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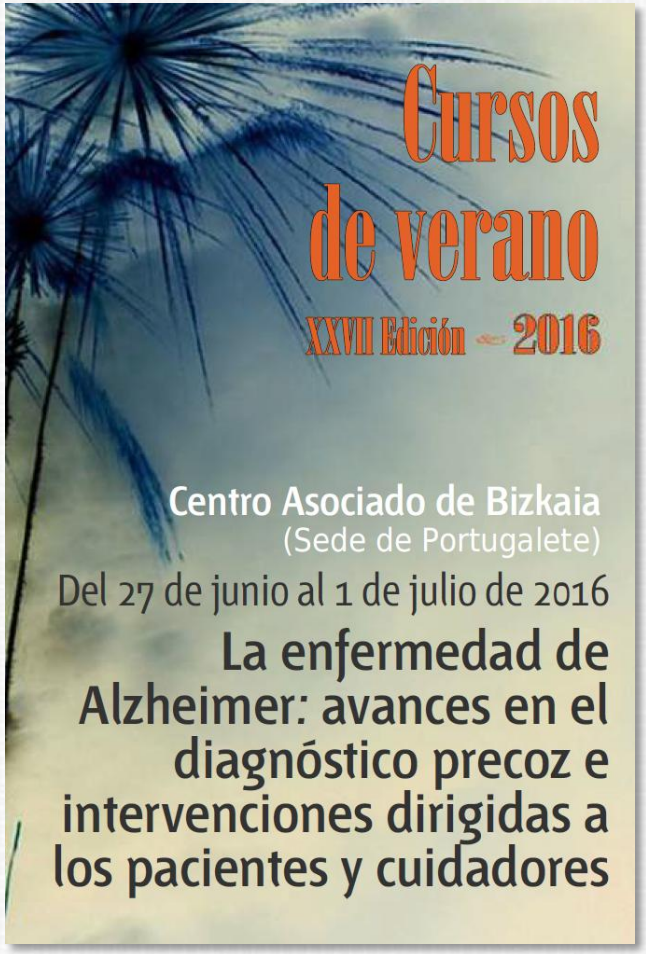

La patología de tipo Alzheimer: un tema con variaciones

Alberto Rábano

Banco de Tejidos CIEN
Fundación CIEN, ISCIII

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Informe anual 2010

Unidad de Investigación Proyecto Alzheimer

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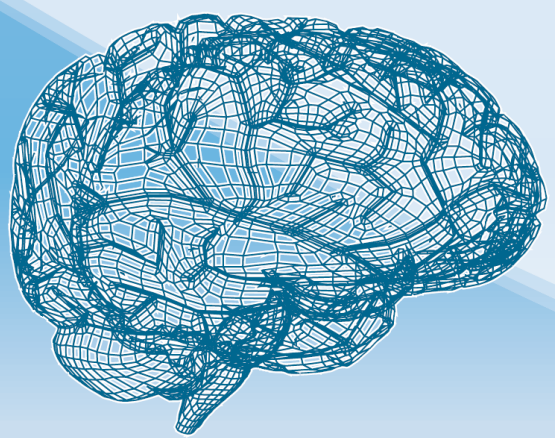

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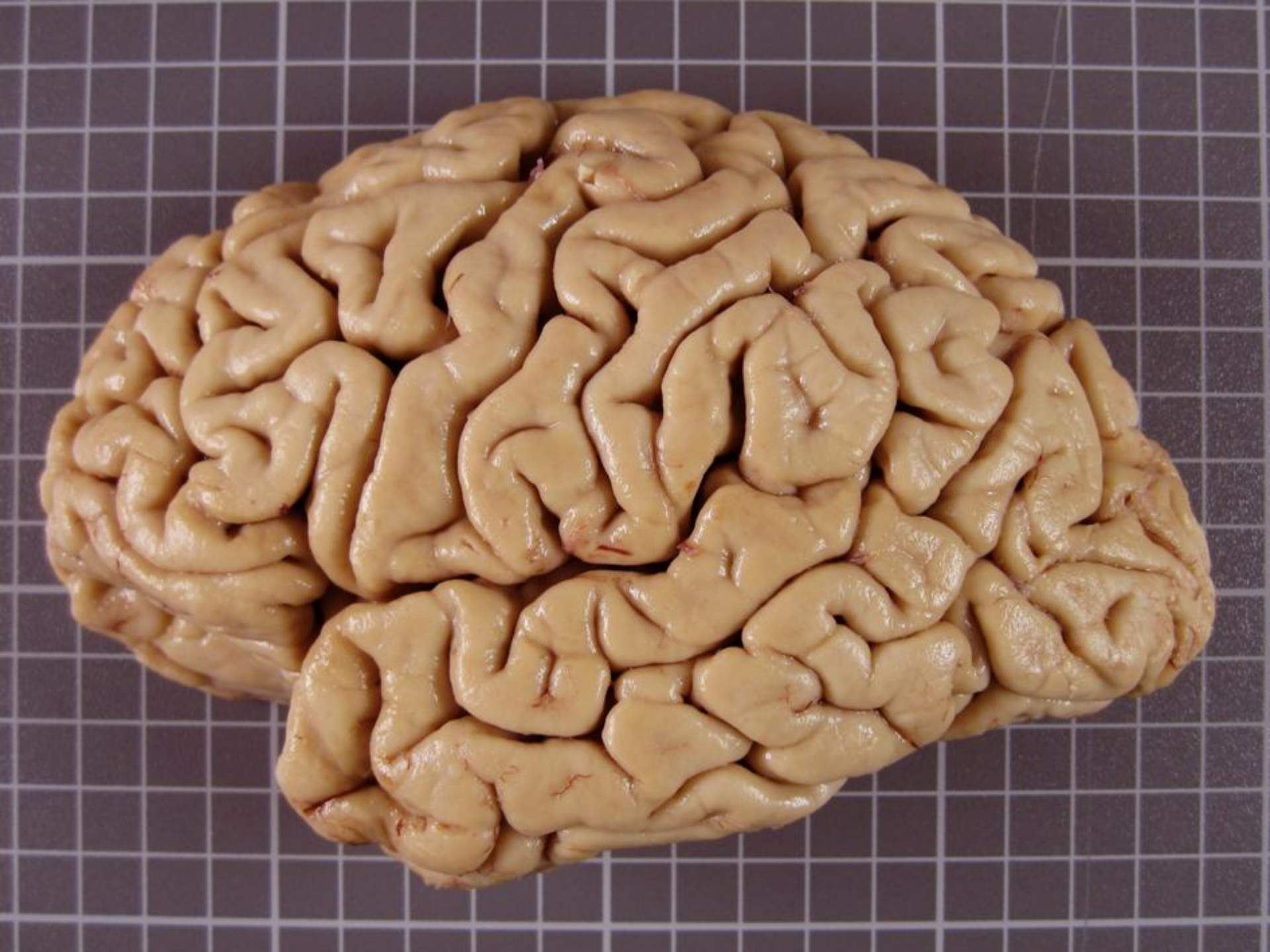

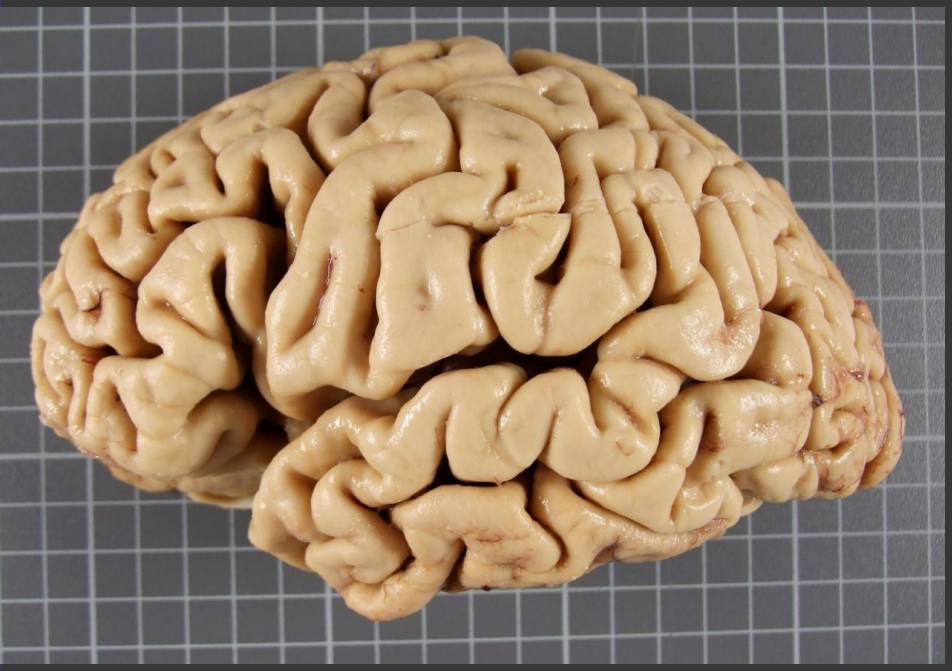
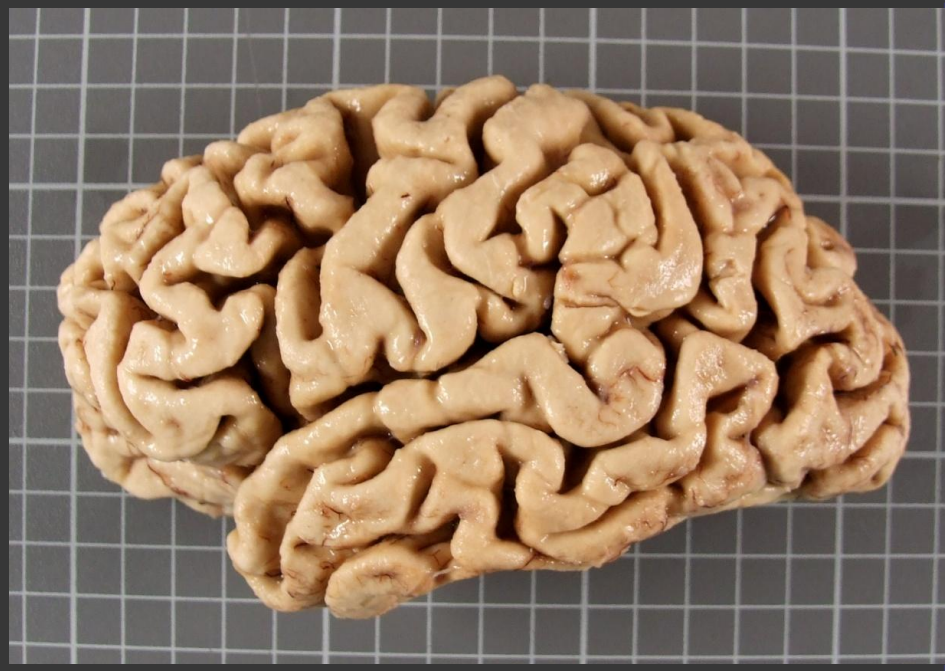
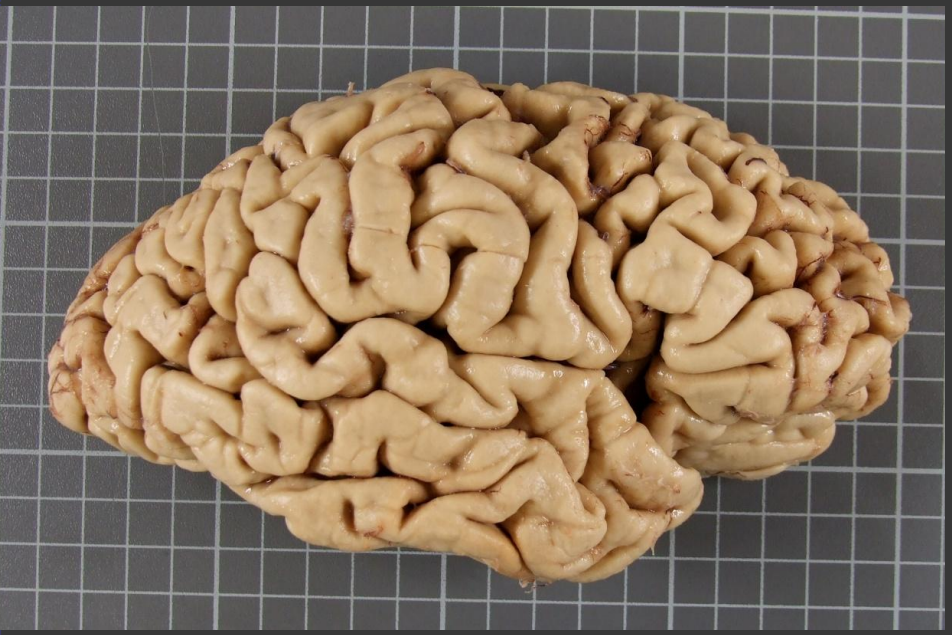
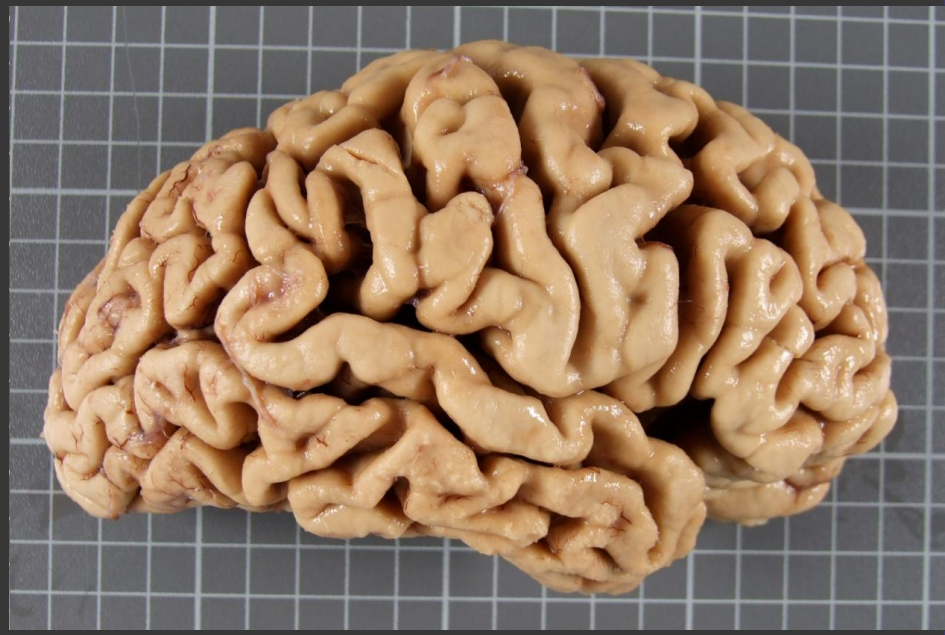

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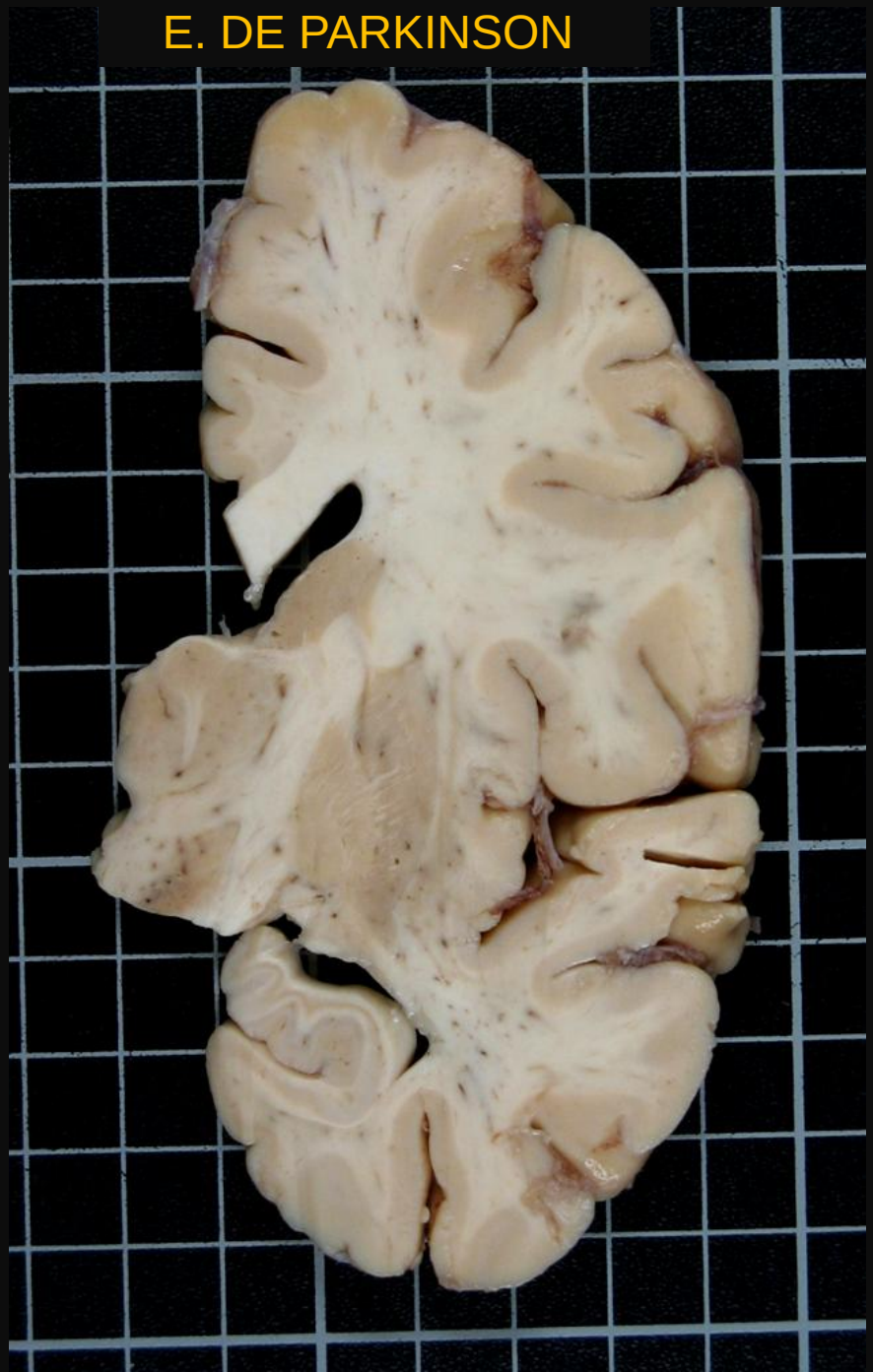

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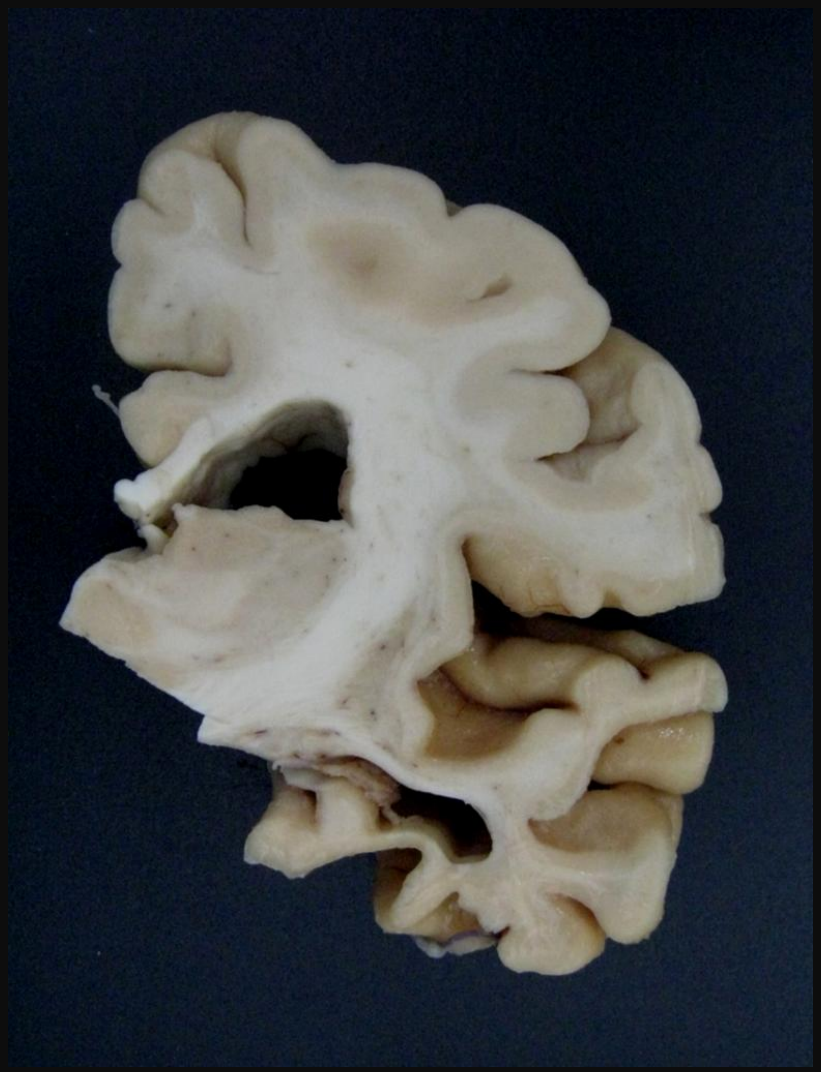

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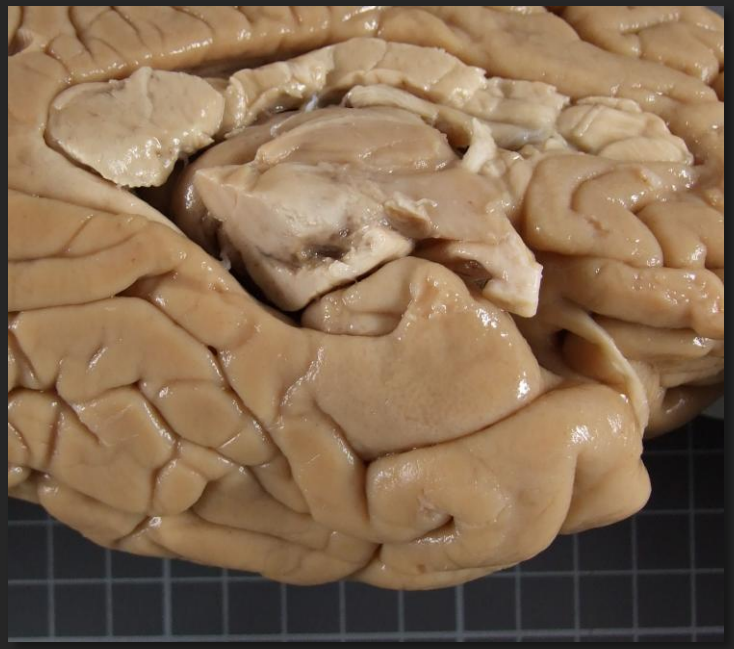
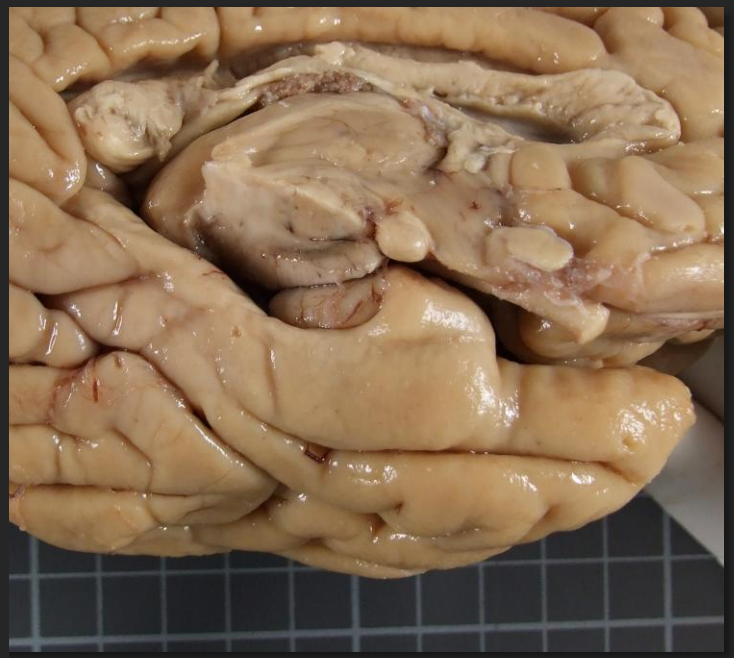
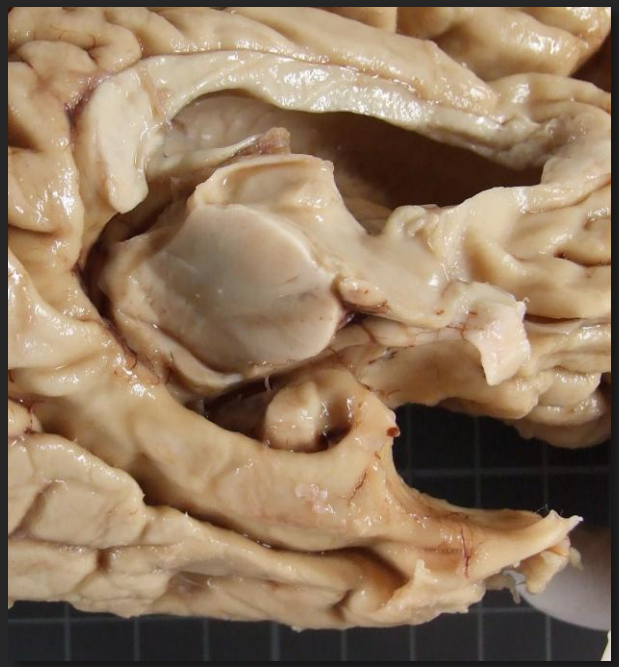


EA

ELA





EA

- **Placas y ovillos, diagnóstico NP de la E. de Alzheimer.**

Metodología y estadiaje de Braak.

Patología típica con distribución atípica.

Otras patologías (tau+) con distribución típica.

Placas sin ovillos.

Ovillos sin placas.

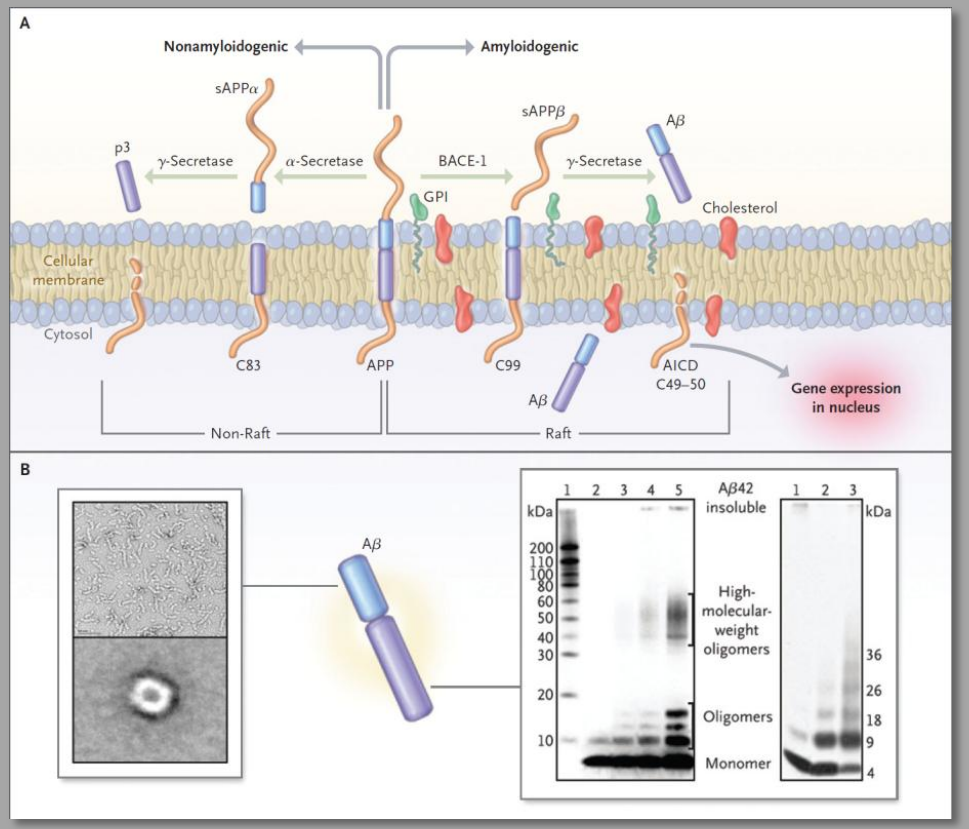
Neuropatología del deterioro cognitivo leve.

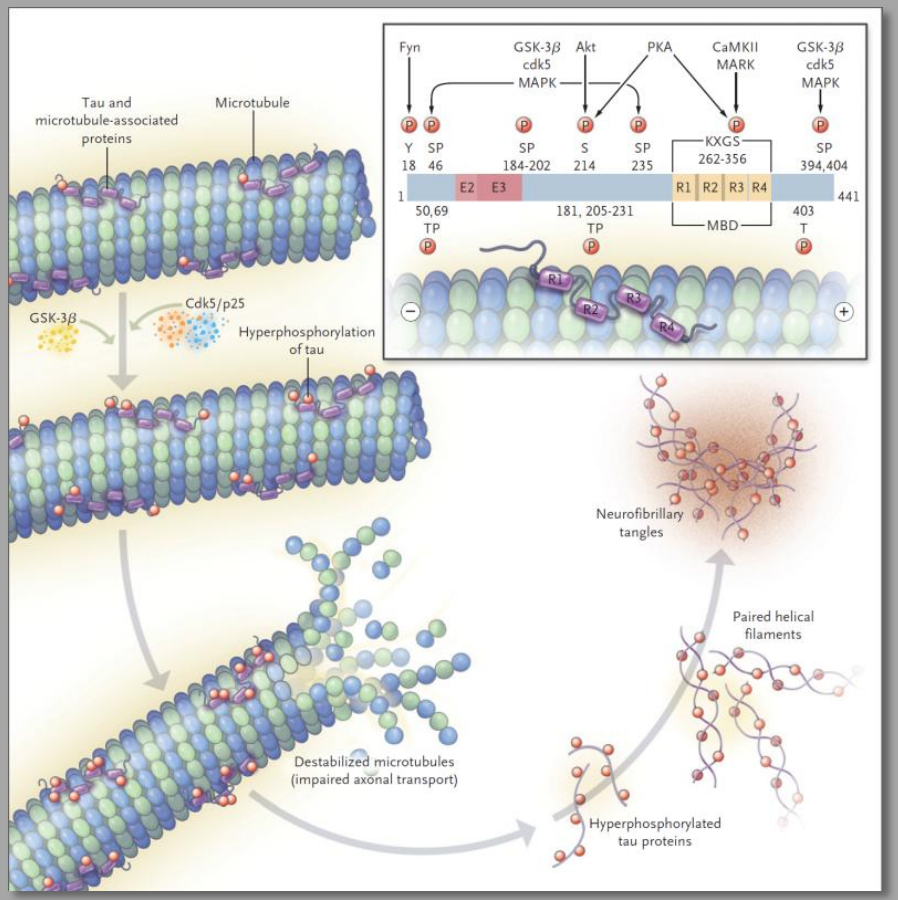
Reserva cognitiva y compensación.

Patología de tipo Alzheimer

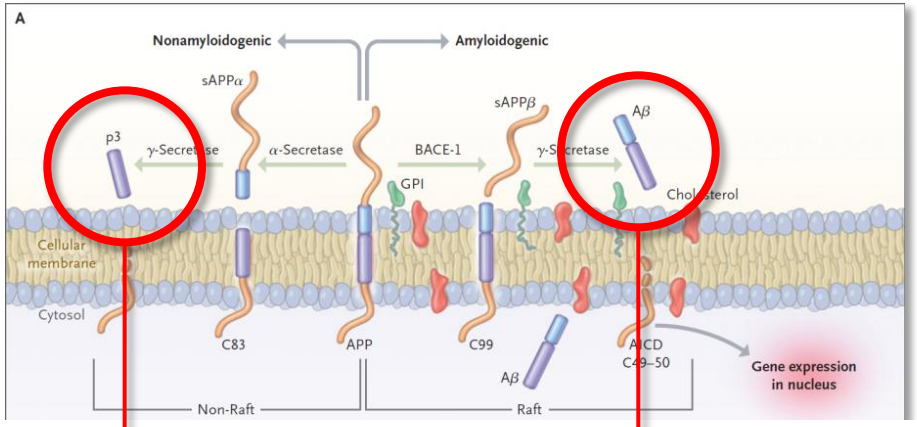
β-amiloide

Tau



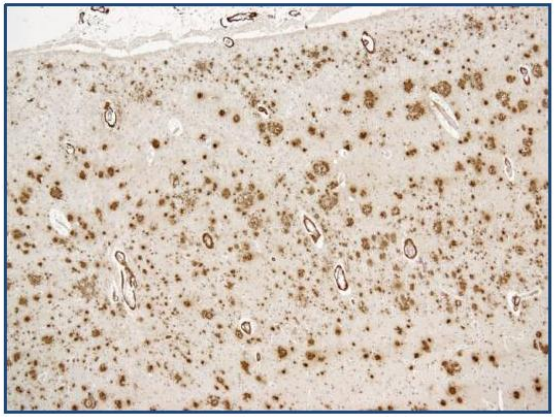


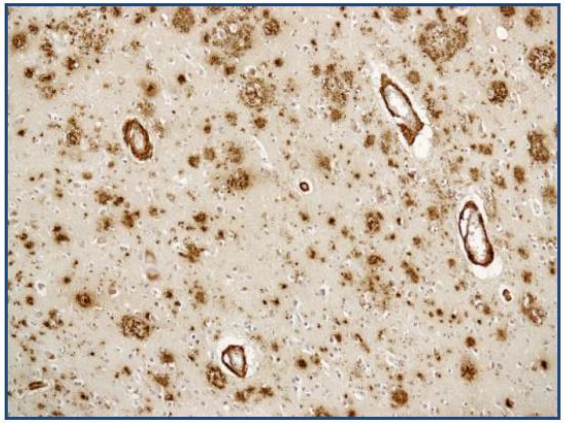
Péptidos de β-amiloide

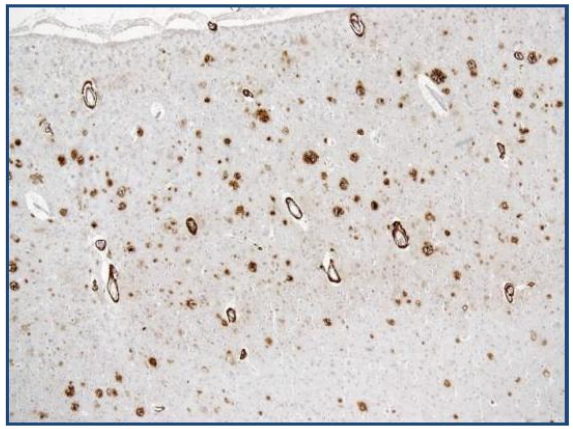


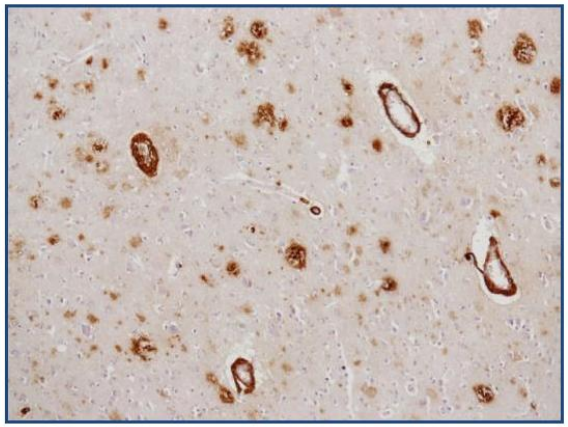
C42

EM5

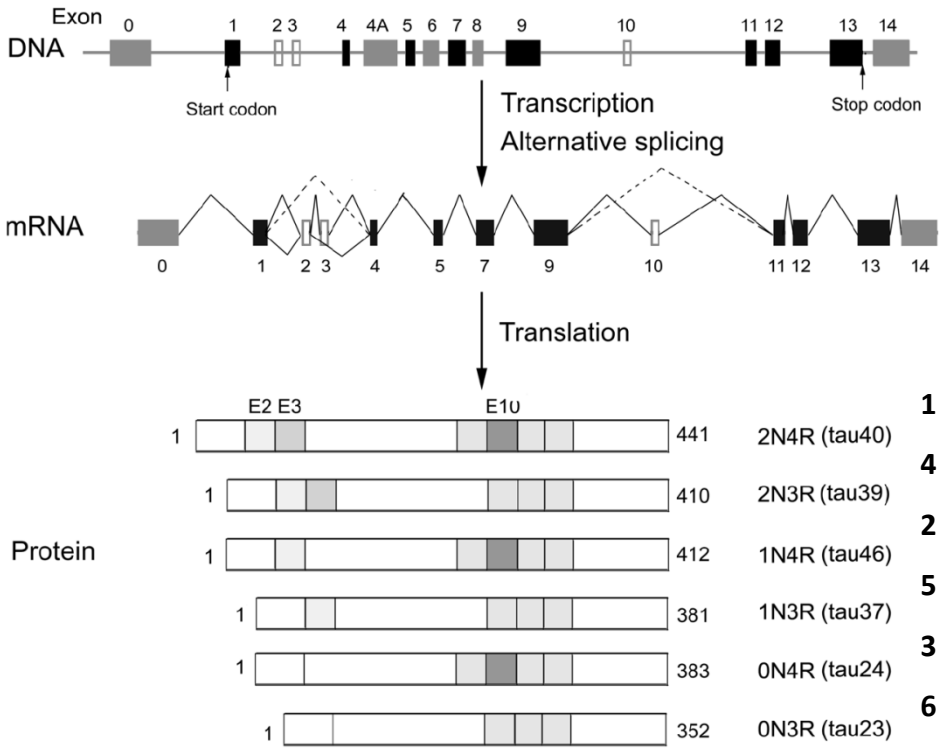


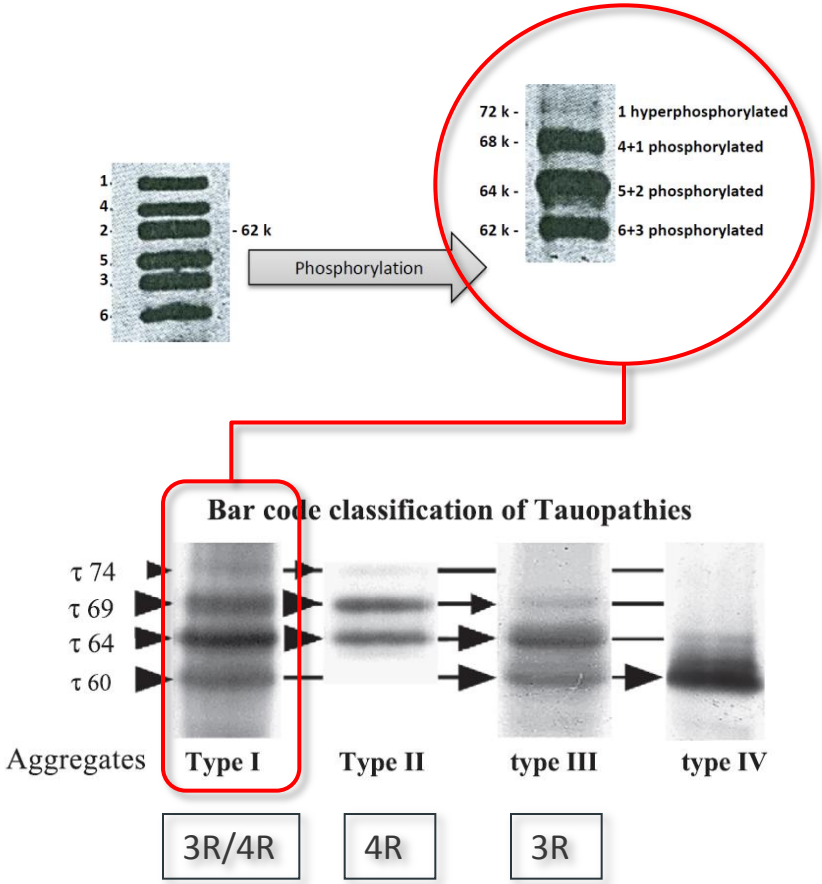






Isoformas de tau

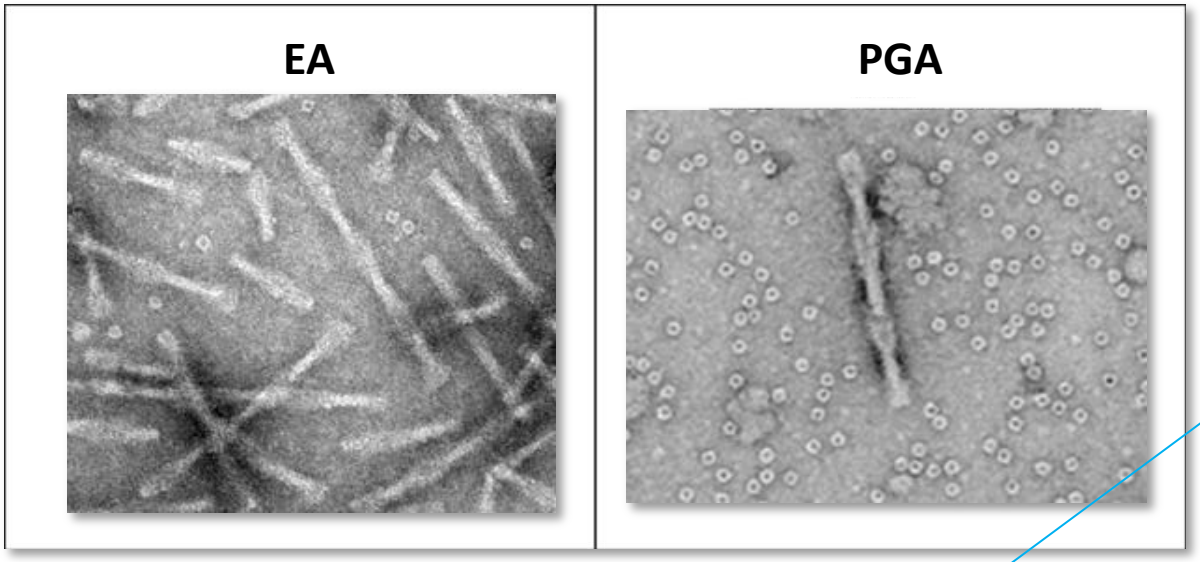


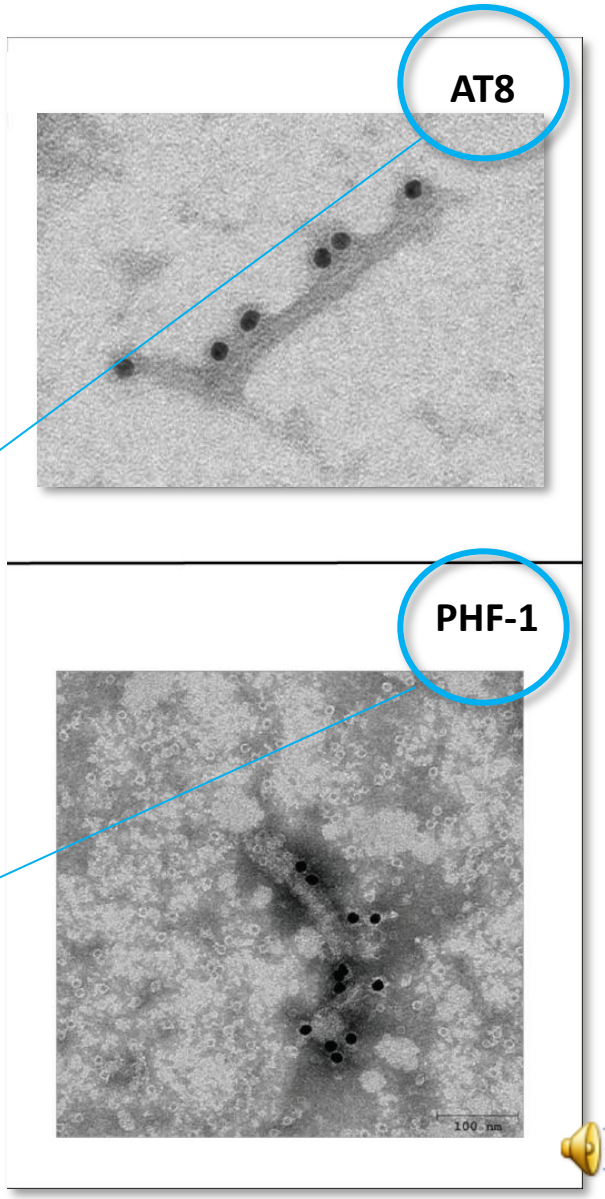


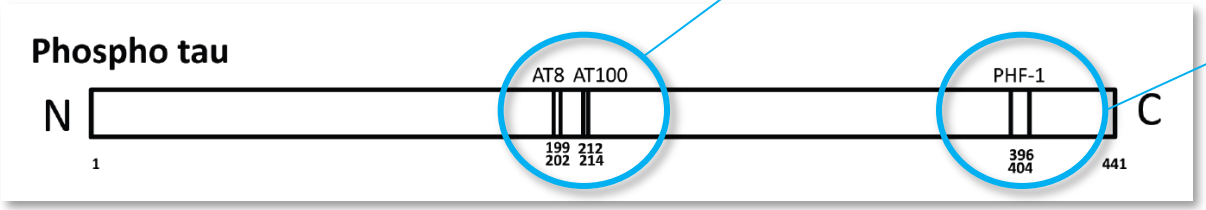
Liu & Gong, 2008

Sergeant *et al.*, 2005

Fosfo-tau: aislamiento de fibras y m. electrónica

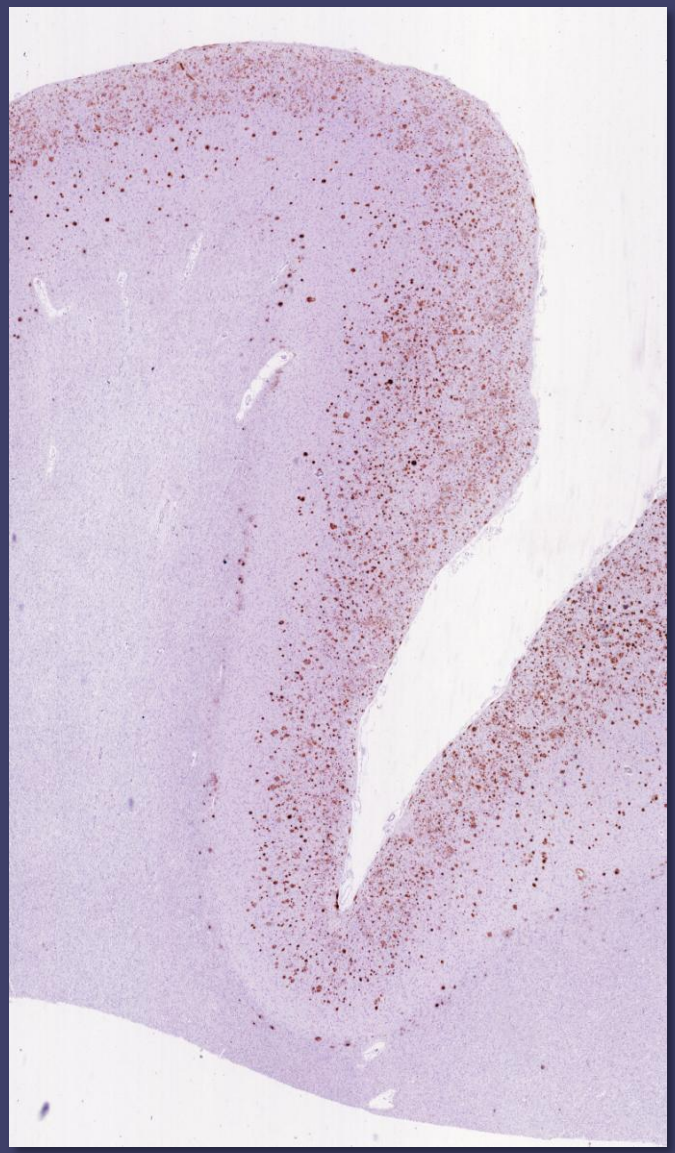




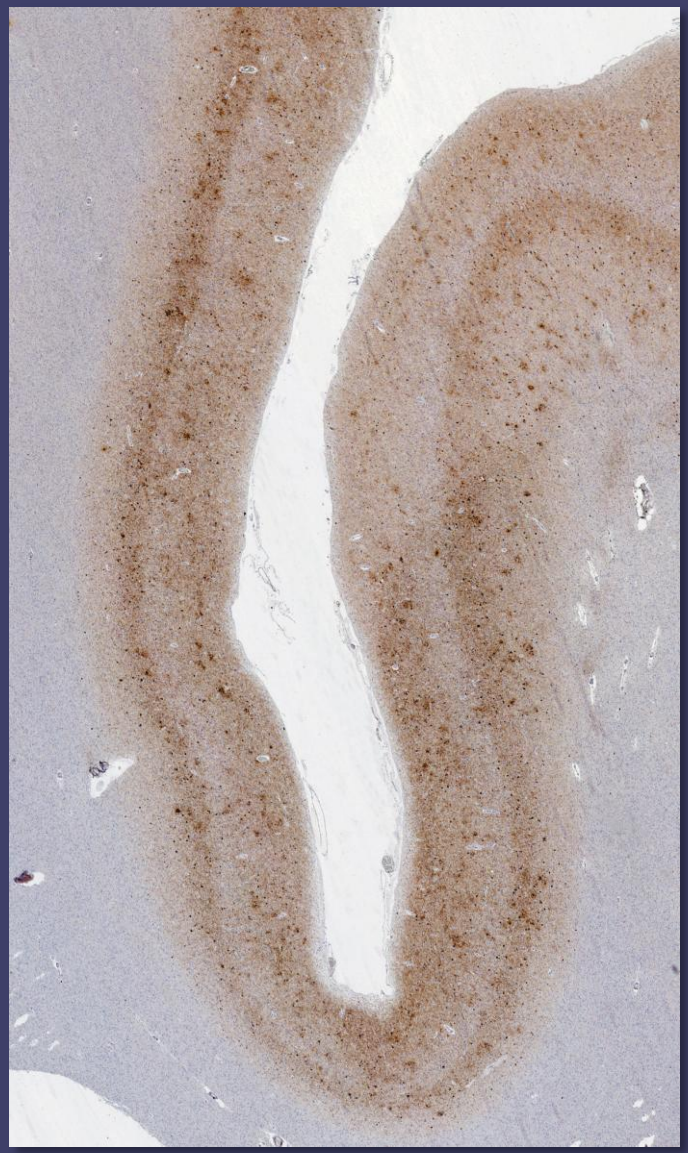


Inmunomicroscopía electrónica sobre polímeros fibrilares mediante tinción de inmuno-oro.

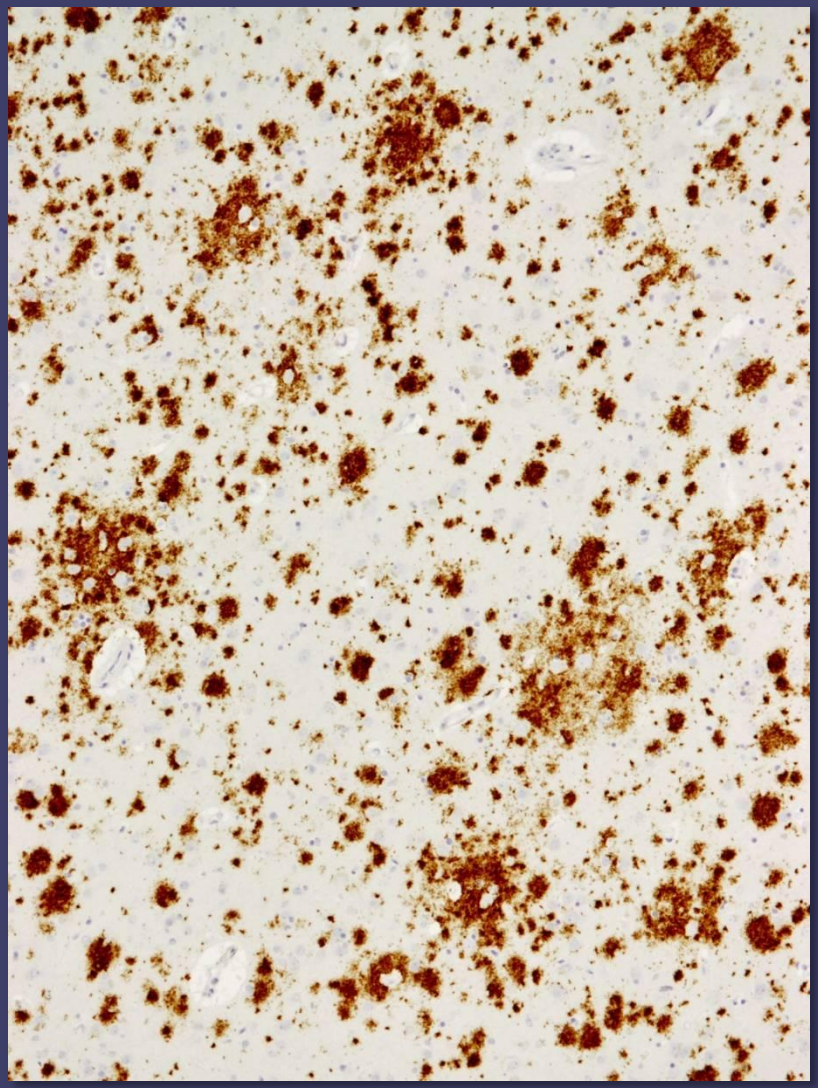
Córtex parietal, β-amiloide



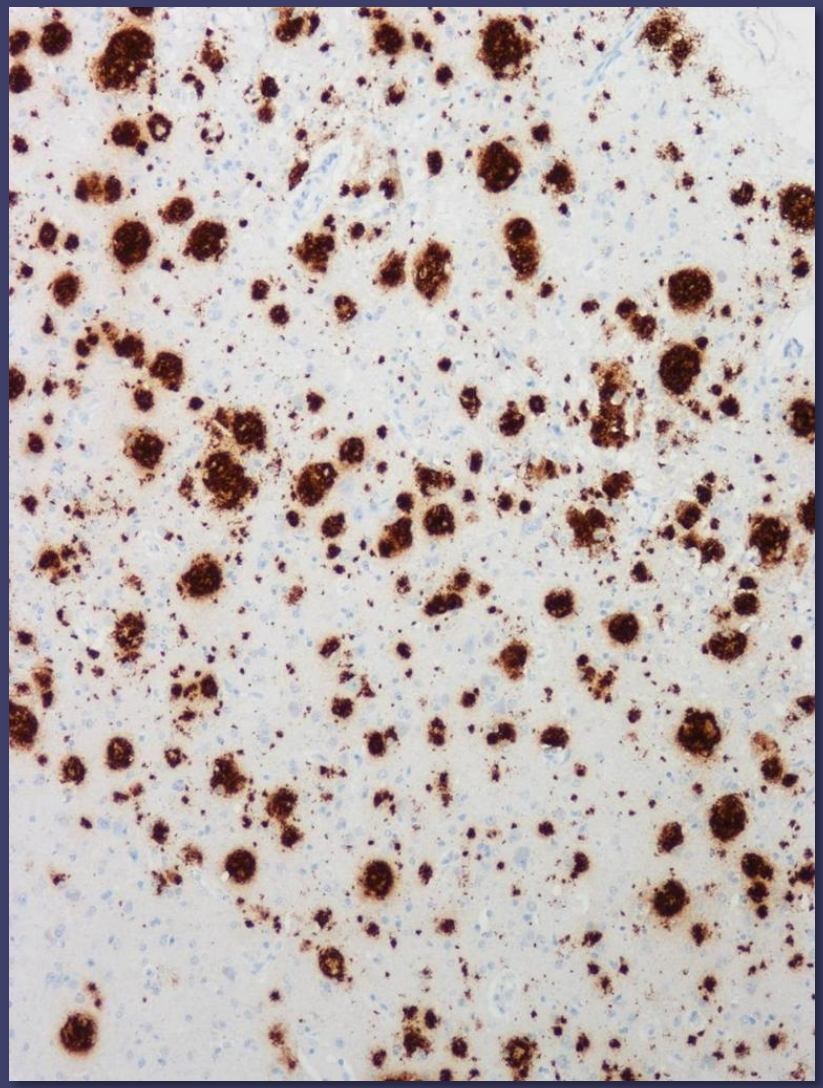
Córtex temporal, Tau AT100

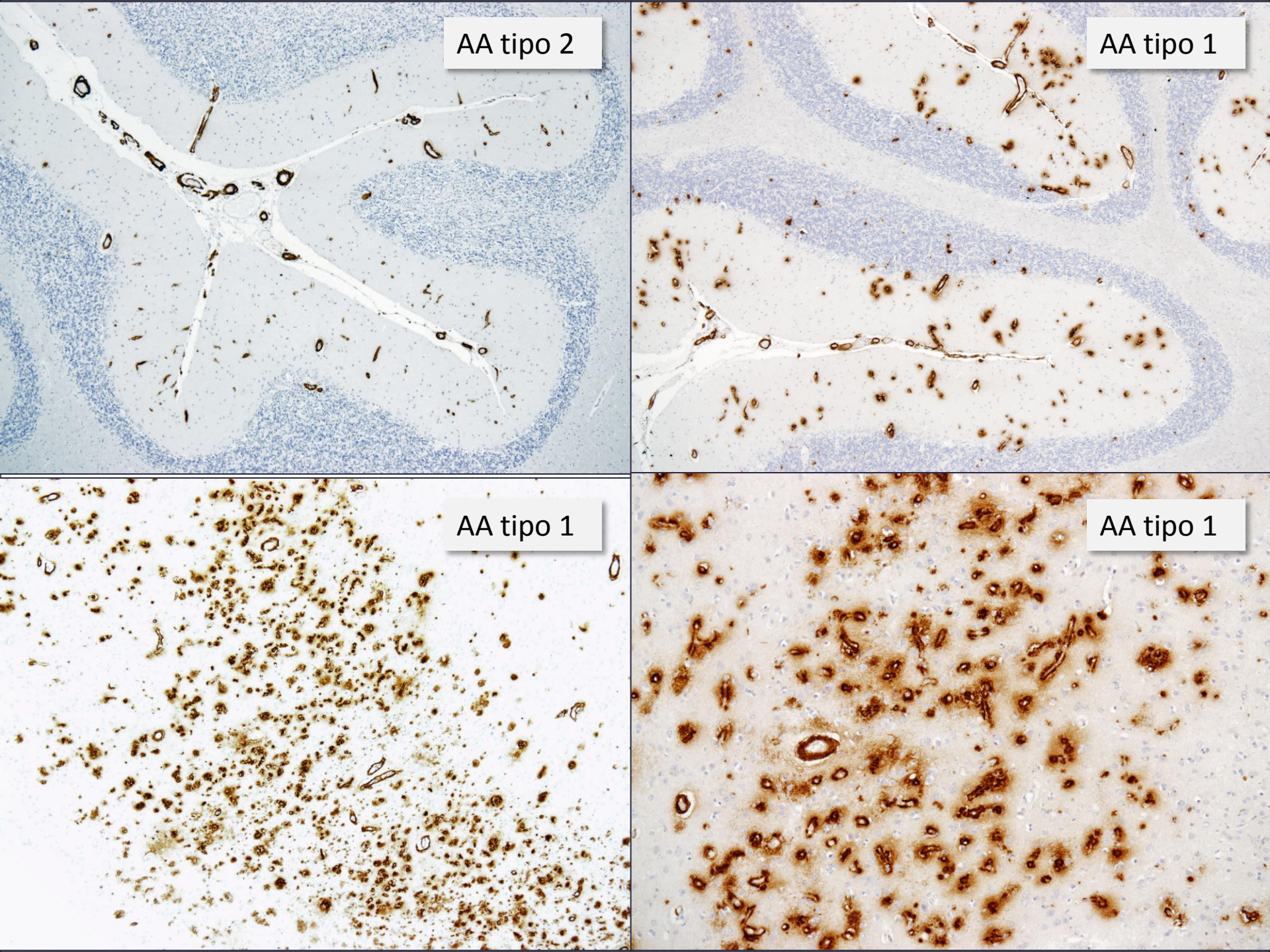


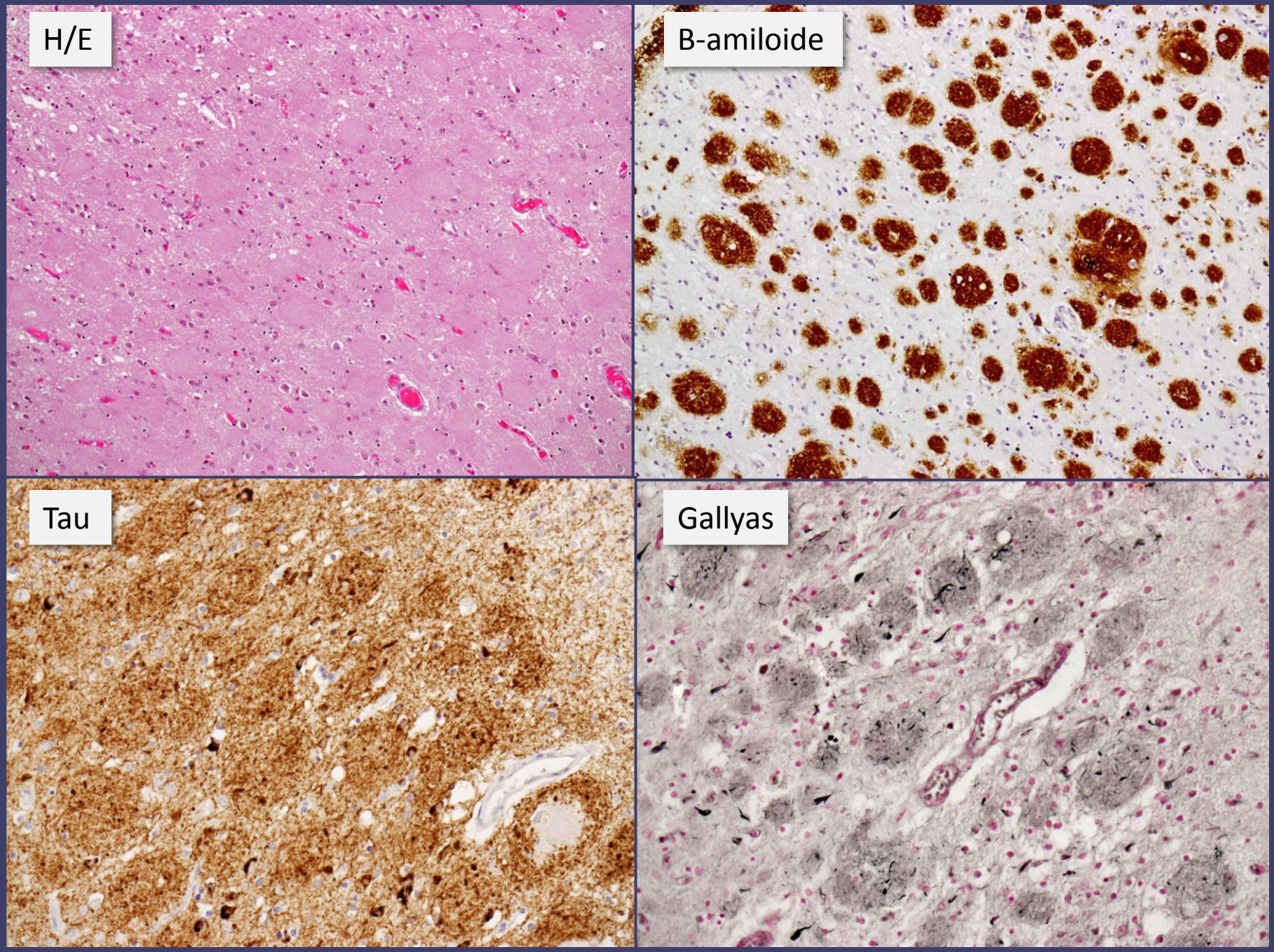
PLACAS DIFUSAS



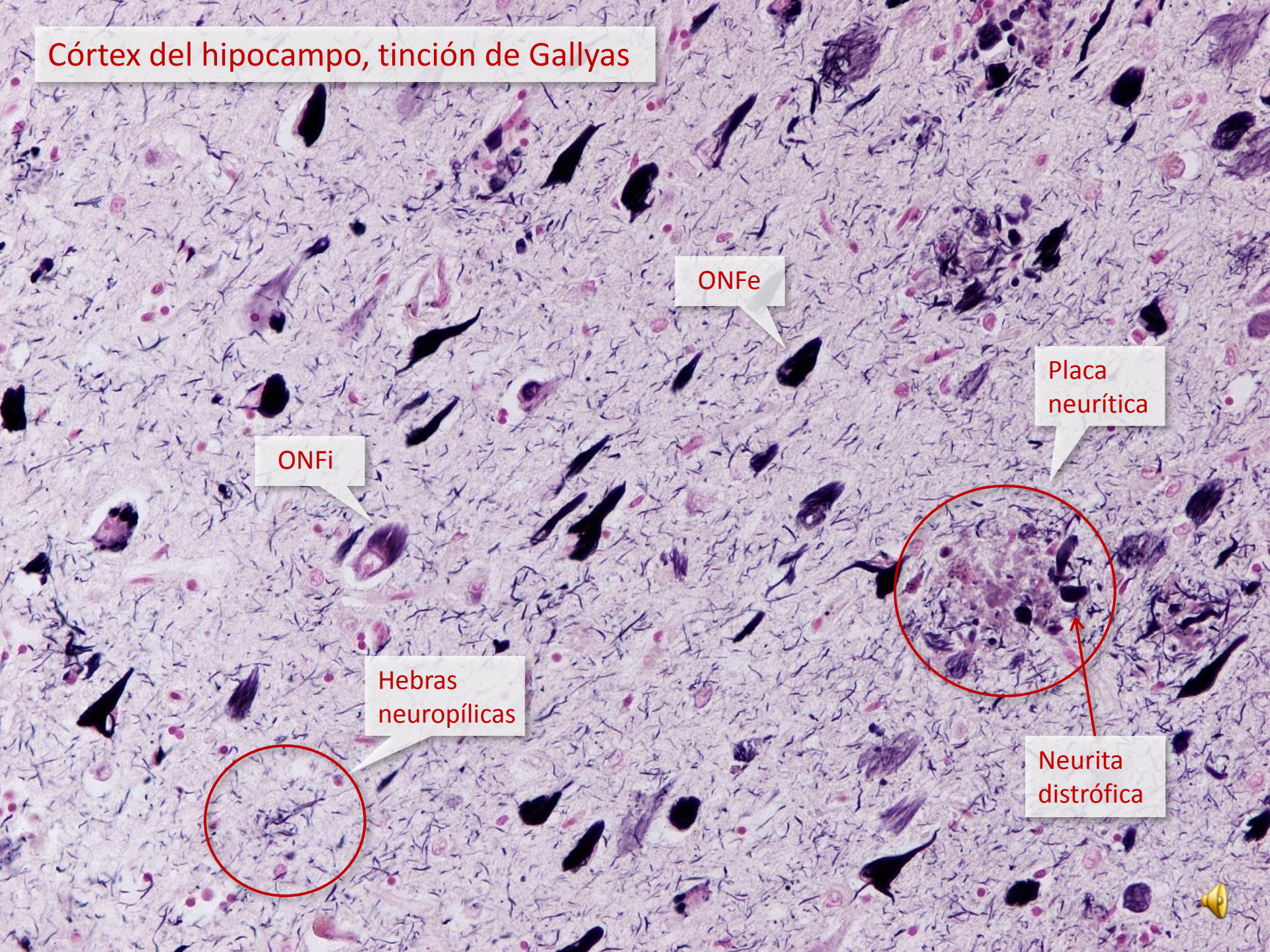
PLACAS FOCALES



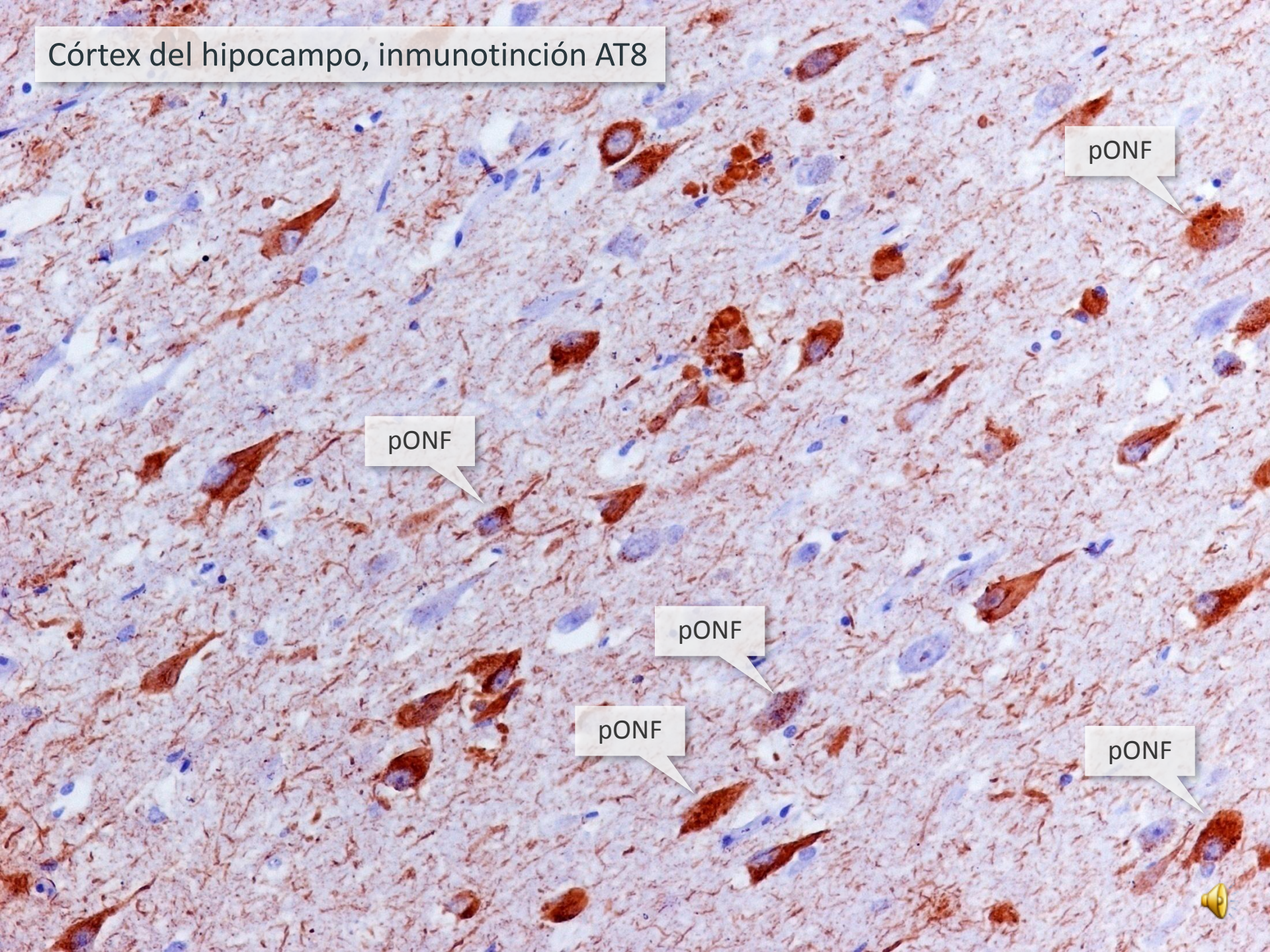

AA tipo 2
AA tipo 1
AA tipo 1
AA tipo 1


H/E
B-amiloide
Tau
Gallyas

Córtex del hipocampo, tinción de Gallyas



Córtex del hipocampo, inmunotinción AT8



ELSEVIER

Alzheimer's & Dementia 8 (2012) 1–13

Alzheimer's & Dementia

Featured Articles

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,*]

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

Se reconoce que los cambios neuropatológicos de la EA pueden darse en ausencia (aparente) de trastorno cognitivo.

Se recomienda el uso de un score “ABC” para la evaluación de los cambios neuropatológicos de EA, que incorpora (A) la evaluación histológica de los depósitos de beta-amiloide, el estadiaje de los ovillos neurofibrilares (B), y la puntuación de placas neuríticas (C).

Se recomienda una evaluación más detallada de otras patologías asociadas, como la enfermedad de cuerpos de Lewy, la patología vascular, la esclerosis del hipocampo, y las inclusiones inmunorreactivas para TDP-43.

Score ABC para cambio neuropatológico de EA

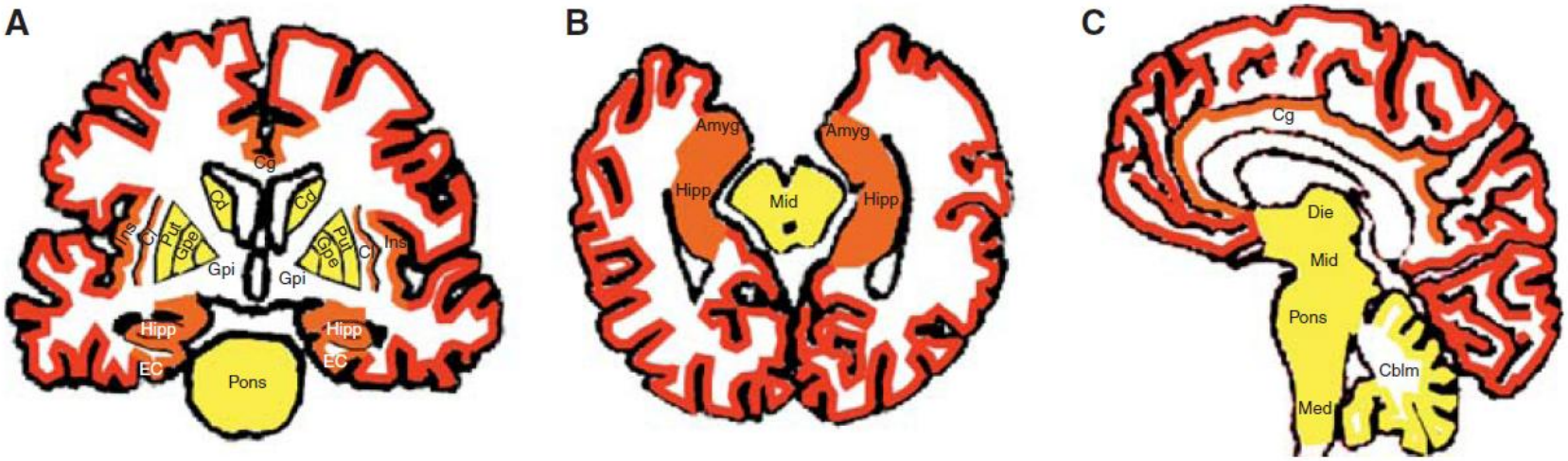
Table 2 "ABC" score for AD neuropathologic change

"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

Ejemplo:
Cambio neuropatológico de EA: A1 B2 C3

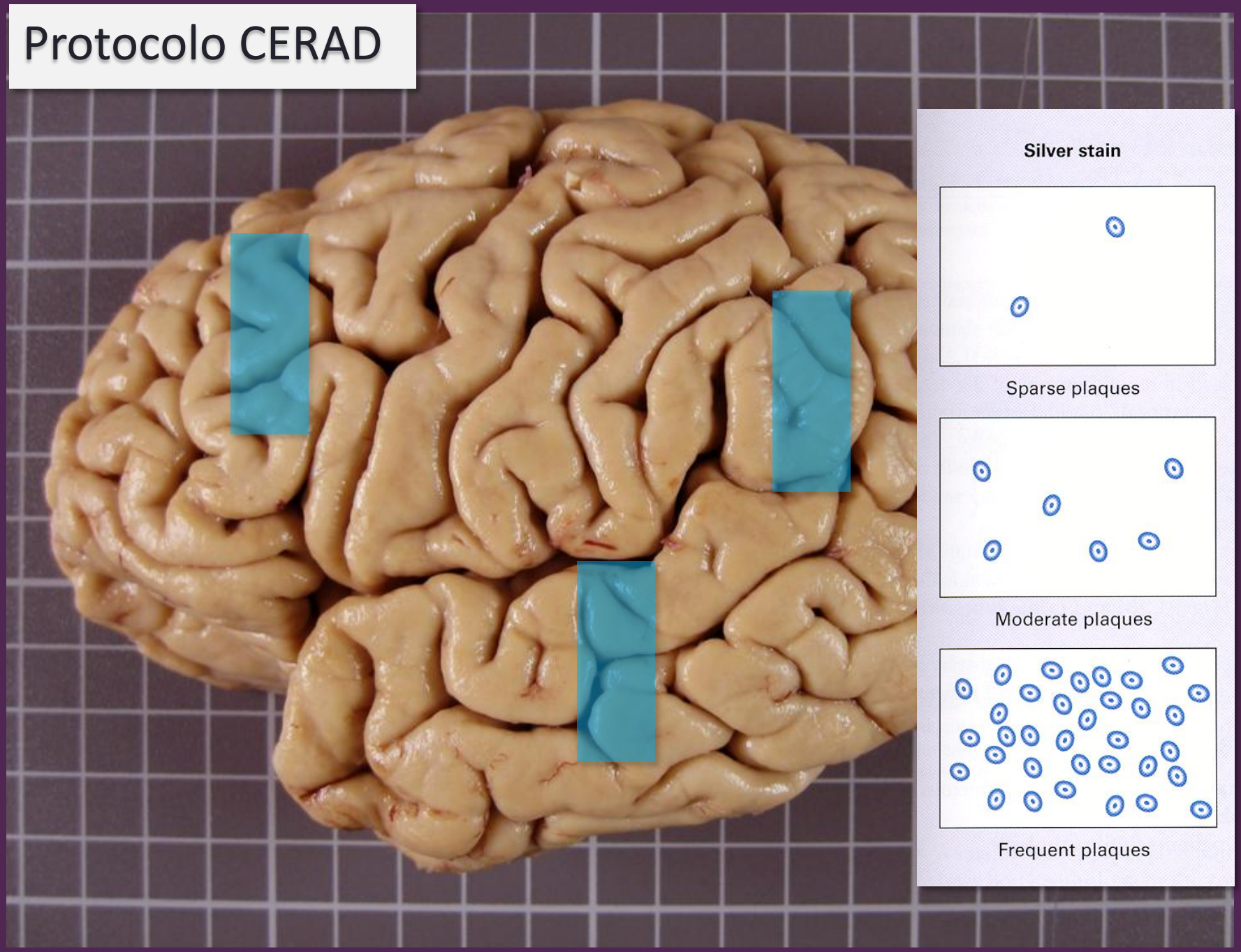
Fases de depósito de β-amiloide

(modificadas a partir de Thal *et al.*, 2002).



Cold Spring Harb Perspect Med 2011;1:a006189

Protocolo CERAD



Estadios de Braak & Braak

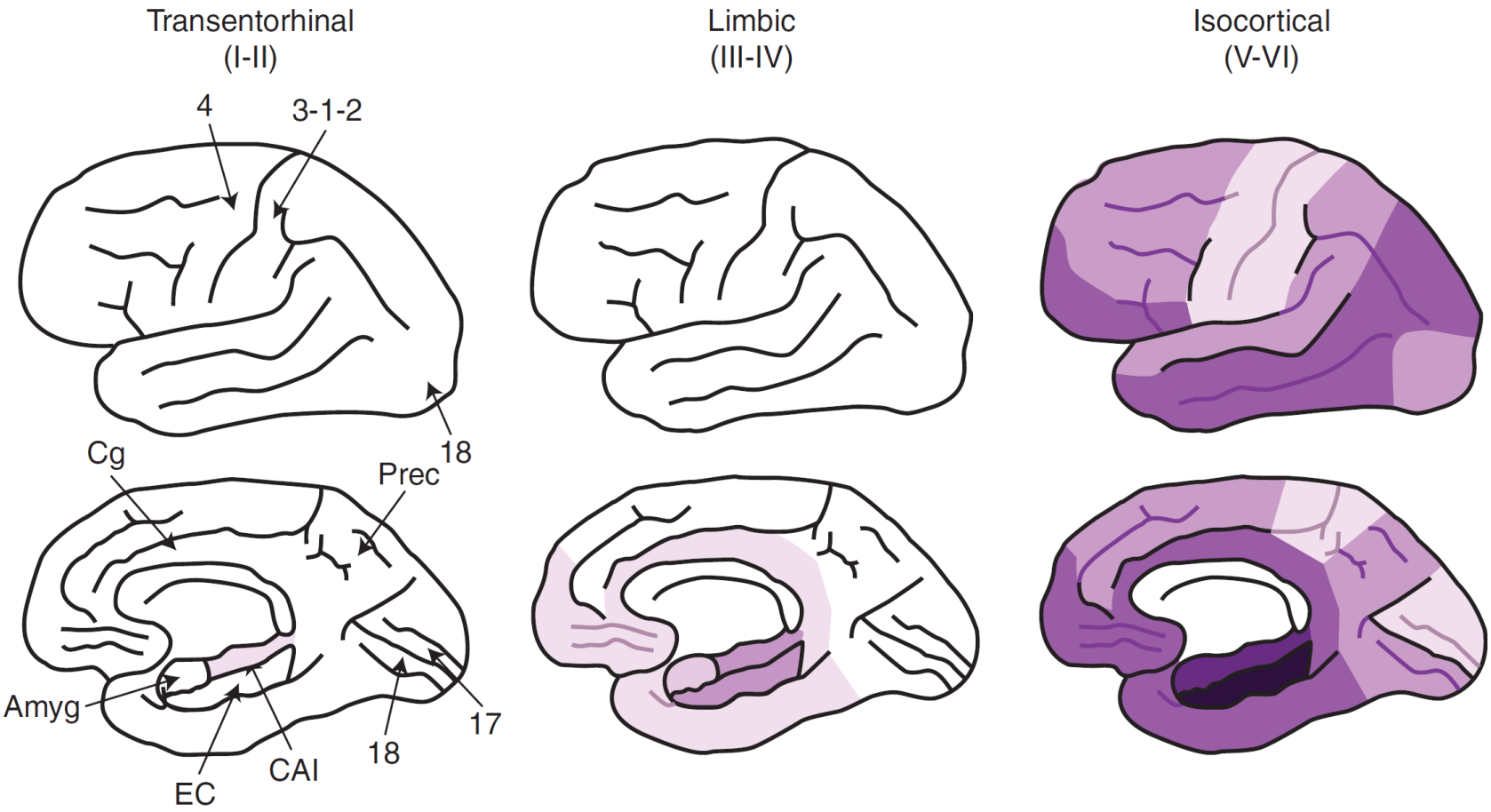
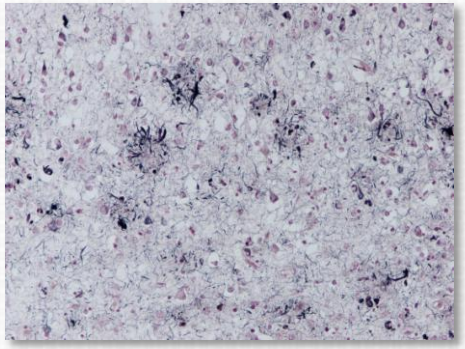
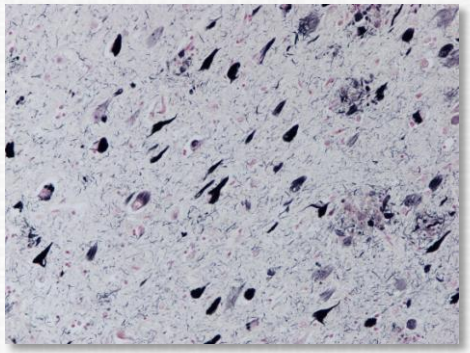


Table 3 "ABC" score for level of AD neuropathologic change

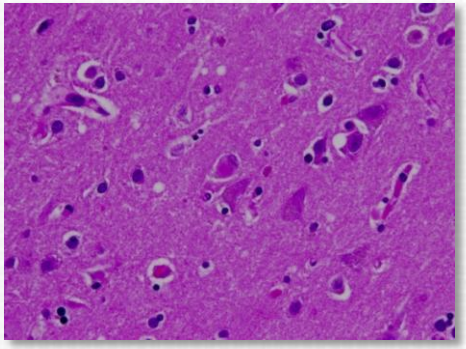
AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

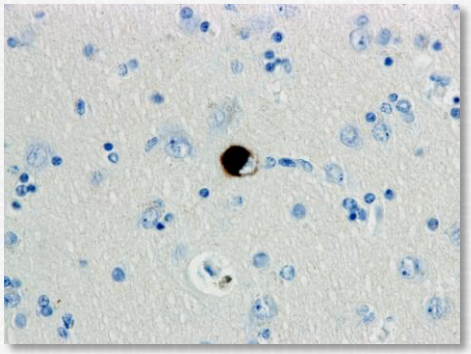
Alzheimer



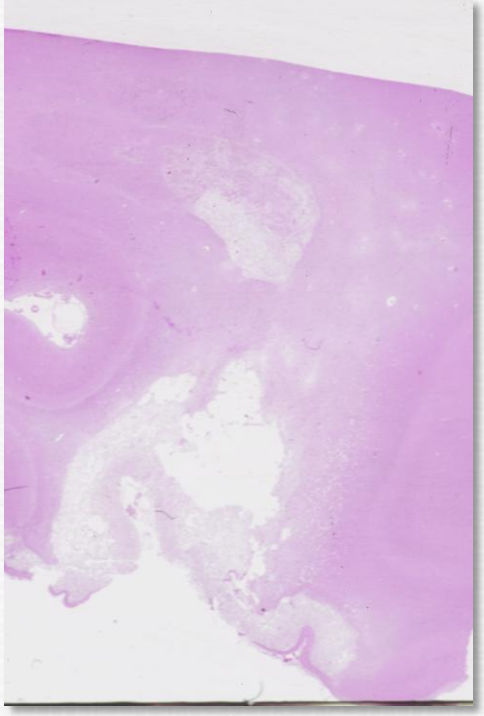


Lewy

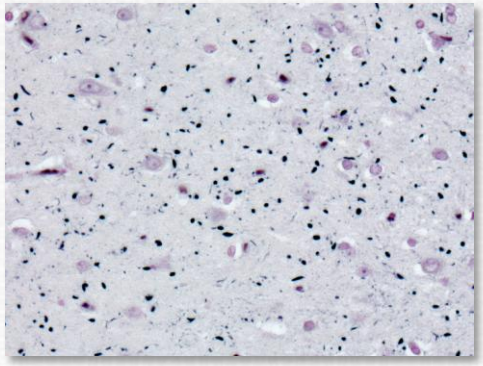




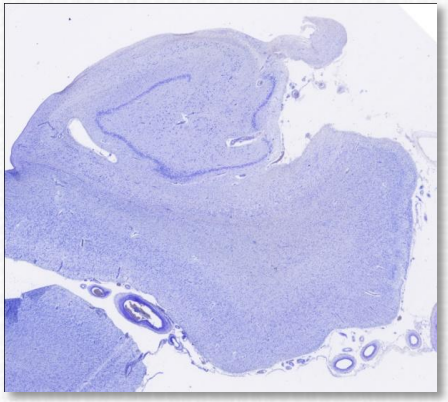
Vascular



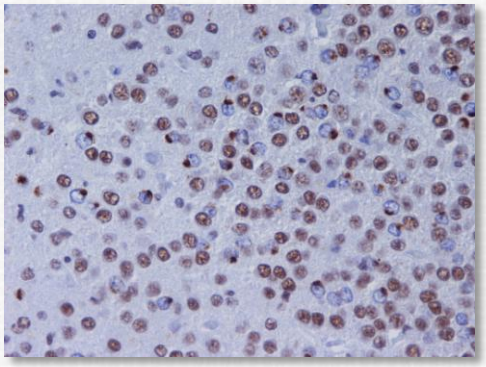
Granos argirófilos



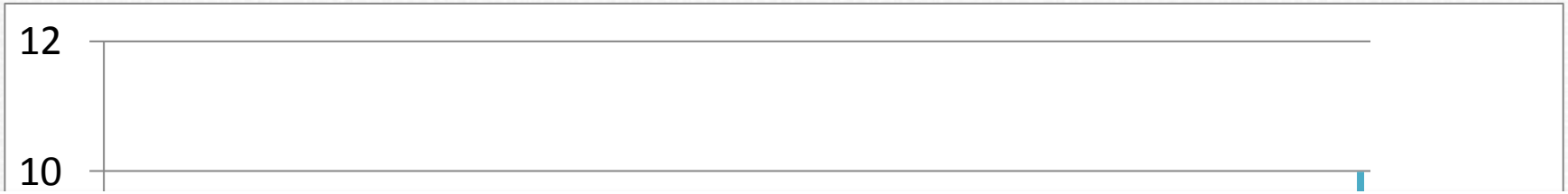
Esclerosis del hipocampo



TDP 43 (+)



Programa CAV: casos ordenados por carga patológica global



ELSEVIER

Alzheimer's & Dementia ■ (2015) 1-9

Alzheimer's & Dementia

Combined Alzheimer's disease and cerebrovascular staging explains advanced dementia cognition

María Ascensión Zea-Sevilla[a,*], Miguel Angel Fernández-Blázquez[a], Miguel Calero[a,b], Pedro Bermejo-Velasco[c], Alberto Rábano[a]

[a]*Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofia Foundation, Madrid, Spain*
[b]*Unidad Funcional de Investigación en Enfermedades Crónicas and CIBERNED, Instituto de Salud Carlos III, Madrid, Spain*
[c]*Hospital Universitario Puerta de Hierro, Neurology Unit, Madrid, Spain*

Placas y ovillos, diagnóstico NP de la E. de Alzheimer.

- **Metodología y estadiaje de Braak.**

Patología típica con distribución atípica.

Otras patologías (tau+) con distribución típica.

Placas sin ovillos.

Ovillos sin placas.

Neuropatología del deterioro cognitivo leve.

Reserva cognitiva y compensación.

Table 1. Stages in the gradual accumulation of neurofibrillary tangles (NFT) and neuropil threads (NT)

Location Stage:	I	II	III	IV	V	VI
Cortical areas:						
Fascia dentata	0	0	0	0	0–i	+–++
CA4: Non-pyramidal cells	0	0	0	i–+	+–++	+++g
CA4/CA3: Pyramidal cells	0	0	0	0	i–+	+–++
CA1: Pyramidal cells	0	i–+	+–++	++	+++	+++g
Subiculum	0	0	0	i	+	+–++
Presubiculum	0	0	0	0	0–i	+
Para-/Transsubiculum	0	0	0	0–i	+	++
Entorhinal-Pre-α	0–i	+	++	+++	+++g	+++g
Entorhinal-Pri-α	0	i	+	+–++	++	+++g
Entorhinal-Pre-β	0	0	i	+	+–++	++
Transentorhinal Pre-α	i–+	+–++	++	+++g	+++g	+++g
Isocortex:						
Association areas	0	0	i	+	+++	+++
Parastriate area	0	0	0–i	i–+	+	++
Striate area	0	0	0	0–i	i–+	+
Subcortical nuclei:						
Striatum	0	0	i	i–+	+	++
Basal magnocellular complex	0	i	+	+–++	++	+++g
Amygdala	0	i	+	++	+++	+++g
Claustrum	0	0	0	i	+	++
Thalamus:						
Antero-dorsal nucleus	i	i–+	+–++	++	+++g	+++g
Reuniens nucleus	0	0	i	+	++	+++
Reticular nucleus	0	0	0	i	+	++
Hypothalamus:						
Tuberomamillary nucleus	0	0	i	+	++	+++
Lateral tuberal nucleus	0	0	0	0	i	+
Pars compacta of substantia nigra	0	0	0	0	i	+–++

The overall amount of NFT and NT is graded and labeled zero (0) with no discernible change, (i) with a few isolated NFT, or (+) with small, (++) moderate, and (+++) large numbers of NFT and NT. (g) points to the presence of ghost tangles

H. Braak & E. Braak, 1991

Table 2. Sex, age, and neuropathological stage of accumulation of both amyloid deposits (A–C) and neurofibrillary (NF) changes (I–VI)

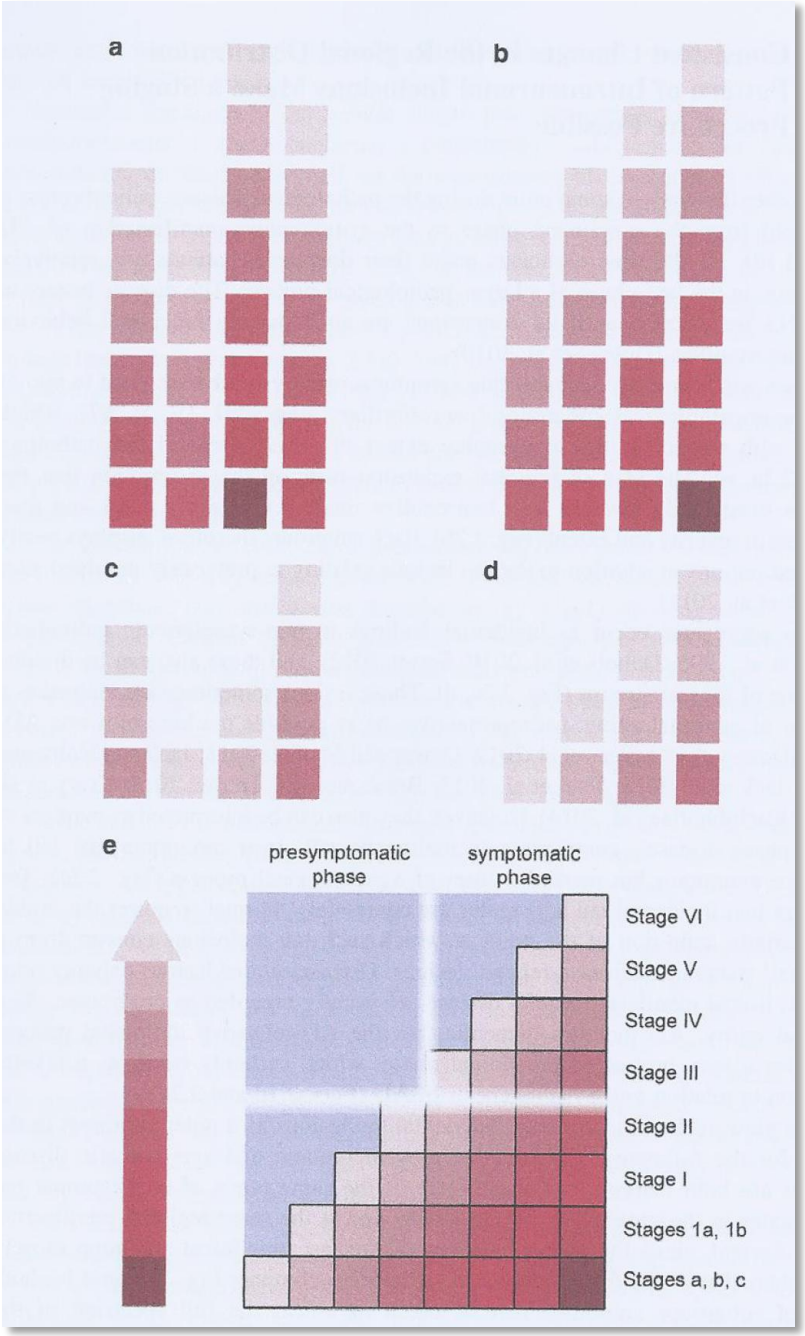
No.	Sex	Age	Clinically proven dementia	Amyloid deposits	NF changes	Deviation from pattern displayed in Table 1
1*	f	47		A	0	
2*	m	56		B	0	
3*	f	58		B	0	
4	m	60		0	0	
5*	f	65		0	0	
6	f	67		A	0	
7	f	67		0	0	
8*	f	81		A	0	
9	f	85		B	0	
10	m	85		0	0	
11*	f	96		A	0	
Mean:		67				
12	f	54		0	I	
13	m	60		0	I	
14*	m	62		A	I	
15	m	63		A	I	
16*	m	67		B	I	
17*	m	71		A	I	
18*	f	74		A	I	
19*	f	75		A	I	
20	m	82		B	I	
21*	f	83		0	I	
22*	m	84		0	I	
23*	m	84		A	I	
24*	f	94		A	I	
Mean:		74				
25	f	47		0	II	CA1 (–)
26	f	57		0	II	
27	m	58		A	II	
28	m	59		B	II	CA1 (–)
29	m	61		0	II	
30	m	65		0	II	
31	m	65		B	II	
32	f	66		B	II	
33*	f	72		B	II	CA1 (+)
34*	m	77		A	II	
35	f	77		A	II	trans e (+)
36	m	78		0	II	
37	m	79		0	II	
38	f	81		B	II	
39*	f	82		A	II	CA4 np (+)
40	f	84		B	II	
41	m	91		0	II	
Mean:		72				
42	m	58		B	III	CA1 (-)
43	m	71		A	III	
44*	f	75		A	III	
45*	m	76	D	B	III	
46*	m	78		C	III	CA4 np (+), parasub (+)
47*	m	79	D	B	III	
48*	f	82	D	C	III	CA1 (–)
49	m	83	D	B	III	CA1 (–)
50	f	84		0	III	
51	f	96	D	B	III	
Mean:		78.5				

Table 2. (continued)

No.	Sex	Age	Clinically proven dementia	Amyloid deposits	NF changes	Deviation from pattern displayed in Table 1
52*	m	64	D	B	IV	CA1 (–)
53*	f	71	D	C	IV	
54*	f	71	D	C	IV	CA4 np (+)
55	f	73		B	IV	CA1 (+), e-Pri-α (+)
56*	m	78	D	C	IV	
57	f	78		C	IV	CA1 (+)
58*	f	85		A	IV	
59	m	83		C	IV	Parasub (–)
60	f	86	D	C	IV	Parasub (–)
61	m	90		C	IV	Parasub (–)
Mean:		78				
62*	m	77	D	C	V	
63	m	78	D	C	V	Sub (+)
64	f	80	D	C	V	Parasub (+)
65	m	81	D	C	V	CA4 np (+)
66	f	81	D	C	V	CA4 np (+), sub (+)
67*	f	81	D	C	V	
68*	f	81	D	C	V	Parasub (+), sub (+)
69*	m	89	D	C	V	Parasub (+), sub (+)
Mean:		81				
70	m	47	D	C	VI	
71*	f	56	D	C	VI	Parasub (+)
72	f	59	D	C	VI	
73	f	59	D	C	VI	
74	f	60	D	C	VI	
75	m	62	D	C	VI	
76	f	64	D	C	VI	
77*	m	64	D	C	VI	
78*	f	69	D	C	VI	Parasub (–)
79*	f	69	D	C	VI	Fd (–)
80*	f	71	D	C	VI	
81*	m	84	D	C	VI	
82*	f	87	D	C	VI	Presub (–)
83*	f	90	D	C	VI	Fd (–), CA4 np (–)
Mean:		64				

Graded series of sections running through an entire hemisphere were evaluated in cases marked by an asterisk. Cases with clinically proven dementia are indicated by "D". Deviations of the cortical involvement displayed in Table 1 are noted with (+) a step more-, or (–) a step less-intensive changes. f: female; m: male; CA1: first sector of the Ammon's horn; CA4 np: non pyramidal cells in the fourth sector of the Ammon's horn; e-Pri-α: entorhinal layer Pri-α; Fd: fascia dentata; Parasub: parasubiculum; Presub: presubiculum; trans e: transentorhinal region; Sub: subiculum

H. Braak & E. Braak, 1991



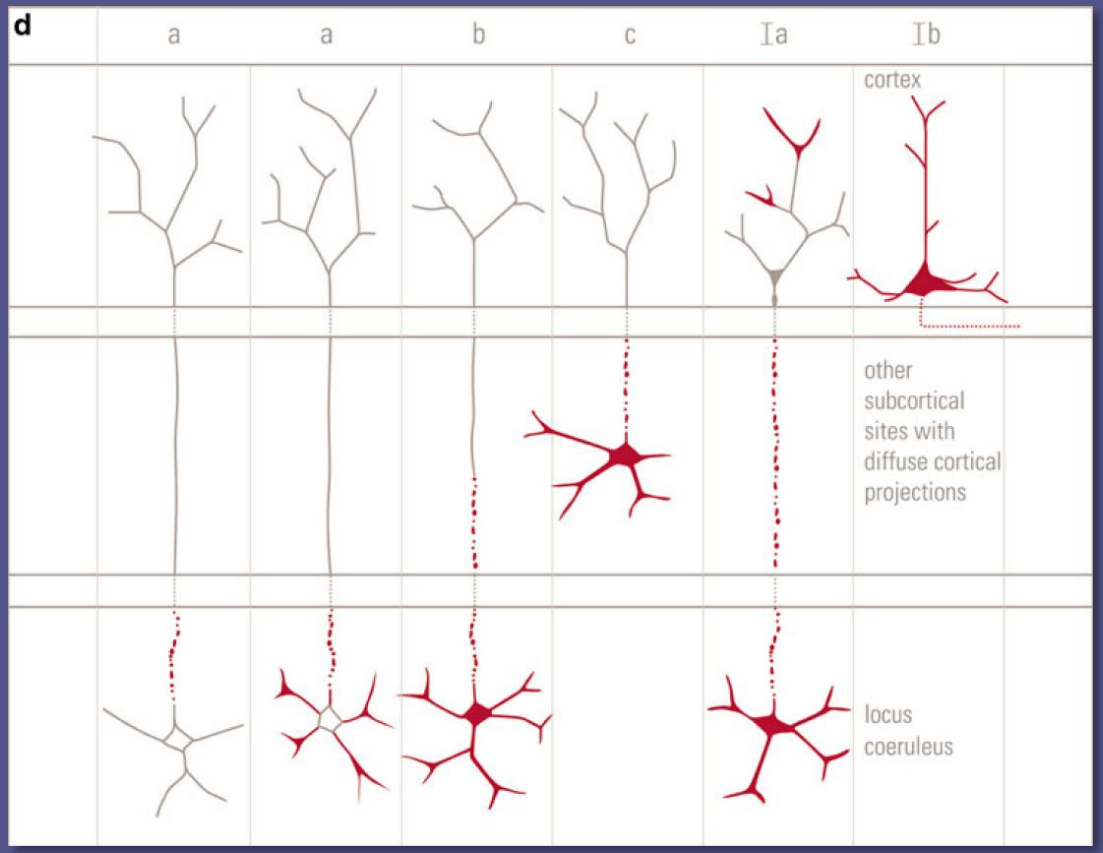
H Braak & K Del Tredici, 2015

Acta Neuropathol (2011) 121:171–181
DOI 10.1007/s00401-010-0789-4

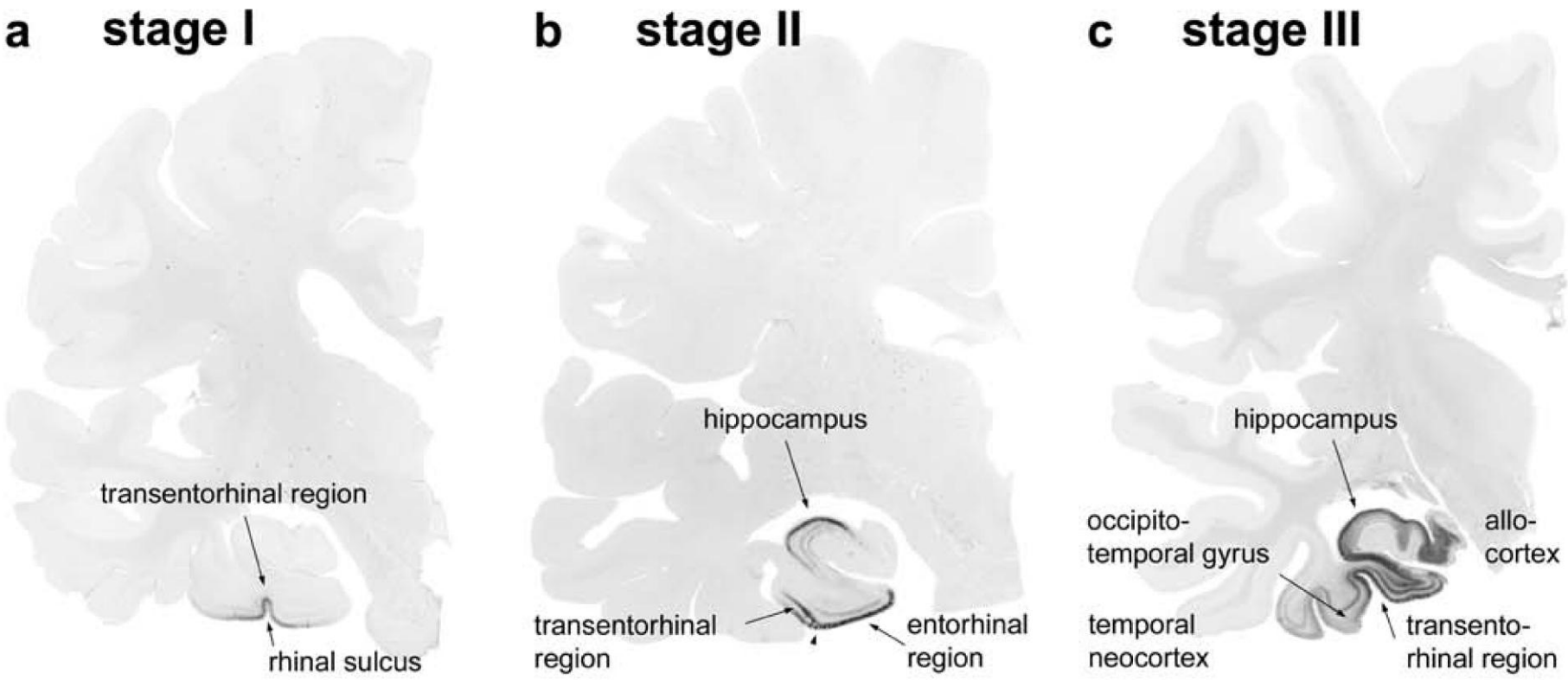
ORIGINAL PAPER

The pathological process underlying Alzheimer's disease in individuals under thirty

Heiko Braak · Kelly Del Tredici

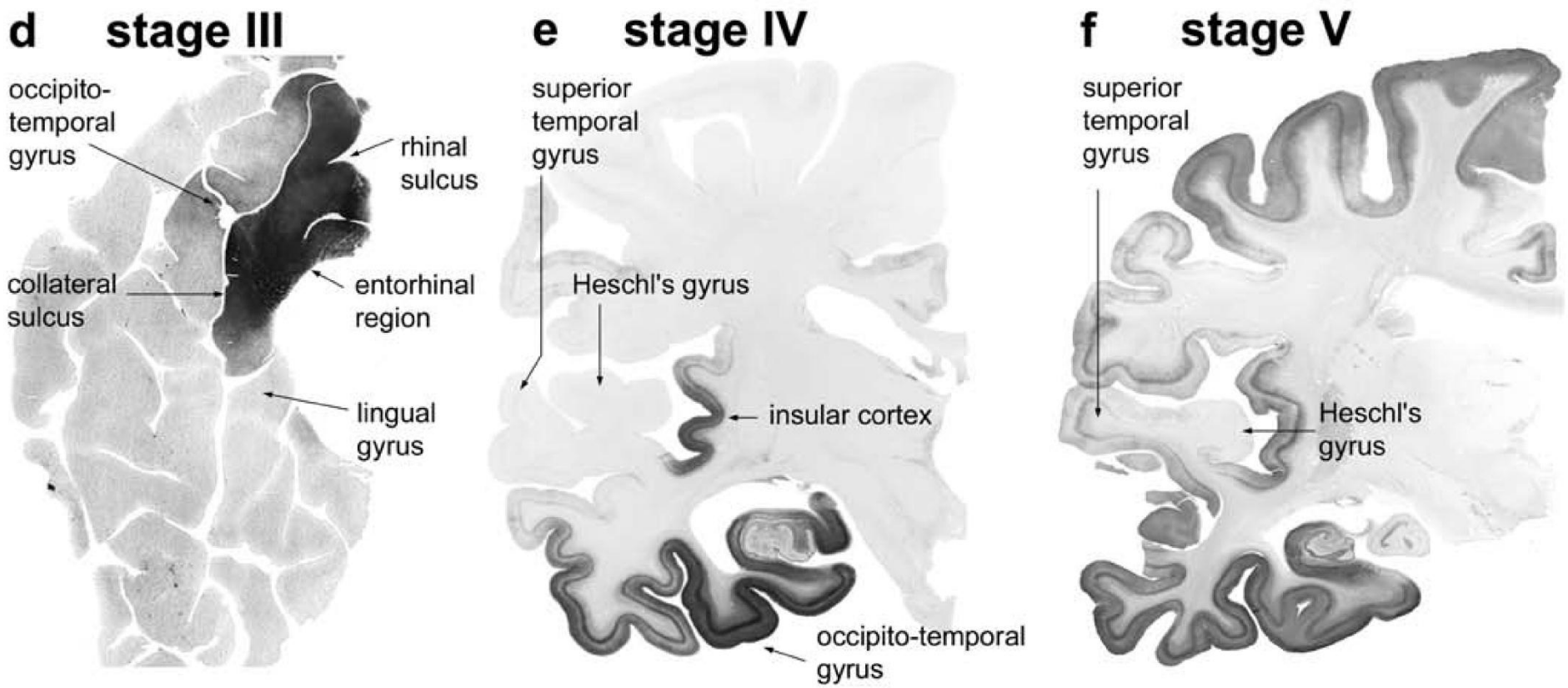


E. de Alzheimer: Estadios de Braak (I-III).



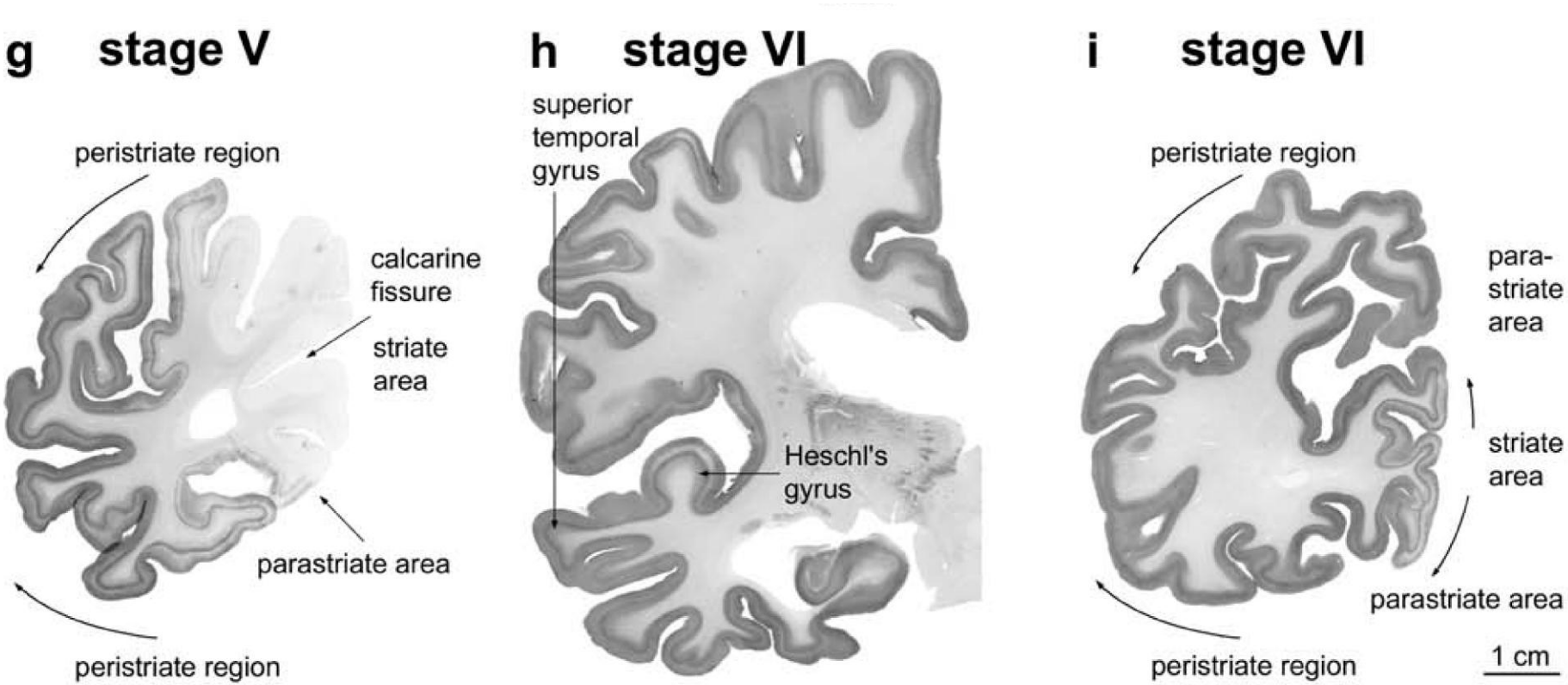
Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry.Acta Neuropathol 2006; 112(4): 389-404.

E. de Alzheimer: Estadios de Braak (III-V).

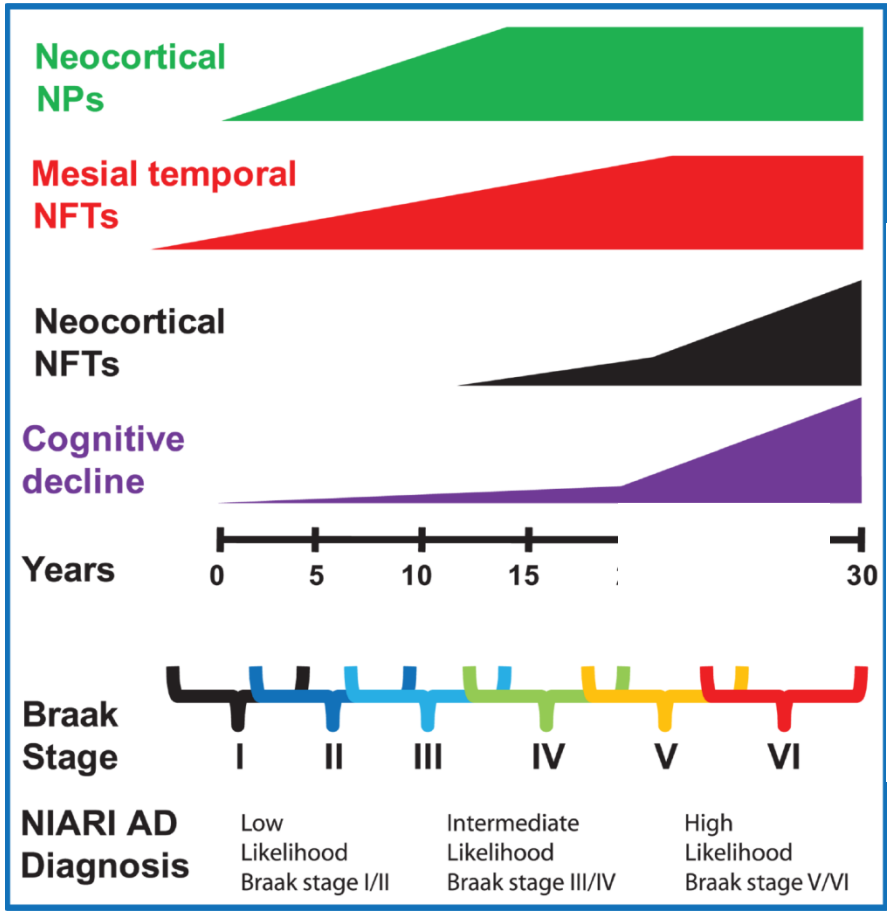


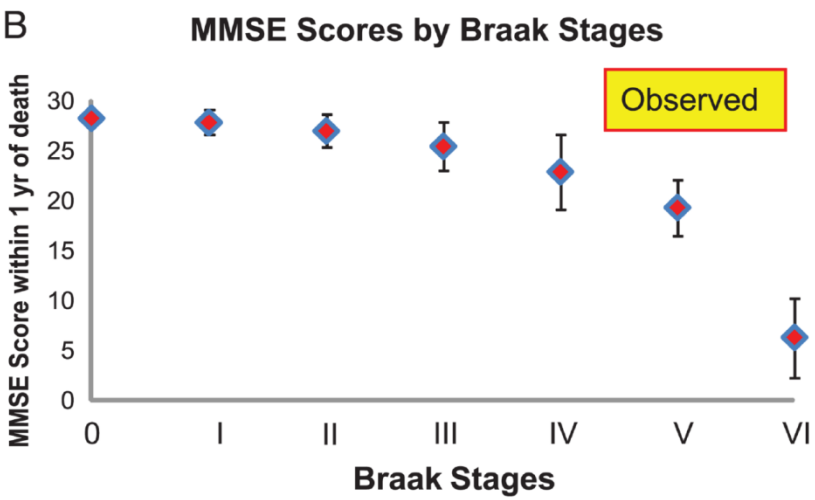
Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry.Acta Neuropathol 2006; 112(4): 389-404.

E. de Alzheimer: Estadios de Braak (V-VI)



Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry.Acta Neuropathol 2006; 112(4): 389-404.



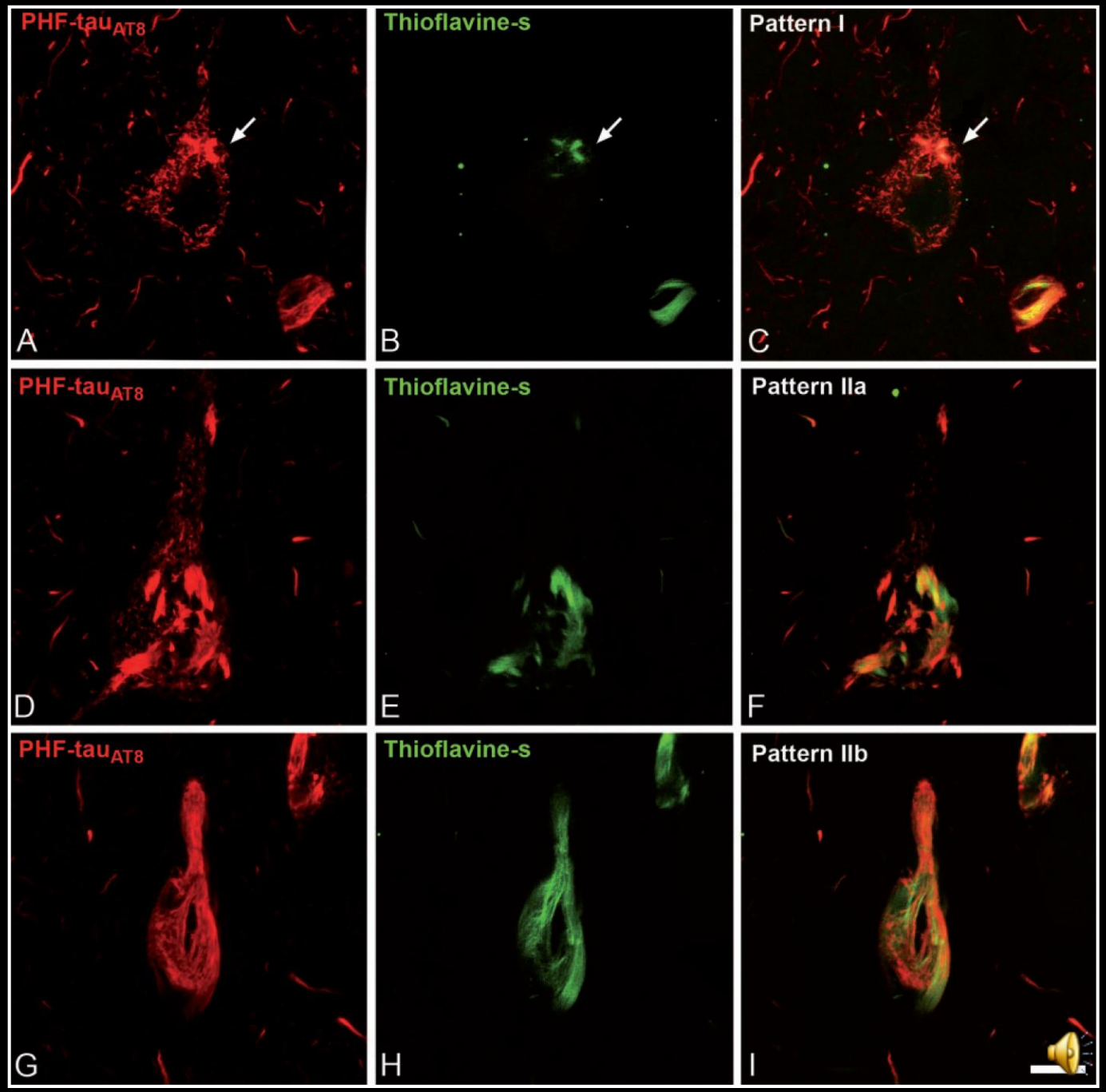


Nelson *et al*., J Neuropathol Exp neurol. 2009; 68(1): 1-14.

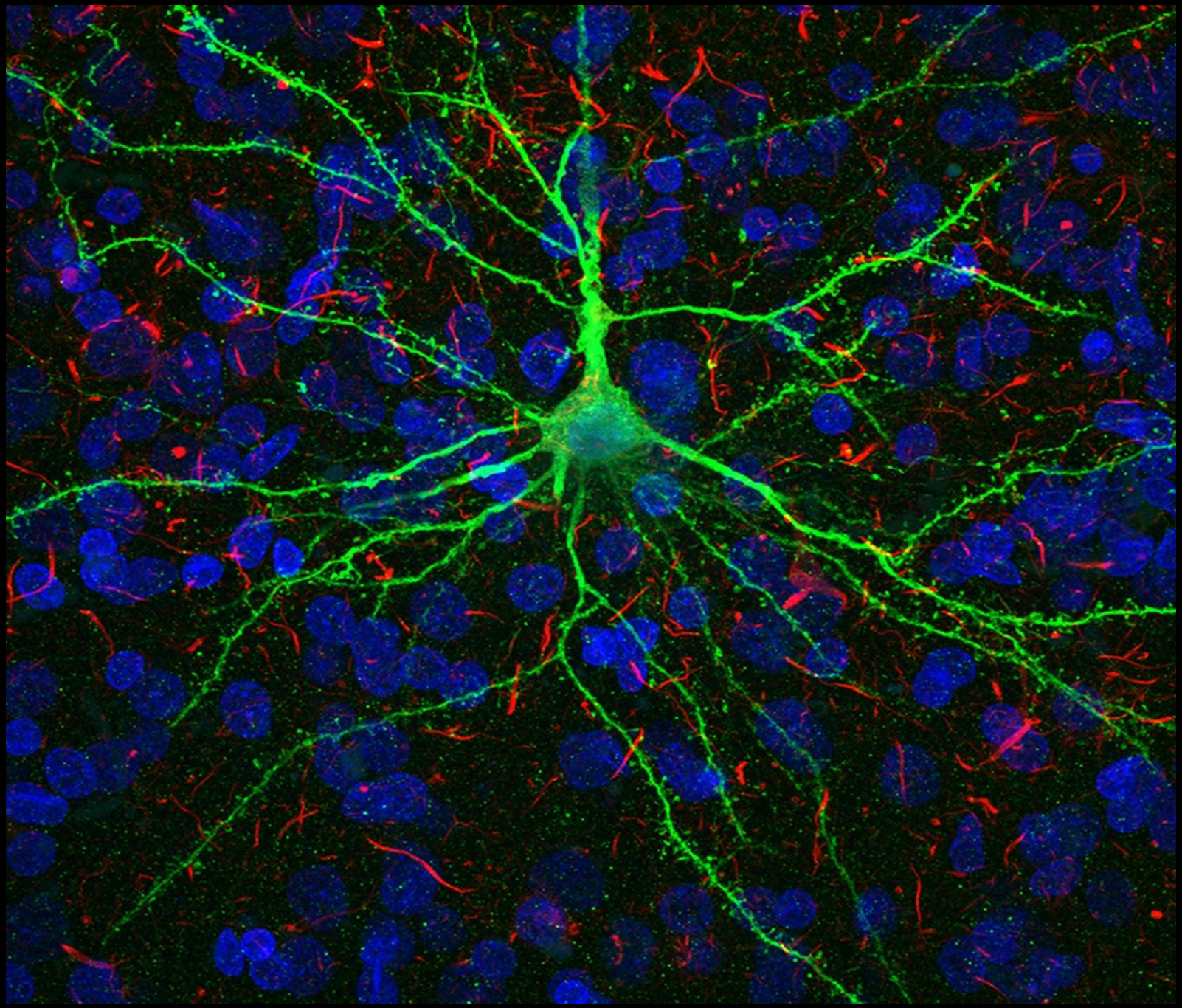
Patrón I

Patrón IIa

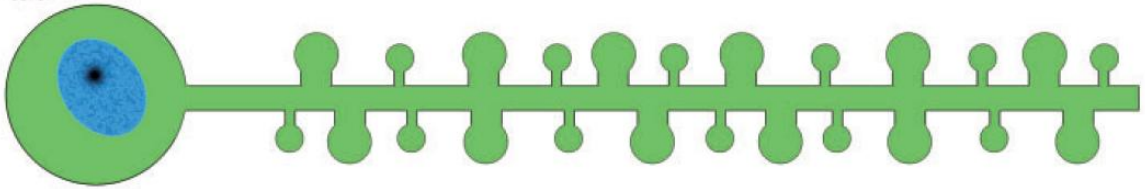
Patrón IIb



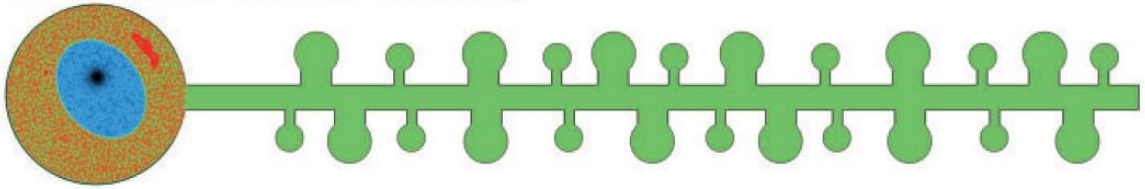
Patrones de inmunotinción , PHF-tau



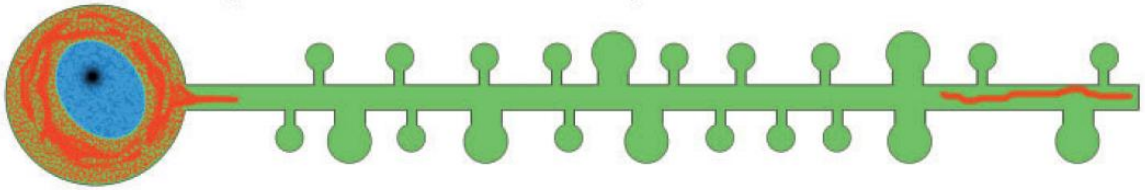
PHF-tau -



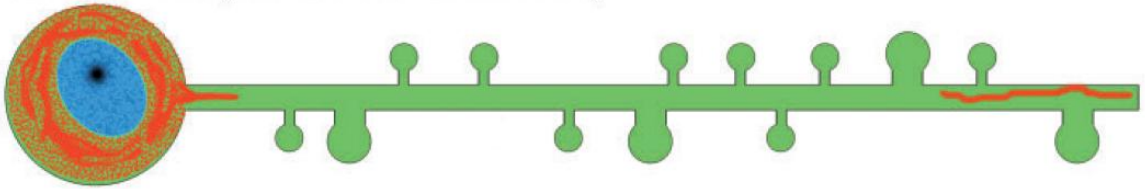
PHF-tau+ Pattern I (no dendritic alterations)



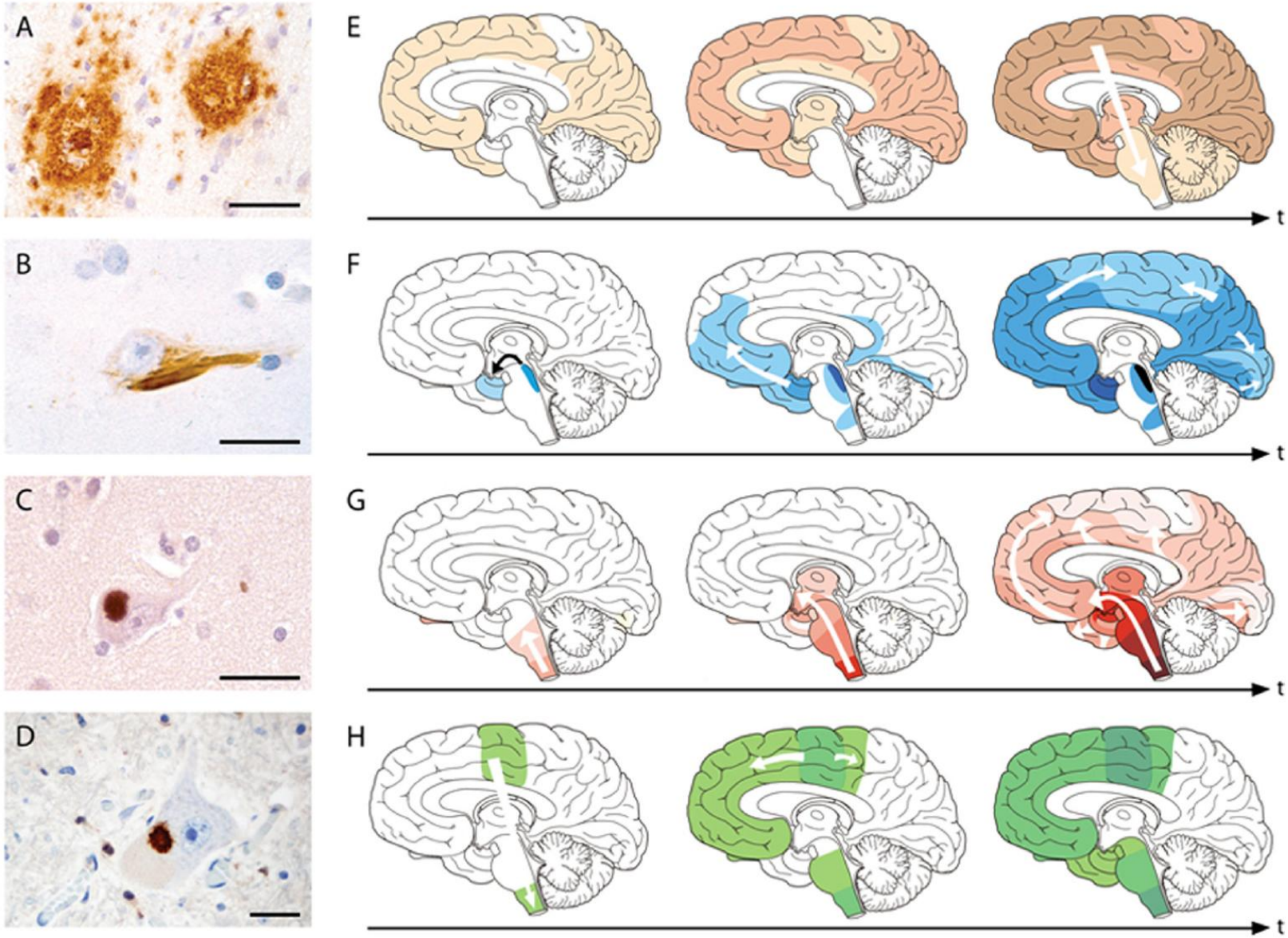
PHF-tau+ Pattern IIa (moderate dendritic alterations)



PHF-tau+ Pattern IIa (severe dendritic alterations)



PHF-tau+ Pattern IIb (extreme dendritic alterations)



Jucker & Walker, 2013

Cell

Leading Edge
Perspective

Transmissible Proteins: Expanding the Prion Heresy

Claudio Soto[1,*]
[1]Mitchell Center for Alzheimer's Disease and Related Brain Disorders, Department of Neurology, University of Texas Houston Medical School, Houston, TX 77030, USA
*Correspondence: claudio.soto@uth.tmc.edu
DOI 10.1016/j.cell.2012.05.007

Annu Rev Genet. 2013 ; 47: 601–623. doi:10.1146/annurev-genet-110711-155524.

Biology and Genetics of Prions Causing Neurodegeneration

Stanley B. Prusiner
Institute for Neurodegenerative Diseases and Department of Neurology, University of California, San Francisco, California

Neurodegenerative diseases caused by prions.

Neurodegenerative diseases	proteins	Percent inherited
Creutzfeldt-Jakob disease	PrP^{Sc}	10–20
Gerstmann-Sträussler-Scheinker		90
Fatal insomnia		90
Bovine spongiform encephalopathy		0
Scrapie		0
Chronic wasting disease		0
Alzheimer's disease	Aβ → tau	10–20
Parkinson's disease	α-synuclein	10–20
Frontotemporal dementia (FTD) Posttraumatic FTD, called chronic traumatic encephalopathy	tau, TDP43, FUS, C9orf72 (progranulin)	10–20
Amyotrophic lateral sclerosis	SOD1, TDP43, FUS, C9orf72	10–20
Huntington's disease	huntingtin	100

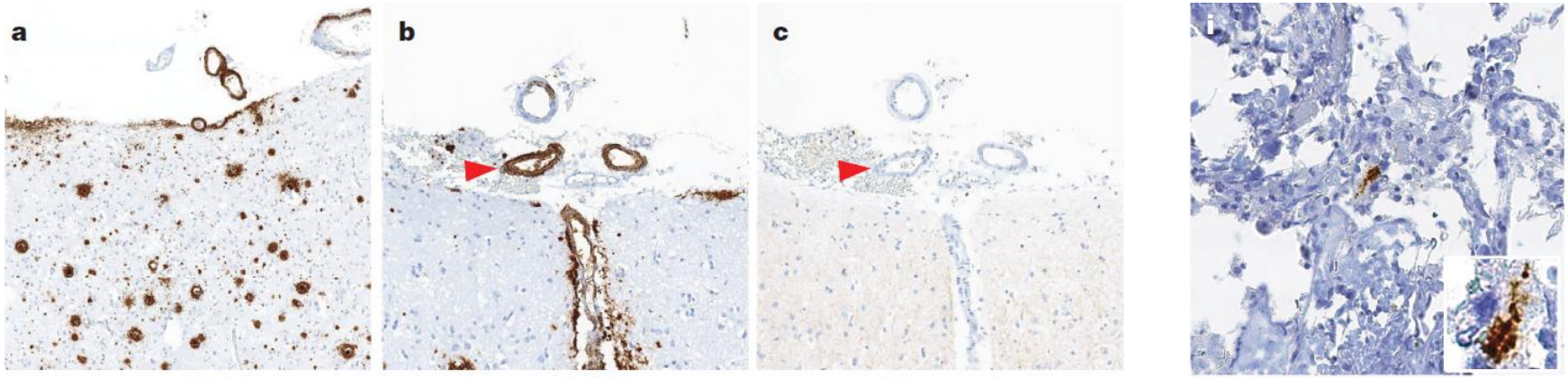
LETTER

doi:10.1038/nature15369

Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy

Zane Jaunmuktane[1], Simon Mead[2,3,4], Matthew Ellis[3], Jonathan D. F. Wadsworth[2,3], Andrew J. Nicoll[2,3], Joanna Kenny[2,4], Francesca Launchbury[3], Jacqueline Linehan[2], Angela Richard-Loendt[3], A. Sarah Walker[5], Peter Rudge[2,4], John Collinge[2,3,4] & Sebastian Brandner[1,2,3]

00 MONTH 2015 | VOL 000 | NATURE | 1



Amyloid β | Amyloid β | Prion protein | Amyloid β in pituitary gland

ition but do not co-localize with Aβ deposits. While there is no suggestion that Alzheimer's disease is a contagious disease and no supportive evidence from epidemiological studies that Alzheimer's disease is transmissible, notably by blood transfusion[28,29], our findings should prompt consideration of whether other known iatrogenic routes of prion transmission, including surgical instruments and blood products, may also be relevant to Aβ and other proteopathic seeds seen in neurodegenerative diseases. Aβ seeds are known, like prions, to adhere to metal surfaces and to resist formaldehyde inactivation and conventional hospital sterilisation[30].

Placas y ovillos, diagnóstico NP de la E. de Alzheimer.

Metodología y estadiaje de Braak.

- **Patología típica con distribución atípica.**

Otras patologías (tau+) con distribución típica.

Placas sin ovillos.

Ovillos sin placas.

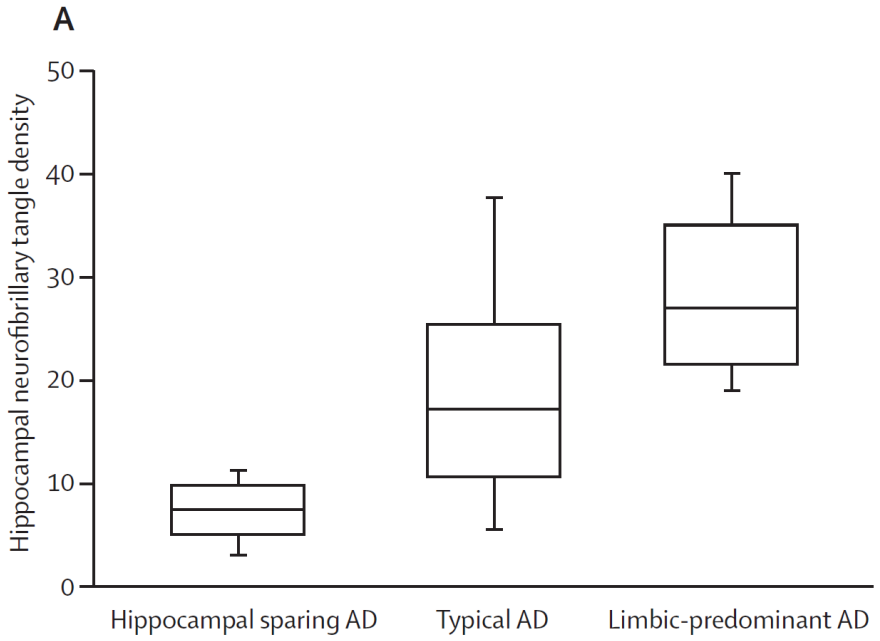
Neuropatología del deterioro cognitivo leve.

Reserva cognitiva y compensación.

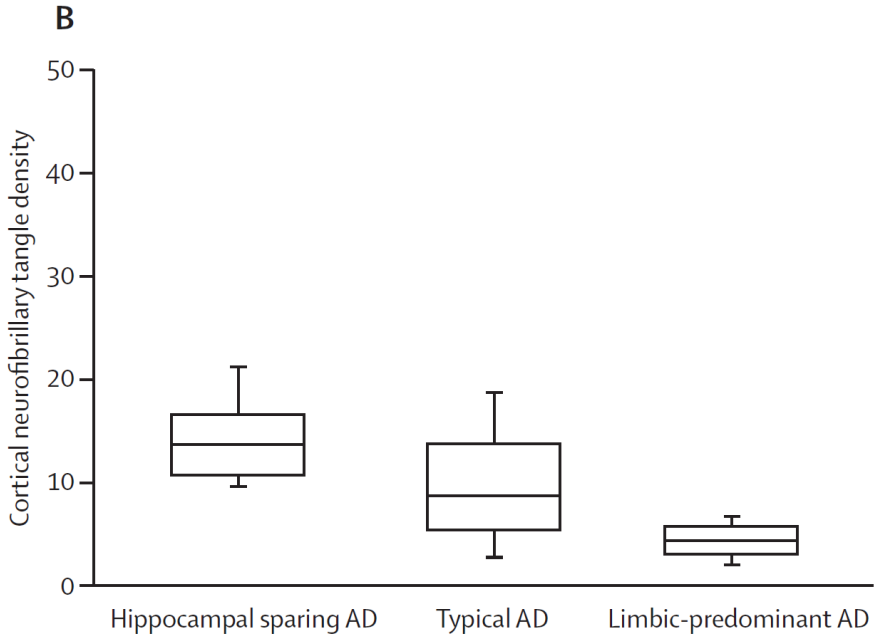
Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study

Melissa E Murray, Neill R Graff-Radford, Owen A Ross, Ronald C Petersen, Ranjan Duara, Dennis W Dickson

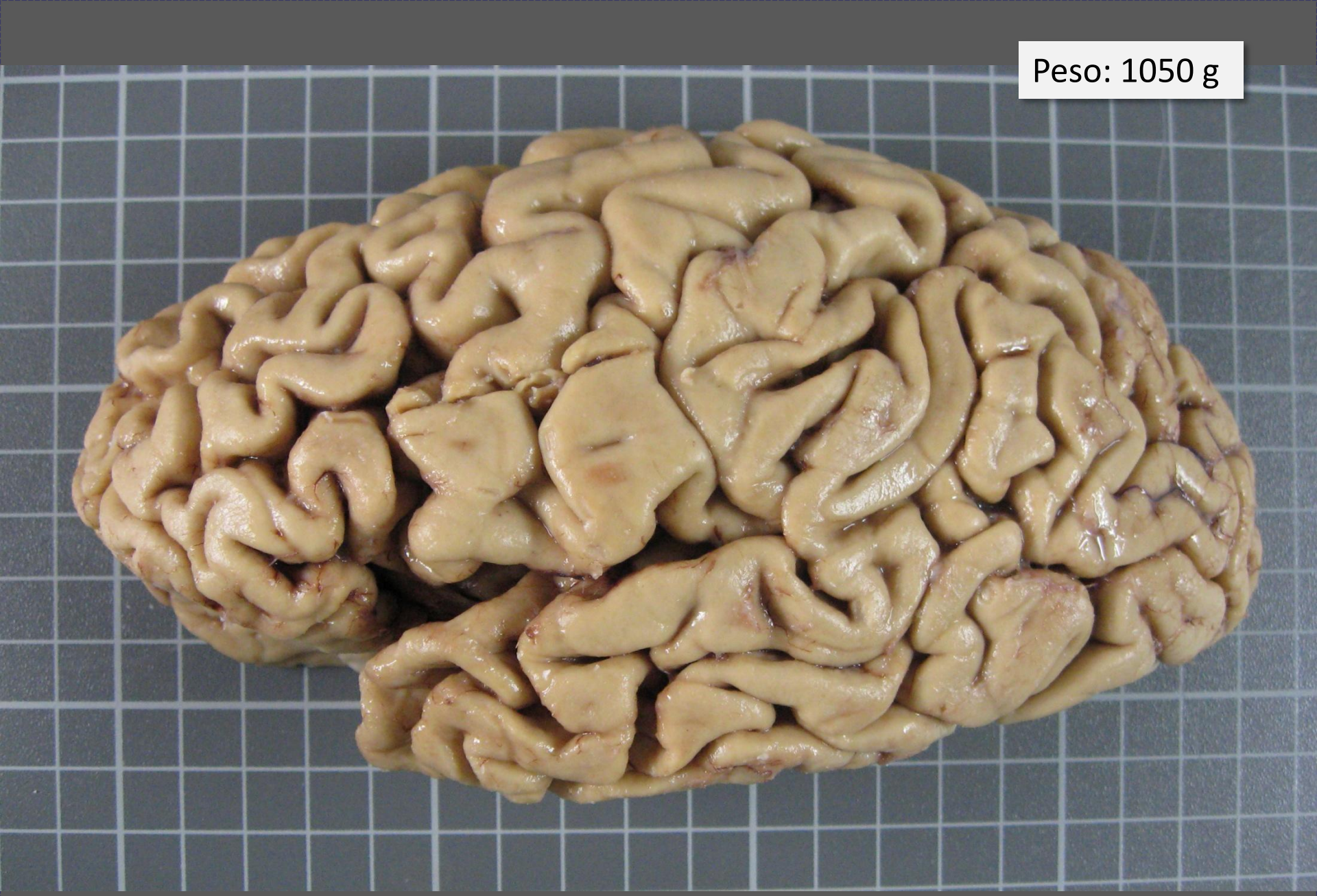
Lancet Neurol 2011; 10: 785–96



Densidad de ONF en hipocampo



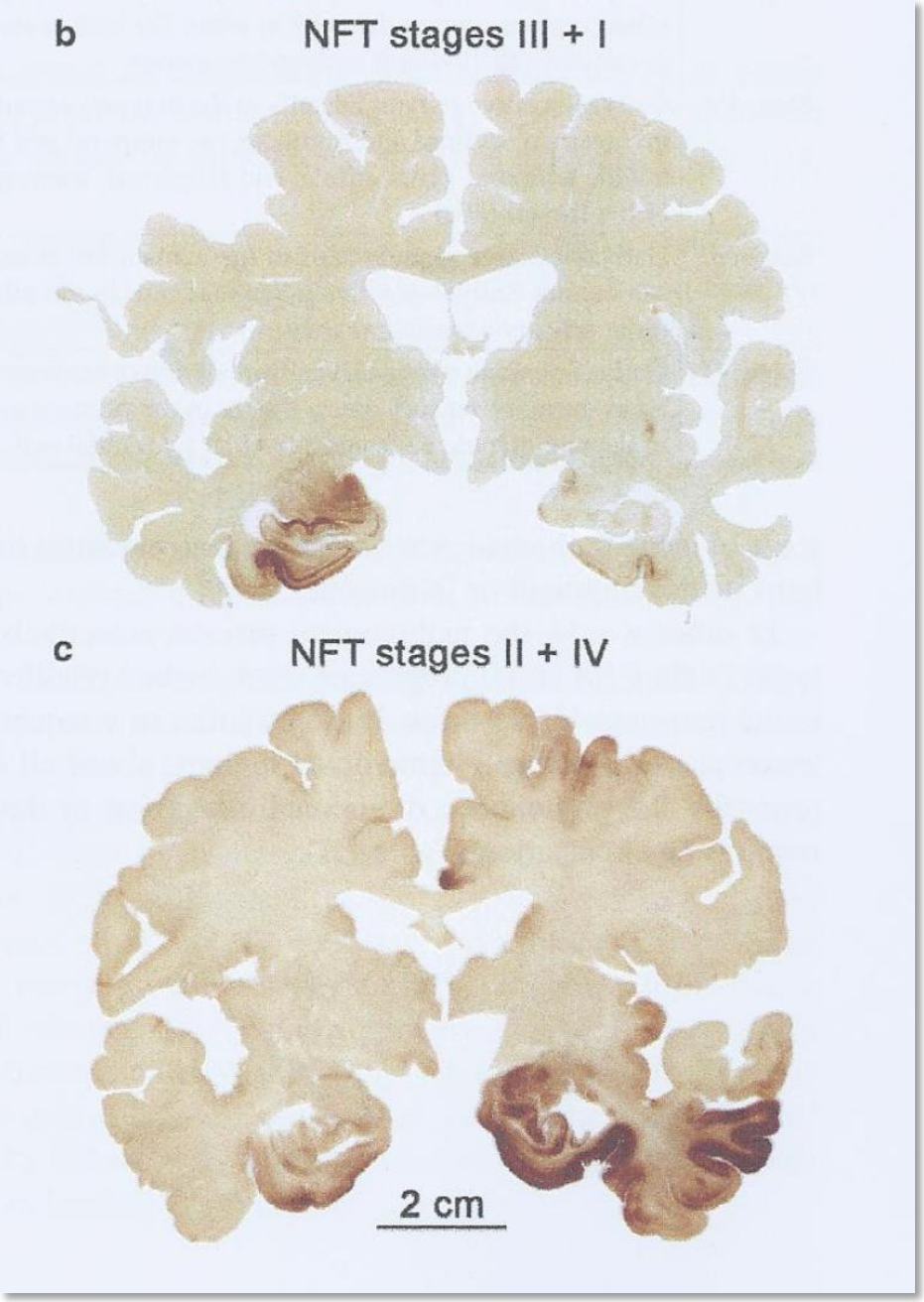
Densidad de ONF en córtex


Peso: 1050 g

Patología de Alzheimer focal

Atrofia perirrolándica

Síndrome córticobasal

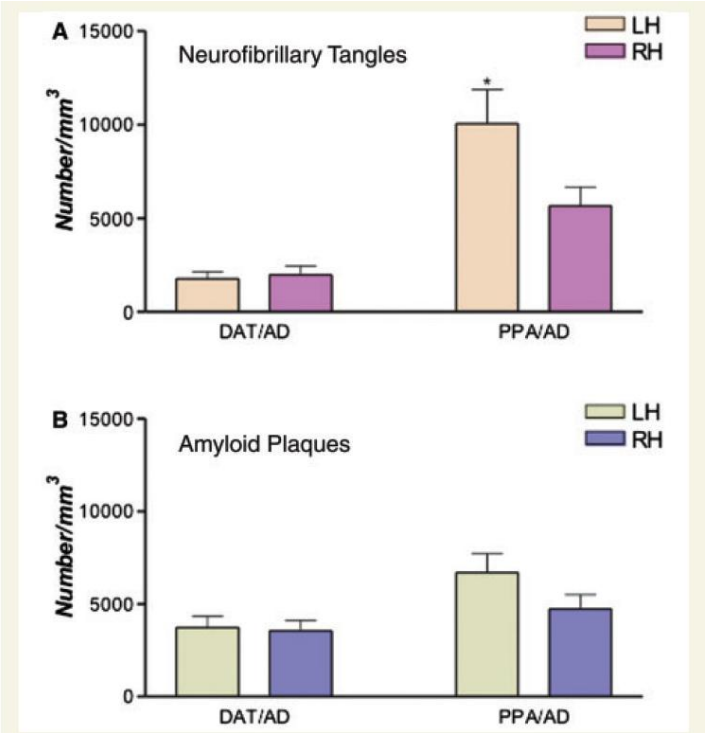


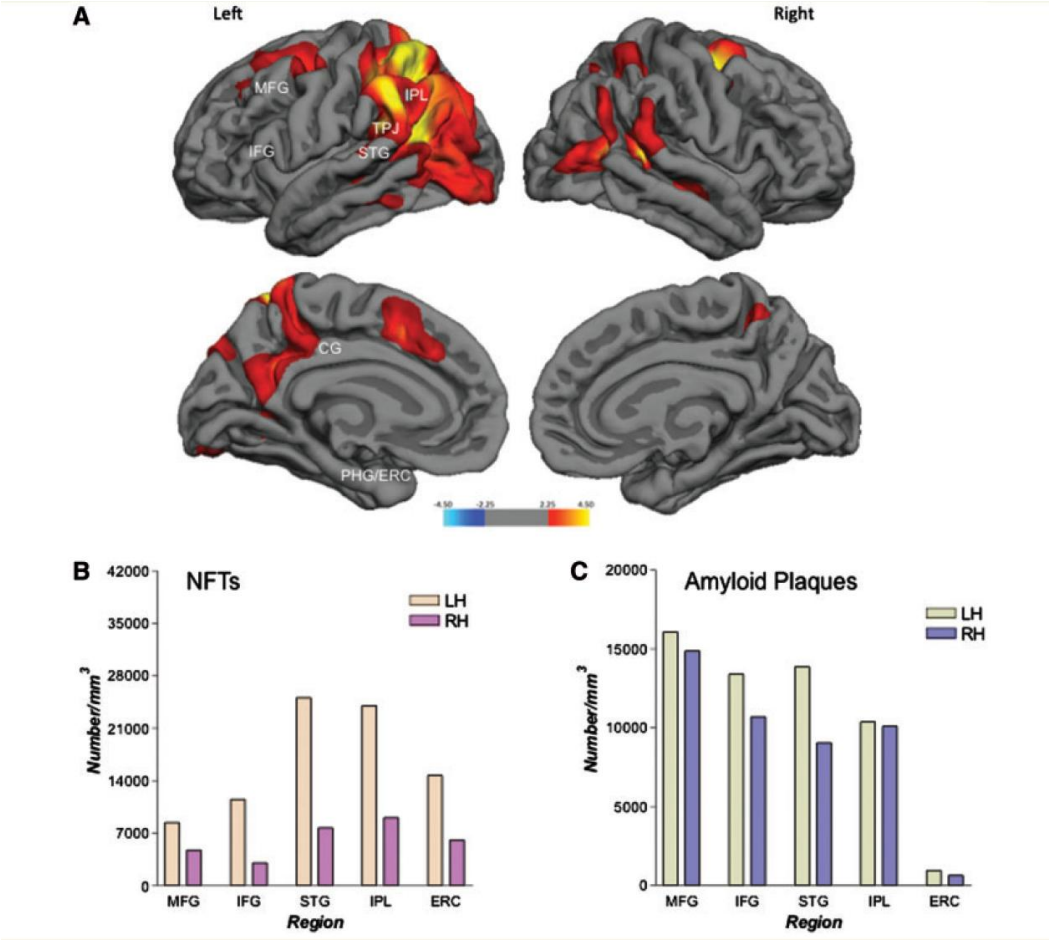
H Braak & K Del Tredici, 2015

Clinically concordant variations of Alzheimer pathology in aphasic versus amnestic dementia

Brain 2012: 135; 1554–1565

Tamar Gefen,[1,2] Katherine Gasho,[1] Alfred Rademaker,[1,3] Mona Lalehzari,[1] Sandra Weintraub,[1,2,4] Emily Rogalski,[1] Christina Wieneke,[1] Eileen Bigio,[1,4] Changiz Geula[1,*] and M.-Marsel Mesulam[1,2,4,*]





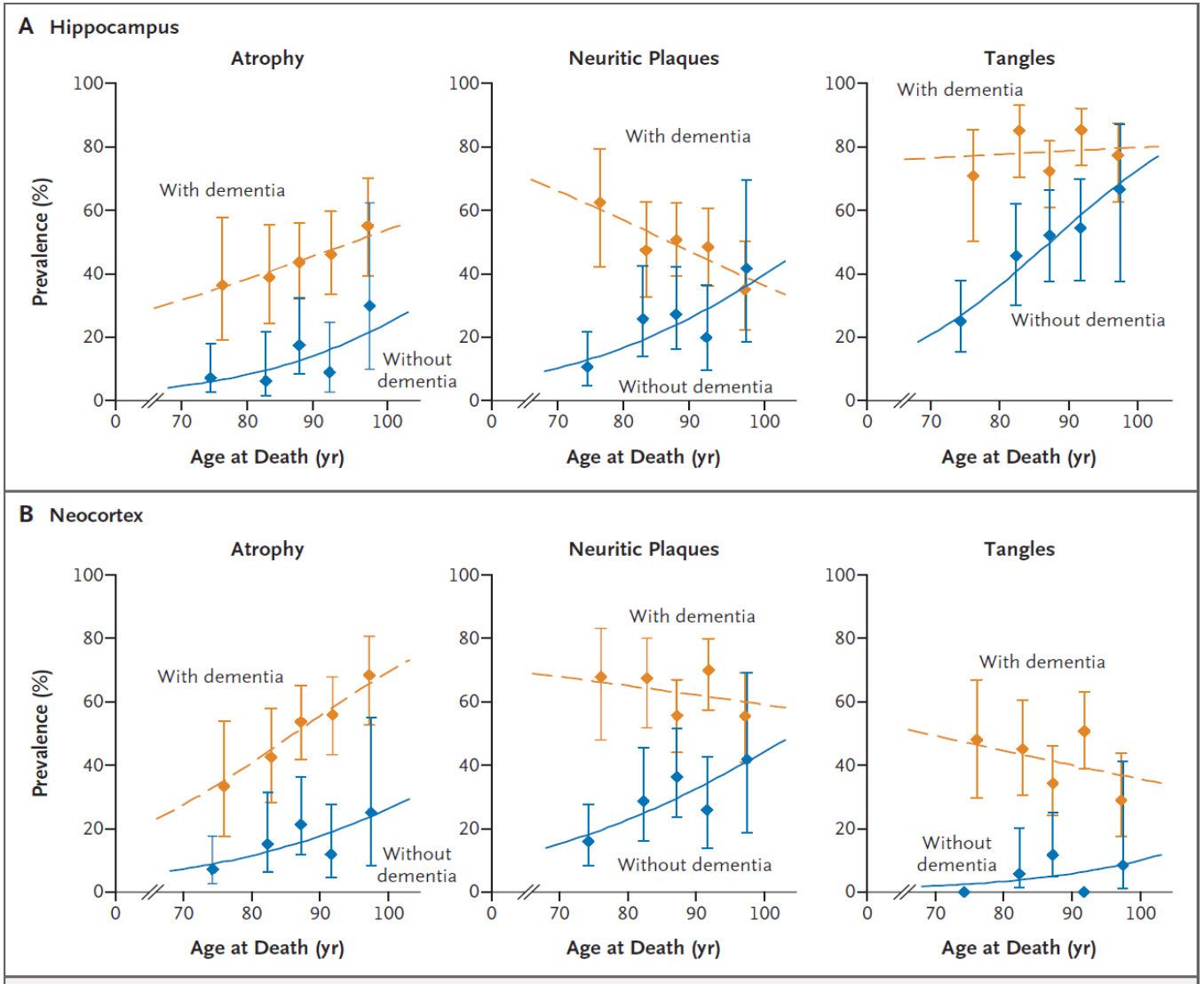


Figure 1. Modeled and Observed Prevalence of Moderate or Severe Pathological Lesions According to Age.
Persons who died with dementia (yellow) are compared with those who died without dementia (blue). Filled symbols represent the observed prevalence of moderate or severe pathological lesions, and I bars show the 95% confidence intervals. The solid and broken lines represent modeled prevalence values.

N Engl J Med 2009;360:2302-09.

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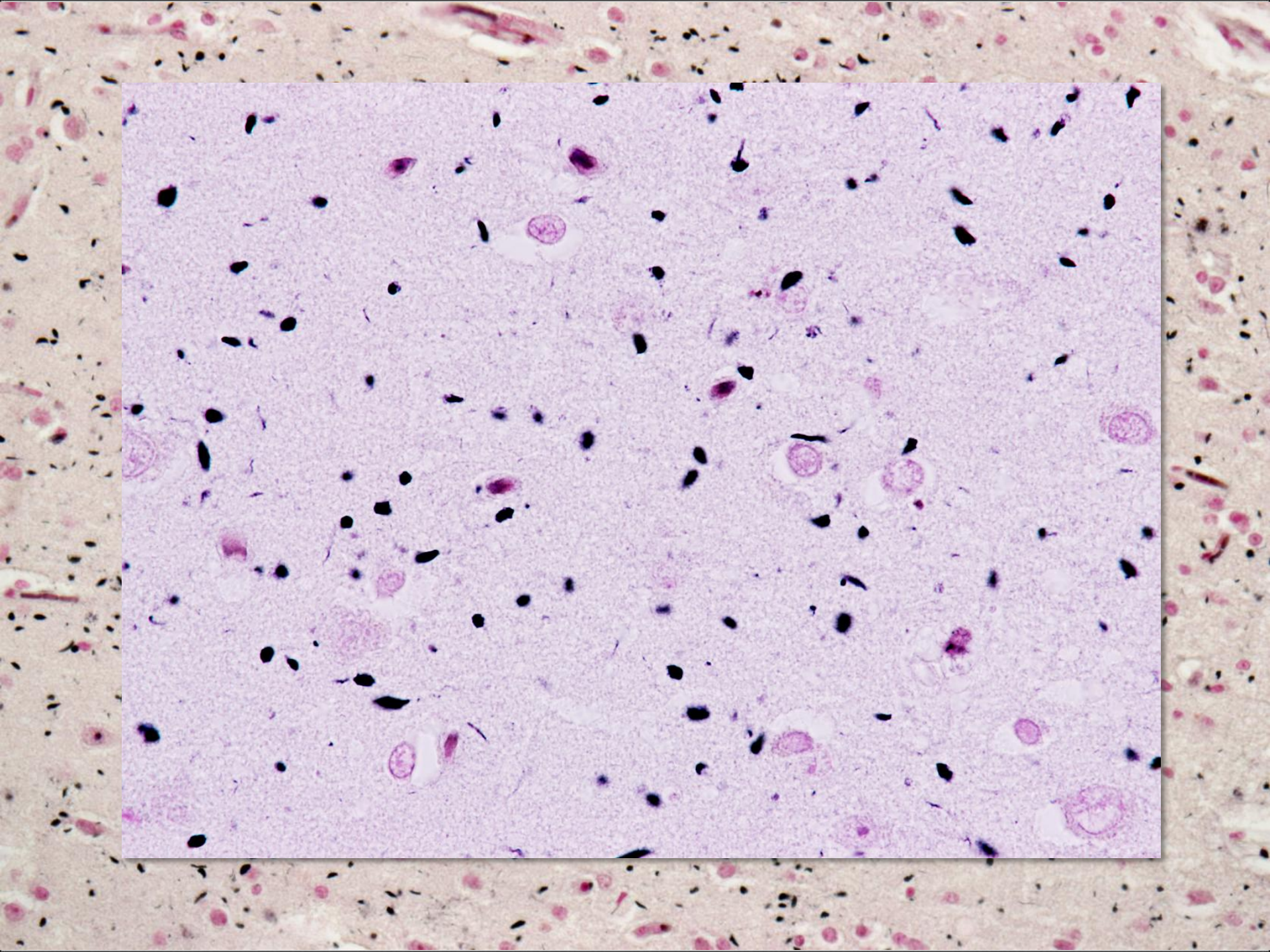
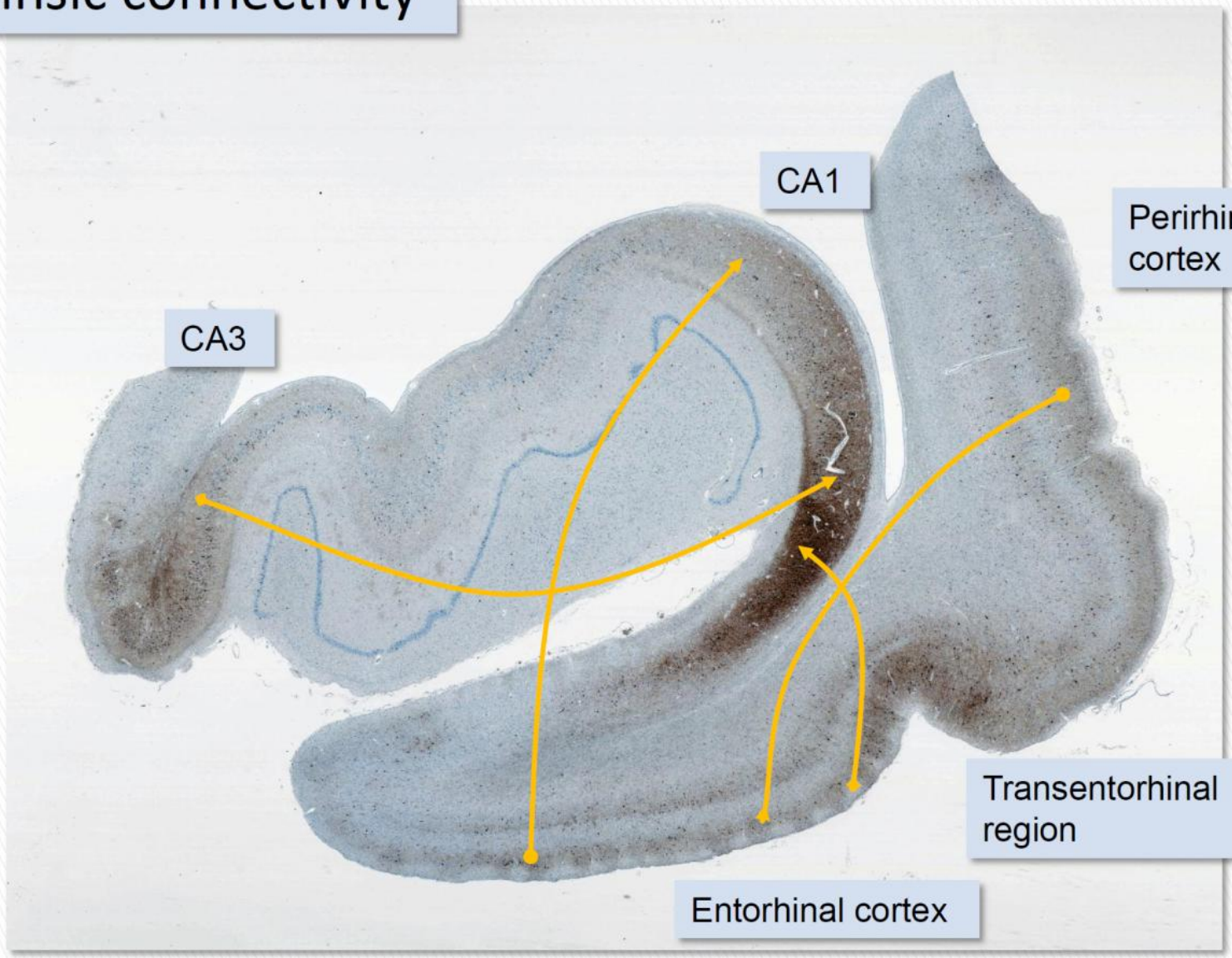
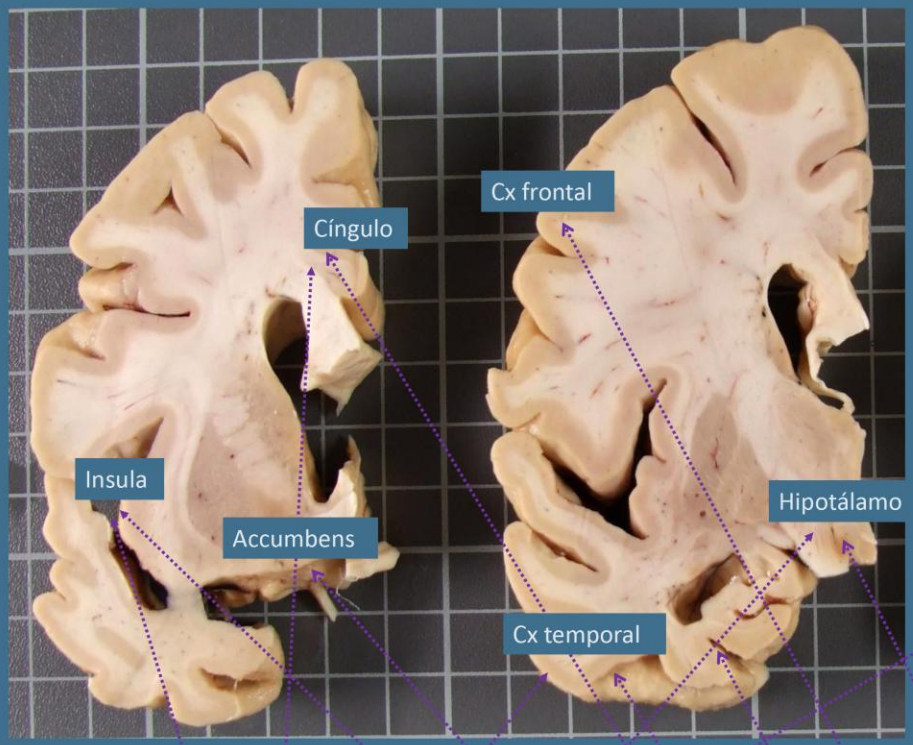


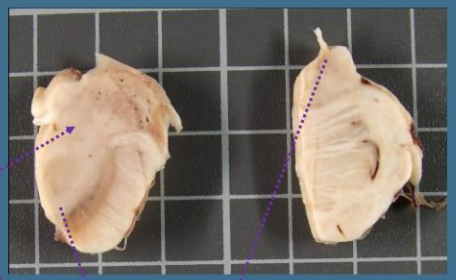
Intrinsic connectivity



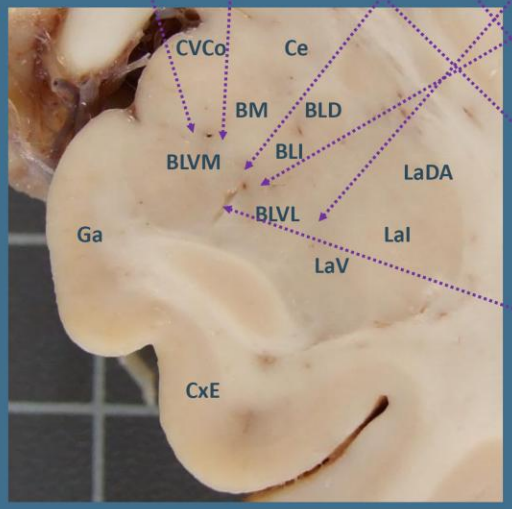
Rábano et al., 2014

Relaciones de conectividad existentes entre distintas regiones y núcleos que participan en la progresión de la patología de granos argirófilos, desde los estadios iniciales limitados a amígdala e hipocampo, hasta los estadios más avanzados, con afectación de neocórtex y tronco.

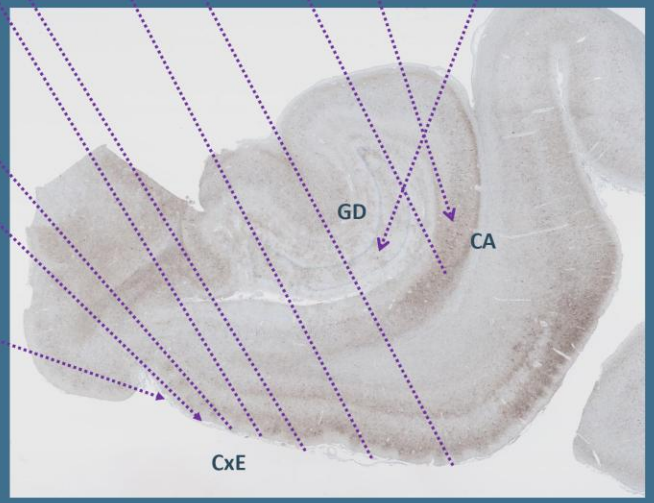




Mesencéfalo Protuberancia

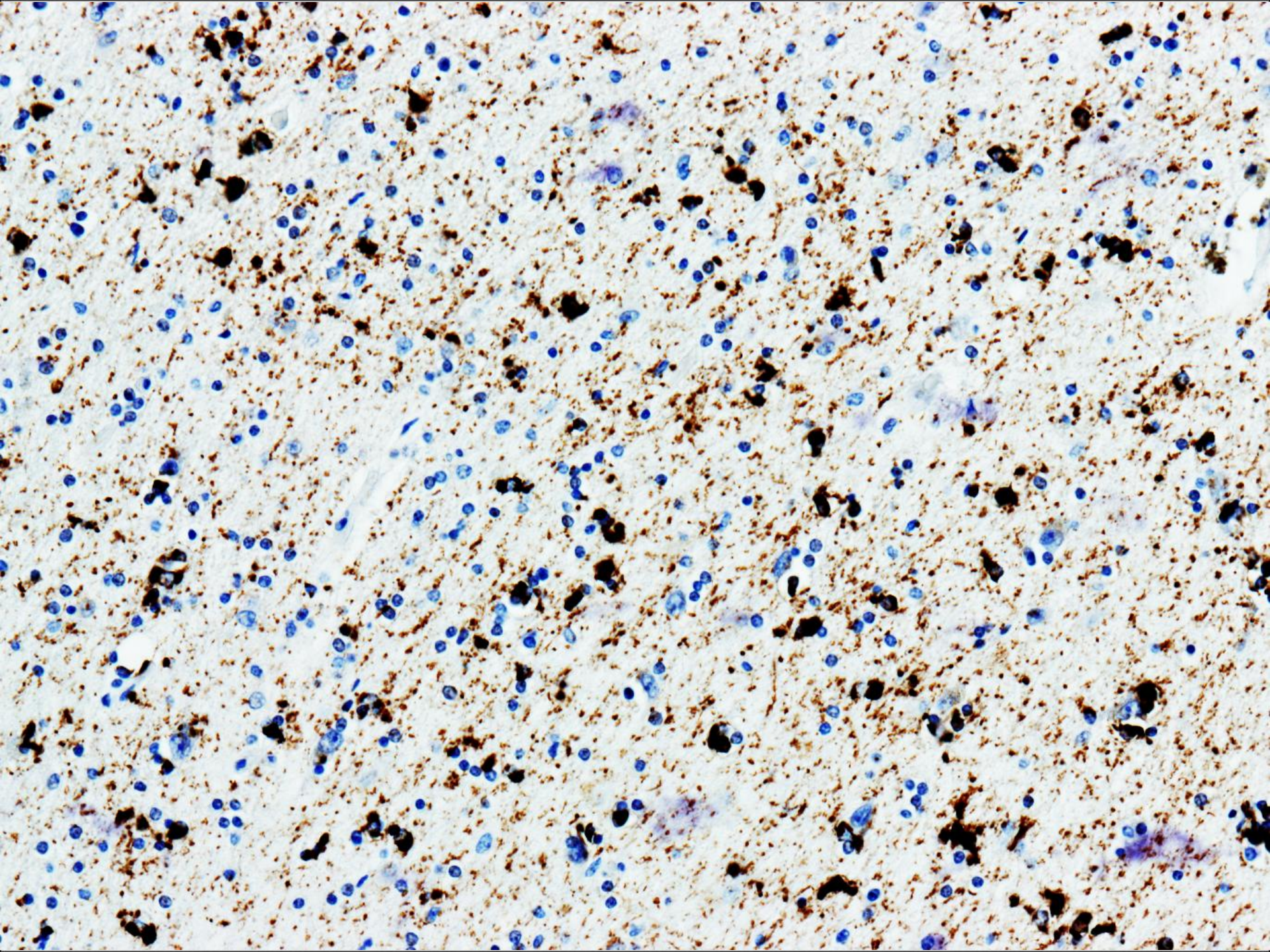


Amígdala



Hipocampo anterior (Tau AT8)

Taupatía con inclusiones gliales globulares (IGG)
Hipocampo, Tau AT8



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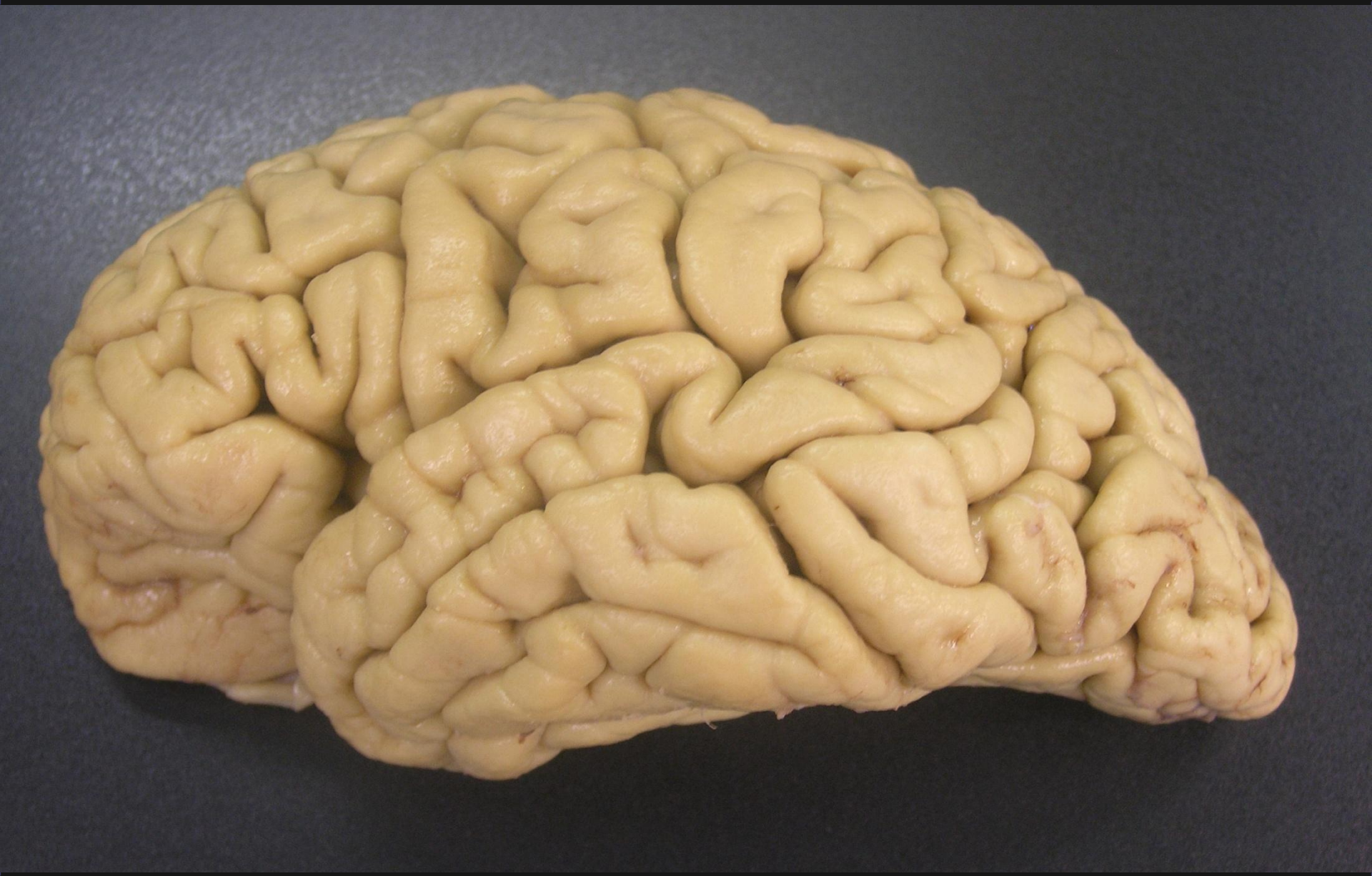
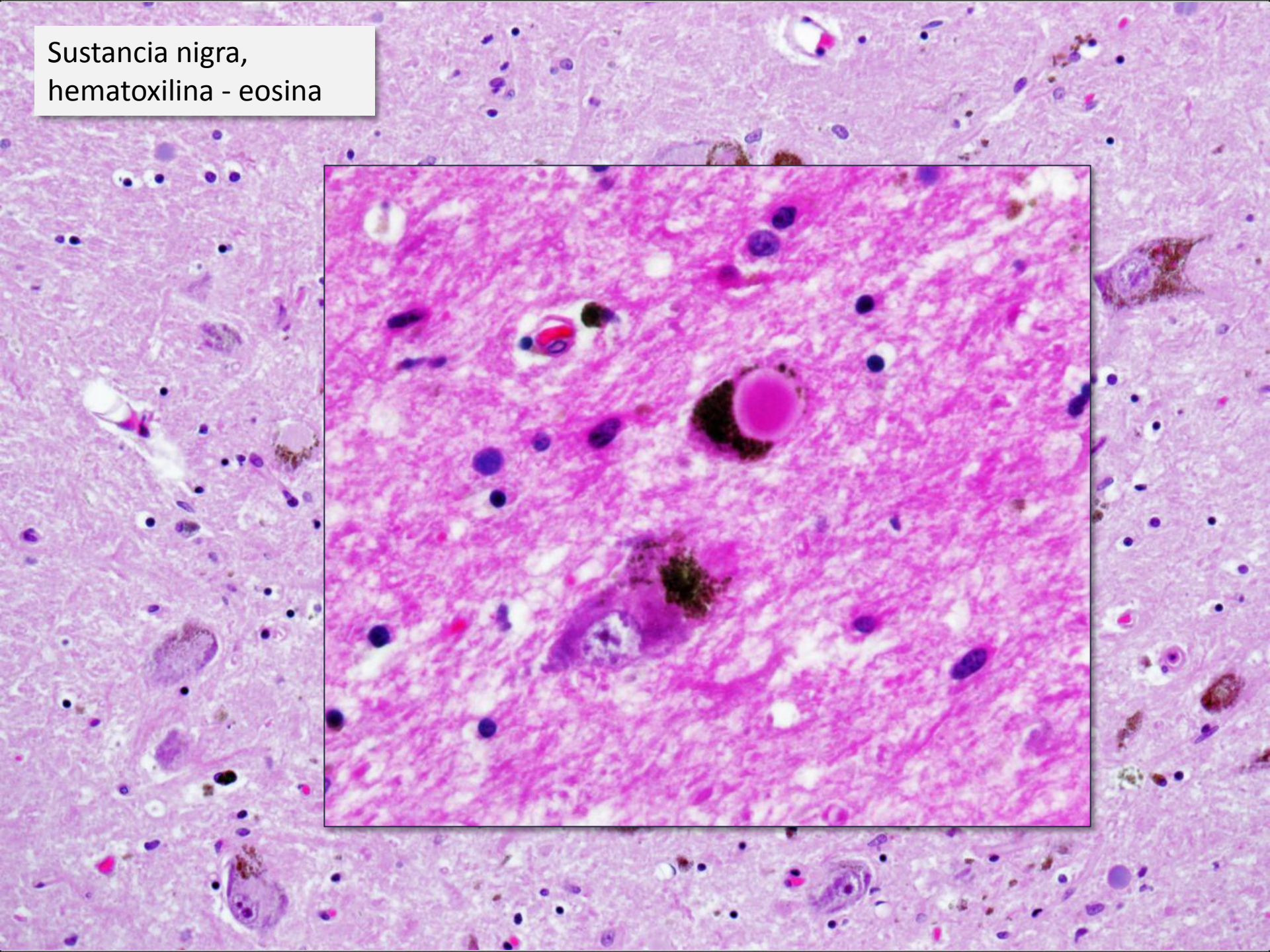
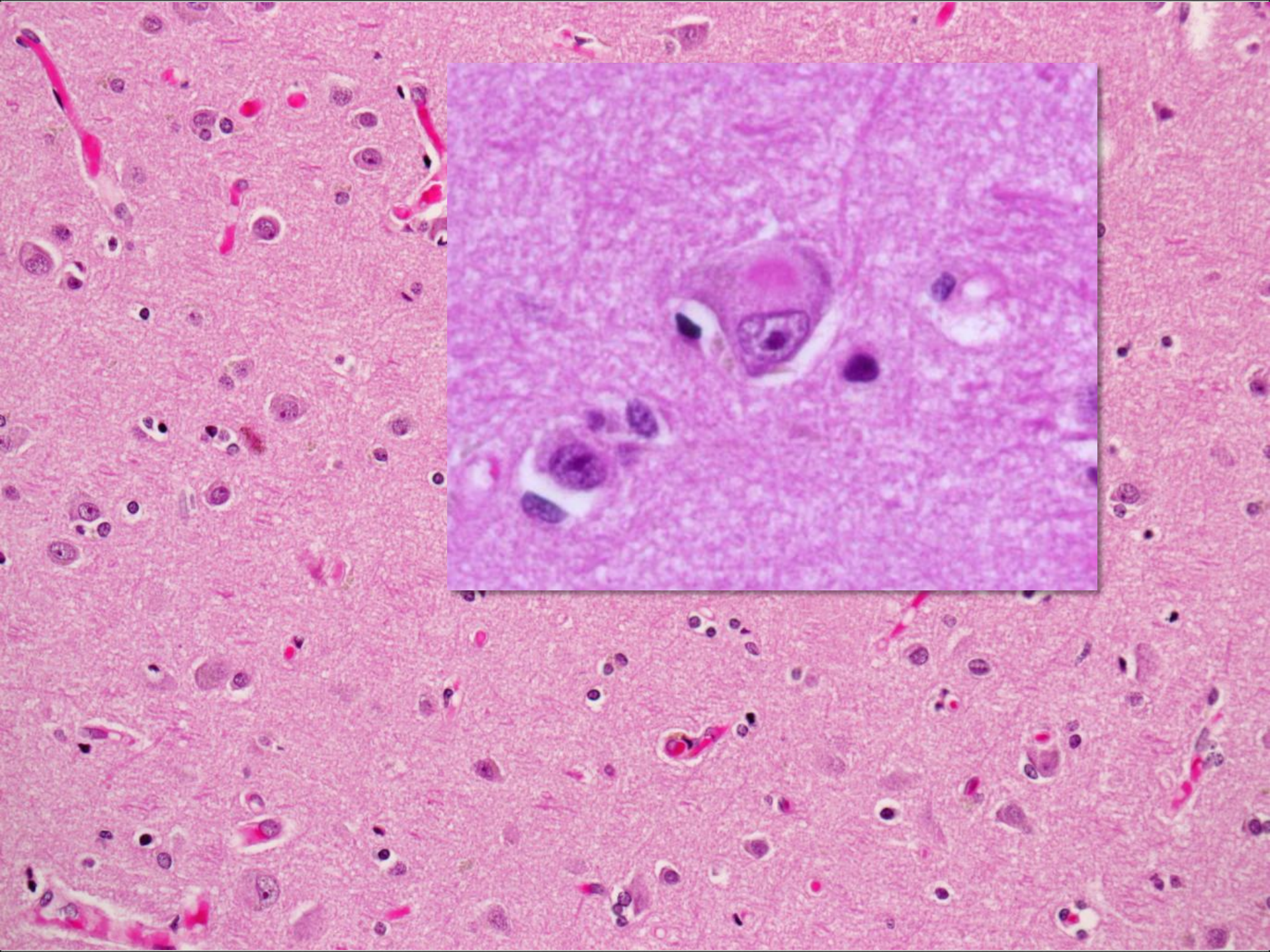
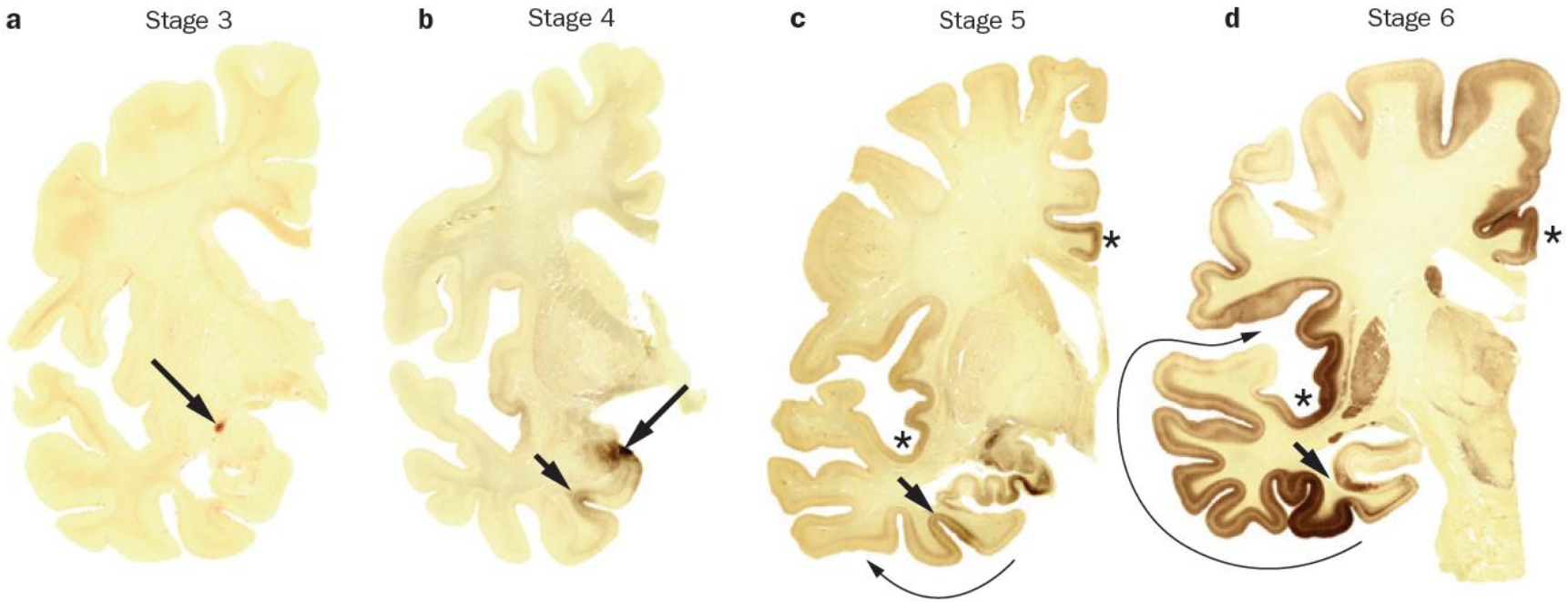


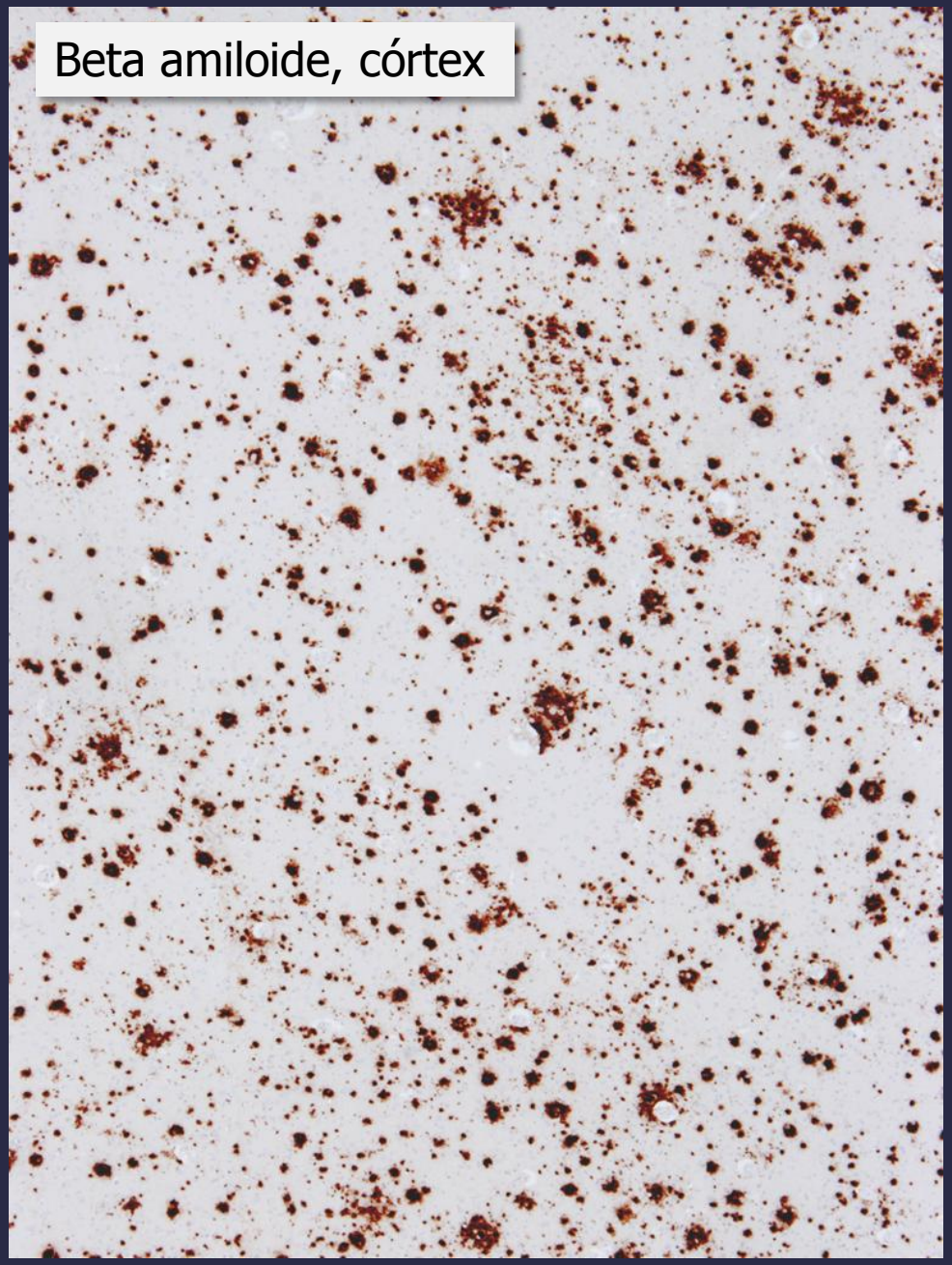
Sustancia nigra,
hematoxilina - eosina

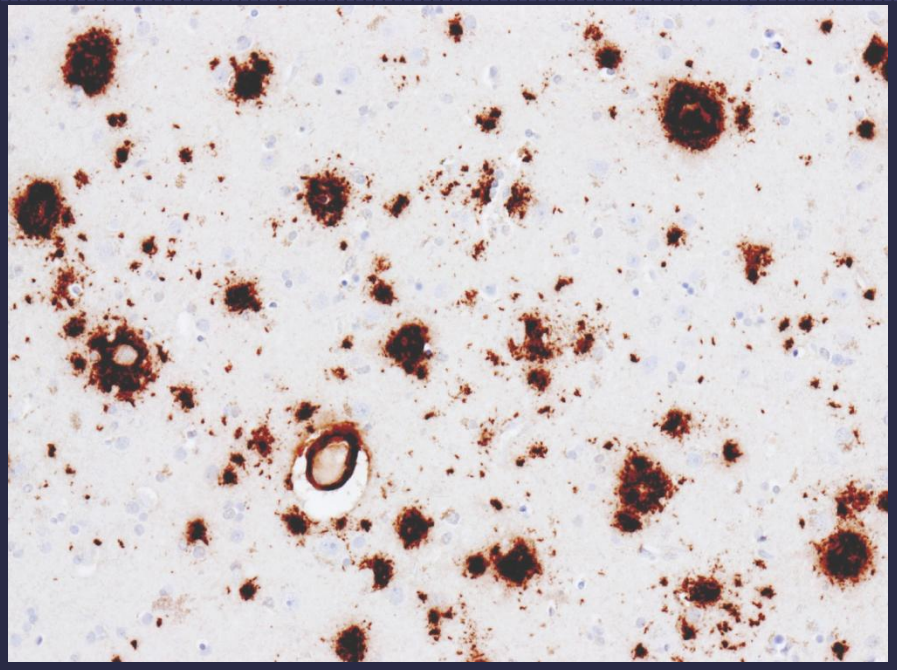


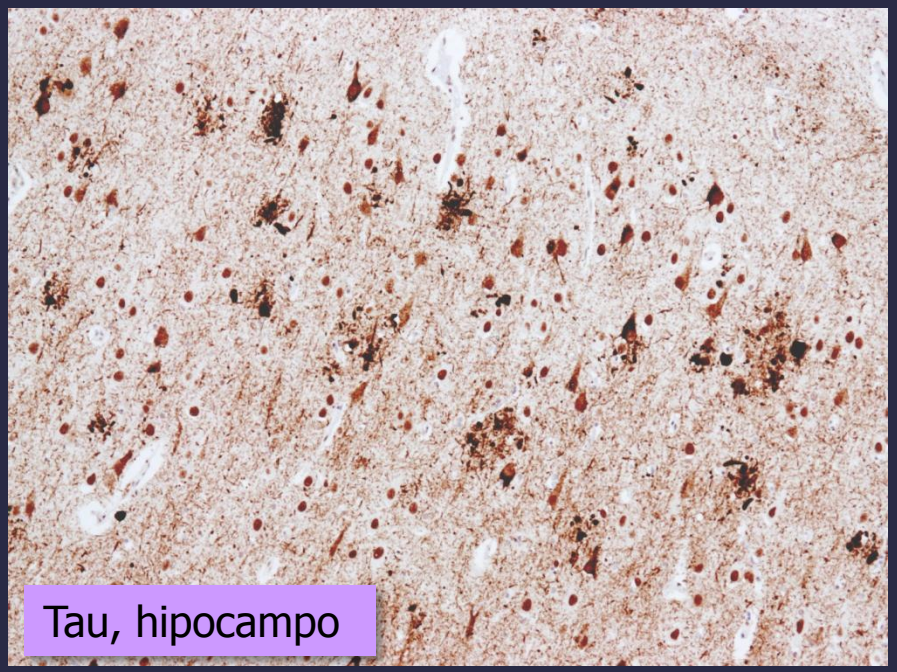




Goedert, M. *et al. Nat. Rev. Neurol.* **9**, 13–24 (2013)


Beta amiloide, córtex




Tau, hipocampo

Placas y ovillos, diagnóstico NP de la E. de Alzheimer.

Metodología y estadiaje de Braak.

Patología típica con distribución atípica.

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Placas sin ovillos.

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Reserva cognitiva y compensación.

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

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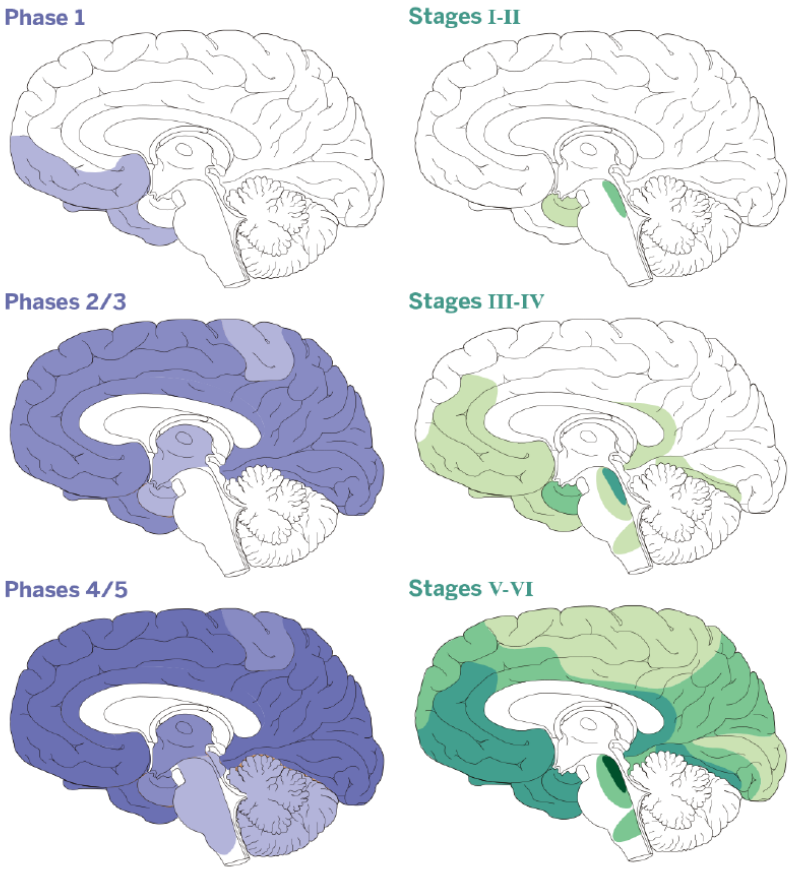
We propose a new term, "primary age-related tauopathy" (PART), to describe a pathologic continuum ranging from focally distributed neurofibrillary tangles (NFTs) observed in cognitively normal aged individuals, through the pathology observed in persons with dementing illnesses that have been referred to as "tangle-predominant senile dementia" (TPSD), "tangle-only dementia", "preferential development of NFT without senile plaques", and "senile dementia of the neurofibrillary tangle type" (SD-NFT), among other names. Here



Thal Braak

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

1. Requires

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

2. Then subclassify as follows

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

Examples

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

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

3. Ancillary studies (not required)

Immunohistochemistry: 3R and 4R tau-positive

Electron microscopy: paired helical filaments present

Genetics: absence of pathogenic FTLD-tau mutation

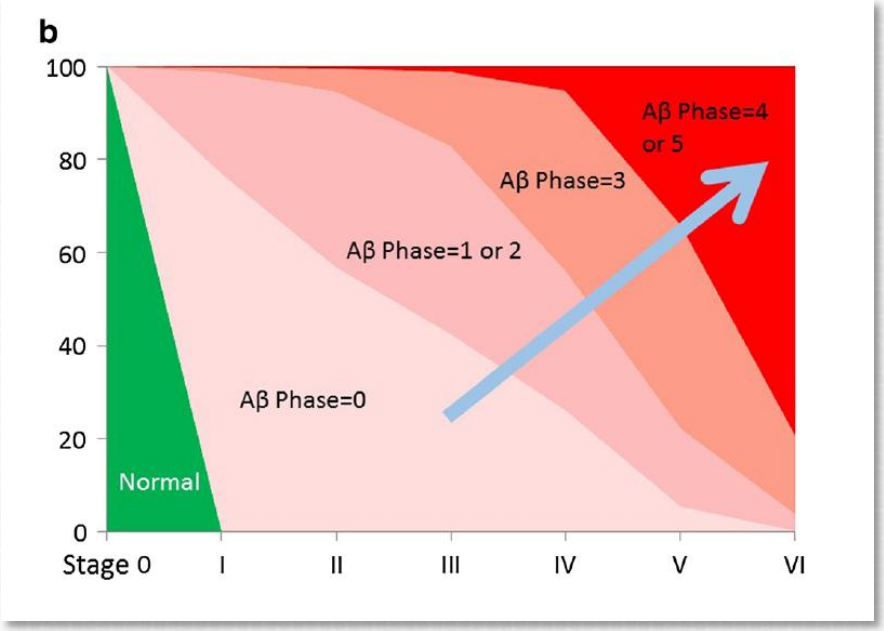
Acta Neuropathol (2015) 129:749–756
DOI 10.1007/s00401-015-1390-7

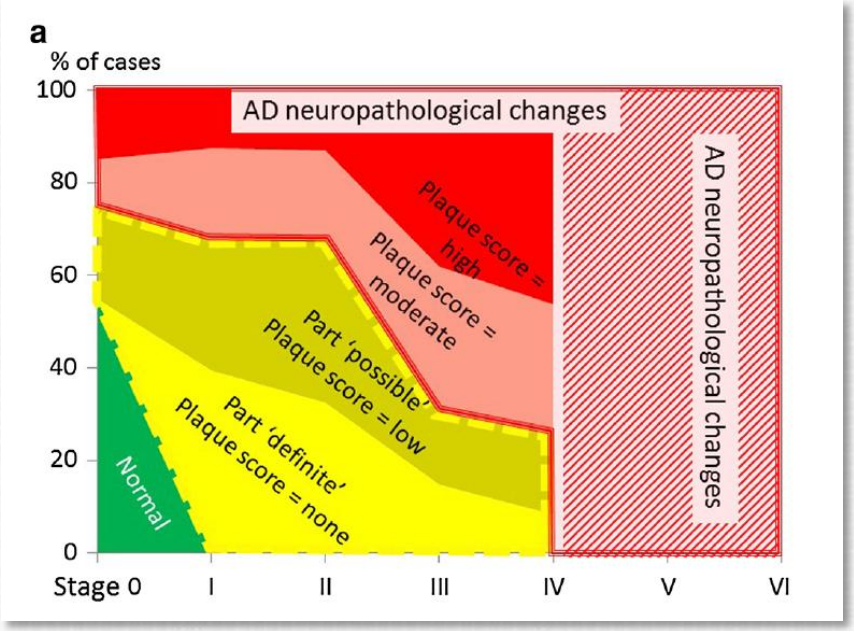
POSITION PAPER

PART is part of Alzheimer disease

Charles Duyckaerts · Heiko Braak · Jean-Pierre Brion · Luc Buée · Kelly Del Tredici · Michel Goedert · Glenda Halliday · Manuela Neumann · Maria Grazia Spillantini · Markus Tolnay · Toshiki Uchihara

We contend first that there is no way, neuropathologically, genetically, or clinically, to differentiate PART from early AD.


b
100
80
60
40
20
0
Stage 0
I
II
III
IV
V
VI
Normal
Aβ Phase=0
Aβ Phase=1 or 2
Aβ Phase=3
Aβ Phase=4
or 5


a
% of cases
100
80
60
40
20
0
Stage 0
I
II
III
IV
V
VI
AD neuropathological changes
Plaque score =
high
Plaque score =
moderate
Part 'possible'
Plaque score = low
Part 'definite'
Plaque score = none
Normal
AD neuropathological changes

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

CORRESPONDENCE

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

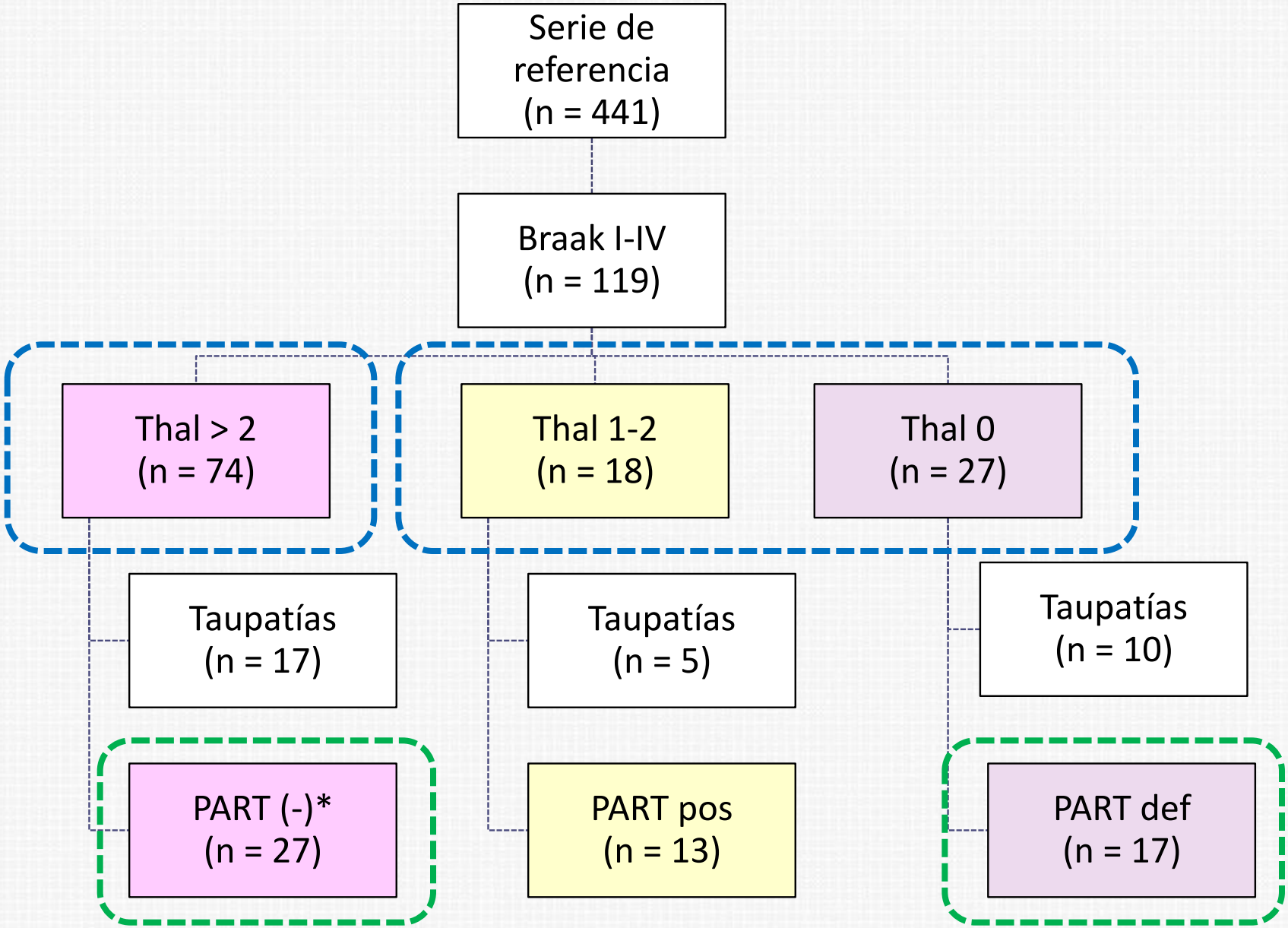
Kurt A. Jellinger[1] · Irina Alafuzoff[2] · Johannes Attems[3] · Thomas G. Beach[4] · Nigel J. Cairns[5] · John F. Crary[6] · Dennis W. Dickson[7] · Patrick R. Hof[8] · Bradley T. Hyman[9] · Clifford R. Jack Jr.[10] · Gregory A. Jicha[11] · David S. Knopman[12] · Gabor G. Kovacs[13] · Ian R. Mackenzie[14] · 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]

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)

This kind of tau pathology is also seen in other neurodegenerative disorders such as Huntington's disease, motor neuron disease, or Guam parkinsonism–dementia complex, where NFTs can be present in the same brain regions, especially in late-onset/longer surviving cases, in the (total or relative) absence of Aβ plaques [11, 41]. These cases might be considered as "coincidental" PART. Thus, further studies are



* Selección aleatoria de casos

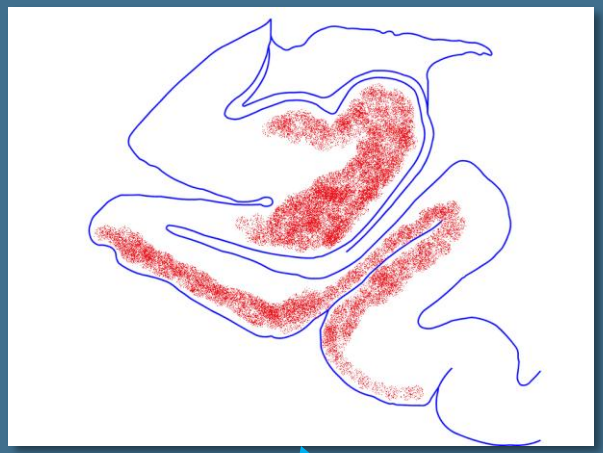
		Thal 0-2	Thal >2	P < 0,05
	N	45	74	
	Edad	74,4 (±8,1)	81,8 (±8,5)	*
	Sexo (V : M)	1,8 : 1	1 : 1,1	P = 0.06
	Estadio Braak (1-4)	1,61	2,76	*
	Estadio Thal (0-5)	0,56	4,06	*
	CERAD (0-3)	0	1,15	*
	Ang. Amiloide (0-3)	0,05	0,9	*
	Score Vascular (0-9)	1,8	2,94	*
	Probabilidad NIA (0-3)	0,44	1,66	*
	Vascular	29	51	*
	Lewy	11	32	*
	Taupatía	31	20	
Dx NPatol	TDP	33	15	*
(%)	Huntington	4	4	
	Inflamatorias	9	0	
	Ataxias	2	5	
	Otros	7	3	

(-) Taupatías

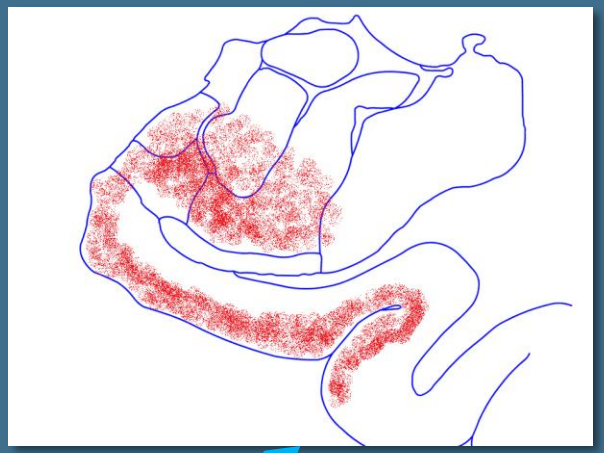
		Thal 0-2	Thal >2	P < 0,05
	N	30	57	
	Edad	73,7 (±8,8)	80,2 (±8,2)	*
	Sexo (V : M)	1,9 : 1	1 : 1,1	
	Estadio Braak (1-4)	1,57	2,72	*
	Estadio Thal (0-5)	0,52	4,04	*
	CERAD (0-3)	0	1,09	*
	Ang. Amiloide (0-3)	0,07	0,98	*
	Score Vascular (0-9)	1,67	3,09	*
	Probabilidad NIA (0-3)	0,43	1,59	*
	Vascular	29	47	P = 0,07
	Lewy	6	37	*
	Taupatía	0	0	
Dx NPatol	TDP	42	17	*
(%)	Huntington	3	5	
	Inflamatorias	10	0	
	Ataxias	0	5	
	Otros	10	3	

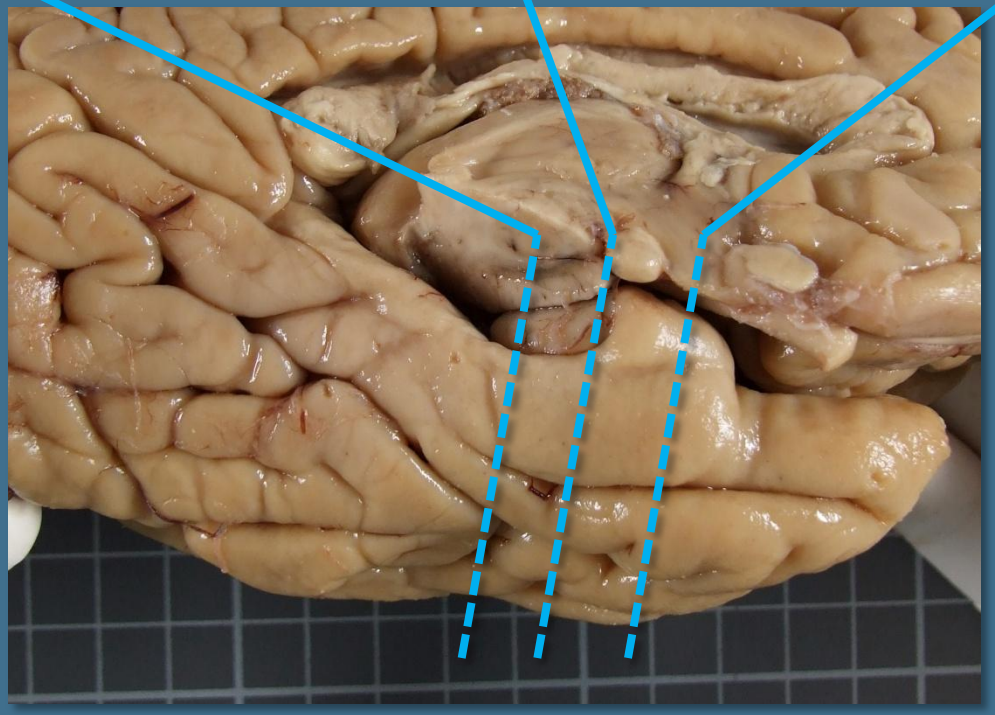
Nivel 3
Hipocampo, cuerpo

Nivel 2
Hipocampo anterior

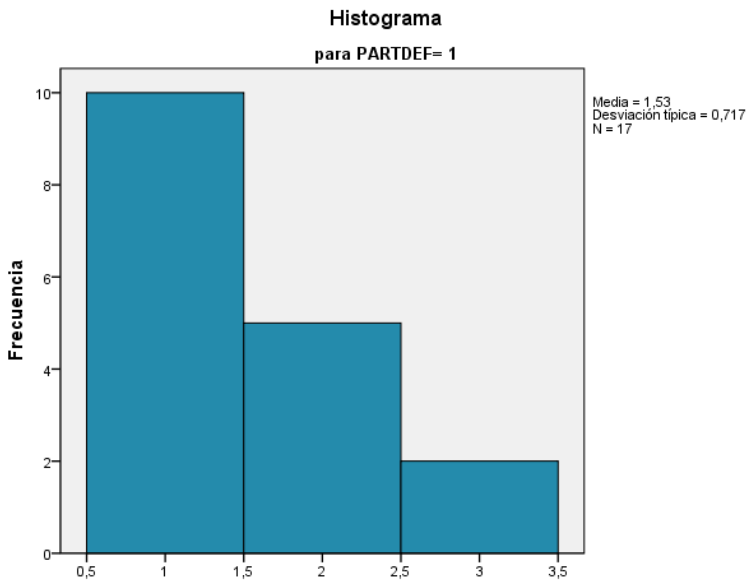


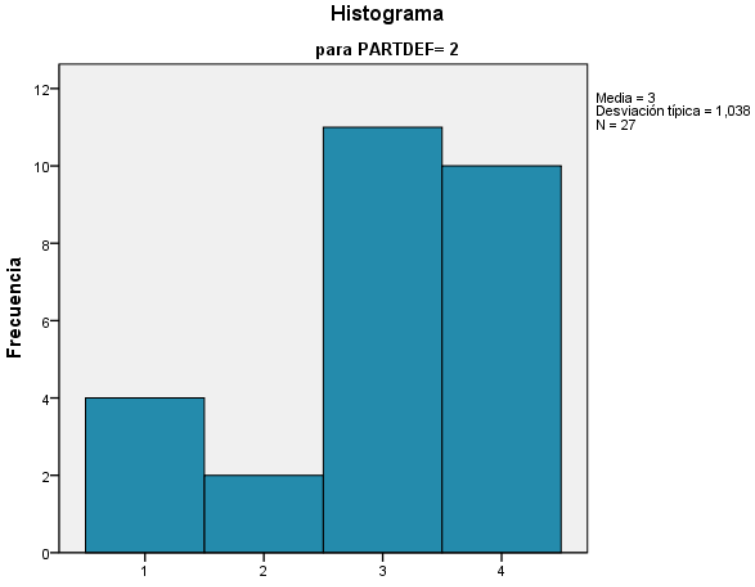
Nivel 1
Amígdala + cx entorrinal





	PART definitivo	PART (-)	P < 0,05
N	17	27	
Edad	73,88 (±7,2)	80,25 (± 8,1)	
Estadio Braak (1-4)	1,53 (± 0,72)	3 (± 1,01)	*
Braak atípico (%)	11,8	33,3	

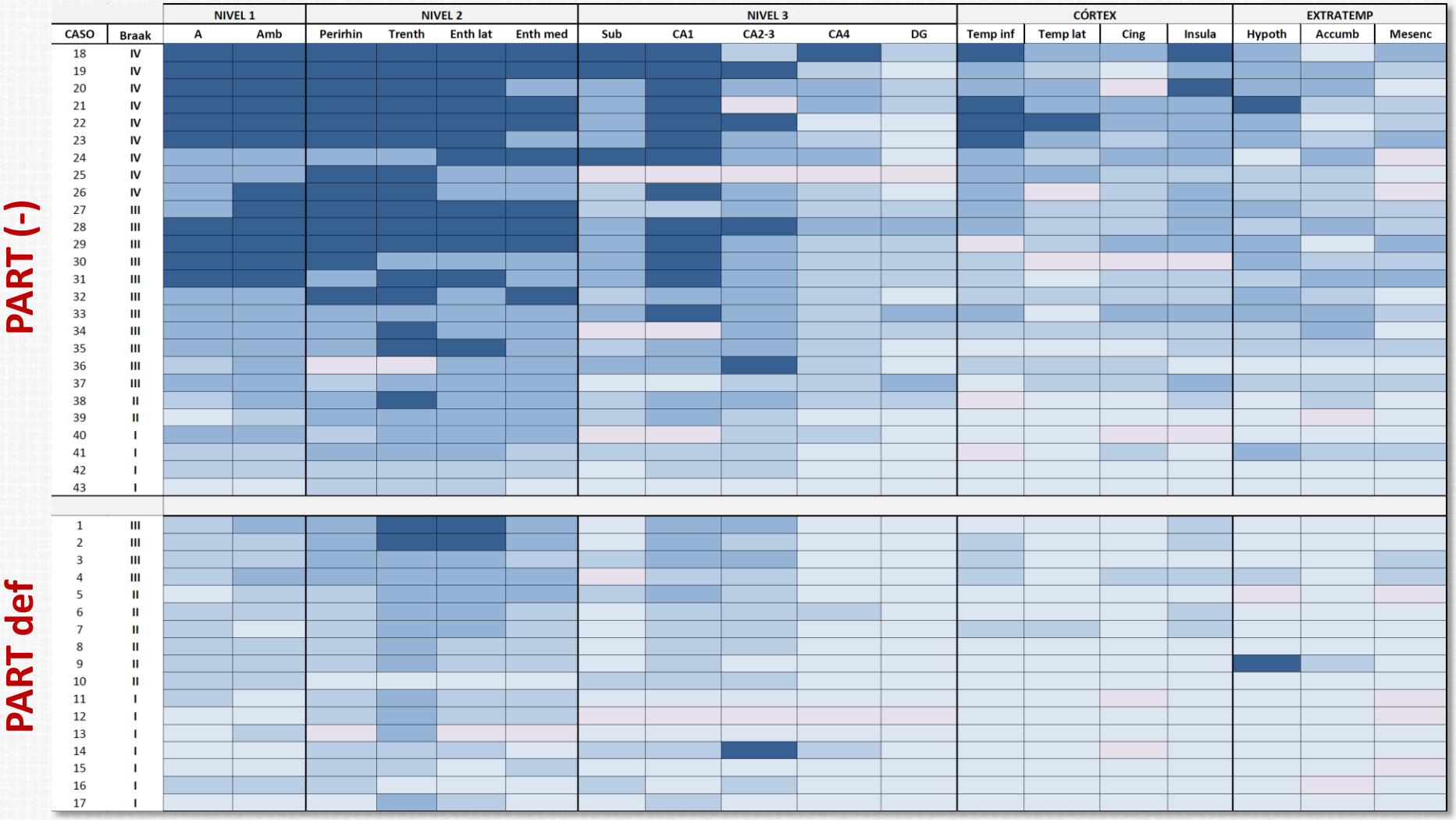




I II III

I II III IV

Estadio de Braak


PART (-)
PART def
NIVEL 1
NIVEL 2
NIVEL 3
CÓRTEX
EXTRATEMP
CASO
Braak
A
Amb
Perirhin
Trenth
Enth lat
Enth med
Sub
CA1
CA2-3
CA4
DG
Temp inf
Temp lat
Cing
Insula
Hypoth
Accumb
Mesenc
18 IV
19 IV
20 IV
21 IV
22 IV
23 IV
24 IV
25 IV
26 IV
27 III
28 III
29 III
30 III
31 III
32 III
33 III
34 III
35 III
36 III
37 III
38 II
39 II
40 I
41 I
42 I
43 I
1 III
2 III
3 III
4 III
5 II
6 II
7 II
8 II
9 II
10 II
11 I
12 I
13 I
14 I
15 I
16 I
17 I

Conclusiones

- En nuestra serie, el grupo PART def (+) presenta una edad al exitus significativamente inferior a PART (-).
- Los casos PART def (+) no muestran un perfil de afectación regional distintivo, y forman un continuo con los casos PART (-) (p. ej., no incluyen casos con Braak IV).
- Ambos grupos difieren significativamente en cuanto a la proporción de casos con diagnóstico NP principal de patología TDP (¿explicable por la Δ edad?).
- Los hallazgos observados en nuestra serie (con elevada edad al exitus global y alta frecuencia de demencia degenerativa), no muestran evidencia de PART.

Placas y ovillos, diagnóstico NP de la E. de Alzheimer.

Metodología y estadiaje de Braak.

Patología típica con distribución atípica.

Otras patologías (tau+) con distribución típica.

Placas sin ovillos.

Ovillos sin placas.

- **Neuropatología del deterioro cognitivo leve.**

Reserva cognitiva y compensación.

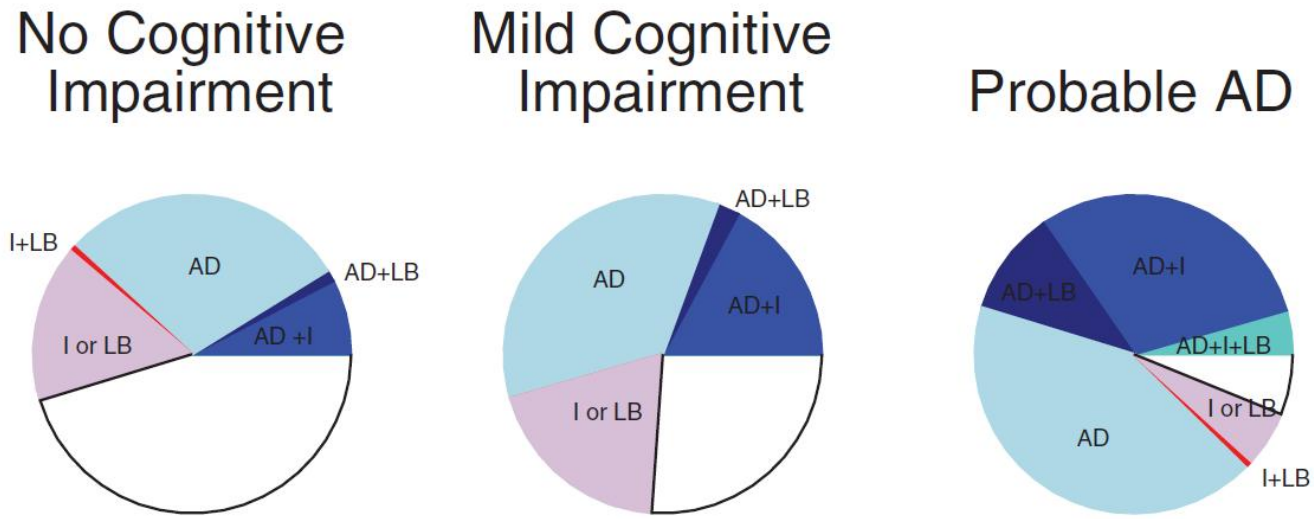


*Fig. Pathology by clinical status proximate to death. (*Blue shades*) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral infarcts (I); aqua = pathologic diagnosis of AD, I, and LB. (*Red shades*) I and/or LB (with no pathologic diagnosis of AD). Clockwise: pink = I or LB; red = I and LB. (*White*) No pathologic diagnosis of AD, no I, no LB.*

Schneider et al., 2009

The neuropathology of older persons with and without dementia from community versus clinic cohorts.

Julie A. Schneider, Neelum T. Aggarwal, Lisa Barnes, Patricia Boyle and David A. Bennett. Journal of Alzheimer's Disease, 2009.

No cognitive impairment

Table 2: Demographics [mean (SD)] and distribution [number (%)] of pathology in persons with no cognitive impairment in community compared to clinic cohorts.

	Community Cohorts	Clinical Cohort
Number	188	14
Age at death	83.8 (SD=6.4)	81.6 (SD=10.7)
Education	17.0 (SD=3.9)	14.7 (SD=3.0)
MMSE	28.3 (SD=1.6)	27.8 (SD=1.6)
Pathologic diagnosis of AD (NIA-Reagan)	73 (38.8%)	8 (57.1%)
High	2 (1.1%)	1 (7.1%)
Intermediate	71 (37.8%)	7 (50.0%)
Infarct (any)	73 (38.8%)	5 (35.7%)
Macroscopic	41 (21.8%)	1 (7.1%)
Microscopic	41 (21.8%)	5 (35.7%)
Lewy bodies (any)	23 (12.2%)	1 (7.1%)
Neocortical	5 (2.7%)	1 (7.1%)
One pathology (AD, infarcts, or Lewy bodies)	87 (46.3%)	6 (42.9%)
Mixed pathology	16 (8.5%)	2 (14.3%)
FTLD or other atypical pathology	0	0

Mild cognitive impairment

Table 3. Demographics [mean (SD)] and distribution [number (%)] with mild cognitive impairment in community compared to clinic cohorts.

	Community Cohorts	Clinical Cohort
Number	141	9
Age at death	87.0 (SD=6.5)	78.9 (SD=10.7)
Education	16.7 (SD=3.8)	16.1 (SD=2.8)
MMSE	26.0 (SD=3.8)	26.8 (SD=1.2)
Pathologic diagnosis of AD (NIA-Reagan)	75 (53.2%)	4 (44.4%)
High	11 (7.8%)	0
Intermediate	64 (45.4%)	4 (44.4%)
Any infarct	60 (42.6%)	2 (22.2%)
Macroscopic	41 (29.1%)	0
Microscopic	32 (22.7%)	2 (22.2%)
Lewy bodies (any)	18 (12.8%)	2 (22.2%)
Neocortical	8 (5.7%)	1 (11.1%)
One pathology (AD, infarcts, or Lewy bodies)	75 (53.2%)	3 (33.3%)
Mixed pathology	27 (19.1%)	1 (11.1%)
FTLD or other atypical pathology	0	2 (22.2%)

BALTIMORE LONGITUDINAL STUDY OF AGING (BLSA)

Table 2. Distribution of Consortium to Establish a Registry for Alzheimer's Disease and Braak Raw Scores per Group

Group	N	Cognitive Decline (+/−)	Neuropathology (+/−)	CERAD[a]	*M* (SD)	Braak[b]	*M* (SD)
Normal	27	−	−	0 or 1	0.26 (0.45)	≤2	1.63 (0.56)
Asymptomatic-AD	21	−	+	2 or 3	2.14 (0.36)	≥2	3.48 (1.17)
MCI/AD	33	+	+	2 or 3	2.64 (0.49)	≥2	4.48 (1.03)
MCI	7				2.43 (0.53)		4.00 (1.00)
AD	26				2.69 (0.47)		4.62 (1.02)

[a]Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores: 0 = none; 1 = rare (A); 2 = moderate (B); 3 = frequent (C).
[b]Braak scores: 0 to 6.

SD = standard deviation; AD = Alzheimer's disease; MCI = mild cognitive impairment; M = mean.

Driscoll I, Resnick SM, Troncoso JC, An Y, O'Brien R, Zonderman AB. Impact of Alzheimer's pathology on cognitive trajectories in nondemented elderly. Ann. Neurol 2006; 60: 688 – 95.

Dugger et al. BMC Neurology (2015) 15:146
DOI 10.1186/s12883-015-0403-4

BMC Neurology

RESEARCH ARTICLE Open Access

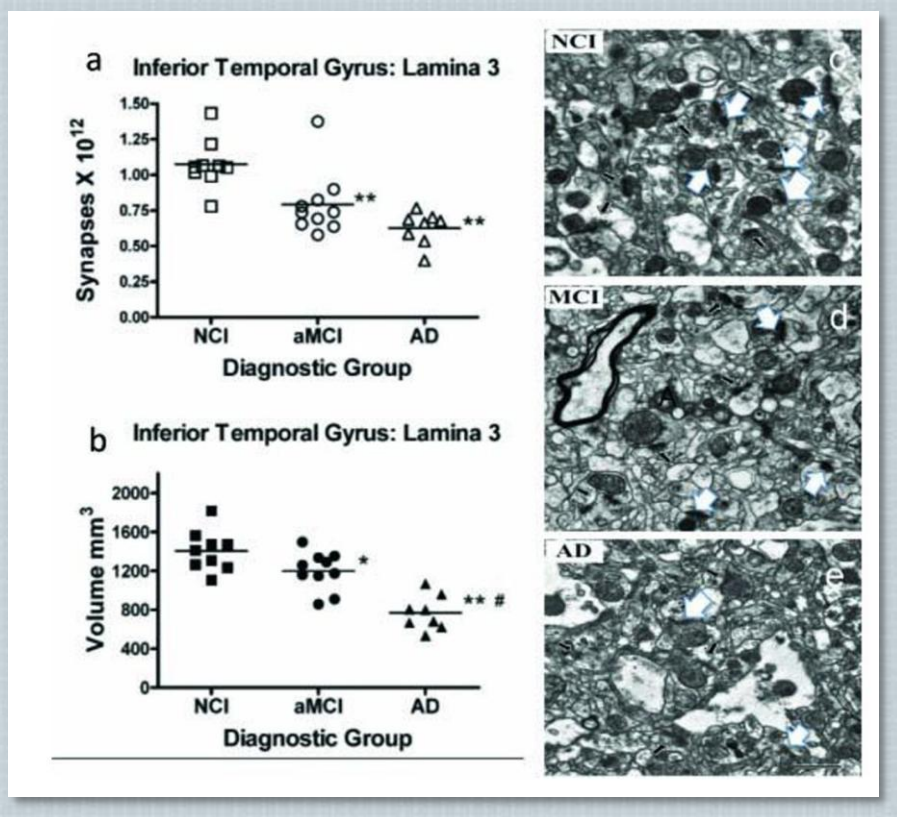
Neuropathological comparisons of amnestic and nonamnestic mild cognitive impairment

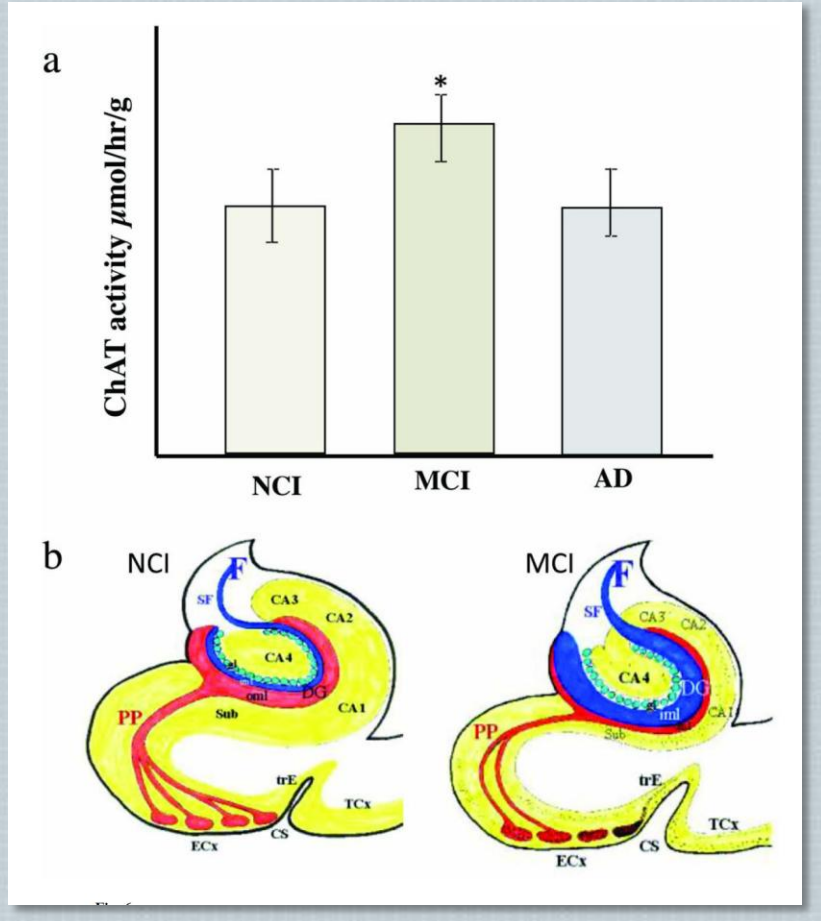
Brittany N. Dugger[1*], Kathryn Davis[2], Michael Malek-Ahmadi[2], Joseph G. Hentz[3], Shawn Sandhu[2], Thomas G. Beach[1], Charles H. Adler[3], Richard J. Caselli[3], Travis A. Johnson[3], Geidy E. Serrano[1], Holly A. Shill[2], Christine Belden[2], Erika Driver-Dunckley[3], John N. Caviness[3], Lucia I. Sue[1], Sandra Jacobson[2], Jessica Powell[2] and Marwan N. Sabbagh[2]

Table 2 Frequencies of pathologies within aMCI ($N = 34$) and naMCI ($N = 15$) cases. All pathology groups are not mutually exclusive; there is considerable overlap with concomitant pathologies

	aMCI	naMCI	*p* value
Clinicopathologic diagnoses			
PD	8 (24 %)[a]	7 (47 %)	0.18
PSP	3 (9 %)[a]	3 (20 %)	0.35
MND	0	1 (7 %)	0.31
MSA	1 (3 %)	0	1.00
Other pathologies			
Met neuropath criteria for AD	18 (53 %)	8 (53 %)	1.00
Braak NFT stage			0.22
I	2 (6 %)	0	
II	2 (6 %)	2 (13 %)	
III	3 (9 %)	5 (33 %)	
IV	23 (68 %)	8 (53 %)	
V	3 (9 %)	0	
VI	1 (3 %)	0	
CERAD NP score			0.90
None	12 (35 %)	6 (40 %)	
Sparse	2 (6 %)	1 (7 %)	
Moderate	8 (24 %)	2 (13 %)	
Frequent	12 (35 %)	6 (40 %)	
Incidental LBs	5 (15 %)	0	0.31
Unified LB staging scheme			0.18
Stage 0. no LBs	21 (62 %)	8 (53 %)	
Stage 1. OBT only	2 (6 %)	0	
Stage IIa. Brainstem	3 (9 %)	1 (7 %)	
Stage IIb. Limbic	3 (9 %)	0	
Stage III. Limbic + Brainstem	3 (9 %)	3 (20 %)	
Stage IV. Neocortical	2 (6 %)	3 (20 %)	

[a]One aMCI case had both PSP and PD; there were no other overlapping clinicopathological diagnoses





Mufson et al., 2012

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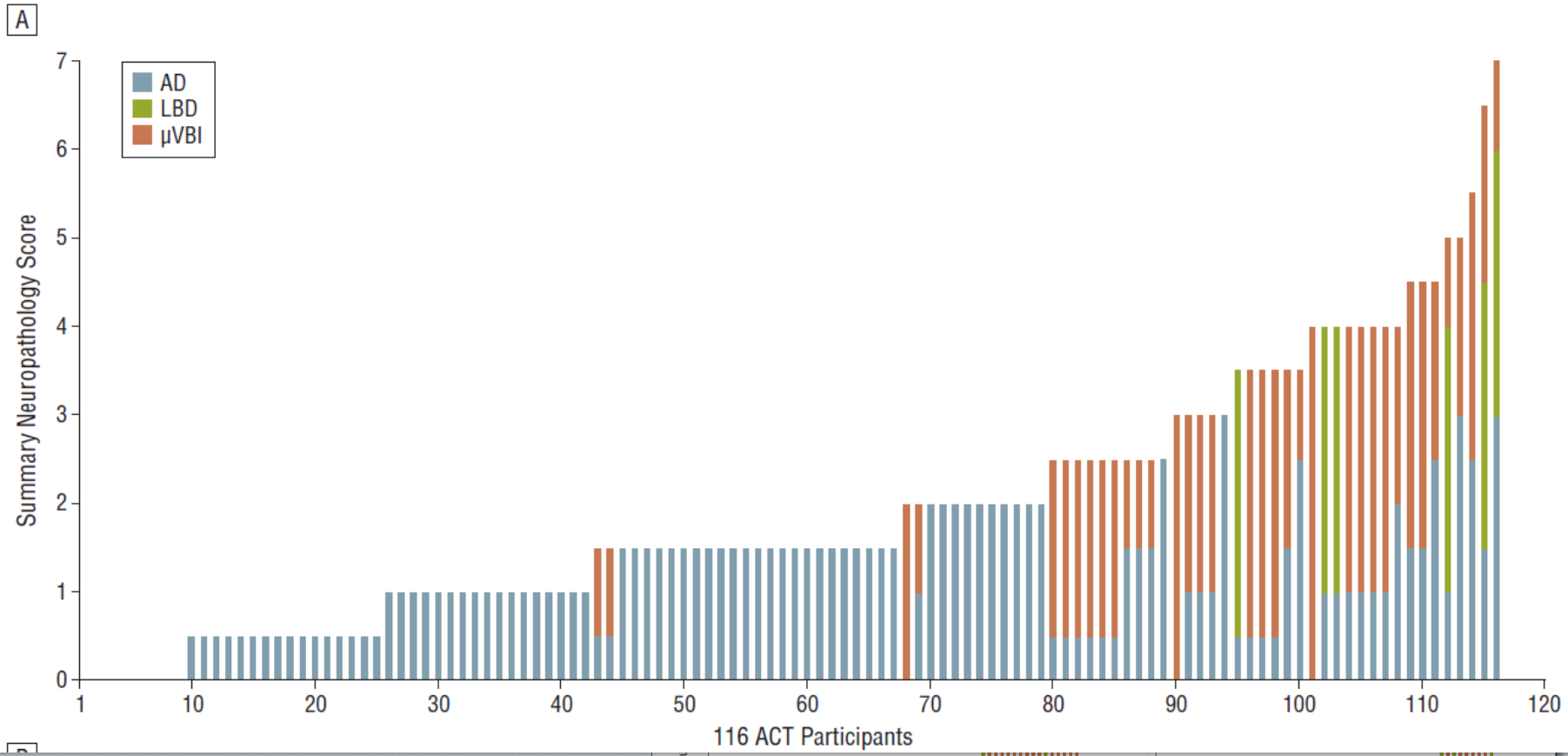
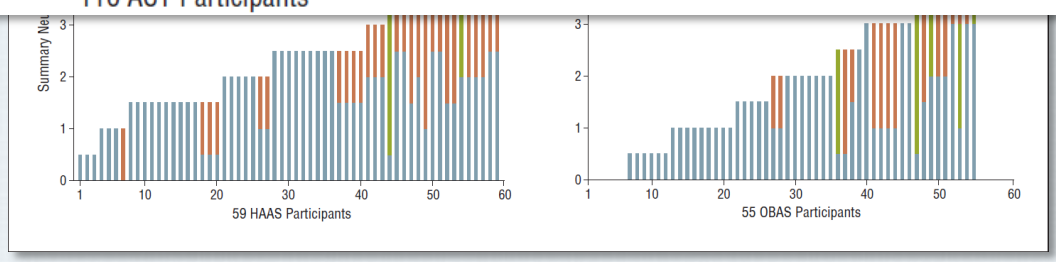
Azul: patología de Alzheimer
Verde: patología de Lewy
Rojo: patología vascular





Arch Neurol. 2011;68(8):1049-1056

Progress in Neurobiology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neurobiology

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

The neurobiology of brain and cognitive reserve: Mental and physical activity as modulators of brain disorders

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[c] Department of Anatomy and Cell Biology, University of Melbourne, Victoria, Australia

RESERVA COGNITIVA

"…cambios que se producen en el cerebro, como respuesta a experiencias crónicas de la vida, que modulan de forma positiva la susceptibilidad a trastornos cerebrales y a la disfunción dependiente de la edad, a través de mecanismos neuroprotectores y/o compensatorios."

Neuropsychologia 47 (2009) 2015–2028

Contents lists available at ScienceDirect

Neuropsychologia

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

Reviews and perspectives

Cognitive reserve☆

Yaakov Stern[a,b,c,*]

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[b] Department of Neurology, Columbia Universit
[c] Department of Psychiatry, Columbia Universit

Brain reserve: Individual differences in the brain itself allow some people to cope better than others with brain pathology. These differences can be quantitative, such as larger brain, more neurons, or synapses. In addition, life experience can influence brain anatomy via neurogenesis, angiogenesis, promoting resistance to apoptosis, and up-regulating compounds that promote neural plasticity.

Cognitive reserve: Individual differences in how people process tasks allow some to cope better than others with brain pathology.

Neural reserve: Inter-individual variability – perhaps in the form of differing efficiency, capacity, or flexibility – in the brain networks or cognitive paradigms that underlie task performance in the healthy brain. An individual whose networks are more efficient, have greater capacity, or are more flexible might be more capable of coping with the disruption imposed by brain pathology.

Neural compensation: Inter-individual variability in the ability to compensate for brain pathology's disruption of standard processing networks by using brain structures or networks not normally used by individuals with intact brains. This compensation may help maintain or improve performance.

JAMA. 1994 Apr 6;271(13):1004-10. Links

Influence of education and occupation on the incidence of Alzheimer's disease.

Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R.
Department of Neurology, Columbia University College of Physicians and Surgeons, Gertrude H. Sergievsky Center, New York, NY 10032.

OBJECTIVE--Several cross-sectional studies have found an association between Alzheimer's disease (AD) and limited educational experience. It has been difficult to establish whether educational experience is a risk factor for AD because educational attainment can influence performance on diagnostic tests. This study was designed to determine whether limited educational level and occupational attainment are risk factors for incident dementia. DESIGN--Cohort incidence study. SETTING--General community. PARTICIPANTS--A total of 593 nondemented individuals aged 60 years or older who were listed in a registry of individuals at risk for dementia in North Manhattan, NY, were identified and followed up. INTERVENTIONS--We reexamined subjects 1 to 4 years later with the identical standardized neurological and neuropsychological measures. MAIN OUTCOME MEASURES--Incident dementia. RESULTS--We used Cox proportional hazards models, adjusting for age and gender, to estimate the relative risk (RR) of incident dementia associated with low educational and occupational attainment. Of the 593 subjects, 106 became demented; all but five of these met research criteria for AD. The risk of dementia was increased in subjects with either low education (RR, 2.02; 95% confidence interval [Cl], 1.33 to 3.06) or low lifetime occupational attainment (RR, 2.25; 95% Cl, 1.32 to 3.84). Risk was greatest for subjects with both low education and low life-time occupational attainment (RR,

The data suggest that increased educational and occupational attainment may reduce the risk of incident AD, either by decreasing ease of clinical detection of AD or by imparting a reserve that delays the onset of clinical manifestations.

N Engl J Med 2003;348:2508-16.

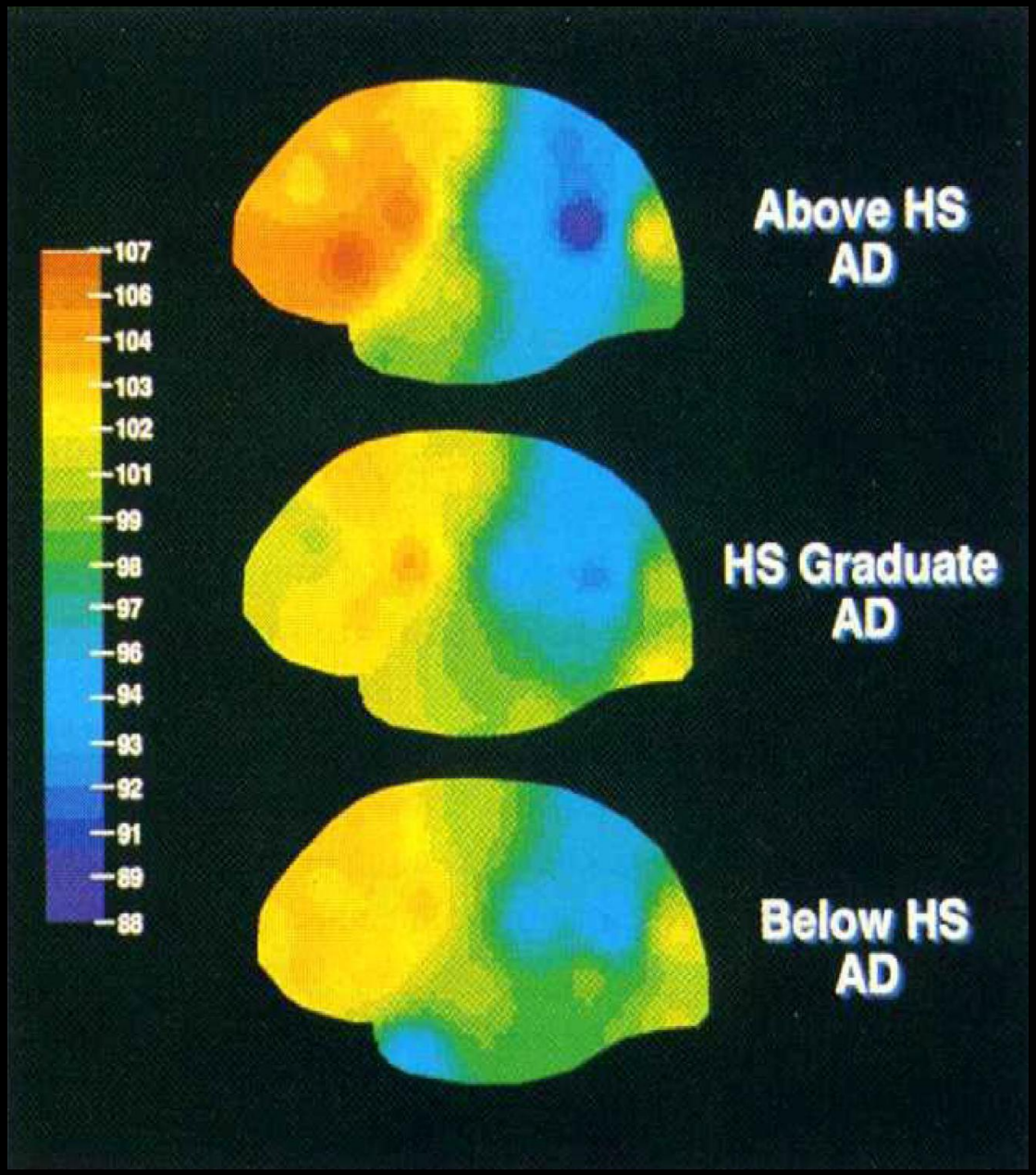
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Leisure Activities and the Risk of Dementia in the Elderly

Joe Verghese, M.D., Richard B. Lipton, M.D., Mindy J. Katz, M.P.H., Charles B. Hall, Ph.D., Carol A. Derby, Ph.D., Gail Kuslansky, Ph.D., Anne F. Ambrose, M.D., Martin Sliwinski, Ph.D., and Herman Buschke, M.D.

Enfermedad de Alzheimer, mismo nivel de deterioro cognitivo



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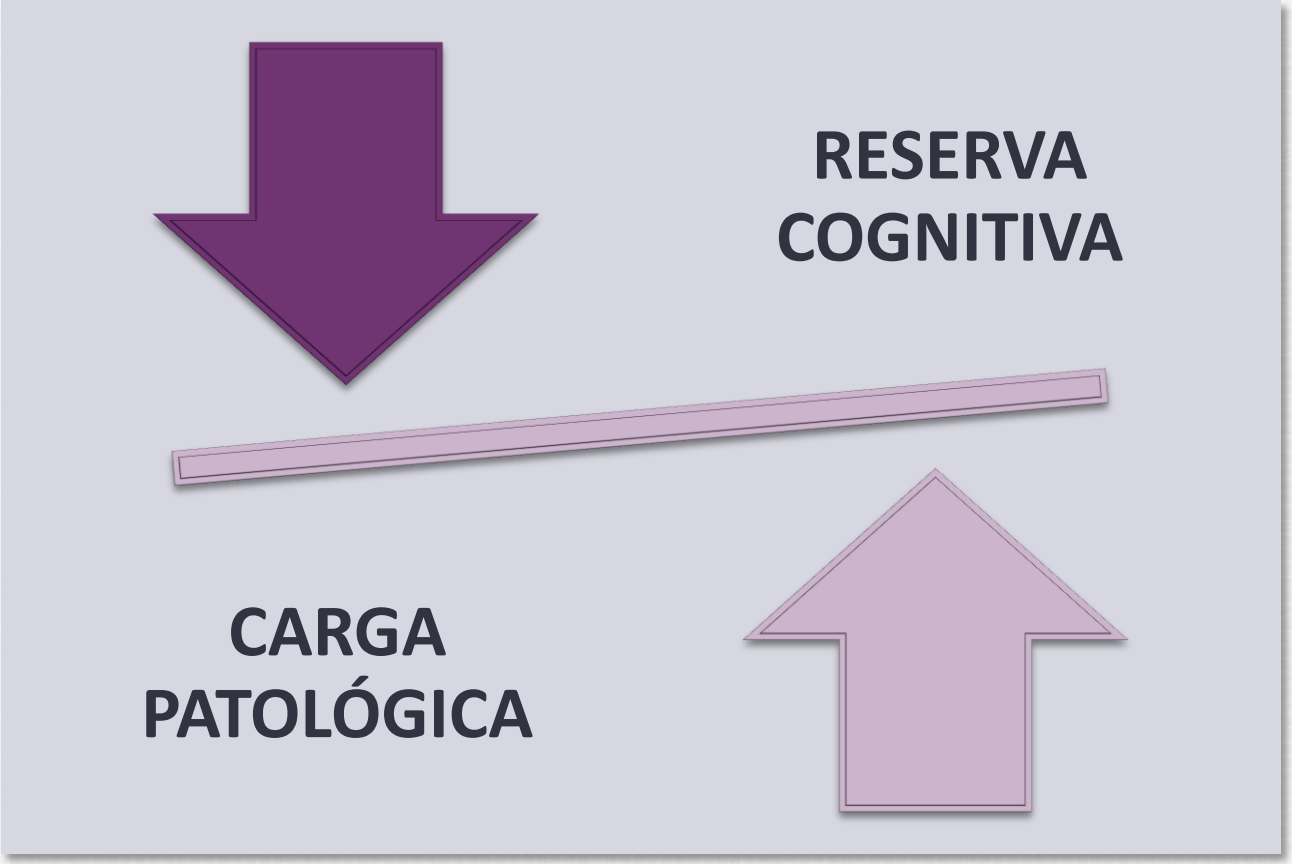
Stern, 2012


RESERVA
COGNITIVA
CARGA
PATOLÓGICA

Factores que aumentan la reserva cognitiva

- Nivel educativo (escolaridad, escolaridad de los padres)
- Ocupación laboral
- Actividad cognitiva (actividad lectora, juegos intelectuales)
- Formación musical (escuchar, tocar música)
- Idiomas (monolingüismo, multilingüismo)
- Actividades de ocio

The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study

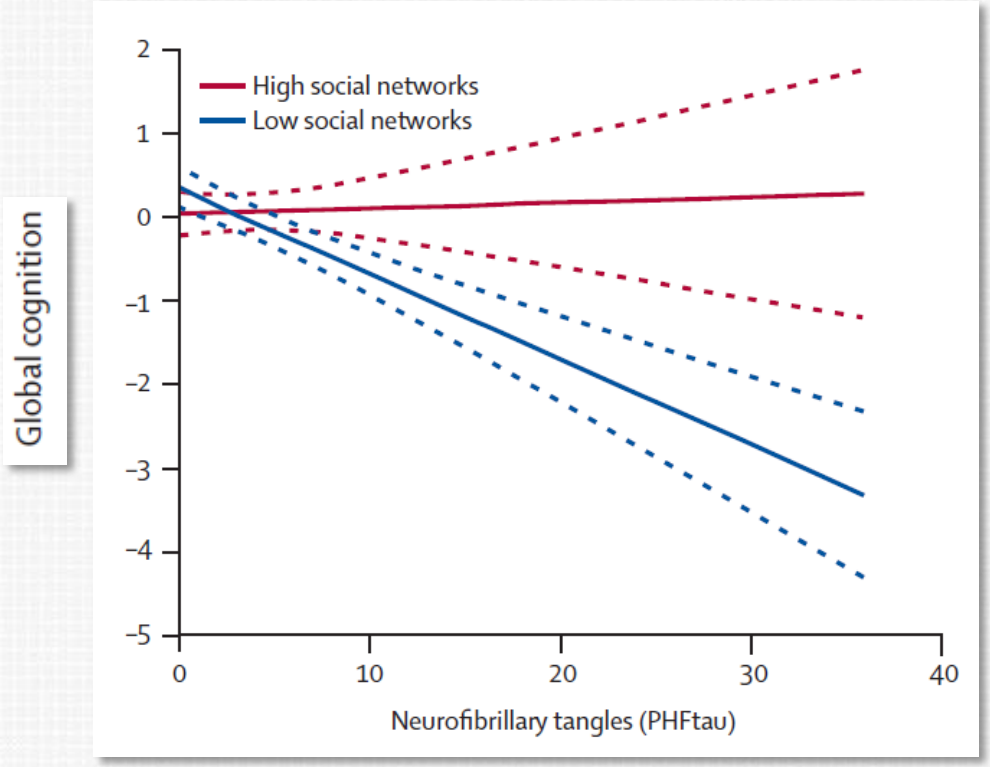
David A Bennett, Julie A Schneider, Yuxiao Tang, Steven E Arnold, Robert S Wilson

Lancet Neurol 2006; 5: 406–12

Summary

Lancet Neurol 2006; 5: 406–12

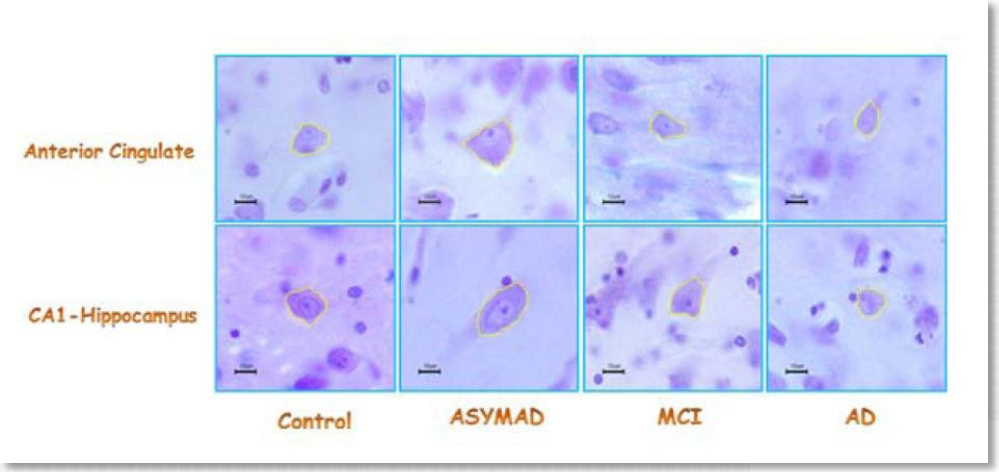
El efecto de las redes sociales sobre la relación entre la patología de la enfermedad de Alzheimer y el nivel de función cognitiva en personas de edad avanzada: un estudio longitudinal de cohortes.

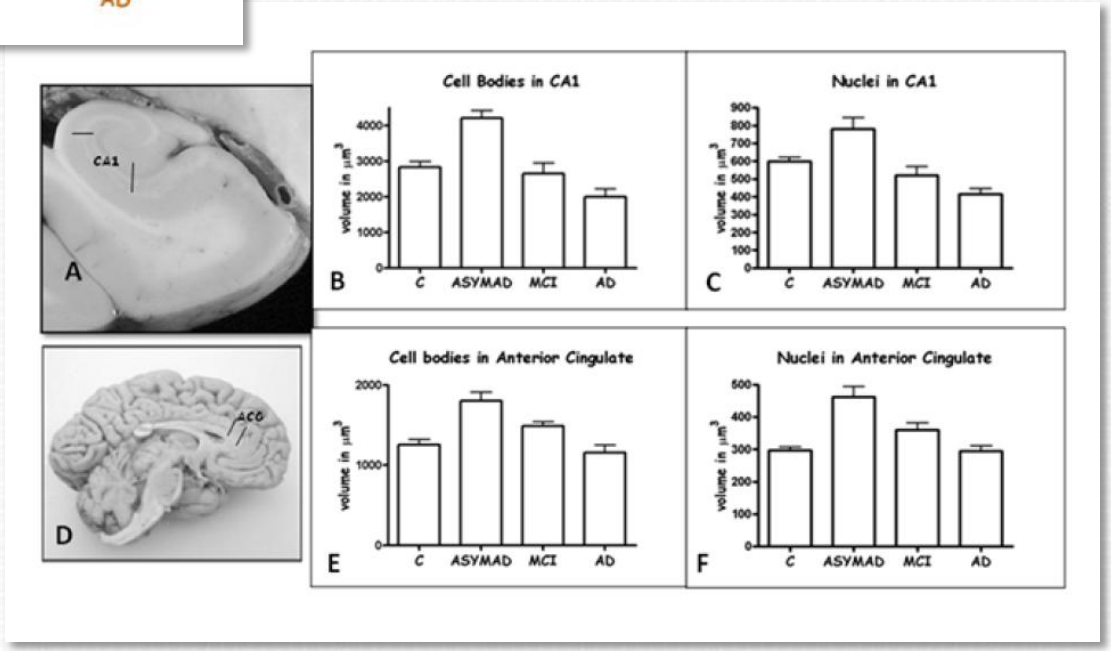


Neuropathologic studies of the Baltimore Longitudinal Study of Aging (BLSA).

Richard J. O'Brien, Susan M. Resnick, Alan B. Zonderman, Luigi Ferrucci, Barbara J. Crain, Olga Pletnikova, Gay Rudow, Diego Iacono, Miguel A. Riudavets, Ira Driscoll, Donald L. Price, Lee J. Martin and Juan C. Troncoso.

Journal of Alzheimer's Disease, 2009.





www.thelancet.com Published online July 16, 2013

A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II

Fiona E Matthews, Antony Arthur, Linda E Barnes, John Bond, Carol Jagger, Louise Robinson, Carol Brayne, on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration

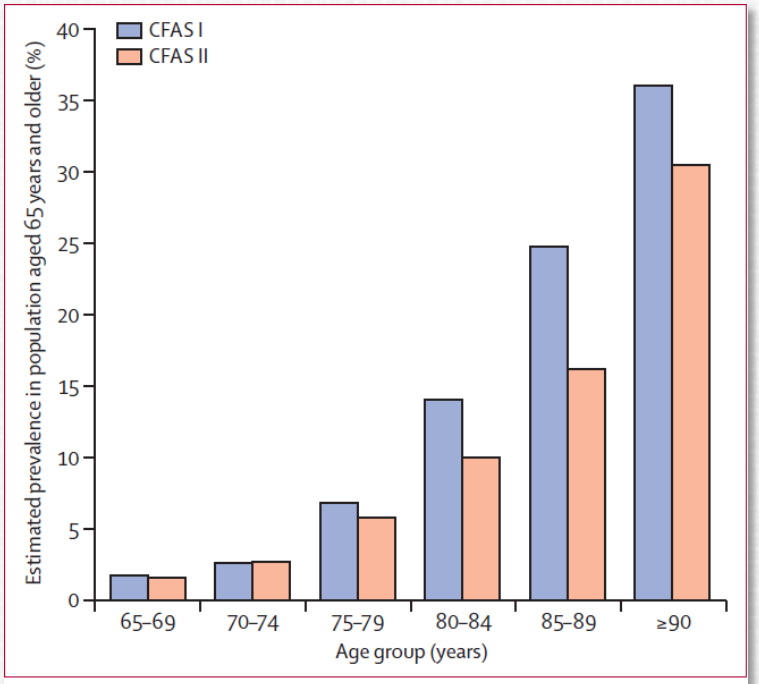


Figure 1: **CFAS I and CFAS II age-specific dementia prevalence**
CFAS=Cognitive Function and Ageing Study.

should be actively pursued.[2] Whether or not the gains that we have identified for the present older population will be borne out in later generations will probably depend on whether further improvements in primary prevention and effective health care for disorders that increase the risk of dementia can be achieved, including addressing inequalities.[35,36]

Heiko Braak, 1937 -


Alzheimer Soria
cien
Fundación Centro Investigación
Enfermedades Neurológicas

¡Gracias!