GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN
Instituto de Salud Carlos III

Neuropatología
ACTUALIZACIÓN EN NEUROPATOLOGÍA

btcïen
Banco de Tejidos de la Fundación Cien

Actualización en patología neurodegenerativa

SEAP-IAP 2023
La patología del futuro

Alberto Rábano
Fundación CIEN, ISCIII, Madrid

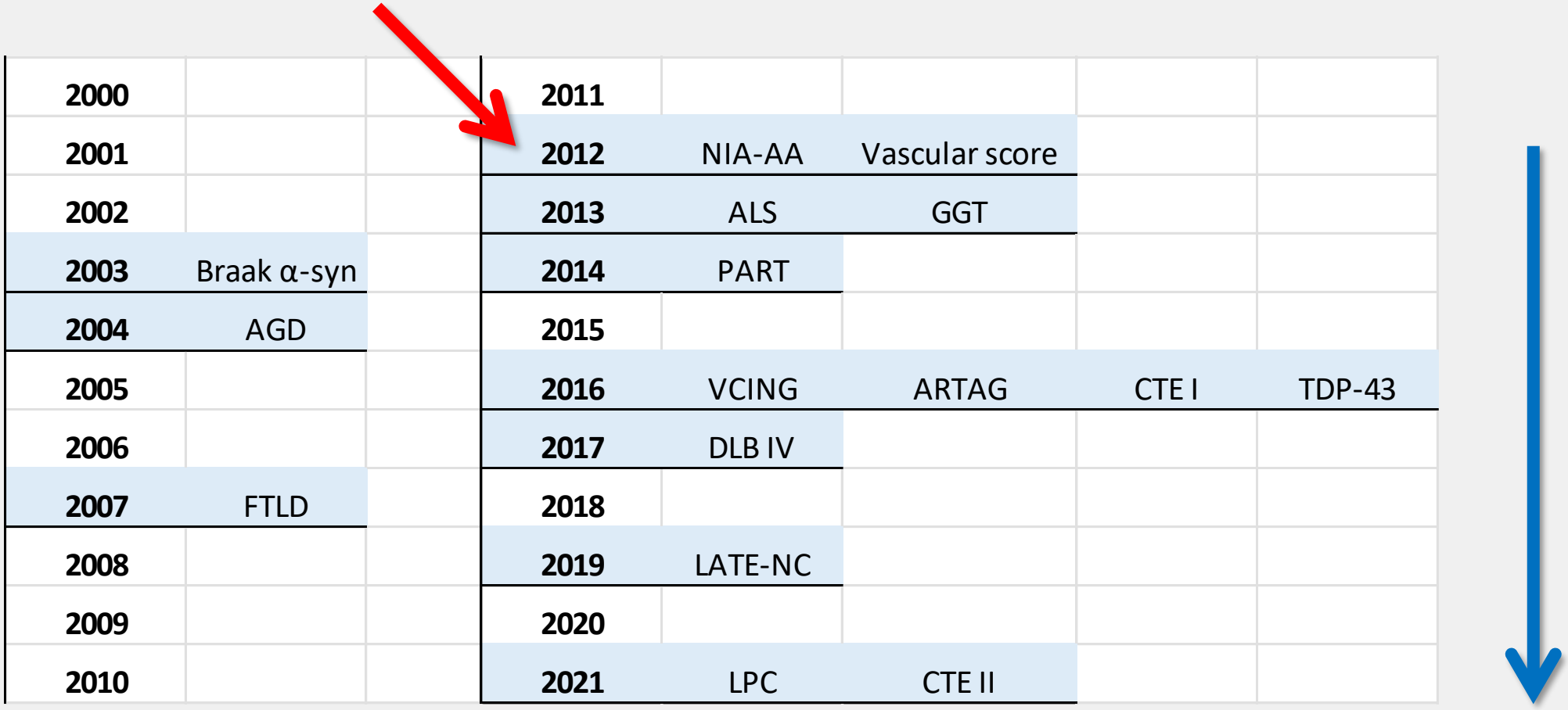
Sevilla, mayo, 2023

Actualización…

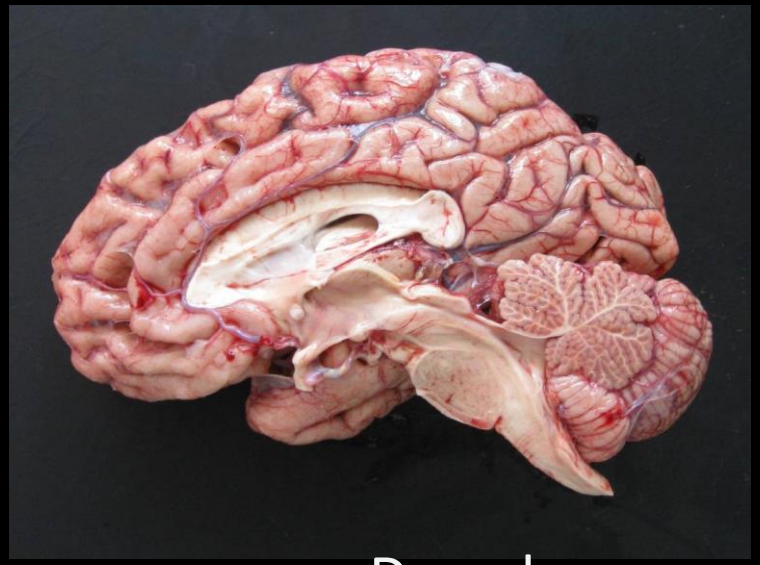
¿de qué?

¿desde cuándo?

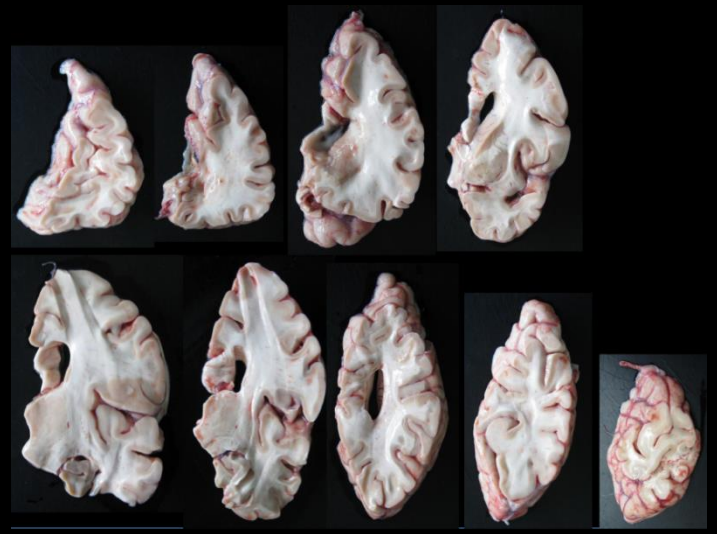
Cronología de los criterios actuales de diagnóstico neuropatológico



2000				
2001				
2002				
2003	Braak α-syn			
2004	AGD			
2005				
2006				
2007	FTLD			
2008				
2009				
2010				
2011				
2012	NIA-AA	Vascular score		
2013	ALS	GGT		
2014	PART			
2015				
2016	VCING	ARTAG	CTE I	TDP-43
2017	DLB IV			
2018				
2019	LATE-NC			
2020				
2021	LPC	CTE II		

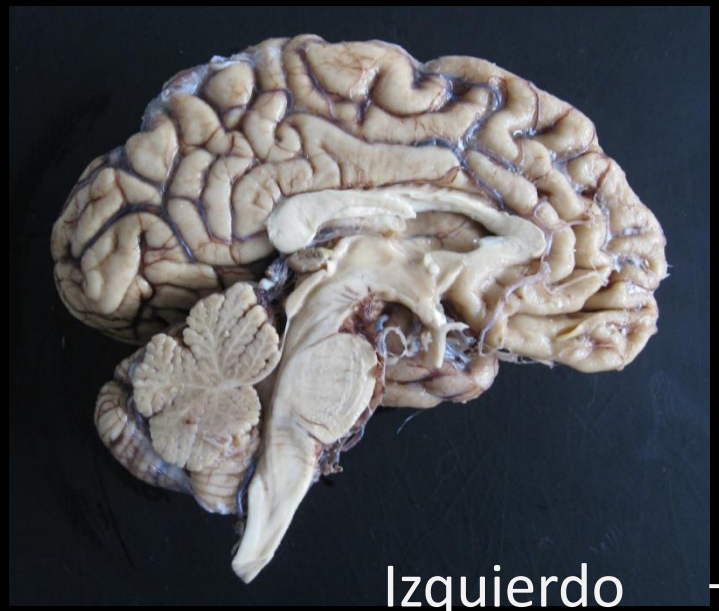


Derecho

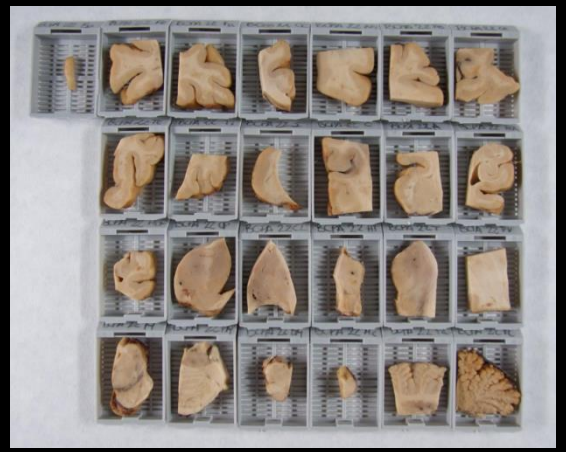


Congelación

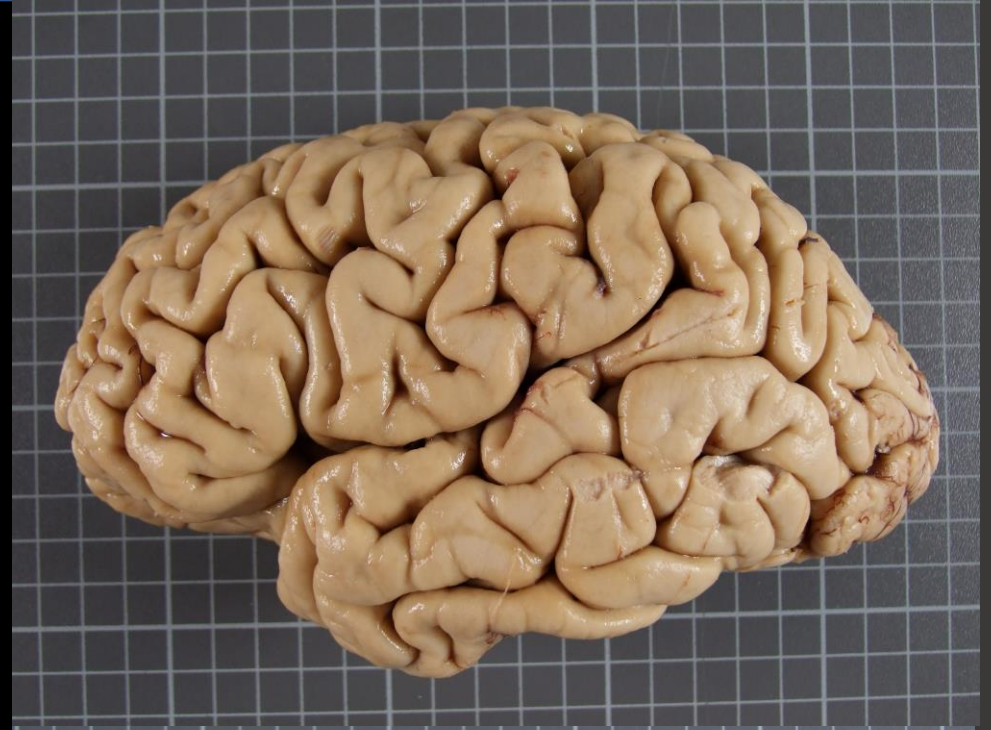
Archivo

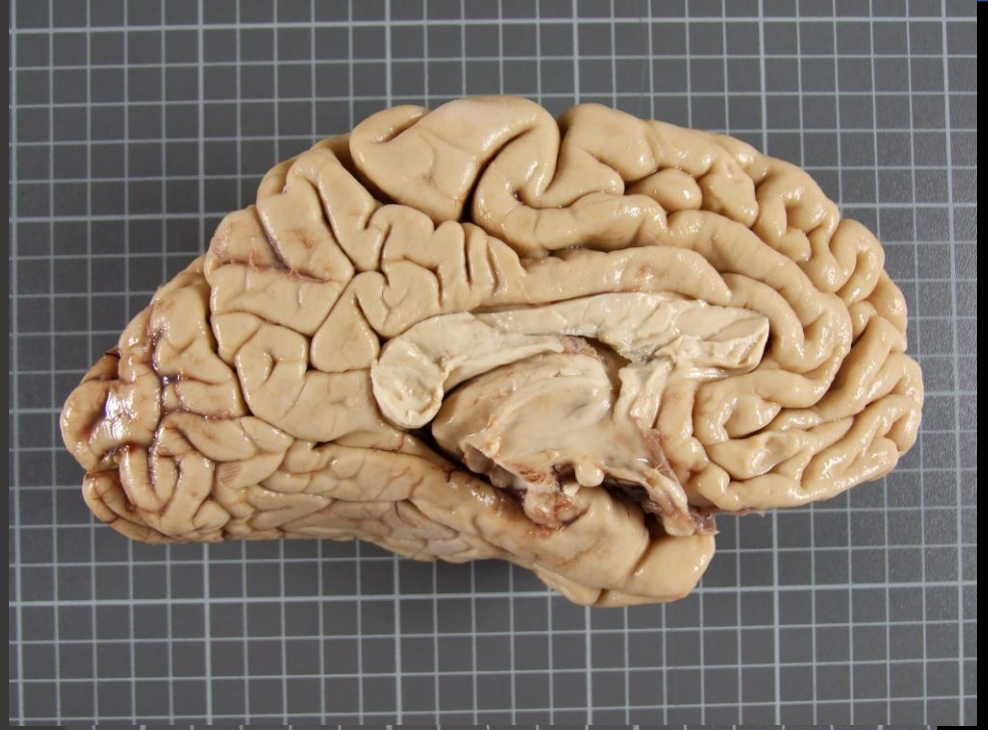


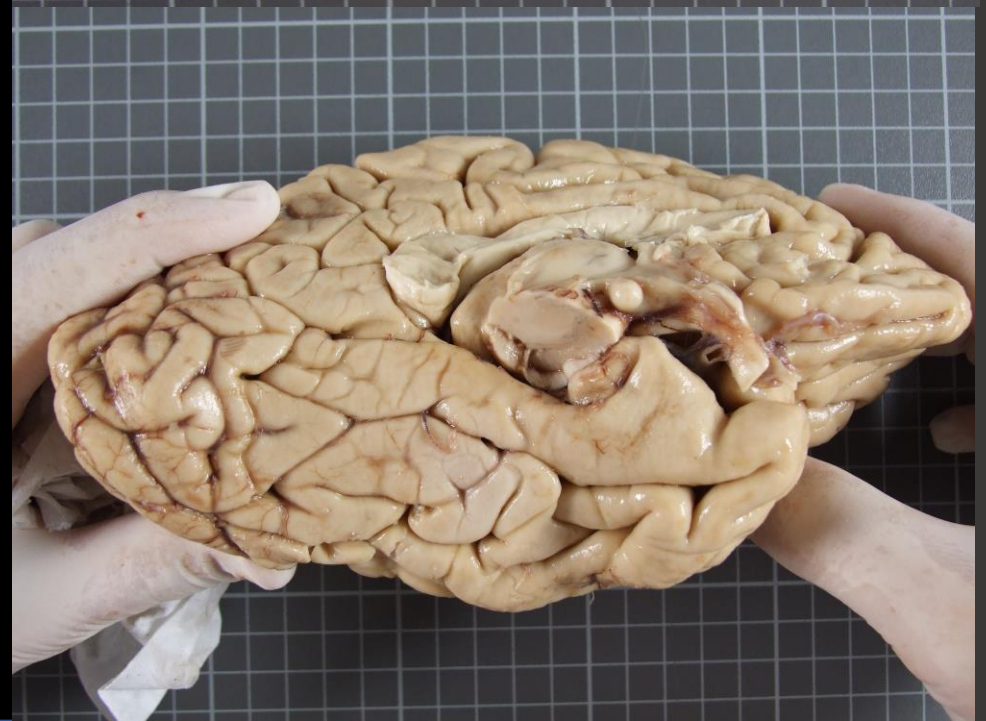
Izquierdo

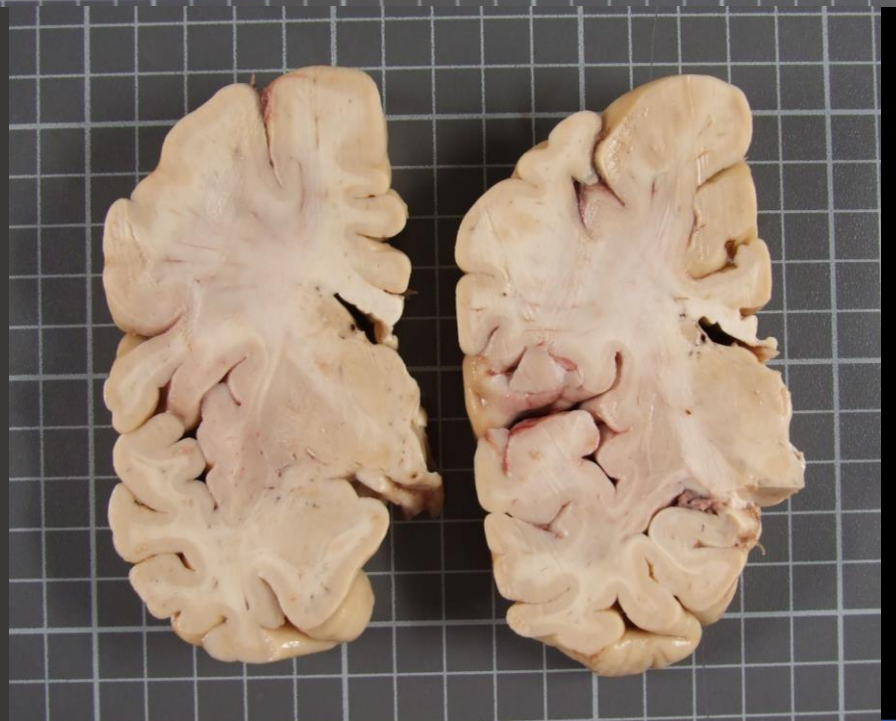


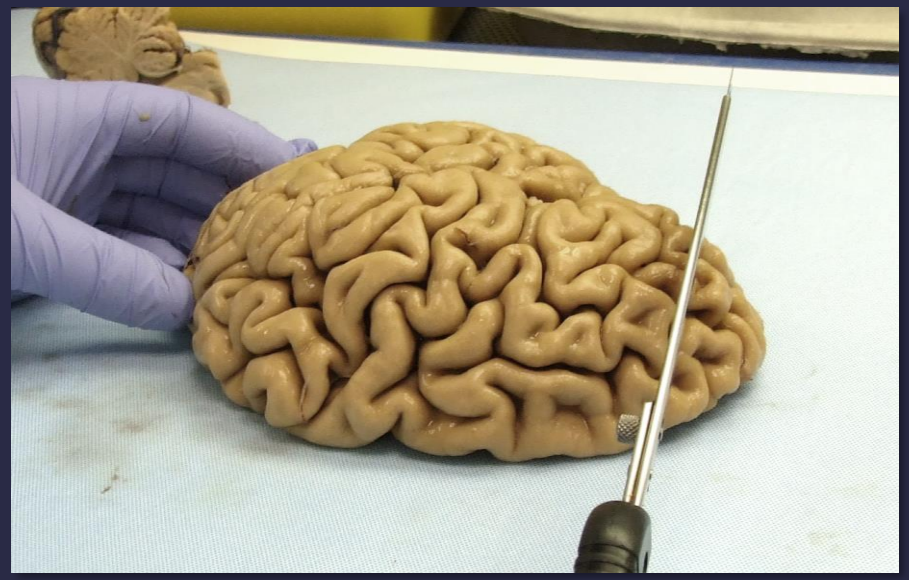
Neuropatología

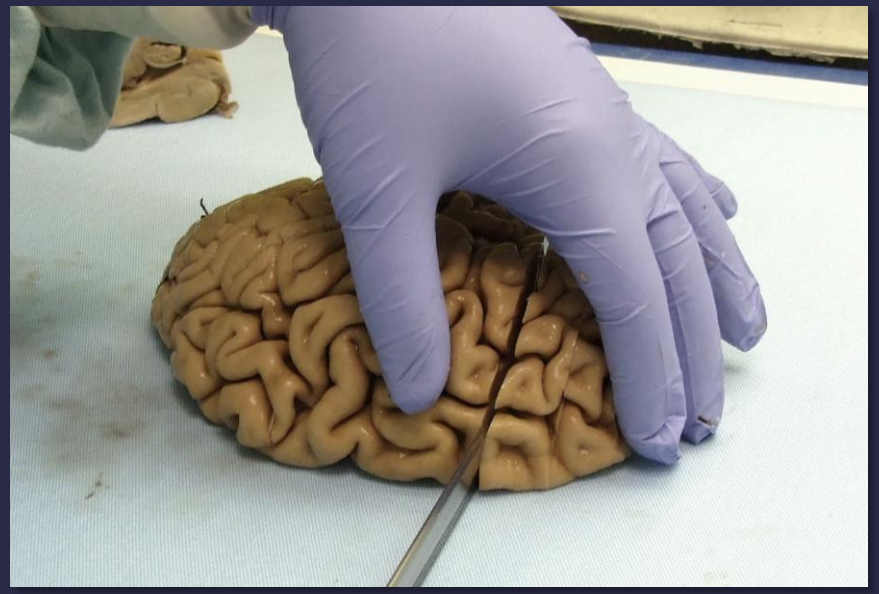


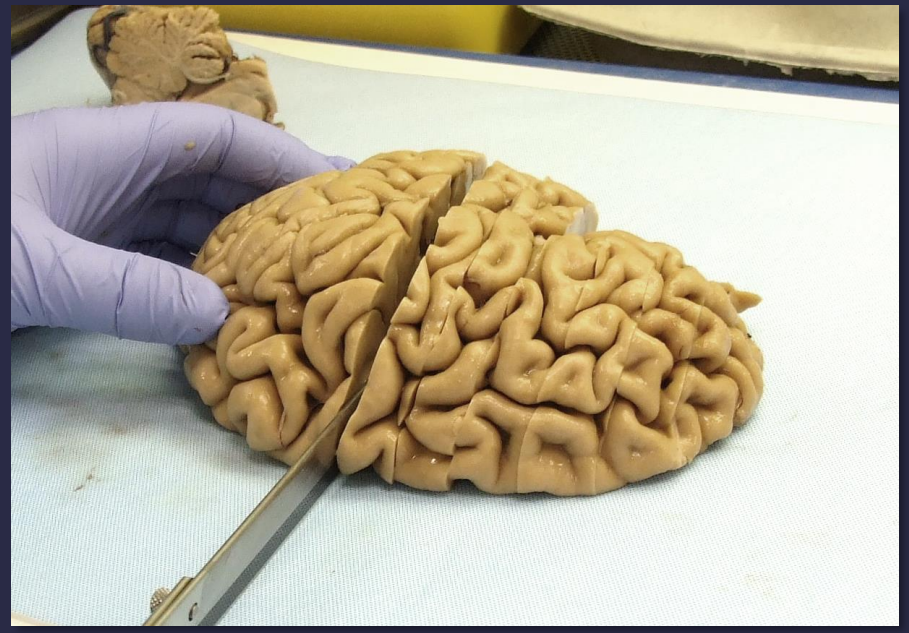


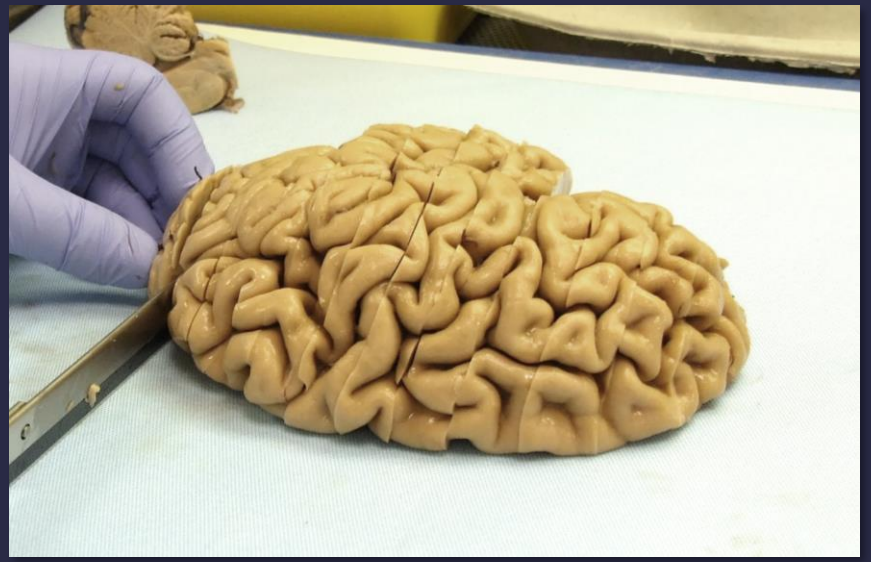






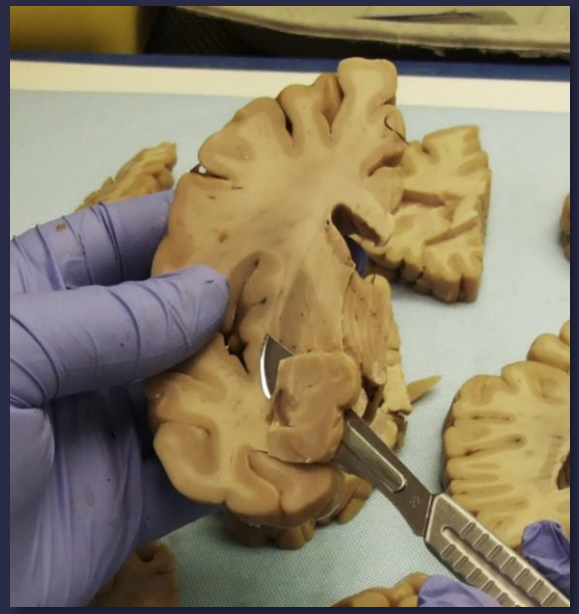




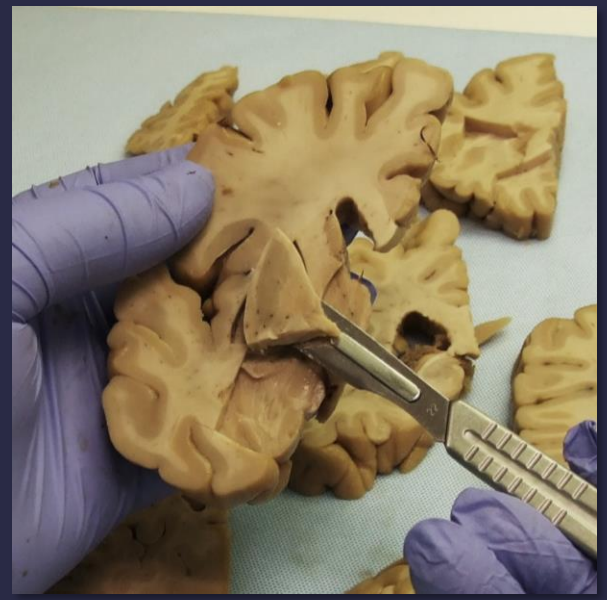


S. blanca periventricular

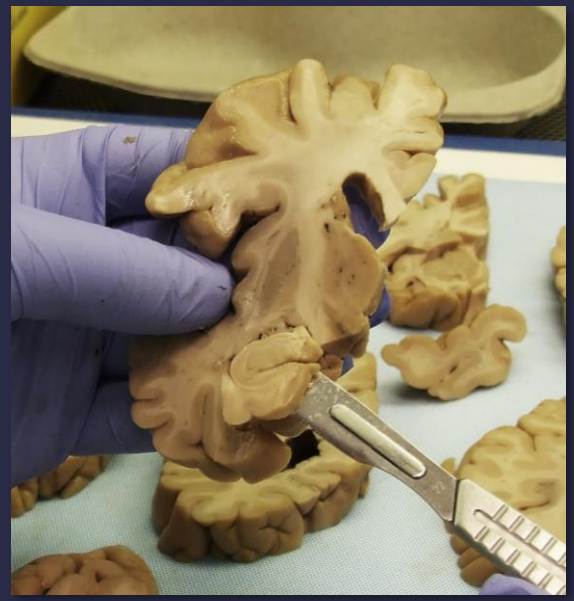
Amígdala



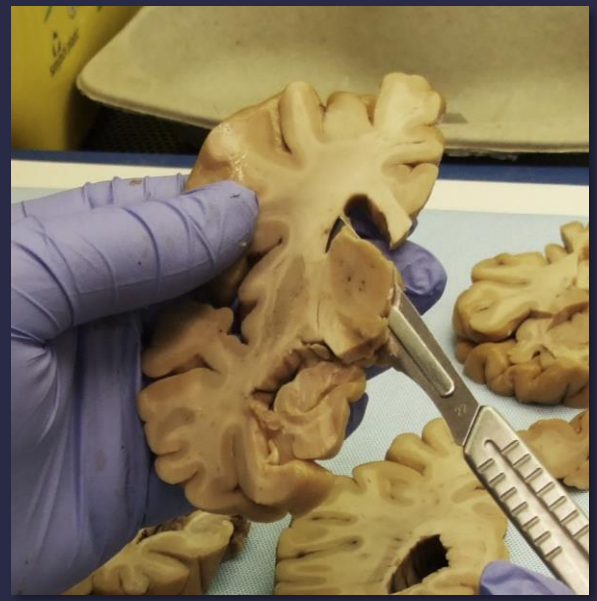
N. lenticular



Hipocampo anterior



Tálamo



Córtex prerrolándico

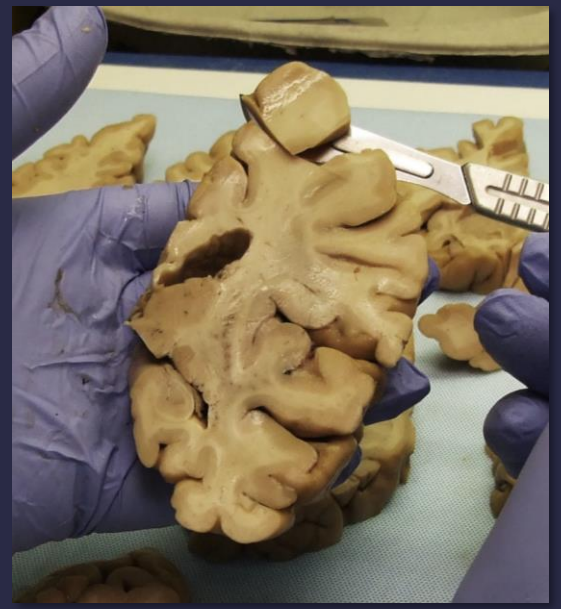
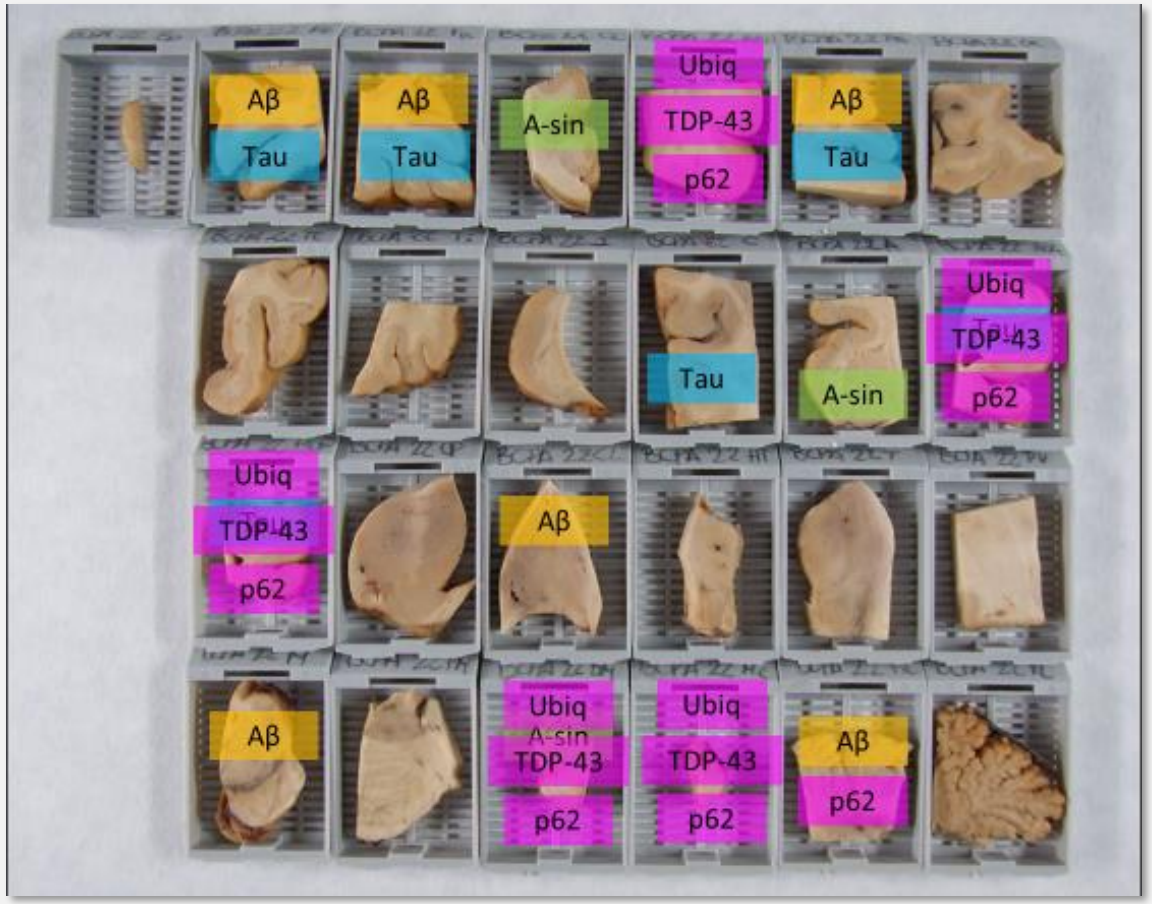


Table 6. Illustrating the blocks routinely taken from fixed post-mortem brains and the stains employed in a suspected case of Alzheimer's Disease.

Block Location	Stains
1. Middle frontal gyrus	H&E, Aβ, HP-tau, p62, pTDP-43
2. Superior and middle temporal gyri	H&E, Aβ, HP-tau, p62, pTDP-43
3. Hippocampus	H&E, Aβ, HP-tau, p62, α-syn, pTDP-43
4. Parietal lobe	H&E, HP-tau, α-syn
5. Mid-brain	H&E, Aβ, α-syn
6. Superior frontal gyrus and cingulate gyrus	H&E, α-syn
7. Occipital including calcarine and paracalcarine	H&E, Aβ, HP-tau
8. Basal Ganglia	H&E, Aβ
9 Amygdala	H&E, Aβ, HP-tau, p62, α-syn, pTDP-43
10. Thalamus	(No stains)
11. Pons	H&E, α-syn
12. Medulla	H&E, α-syn
13. Cerebellar hemisphere	H&E, Aβ, p62
14. Frontal deep white matter	H&E (LFB/N-if evidence of CVD)
15. Occipital deep white matter	H&E (LFB/N-if evidence of CVD)
16. Motor cortex	(No stains)

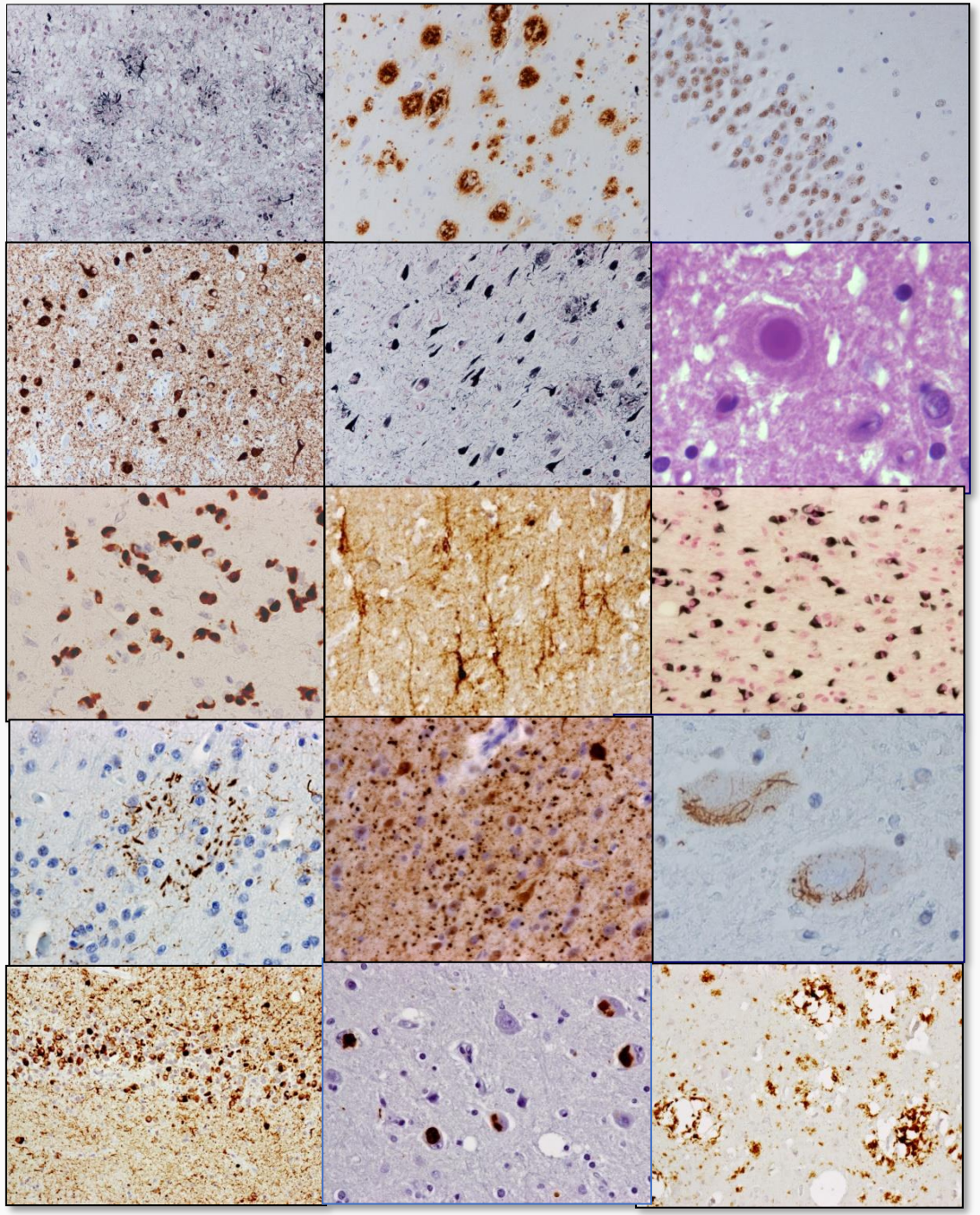
(No stains)-indicate block is taken and not routinely stained but may be if need arises. CVD-cerebrovascular disease, α-syn-α-synuclein, LFB/N-Luxol Fast Blue/Nissl.



King A *et al.*, 2020

Tinción de rutina, hematoxilina - eosina

Técnicas especiales, de plata y de inmunohistoquímica



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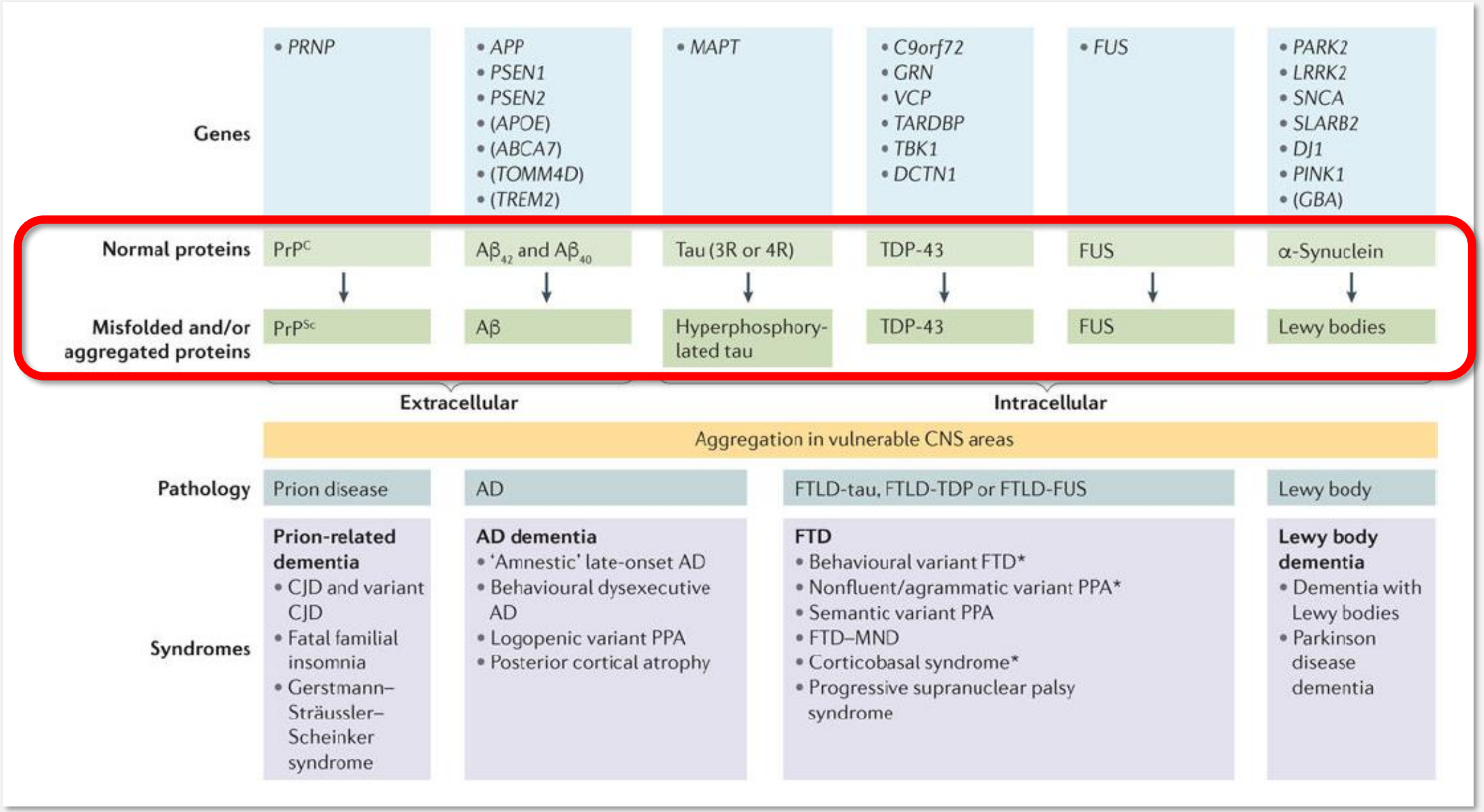
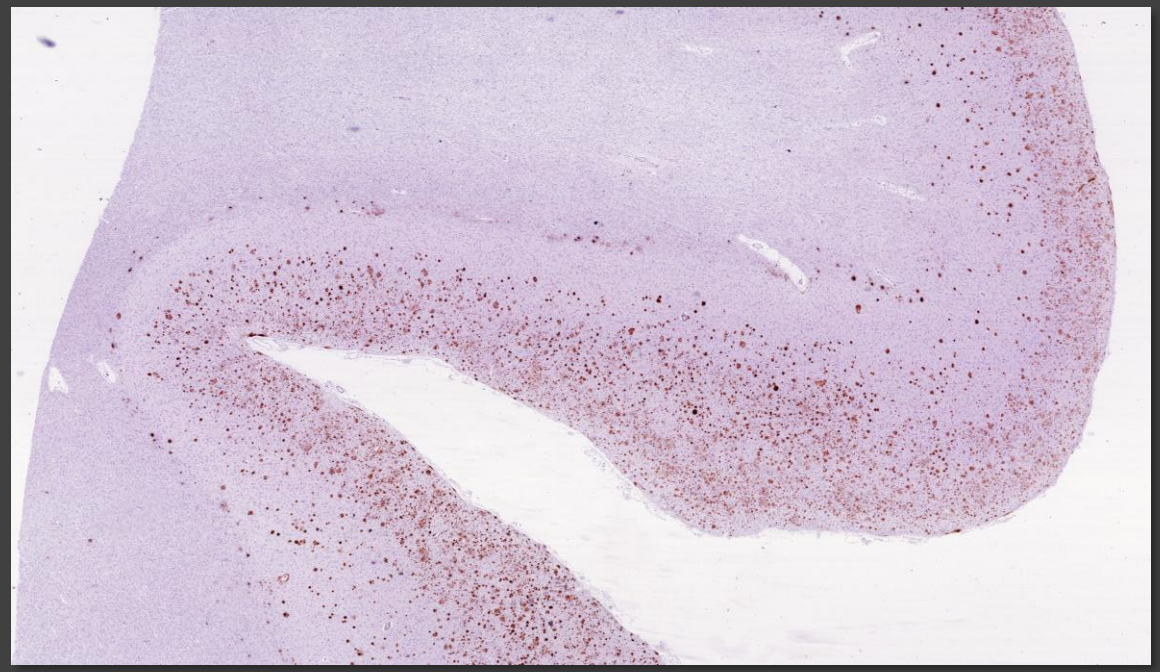
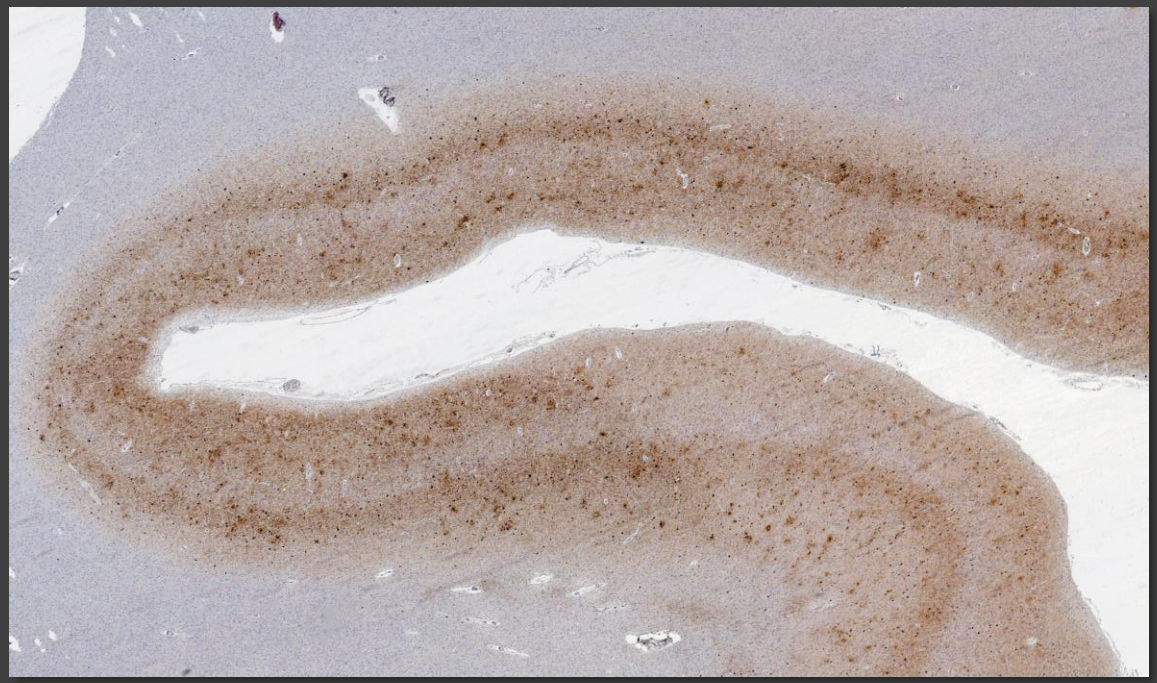
Banco de Tejidos de la Fundación Cien



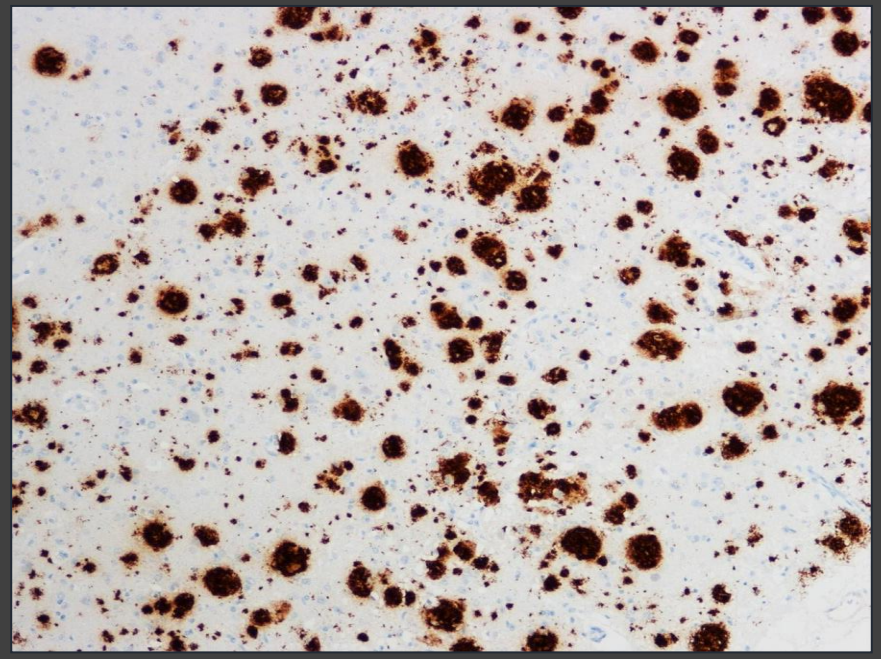
Elahi FM & Miller BL, 2017

Enfermedad / patología	Pat. molecular/ inmunohistoquímica	Lesiones histológicas características
E. de Alzheimer (esporádica o genética)	Beta-amiloide	Placas neuríticas, angiopatía amiloide cerebral (AAC)
	Tau 3R/4R	Ovillos neurofibrilares (ONF), hebras neuropílicas
Enfermedad de cuerpos de Lewy (E. de Parkinson, Demencia con cuerpos de Lewy)	Alfa-sinucleína	Cuerpos de Lewy, neuritas de Lewy, cuerpos pálidos
Atrofia multisistémica	Alfa-sinucleína	Inclusiones gliales citoplásmicas (GCI) e inclusiones neuronales
Parálisis supranuclear progresiva	Tau 4R	Astrocitos en penacho, coiled bodies, ONF globosos.
Degeneración córticobasal	Tau 4R	Placas astrocitarias, neuronas balonizadas, cuerpos Pick-like
Enfermedad de granos argirófilos	Tau 4R	Granos argirófilos, pre-ONF, coiled bodies
Taupatía con inclusiones gliales globulares	Tau 4R	Inclusiones gliales globulares (IGG)
Enfermedad de Pick	Tau 3R	Cuerpos de Pick, astrocitos en espina
Aging-related tau astrogliopathy (ARTAG)	Tau 4R>3R	Fuzzy-granular astrocytes
Primary age-related tauopathy (PART)	Tau 3R/4R	ONF
Degeneración lobar frontotemporal – TDP (subtipos A, B, C y D)	TDP-43	Inclusiones neuronales (citoplásmicas y nucleares) y gliales, fibras +
Esclerosis lateral amiotrófica – TDP	TDP-43, p62	Inclusiones neuronales y gliales, fibras +
Limbic-predominant age-related TDP-43 encepha-lopathy (LATE)	TDP-43	Inclusiones neuronales, fibras +
Enfermedad de Huntington	Huntingtina	Inclusiones neuronales, fibras +
Enfermedad de Creutzfeldt-Jakob	Proteína priónica patológca (PrP^{Sc})	Depósitos de tipo sináptico, perineuronal, perivacuolar, placas tipo kuru,

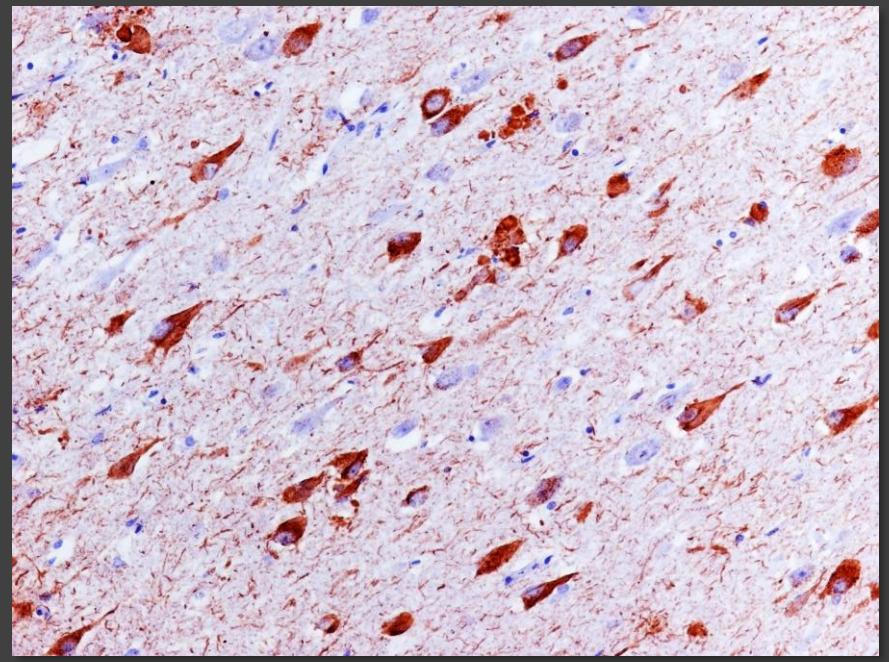




Aβ



Tau



2012

Acta Neuropathol (2012) 123:1–11
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

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

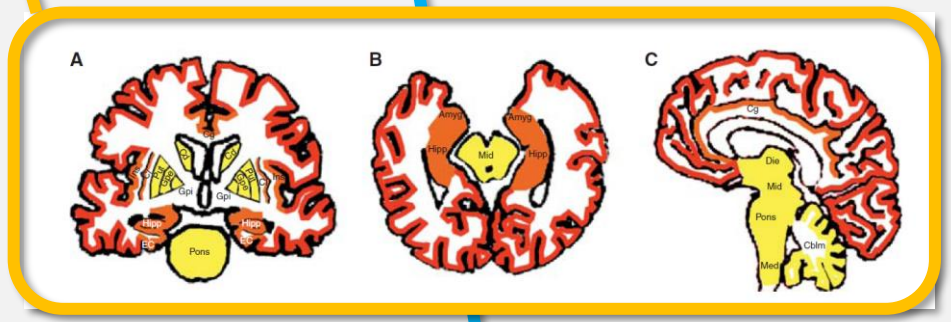
Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley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

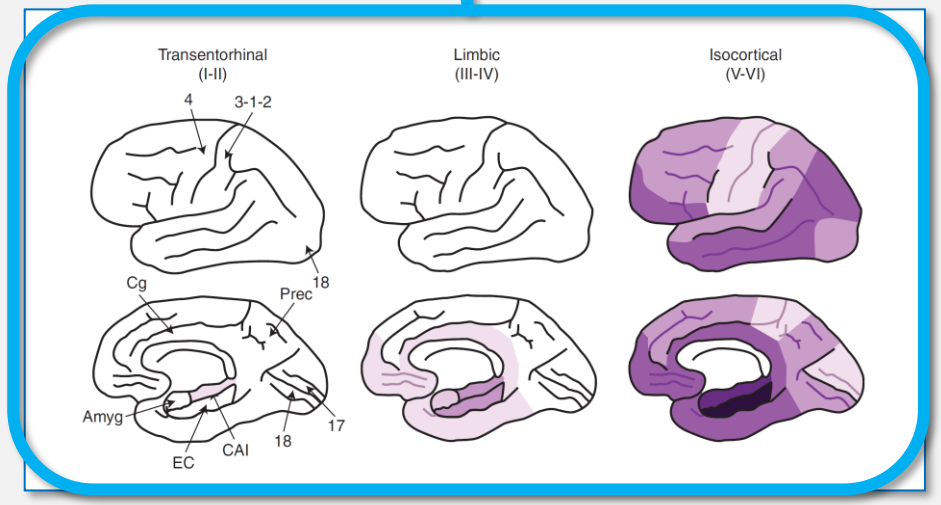
Table 2 "ABC" score for AD neuropathologic change

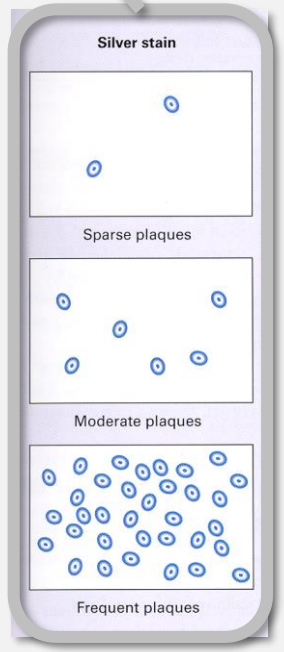
"A"	Thal Phase for Aβ plaques [57]	"B"	Braak and Braak NFT stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

Table 3 "ABC" score for level of AD neuropathologic change

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







Alzheimer's disease neuropathological change: A1 B2 C3

nature medicine

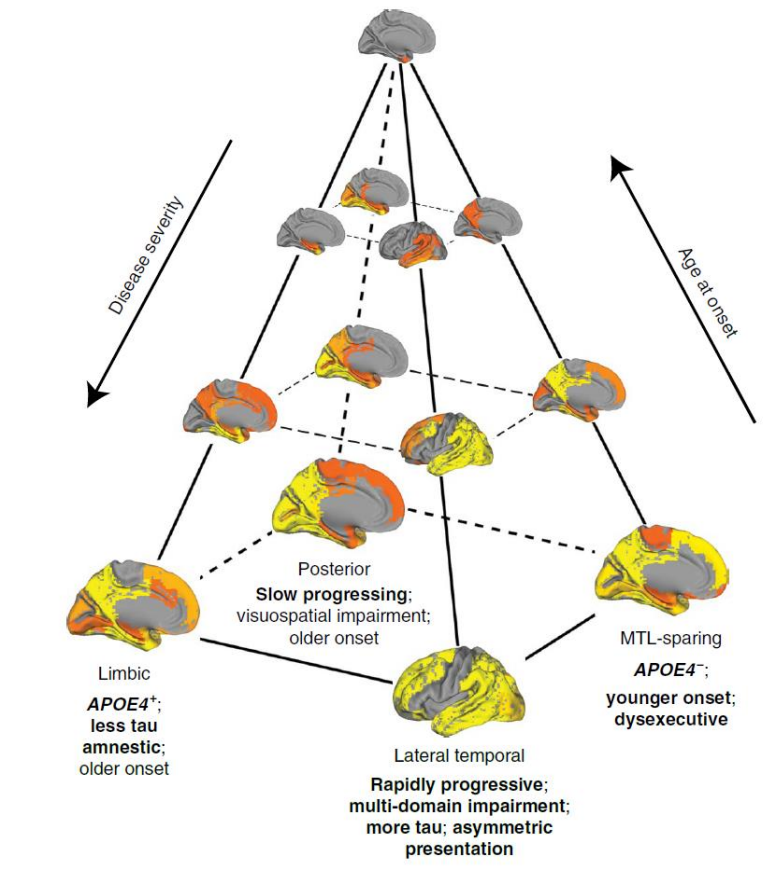
ARTICLES

https://doi.org/10.1038/s41591-021-01309-6

Check for updates

Four distinct trajectories of tau deposition identified in Alzheimer's disease

Jacob W. Vogel[1]✉, Alexandra L. Young[2], Neil P. Oxtoby[3,4], Ruben Smith[5,6], Rik Ossenkoppele[5,7], Olof T. Strandberg[5], Renaud La Joie[8], Leon M. Aksman[3,9], Michel J. Grothe[10,11], Yasser Iturria-Medina[1], the Alzheimer's Disease Neuroimaging Initiative*, Michael J. Pontecorvo[12], Michael D. Devous[12], Gil D. Rabinovici[8,13], Daniel C. Alexander[3,4], Chul Hyoung Lyoo[14], Alan C. Evans[1] and Oskar Hansson[5,15]✉



CellPress
OPEN ACCESS

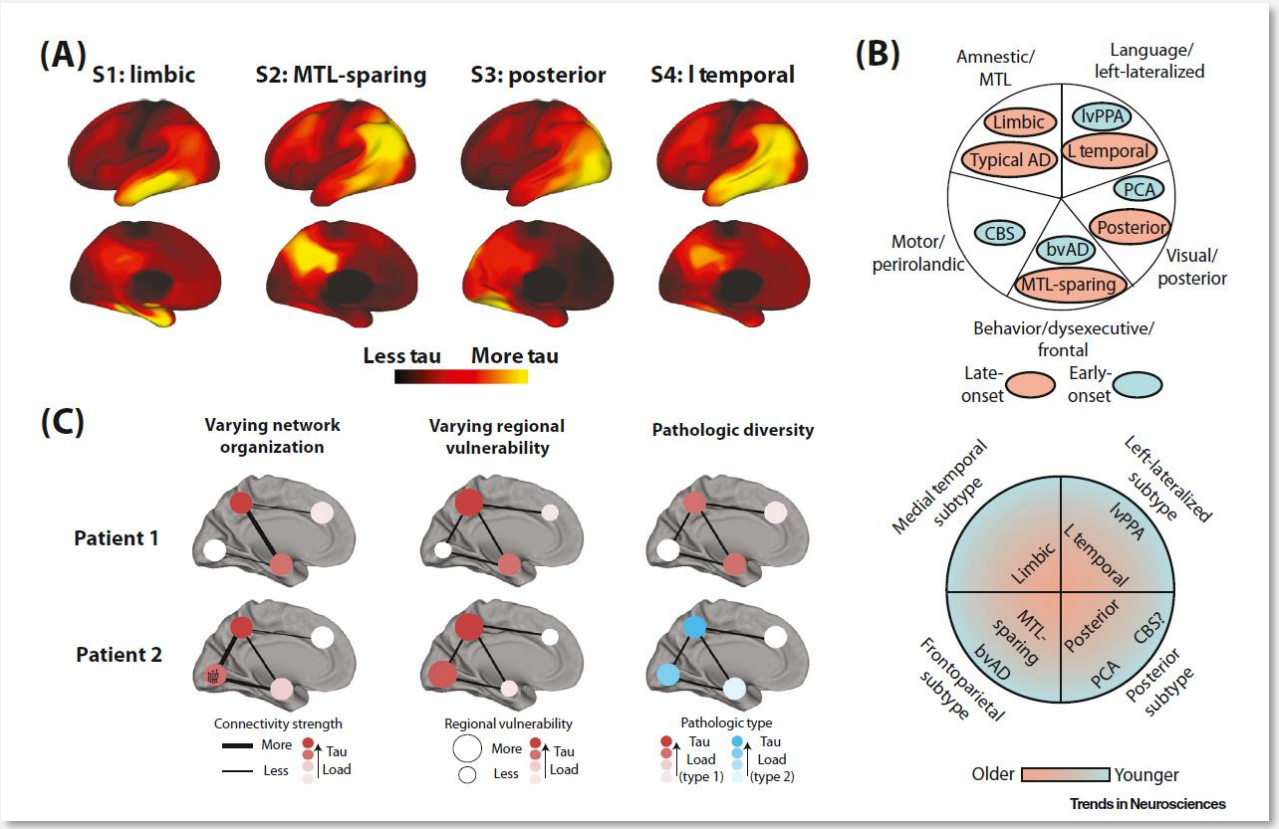
Forum

Subtypes of Alzheimer's disease: questions, controversy, and meaning

Jacob W. Vogel[1,2,*] and Oskar Hansson[3,4,*]

Trends in Neurosciences

Trends in Neurosciences, May 2022, Vol. 45, No. 5



2020

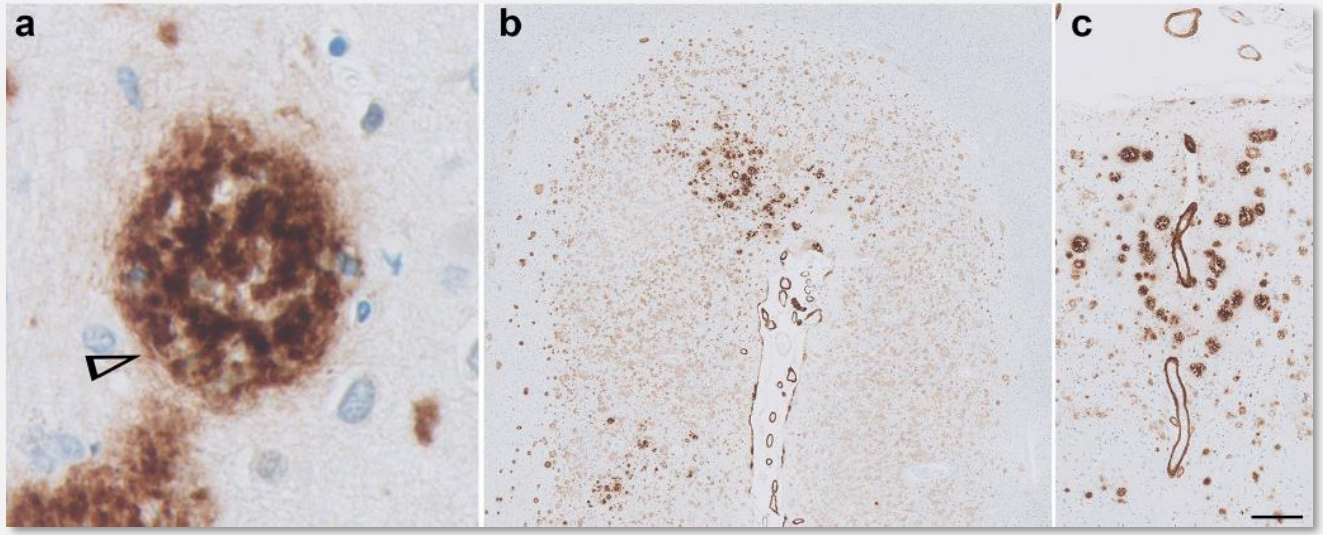
Acta Neuropathologica (2020) 140:811–830
https://doi.org/10.1007/s00401-020-02198-8

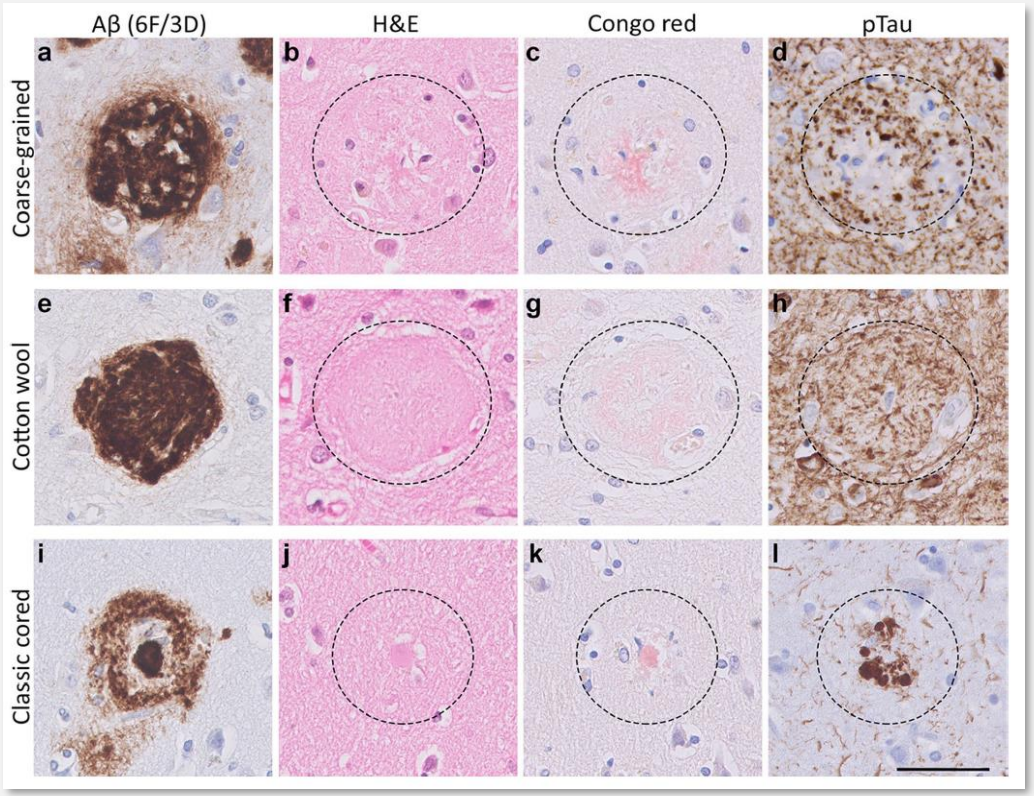
ORIGINAL PAPER

Check for updates

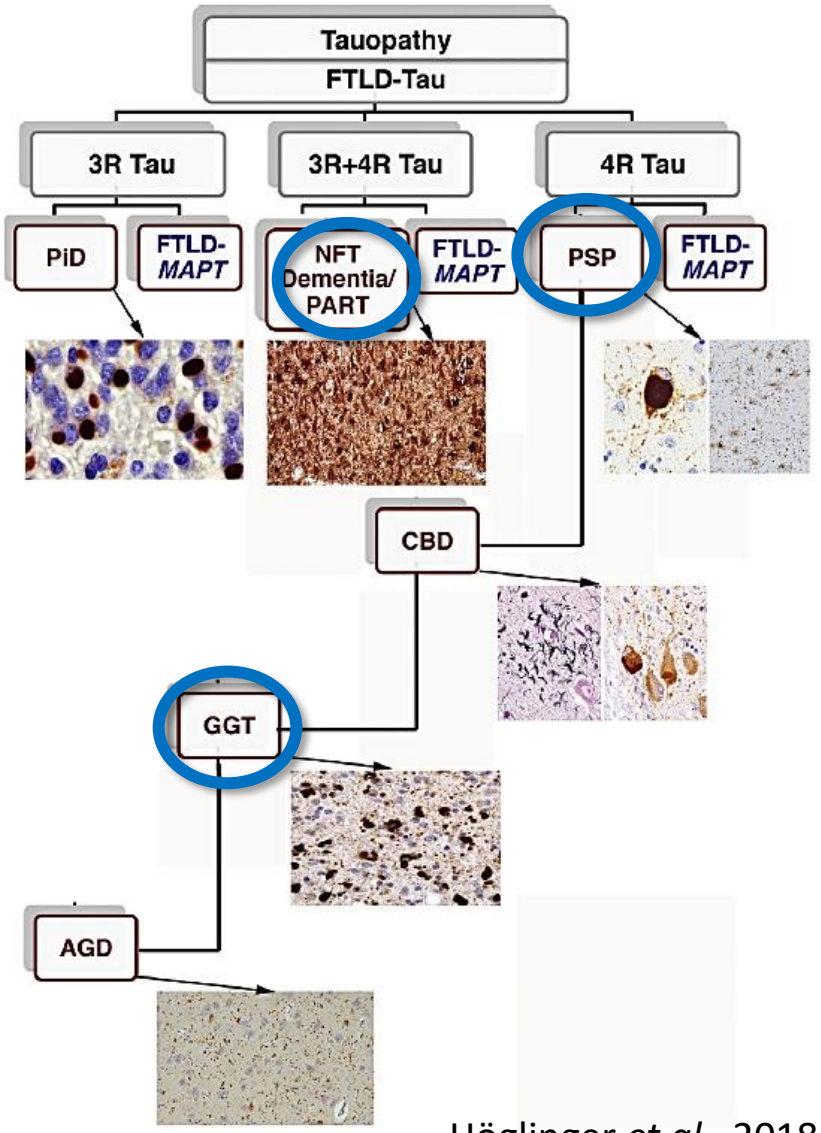
The coarse-grained plaque: a divergent Aβ plaque-type in early-onset Alzheimer's disease

Baayla D. C. Boon[1,2] · Marjolein Bulk[3] · Allert J. Jonker[4] · Tjado H. J. Morrema[2] · Emma van den Berg[4] · Marko Popovic[5] · Jochen Walter[6] · Sathish Kumar[6] · Sven J. van der Lee[1,7] · Henne Holstege[1,7] · Xiaoyue Zhu[8] · William E. Van Nostrand[8] · Remco Natté[9] · Louise van der Weerd[3,10] · Femke H. Bouwman[1] · Wilma D. J. van de Berg[4] · Annemieke J. M. Rozemuller[2] · Jeroen J. M. Hoozemans[2]





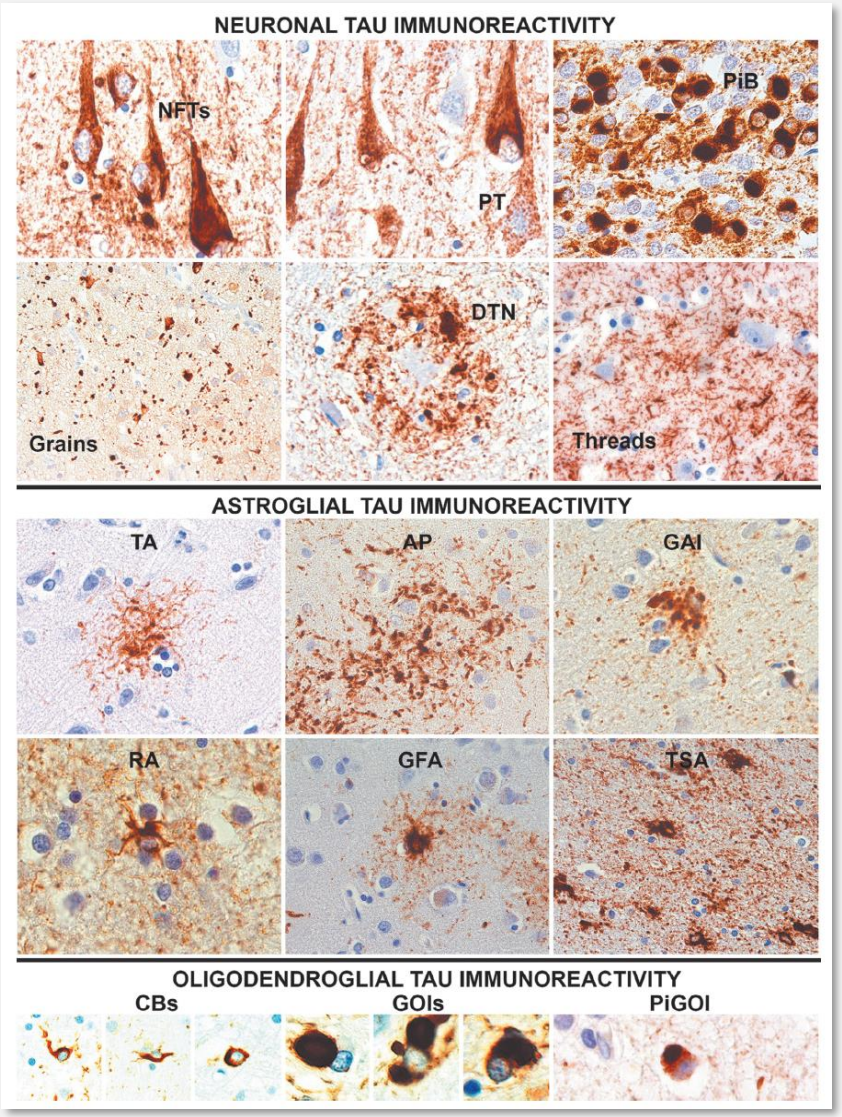
Taupatías primarias *vs*. secundarias

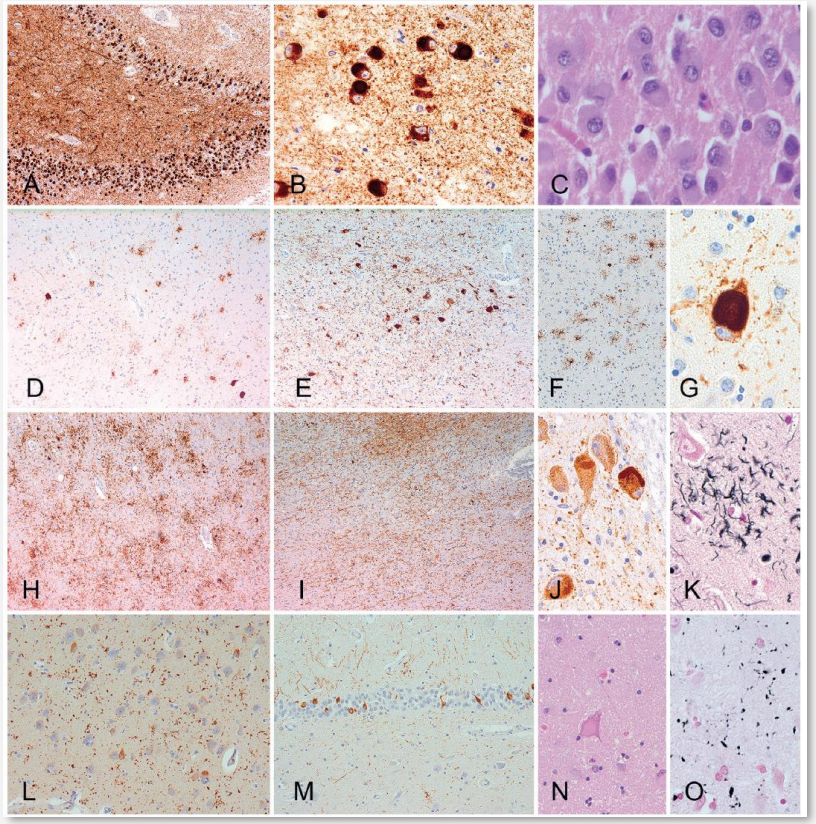


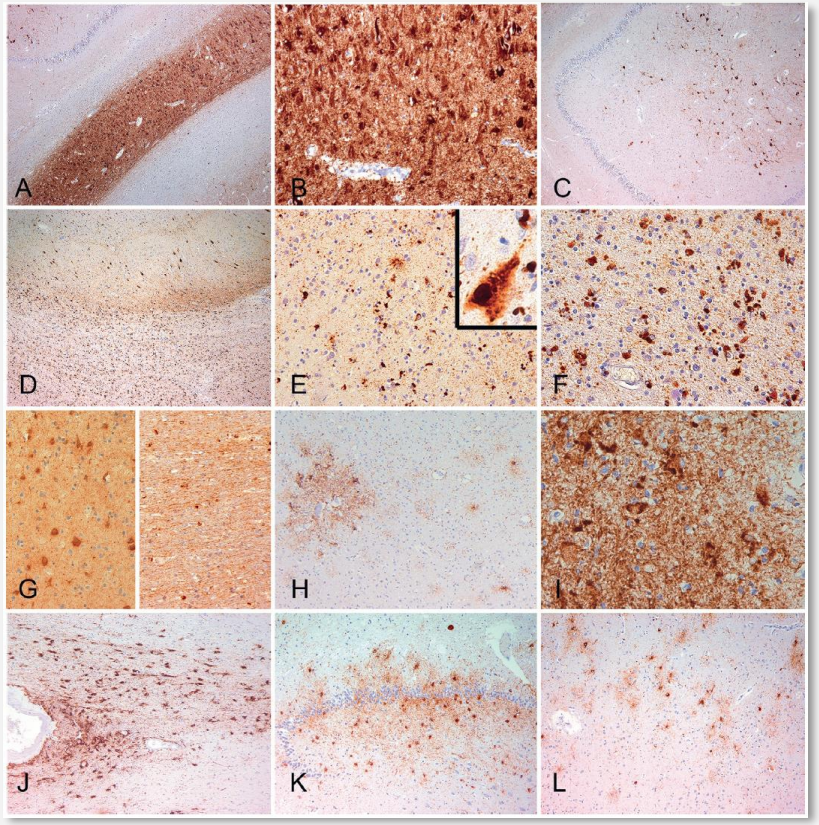
Höglinger *et al*., 2018

List of disorders associated with various tau pathologies (Murray et al., 2014; Kovacs, 2015; Tacik et al., 2016)

Alzheimer disease (sporadic and hereditary: *APP*, *PSEN1*, *PSEN2*)
Down syndrome
Prion diseases (sCJD, vCJD, gCJD, GSS, FFI)
Diffuse neurofibrillary tangles with calcification
Familial British and Danish dementia
Postencephalitic parkinsonism
Subacute sclerosing panencephalitis
Myotonic dystrophy (DM1) and PROMM (DM2)
Aging-related tau astrogliopathy → ARTAG
Traumatic brain injury
Chronic traumatic encephalopathy → Encefalopatía traumática crónica
IgLON5-related tauopathy → Taupatía relacionada con IgLON5
Guadeloupean parkinsonism
Parkinson–dementia complex of Guam
Non-Guamanian motor neuron disease with NFTs
Amyotrophic lateral sclerosis of Guam
X-linked parkinsonism with spasticity
Cerebrotendinous xanthomatosis
Niemann–Pick disease type C
NBIA *PANK2* and *PLA2G6*
SLC9A6 mental retardation
LRRK2, *PRKN*, *SNCA*, *TARDBP*, *C9orf72* gene mutations







Kovacs GG, 2017

Primary age-related tauopathy (PART)

2014

Acta Neuropathol (2014) 128:755–766
DOI 10.1007/s00401-014-1349-0

CONSENSUS PAPER

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

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F.
Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen F
Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hy
Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. K
Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H.
Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masal
Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · T
Masahito Yamada · Peter T. Nelson

Acta Neuropathol (2015) 129:749–756
DOI 10.1007/s00401-015-1390-7

POSITION PAPER

PART is part of Alzheimer dis

Charles Duyckaerts · Heiko Braak · Jean-Pierr
Michel Goedert · Glenda Halliday · Manuela Neumann · Maria Grazia Spillantini ·
Markus Tolnay · Toshiki Uchihara

Acta Neuropathol
DOI 10.1007/s00401-015-1407-2

CORRESPONDENCE

PART, a distinct tauopathy, different from classical sporadic Alzheimer disease

Kurt A. Jellinger[1] · Irina Alafuzoff[2] · Johannes Attems[3] · Thomas G. Beach[4] · Nigel J. Cairns[5] · John F. Crary[6] · Dennis W. Dickson[7] · Patrick R. Hof[8] · Bradley T. Hyman[9] · Clifford R. Jack Jr.[10] · Gregory A. Jicha[11] · David S. Knopman[12] · Gabor G. Kovacs[13] · Ian R. Mackenzie[14] · Eliezer Masliah[15,16] · Thomas J. Montine[17] · Peter T. Nelson[18] · Frederick Schmitt[11] · Julie A. Schneider[19,20] · Albert Serrano-Pozo[21] · Dietmar R. Thal[22] · Jonathan B. Toledo[23] · John Q. Trojanowski[23] · Juan C. Troncoso[24] · Jean Paul Vonsattel[6] · Thomas Wisniewski[25,26,27]

Acta Neuropathol

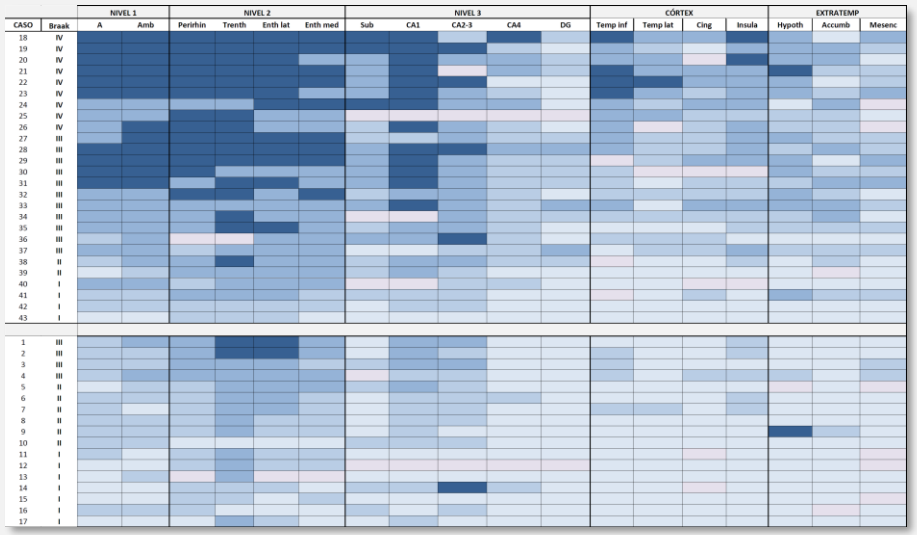
Table 1 Hypothetical correlation between PART and AD

	No AD/no PART	Asymptomatic PART	p-preAD	NFT-predominant Dementia (symptomatic PART)	Symptomatic AD
Aβ phase	0	0–2	1–5	0–2	3–5
Braak-NFT-stage	0	I–IV	0–VI	III, IV	III–VI
Degree of AD pathology	No AD	No or low AD	Low–high AD	No AD or low	Intermediate–high AD
Clinical signs of dementia or cognitive decline	No	No	No	Yes	Yes

PART vs. AD: symptomatic PART and symptomatic AD can be distinguished by Aβ pathology. Asymptomatic PART and p-preAD overlap in those cases with initial Aβ pathology (Aβ phases 1, 2)

PART (-)

PART def



Acta Neuropathol. 2013 October ; 126(4): 537–544. doi:10.1007/s00401-013-1171-0.

Ahmed Z et al.

Globular glial tauopathies (GGT): consensus recommendations

2013

Taupatía con inclusiones gliales globulares (GGI)

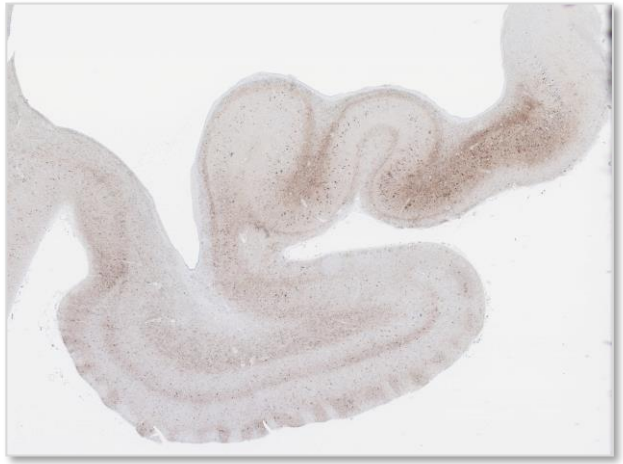
1) oligodendrogliales (GOI), con una morfología similar a las inclusiones de la AMS, argirófilas (Gallyas) e inmunorreactivas para fosfo-tau y tau 4R; o

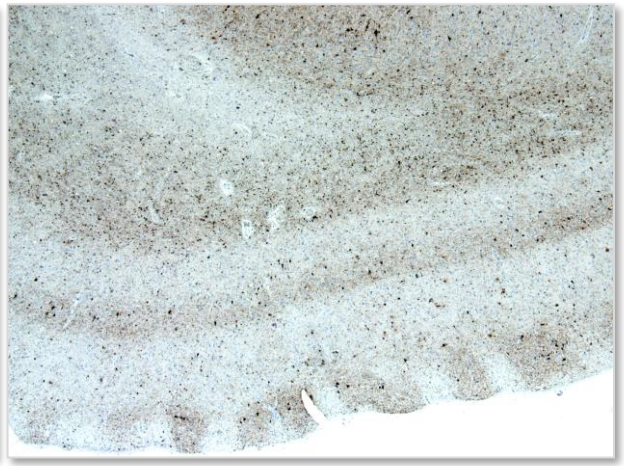
2) astrogliales (GAI), fosfo-tau+, no suelen ser argirófilas.

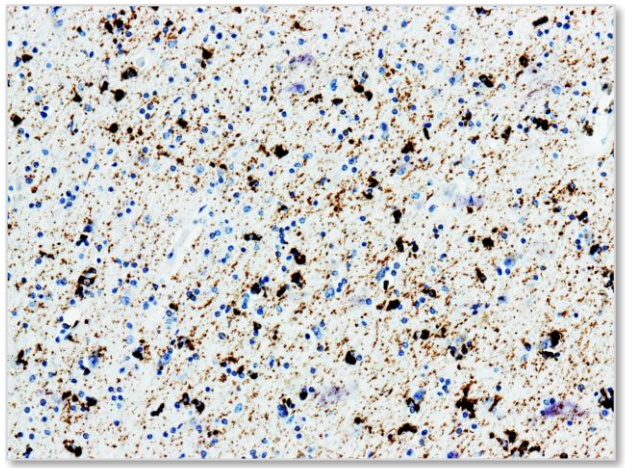
Tipo I. Casos con afectación predominantemente frontotemporal, sin afectación córticoespinal. Abundantes GOI.

Tipo II. Casos con afectación predominante del córtex motor y del tracto córticoespinal. GOI/GAI

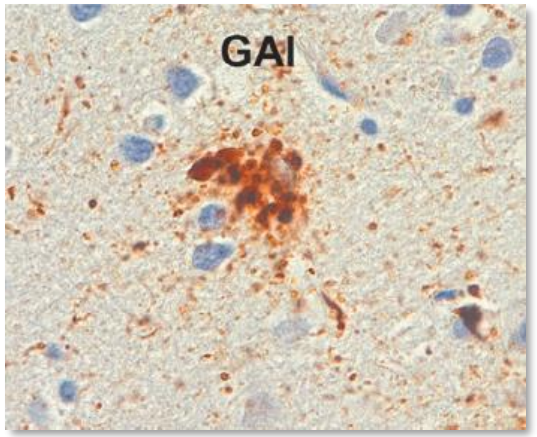
Tipo III. Casos que presentan tanto afectación frontotemporal como del sistema córticoespinal. GAI > GOI corticales







GOI



Kovacs GG, 2017

Encefalopatía traumática crónica

2016

Acta Neuropathol
DOI 10.1007/s00401-015-1515-z

CrossMark

CONSENSUS PAPER

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

Ann C. McKee[1,2,3,4,5] · Nigel J. Cairns[6] · Dennis W. Dickson[7] · Rebecca D. Folkerth[8] · C. Dirk Keene[9] · Irene Litvan[10] · Daniel P. Perl[11] · Thor D. Stein[2,3,4,5] · Jean-Paul Vonsattel[12] · William Stewart[13] · Yorghos Tripodis[3,14] · John F. Crary[15] · Kevin F. Bieniek[7] · Kristen Dams-O'Connor[16] · Victor E. Alvarez[1,2,3,4] · Wayne A. Gordon[16] · the TBI/CTE group

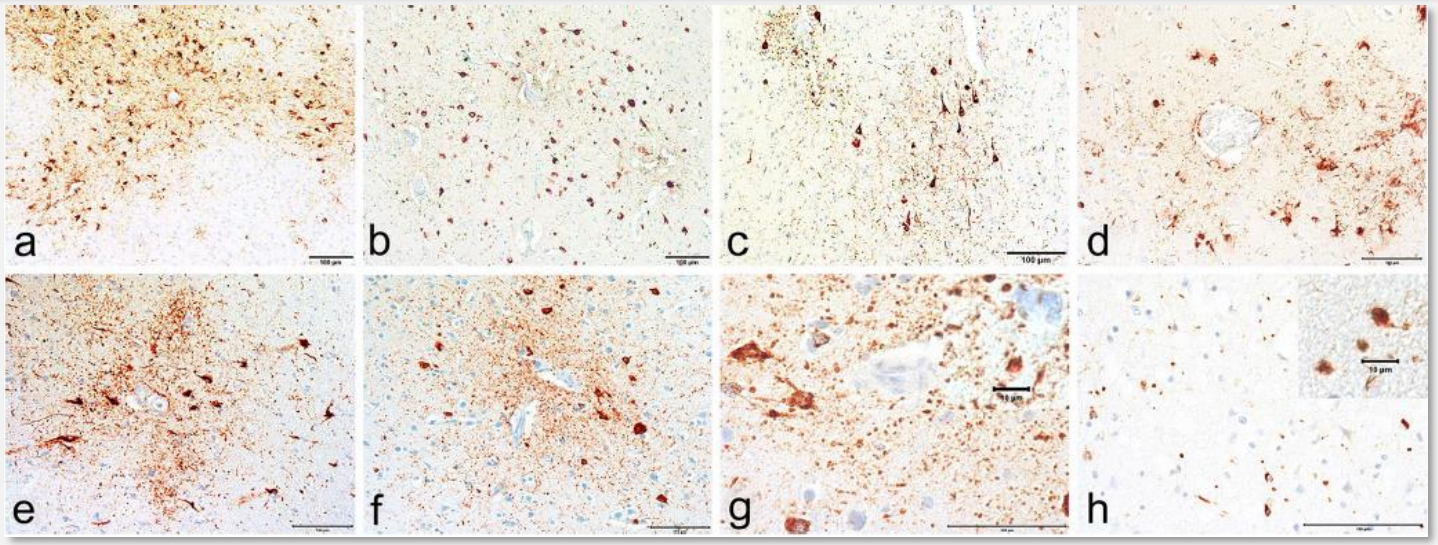


TABLE 1. Preliminary NINDS Criteria for the Pathological Diagnosis of Chronic Traumatic Encephalopathy (CTE) (31)

Required for the diagnosis of CTE (pathognomonic CTE lesion):*

1) Phosphorylated tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci.

Supportive tau-related neuropathological features of CTE:

1) Abnormal tau-immunoreactive pretangles and neurofibrillary tangle (NFTs) preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD.
2) In the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4. These regional p-tau pathologies differ from the preferential involvement of CA1 and subiculum found in AD.
3) Abnormal p-tau immunoreactive neuronal and astrocytic aggregates in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and isodendritic core (nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus).
4) Tau-immunoreactive thorny astrocytes at the glial limitans most commonly found in the subpial and periventricular regions.
5) Tau-immunoreactive large grain-like and dot-like structures (in addition to some threadlike neurites).

Supportive nontau-related neuropathological features of CTE:

1) Macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury.
2) TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala.

Aging-related tau astrogliopathy (ARTAG) may be present but is neither diagnostic nor supportive (40)

*The second consensus panel made refinements in the description of a pathognomonic lesion. They determined that the perivascular p-tau aggregates should include neurofibrillary tangles, with or without astrocytes, and that the focus had to be in deeper cortical layers not restricted to subpial and superficial regions.

2021

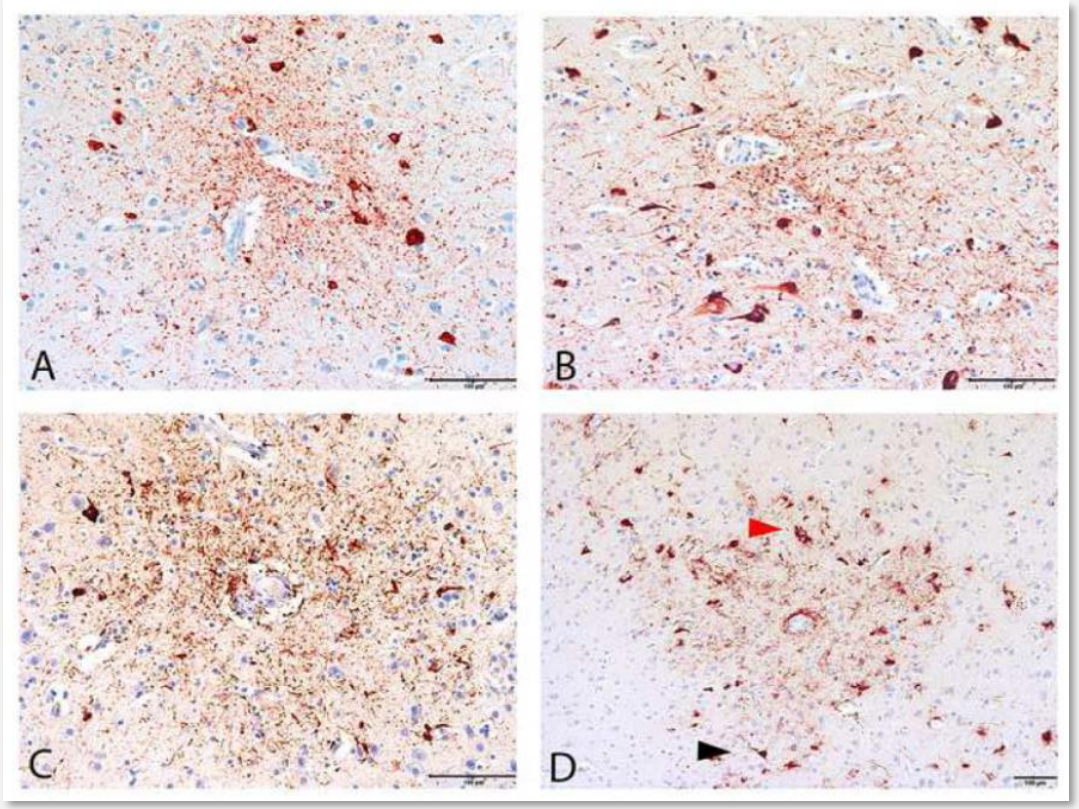
J Neuropathol Exp Neurol
Vol. 80, No. 3, March 2021, pp. 210–219
doi: 10.1093/jnen/nlab001

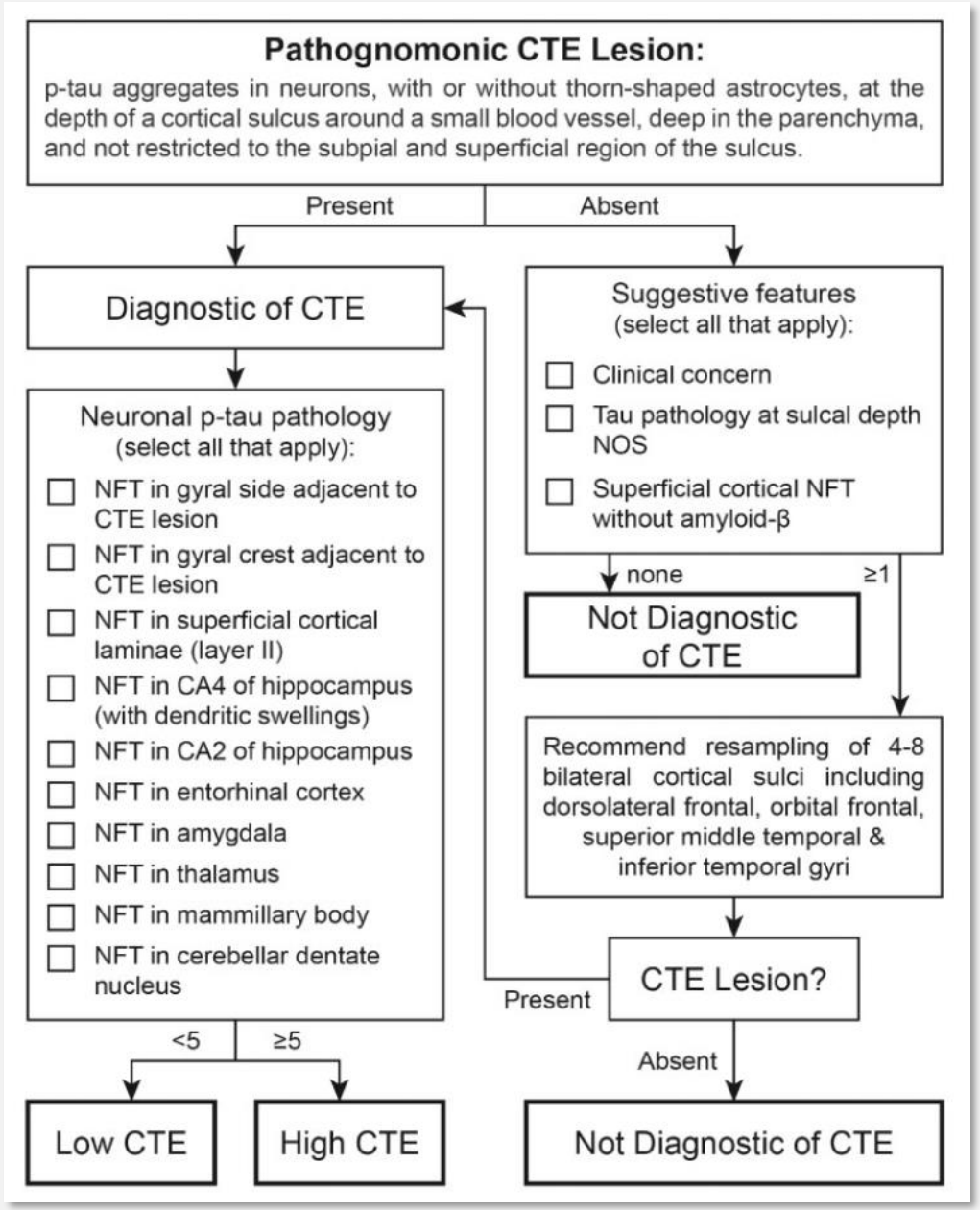
OXFORD

ORIGINAL ARTICLE

The Second NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

Kevin F. Bieniek, PhD, Nigel J. Cairns, PhD, FRCPath, John F. Crary, MD, PhD, Dennis W. Dickson, MD, Rebecca D. Folkerth, MD, C. Dirk Keene, MD, PhD, Irene Litvan, MD, Daniel P. Perl, MD, Thor D. Stein, MD, PhD, Jean-Paul Vonsattel, MD, William Stewart, PhD, FRCPath, Kristen Dams-O'Connor, PhD, Wayne A. Gordon, PhD, Yorghos Tripodis, PhD, Victor E. Alvarez, MD, Jesse Mez, MD, Michael L. Alosco, PhD, Ann C. McKee, MD, and the TBI/CTE Research Group





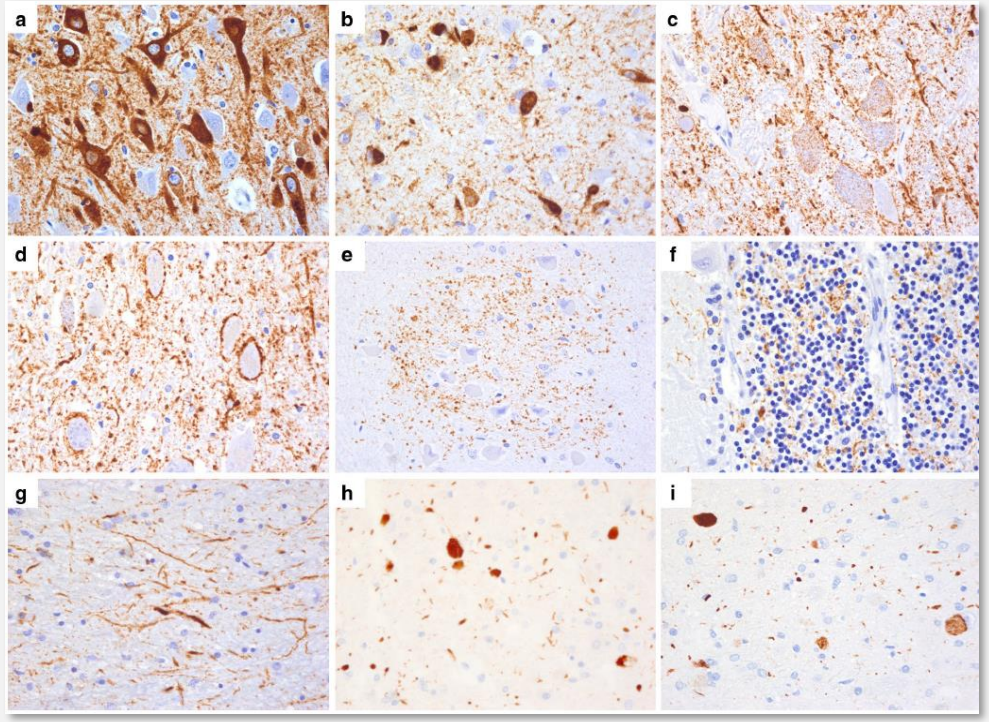
2016

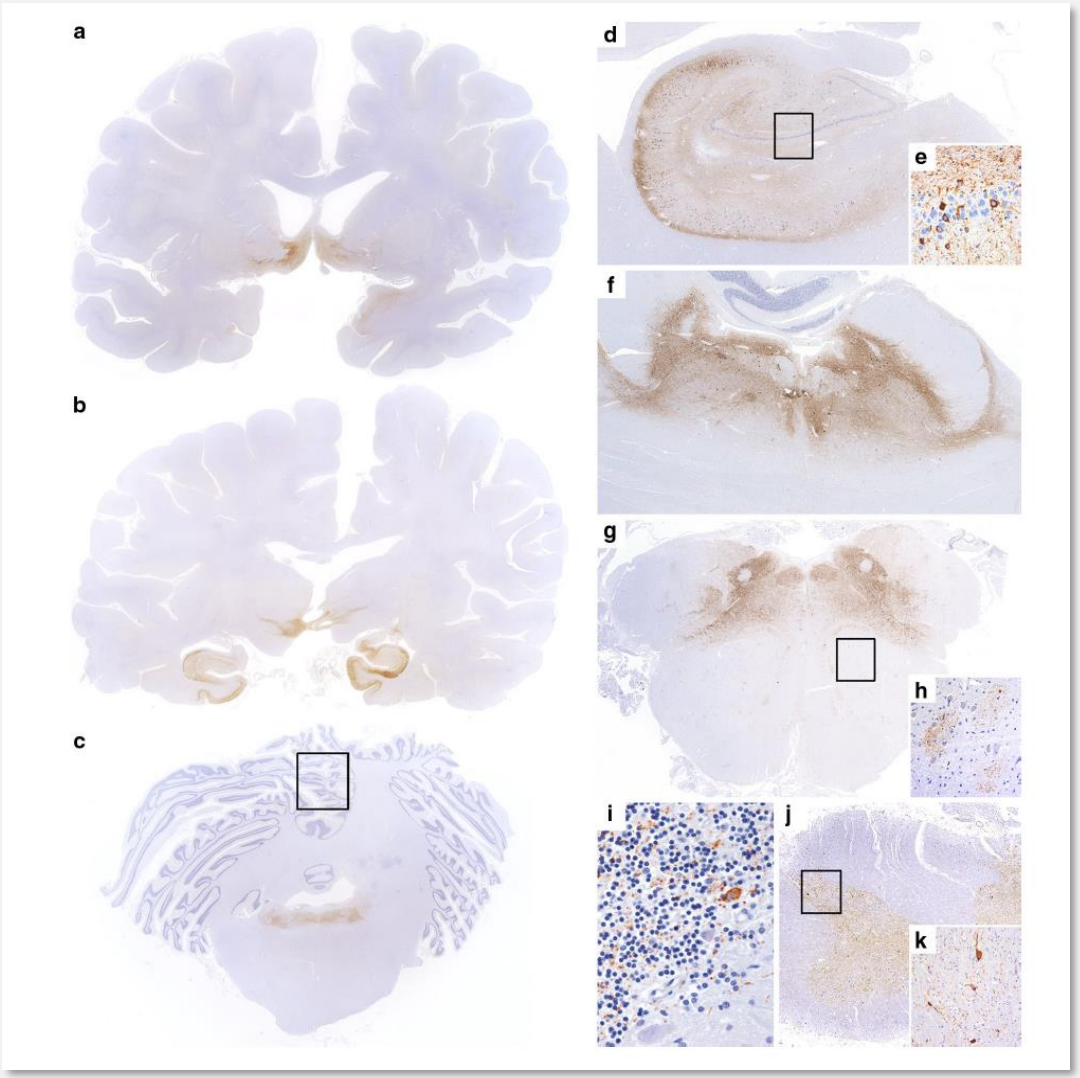
Acta Neuropathol (2016) 132:531–543
DOI 10.1007/s00401-016-1591-8

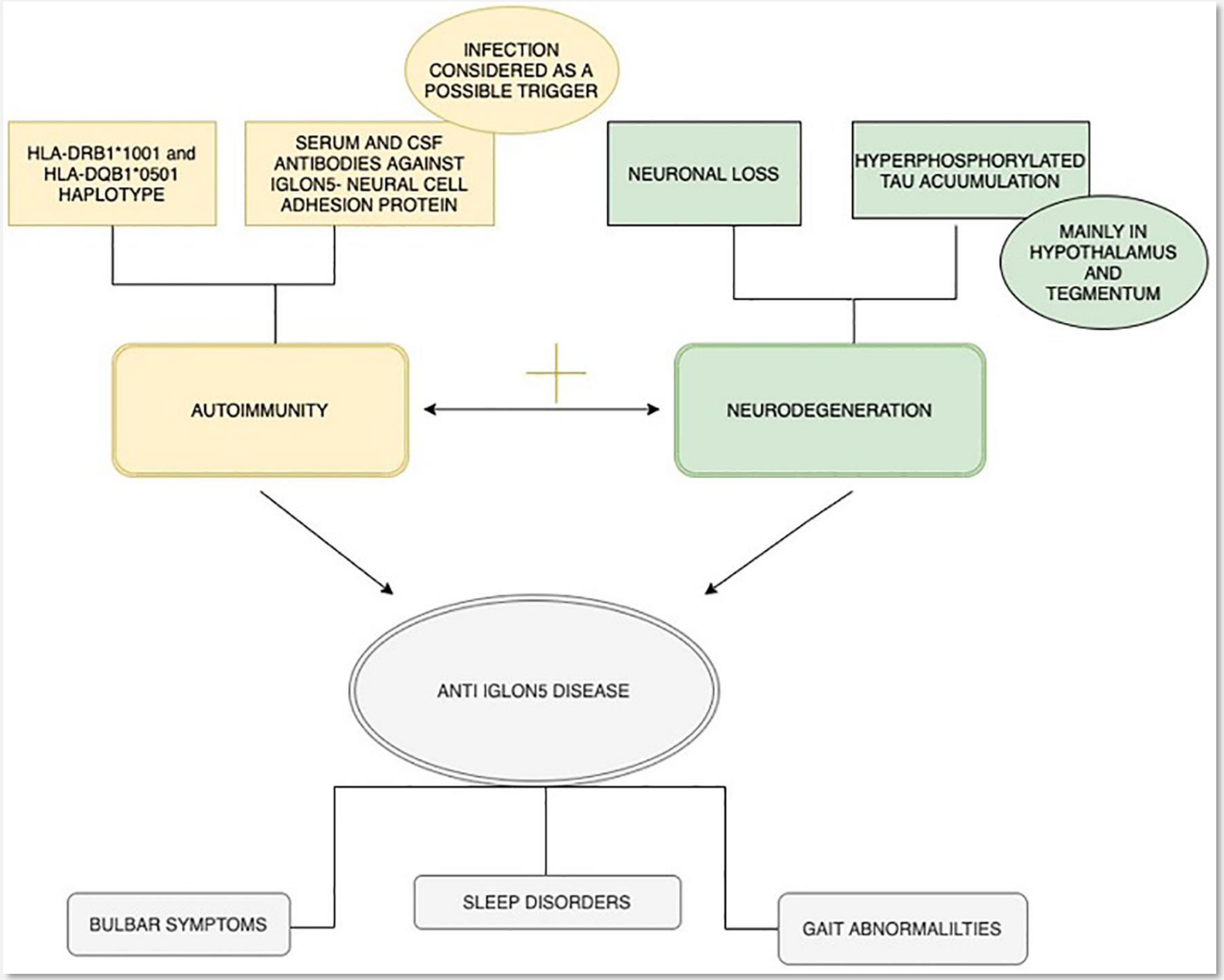
ORIGINAL PAPER

Neuropathological criteria of anti-IgLON5-related tauopathy

Ellen Gelpi[1] · Romana Höftberger[2,4] · Francesc Graus[3,4] · Helen Ling[5] · Janice L. Holton[5] · Timothy Dawson[6] · Mara Popovic[7] · Janja Pretnar-Oblak[8] · Birgit Högl[9] · Erich Schmutzhard[9] · Werner Poewe[9] · Gerda Ricken[2] · Joan Santamaria[3] · Josep Dalmau[4,10,11] · Herbert Budka[12] · Tamas Revesz[5] · Gabor G. Kovacs[2]







Madetko N *et al*., 2022

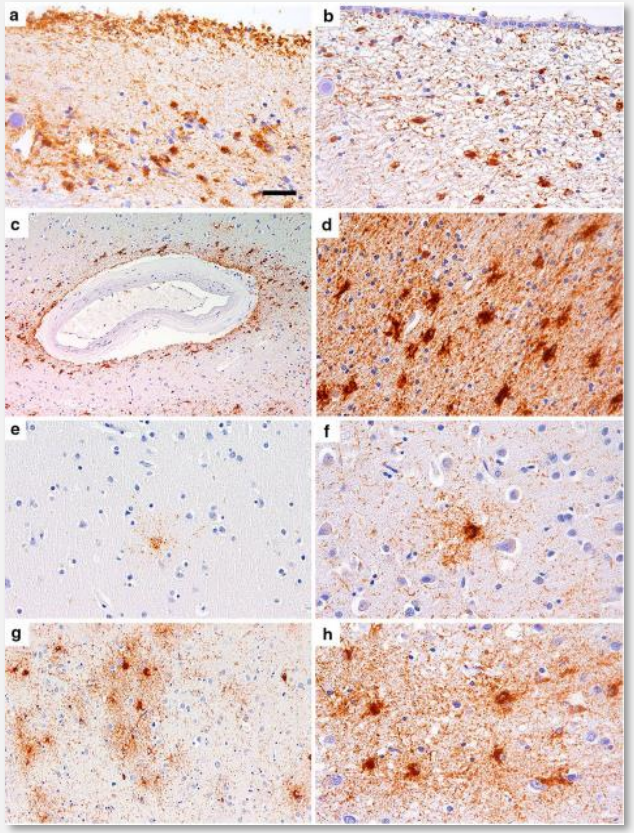
Aging-related tau astrogliopathy (ARTAG)

2016

Acta Neuropathol. 2016 January ; 131(1): 87–102. doi:10.1007/s00401-015-1509-x.

Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy

A full list of authors and affiliations appears at the end of the article.



Kovacs *et al. Acta Neuropathologica Communications* (2018) 6:50
https://doi.org/10.1186/s40478-018-0552-y

Acta Neuropathologica Communications

RESEARCH Open Access

Sequential stages and distribution patterns of aging-related tau astrogliopathy (ARTAG) in the human brain

Gabor G. Kovacs[1,2*], Sharon X. Xie[3], John L. Robinson[2], Edward B. Lee[2], Douglas H. Smith[4], Theresa Schuck[2], Virginia M.-Y. Lee[2] and John Q. Trojanowski[2*]

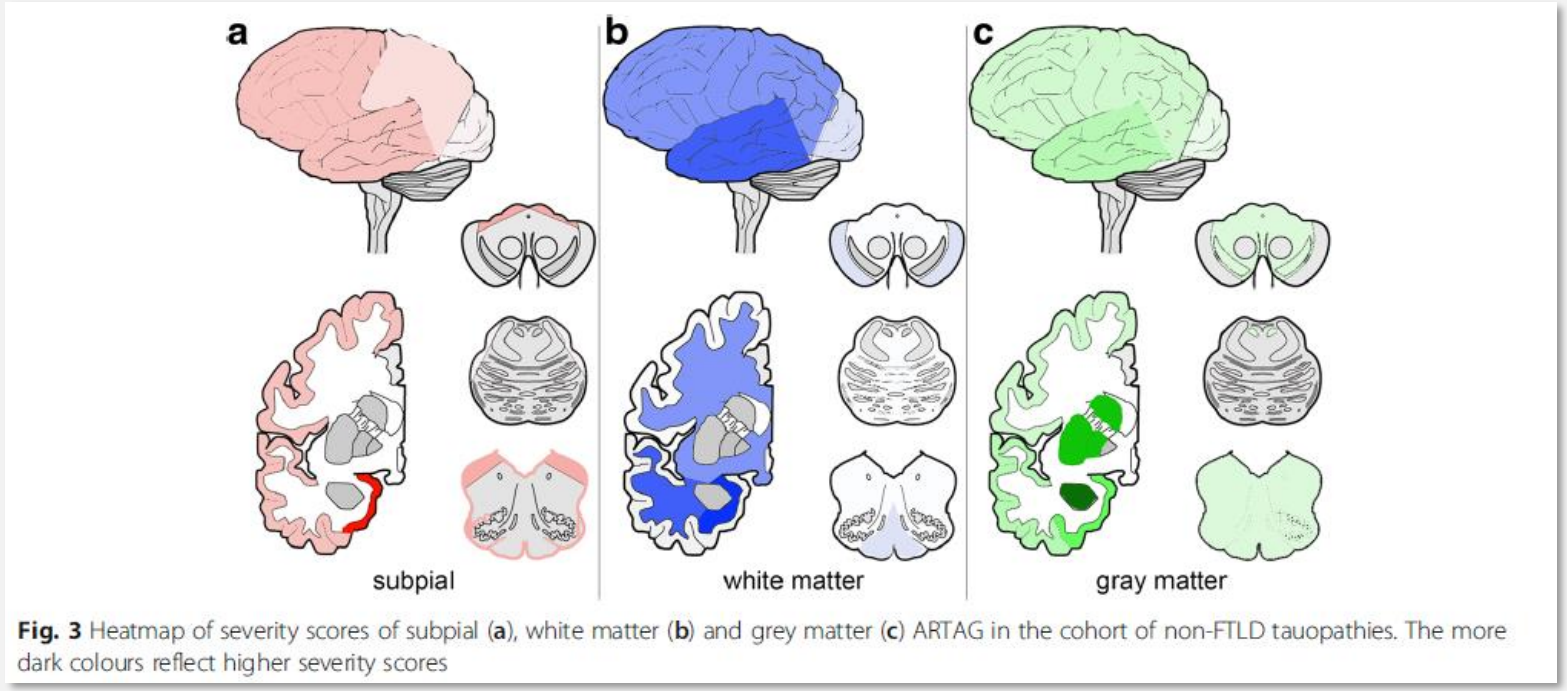


Fig. 3 Heatmap of severity scores of subpial (**a**), white matter (**b**) and grey matter (**c**) ARTAG in the cohort of non-FTLD tauopathies. The more dark colours reflect higher severity scores

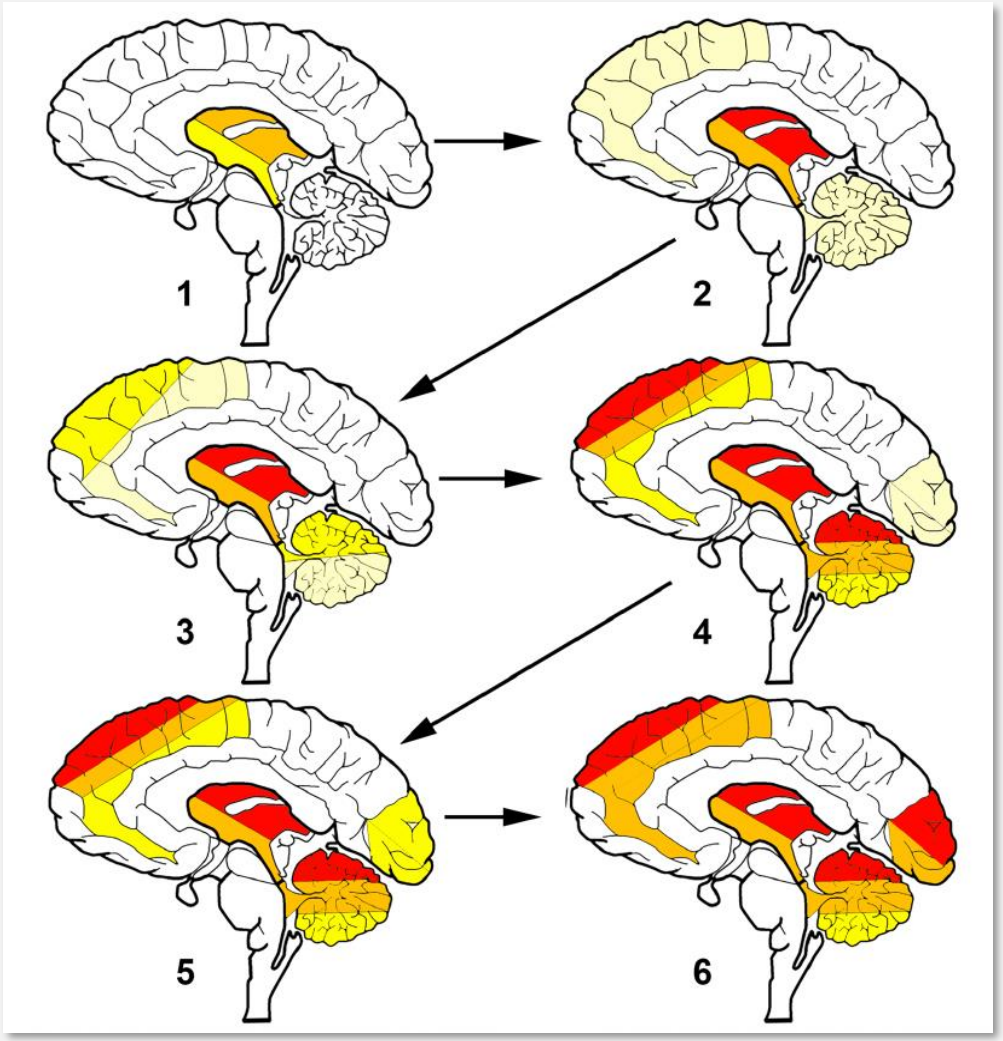
Parálisis supranuclear progresiva

2020

Steps	Neuronal
1	Globus pallidus Subthalamic nucleus Substantia nigra *Locus coeruleus*
2	Midbrain tegmentum Medulla oblongata Pons base
3	Amygdala Striatum Dentate nucleus
4	Frontal lobe
5	Parietal lobe Temporal lobe
6	Occipital lobe

Steps	Astroglial
1	Striatum
2	Striatum
3	Frontal lobe Thalamus
4	Parietal lobe Temporal lobe Amygdala
5	Occipital lobe Midbrain tegmentum
6	Subtantia nigra Globus pallidus Pons Medulla oblongata Dentate nucleus Hippocampus

Steps	Oligodendroglial
1	Globus pallidus
2	Globus pallidus
3	Thalamus
4	Striatum Cerebellum
5	Frontal lobe Parietal lobe Midbrain Pons Medulla oblongata Amygdala Hippocampus
6	Temporal lobe Occipital lobe



Sistema de estadios para la PSP-RS (aplicables a otros subtipos)

Eje principal de variación:

rostral predominant
vs.
caudal predominant

Kovacs GG *et al*., 2020

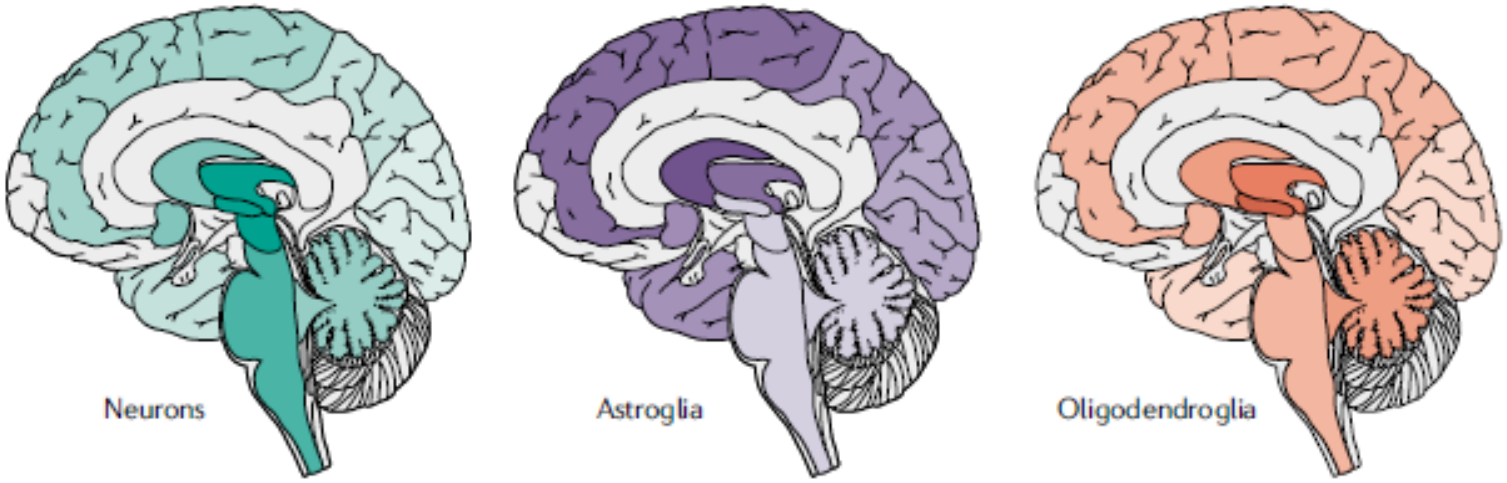
NATURE REVIEWS | NEUROLOGY

Check for updates

Evolving concepts in progressive supranuclear palsy and other 4-repeat tauopathies

Maria Stamelou[1,2,3]✉, Gesine Respondek[4], Nikolaos Giagkou[1], Jennifer L. Whitwell[5], Gabor G. Kovacs[6,7] and Günter U. Höglinger[4,8]

b Tau distribution in PSP-RS



c Neuropathology staging scheme

Stage	1 → 2			3 → 4		5 → 6
Region	Globus pallidus	Subthalamic nucleus	Striatum	Frontal cortex	Dentale Cerebellum	Occipital cortex
Cell	Neurons Oligodendroglia	Neurons	Astroglia	Astroglia	Neurons Oligodendroglia	Astroglia

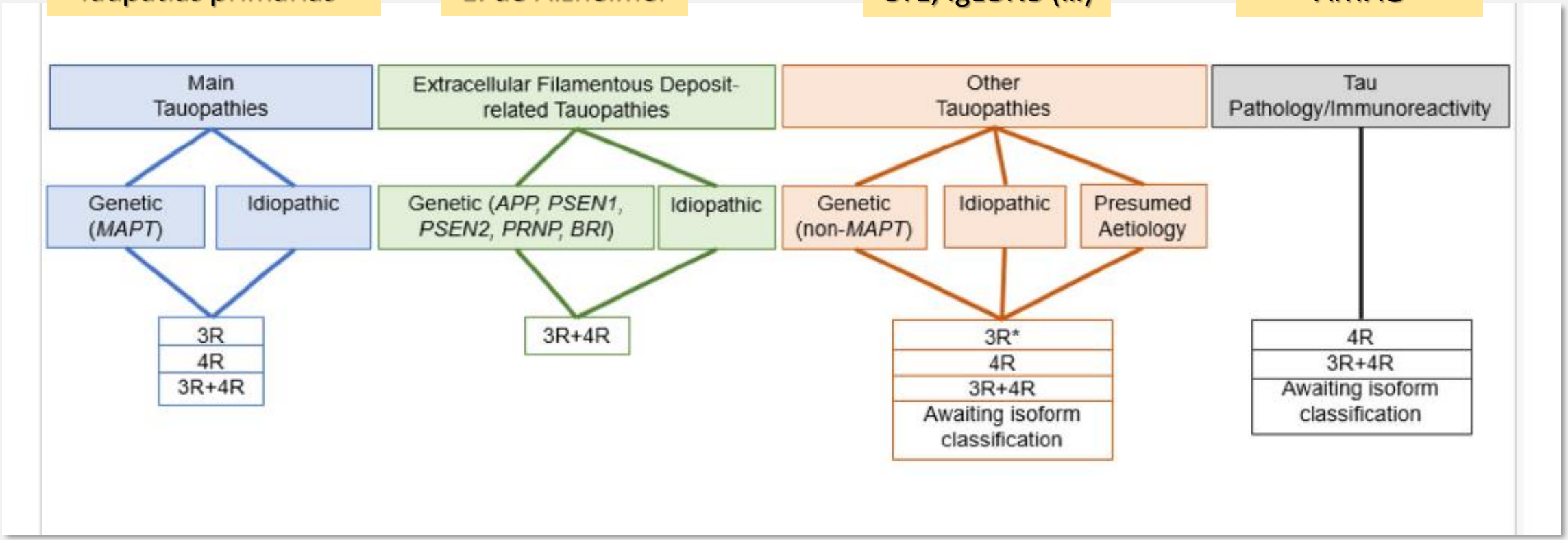
Neuropathol Appl Neurobiol. 2022 April ; 48(3): e12792. doi:10.1111/nan.12792.

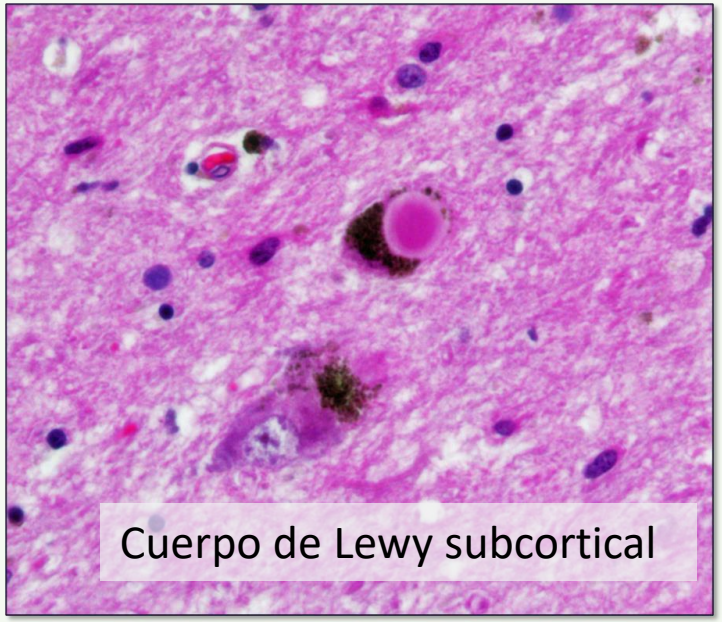
2022

Classification of Diseases with Accumulation of Tau Protein

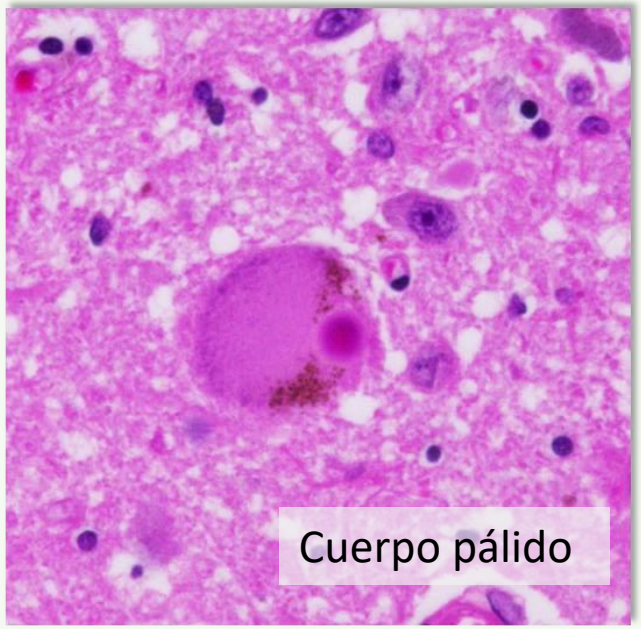
Gabor G. Kovacs, MD PhD[1,2], Bernardino Ghetti, MD[3], Michel Goedert, MD PhD[4]

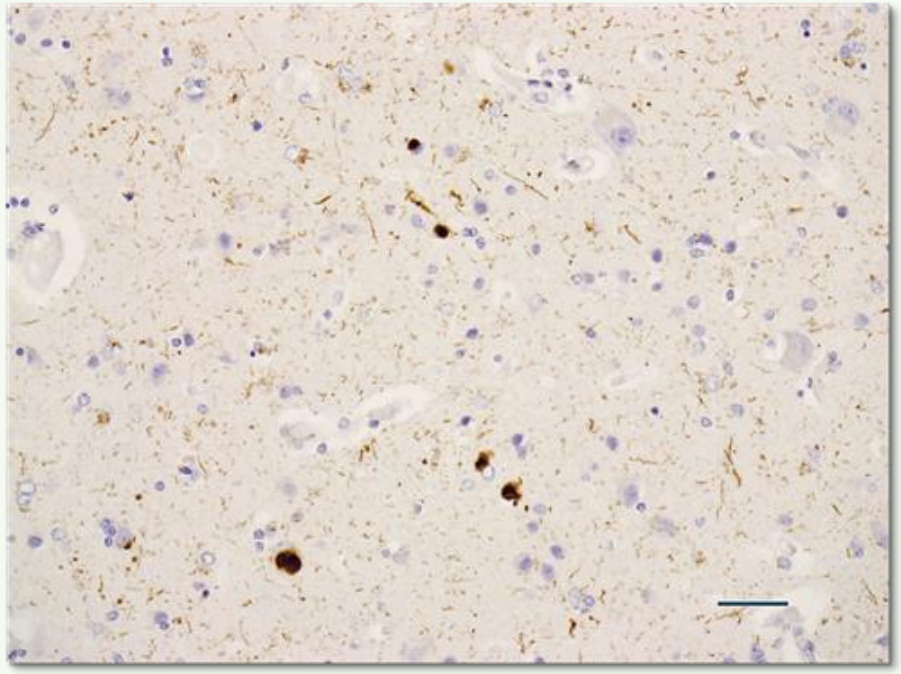
"Taupatías primarias" | E. de Alzheimer | CTE, IgLON5 (…) | ARTAG

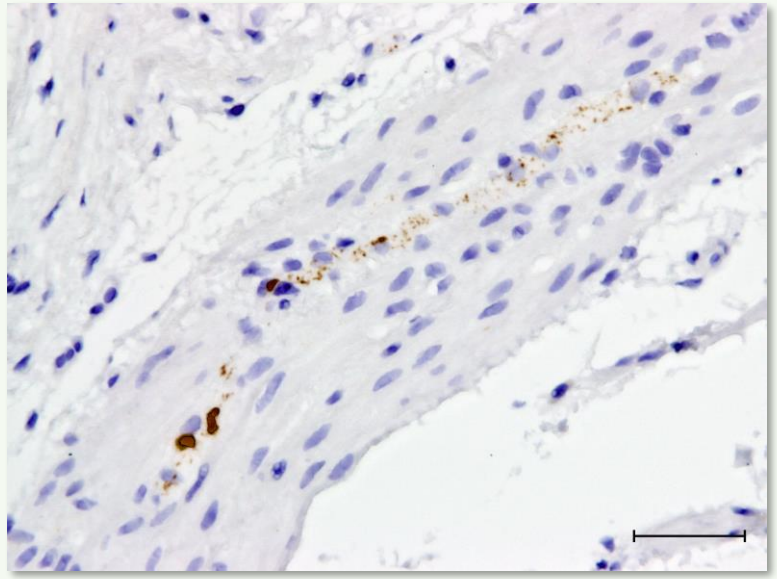



Cuerpo de Lewy subcortical


Cuerpo de Lewy cortical


Cuerpo pálido


Patología de Lewy cortical, α-sinucleína total


Fibras + en la mucosa gástrica, α-sinucleína fosforilada

Sánchez-Ferro Á, Rábano A *et al*., Mov Disord, 2015

VIEWS & REVIEWS

Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

OPEN

McKeith IG *et al.*, 2017

2017

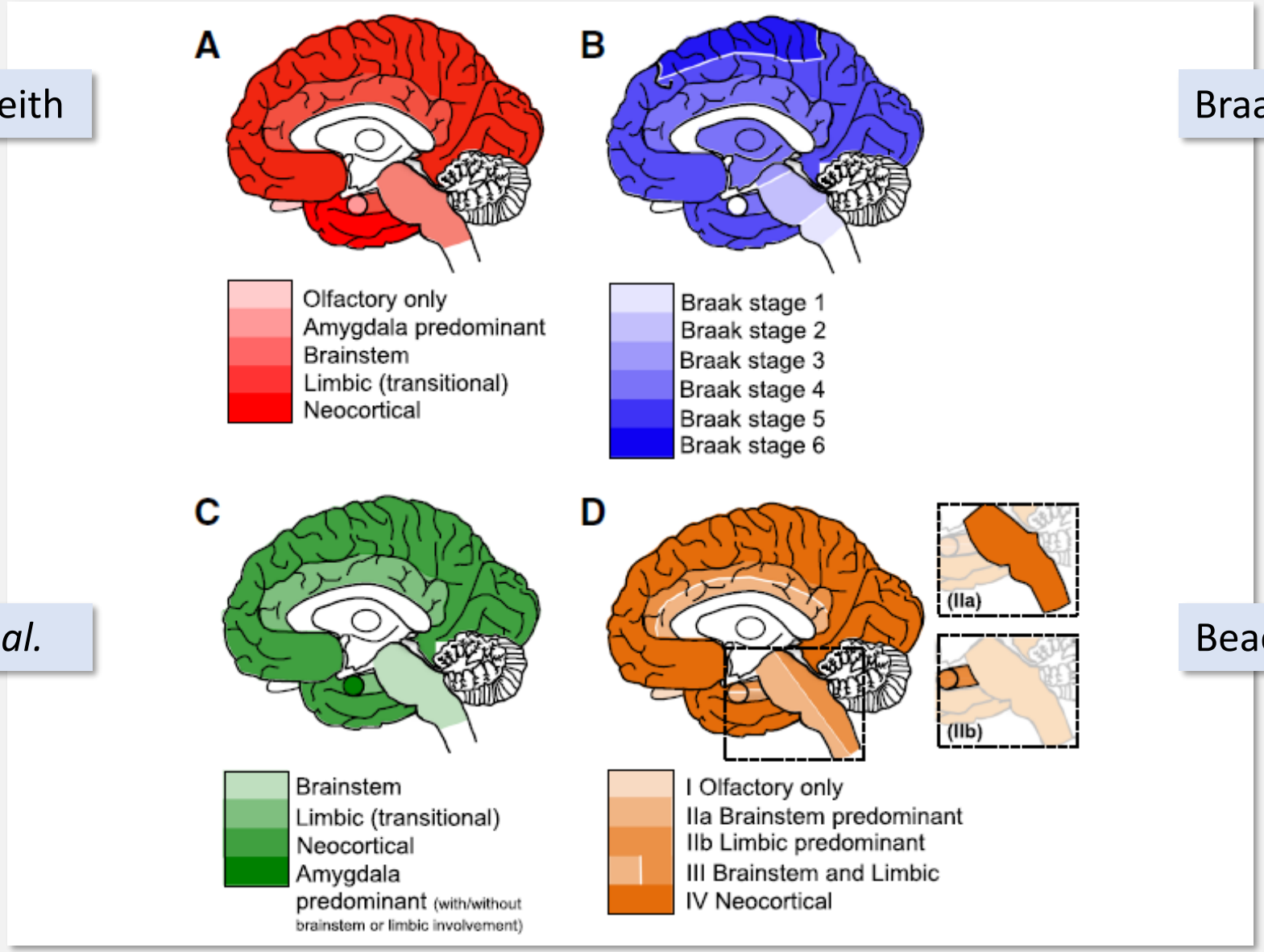
Table 2 Assessment of the likelihood that the pathologic findings are associated with a typical, dementia with Lewy bodies, clinical syndrome

Alzheimer disease neuropathologic change	NIA-AA none/low (Braak stage 0-II)	NIA-AA intermediate (Braak stage III-IV)	NIA-AA high (Braak stage V-VI)
Lewy-related pathology			
Diffuse neocortical	High	High	Intermediate
Limbic (transitional)	High	Intermediate	Low
Brainstem-predominant	Low	Low	Low
Amygdala-predominant	Low	Low	Low
Olfactory bulb only	Low	Low	Low
Substantia nigra neuronal loss to be assessed (as none, mild, moderate, and severe)[59] in order to subclassify cases into those likely or not to have parkinsonism			

Abbreviation: NIA-AA = National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer disease.[55]

Newcastle-McKeith

Braak



Leverenz *et al.*

Beach *et al.*

2021

Lewy Pathology Consensus Criteria (LPC)

Acta Neuropathologica (2021) 141:159–172
https://doi.org/10.1007/s00401-020-02255-2

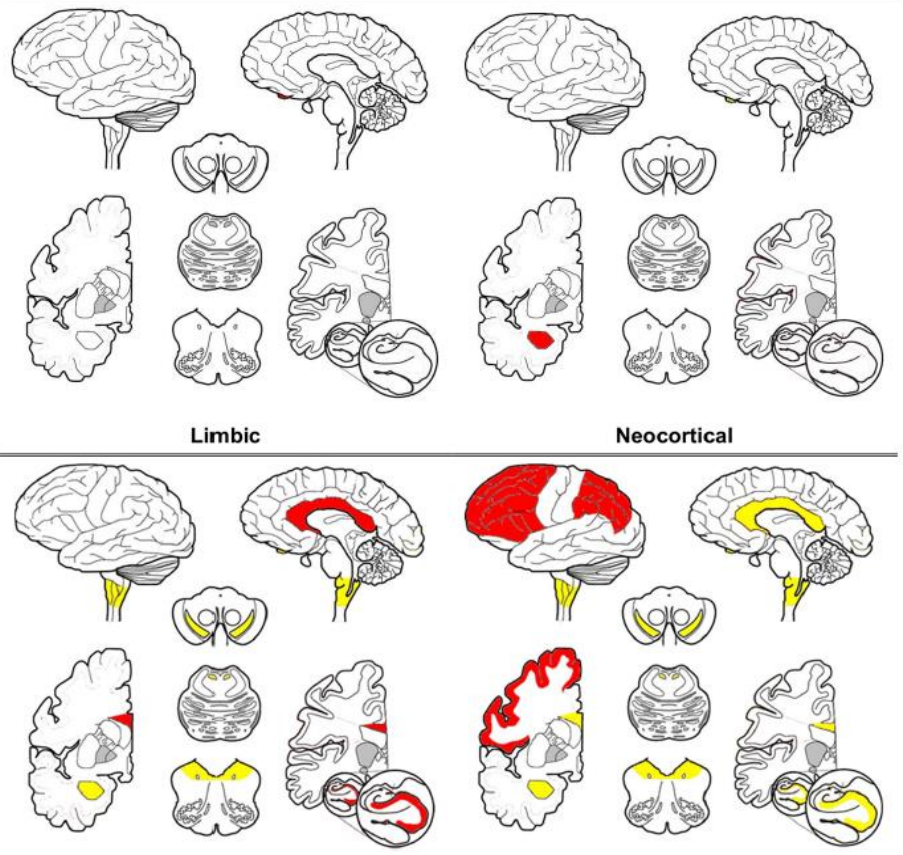
ORIGINAL PAPER

Neuropathological consensus criteria for the evaluation of Lewy pathology in post-mortem brains: a multi-centre study

Johannes Attems[1] · Jon B. Toledo[2,3] · Lauren Walker[1] · Ellen Gelpi[4,5] · Steve Gentleman[6] · Glenda Halliday[7] · Tibor Hortobagyi[8,9,10,11] · Kurt Jellinger[12] · Gabor G. Kovacs[13,14] · Edward B. Lee[3] · Seth Love[15] · Kirsty E. McAleese[1] · Peter T. Nelson[16] · Manuela Neumann[17,18] · Laura Parkkinen[19,20] · Tuomo Polvikoski[1] · Beata Sikorska[21] · Colin Smith[22] · Lea Tenenholz Grinberg[23,24] · Dietmar R. Thal[25] · John Q. Trojanowski[3] · Ian G. McKeith[1]

Category of LP	OB	Amy.	dmX or SN (1)	MTL or Cing. (1)	Fr. or Pa. ctx (1)
Olfactory only	+	-	-	-	-
Amygdala predominant	- / +	+	-	-	-
Brainstem predominant	- / +	- / +	+	-	-
Limbic	- / +	- /+	- / +	+	-
Neocortical	- / +	- / +	- / +	- /+	+

Lewy Pathology Consensus Criteria (LPC)



Ann Neurol. 2013 July ; 74(1): 20–38. doi:10.1002/ana.23937.

Stages of pTDP-43 pathology in amyotrophic lateral sclerosis

Johannes Brettschneider, MD[#1,4], Kelly Del Tredici, MD, PhD[#4], Jon B. Toledo, MD[1], John L. Robinson, BS[1], David J. Irwin, MD[1,3], Murray Grossman, MD[3], EunRan Suh, PhD[1], Vivianna M. Van Deerlin, MD, PhD[1,2], Elisabeth M. Wood, MS[1], Young Baek, MS[1], Linda Kwong, PhD[1,2], Edward B. Lee, MD, PhD[1,2], Lauren Elman, MD[3], Leo McCluskey, MD[3], Lubin Fang, MD[4], Simone Feldengut[4], Albert C. Ludolph, MD[5], Virginia M.-Y. Lee, PhD[1,2], Heiko Braak, MD[4,]**, and **John Q. Trojanowski, MD, PhD[1,2,**]**

2013

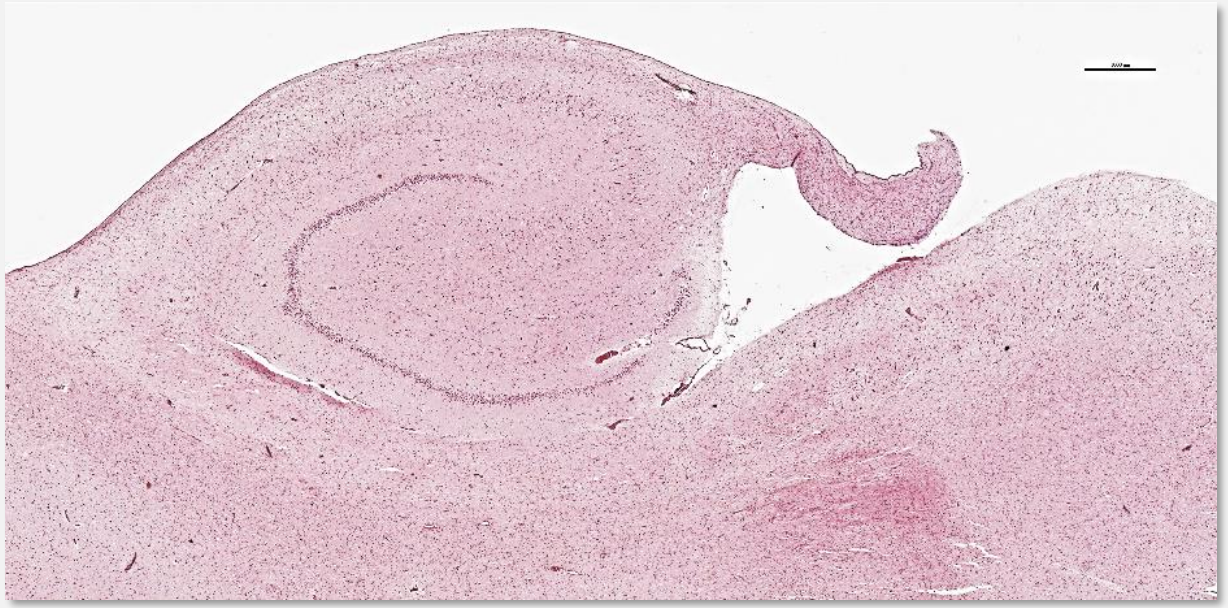
Estadios de patología TDP-43 en ELA

Tissue blocks and regions for staging of pTDP-43 pathology in ALS

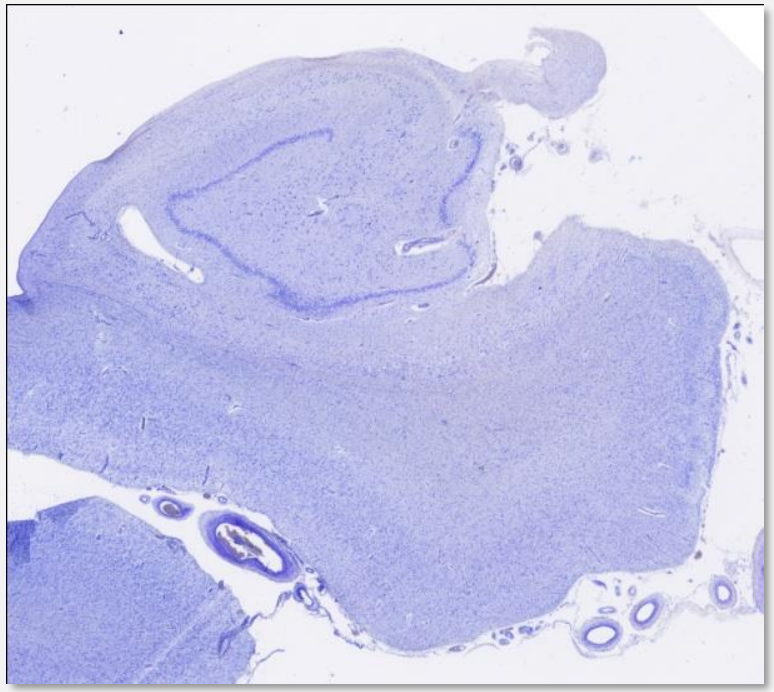
Stage 1:	block 1: agranular motor neocortex – Brodmann areas 4, 6 block 2: medulla oblongata at the level of N. XII – bulbar somatomotor neurons of N. XII optional: spinal cord layer 9 – ventral horn α-motoneurons
Stage 2:	block 1 block 2: inferior olive, medullary reticular formation optional: parvocellular portion of the red nucleus
Stage 3:	blocks 1 and 2 block 3: prefrontal neocortex (e.g., gyrus rectus, orbital gyri) block 4: striatum optional: postcentral neocortex
Stage 4:	blocks 1-4 block 5: hippocampal formation, entorhinal region, adjoining temporal neocortex

Staging is based on a minimum of five tissue blocks, additional blocks, e.g., from the spinal cord or midbrain, are optional. When assigning stages, the extent (topographical distribution pattern) is accorded more weight than the degree (severity) of the pTDP-43 pathology in each region.

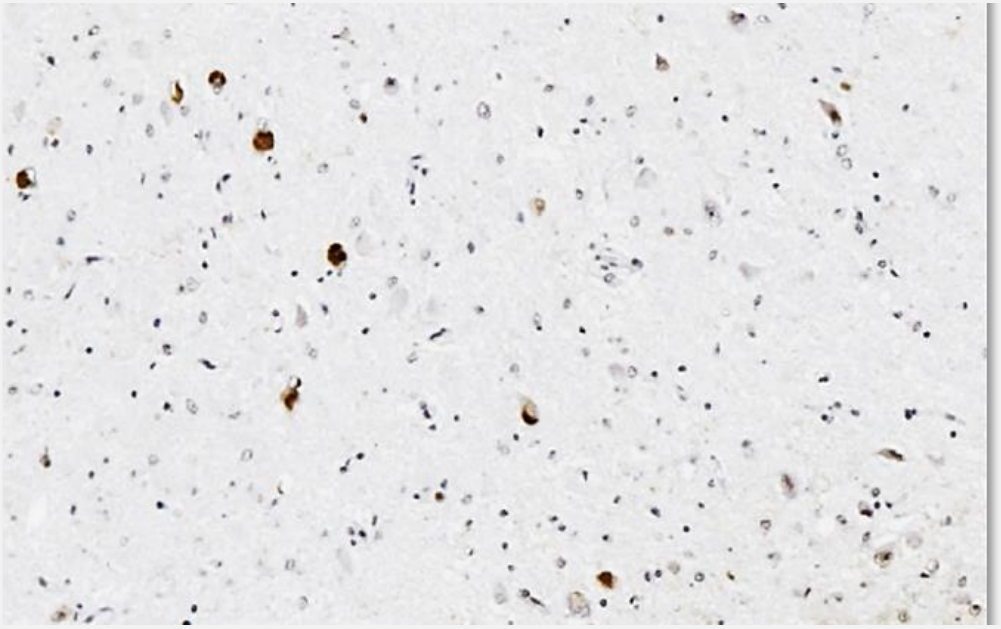
Esclerosis del hipocampo



HE



Nissl



TDP-43

2019

doi:10.1093/brain/awz099 BRAIN 2019: Page 1 of 25 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

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

Peter T. Nelson,[1] Dennis W. Dickson,[2] John Q. Trojanowski,[3] Clifford R. Jack Jr.,[4] Patricia A. Boyle,[5] Konstantinos Arfanakis,[5,6] Rosa Rademakers,[2] Irina Alafuzoff,[7] Johannes Attems,[8] Carol Brayne,[9] Ian T.S. Coyle-Gilchrist,[9] Helena C. Chui,[10] David W. Fardo,[1] Margaret E. Flanagan,[11] Glenda Halliday,[12] Suvi R.K. Hokkanen,[9] Sally Hunter,[9] Gregory A. Jicha,[1] Yuriko Katsumata,[1] Claudia H. Kawas,[13] C. Dirk Keene,[14] Gabor G. Kovacs,[15] Walter A. Kukull,[14] Allan I. Levey,[16] Nazanin Makkinejad,[6] Thomas J. Montine,[17] Shigeo Murayama,[18] Melissa E. Murray,[2] Sukriti Nag,[5] Robert A. Rissman,[19] William W. Seeley,[20] Reisa A. Sperling,[21] Charles L. White III,[22] Lei Yu[5] and Julie A. Schneider[5]

Limbic-predominant age-related TDP-43 encephalopathy (LATE)

LATE-NC
Stages 0 → 3
HS +/-

B LATE-NC related stages based on anatomic distribution of TDP-43 pathology

Simplified staging of TDP-43 proteinopathy* for routine LATE-NC diagnosis (consensus recommendation)		Josephs TDP-43 proteinopathy staging (KA Josephs et al, 2013)		Rush University TDP-43 proteinopathy staging (S Nag et al, 2017)	
0	None	0	None	0	None
1	Amygdala	1	Amygdala	1	Amygdala
2	Hippocampus	2	Entorhinal cortex, subiculum	2	Entorhinal cortex, CA1
		3	Dentate, Occipitotemporal cortex	3	Anterior temporal cortex
		4	Insula, Inf temporal cortex	4	Midtemporal and orbitofrontal cortex
		5	Inf olive, midbrain		
3	Middle frontal gyrus (MFG)	6	Basal ganglia, MFG	5	MFG

*-*Any* TDP-43 proteinopathy is seen in that anatomic region

2023

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https://doi.org/10.1007/s00401-022-02524-2

ORIGINAL PAPER

LATE-NC staging in routine neuropathologic diagnosis: an update

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Table 1 Specific pathological combinations and corresponding recommendations for LATE-NC staging

	Amygdala region*		Hippocampal region*		Middle frontal gyrus	LATE-NC Stage
	NCI(s)	Process(es)	NCI(s)	Process(es)	NCI(s)	
TDP-43 pathology: present (+) or absent (-)	+	Either + or -	-	Either + or -	-	1 (optional 1a)
	-	Either + or -	+	Either + or -	-	1 (optional 1b)
	-	+	-	Either + or -	-	1 (optional 1c)
	-	Either + or -	-	+	-	1 (optional 1c)
	+	Either + or -	+	Either + or -	-	2
	+	Either + or -	+	Either + or -	+	3**

*Amygdala region and hippocampal region refer to anatomical areas on the same slide

**See recommendations to distinguish LATE-NC Stage 3 from FTLD-TDP and ALS

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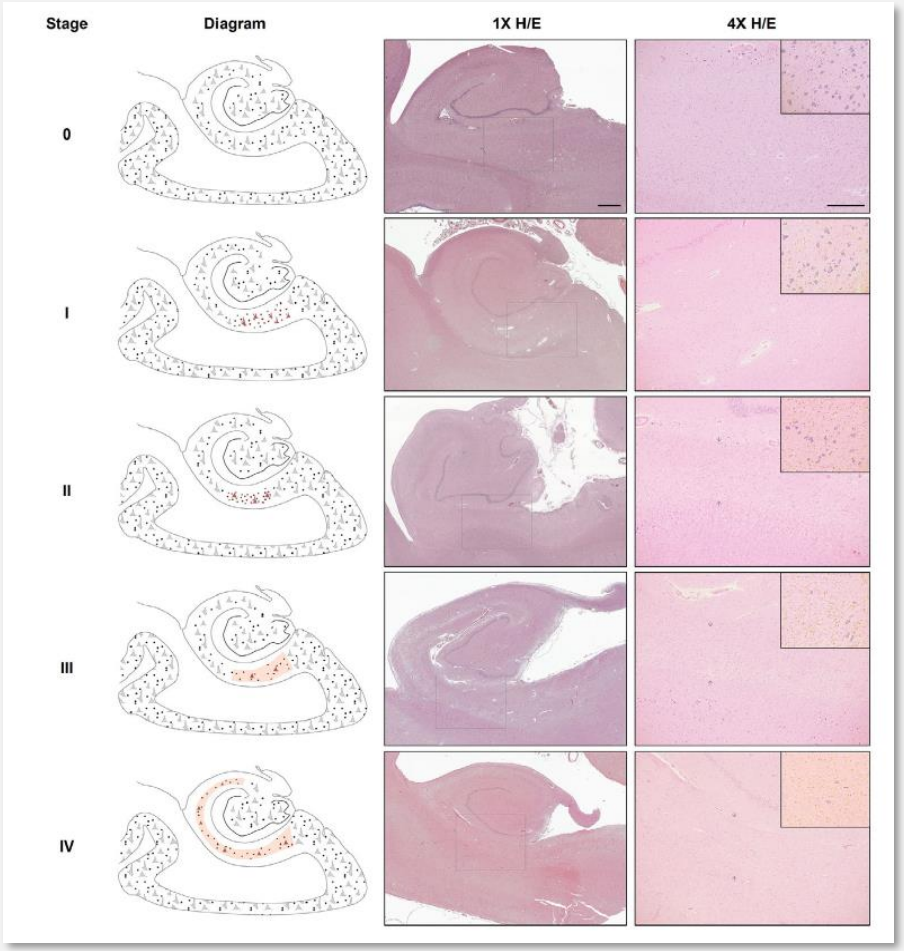
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

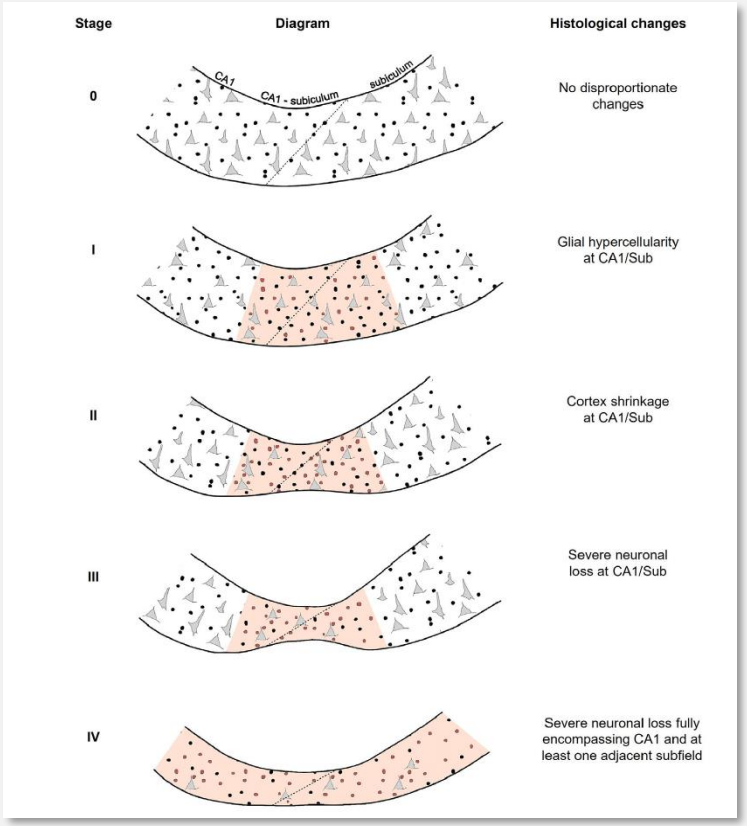
RESEARCH ARTICLE

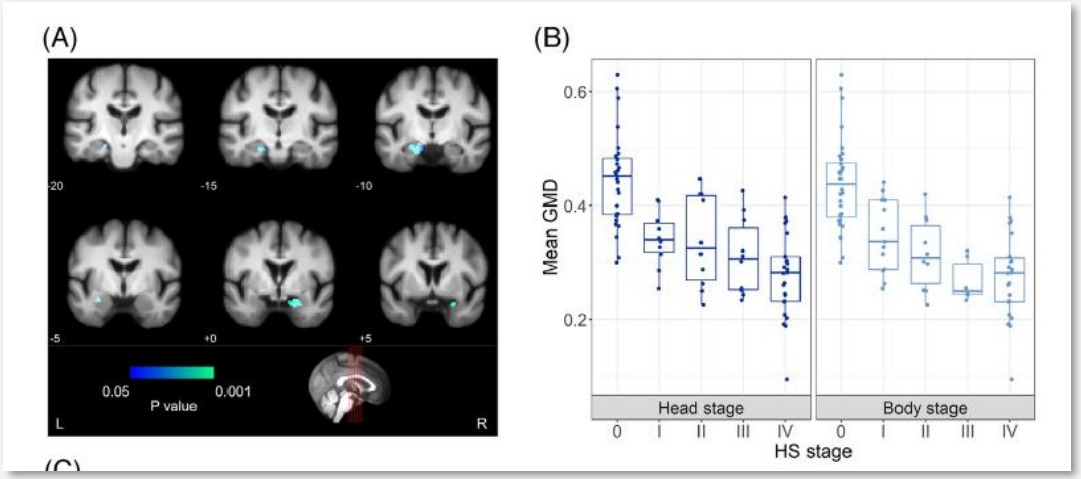
A novel histological staging of hippocampal sclerosis that is evident in gray matter loss in vivo

Diana Ortega-Cruz[1,2] | Alicia Uceda-Heras[2,3] | Juan Eugenio Iglesias[4,5] | María Ascensión Zea-Sevilla[2] | Bryan Strange[1,2] | Alberto Rabano[2]

2022







doi:10.1093/brain/aww214 BRAIN 2016: Page 1 of 13 | 1

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]

2016

Evaluación de la patología cerebrovascular asociada a deterioro cognitivo (VCING)

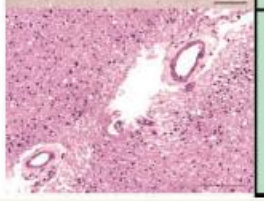
Likelihood that cerebral vascular disease contributed to cognitive impairment		Low (<50%)			Moderate (50-80%)		High (>80%)		
One or more large (> 10 mm) subcortical cerebral infarcts		-	-	-	+	-	+	+	+
Moderate or severe occipital leptomeningeal CAA		-	+	-	-	+	+	-	+
Moderate or severe occipital white matter arteriolosclerosis		-	-	+	-	+	-	+	+

Figure 1 VCING model estimating the likelihood that cerebrovascular disease contributed to cognitive impairment. Combinations of the three main determinants—at least one large (>10 mm diameter) infarct, moderate/severe occipital leptomeningeal CAA, and moderate/severe arteriolosclerosis in the occipital white matter—are used to assign a low, intermediate or high likelihood that cerebrovascular disease contributed to cognitive impairment in an individual case. Scale bars in the *top*, *middle* and *bottom* photomicrographs represent 1 mm, 250 μm and 100 μm, respectively.

ELSEVIER
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Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 83-91
Alzheimer's & Dementia

Perspective

Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development

Gil D. Rabinovici[a], Maria C. Carrillo[b], Mark Forman[c], Susan DeSanti[d], David S. Miller[e], Nicholas Kozauer[f], Ronald C. Petersen[g], Christopher Randolph[h,i], David S. Knopman[g], Eric E. Smith[j], Maria Isaac[k], Niklas Mattsson[l,m], Lisa J. Bain[n], James A. Hendrix[b,*], John R. Sims[o]

Alzheimers Dement. 2017 June ; 13(6): 654–662. doi:10.1016/j.jalz.2016.09.015.

Mixed neuropathologies and estimated rates of clinical progression in a large autopsy sample

Willa D. Brenowitz[1], **Rebecca A. Hubbard**[2], **C. Dirk Keene**[3], **Stephen E. Hawes**[4], **W.T. Longstreth Jr**[1,5], **Randy L. Woltjer**[6], and **Walter A. Kukull**[1]

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Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+ Study

John L. Robinson[1], **Maria M. Corrada**[2], **Gabor G. Kovacs**[1,3], **Myrna Dominique**[1], **Carrie Caswell**[4], **Sharon X. Xie**[4], **Virginia M.-Y. Lee**[1], **Claudia H. Kawas**[5], and **John Q. Trojanowski**[1]

doi:10.1093/brain/awab099 BRAIN 2021: 144; 2186–2198 | 2186
BRAIN
ORIGINAL ARTICLE

Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease

Salvatore Spina,[1,†] Renaud La Joie,[1,†] Cathrine Petersen,[1] Amber L. Nolan,[1] Deion Cuevas,[1] Celica Cosme,[1] Mackenzie Hepker,[1] Ji-Hye Hwang,[1] Zachary A. Miller,[1] Eric J. Huang,[2] Anna M. Karydas,[1] Harli Grant,[1] Adam L. Boxer,[1] Maria Luisa Gorno-Tempini,[1] Howard J. Rosen,[1] Joel H. Kramer,[1] Bruce L. Miller,[1] William W. Seeley,[1,2] Gil D. Rabinovici[1,3] and Lea T. Grinberg[1,2]

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

John L. Robinson,[1,2,3,4] Edward B. Lee,[1,2,3,4] Sharon X. Xie,[1,2,3,4,5] Lior Rennert,[1,2,3,4,5] EunRan Suh,[1,2,3,4] Colin Bredenberg,[1,2,3,4] Carrie Caswell,[1,2,3,4,5] Vivianna M. Van Deerlin,[1,2,3,4] Ning Yan,[1,2,3,4,6] Ahmed Yousef,[1,2,3,4] Howard I. Hurtig,[1,2,3,7] Andrew Siderowf,[1,2,3,7] Murray Grossman,[1,2,3,7,8] Corey T. McMillan,[7,8] Bruce Miller,[9] John E. Duda,[3,10] David J. Irwin,[1,2,3,7,8] David Wolk,[1,2,3,7,8,11] Lauren Elman,[3,7] Leo McCluskey,[3,7] Alice Chen-Plotkin,[1,2,3,7] Daniel Weintraub,[2,3,12] Steven E. Arnold,[13] Johannes Brettschneider,[14] Virginia M.-Y. Lee[1,2,3,4,7] and John Q. Trojanowski[1,2,3,4,7]

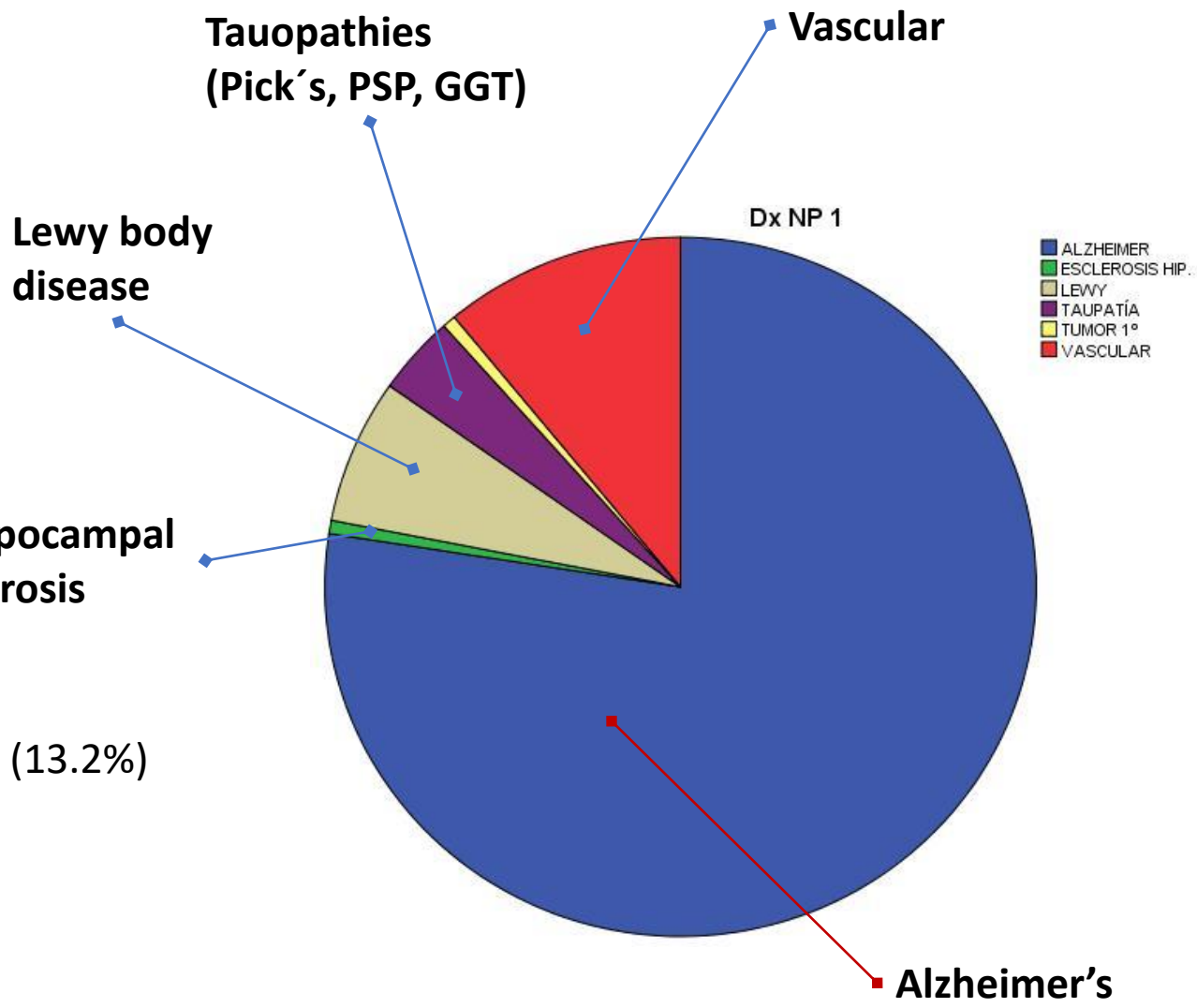
Heterogeneidad patológica y comorbilidad en demencia

- Patología de tipo Alzheimer
- Patología cerebrovascular
- Patología de tipo Lewy
- Limbic-predominant age-related TDP-43 encephalopathy (LATE)
- Aging-related tau astrogliopathy (ARTAG)
- Enfermedad de granos argirófilos
- Otras patologías

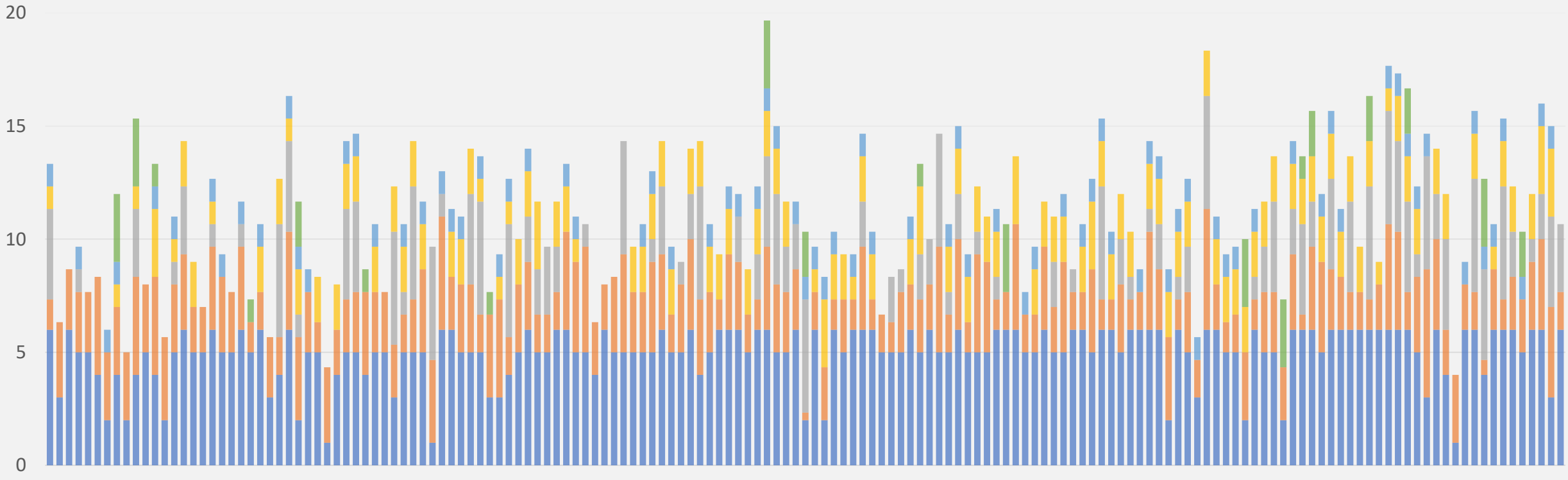
N	167
Sex	79% female
T in CAFRS (mths)	52.9 (38.6)
Age at onset	75.4 (7.3)
Age at death	87.2 (6.5)
Survival time	11.9 (4.4)
PMI (hrs.)	4.5 (2.1)
APOE e4	45.2%
High ADNC	75.8%
High vascular path.	54.5%
Lewy path. (LPC>1)*	37.8%
LATE (HS)	71.2% (45.2%)
ARTAG	52.7%
AGD	12%

*LPC =1 (13.2%)

Main neuropathological diagnosis



Vallecas Alzheimer's Study



- Alzheimer' pathology (Braak stage 0 – 6)
- Cerebrovascular pathology (0 – 5)
- Lewy type pathology (0 – 6)
- TDP-43 pathology (LATE) (0 – 3)
- ARTAG (0 – 1)
- Argyrophilic grain disease (0 – 3)

Lancet Healthy Longev. 2023 Mar; 4(3): e115–e125.
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PMCID: PMC9977689
PMID: 36870337

The prevalence, correlation, and co-occurrence of neuropathology in old age: harmonisation of 12 measures across six community-based autopsy studies of dementia

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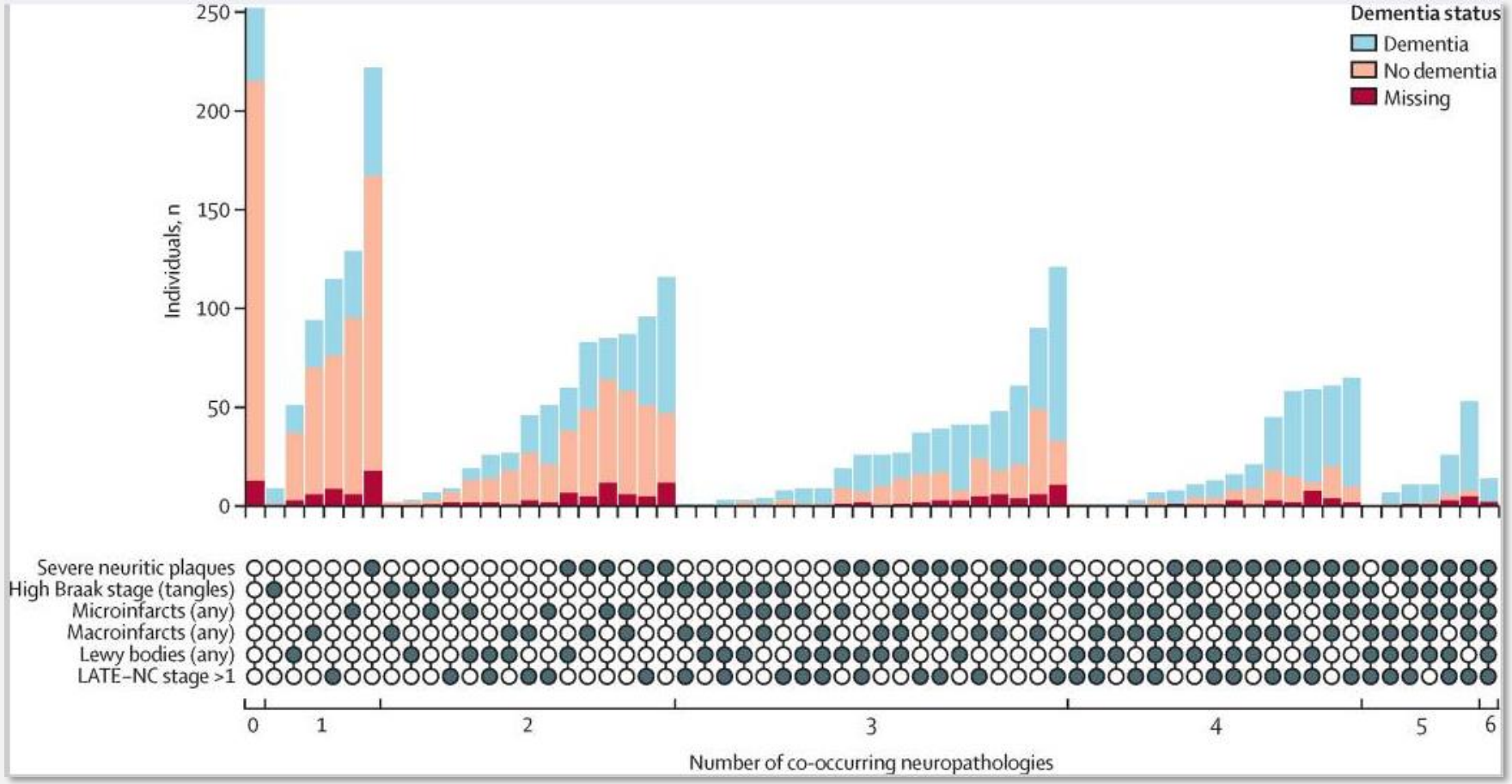
2023

6 cohortes
4354 sujetos >80 años
6 hallazgos patológicos
demencia vs. no demencia



El futuro…

Perosa *et al. acta neuropathol commun* (2021) 9:141
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Acta Neuropathologica Communications

METHODOLOGY ARTICLE Open Access

Deep learning assisted quantitative assessment of histopathological markers of Alzheimer's disease and cerebral amyloid angiopathy

Valentina Perosa[1,2*†], Ashley A. Scherlek[3,4†], Mariel G. Kozberg[4], Lindsey Smith[5], Thomas Westerling-Bui[5], Corinne A. Auger[4], Serge Vasylechko[6], Steven M. Greenberg[1] and Susanne J. van Veluw[1,4*]

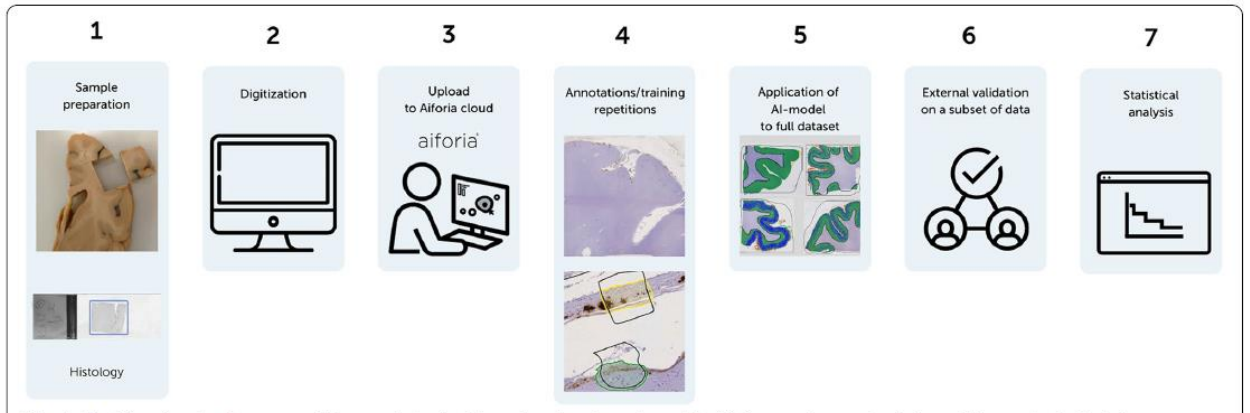
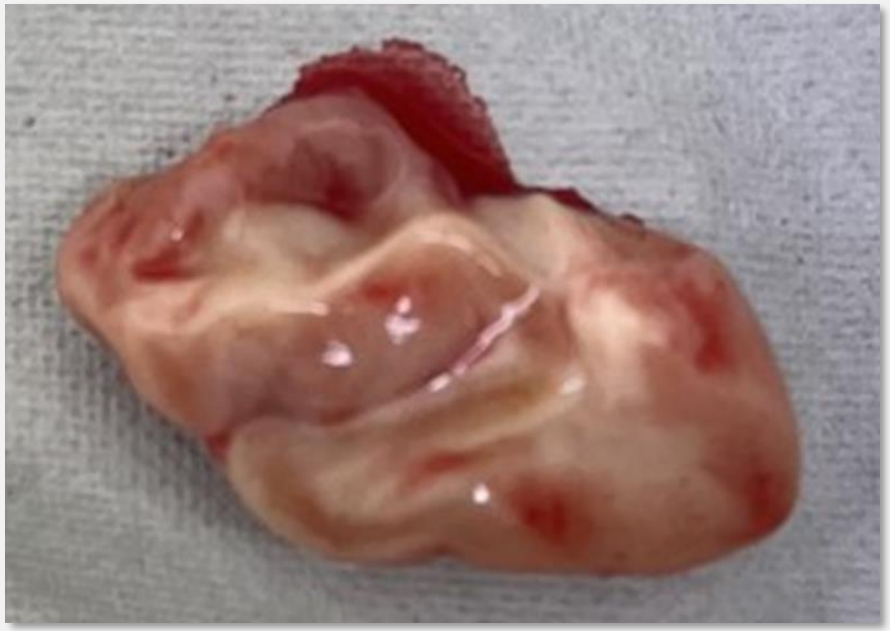
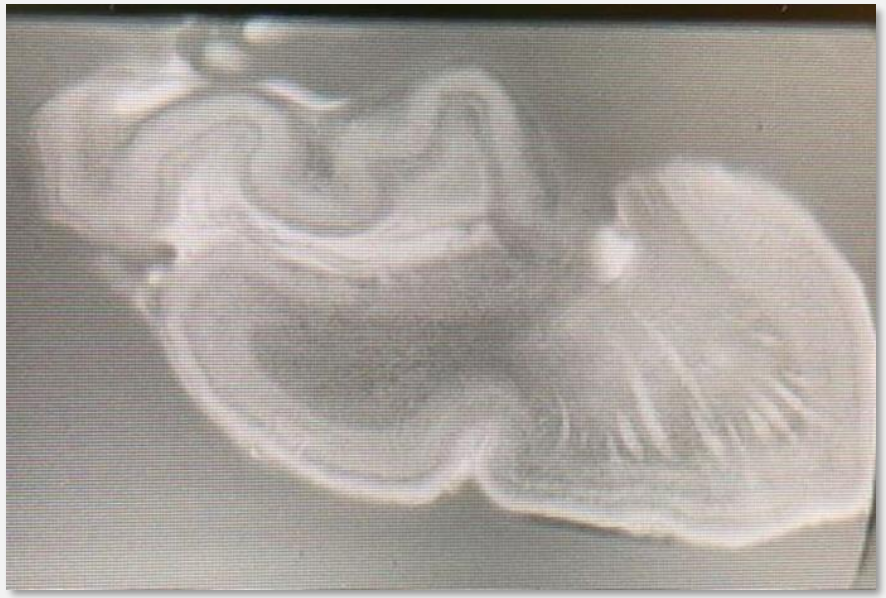


Fig. 1 Workflow for development of histopathological deep learning-based models. (1) Preparation and staining of histopathological tissue sections; (2) Digitization of high resolution whole slide images; (3) Uploading on the Aiforia ® cloud based platform; (4) Annotations on a representative subset (approximately 10%) of the whole dataset and repetitive training of the separate convolutional neural networks (CNNs), that constitute the deep learning-based model (AI-model); (5) Application of the model on the whole dataset; (6) Validation of each CNN; (7) Statistical analysis





Gracias!

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