IC InterCol.legial DE PROFESSIONALS SENIOR DE CATALUNYA

Fundació ACE

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BARCELONA ALZHEIMER TREATMENT & RESEARCH CENTER

making Alzheimer history

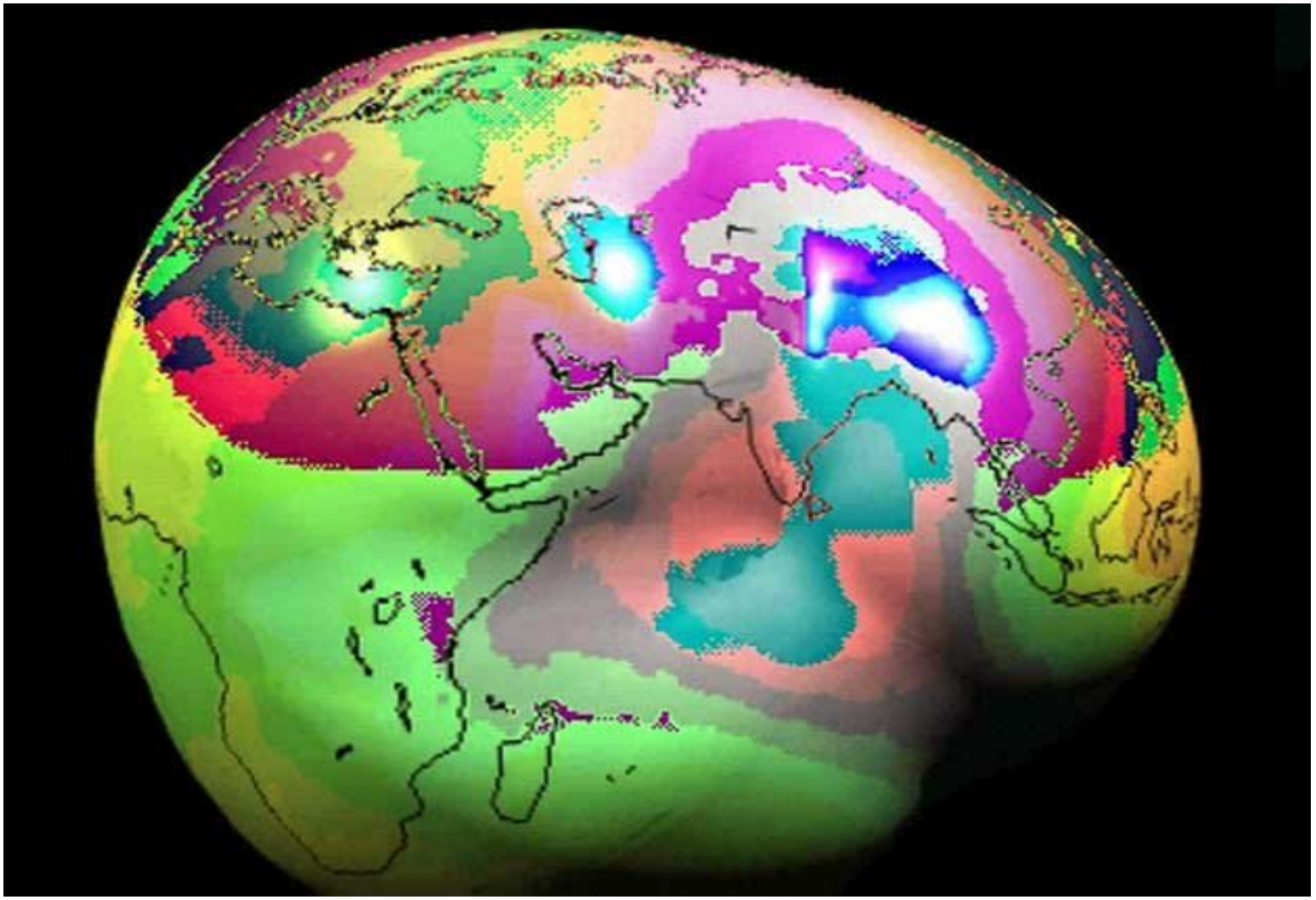
Neurologia a la tercera edat

Mercè Boada, MD, PhD

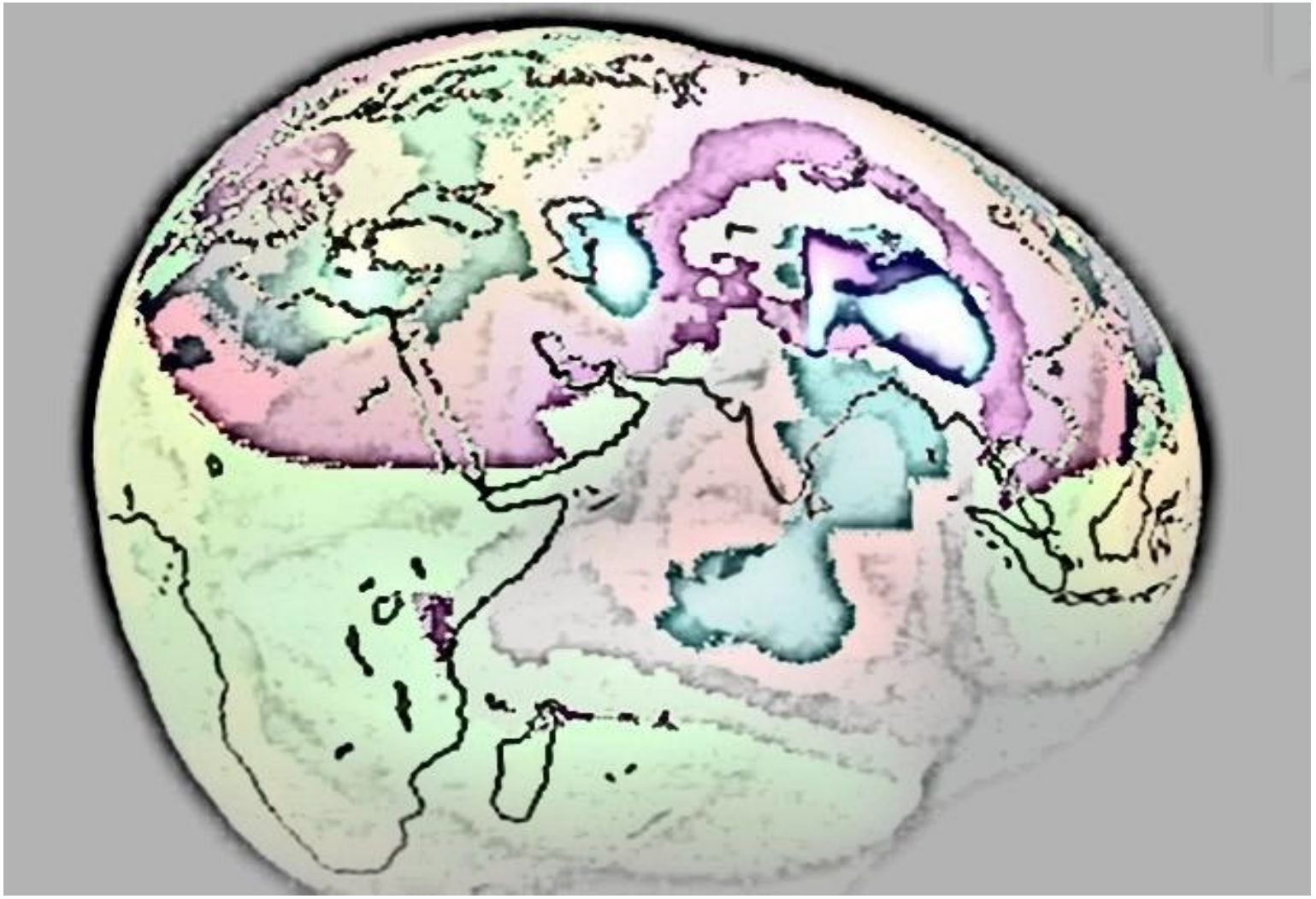
CMO. Fundació ACE. Barcelona Alzheimer Treatment & Research Center
Cap Clínic. Servei Neurologia. Área Malalties Neurodegeneratives .
HVH-IR-UAB

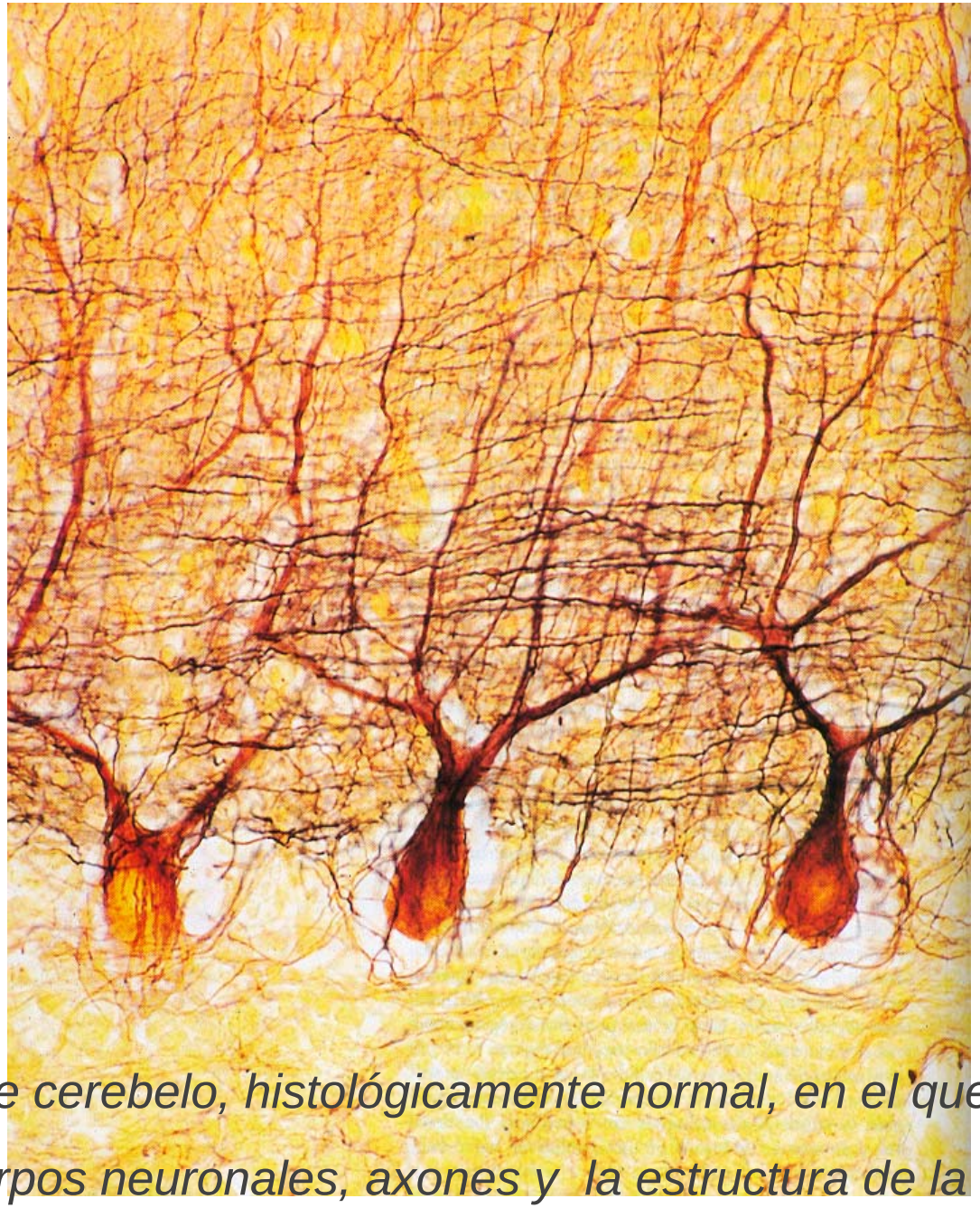
Barcelona, 28 novembre 2012

Com envelleix el nostre cervell?

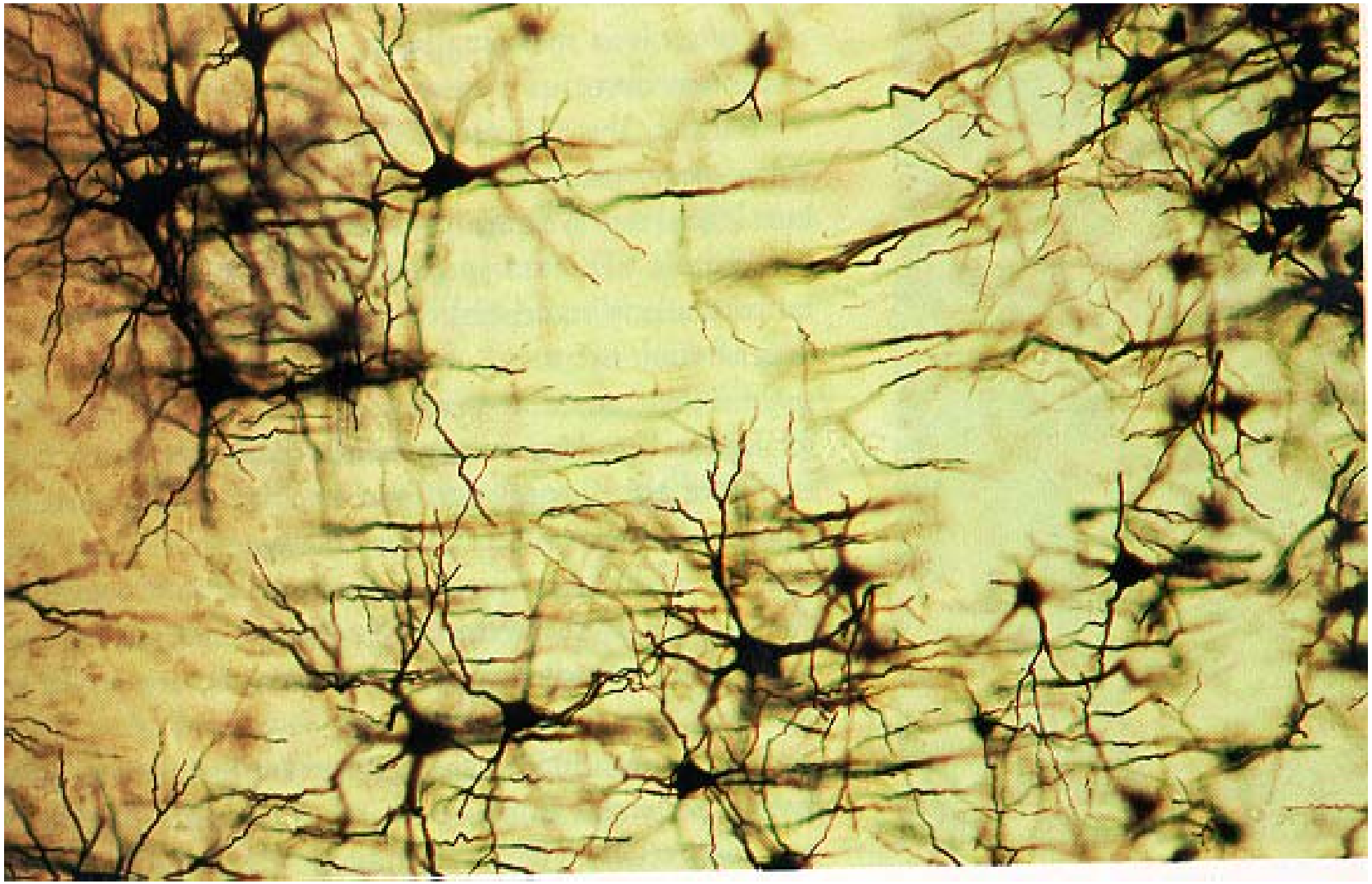


Perden llum, definició i precisió de funcions i deixant de comunicar-se



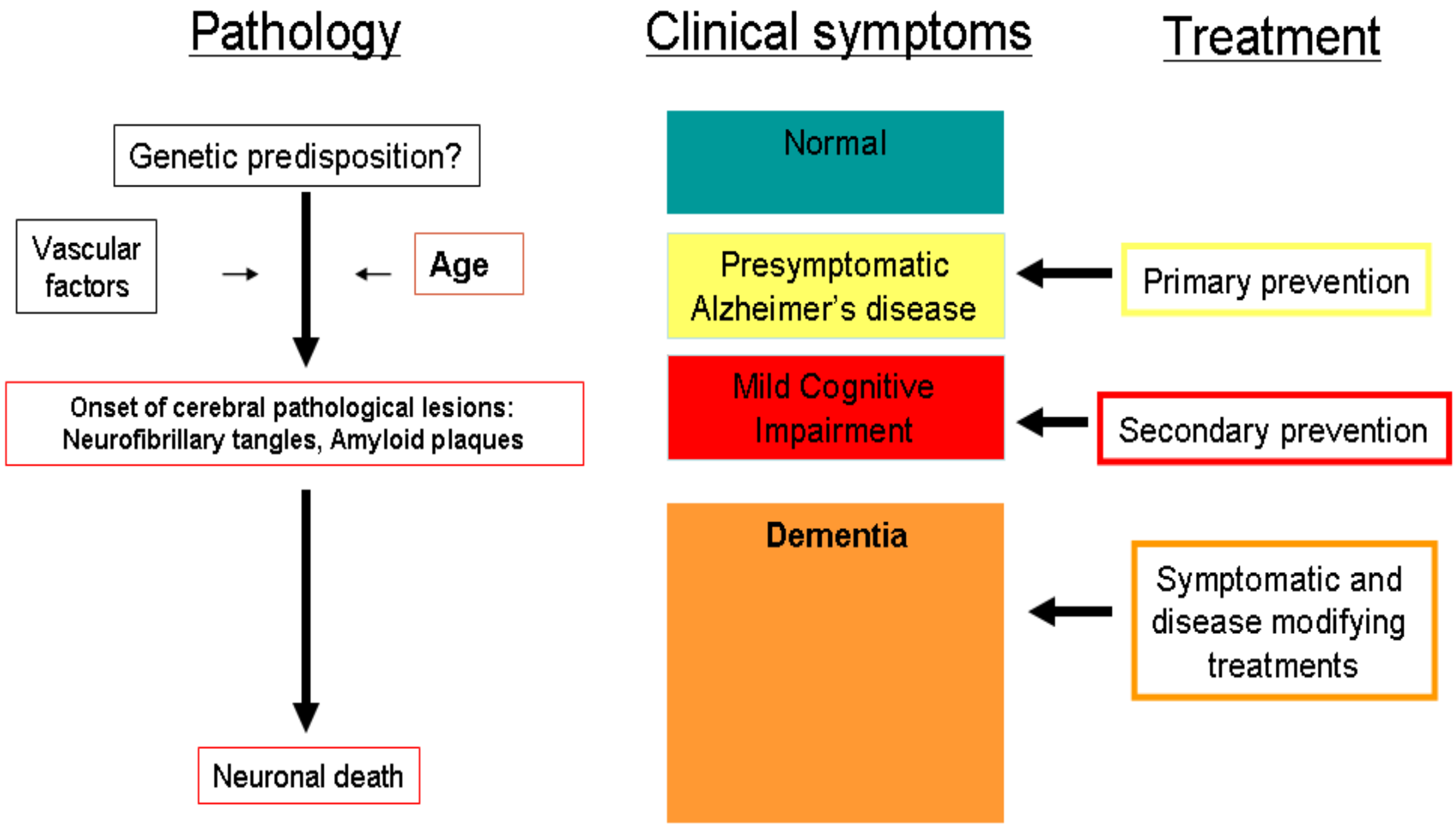


Corte de cerebelo, histológicamente normal, en el que se observan los cuerpos neuronales, axones y la estructura de la red neurítica.



Con la vejez y/o en la EA, se observa una marcada pérdida dendrítica y reducción de las conexiones interneuronales.

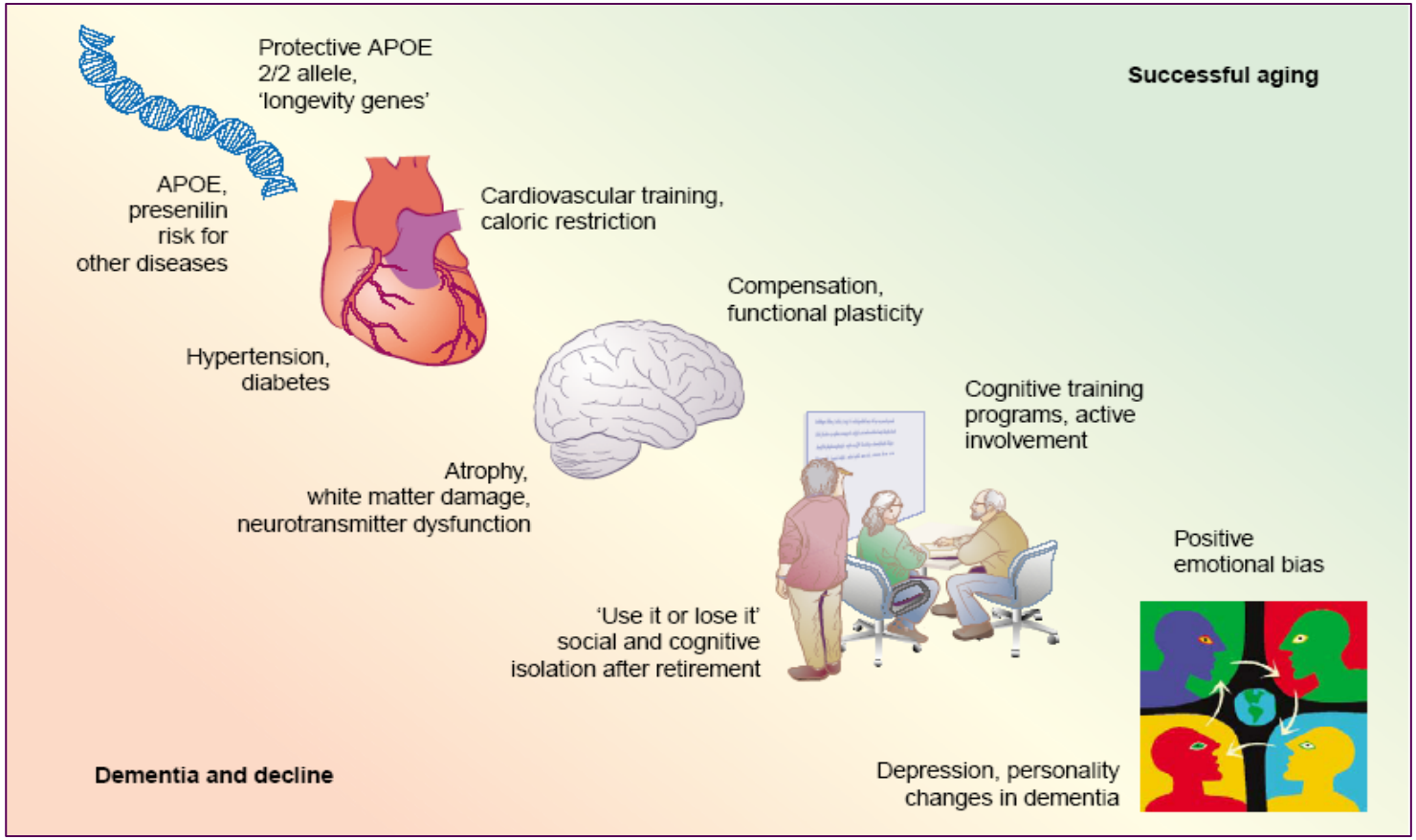
Relationship between primary and secondary prevention, clinical symptoms, and the pathological cascade



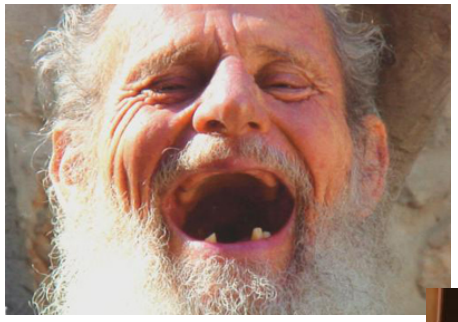
Variabilidad Interindividual

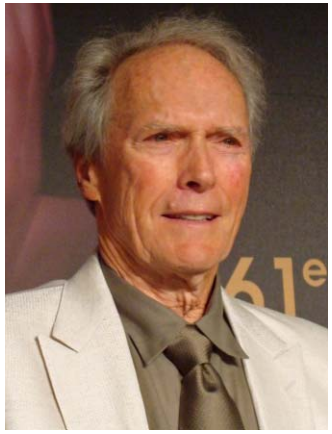
Predicting the rate of cognitive decline in aging and early Alzheimer disease

S. Adak, PhD; K. Illouz, MS; W. Gorman, MS; R. Tandon, MS; E.A. Zimmerman, MD; R. Guariglia, BSN; M.M. Moore, BS; and J.A. Kaye, MD

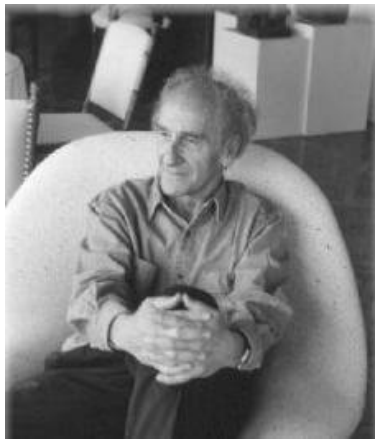


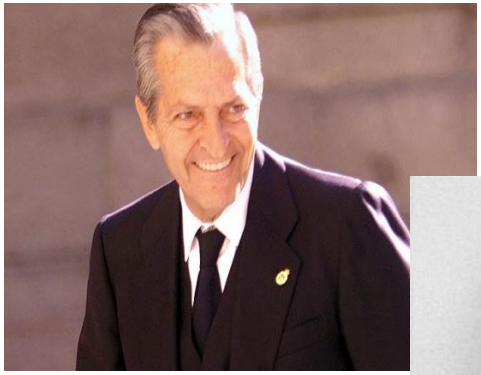
No hay dos personas iguales





No hay dos demencias iguales





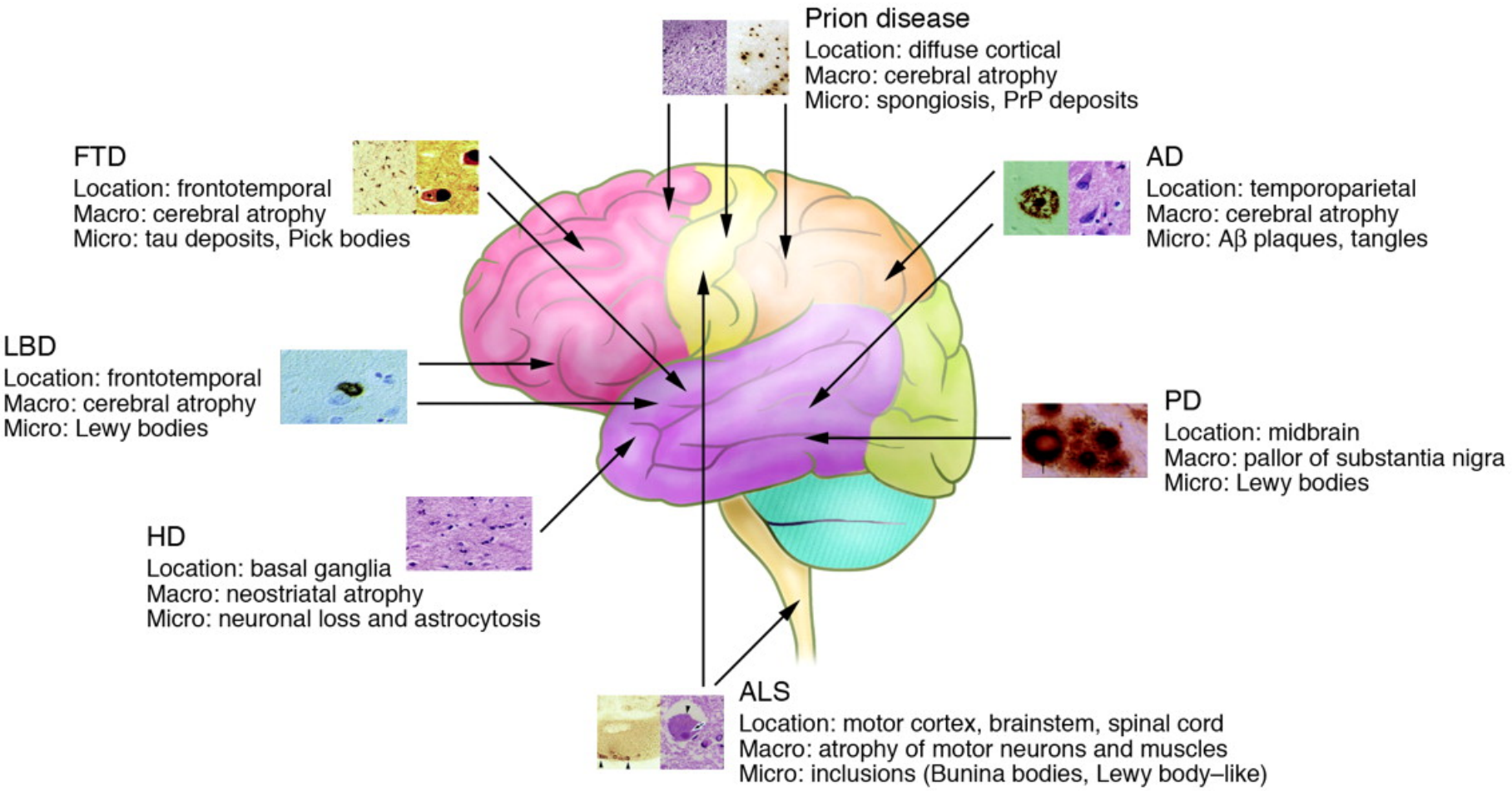
Enfermedades neurodegenerativas

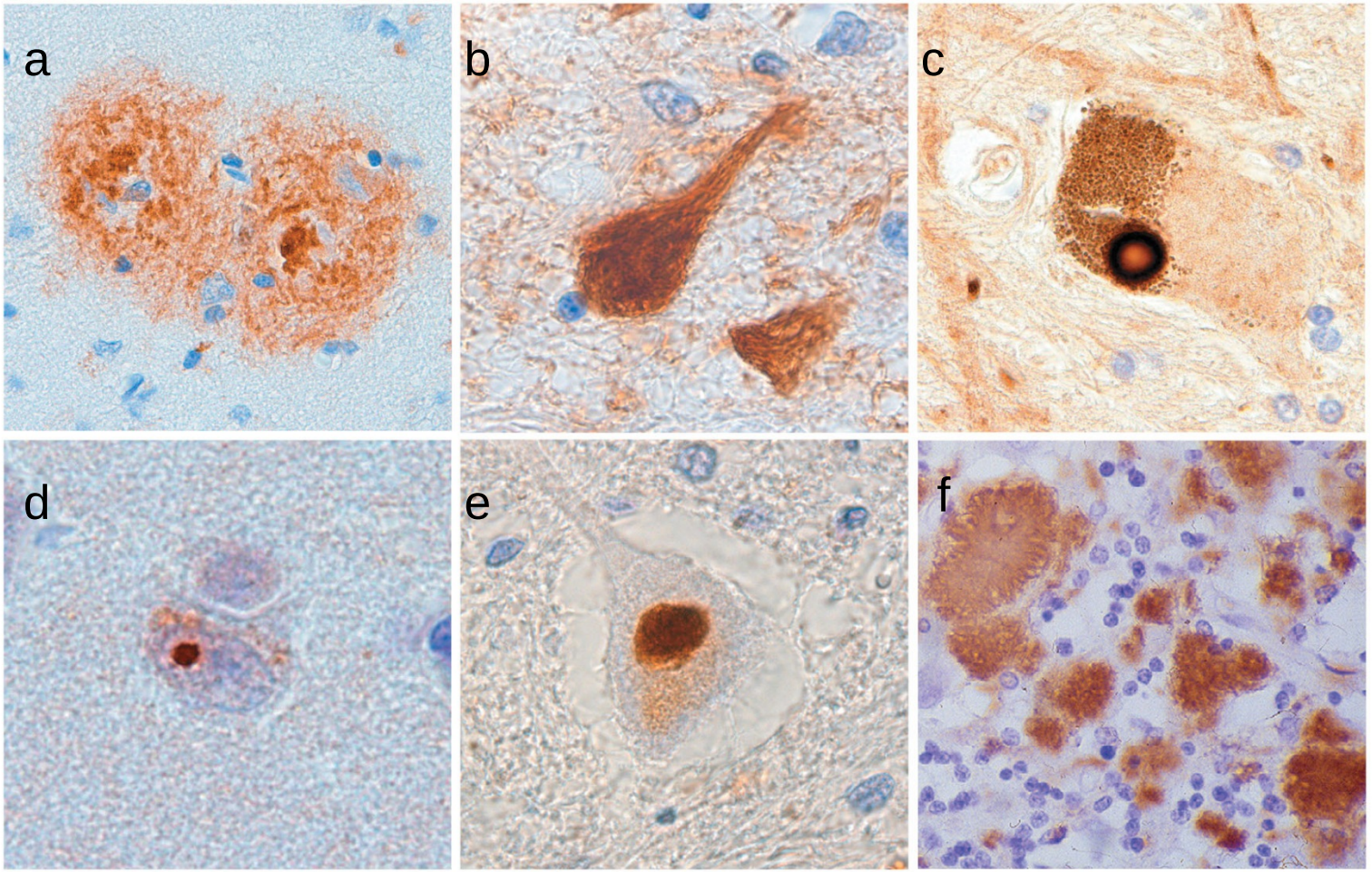
Enfermedad de Alzheimer	Enfermedad con cuerpos de LEWY Parkinson	Demencias Frontotemporales Enf. de PICK, otras

Pérdida de memoria – otros cambios cognitivos – conducta – aspectos motores

Memoria	Memoria	Carácter
Lenguaje	Lenguaje	Conducta
Orientación	Orientación	Psiquiátricos
Carácter	Carácter	
Apatía	Apatía	Lenguaje
Depresión	Depresión	
Etc.		Parkinsonismo
	Parkinsonismo	Movimientos
	Alucinaciones	anormales
	Fluctuaciones	

Enfermedades neurodegenerativas primarias de inicio tardío

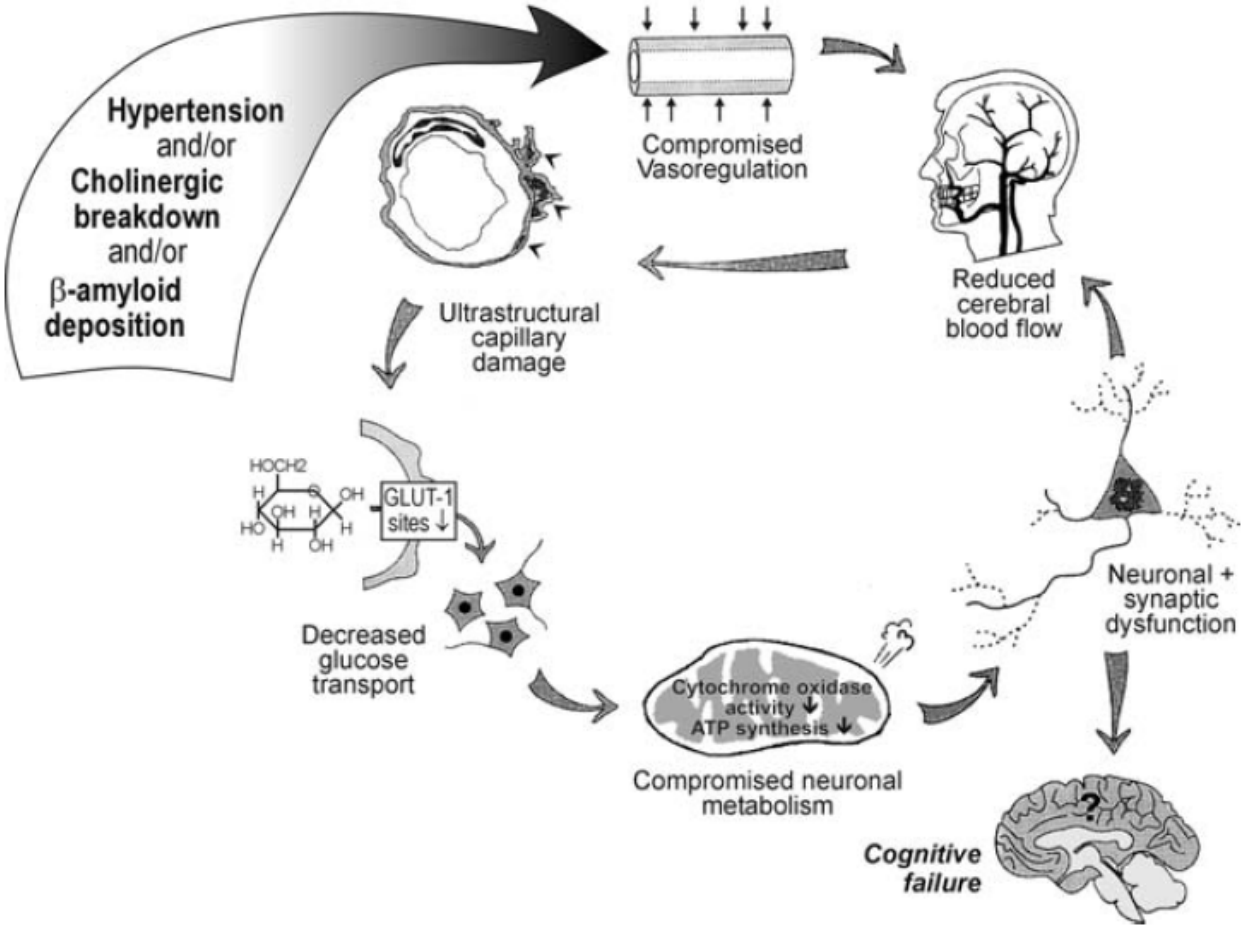




Protein aggregates in neurodegenerative disease. (**a**) Senile plaques in neocortex of Alzheimer disease. (**b**) NFTs in hippocampus of FTDP-17 (R406W mutation). (**c**) Lewy body in substantia nigra of Parkinson disease. (**d**) Intranuclear polyglutamine inclusion in neocortex of Huntington disease. (**e**) Ubiquitinylated inclusion in spinal cord motor neuron of ALS. (**f**) Protease-resistant PrP in cerebellum of CJD (panel **f** courtesy of Nigel Cairns).

Mark S Forman, John Q Trojanowski & Virginia M-Y Lee. ***Neurodegenerative diseases: a decade of discoveries paves the way for therapeutic breakthroughs.*** Nature Medicine. Vol. 10. Number 10. October 2004

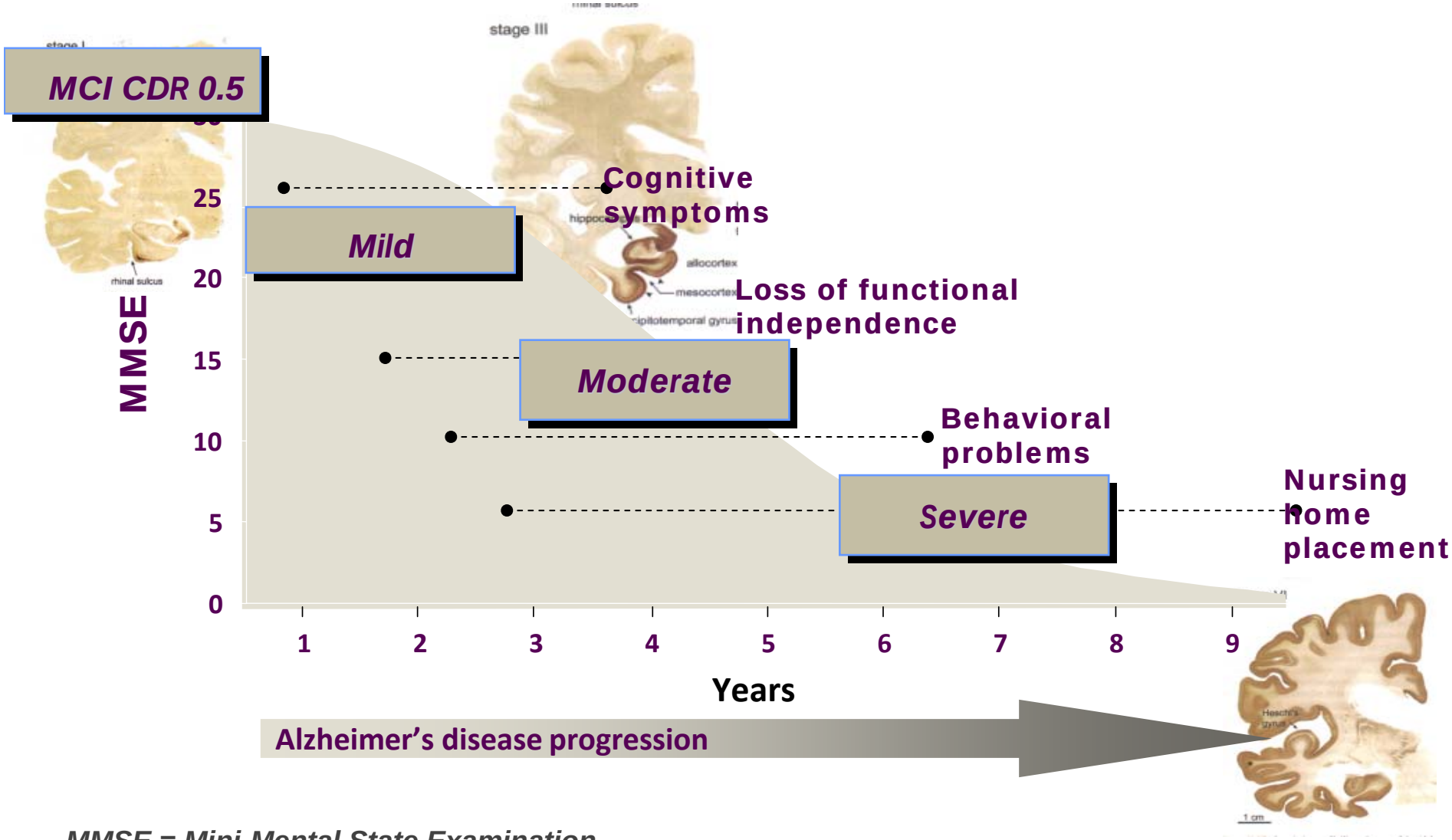
Scheme of cerebral microvascular pathology



Kurt. A. Jellinger. The enigma of vascular cognitive disorders and vascular dementia
Acta Neuropathol (2007) 113:349–388

Del olvido benigno a la pérdida del YO

Symptomatic Course and Progression of AD



MMSE = Mini-Mental State Examination.

Feldman and Grundman. In: Gauthier, ed. Clinical Diagnosis and Management of Alzheimer's Disease. London: Martin Dunitz; 1999:249-268.

ATENCIÓ ESPECIALITZADA:FUNDACIÓ ACE. ACTIVITAT 2011

TOTAL PACIENTS VISITATS en el 2011 segons diagnòstic i gravetat (CDR)

	CDR 0	CDR 0,5	CDR 1: lleu	CDR 2: Moderat	CDR 3: greu	Total	
DETERIORAMENT COGNITIU AMB DEMÈNCIA							
Malaltia d'Alzheimer	**0**	**35**	**671**	**1044**	**505**	**2255**	
Alzheimer probable	0	5	409	761	434	**1609**	
Alzheimer possible	0	28	262	283	71	**644**	
Síndrome Down con Alzheimer	0	2	0	0	0	**2**	
Cosos de Lewy i Parkinson	**0**	**1**	**81**	**89**	**48**	**219**	
Cossos Lewy probable	0	0	11	35	12	**58**	
Cossos Lewy possible	0	0	51	45	31	**127**	
Demència Parkinson	0	1	19	9	5	**34**	
Degeneracio Lobular Fronto-temporal	**0**	**15**	**118**	**79**	**38**	**250**	
DFT variable conducta	0	7	75	43	25	**150**	
APNF (afàsia progressiva no fluent)	0	5	13	10	6	**34**	
D. Semàntica	0	1	18	15	6	**40**	
PSP (paràlisis supranuclear progressiva)	0	2	6	7	0	**15**	
DCB (degenericó còrtico-basal)	0	0	6	4	1	**11**	
Malaltia Vascular Cerebral	**0**	**18**	**301**	**132**	**50**	**501**	
MVC (cortical) probable	0	2	23	14	2	**41**	
MVC (cortical) possible	0	0	4	1	21	**26**	
MVS (subcortical) probable	0	10	126	75	17	**228**	
MVS (subcortical) possible	0	6	145	40	10	**201**	
MV infart estratègic	0	0	3	2	0	**5**	
Demència per altres entitats	**0**	**3**	**53**	**19**	**8**	**83**	
TOTAL D.C. AMB DEMÈNCIA	**0**	**72**	**1224**	**1363**	**649**	**3308**	**64%**
		2%	**37%**	**41%**	**20%**		
DETERIORAMENT COGNITIU SENSE DEMÈNCIA							
DCL probable	0	132	0	0	0	**132**	
DCL possible	0	408	0	0	0	**408**	
DCL no amnesic	0	656	0	0	0	**656**	
DCL per M. Parkinson	0	3	0	0	0	**3**	
DCL per malaltias psiquiatriques	0	8	0	0	0	**8**	
Fibromiàlgia / Fatiga Crònica	0	1	0	0	0	**1**	
DCL per altres entitats mèdiques	0	7	0	0	0	**7**	
TOTAL D.C. SENSE DEMÈNCIA	**0**	**1215**	**0**	**0**	**0**	**1215**	**24%**

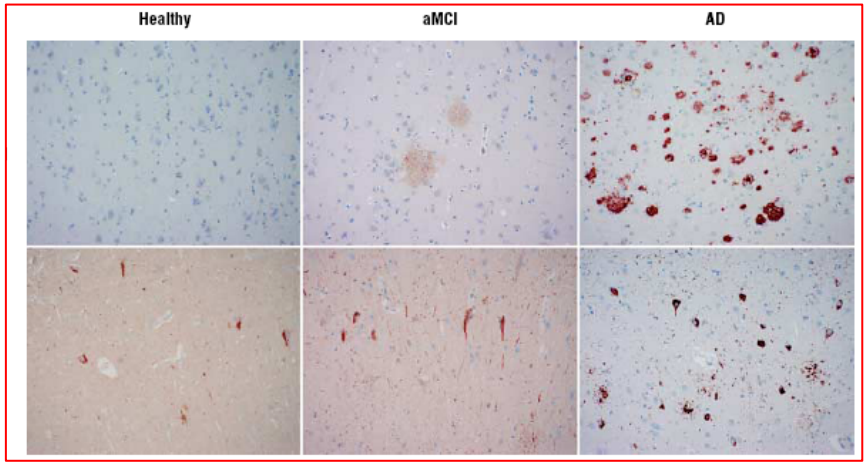
Proportion of Diagnoses of Cognitive Dysfunction in AD

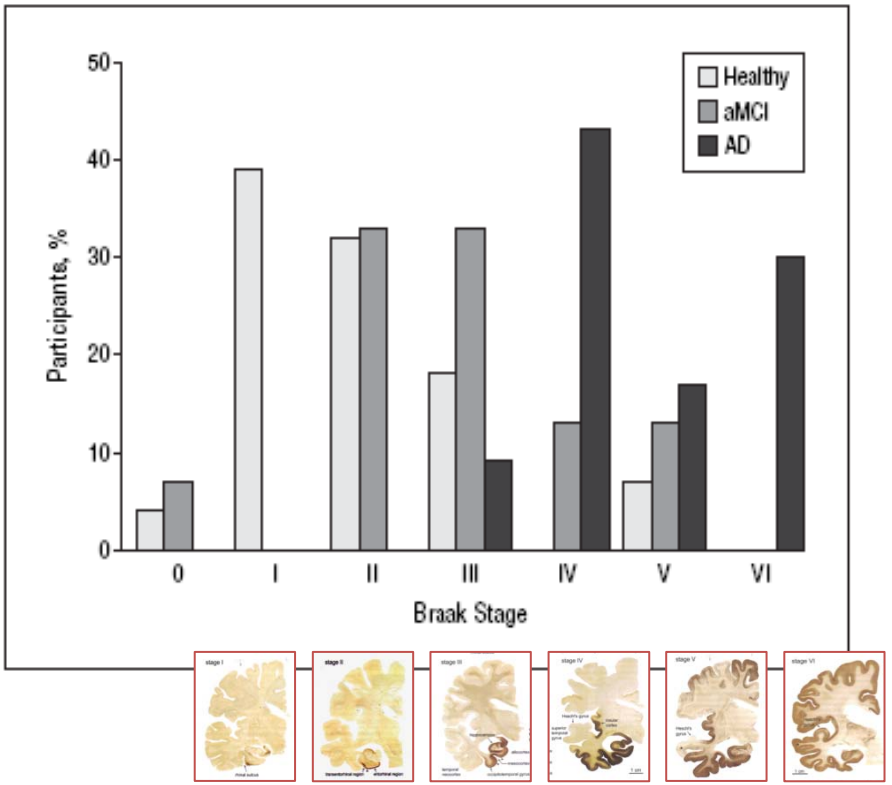
Diagnosed disorder	Level of impairment: None (*n* = 563)	Mild (*n* = 154)	Moderate (*n* = 279)	Severe (*n* = 308)
Agnosia	.000	.07	.30	.87
Apraxia	.003	.30	.52	.90
Aphasia	.011	.48	.51	.82
Judgement	.004	.52	.88	.996
Constructional defect	.007	.62	.77	.97
Abstract thinking	.011	.80	.97	1.00

Source: Helmes E., Østbye T. Beyond memory impairment. Cognitive changes in Alzheimer's disease. Arch Clin Neuropsychology 2002; 17: 179-193.

Neuropathologic Features of Amnestic Mild Cognitive Impairment

Conclusions: The neuropathologic features of aMCI matched the clinical features and seemed to be intermediate between the neurofibrillary changes of aging and the pathologic features of very early AD.





Ronald C. Petersen, PhD, MD; Joseph E. Parisi, MD; Dennis W. Dickson, MD; Kris A. Johnson, RN; David S. Knopman, MD; Bradley F. Boeve, MD; Gregory A. Jicha, MD, PhD; Robert J. Ivnik, PhD; Glenn E. Smith, PhD; Eric G. Tangalos, MD; Heiko Braak, MD; Emre Kokmen, MD†

Arch Neurol. 2006;63:665-672

Cognition shares different pathologies.

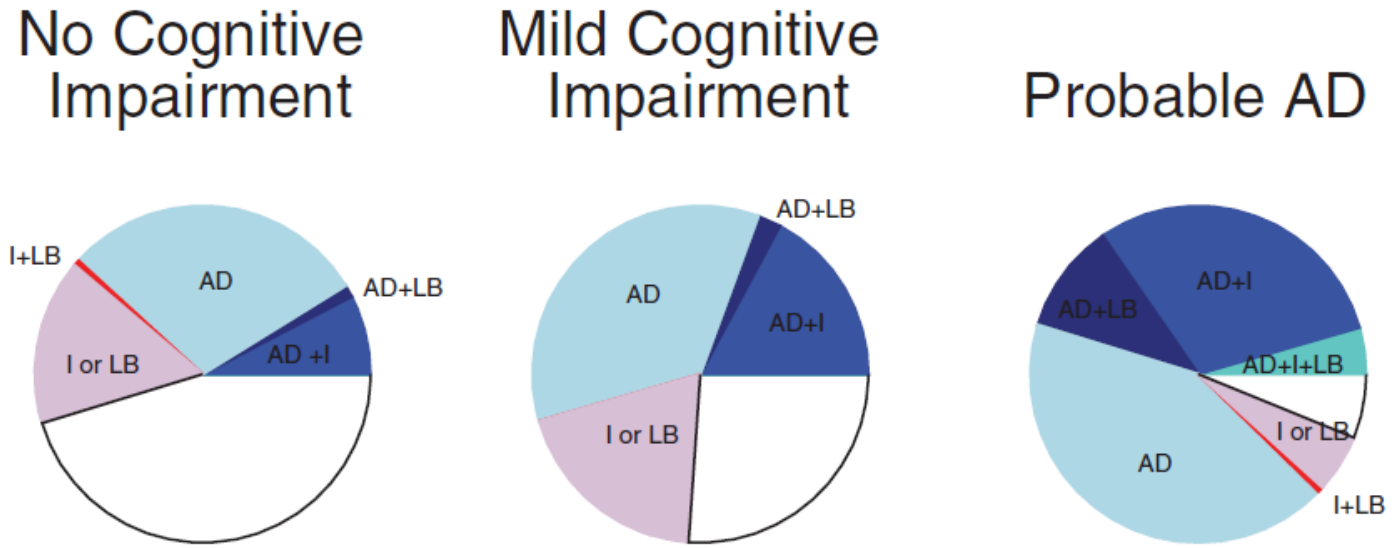


*Fig. Pathology by clinical status proximate to death. (*Blue shades*) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral 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.*

The study included 483 autopsied participants from the Religious Orders Study and the Rush Memory and Aging Project with probable AD; MCI (amnestic and non amnestic), or no cognitive impairment.

.

Julie A. Schneider, Zoe Arvanitakis,Sue E. Leurgans, and David A. Bennett . The Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment. Ann Neurol 2009;66:200–208

Exploración Neuropsicológica

Protocolo neuropsicológico para el deterioro cognitivo ligero.

- Memoria lógica e immediata
- Memoria lógica diferida
- Weschler's Vocabulary Subtest
- Letter & number sequence (*Weschler 1987)*
- Block desing *(WAIS,1981)*
- ADCS Cancelation test *(Mohs 1997)*
- Colour trials *(D'Elia,1996)*
- Free cued selective remainding test *(Buschke)*
- Semantic category fluence *(Ranier,1974)*

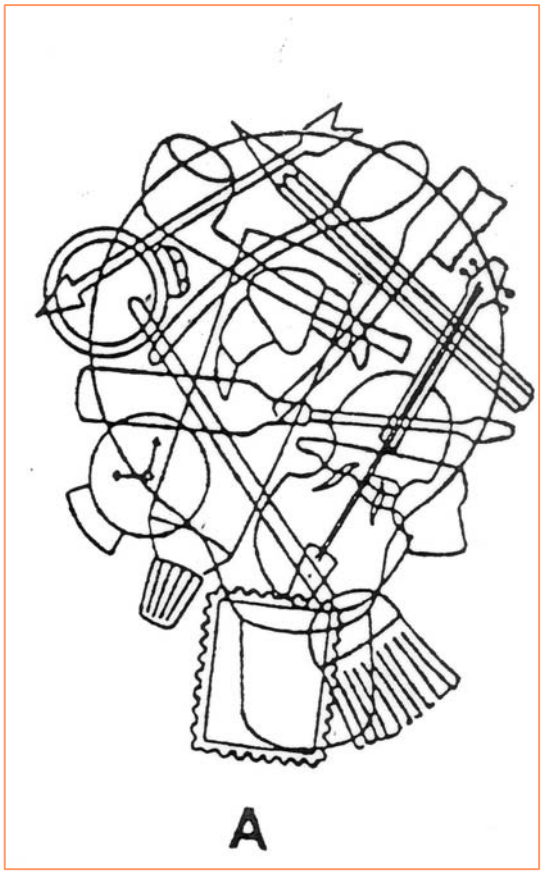
Test 15-Objetos

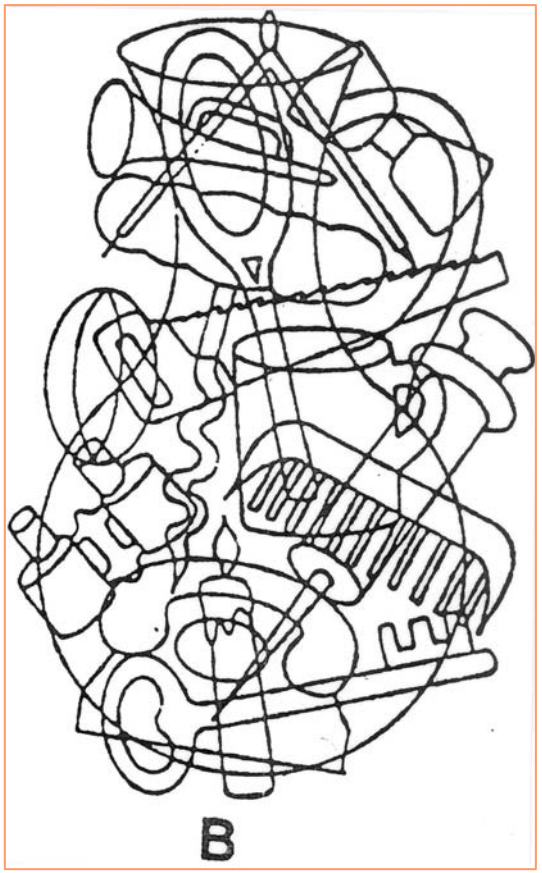
APLICACIÓN

A continuación, le enseñaré una hoja en la que aparecen objetos sobrepuestos. Por favor, sin girar el papel, dígame lo que va viendo.

El sujeto no puede girar la hoja.

Se anotarán todas las respuestas y se contarán las correctas y las neoformas.





***Alegret M**, Vinyes-Junqué G, **Boada M**, Martínez-Lage P, Cuberas G, Espinosa A, Roca I, Hernández I, Valero S, Rosende-Roca M, Becker J T, Tárraga L. **Brain perfusion correlates of visuoperceptual deficits in preclinical and mild Alzheimer disease**. Journal of Alzheimer's Disease 21 (2010) 557-567.*

***Alegret M, Boada M**, Viñas G, Valero S, Espinosa A, Hernández I, Modinos G, Rosende-Roca M, Mauleón A, Becker J T, Tárraga L. **Detection of visuoperceptual deficits in preclinical and mild Alzheimer's disease**. J Clin Exp Neuropsychol. 2009,31(7), 860-7.*

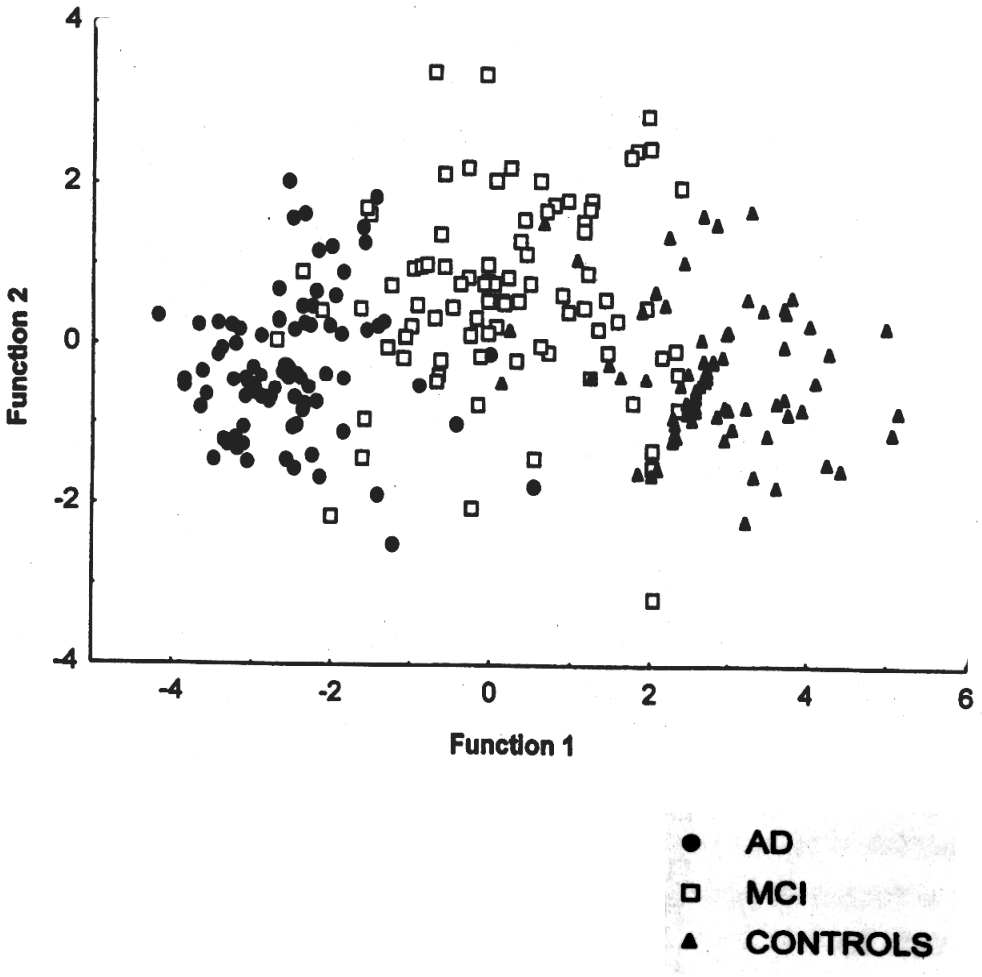
Test 15-Objetos (A ó B)

FORMA A	FORMA B
1. Bombilla 2. Flecha, lanza 3. Pipa 4. Anillo 5. Reloj, despertador 6. Tubo (pasta dientes…) 7. Destornillador 8. Sello, marco 9. Violín, guitarra, violonchelo 10. Pistola 11. Escoba 12. Croissant 13. Cuchara 14. Cepillo dientes 15. Lápiz	1. Jarrón, botijo 2. Raqueta, matamoscas, espejo, pala 3. Compás 4. Trompeta 5. Lazo, diábolo 6. Jeringa 7. Pelota, melón 8. Sierra, serrucho 9. Sacacorchos 10. Llave 11. Vela 12. Prismáticos 13. Taza, vaso 14. Peine 15. Teléfono

PUNTUACIÓN TOTAL

Respuestas correctas _____ y NEOFORMAS _____

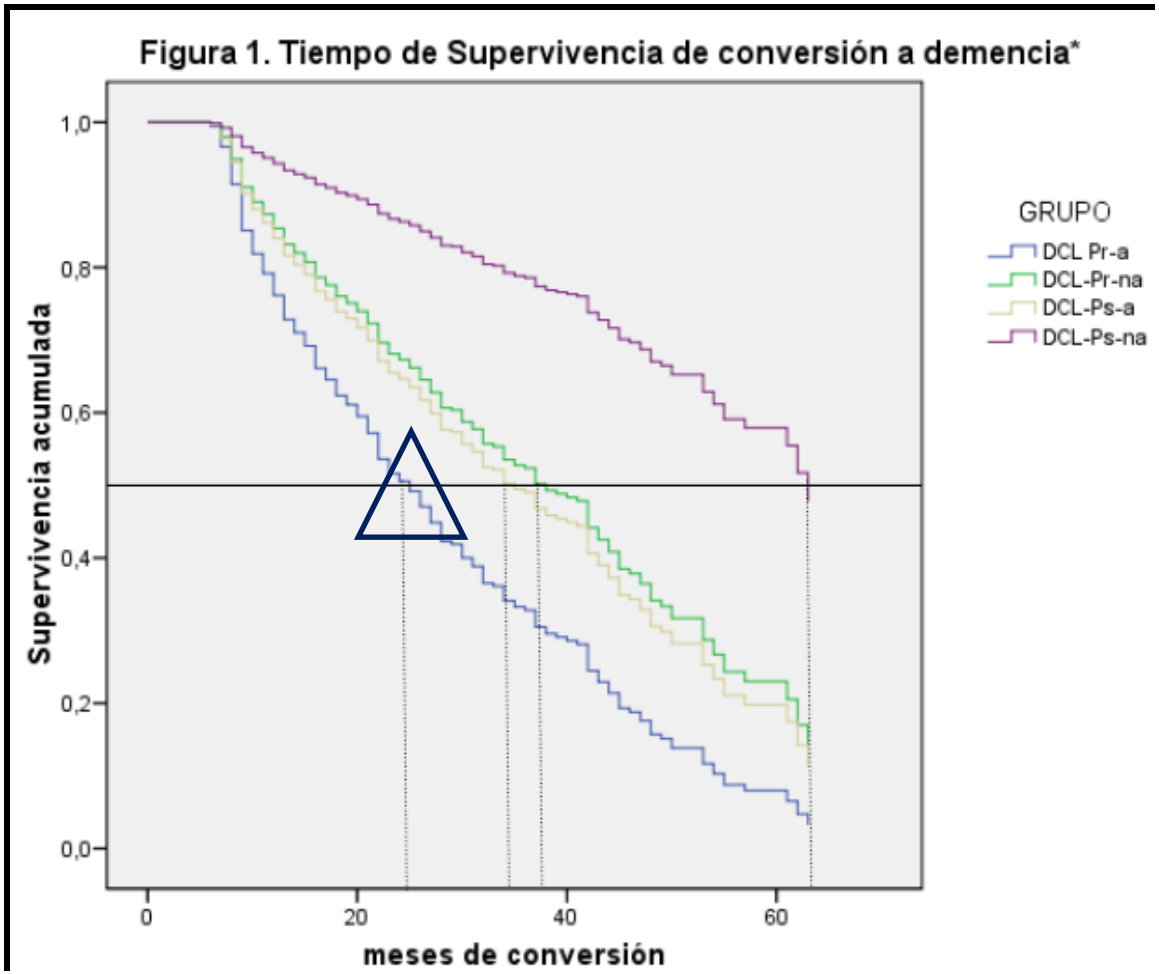
Neuropsychological phenotype of MCI



Discriminant Functions
(prop. expl. variance 0.94)

- EPISODIC MEMORY
  (AVLT5, WMS: Immediate Recall)
- SEMANTIC MEMORY
  (WAIS-R: Similarities)
- VISUOSPATIAL FUNCTIONS
  (WAIS-R: Block Design)
- ATTENTION
  (TMT B)

Arnaiz E. et al, Alzheimer Reports, 2000; 3:97-104

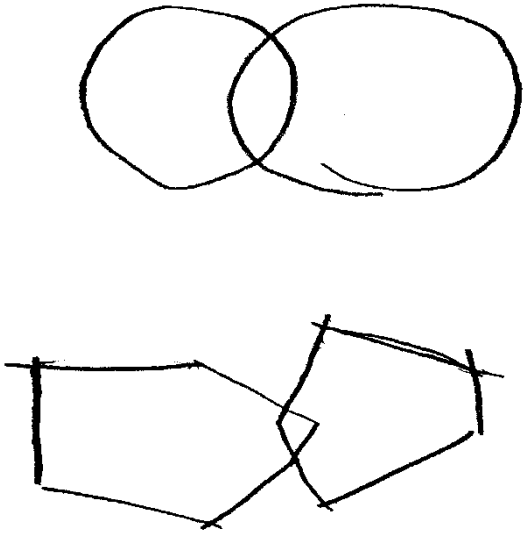


Estudio longitudinal de 550 DCL y conversión a demencia. Poster SEN 76H/1410

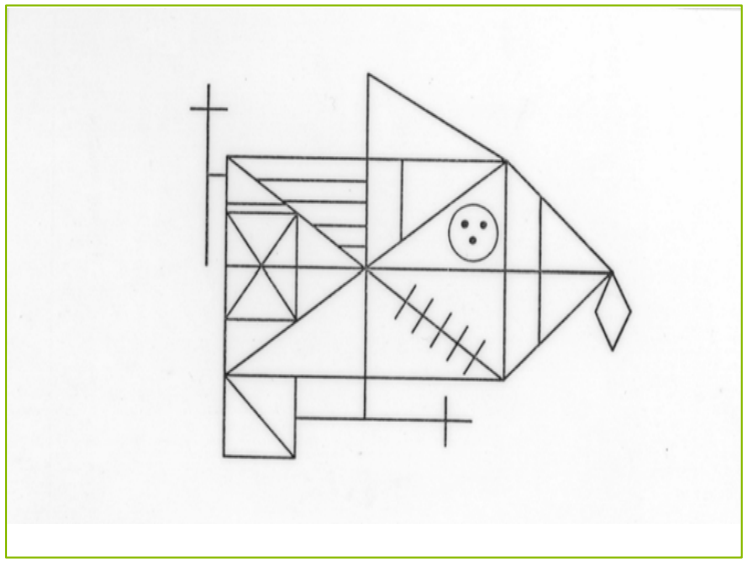
Se analizaron 550 sujetos con diagnóstico de DCL y genotipo APOE, reclutados en la Unidad de Diagnóstico de Fundació ACE entre 2006 y 2011, clasificados siguiendo los criterios de Petersen (2004) y de López y cols. (2003.

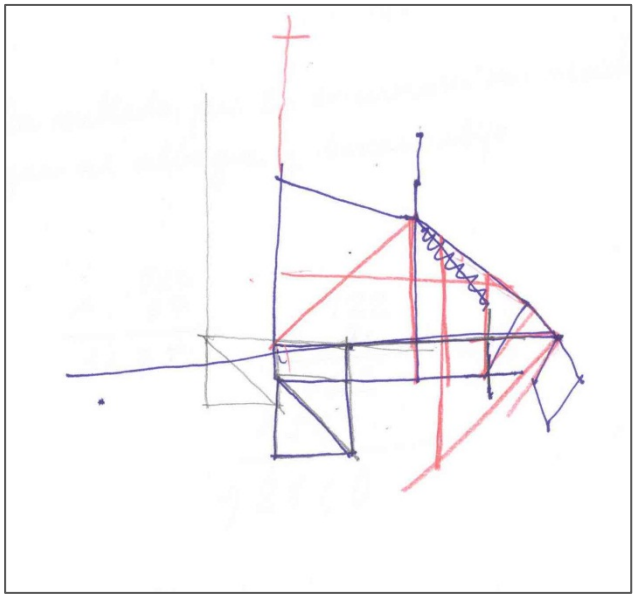
***El grupo DCL-Pr-a mostró un riesgo 8,5 veces mayor de convertir a demencia que el grupo DCL-Ps-na, que mostró la tasa más lenta de conversión a demencia*.**

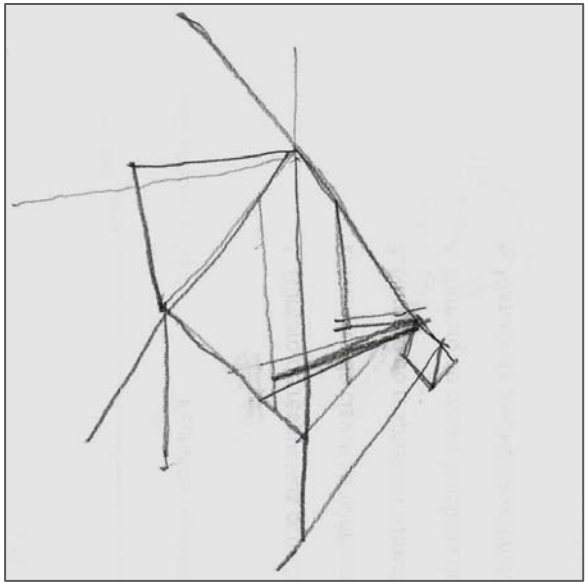
Paciente de 77 años con EA (MMSE 20/30)



…el dibujo del reloj requiere la puesta en marcha de numerosos procesos cognitivos, como la planificación, secuenciación, y abstracción (…) que no son necesarios para realizar otros dibujos más simples (Shullman, 2000).



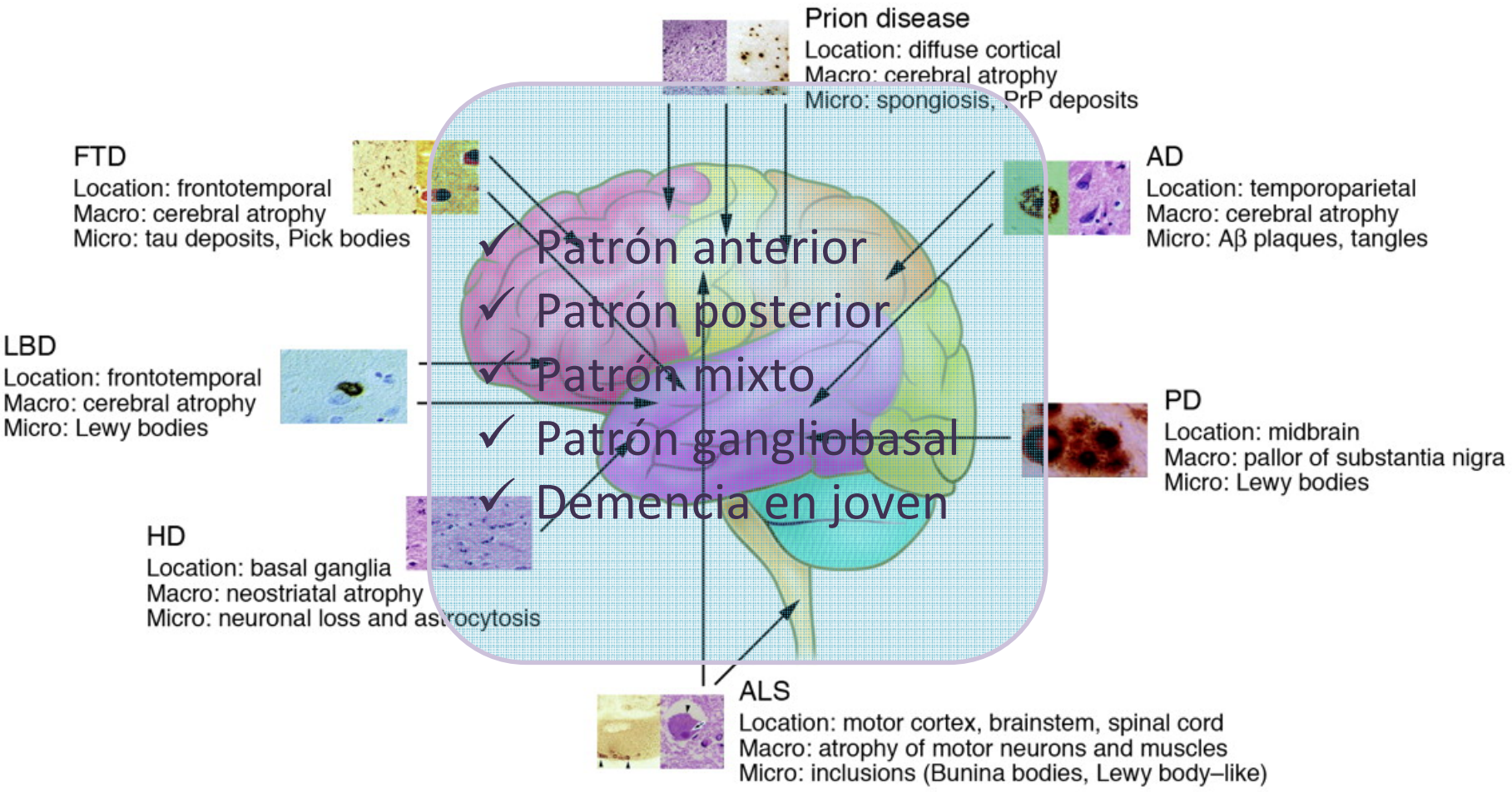




Paciente de 48 años , arquitecto.
Apraxia progresiva

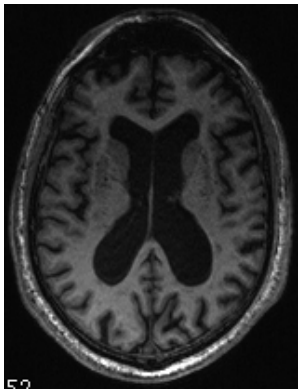
Enfermedades neurodegenerativas. Diagnóstico por la imagen

Enfermedades neurodegenerativas.
Diagnóstico por la imagen

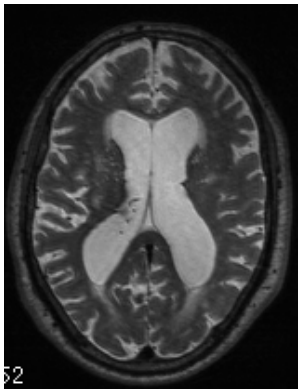


Multimodality Neuroimaging

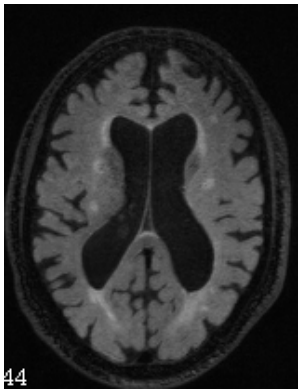
Structural imaging



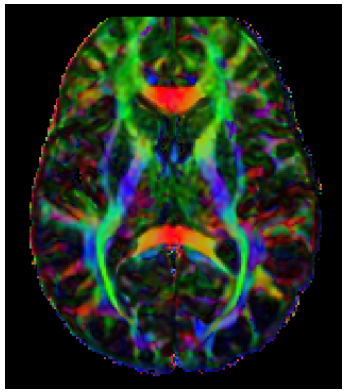
T_1weighted



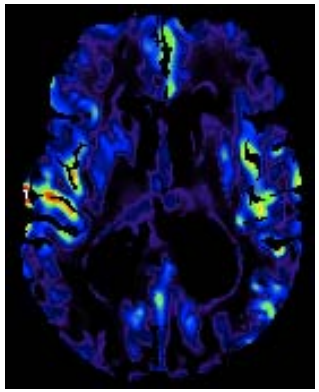
T_2 weighted



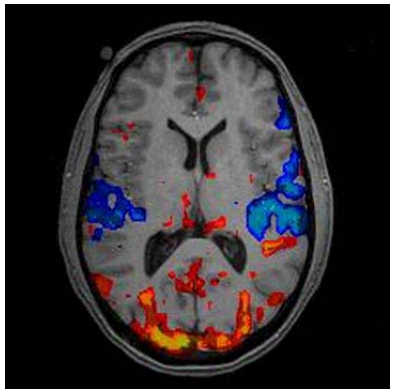
FLAIR



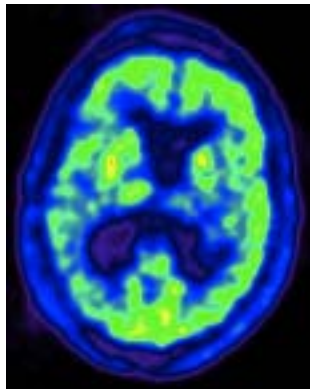
DTI



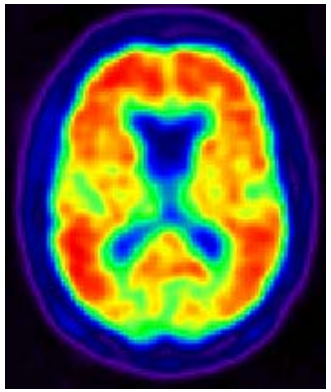
ASL MRI



fMRI



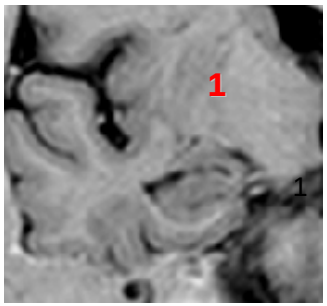
FDG PET

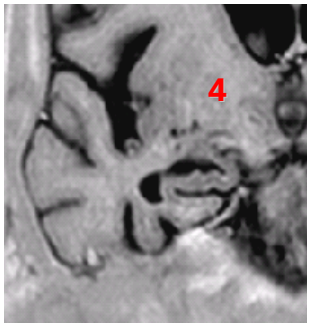


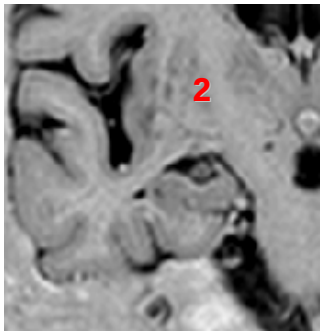
^{11}C-PiB PET

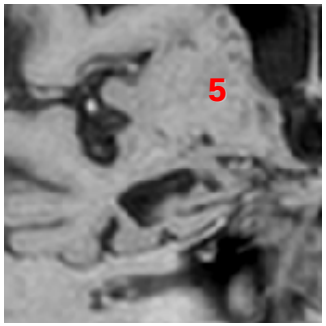
Medial Temporal Lobe (MTL)atrophy: Visual analysis scale

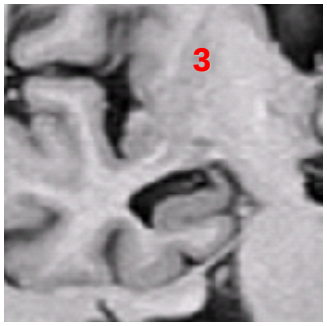
Korf E. et al. Medial temporal lobe atrophy on MRI predicts dementia with mild cognitive impairment. Neurology 2004;63:94-100 ***Scheltens et al. J Neurol Neurosurg Psychiatry 1992***

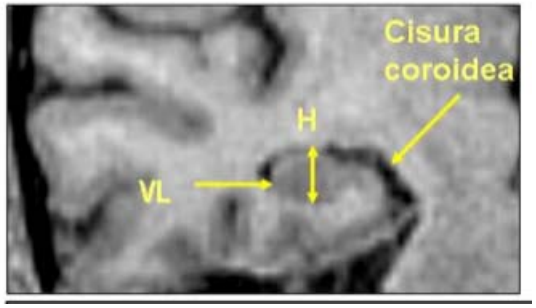


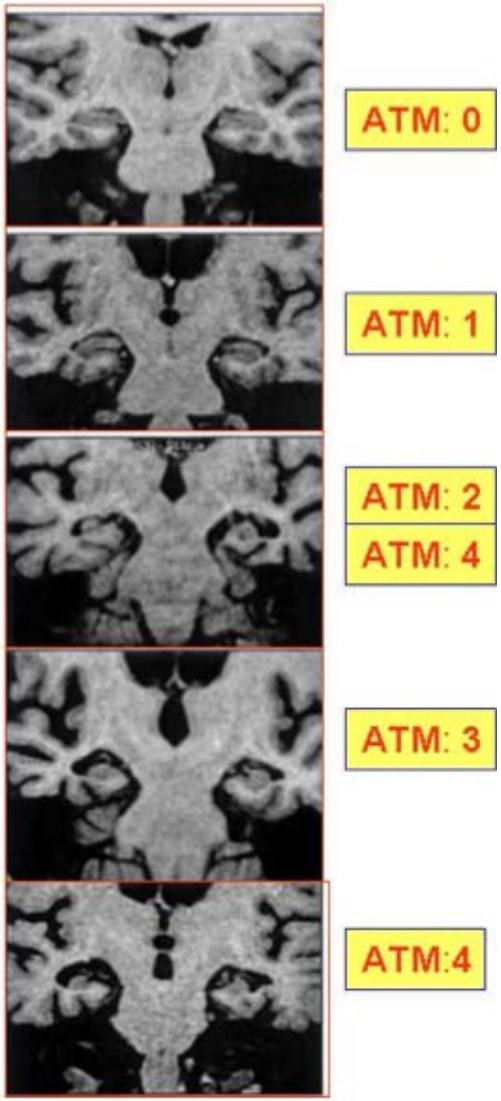




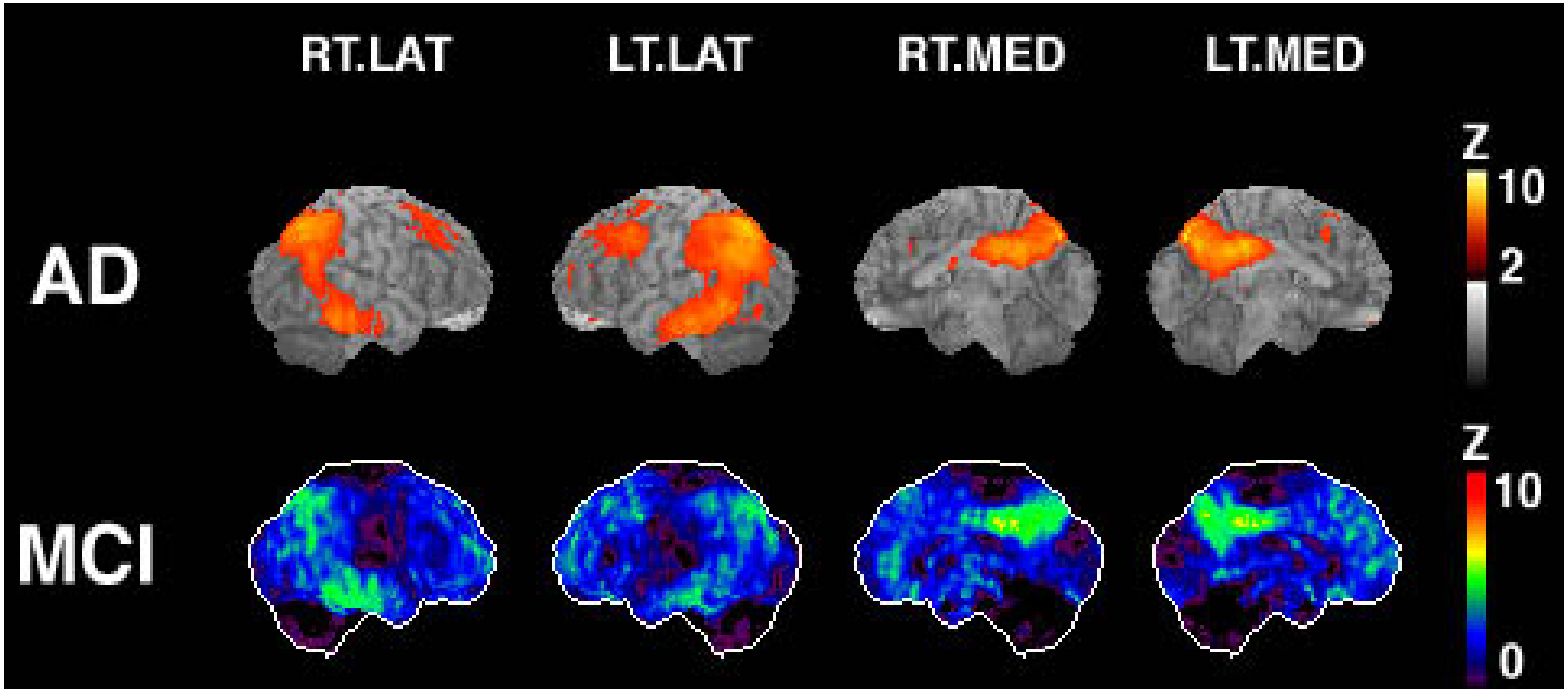






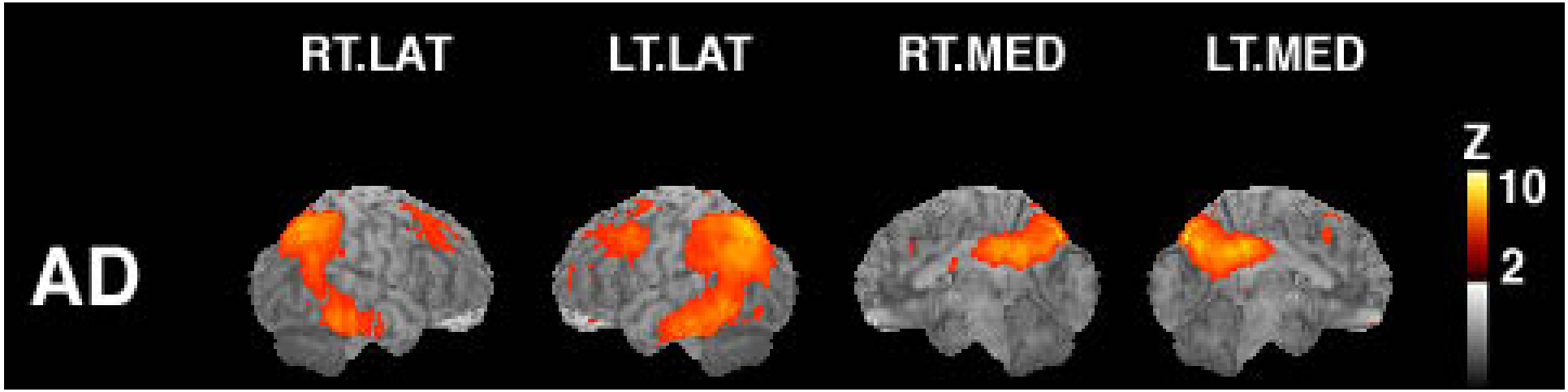


FDG-PET in AD and MCI



Courtesy of S. Minoshima, University of Washington

FDG-PET in AD and MCI



Courtesy of S. Minoshima, University of Washington

DETECTING AMYLOID IN THE BRAIN

Amyloid in the brain means Alzheimer's Disease

Amyloid PET

Pittsburg compound B C-11

Florbetair F18 /AVID 45

F 18 Flutemetanol

- CSF AB

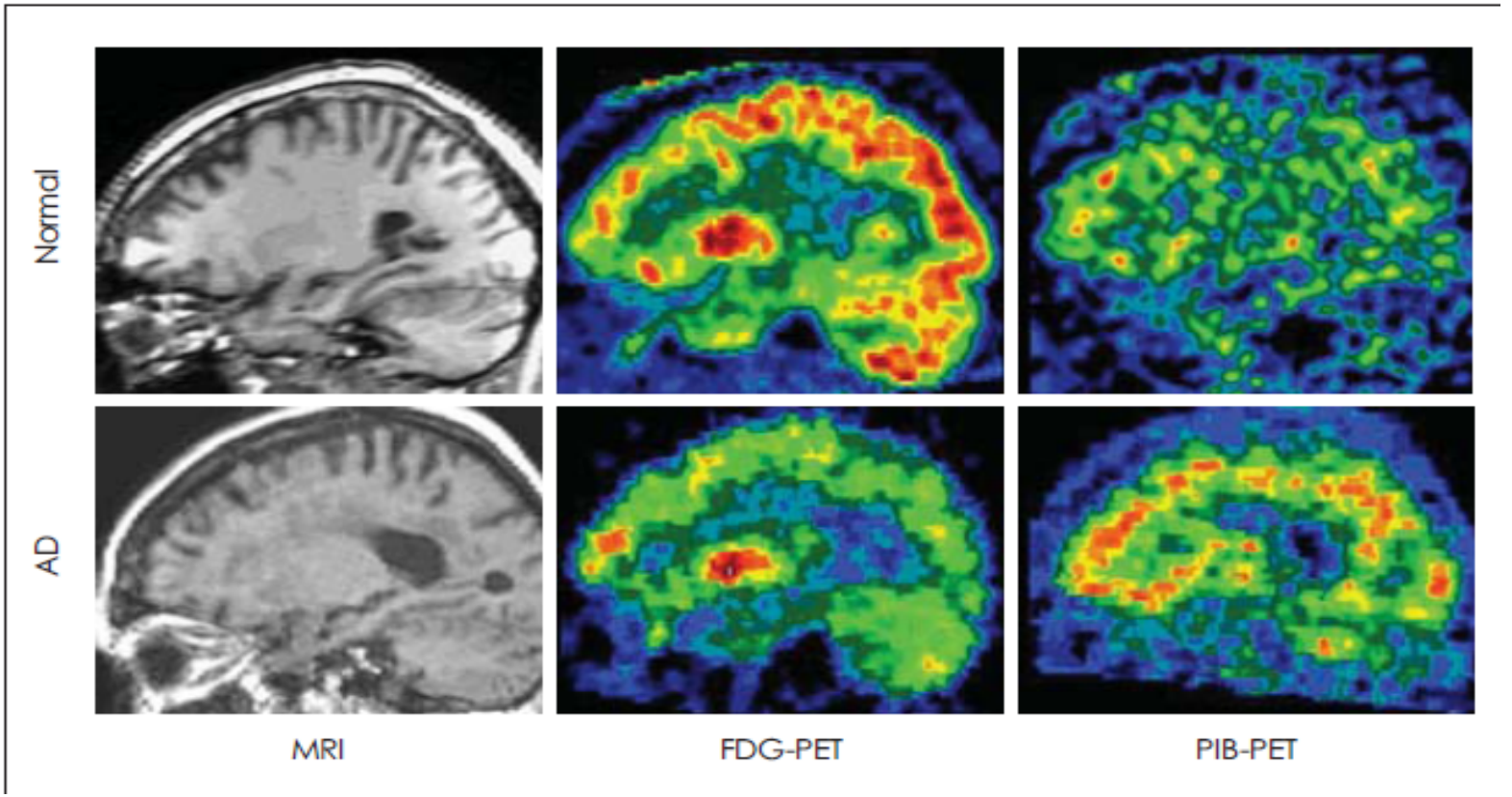
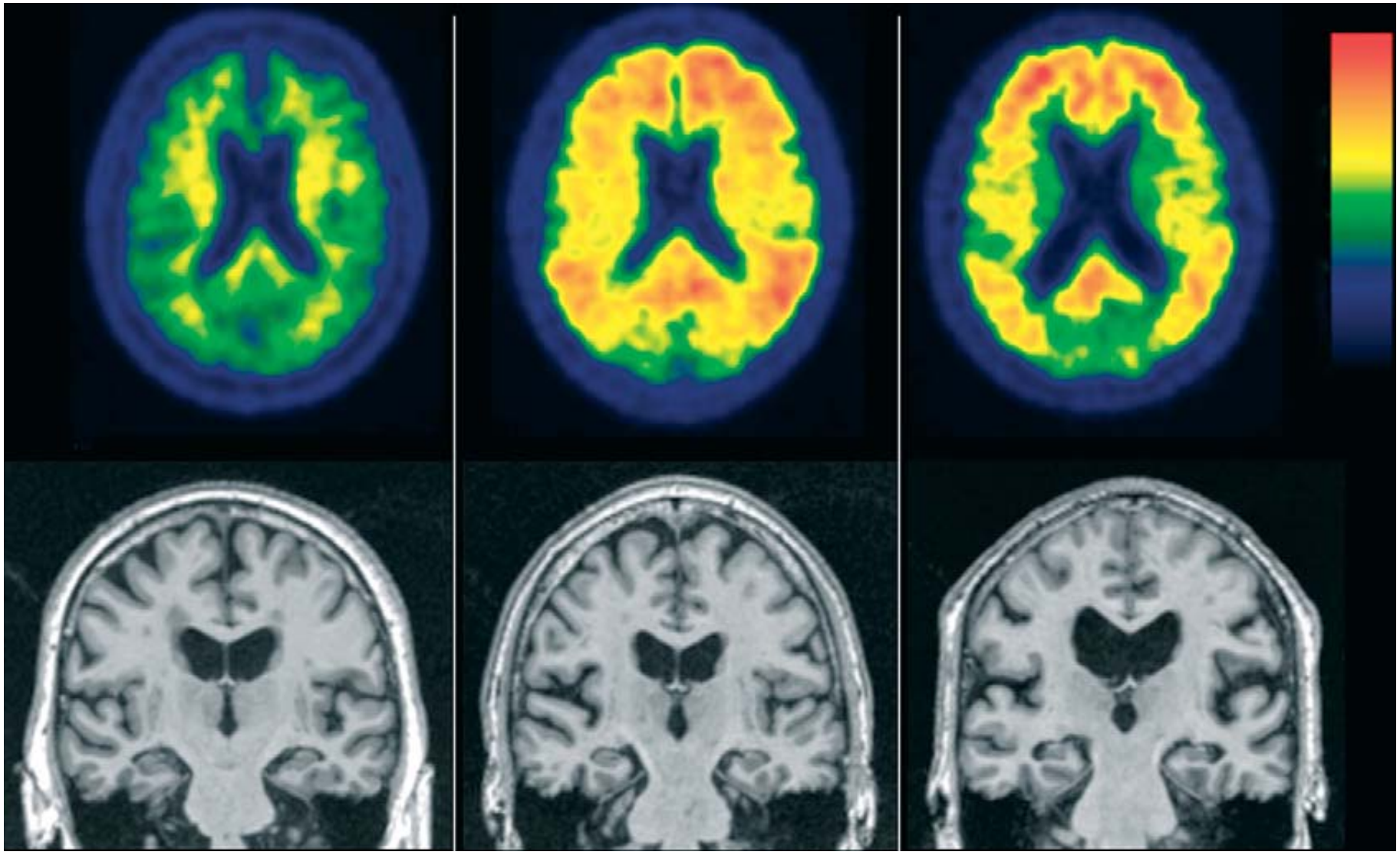


Fig. 1. Two representative cases: magnetic resonance image (MRI, left column), FDG-PET (middle column) and PIB-PET (right column) of a normal control (top row) and an AD patient (bottom row). FDG: 2-[^{18}F]fluoro-2-Deoxy-D-glucose, PIB: Pittsburgh Compound-B, AD: Alzheimer's disease.

Raquel Mistur, Lisa Mosconi, Susan De Santi, María Guzman, Yi Li, Wai Tsui, Mony J. De Leon.
Current Challenges for the Early Detection of AD: Brain Imaging and CSF Studies. J. Clin Neurol 2009;5:153-166



Ilustration of biomarkers staging of Alzheimer's disease.

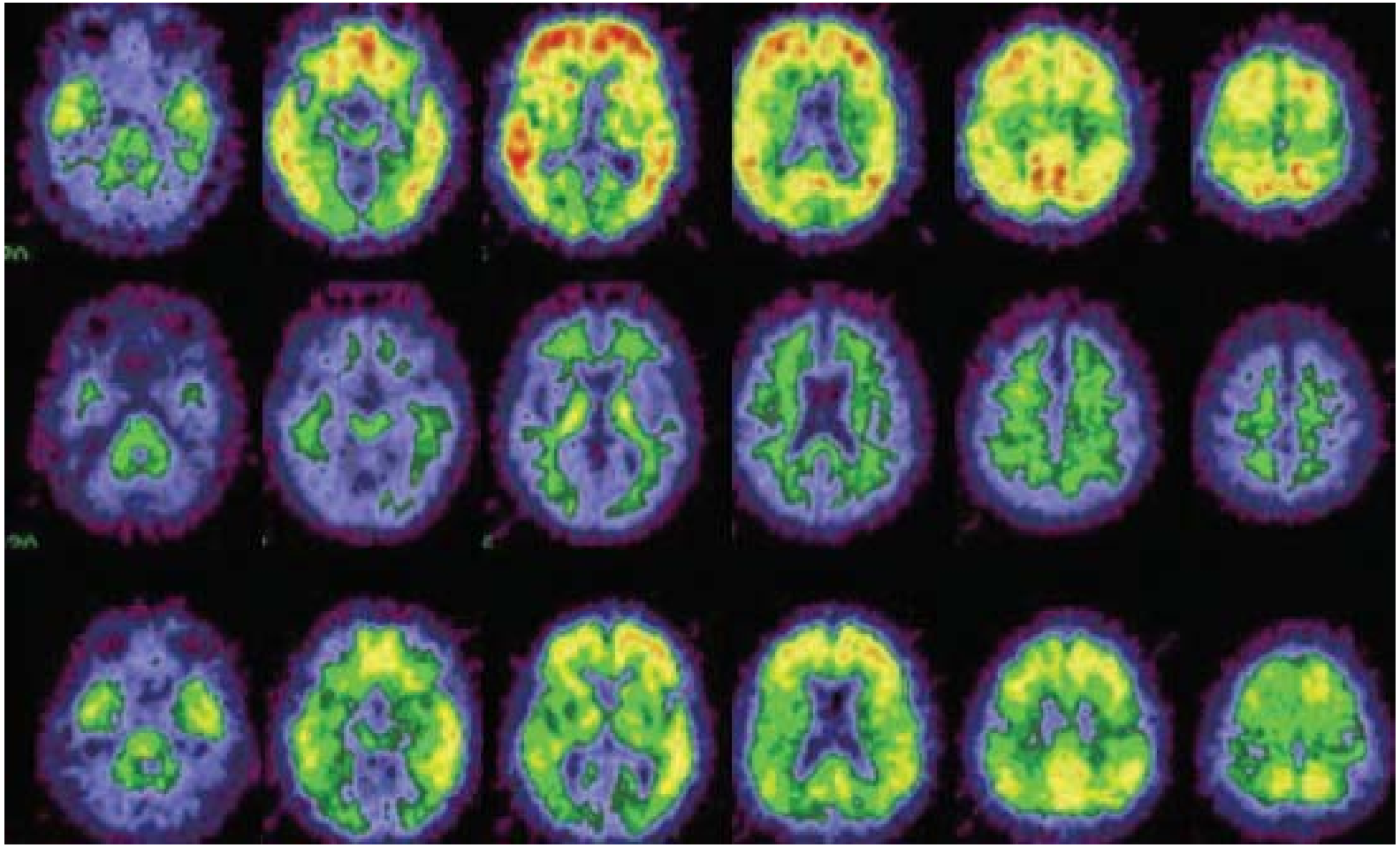
Clifford R Jack jr, David S Knopman, Willian J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner et al. ***Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade***. Lancet Neurol. 2010;9:119-28

HIGH LIGHT

[^{11}C]PIB in a nondemented population

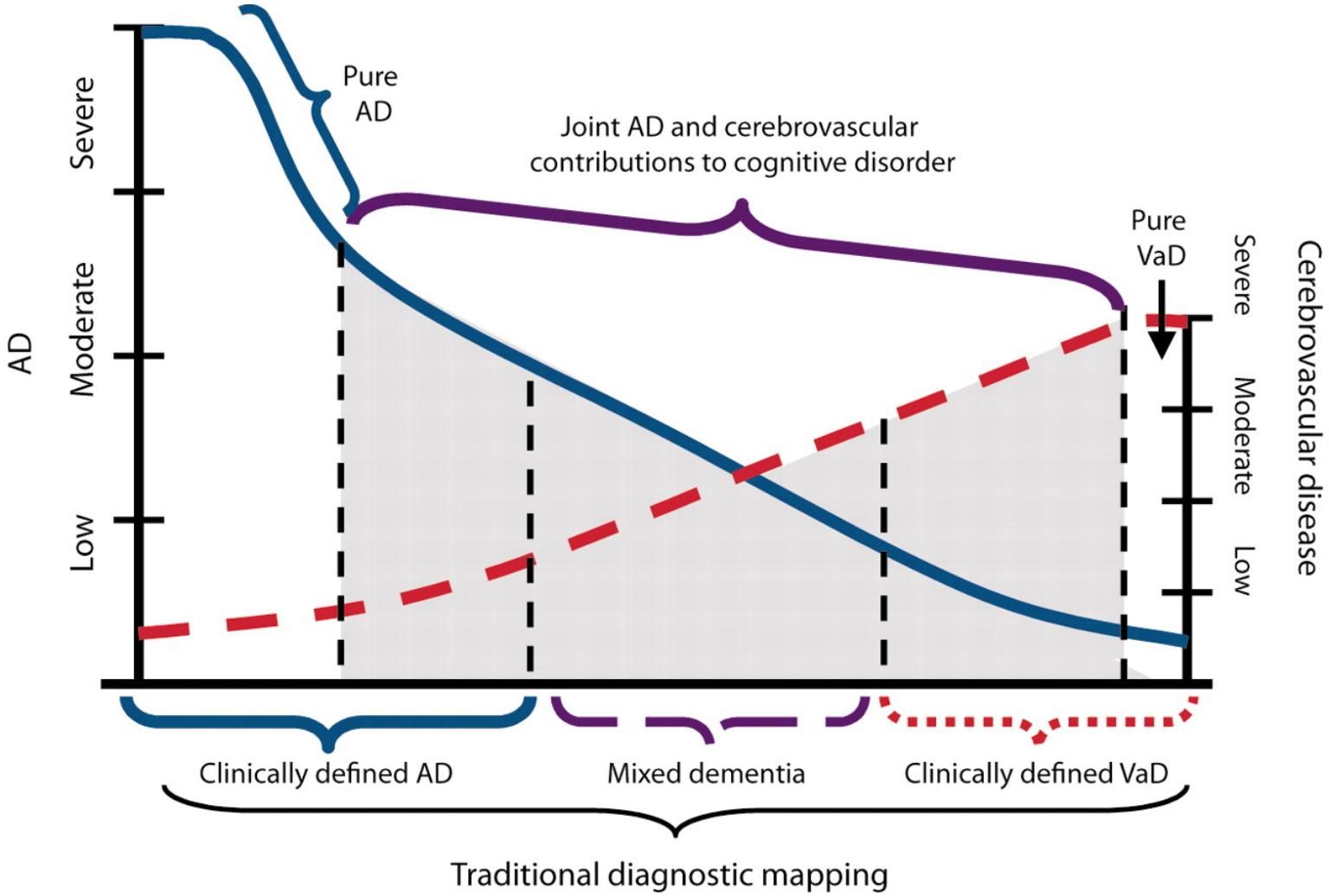
Potential antecedent marker of Alzheimer disease

M.A. Mintun, MD; G.N. LaRossa; Y.I. Sheline, MD; C.S. Dence, MS; S.Y. Lee, PhD; R.H. Mach, PhD; W.E. Klunk, MD, PhD; C.A. Mathis, PhD; S.T. DeKosky, MD; and J.C. Morris, MD



NEUROLOGY 2006;67:446–452

Balance between Alzheimer disease (AD) and cerebrovascular disease and the mapping of clinical diagnoses on the pathologic findings



Knopman D S Mayo Clin Proc. 2006;81:223-230

Cognition shares different pathologies.

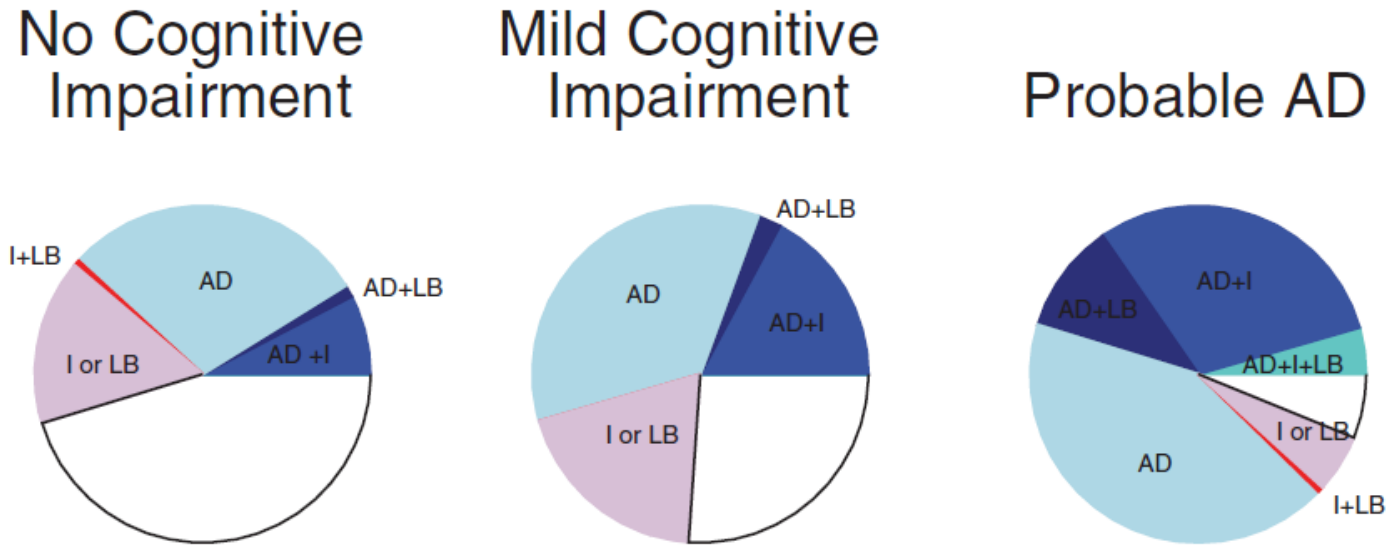


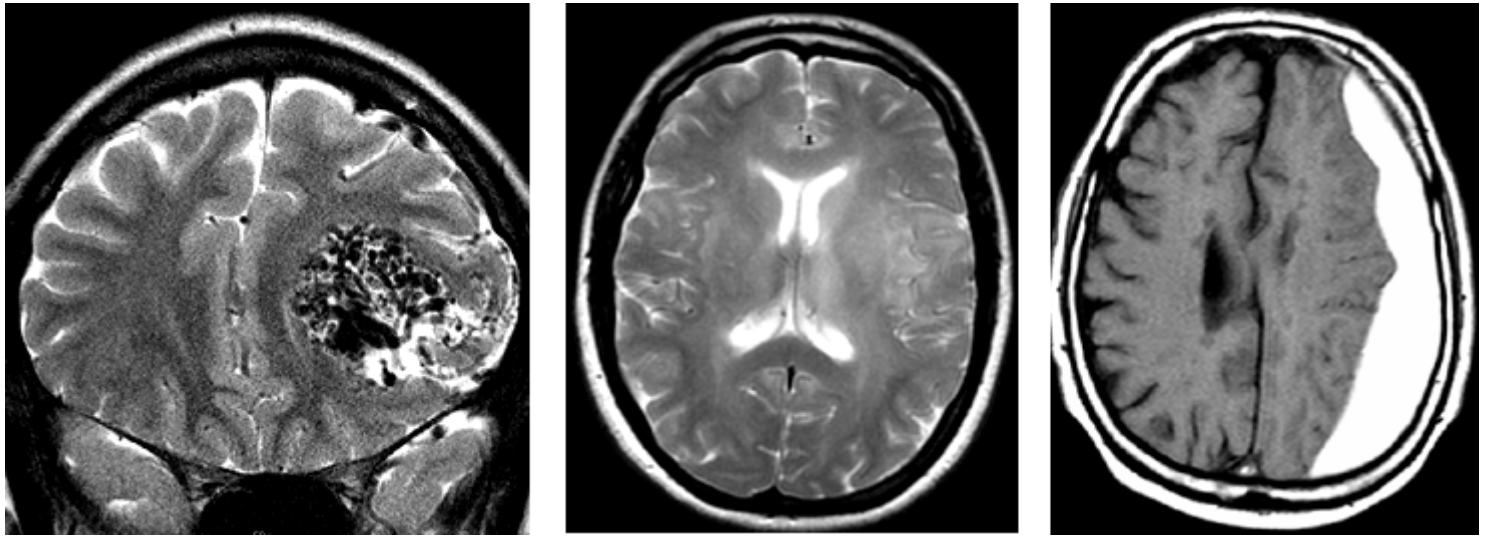
*Fig. Pathology by clinical status proximate to death. (*Blue shades*) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral 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.*

The study included 483 autopsied participants from the Religious Orders Study and the Rush Memory and Aging Project with probable AD; MCI (amnestic and non amnestic), or no cognitive impairment.

.

Julie A. Schneider, Zoe Arvanitakis,Sue E. Leurgans, and David A. Bennett . The Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment. Ann Neurol 2009;66:200–208

Otras patologías que cursan con demencia



A) Malformación arterio-venosa
B) B) Gliomatosis cerebri C)
C) Hematoma subdural

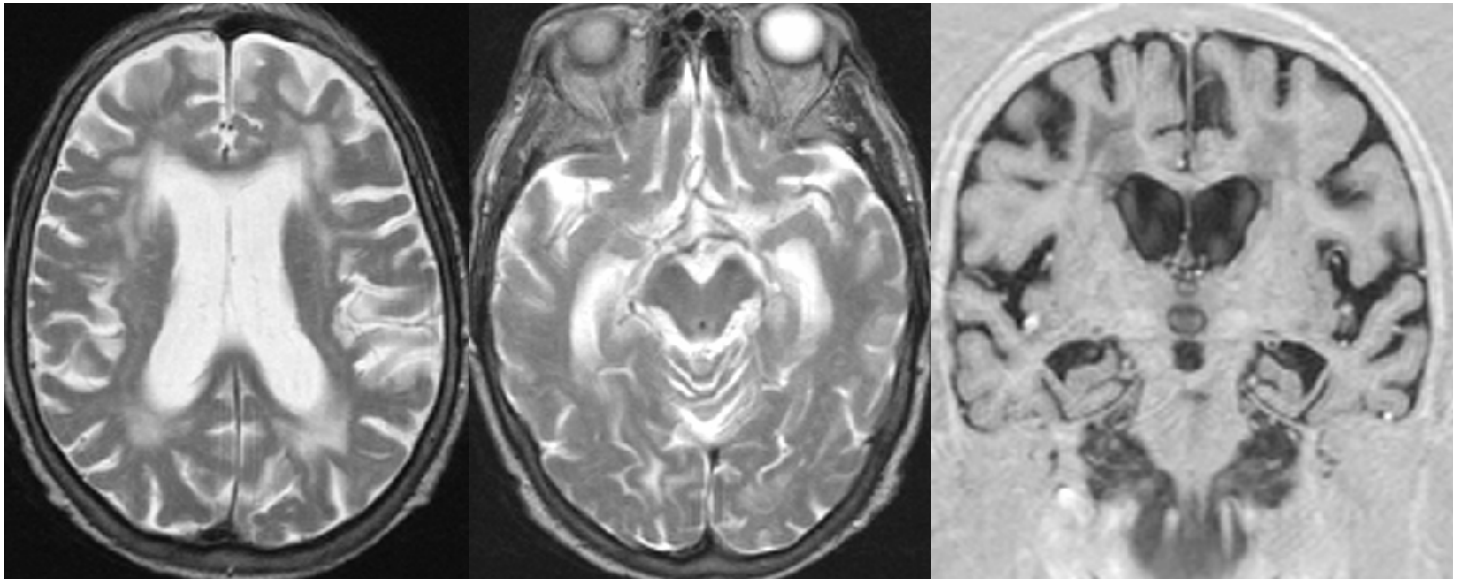
Amb el permís Dr. P Munuera. Hospital Trias i Pujols & Fundació ACE. Barcelona

Demencia Mixta

NINDS AIREN: EA con enfermedad CV

- EA: deterioro de la memoria
- CV: deterioro fx ejecutivas

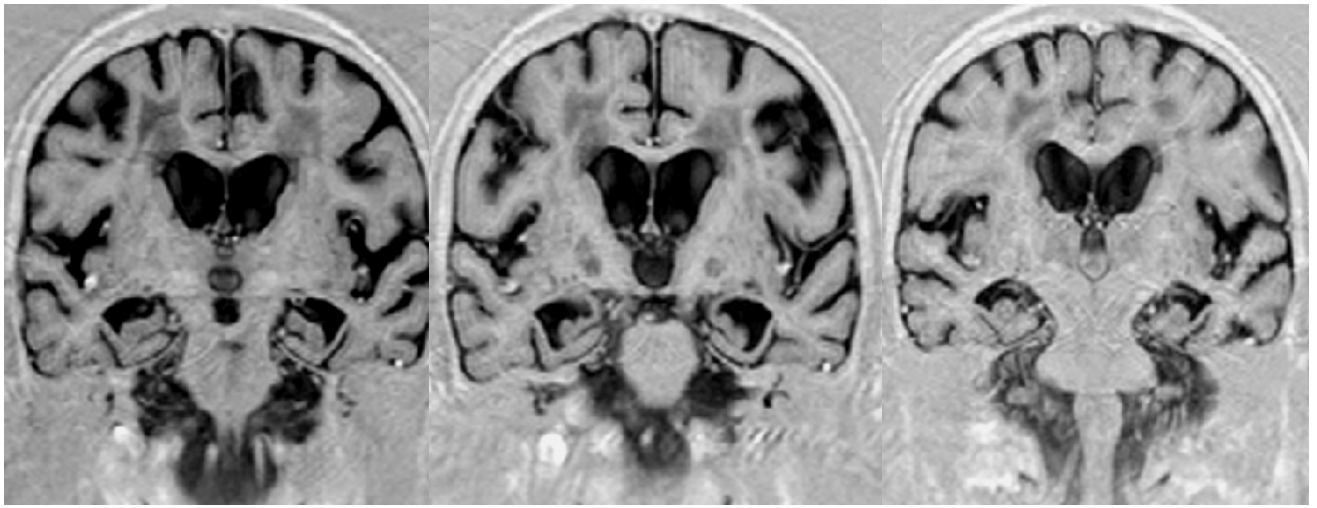
Forma clínica: paciente con sintomatología de EA (incluído el DCL) que empeora de forma brusca coincidiendo con ictus.
NRX: atrofia hipocampal+lesiones vasculares silentes RM



DV & Alzheimer

Mecanismos patogénicos comunes
Efecto sinérgico entre EA y patología vascular

- ✓ microinfartos corticales (no visibles en RM)
- ✓ AAC-hipoperfusión cerebral (disfunción vascular)
- ✓ enfermedad de pequeño vaso



Kövari et al. Stroke 2004 ; Kövari et al. Neurology 2007

Conocer el contexto social

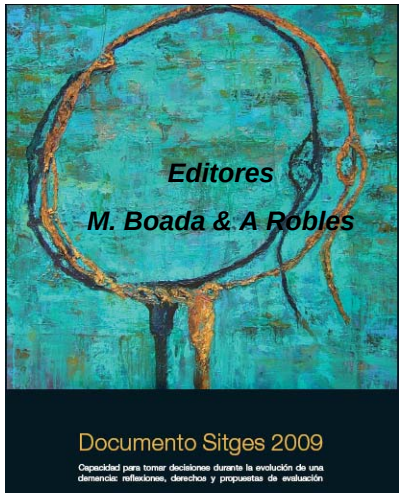
ACE

HEALTH CARE SYSTEMS:

- Definition of “quality of life”.
- Optimization of the quality of resources and services for patients and carers throughout AD care.

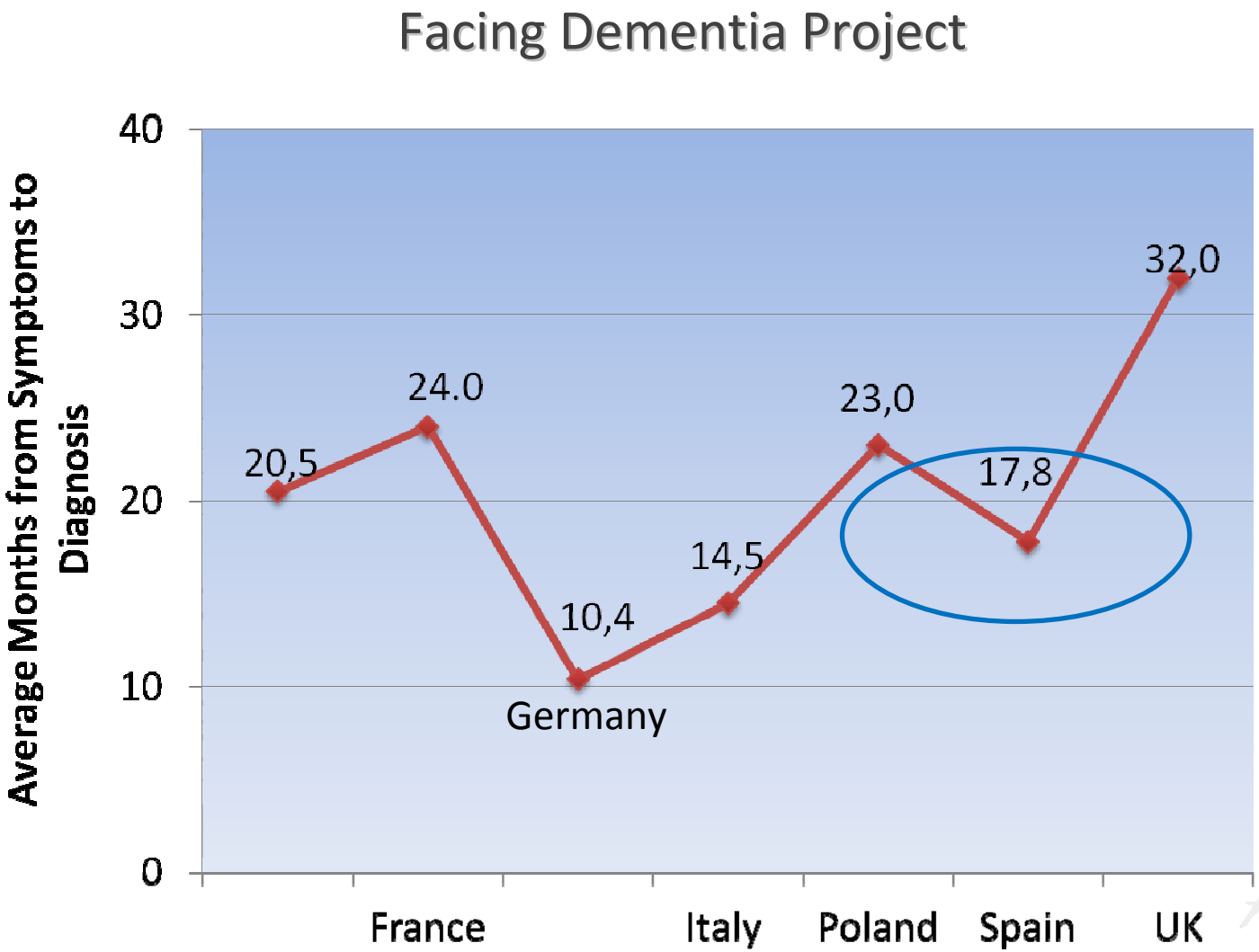
ETHICS AND HEALTH ECONOMICS:

- Ethics of clinical research and in clinical care.
- Definition of cost effectiveness.



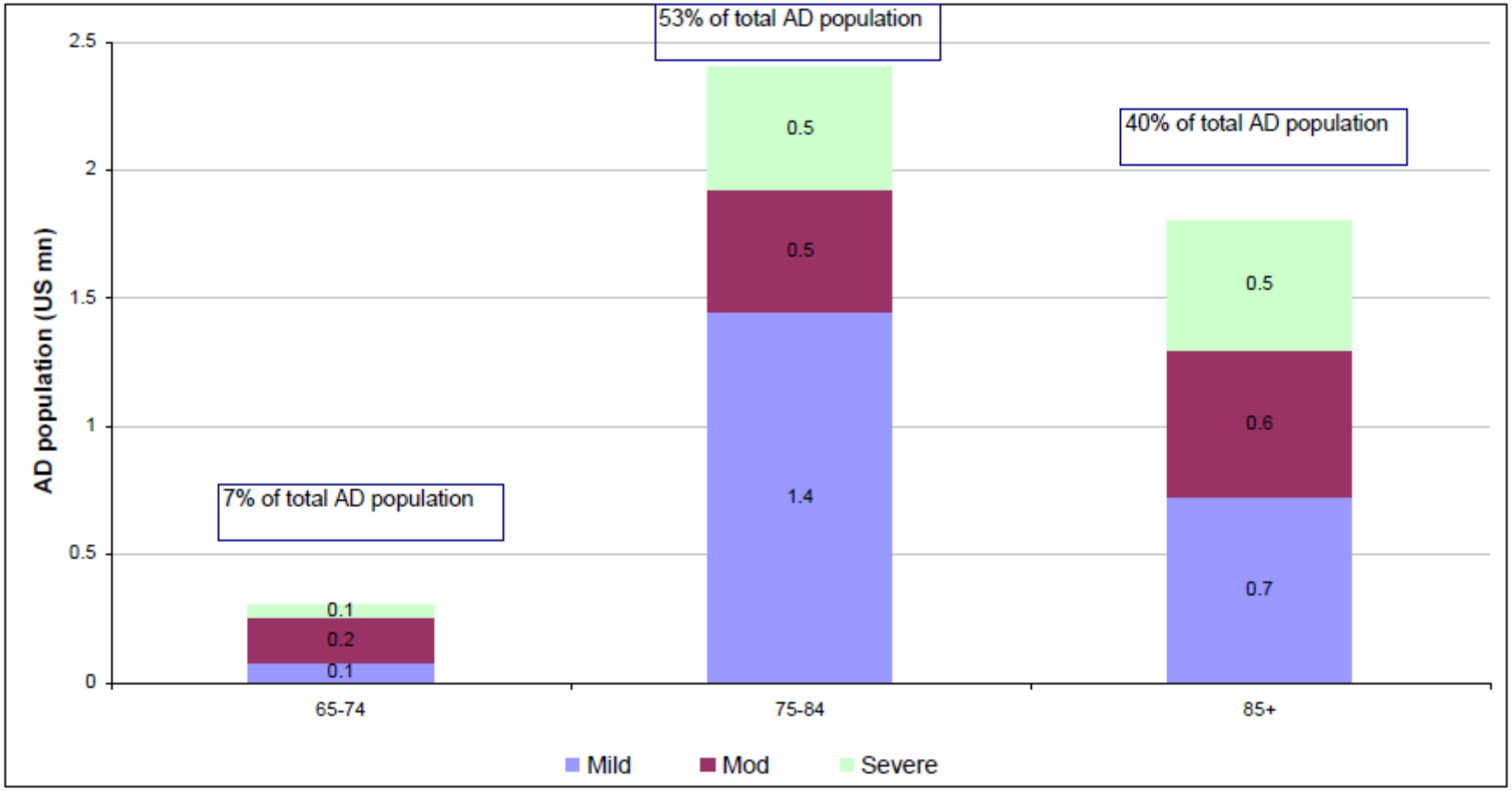
Grupo “Documento Sitges” 2009 (por orden alfabético)
R. Alberca, M. Alegret, C. Antunez, J.R. Ara, S. Barquero, M. Boada, A. Bosch, P..Cañabate, E. Corral, A. Cruz-Jentoff, J. L Dobato, B. Fontecha, J. Gabrieli, P. Martinez-Lage, J.L.Molinuevo, F. Quinzá, A. Robles, A. Rovira, F. Santos-Urbaneja, G. Tomé, S. Ventura,

Conocer el contexto europeo



Prevalence of AD as well as proportion of severe disease increases with age. In 2000, of the 4.5mn people suffering from Alzheimer's, 7% (about 300k) were aged 65-74, 2.4mn (53%) were aged 75-84 while the remaining 40% (1.8mn) were 85 years or older (**Figure 15**).

Figure 15: Prevalence of mild, moderate and severe AD in the US (based on 2000)



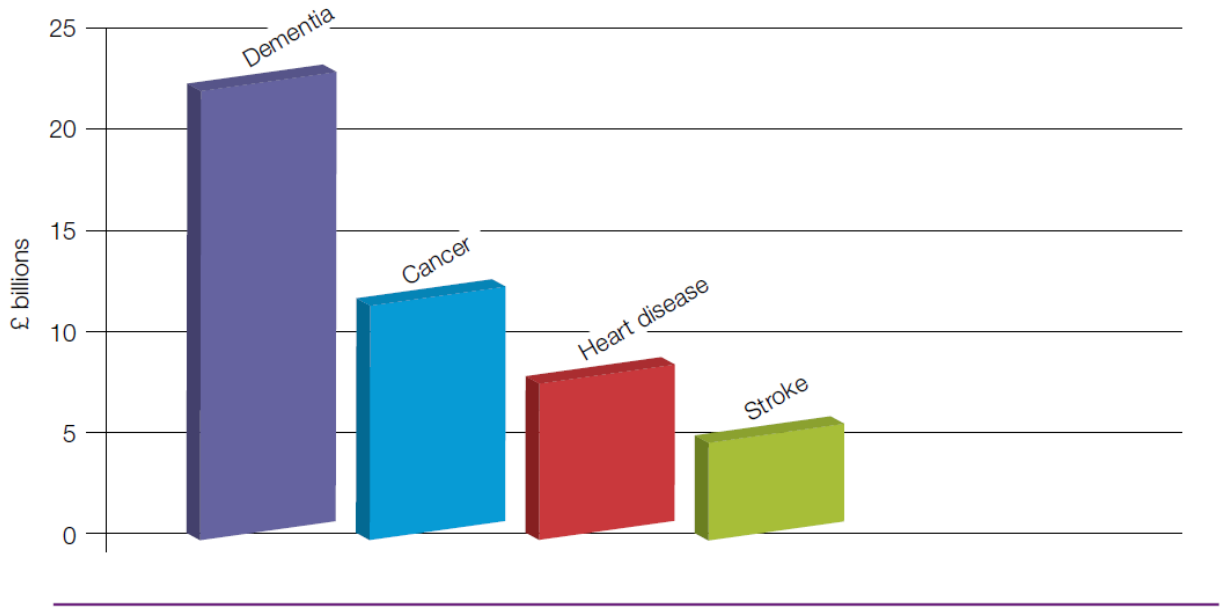
COST

Cost nacional anual: demències, £23 bilions.

càncer, £12 bilions.

malalties de cor, £8 bilions

ictus, £5 bilions



Dementia 2010 Report.
Alzheimer's Research Trust. UK

WolframAlpha computational knowledge engine

Alzheimer's disease

Input interpretation:

Alzheimer's disease

Medical codes:

ICD–9 code	331.0

Patients with diagnosis in a given year:

	male	female	all
fraction of US population	1 in 2010 ≈ 0.05%	1 in 1240 ≈ 0.08%	1 in 1480 ≈ 0.068%
number of US patients	89 200 per year	198 900 per year	288 000 per year
average patient age	74 years	76 years	75 years
diagnosis sample size	47 visits	80 visits	127 visits

(estimates based on 131 748 patient visits to healthcare providers from NAMCS and NHAMCS, weighted for USA demographics, 2006 to 2007)

Reasons for patient visit:

	male	female	all
memory disturbance	≈ 36%	≈ 22%	26%

Generated by Wolfram|Alpha (www.wolframalpha.com) on July 22, 2010 from Champaign, IL.

Població nord-americana - 2010