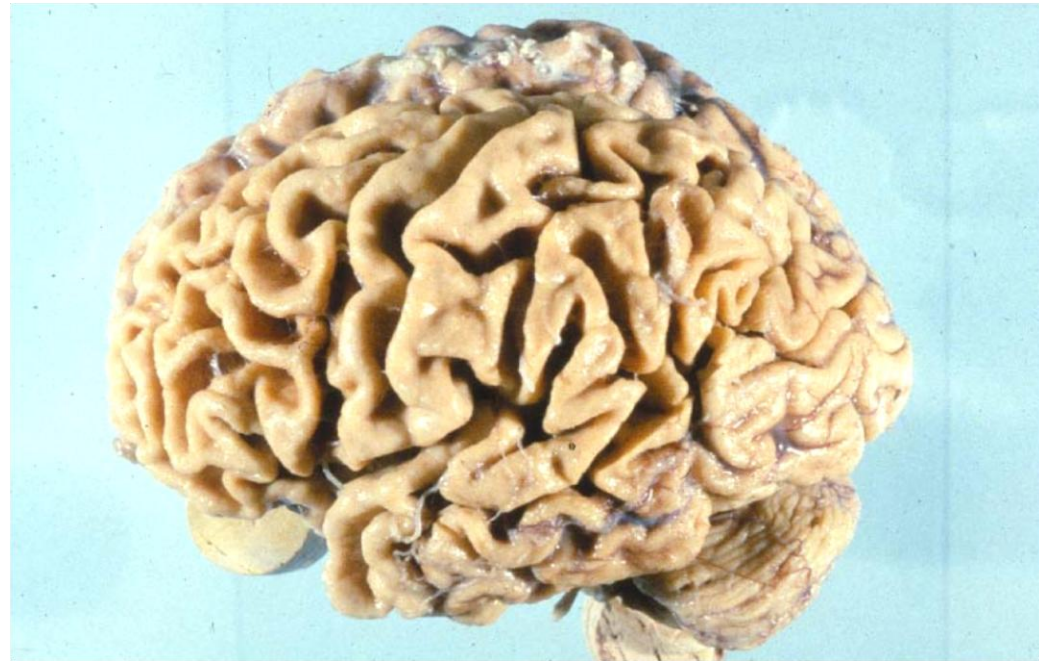
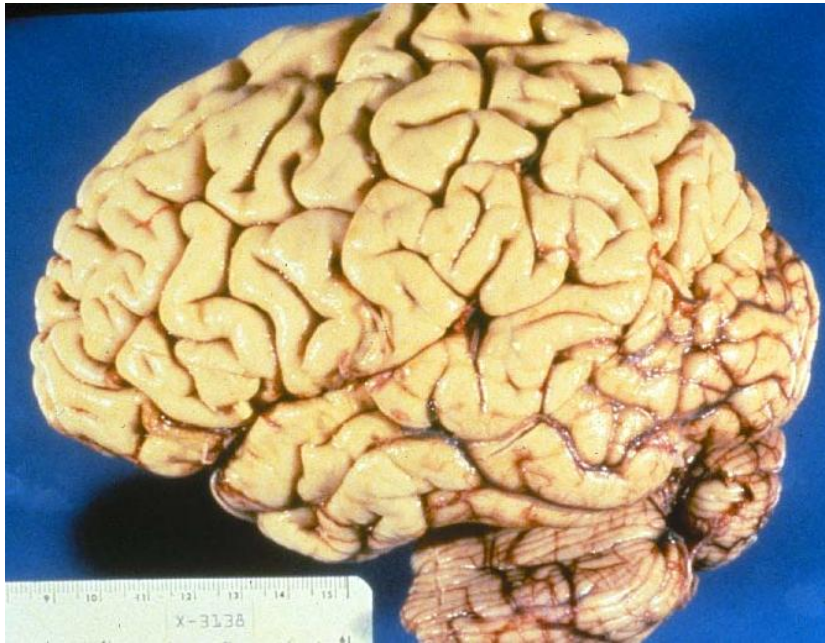
PiD
FTDP-17

CBD
PSP
FTDP-17

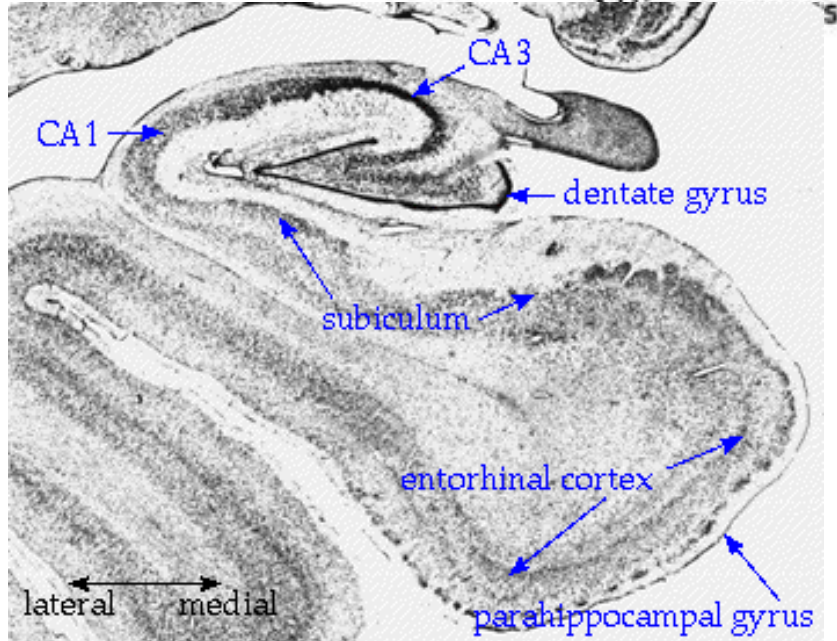
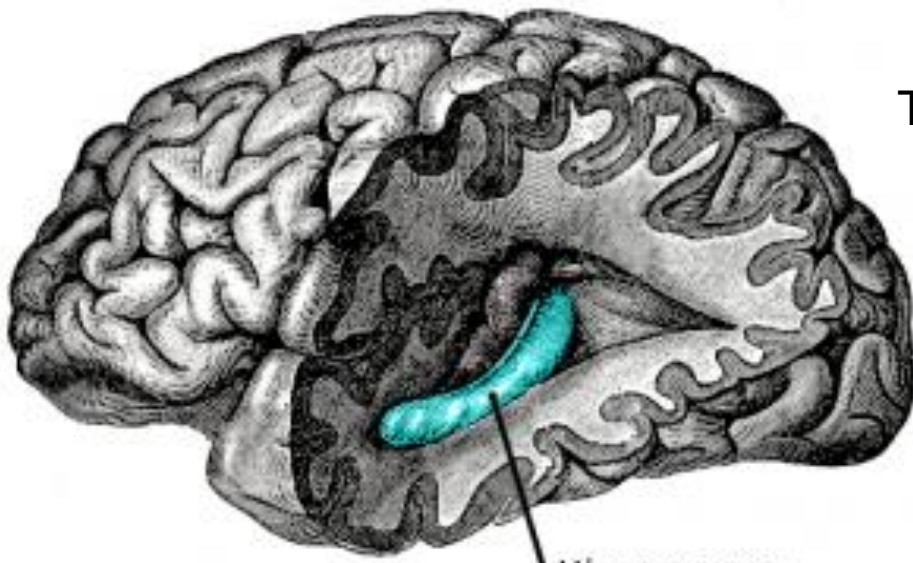
FTD
+/- MND

PD
DLB
MSA

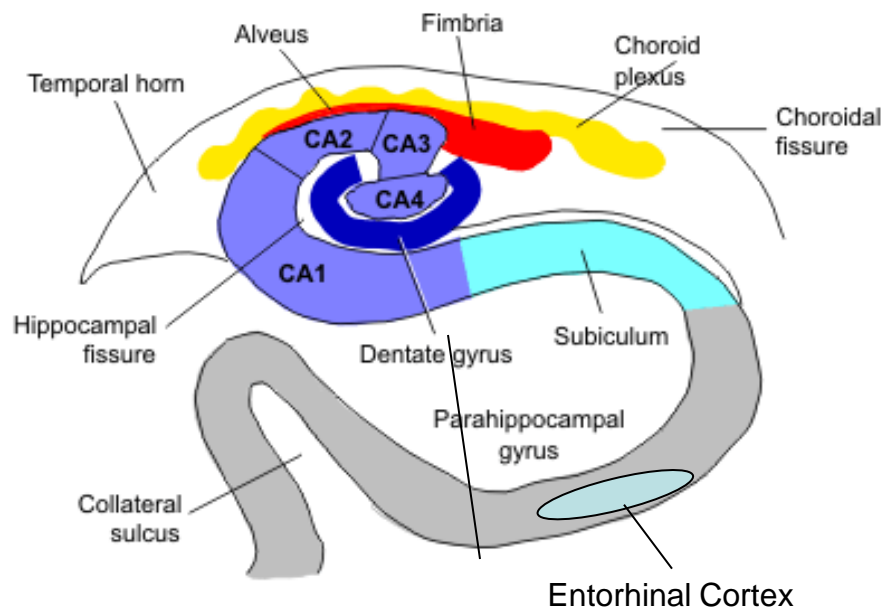
Alzheimer's disease

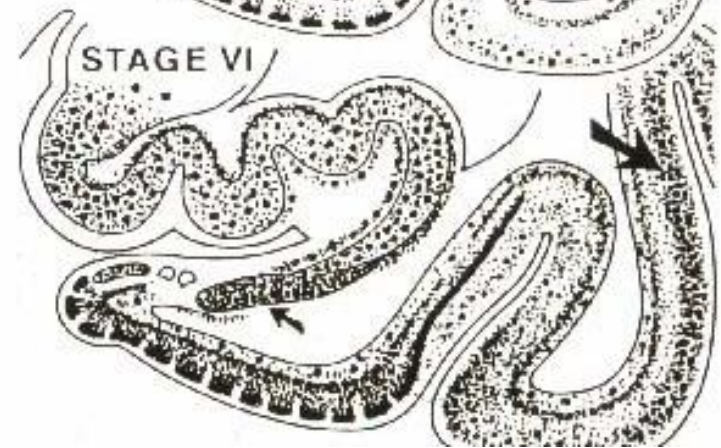
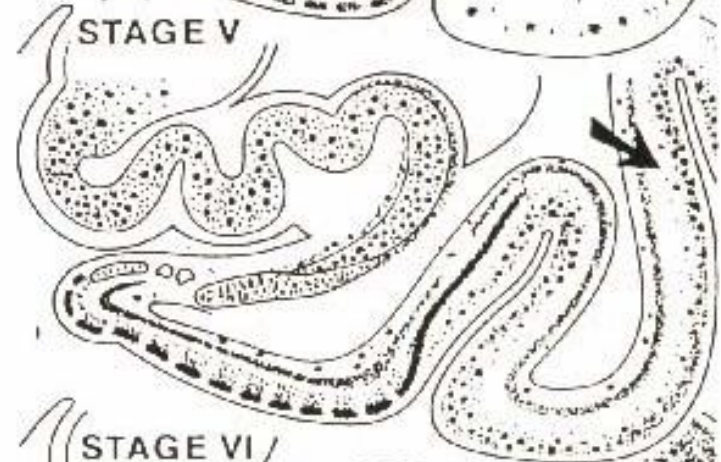
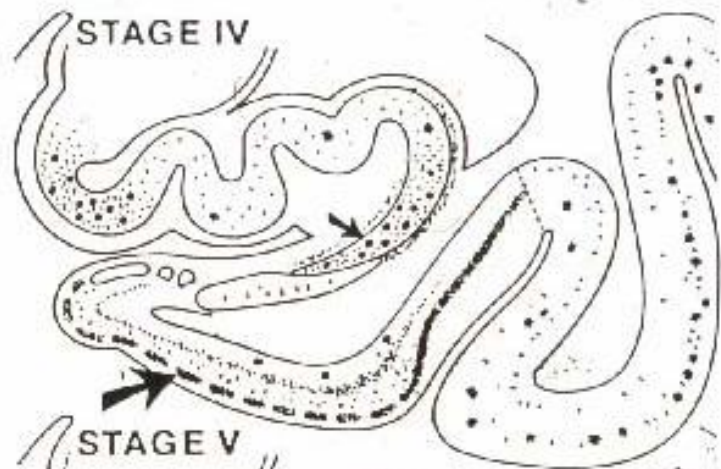
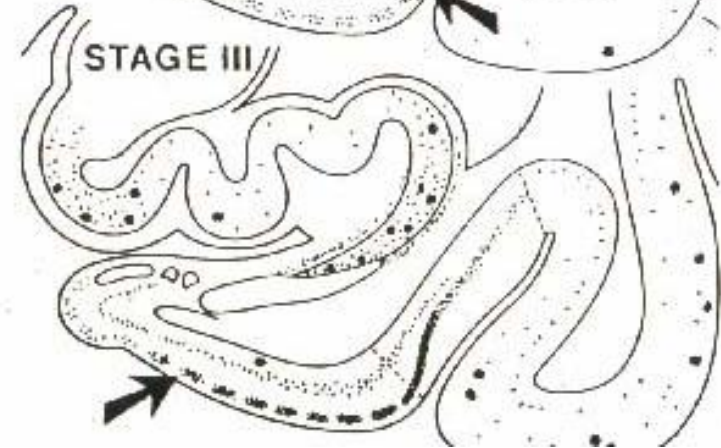
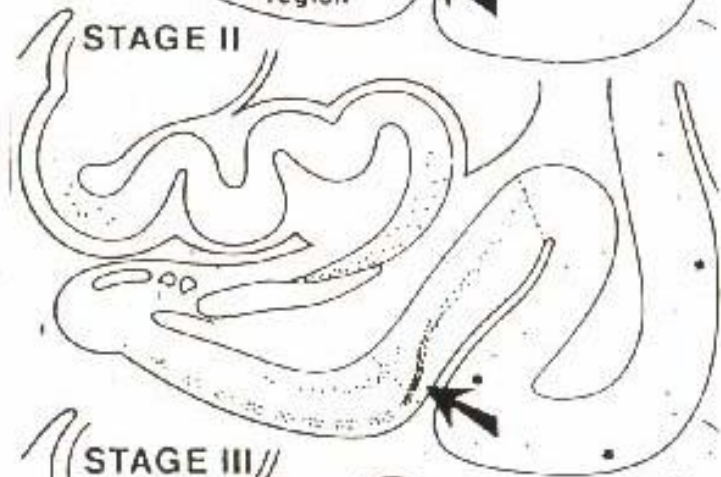
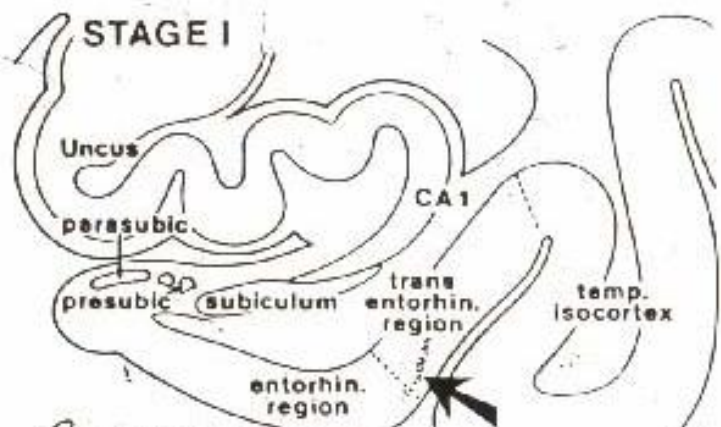


Tangles predictive of AD progression



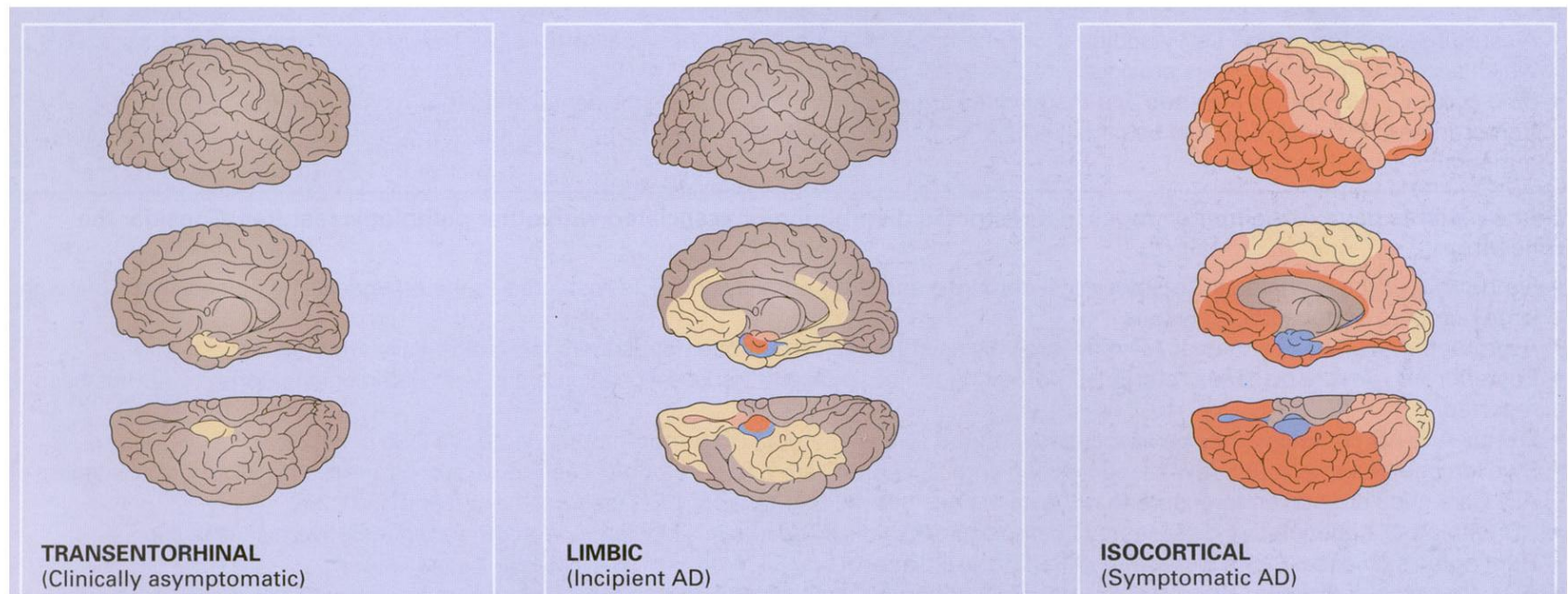
Hippocampal Anatomy





Alzheimer's Disease

Braak & Braak staging of NFTs

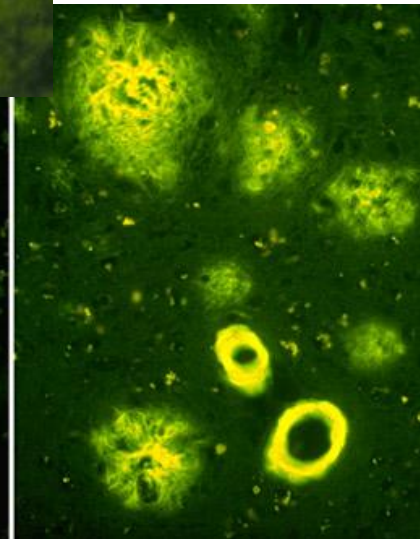
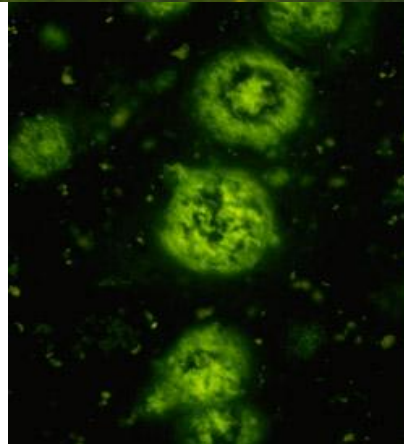
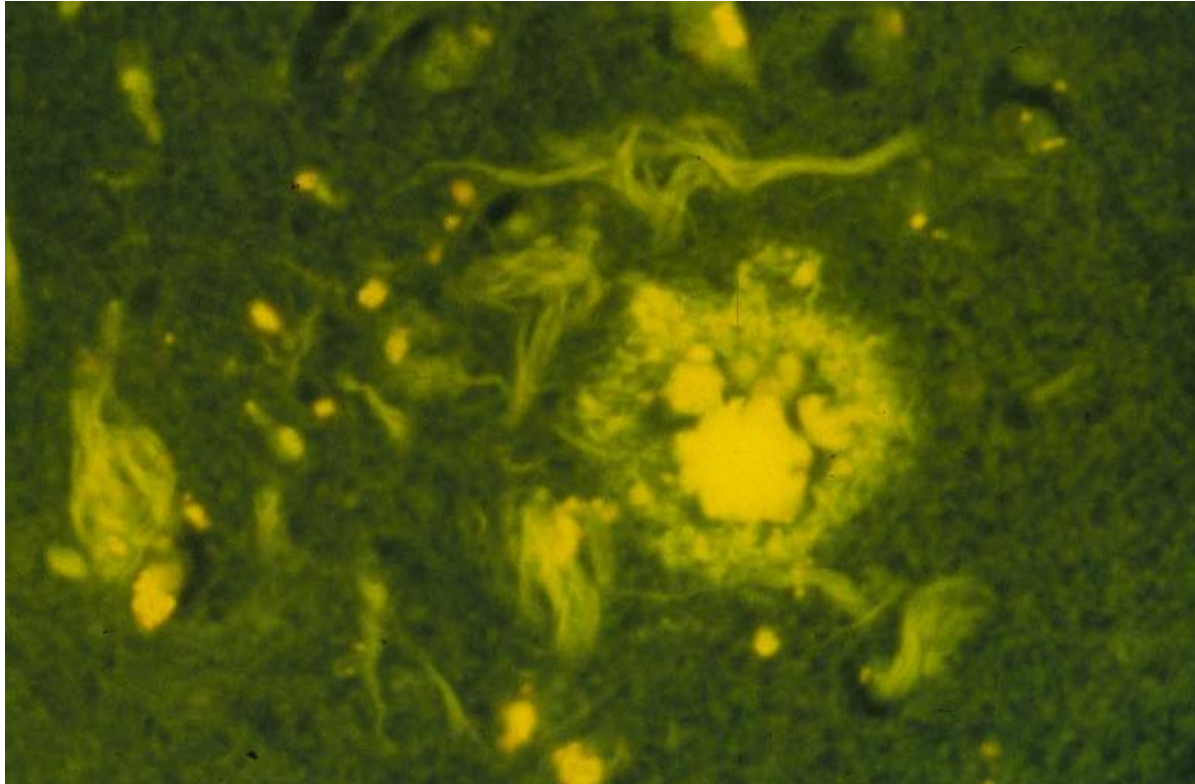


I-II

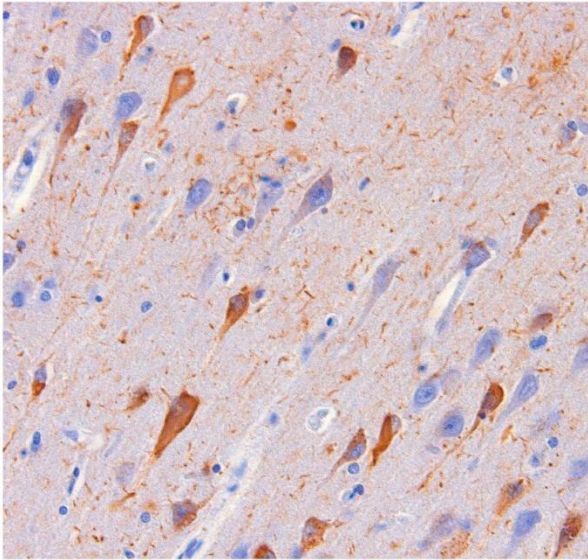
III-IV

V-VI

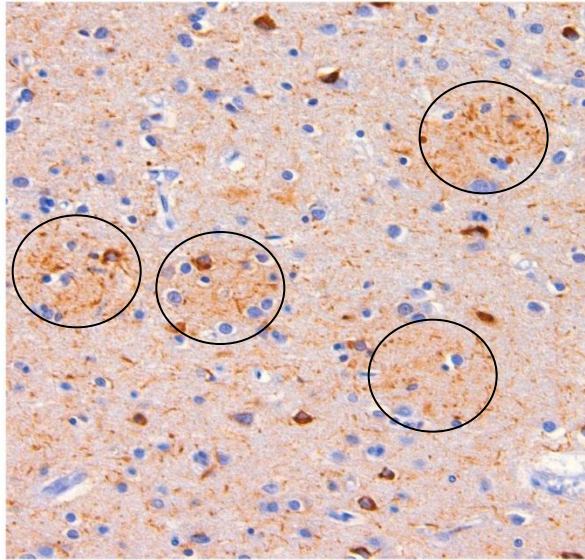
Thioflavin stains



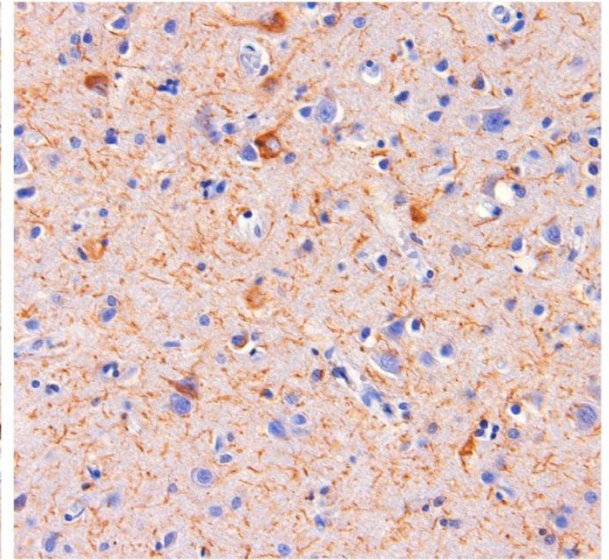
Tau pathology



Neurofibrillary tangles

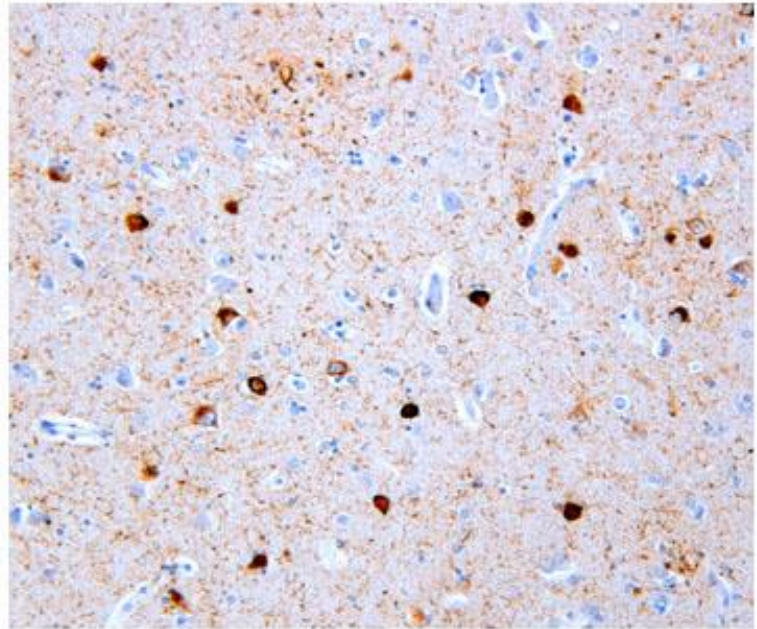
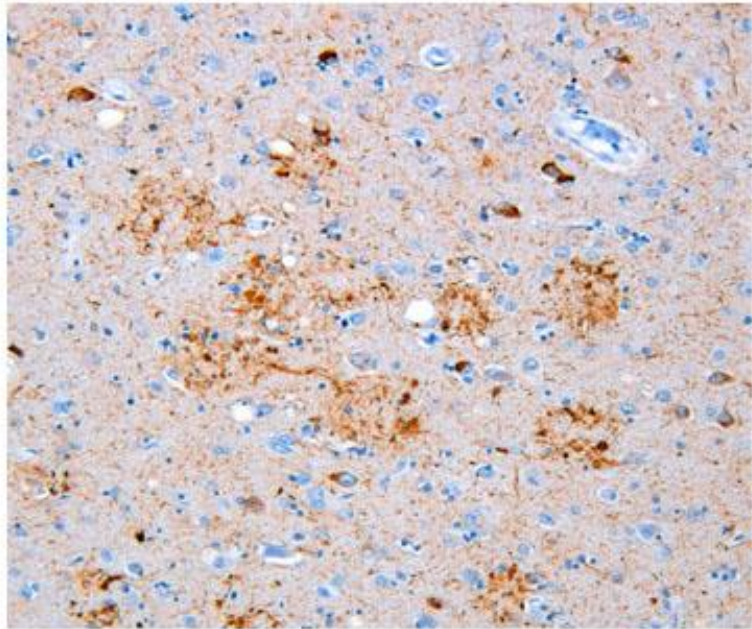


Neuritic plaques

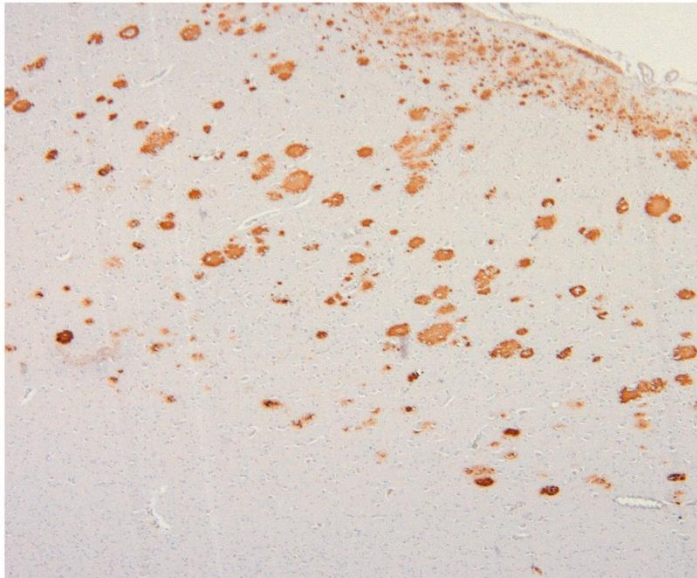


Neuropil threads

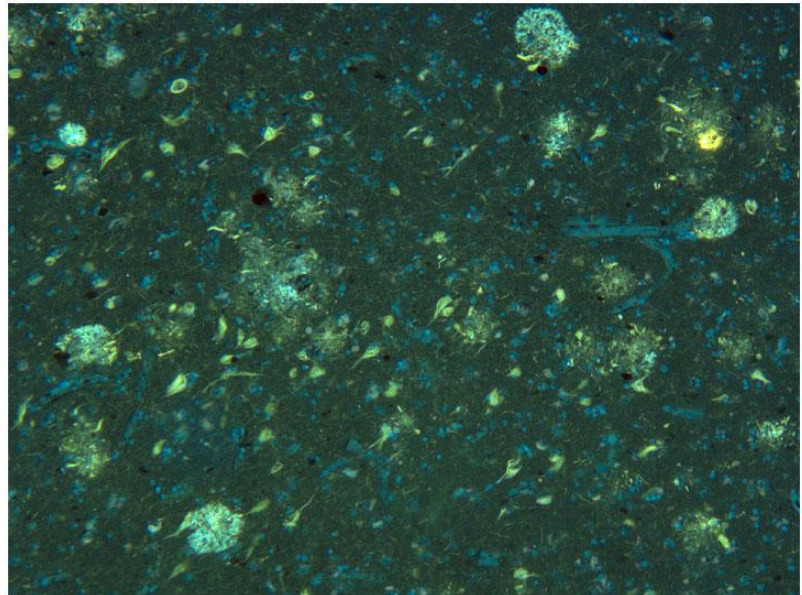
Tau immunostain



Abeta immunostain



Thioflavin



Neuropathologic Diagnosis of Dementias

Tau positive inclusions -
composed predominantly of:

NFTs
3R/4R-tau

Pick bodies
3R-tau

Neuronal/glia
inclusions
4R-tau

Ubiquitinated
Inclusions
TDP43+

α -synuclein
inclusions

Other
NFID, DLHD

+ senile plaques

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AGD*
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CBD
PSP
FTDP-17

FTD
+/- MND

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DLB
MSA

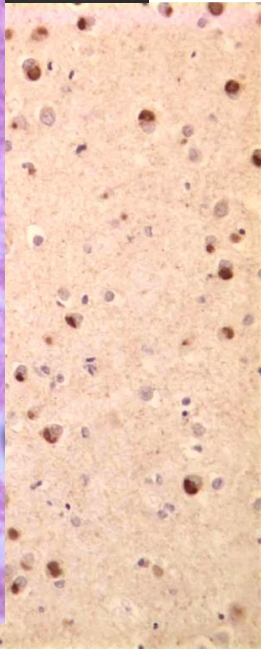
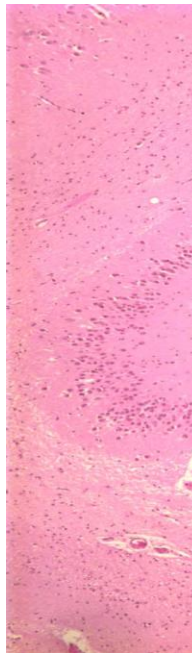
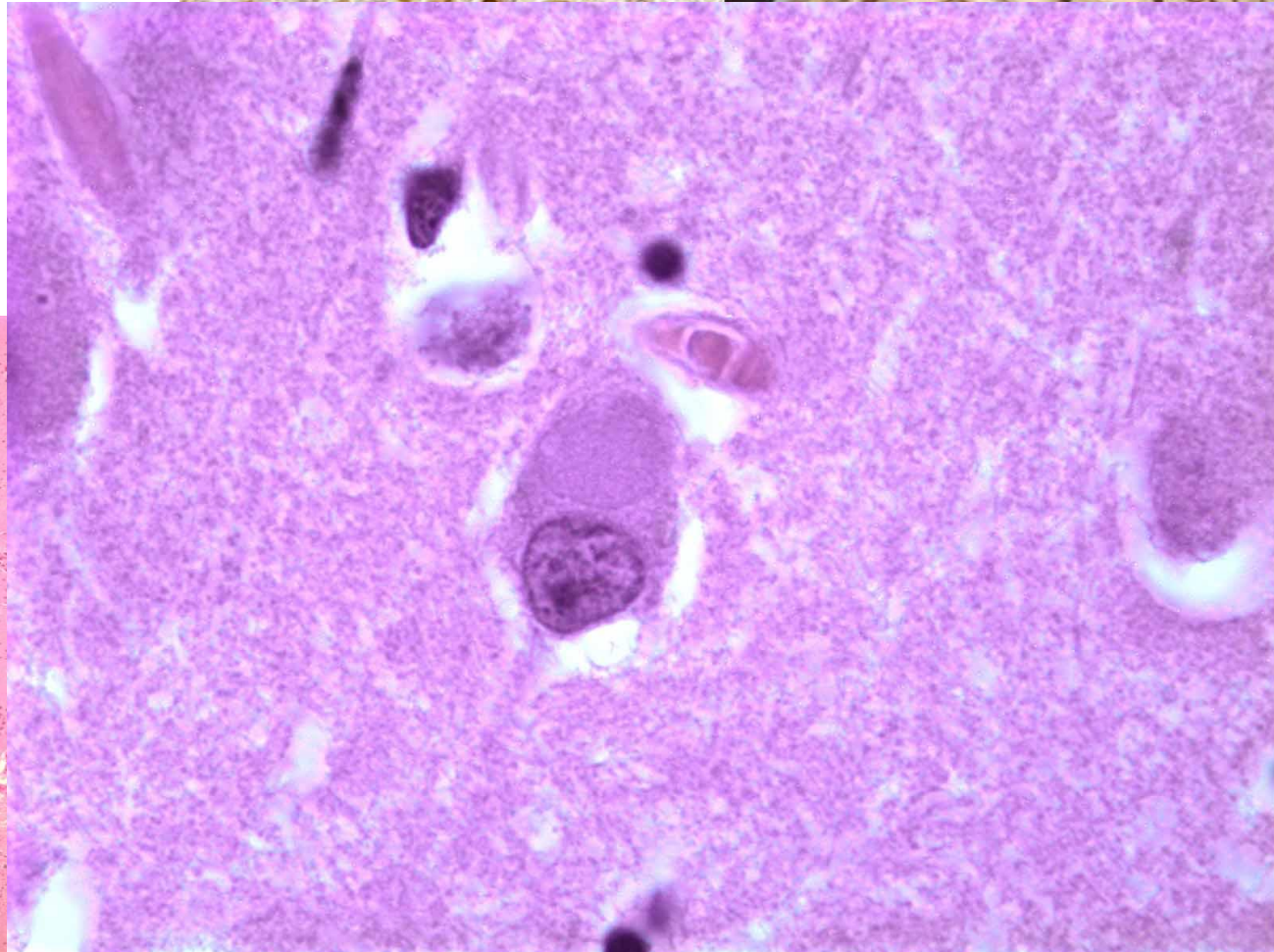
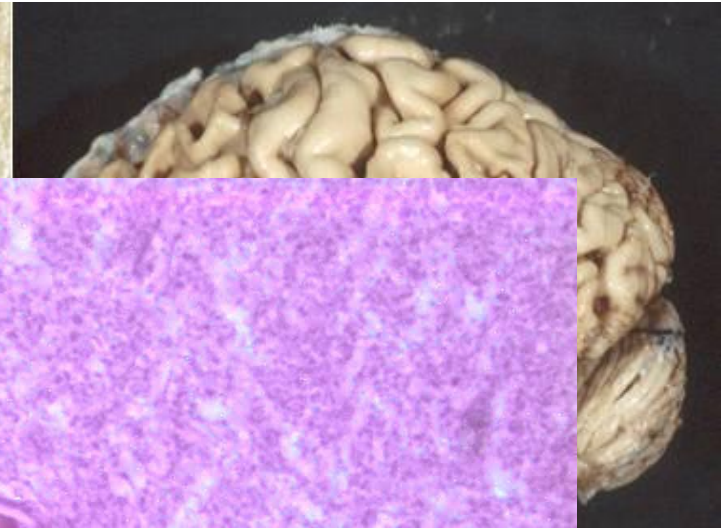
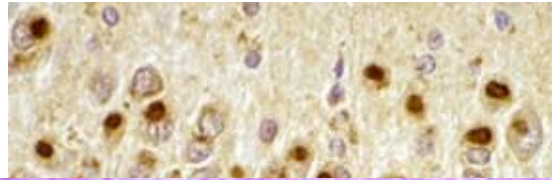
“other”
tauopathies

AD v/s Frontotemporal dementia

- Memory loss v/s 'bizarre' symptoms

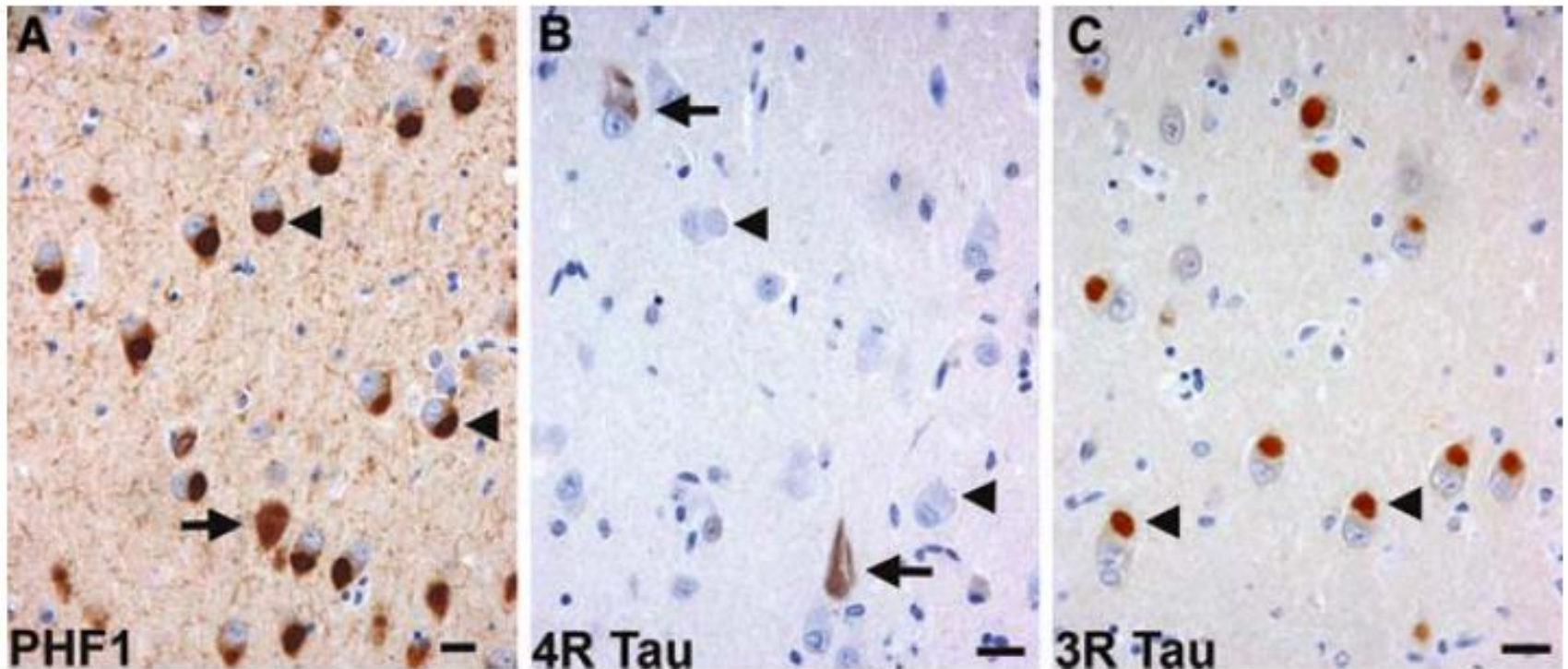
“Other tauopathies”- Pick’s disease

- Tau positive “Pick bodies”



Picks case

Predominantly 3R tau present!



Acta Neuropathol (2007) 114:5–22
DOI 10.1007/s00401-007-0237-2

CONSENSUS PAPER

Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration

Nigel J. Cairns · Eileen H. Bigio · Ian R. A. Mackenzie · Manuela Neumann · Virginia M. -Y. Lee ·
Kimmo J. Hatanpää · Charles L. White III · Julie A. Schneider · Lea Tenenholz Grinberg · Glenda Hall

“Other tauopathies”- Corticobasilar degeneration (CBD) and Progressive Supranuclear Palsy (PSP)

Clinical: rigidity, speech disorder (apraxia, aphasia),

CBD (more cortical pathology):

- 1) Tau + “coiled bodies” in white matter
- 2) Tau + “thread pathology” in white matter
- 3) Tau + “pre-tangles” in cortex
- 4) Tau + “astrocytic plaques” in cortex

PSP (less/no cortical pathology):

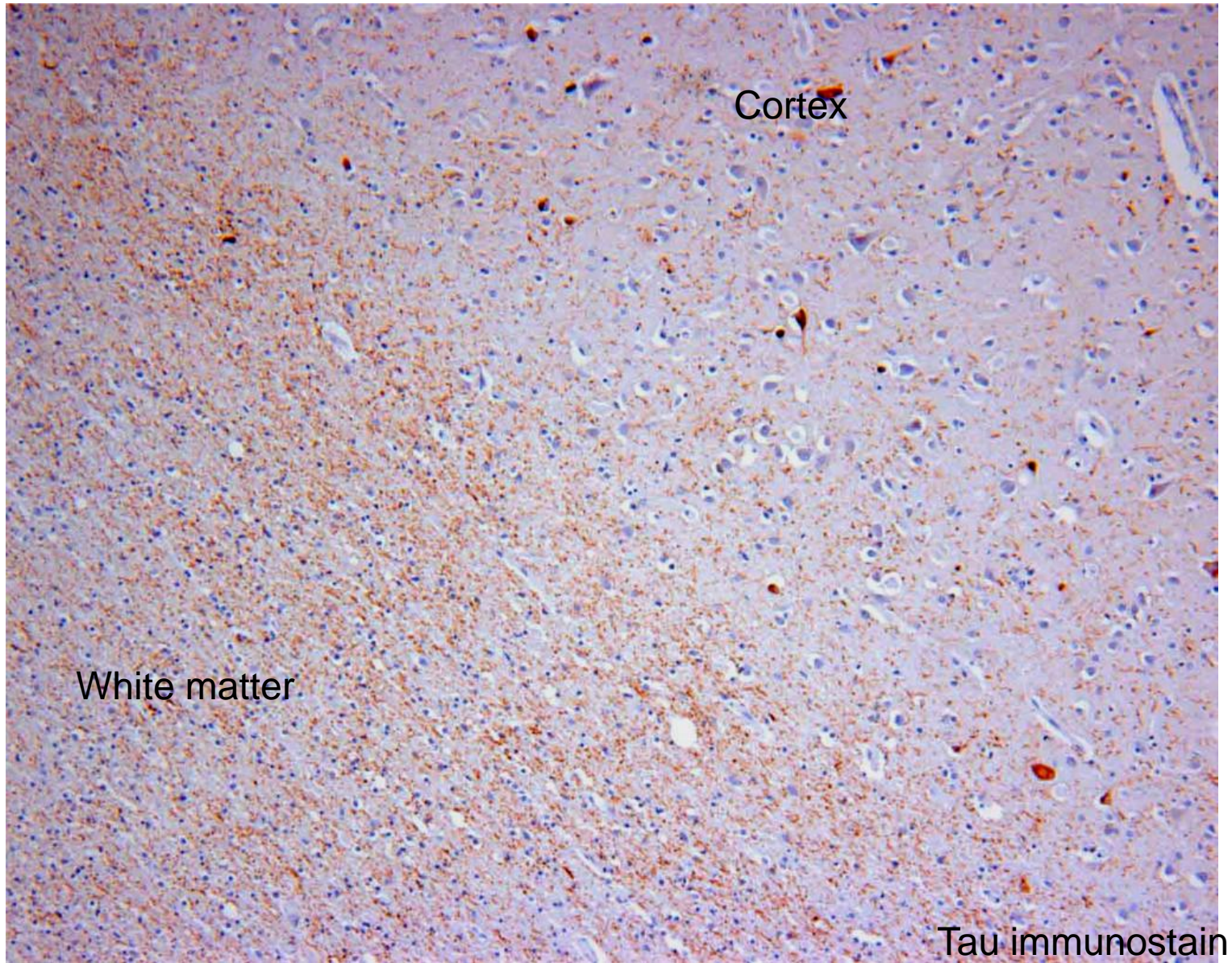
- 1) Tau + “globose tangles” in brainstem nuclei
- 2) Tau + “tufted astrocytes” in peri-Rolandic cortex and striatum

Office of Rare Diseases Neuropathologic Criteria for Corticobasal Degeneration

D. W. DICKSON, MD, C. BERGERON, MD, S. S. CHIN, MD, PHD, C. DUYNCKAERTS, MD, D. HOROUPIAN, MD, K. IKEDA, MD, K. JELLINGER, MD, PHD, P. L. LANTOS, MD, PHD, C. F. LIPPA, MD, S. S. MIRRA, MD, M. TABATON, MD, J. P. VONSATTEL, MD, K. WAKABAYASHI, MD, AND I. LITVAN, MD

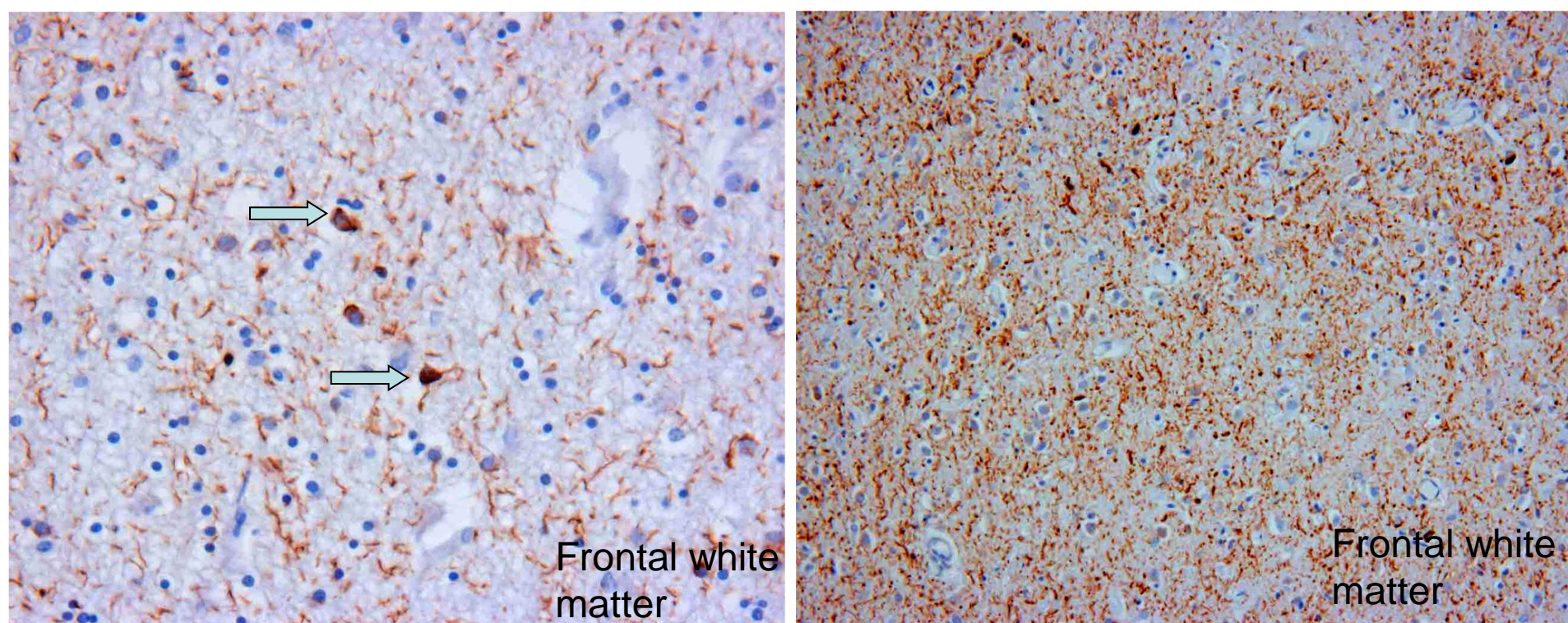
Abstract. A working group supported by the Office of Rare Diseases of the National Institutes of Health formulated neuropathologic criteria for corticobasal degeneration (CBD) that were subsequently validated by an independent group of neuropathologists. The criteria do not require a specific clinical phenotype, since CBD can have diverse clinical presentations, such as progressive asymmetrical rigidity and apraxia, progressive aphasia, or frontal lobe dementia. Cortical atrophy, ballooned neurons, and degeneration of the substantia nigra have been emphasized in previous descriptions and are present in

CBD (a low-power diagnosis!)



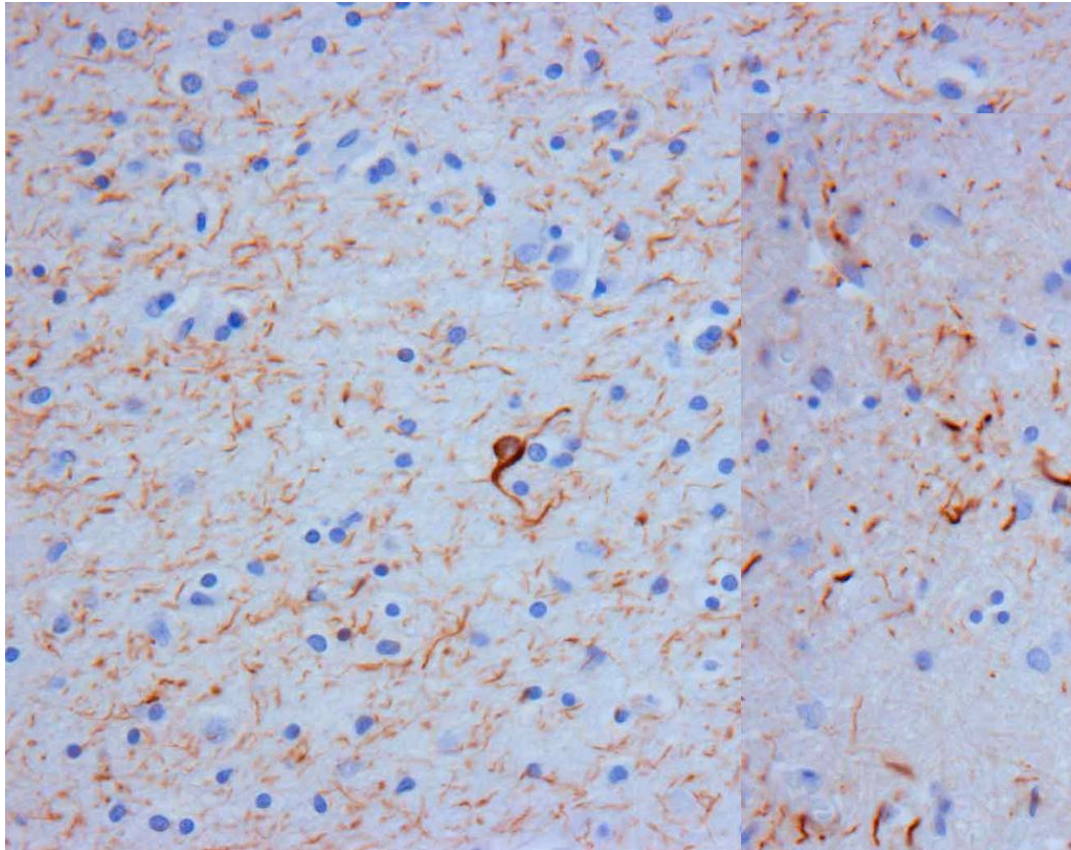
CBD case

CBD

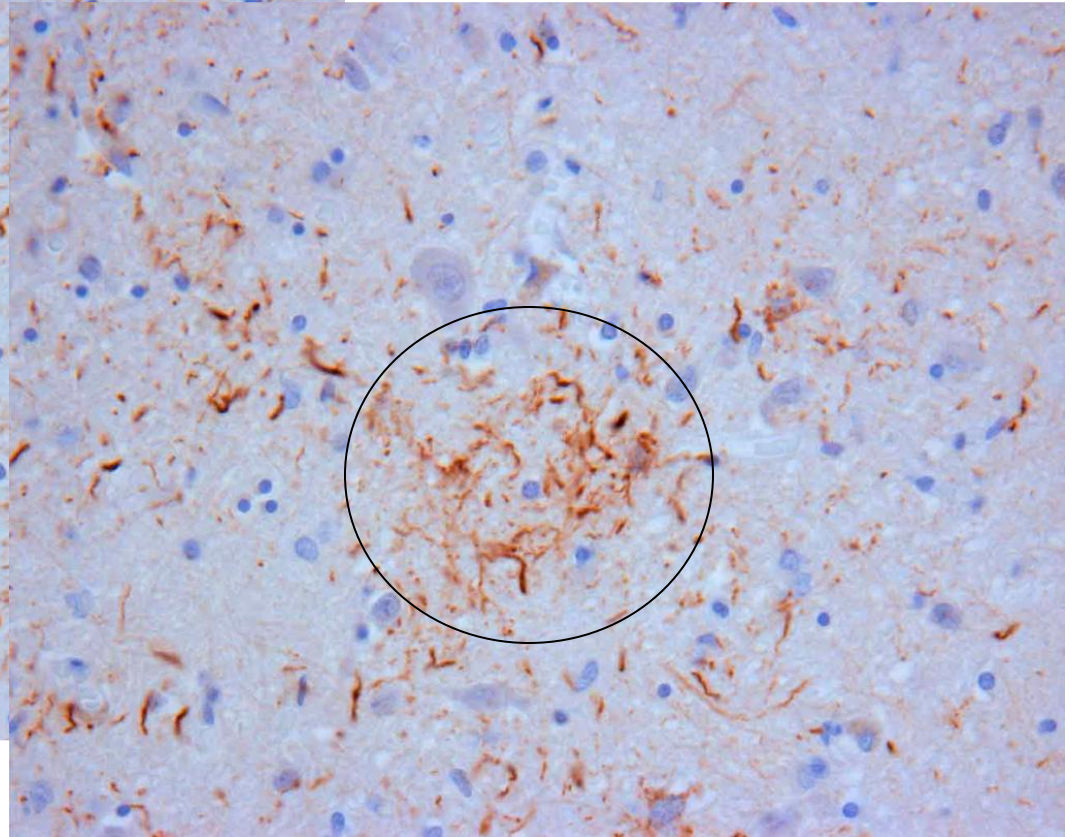


Extensive tau pathology in white matter, arrows show “coiled bodies”

CBD

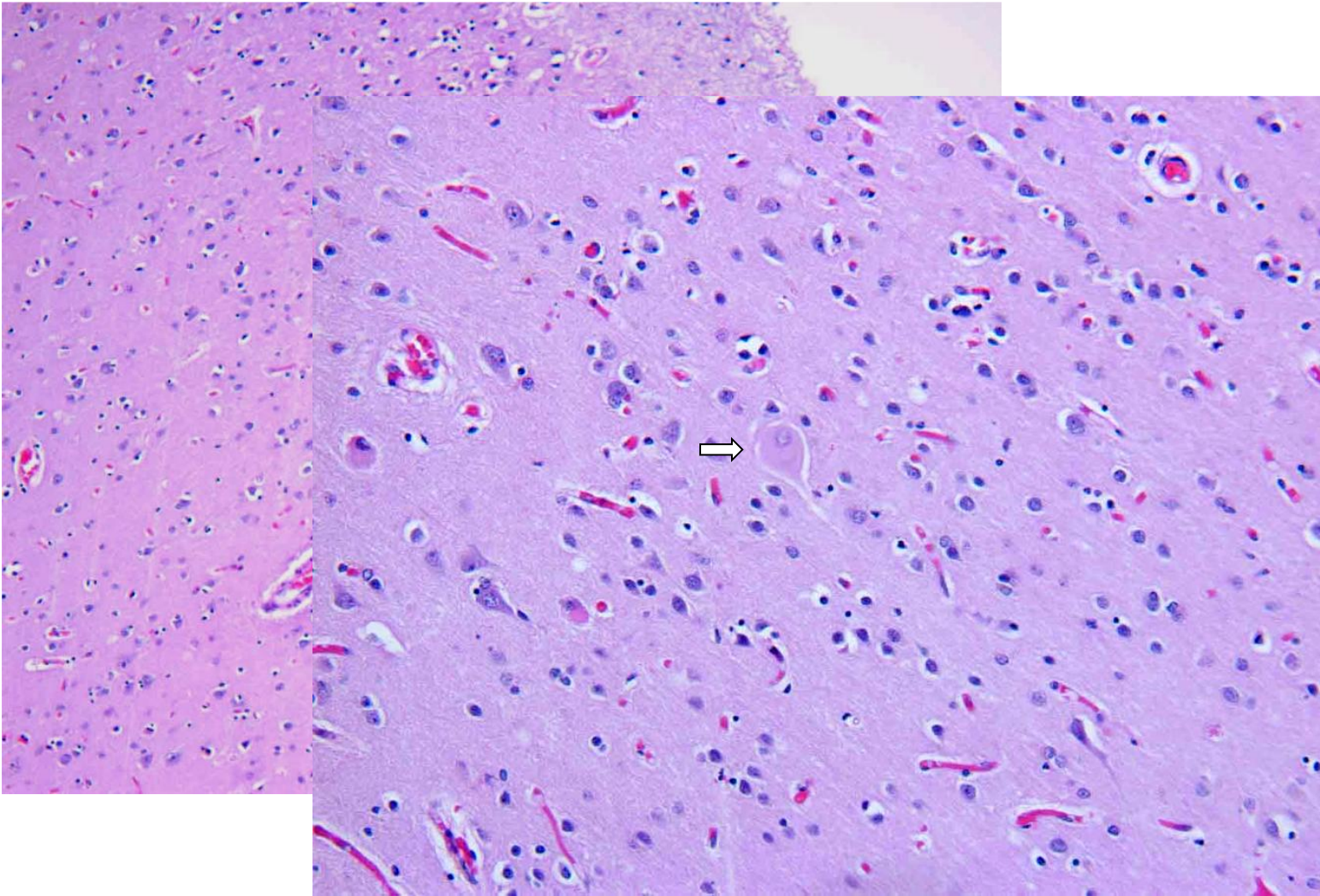


“Coiled bodies”



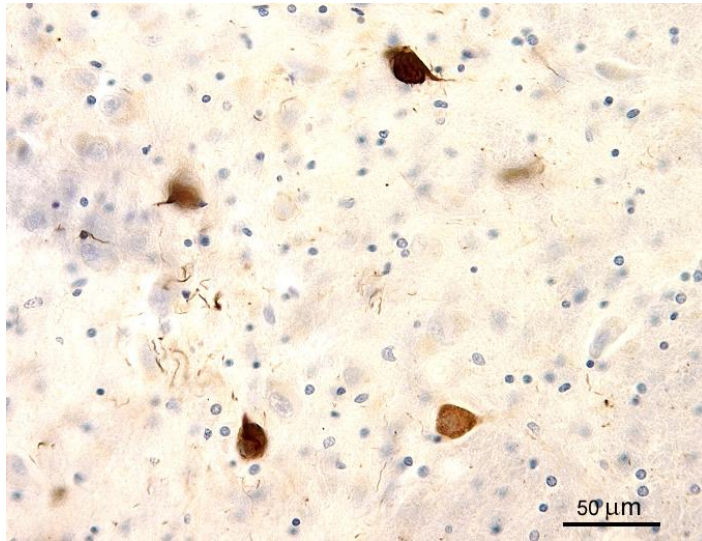
“Astrocytic plaques”

Frontal gliosis and neuronal loss

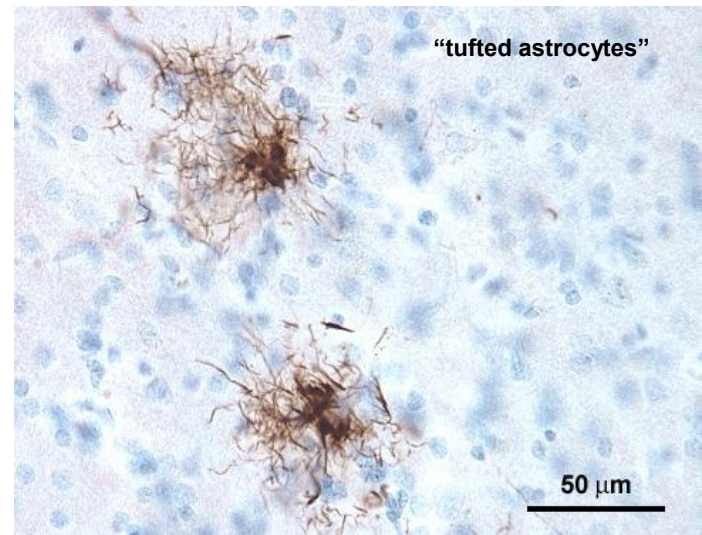


“Ballooned” neuron in frontal cortex

“Other tauopathy”- PSP



Pons- tau immunostain



Striatum- tau immunostain

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3R-tau

Neuronal/glial
inclusions
4R-tau

Ubiquitinated
Inclusions
TDP43+

α -synuclein
inclusions

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AD+LBD

AGD*
FTDP-17

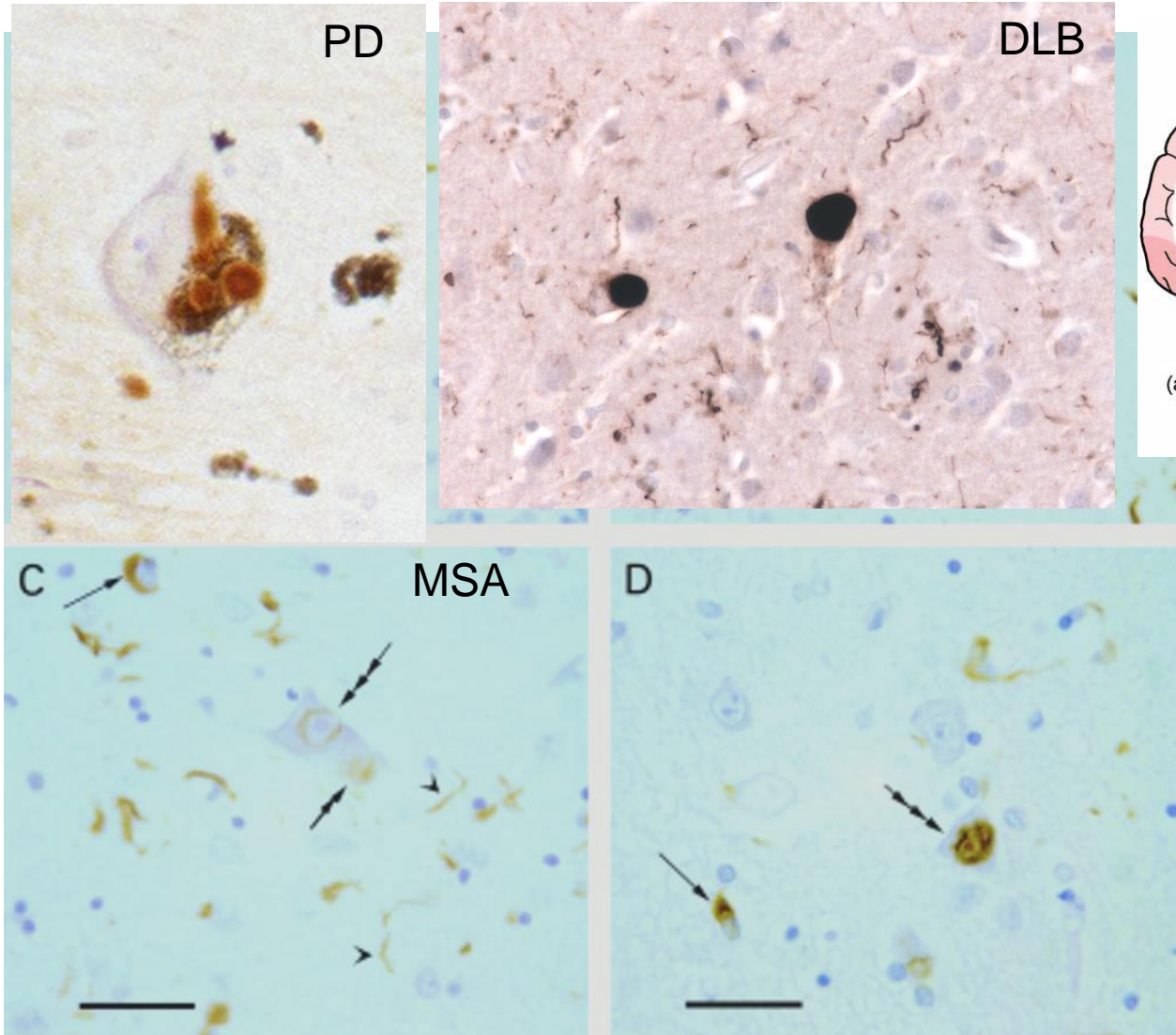
PiD
FTDP-17

CBD
PSP
FTDP-17

FTD
+/- MND

PD
DLB
MSA

Alpha-synuclein and “Lewy body” diseases



Neuropathologic Diagnosis of Dementias

Tau positive inclusions -
composed predominantly of:

Absence of **tau** positive inclusions

NFTs
3R/4R-tau

Pick bodies
3R-tau

Neuronal/glial
inclusions
4R-tau

Ubiquitinated
Inclusions
TDP43+

α -synuclein
inclusions

Other
NFID, DLBH

+ senile plaques

No senile plaques

AD
AD+LBD

AGD*
FTDP-17

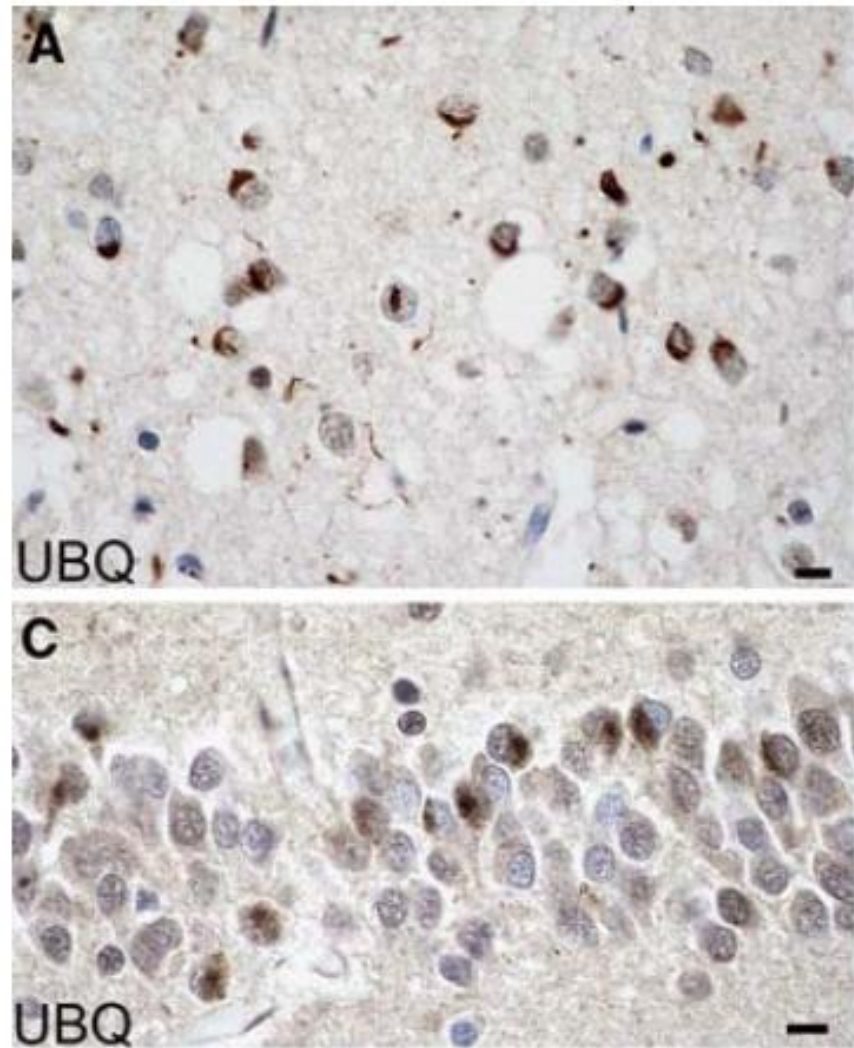
PiD
FTDP-17

CBD
PSP
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FTD
+/- MND

PD
DLB
MSA

Story of TDP-43: a first-hand perspective



Formerly “FTD-U”

Neuropathologic Diagnosis of Dementias

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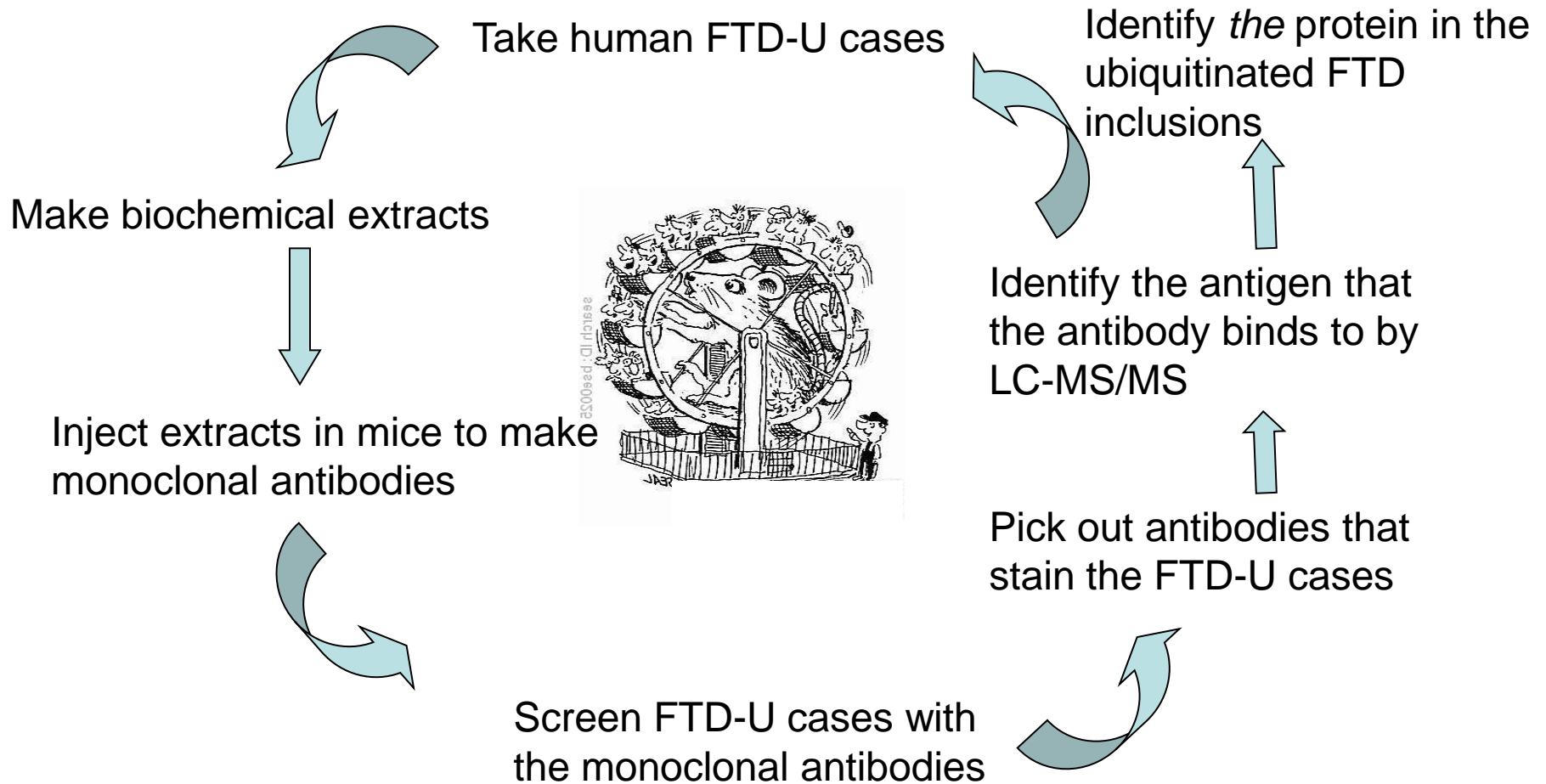
PiD
FTDP-17

CBD
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FTD
+/- MND

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MSA

Story of TDP-43: a first-hand perspective



Story of TDP-43: a personal perspective

REPORTS

Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

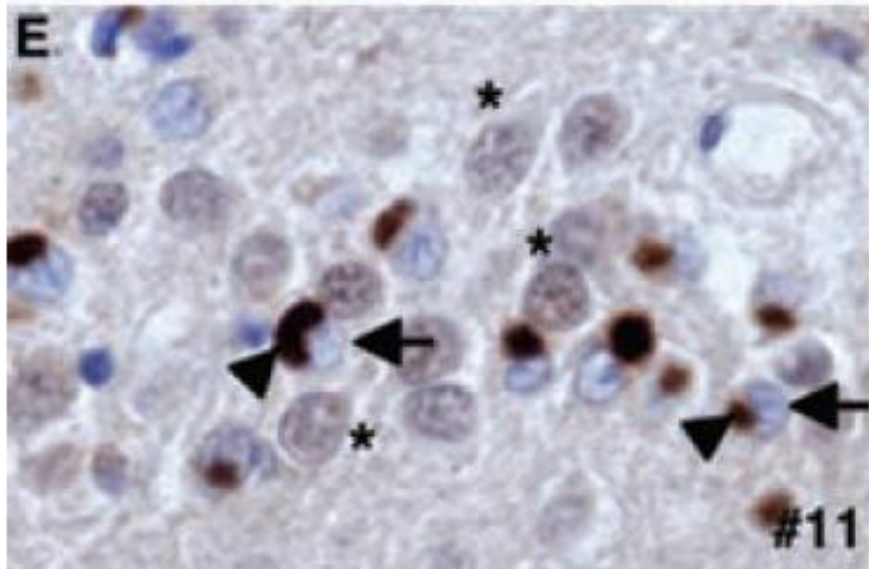
Manuela Neumann,^{1,11*} Deepak M. Sampathu,^{1*} Linda K. Kwong,^{1*} Adam C. Truax,¹ Matthew C. Micsenyi,¹ Thomas T. Chou,² Jennifer Bruce,¹ Theresa Schuck,¹ Murray Grossman,^{3,4} Christopher M. Clark,^{3,4} Leo F. McCluskey,³ Bruce L. Miller,⁶ Eliezer Masliah,⁷ Ian R. Mackenzie,⁸ Howard Feldman,⁹ Wolfgang Feiden,¹⁰ Hans A. Kretschmar,¹¹ John Q. Trojanowski,^{1,4,5} Virginia M.-Y. Lee^{1,4,5†}

Ubiquitin-positive, tau- and α -synuclein-negative inclusions are hallmarks of frontotemporal lobar degeneration with ubiquitin-positive inclusions and amyotrophic lateral sclerosis. Although the identity of the ubiquitinated protein specific to either disorder was unknown, we showed that TDP-43 is the major disease protein in both disorders. Pathologic TDP-43 was hyper-

different manifestations of the same neurodegenerative disorder.

More than 30% of FTDs are familial, and many kindreds show linkage to chromosome 17 (6, 11, 12). However, FTD with parkinsonism linked to chromosome 17 (FTDP-17) usually shows tau pathology caused by pathogenic mutations in the microtubule-associated protein tau gene (*MAPT*) (13, 14), FTDP-17T, but several FTDP-17 families are characterized by UBIs (FTDP-17U) without *MAPT* mutations (15–17). Recently, mutations in the progranulin gene (*PGRN*) were shown to be pathogenic for FTDP-17U (11, 12). Because *PGRN* is not incorporated into UBIs in FTDP-17U (11, 12), the FTLD-U disease protein remains to be identified.

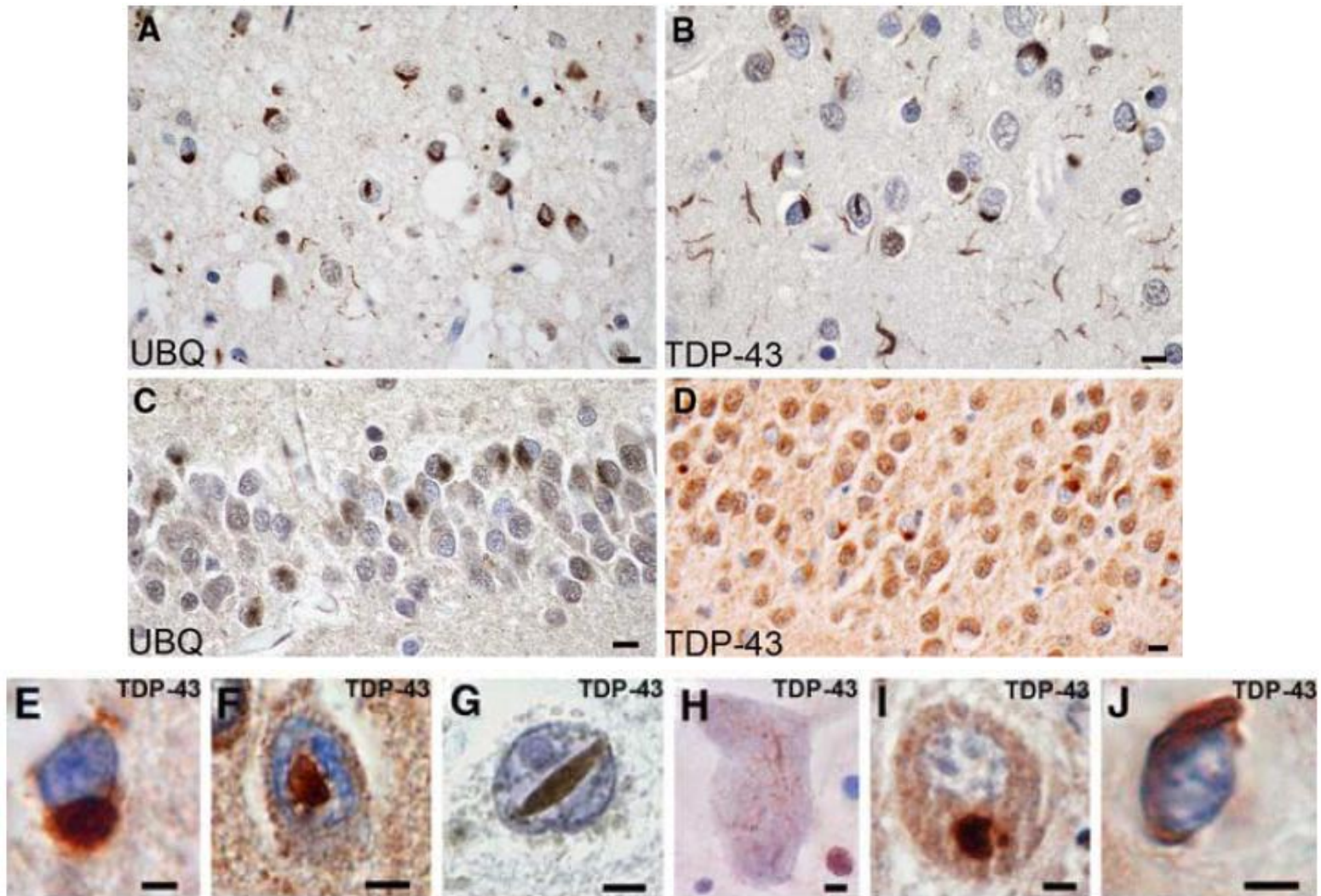
On the basis of immunohistochemistry with



PubMed citations of “TDP-43”:
>1000

Science 314, 130 (2006);

Adjacent sections stained with Ubiquitin and TDP-43



Acta Neuropathol (2007) 114:5–22
DOI 10.1007/s00401-007-0237-2

CONSENSUS PAPER

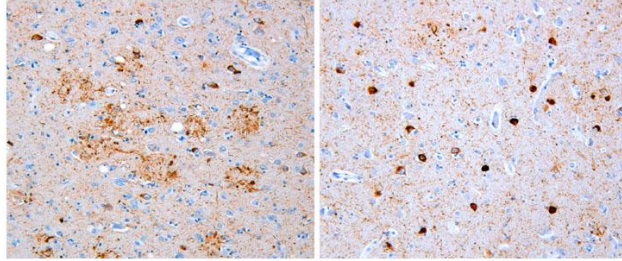
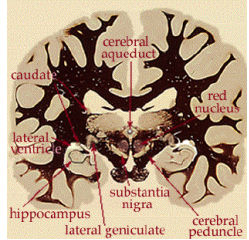
Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration

Nigel J. Cairns · Eileen H. Bigio · Ian R. A. Mackenzie · Manuela Neumann · Virginia M. -Y. Lee · Kimmo J. Hatanpää · Charles L. White III · Julie A. Schneider · Lea Tenenholz Grünberg · Glenda Hall

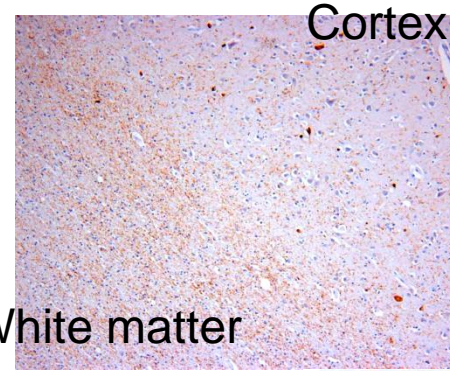
QUIZ

TAU + α -SYNUCLEIN

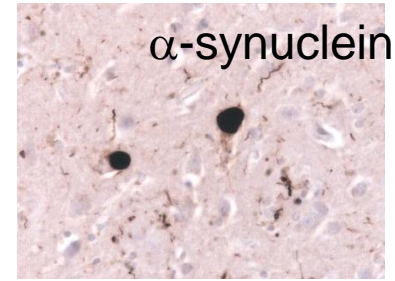
FRONTAL/TEMPORAL



= AD Braak V-VI

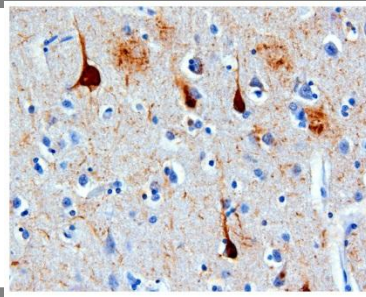
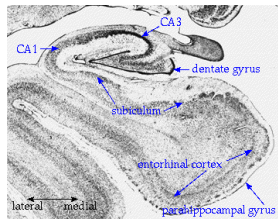


White matter

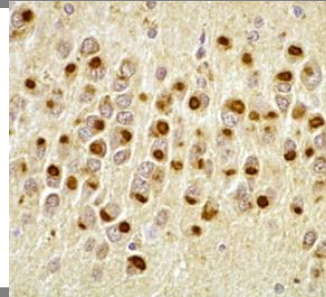


= DLB

HIPP

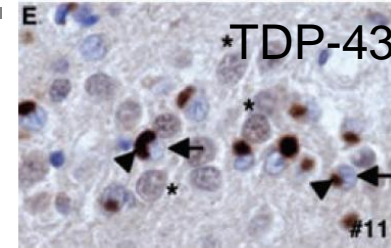


= AD Braak II-IV



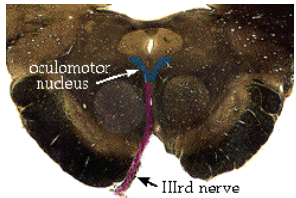
= Pick's disease

= CBD

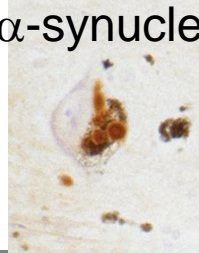


= FTD-TDP-43

MIDBRAIN

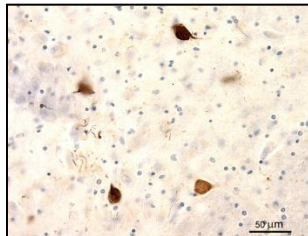
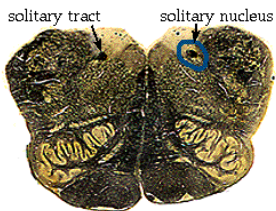


α -synuclein



= PD

PONS/MEDULLA



= PSP

6 sections, 2 immunostains

Neuropathologic Diagnosis of Dementias

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"Sorting through the
nomenclature quagmire of
neurodegenerative diseases using
neuropathology"

Alzheimer's Disease Centers

- Clinical core – patient follow-up
- Administrative/education core
- Neuropathology core

Brain → Dissected, ½ fixed, half stored in formalin → Tissue sections from fixed brains → Slides H&E and immunostains (tau, amyloid beta, synuclein) → Final diagnosis to patient family

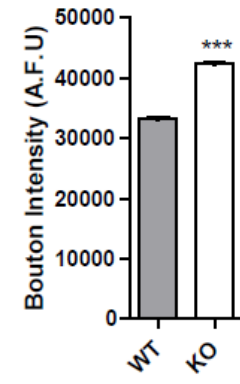
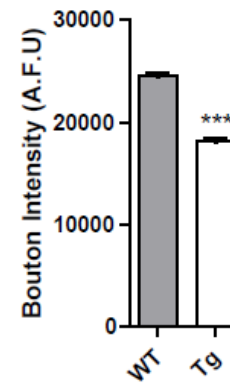
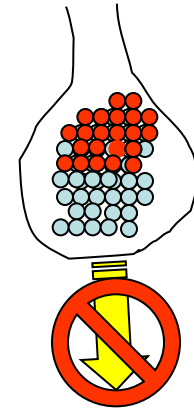
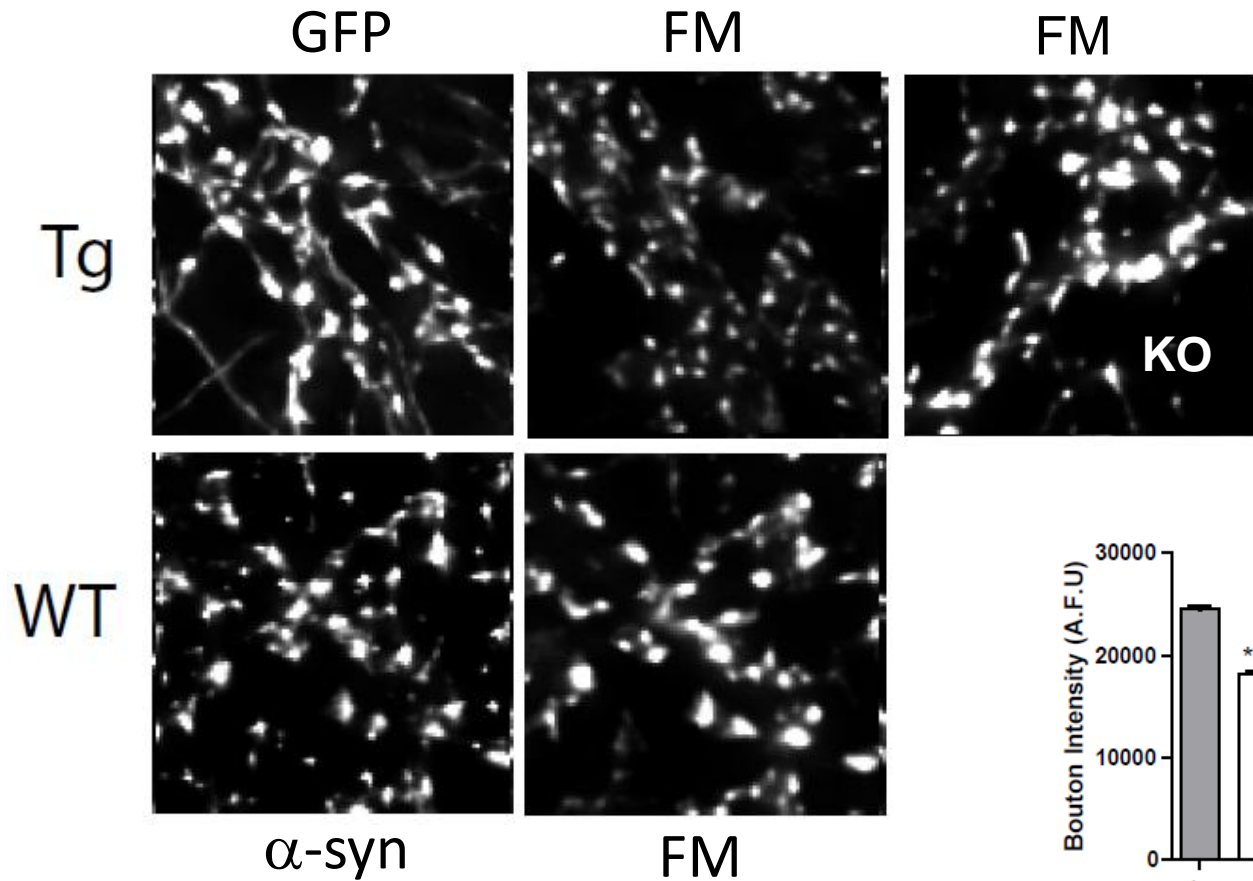
- Tissue exchange between centers
- Numerous research projects supported within and outside institution

Caveats to the “aggregation = disease” concept

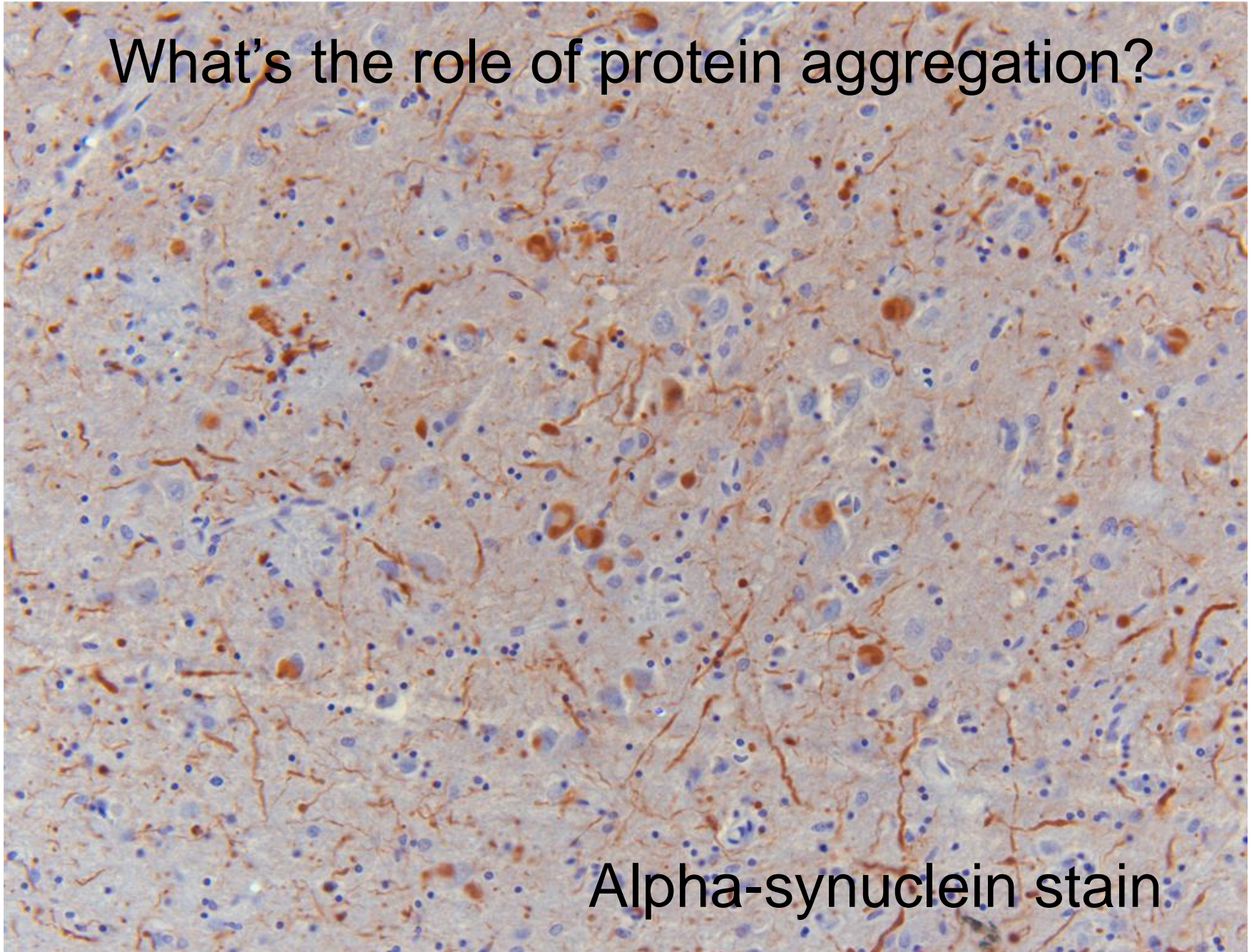
- The “anti-amyloid cascade” movement: the tauists and the β aptists
- Rise of the “oligomeric $A\beta$ ” and “intracellular $A\beta$ ”
- Alpha-synuclein

Patho-physiologic role of alpha-synuclein

Experiment: Load WT or Tg boutons with FM4-64



What's the role of protein aggregation?



Alpha-synuclein stain

“Behind every beautiful hypothesis
there is an ugly fact”.

Summary

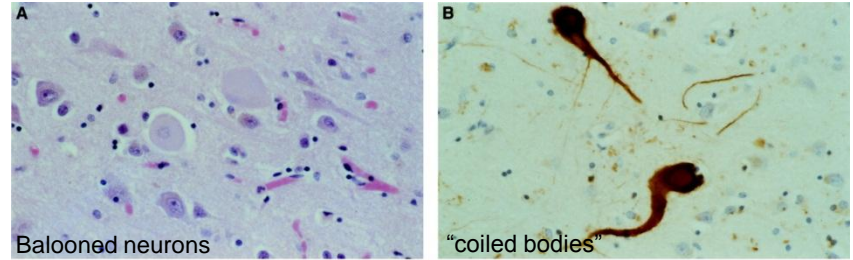
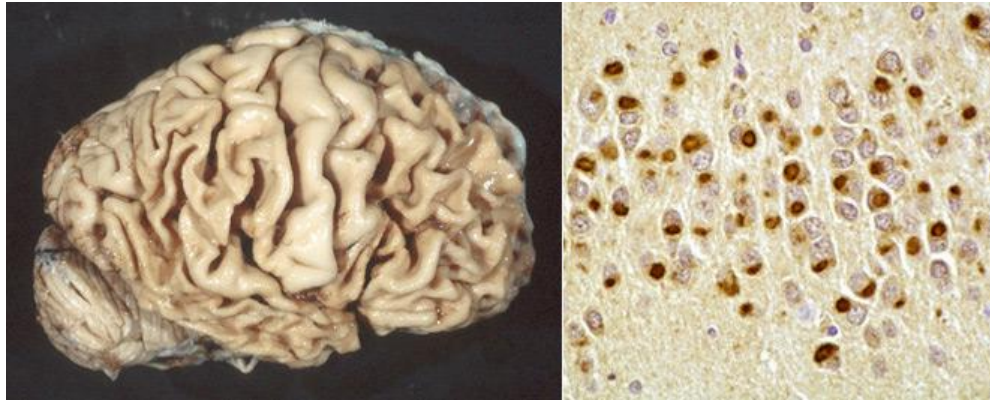
- Protein aggregation and dementias
- A diagnostic algorithm for dementias using immunohistochemistry
- Emerging evidence that aggregation \neq disease pathogenesis

Other tauopathies

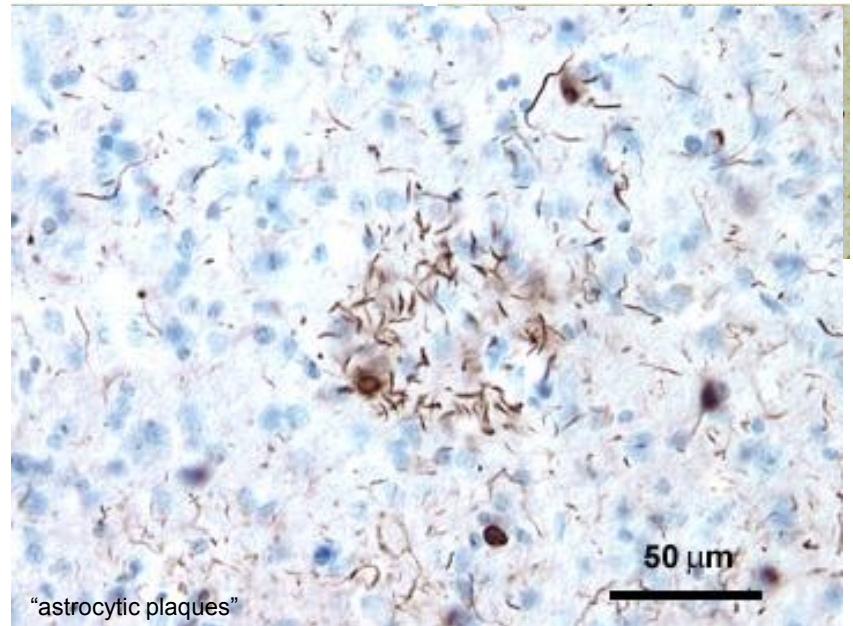
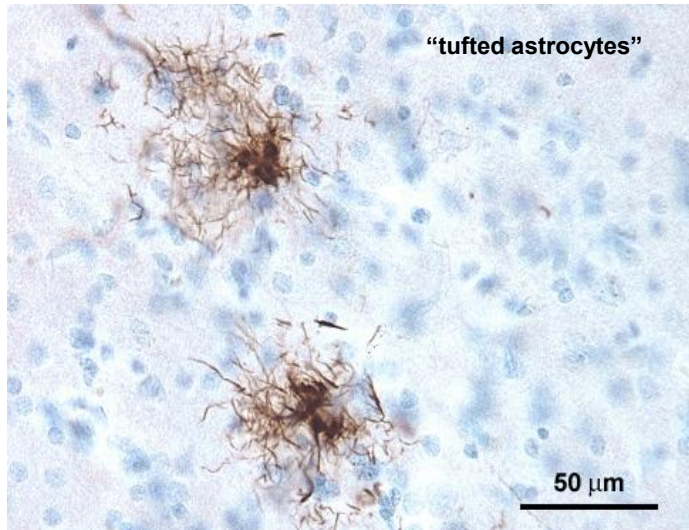
- Pick's disease (AD v/s FTD), CBD, PSP

Pick's

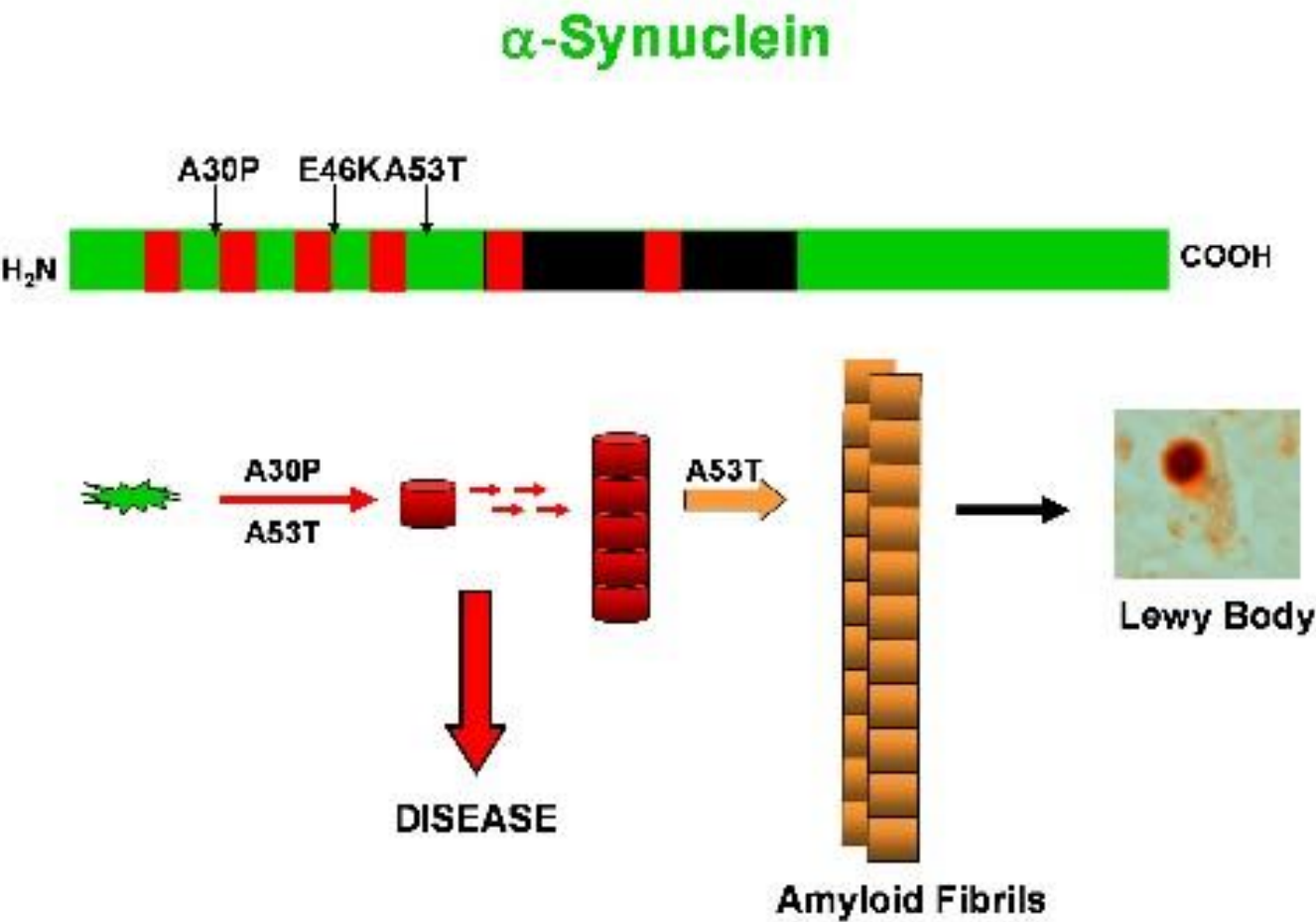
CBD



PSP



Alpha-synuclein and “Lewy body” diseases



Conway, et al Nat Med 1998

Conway et al PNAS 2000

Goldberg and Lansbury, Nat Cell Biol 2001