huca hospital universitario central asturias

SESIÓN CLÍNICA GENERAL

CONFERENCIA:

"LA ENFERMEDAD DE ALZHEIMER, UNA PREGUNTA QUE NOS HACEMOS TODOS"

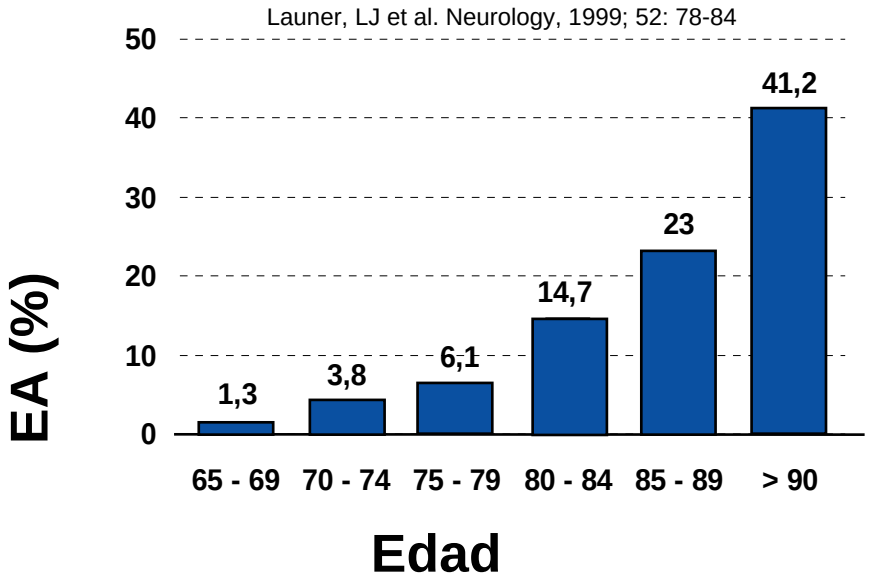
DR. RAFAEL BLESA
Director del Servicio de Neurología.
Hospital de la Santa Creu i de Sant Pau.
Facultad de Medicina UAB. Barcelona

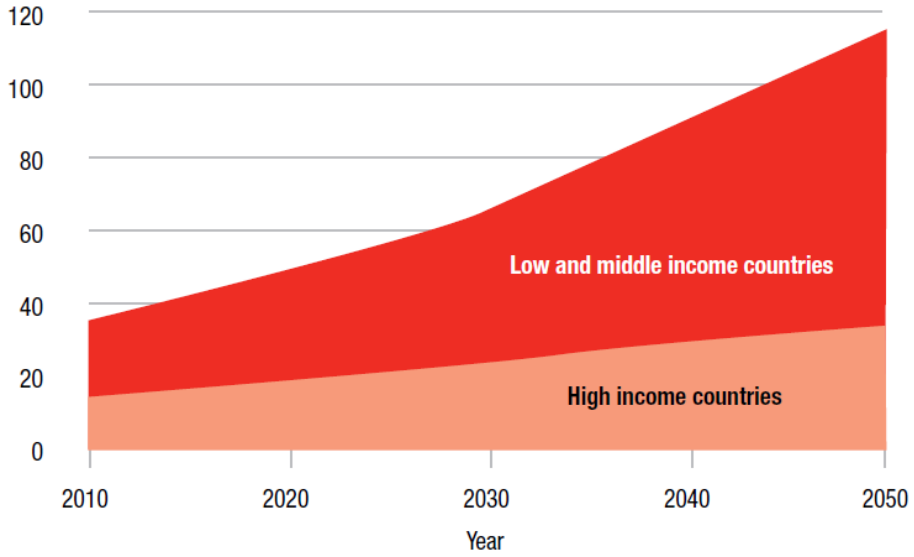
Jueves, 20 de enero de 2011, a las 13:30 horas
Salón de Actos "Luis Estrada" del Centro General

ORGANIZA:
COMISIÓN DE DOCENCIA Y FORMACIÓN CONTINUADA

- Epidemiología
- Clasificación de les demencias
- Diagnóstico precoz
- Tratamientos No específicos:
- Tratamients específicos

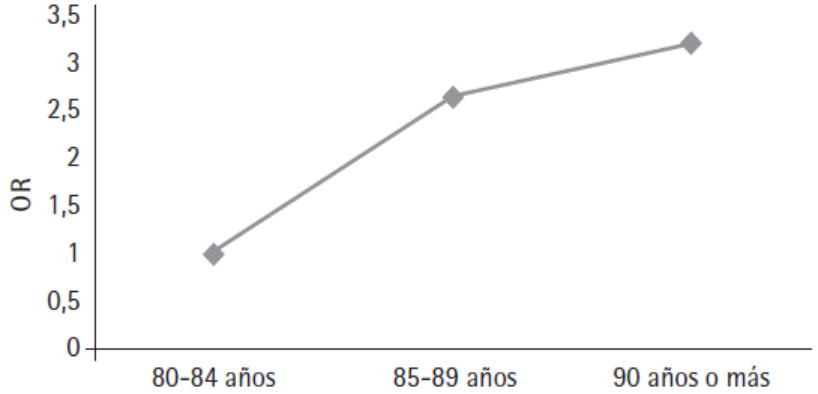
Epidemiología



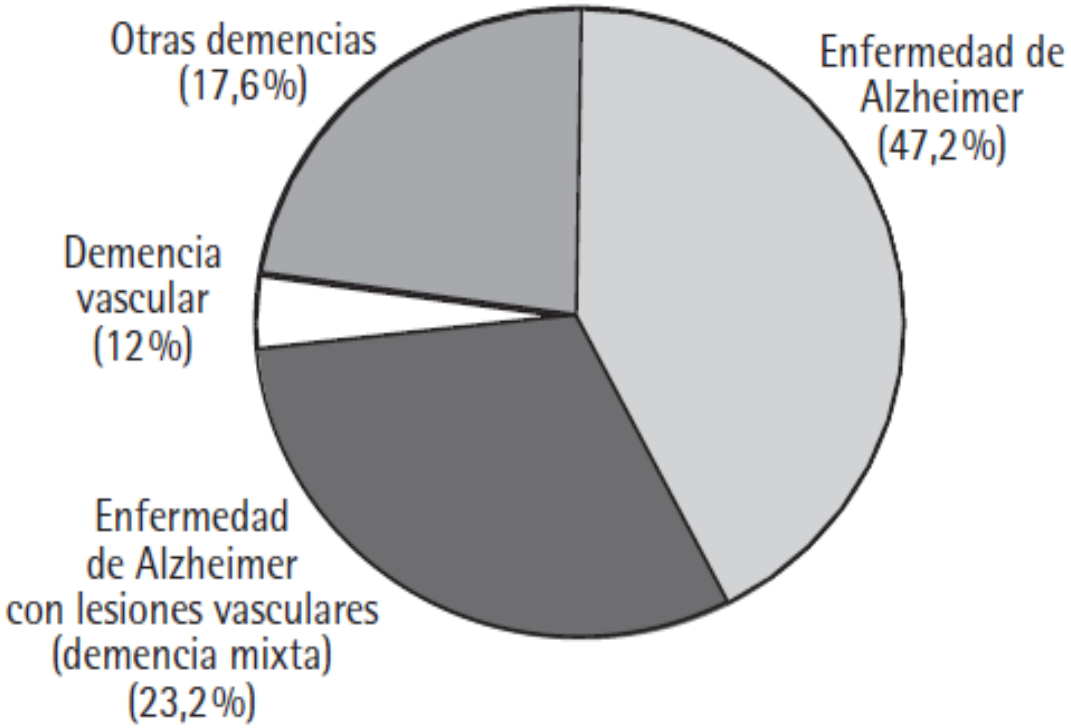


35.6 millones de personas de todo el mundo sufren demencia en el año 2010.
Este número se doblará cada 20 años, alcanzando los 65.7 millones el 2030 y 115.4 millones el 2050.

50% de mayores de 80 años:
Det Cog (25% demencia)



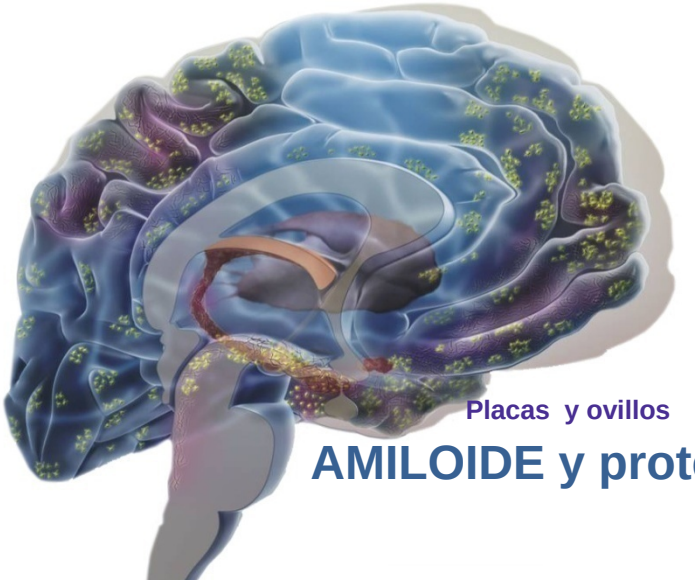
Bufill E, et al. *Neurología 2009;24(2):102-107*



¿Cuántas enfermedades son el alzheimer?

Hablamos de enfermedades Neurodegenerativas: Hablamos de Proteinopatías

Atrofia cerebral y pérdida de capacidades cognitivas y funcionales: **Alzheimer**



Placas y ovillos

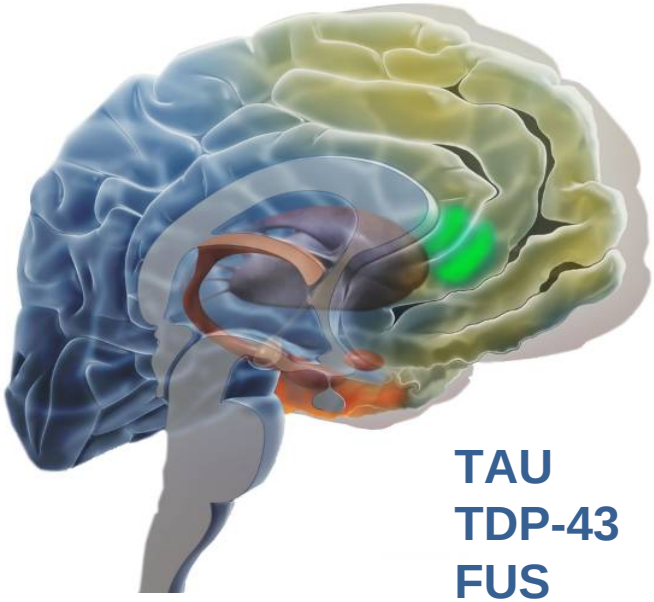
AMILOIDE y proteína Tau

Atrofia de la parte anterior del cerebro(frontal): trastornos conductuales y del lenguaje

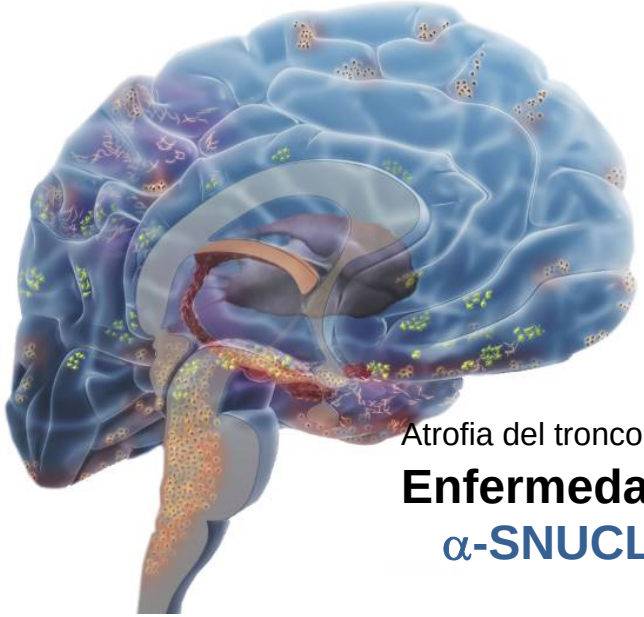
Degeneración lobular frontotemporal

Médula espinal i pérdida de fuerza muscular:

Esclerosis Lateral Amiotrófica



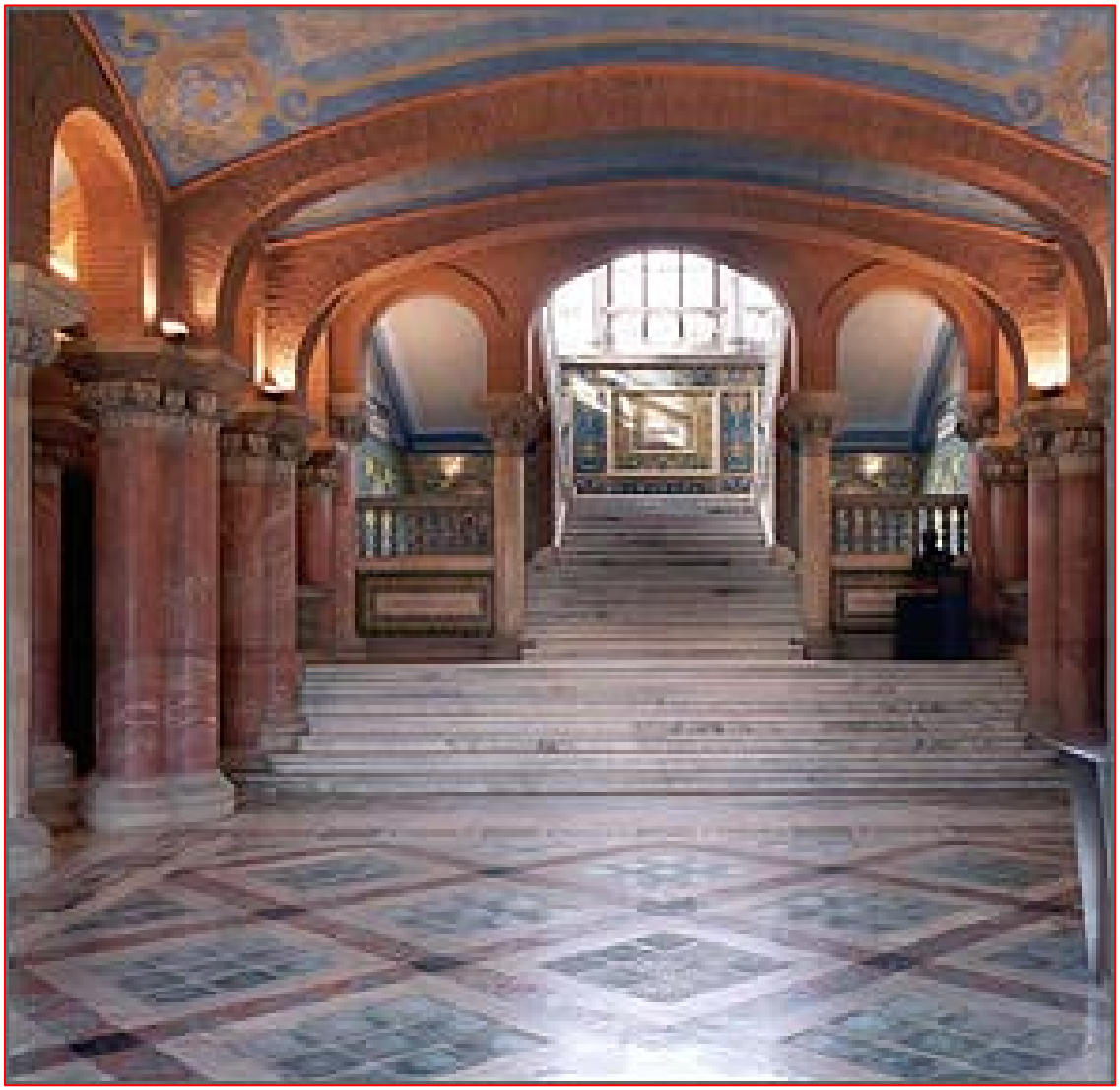
TAU
TDP-43
FUS

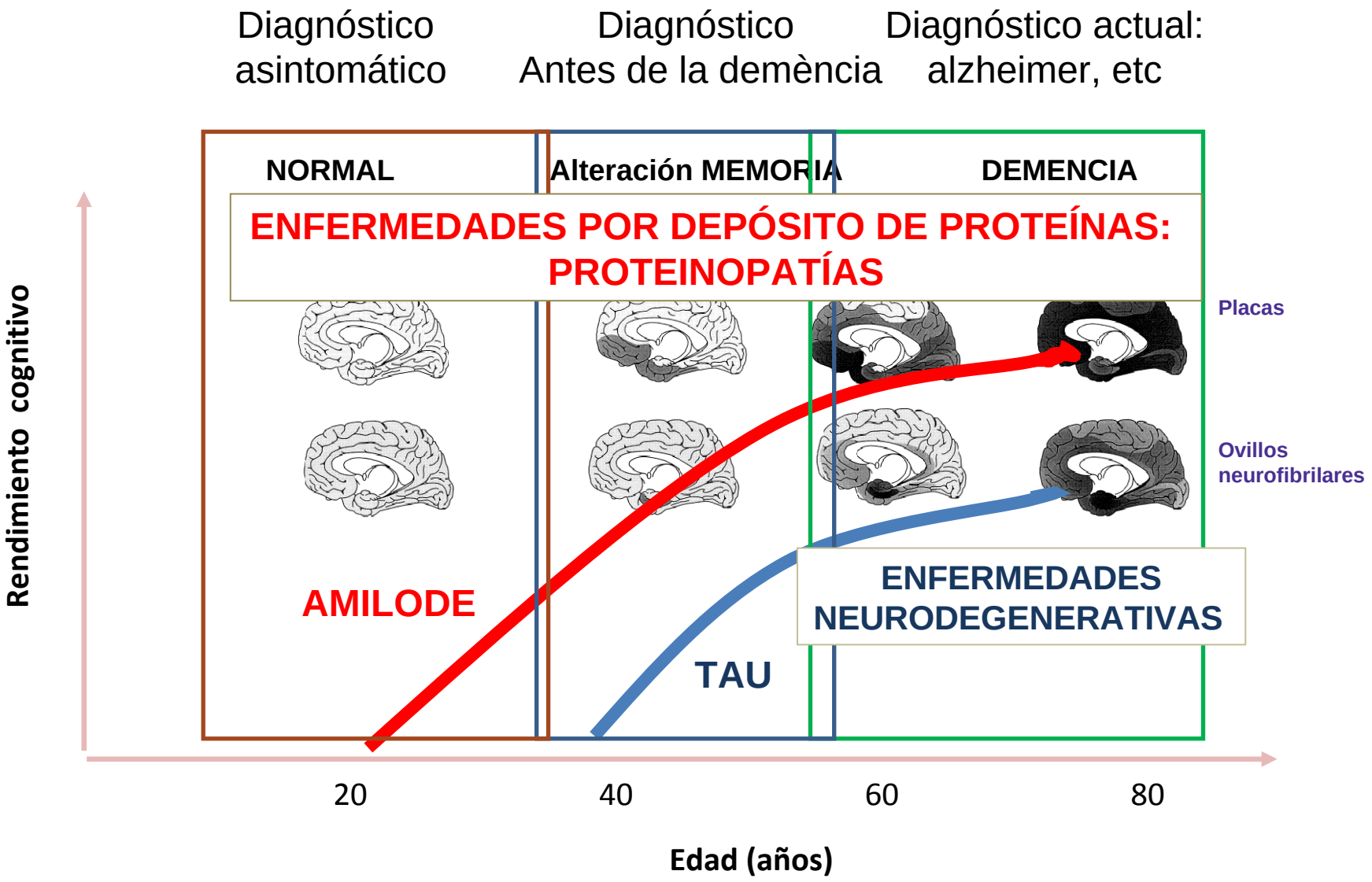


Atrofia del tronco cerebral y cerebral: **Parkinson - Enfermedad con Cuerpos de Lewy**

α-SNUCLEINA

Diagnóstico




Diagnóstico asintomático
Diagnóstico Antes de la demència
Diagnóstico actual: alzheimer, etc
NORMAL
Alteración MEMORIA
DEMENCIA
ENFERMEDADES POR DEPÓSITO DE PROTEÍNAS: PROTEINOPATÍAS
Placas
Ovillos neurofibrilares
AMILODE
TAU
ENFERMEDADES NEURODEGENERATIVAS
Rendimiento cognitivo
20
40
60
80
Edad (años)

Ahora diagnosticamos de alzheimer a los que tienen demencia, ¿podremos diagnosticar de alzheimer en etapas asintomáticas?

New research diagnostic criteria for AD

1 major criterion

A. An episodic memory disorder

- Progressive change in memory function (patient or informant)
- Evidence of a recall deficit that does not normalize with cueing
- Deficit isolated or associated with other cognitive changes

+1 or more minor criteria

B. Structural: atrophy of medial temporal lobe (MRI)

or

C. Biochemical: changes in biomarkers (CSF)

or

D. Functional: neuroimaging pattern on PET or SPECT

or

E. Genetic: autosomal dominant mutation in immediate family

Dubois B, et al. *Lancet Neurol* 2007;6:734–46

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Archives
of
CLINICAL
NEUROPSYCHOLOGY

Archives of Clinical Neuropsychology Advance Access published June 23, 2009

Spanish Multicenter Normative Studies (NEURONORMA Project): Methods and Sample Characteristics

Jordi Peña-Casanova[a,b,*], Rafael Blesa[c], Miquel Aguilar[d], Nina Gramunt-Fombuena[b], Beatriz Gómez-Ansón[e], Rafael Oliva[f], José Luis Molinuevo[g], Alfredo Robles[h], María Sagrario Barquero[i,†], Carmen Antúnez[j], Carlos Martínez-Parra[k], Anna Frank-García[l], Manuel Fernández[m], Verónica Alfonso[n], Josep M. Sol[n], for the NEURONORMA Study Team

[a]*Section of Behavioral Neurology and Dementias, Hospital del Mar, Barcelona, Spain*
[b]*Behavioral Neurology Group, Institut Municipal d'Investigació Mèdica, Barcelona, Spain*

Archives of Clinical Neuropsychology Advance Access published August 1, 2009

Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for Boston Naming Test and Token Test

Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for the Visual Object and Space Perception Battery-Abbreviated, and Judgment of Line Orientation

Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for Verbal Fluency Tests

Archives of Clinical Neuropsychology Advance Access published August 5, 2009

Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for Verbal Span, Visuospatial Span, Letter and Number Sequencing, Trail Making Test, and Symbol Digit Modalities Test

Archives of Clinical Neuropsychology Advance Access published August 6, 2009

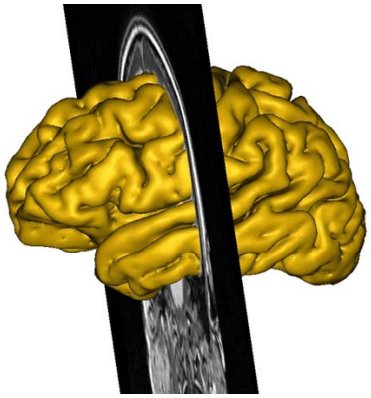
Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for the Rey–Osterrieth Complex Figure (Copy and Memory), and Free and Cued Selective Reminding Test

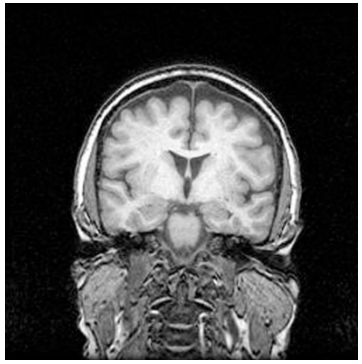
Spanish Multicenter Normative Studies (NEURONORMA Project): Norms for the Stroop Color-Word Interference Test and the Tower of London-Drexel

RM

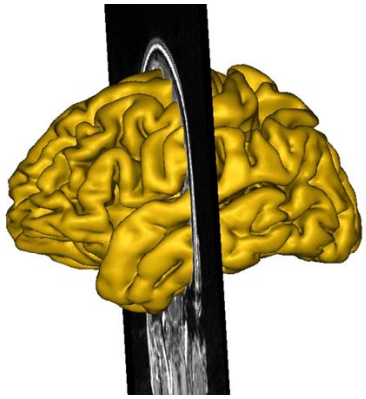
MRIs: Hippocampal Atrophy in AD

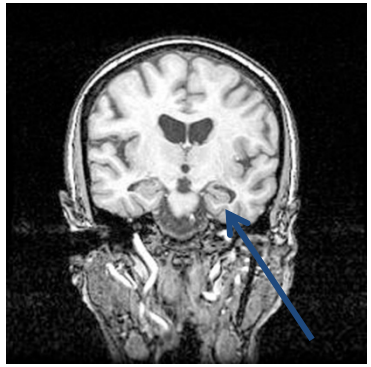
Normal



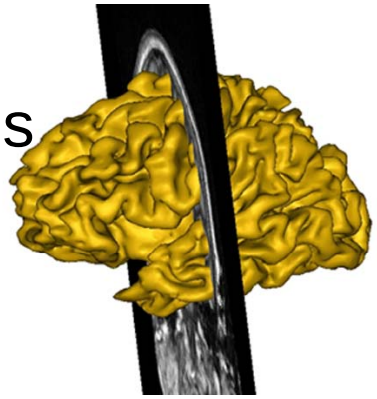


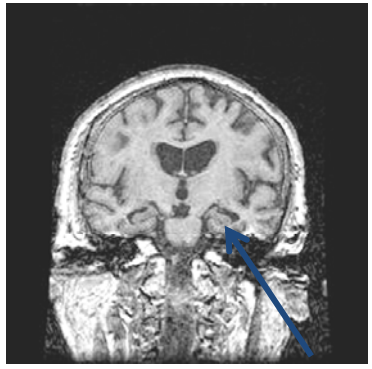
Mild Atrophy





Alzheimer's Disease



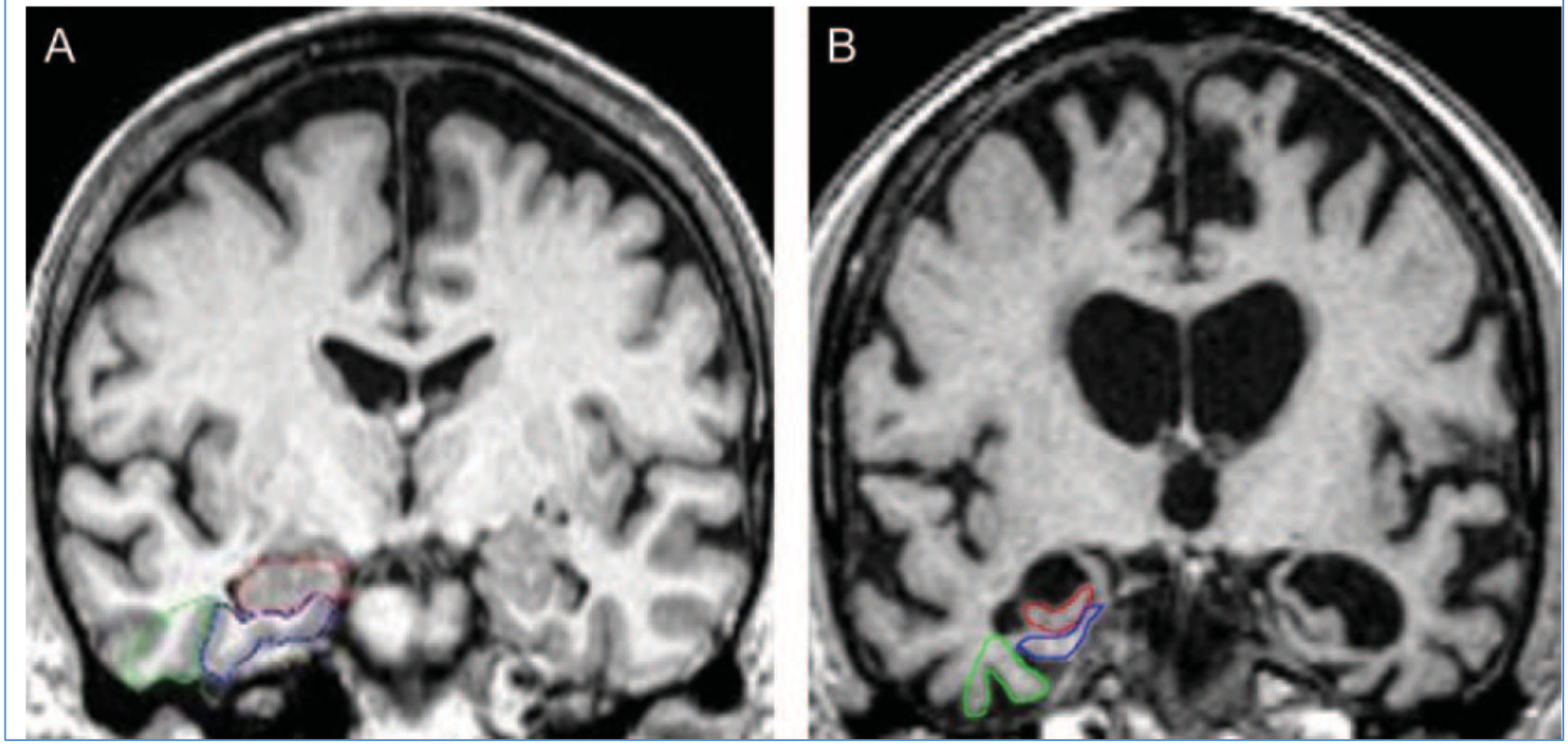


Good correlation with neurofibrillary pathology in aging and dementia

Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease

Duara R, et al. *Neurology 2008;71:1986–1992*

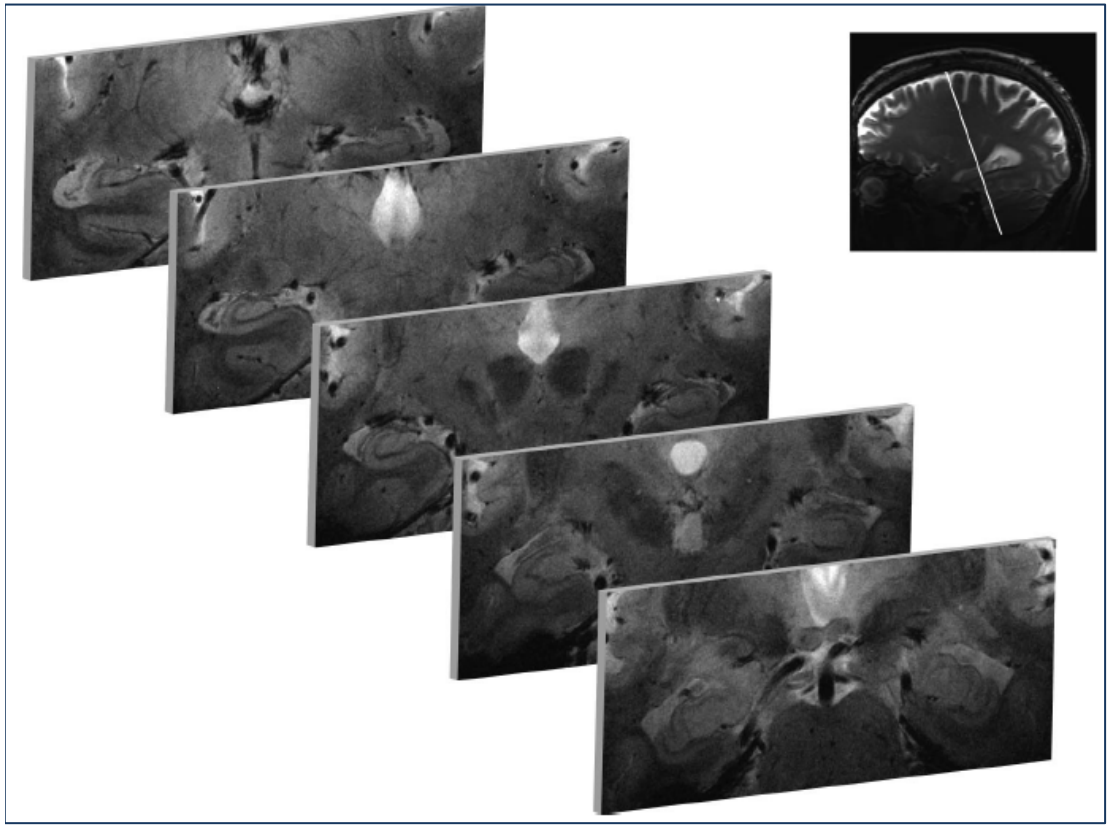
Figure 1 Visual rating system for assessing medial temporal atrophy

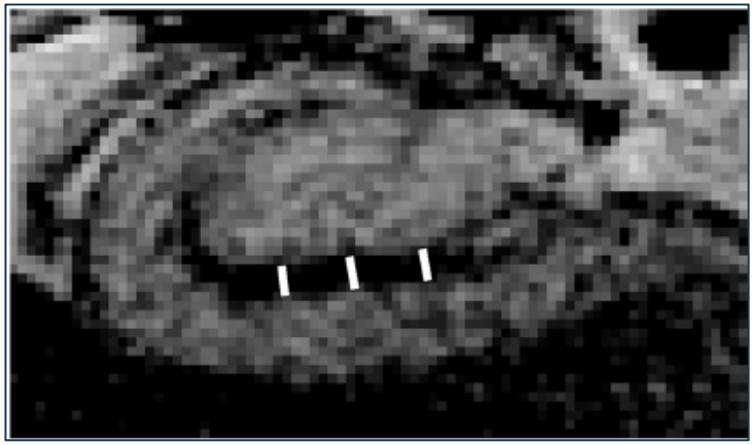


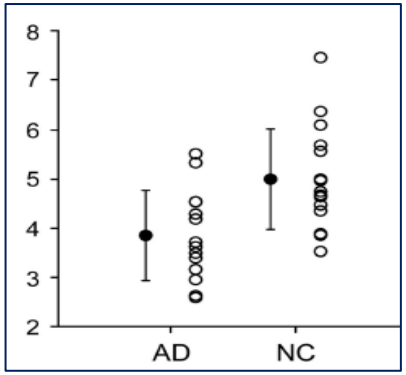
Medial temporal lobe atrophy scores distinguish probable Alzheimer disease and amnestic mild cognitive impairment subjects from nonamnestic MCI and no cognitive impairment subjects.

Hippocampal CA1 apical neuropil atrophy in mild Alzheimer disease visualized with 7-T MRI

G.A. Kerchner, **Neurology 2010**;75:1381–1387

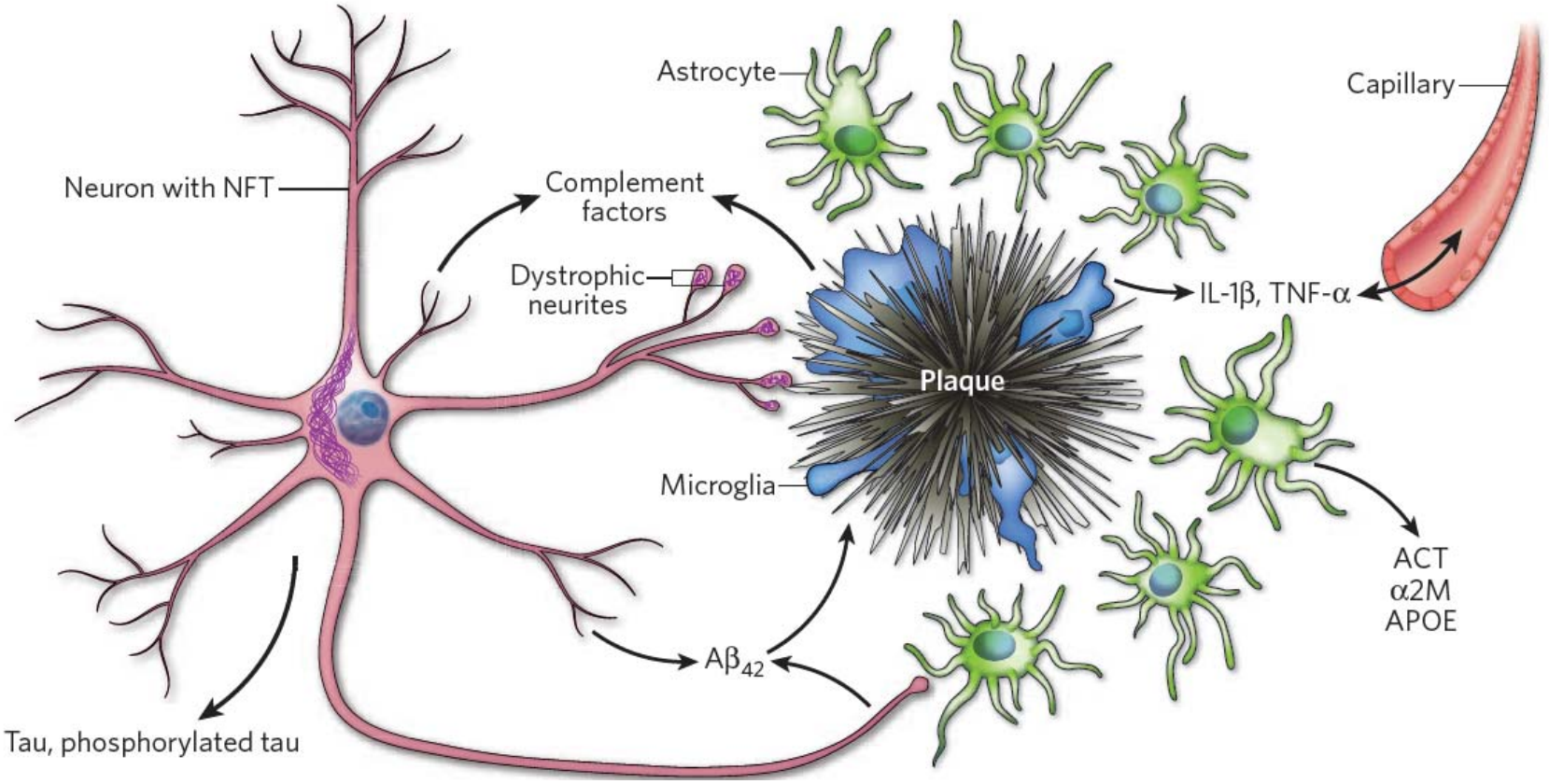


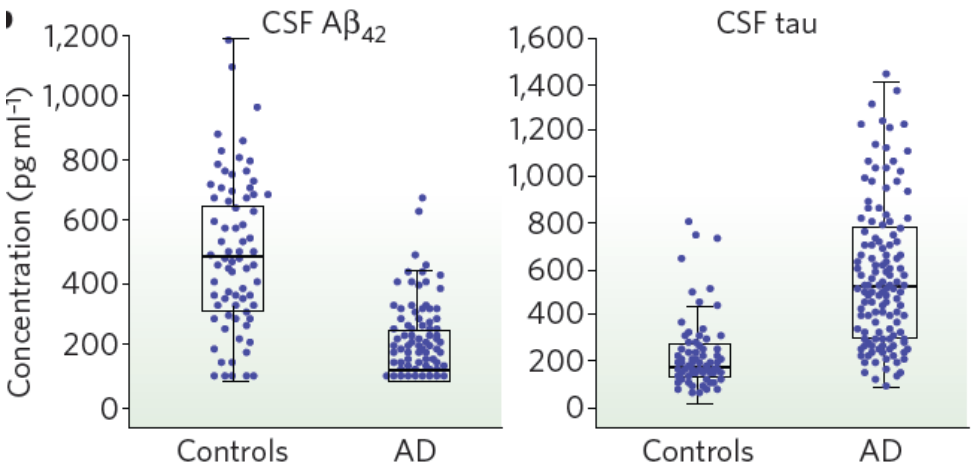


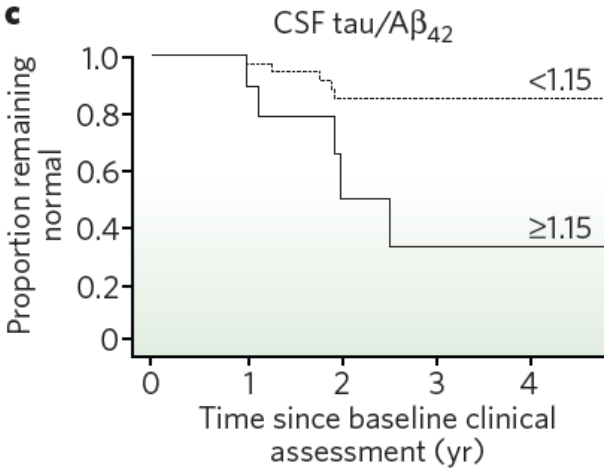


CA1 apical neuropil atrophy is apparent in patients with mild AD. With its superior spatial resolution, 7-T MRI permits in vivo analysis of a very focal, early site of AD pathology.

Richard J. Perrin et al. **NATURE** |Vol 461|15 **October 2009|**



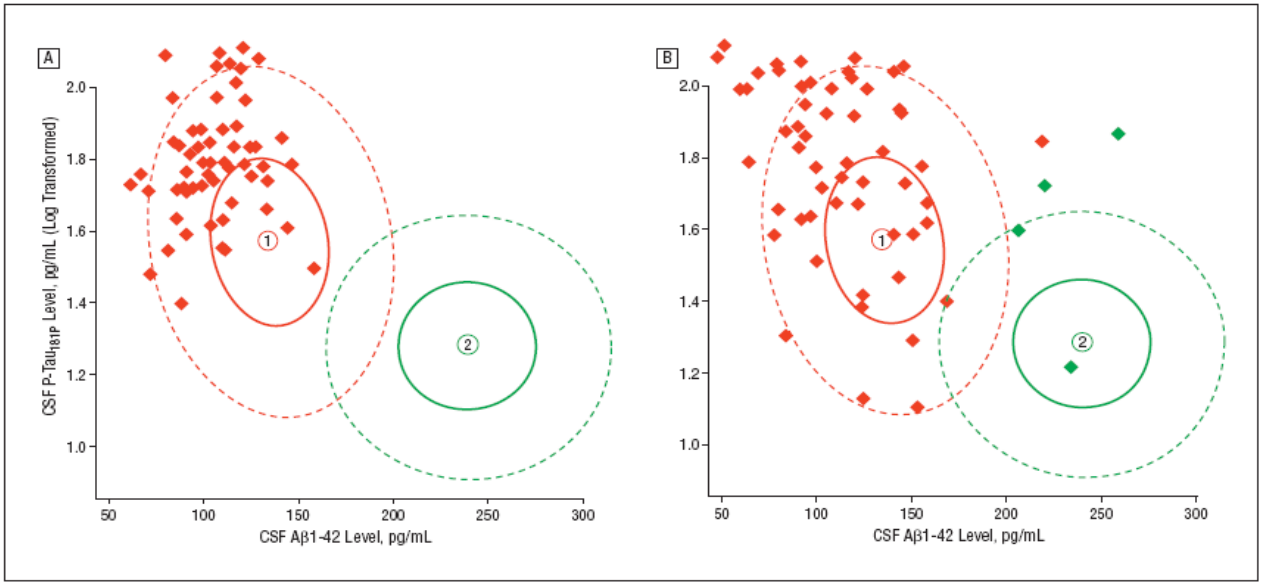




Diagnosis-Independent Alzheimer Disease Biomarker Signature in Cognitively Normal Elderly People

De Meyer G et al. **Arch Neurol**. 2010;67(8):949-956

Validation of the combined cerebrospinal fluid–derived -amyloid protein 1-42 (CSF A1-42)/CSF phosphorylated tau181P (CSF P-Tau181P) mixture model in 2 data sets.



Alzheimer disease signature(red)

Healthy signature (green).

A, Patients with mild cognitive impairment who developed Alzheimer disease within 5 years after the CSF sample

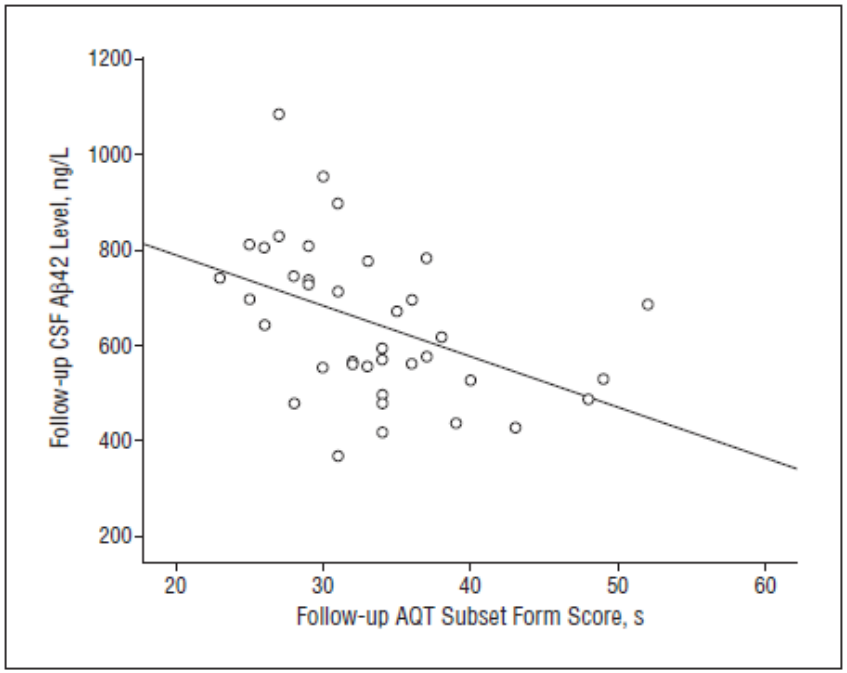
B, Patients with autopsy-confirmed Alzheimer disease with mostly less than 1 year between CSF sample and autopsy (n=68).

Conclusions: The mixture modeling approach, totally independent of clinical AD diagnosis, correctly classified patients with AD. The unexpected presence of the AD signature in more than one-third of cognitively normal subjects suggests that AD pathology is active and detectable earlier than has heretofore been envisioned.

Correlation of Longitudinal Cerebrospinal Fluid Biomarkers With Cognitive Decline in Healthy Older Adults

Erik Stomrud, ***Arch Neurol****. 2010;67(2):217-223*

Distribution of follow-up scores on A Quick Test of Cognitive Speed subset form (AQT Subset Form) in relation to follow-up cerebrospinal fluid - amyloid1-42 protein (CSF A42)



In this group of healthy older adults, changes in CSF biomarker levels previously associated with Alzheimer disease correlated with a decline in cognitive functions. Changes in CSF biomarker levels may identify early neurodegenerative processes of Alzheimer disease.

Increased Brain Atrophy Rates in Cognitively Normal Older Adults with Low Cerebrospinal Fluid Ab1-42

Schott JM et al. **ANN NEUROL** 2010;68:825–834

- **Objective:**

  To identify cognitively normal individuals at risk of Alzheimer disease (AD) based on cerebrospinal fluid (CSF) Ab1-42, and to determine rates of cerebral atrophy.

- **Methods:**

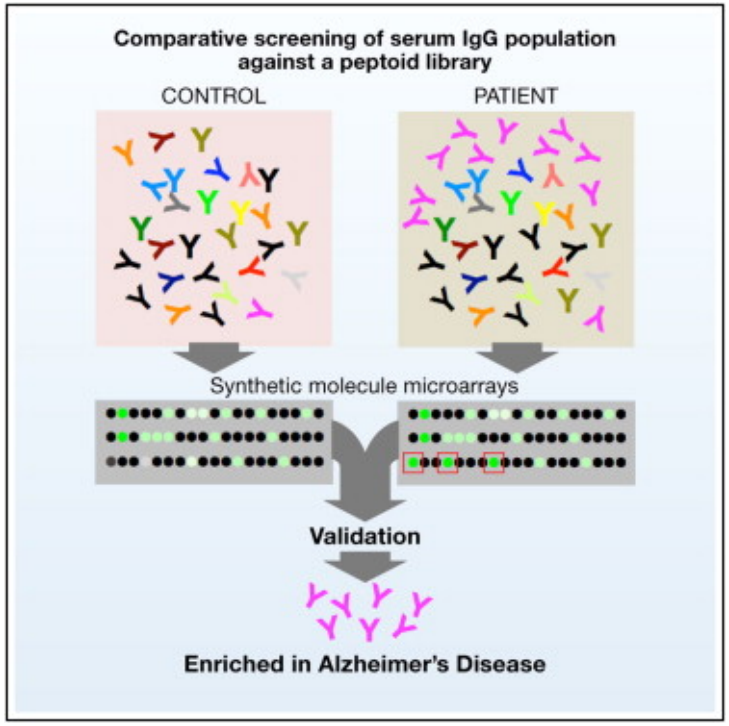
  Control subjects were dichotomized on CSF Ab1-42: NC-high >192pg/ml; NC-low 192pg/ml

- **Results:**
  - 40/105 (38%) were classified as NC-low, and 65 (62%) as NC-high, age, gender, brain volumes, and cognitive score
  - The NC-low group had higher tau and p-tau and was more likely to be APOE4 positive (48% vs 11%.)
  - The Nclow group had significantly higher whole brain loss, ventricular expansion and hippocampal atrophy rate
  - Baseline Ab1-42 level was strongly correlated with rate of brain atrophy only in the NC-low group.

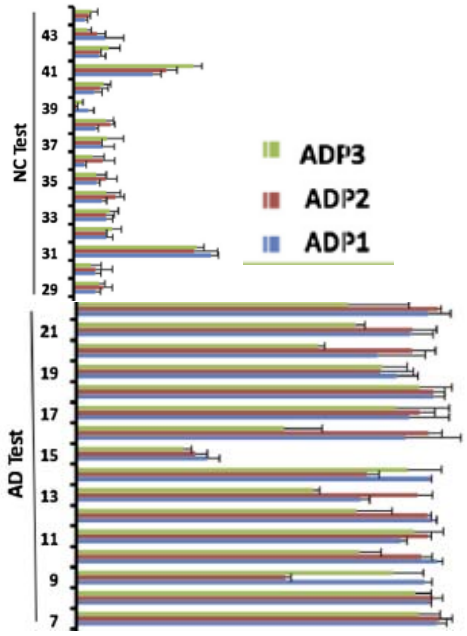
A significant percentage of healthy older adults have CSF profiles consistent with AD and increased rates of brain atrophy, suggesting that they may be in the earliest stages of neurodegeneration. Brain atrophy may be a feasible outcome measure for AD prevention studies.

Identification of Candidate IgG Biomarkers for Alzheimer's Disease via Combinatorial Library Screening

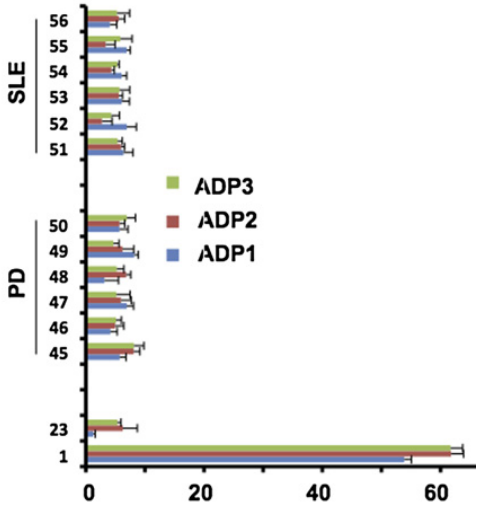
Muralidhar Reddy M et al., **Cell** January 7, 2011; 144, 132–142



Peptoids that Retain Antibodies from the Serum of Patients with AD



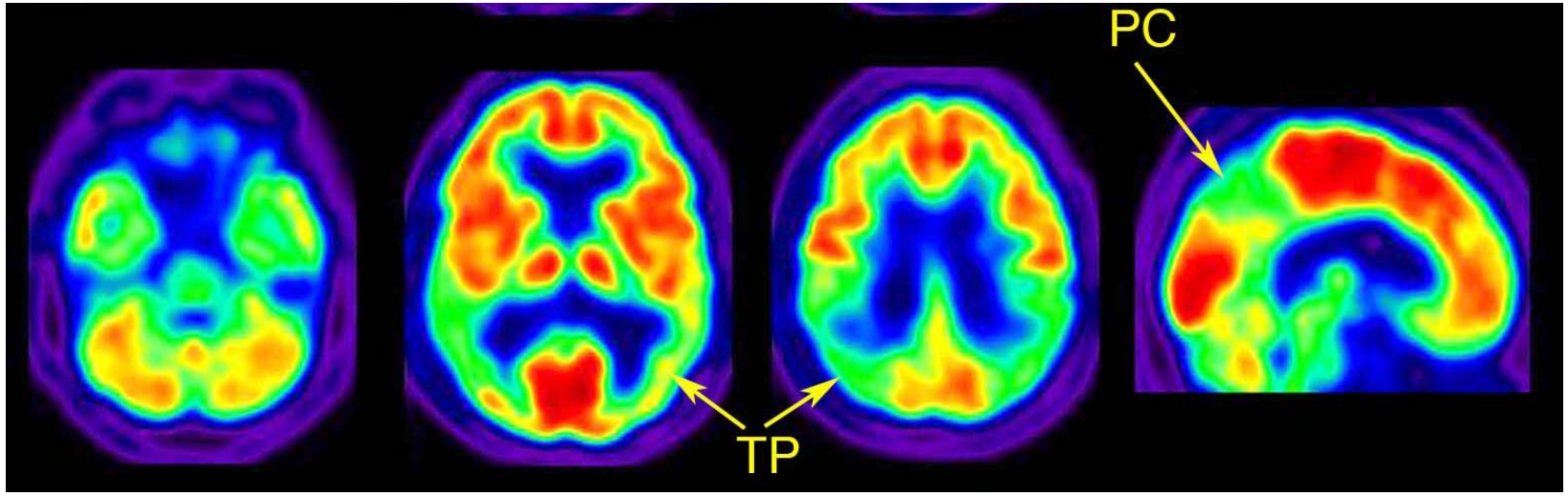
Peptoids ADP1–3 Bind Two Different Antibodies that Are Present in the Serum of Patients with Alzheimer's Disease, but Not Patients with PD or Lupus



Molecules that retain far more IgG antibodies from the case samples than the controls are identified and subsequently tested as capture agents for diagnostically useful antibodies. The utility of this method is demonstrated using a mouse model for multiple sclerosis and via the identification of two candidate IgG biomarkers for Alzheimer's disease.

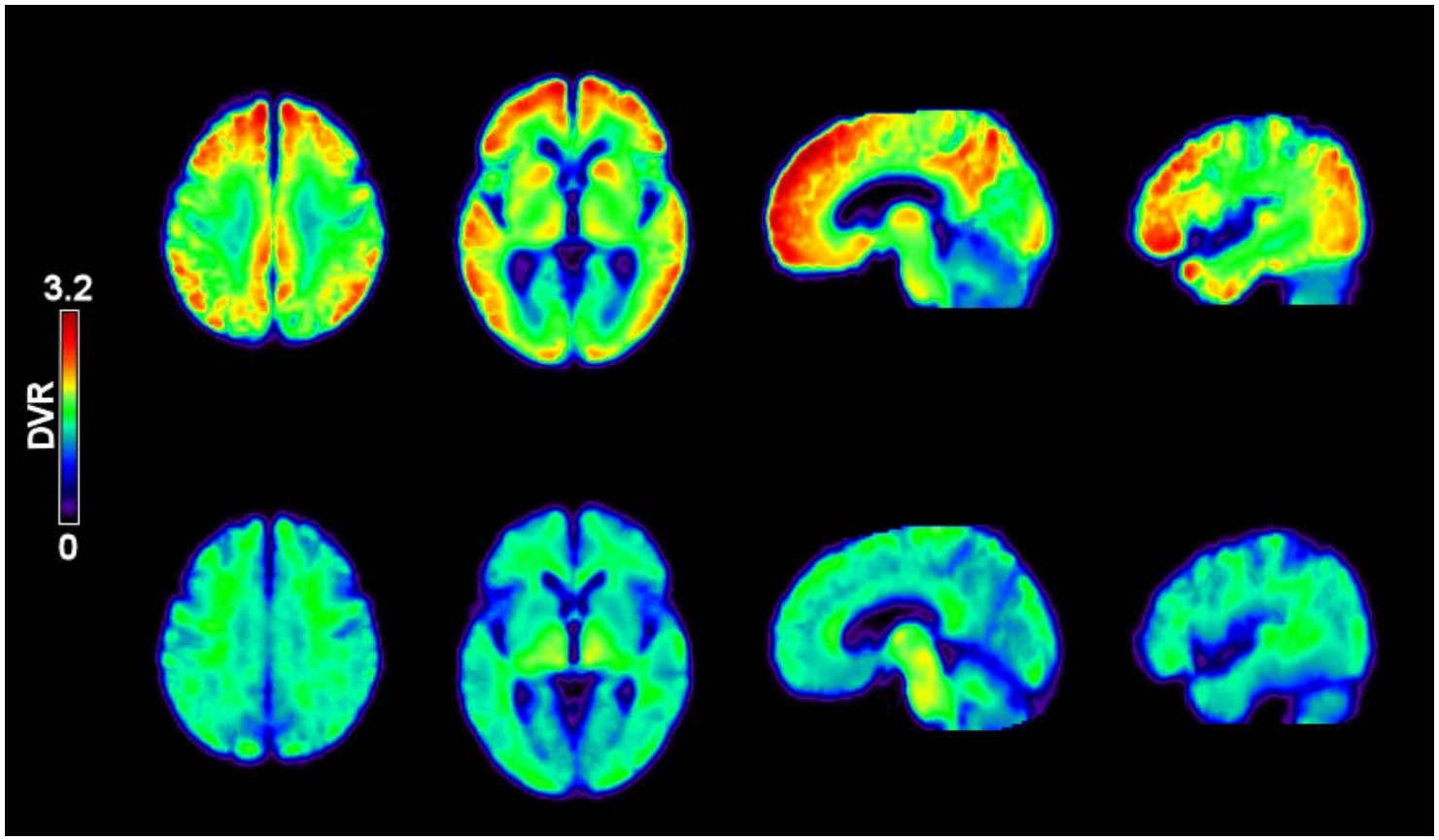
PET (tomografía por emisón de positrones)

FDG-PET in Alzheimer's Disease



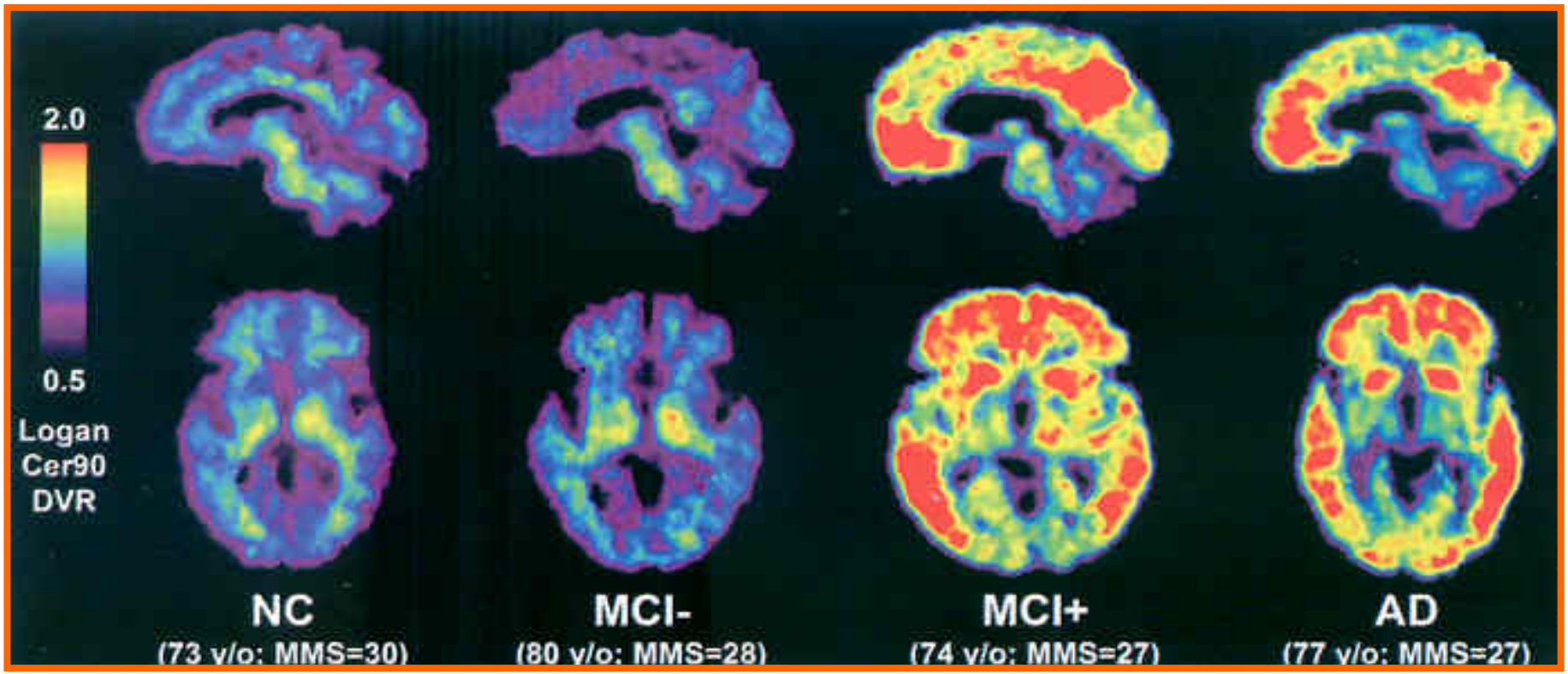
Hypometabolism in TP = Temporoparietal cortex,
PC = posterior cingulate/precuneus

PIB in AD and Normal Aging



AD

Normal Aging

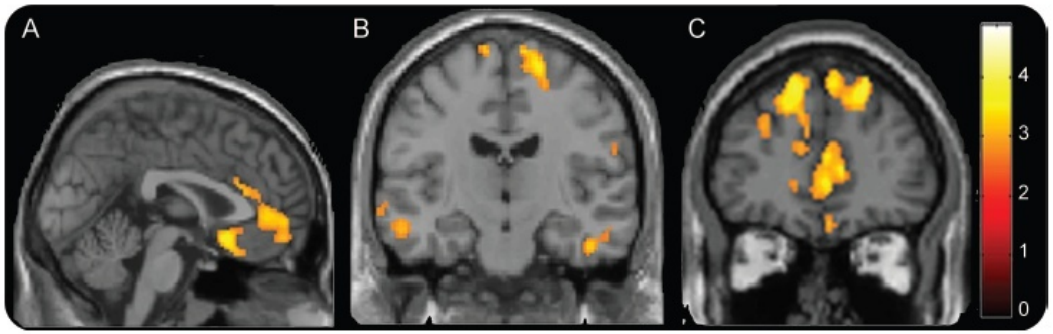


Blennow K, Zetterberg H. Nat Medicine 2006;12:753

Conversion of amyloid positive and negative MCI to AD over 3 years. An 11C-PIB PET study

Okello, A, et al. Neurology 2009 early ed

31 MCI with 11C-PIB PET, MRI, and neuropsychometry have been clinically followed up for 1 to 3 years.

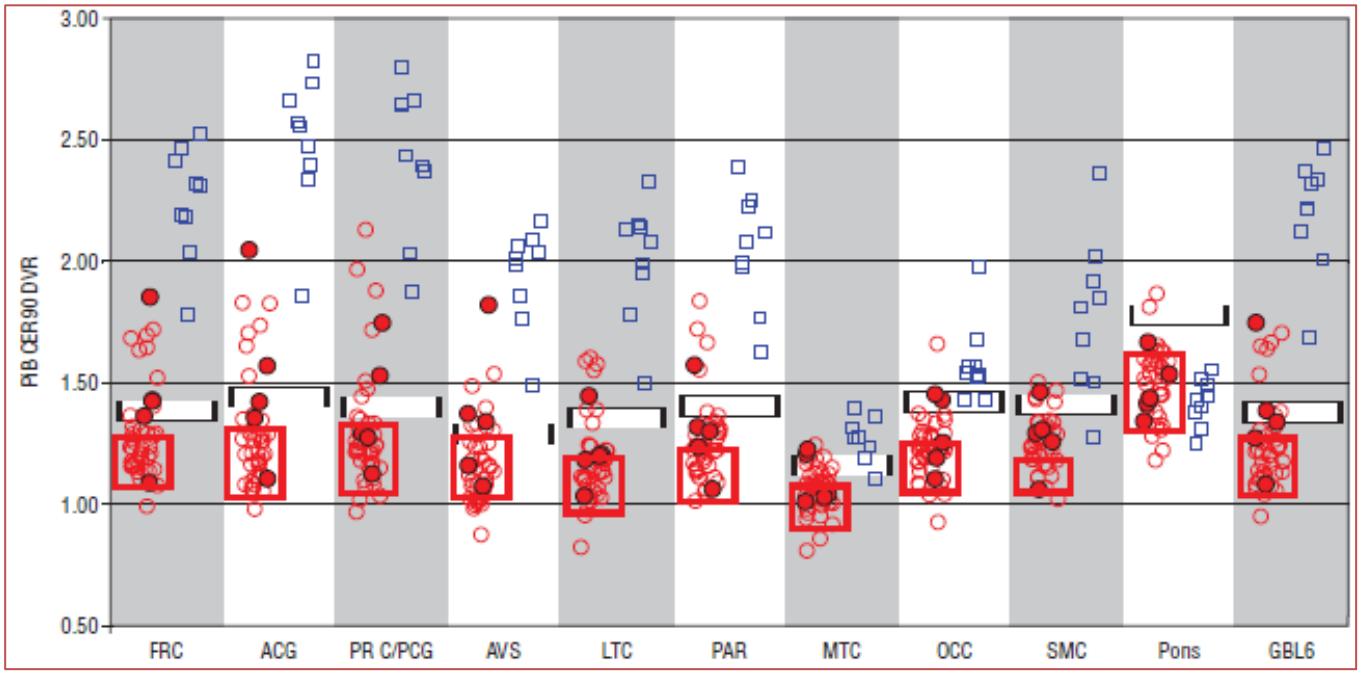


1. **55% with MCI had increased 11C-PIB retention at baseline and 82% clinically converted to AD during follow-up.**
2. **Only one PIB negative MCI cases converted to AD.**
3. **PIB-positive MCI, 47% converted to AD within 1 year of baseline PIB PET,**

Frequent Amyloid Deposition Without Significant Cognitive Impairment Among the Elderly

Aizenstein HJ et al. Arch Neurol. 2008;65(11):1509-1517

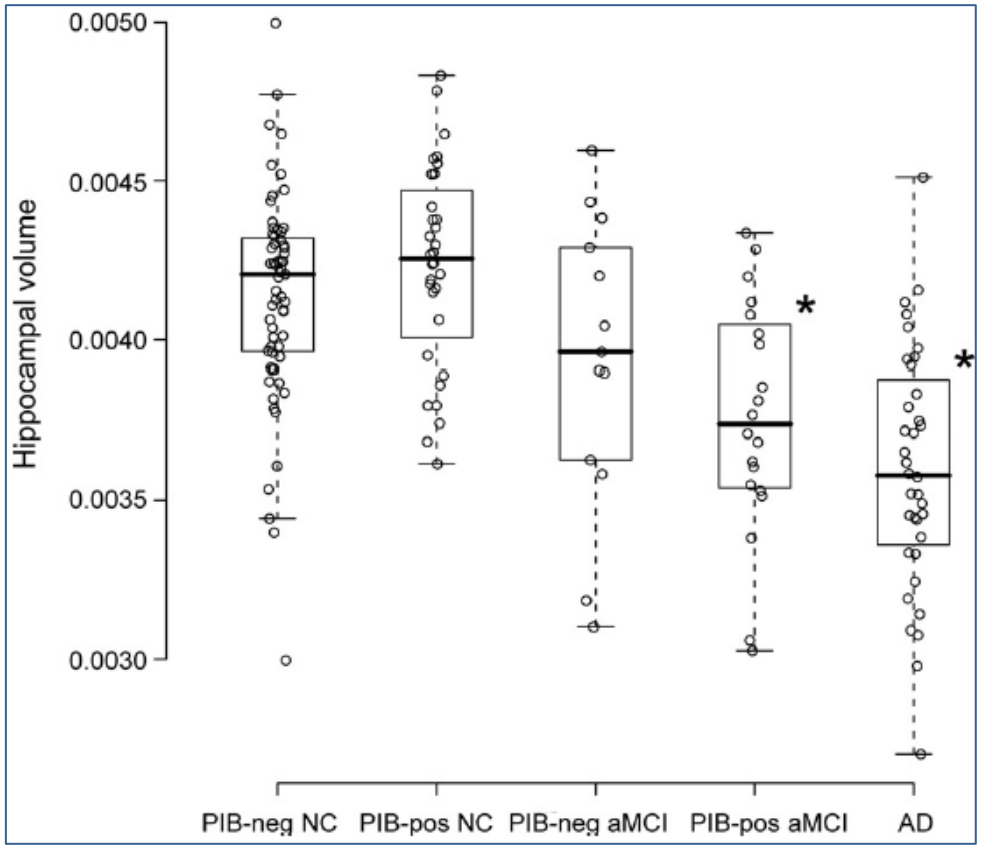
Of 43 clinically unimpaired elderly persons imaged, 9 (21%) showed evidence of early amyloid deposition in at least 1 brain area



Amyloid can be identified among cognitively normal elderly and the prevalence of asymptomatic amyloid may be similar to that of symptomatic amyloid deposition.

Amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia

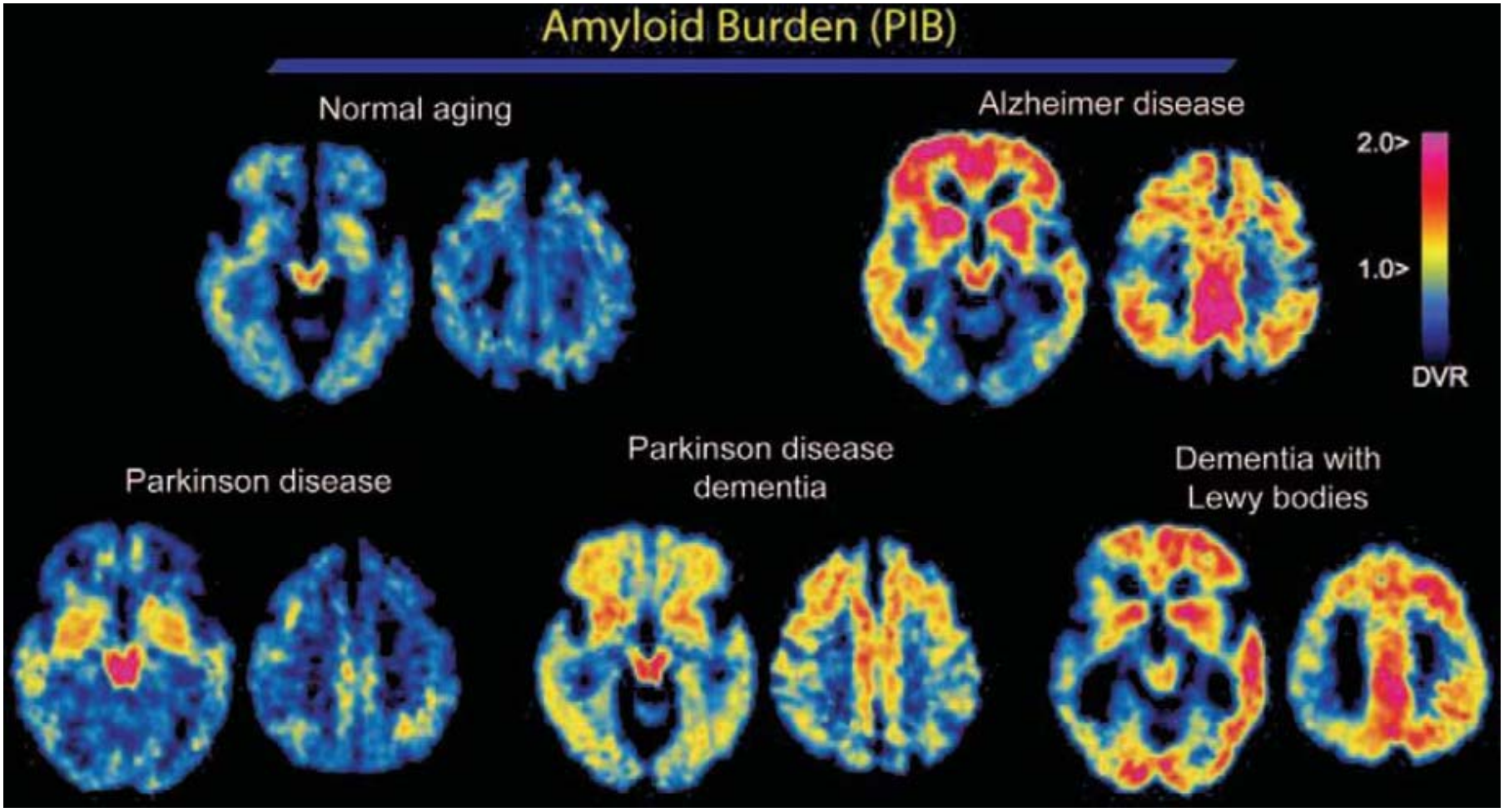
Bourgeat P et al. **Neurology** 2010;74:121–127



The strong correlation between hippocampal atrophy and -amyloid (A) burden in the Pittsburgh compound B–positive healthy control group suggests that A deposition in the inferior temporal neocortex is related to hippocampal synaptic and neuronal degeneration

Imaging amyloid deposition in Lewy body diseases

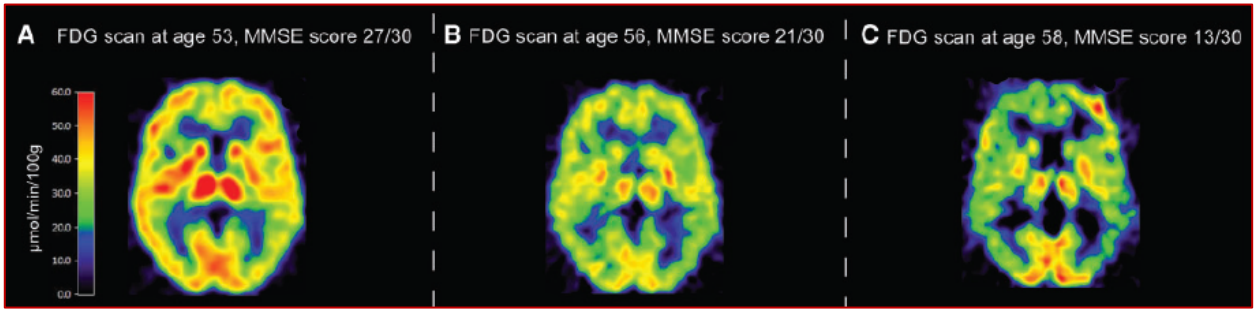
Gomperts S, et al. *Neurology 2008;71:903–910*

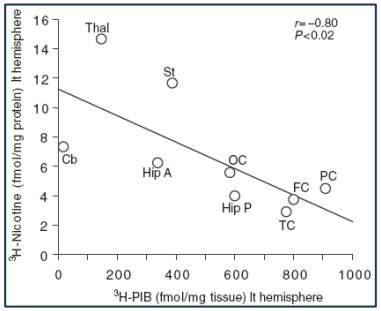


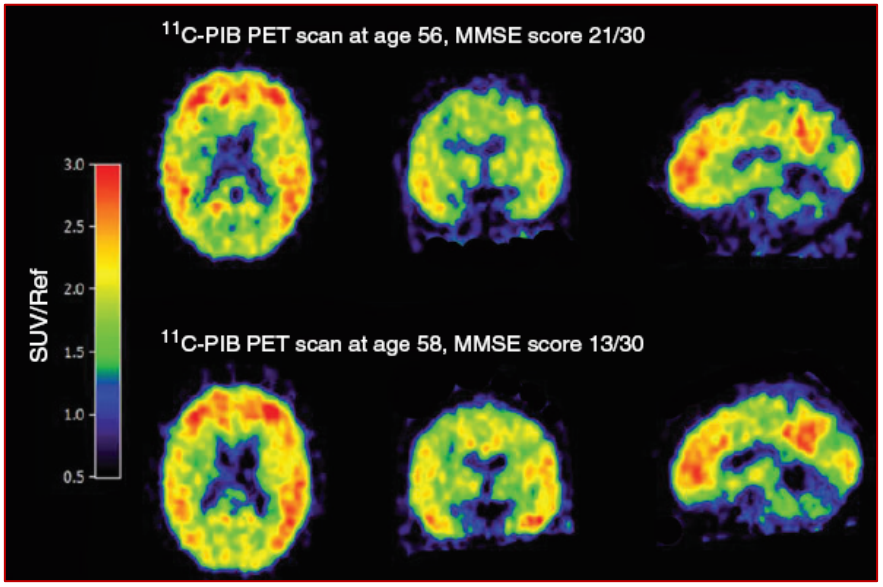
Global cortical amyloid burden is high in dementia with Lewy bodies (DLB) but low in Parkinson disease dementia.

PET imaging and clinical progression in relation to molecular pathology in the first Pittsburgh Compound B PET patient with Alzheimer's disease

Kadir A et al., **Brain** 2011: 134; 301–317





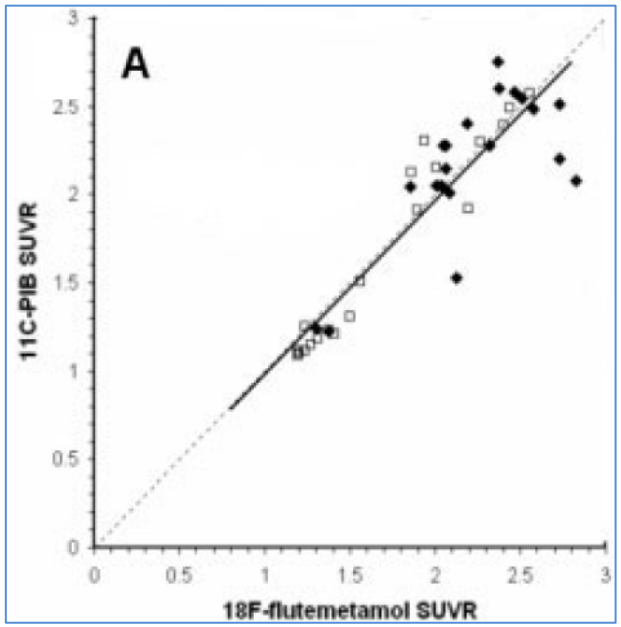


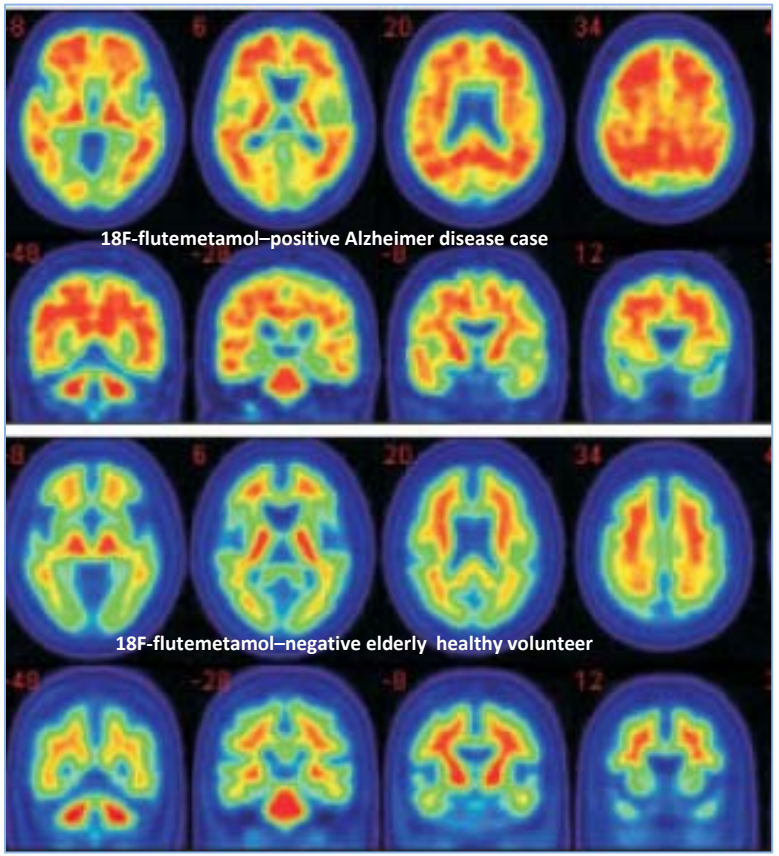
High 11C-PIB PET retention significantly correlates with both fibrillar b-amyloid and losses of neuronal nicotinic acetylcholine receptor subtypes at autopsy, suggesting a involvement of b-amyloid pathology with neuronal nicotinic acetylcholine receptor subtypes

18F-Flutemetamol Amyloid Imaging in Alzheimer Disease and Mild Cognitive Impairment. A Phase 2 Trial

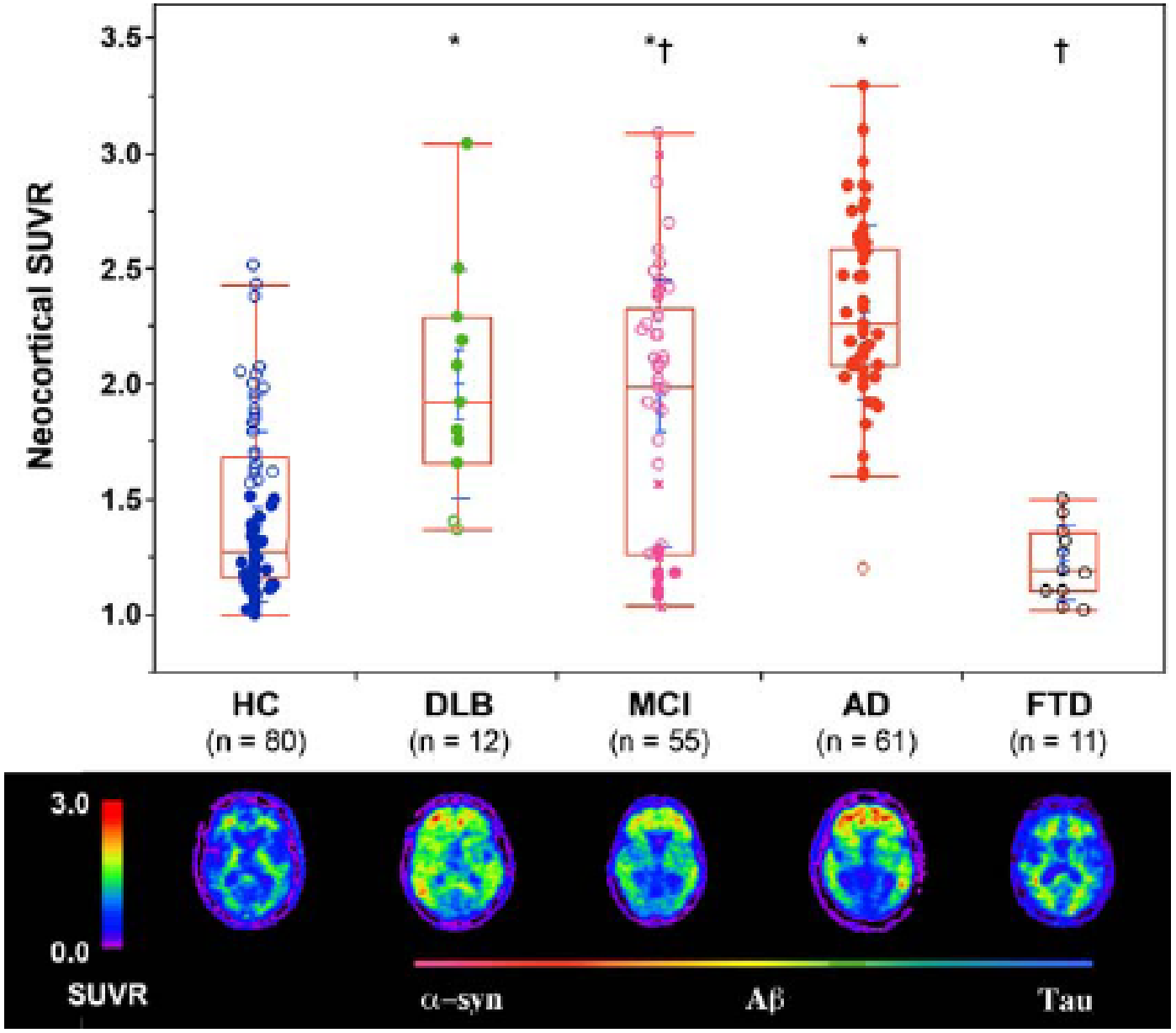
Vandenberghe R, et al. **ANN NEUROL** 2010; Published DOI: 10.1002/ana.22068

Correlation between 18F-flutemetamol and 11C-PIB from 20 AD and 20 MCI subjects.



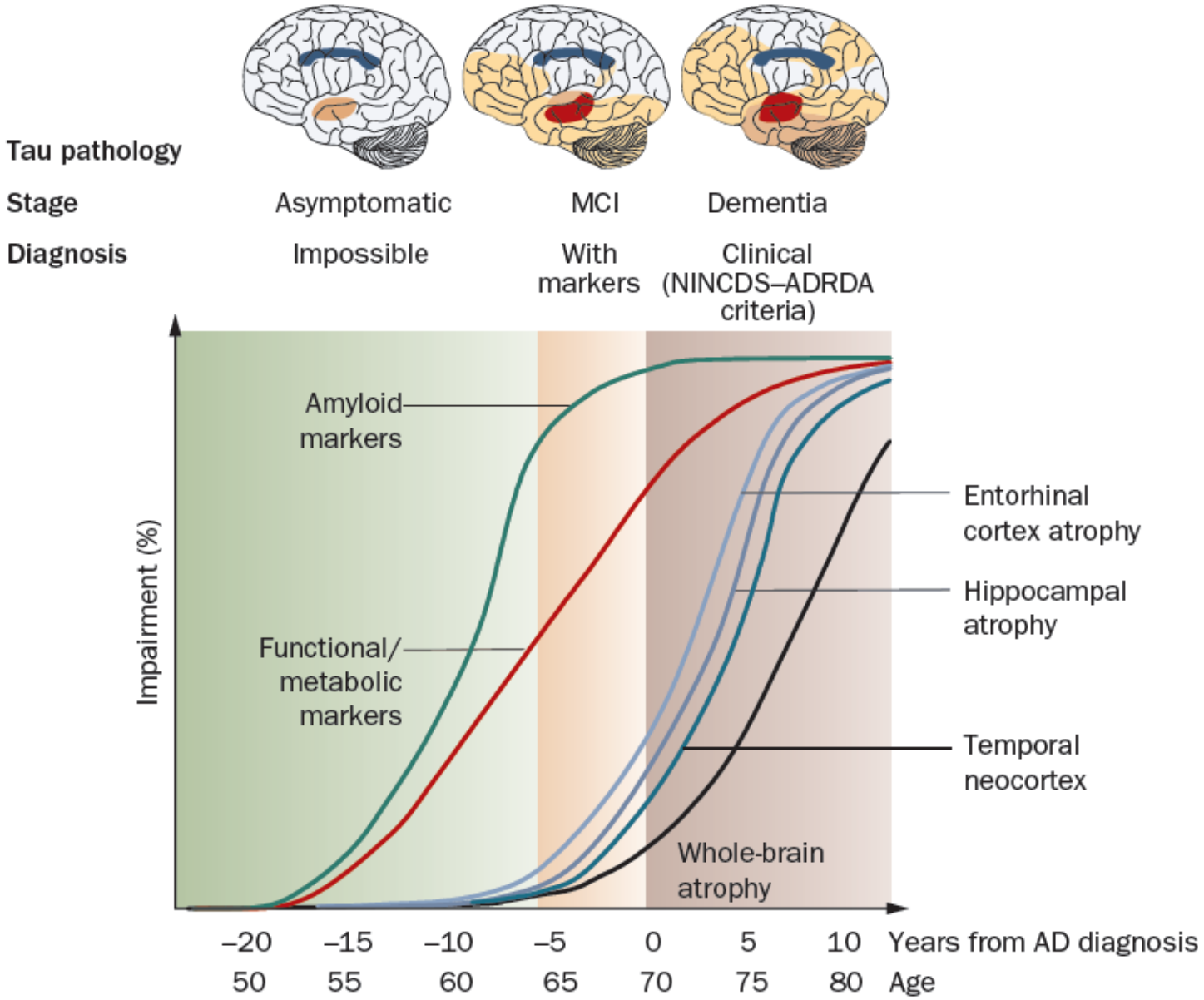


18F-Flutemetamol performs similarly to the 11C-PIB parent molecule within the same subjects and provides high test-retest replicability and potentially much wider accessibility for clinical and research use.



Villemagne VL et al. Mol Neurobiol (2008) 38:1–15

Frisoni, G. B. *et al.* ***Nat. Rev. Neurol.*** 6, 67–77 (2010)



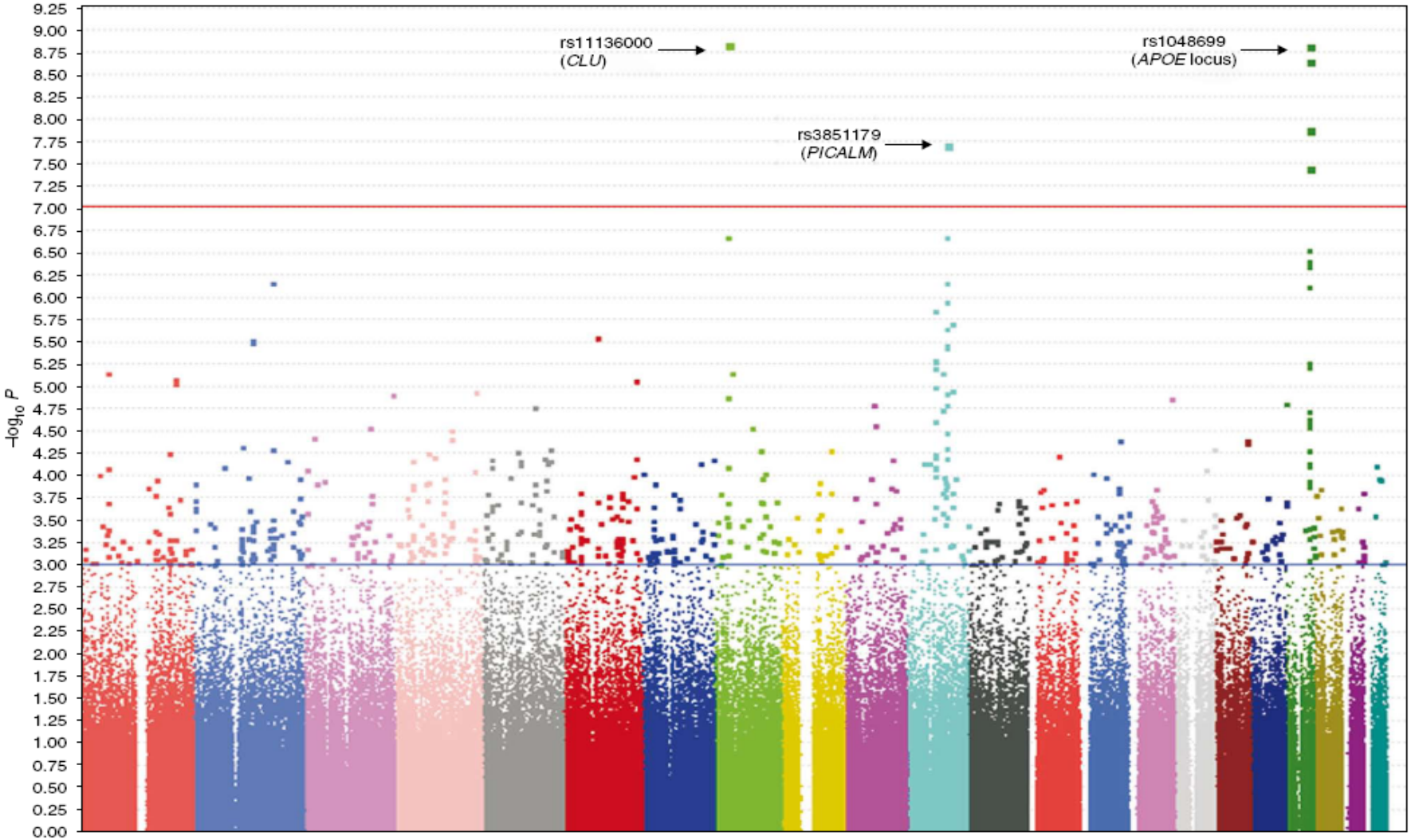

Genética

Confirmed Genetic Variants Associated With Alzheimer's Disease

chromosome	***gene***	***age-at-onset***	***pattern***	***variants***
ch21q21.3	*APP*	30 to 60	AD	20 mutations
ch14q24.13	*PSEN1*	30 to 50	AD	>150 mutations
ch1q31.42	*PSEN2*	50 to 70	AD	12 mutations
ch19q13.2	*APOE*	50 to 80+	familial/sporadic	3 isoforms
ch11q23.3	*SORL1*	LOAD	familial/sporadic	2 haplotypes

Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease

Harold D et al, Nature GeNetics, 6 September 2009; doi:10.1038/ng.440



Meta-analysis Confirms *CR1, CLU, and PICALM* as Alzheimer Disease Risk Loci and Reveals Interactions With *APOE Genotypes*

Gyungah Jun, PhD; Adam C. Naj, PhD; Gary W. Beecham, PhD; Li-San Wang, PhD; Jacqueline Buros, BS; Paul J. Gallins, MS; Joseph D. Buxbaum, PhD; Nilufer Ertekin-Taner, MD, PhD; M. Daniele Fallin, PhD; Robert Friedland, MD; Rivka Inzelberg, MD; Patricia Kramer, PhD; Ekaterina Rogaeva, PhD; Peter St. George-Hyslop, MD, FRCP; Alzheimer's Disease Genetics Consortium; Laura B. Cantwell, MPH; Beth A. Dombroski, PhD; Andrew J. Saykin, PsyD; Eric M. Reiman, MD; David A. Bennett, MD; John C. Morris, MD; Kathryn L. Lunetta, PhD; Eden R. Martin, PhD; Thomas J. Montine, MD, PhD; Alison M. Goate, DPhil; Deborah Blacker, MD; Debby W. Tsuang, MD; Duane Beekly, BS; L. Adrienne Cupples, PhD; Hakon Hakonarson, MD, PhD; Walter Kukull, PhD; Tatiana M. Foroud, PhD; Jonathan Haines, PhD; Richard Mayeux, MD; Lindsay A. Farrer, PhD; Margaret A. Pericak-Vance, PhD; Gerard D. Schellenberg, PhD

***Arch Neurol**. 2010;67(12):1473-1484.*

- 7.070 cases with AD, 3055 with autopsies
- 8169 elderly cognitively normal controls, 1092 with autopsies,
- from 12 different studies, including white, African American, Israeli-Arab, and Caribbean Hispanic individuals.

CR1, CLU, and PICALM are AD susceptibility loci in European ancestry populations. Genotypes at PICALM confer risk predominantly in APOE ε4–positive subjects. Thus, APOE and PICALM synergistically interact.

A Megalin Polymorphism Associated With Promoter Activity and Alzheimer's Disease Risk

Vargas T et al. **Am J Med Genet Part B,** 2010 153B:895–902

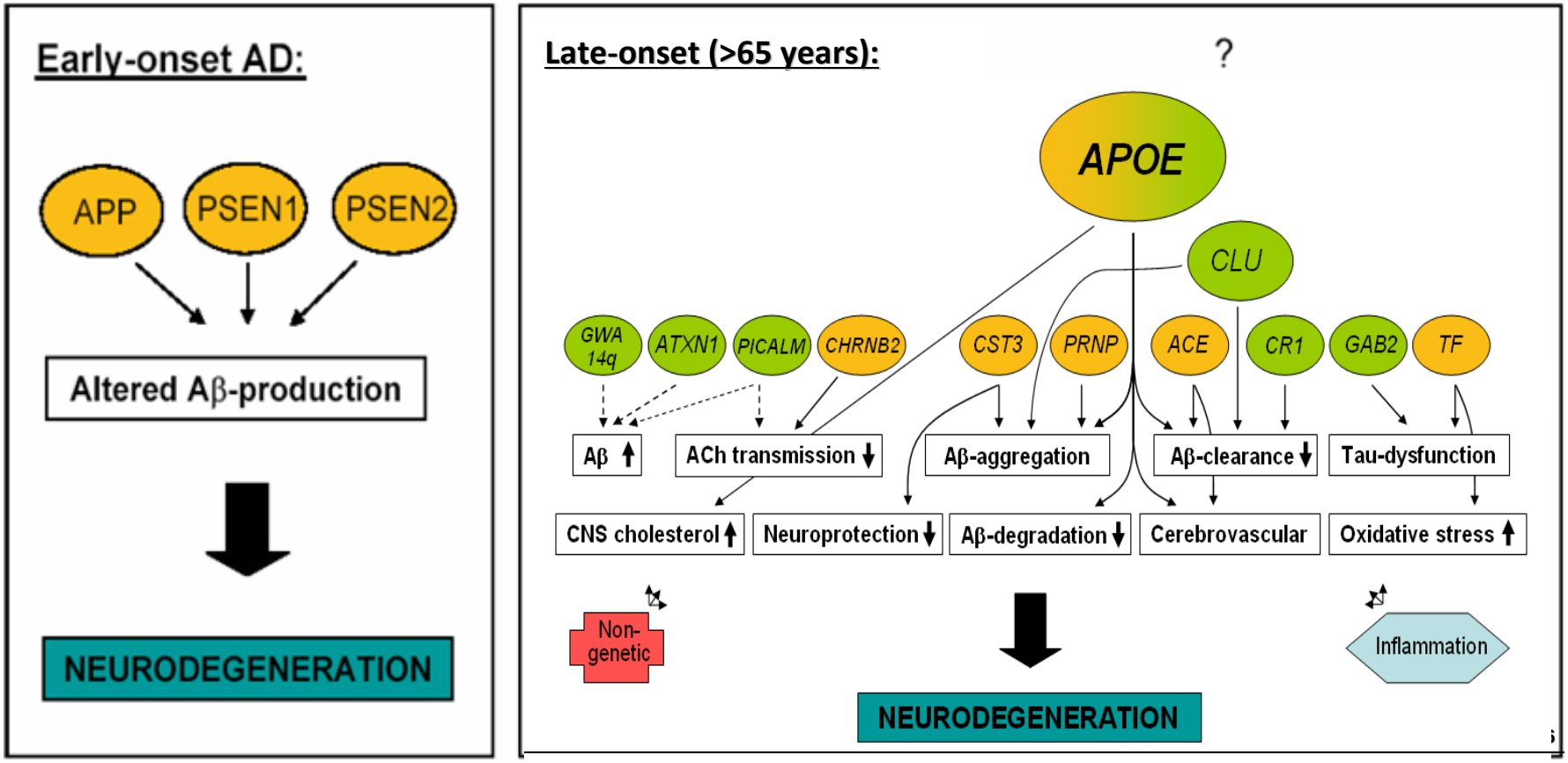
rs3755166 (G/A) polymorphismin the megalin promoter is associated with AD, and that this association is more evident in the absence of the APOE e4 allele.

		Megalin rs3755166 (G/A)[b]				Crude odds ratio[d]		Adjusted odds ratio[e]	
	n[a]	GG	GA	AA	χ^c	OR (95% CI)	*P*	OR (95% CI)	*P*
Test sample									
APOE									
No *E4* alleles									
Cases	574	0.37	0.46	0.17	0.06	1.38 (1.1–1.9)	0.03	1.41 (1.1–1.9)	0.03
Controls	864	0.38	0.49	0.13					
At least one E4 allele									
Cases	584	0.38	0.46	0.16	ns	1.01 (0.6–1.6)	ns	1.06 (0.7–1.7)	ns
Controls	161	0.34	0.50	0.16					

ns, no significant

This study provides strong evidence that this megalin polymorphism confers a greater risk for AD, and supports a biological role for megalin in the neurodegenerative processes involved in AD.

The dichotomy of AD genetics



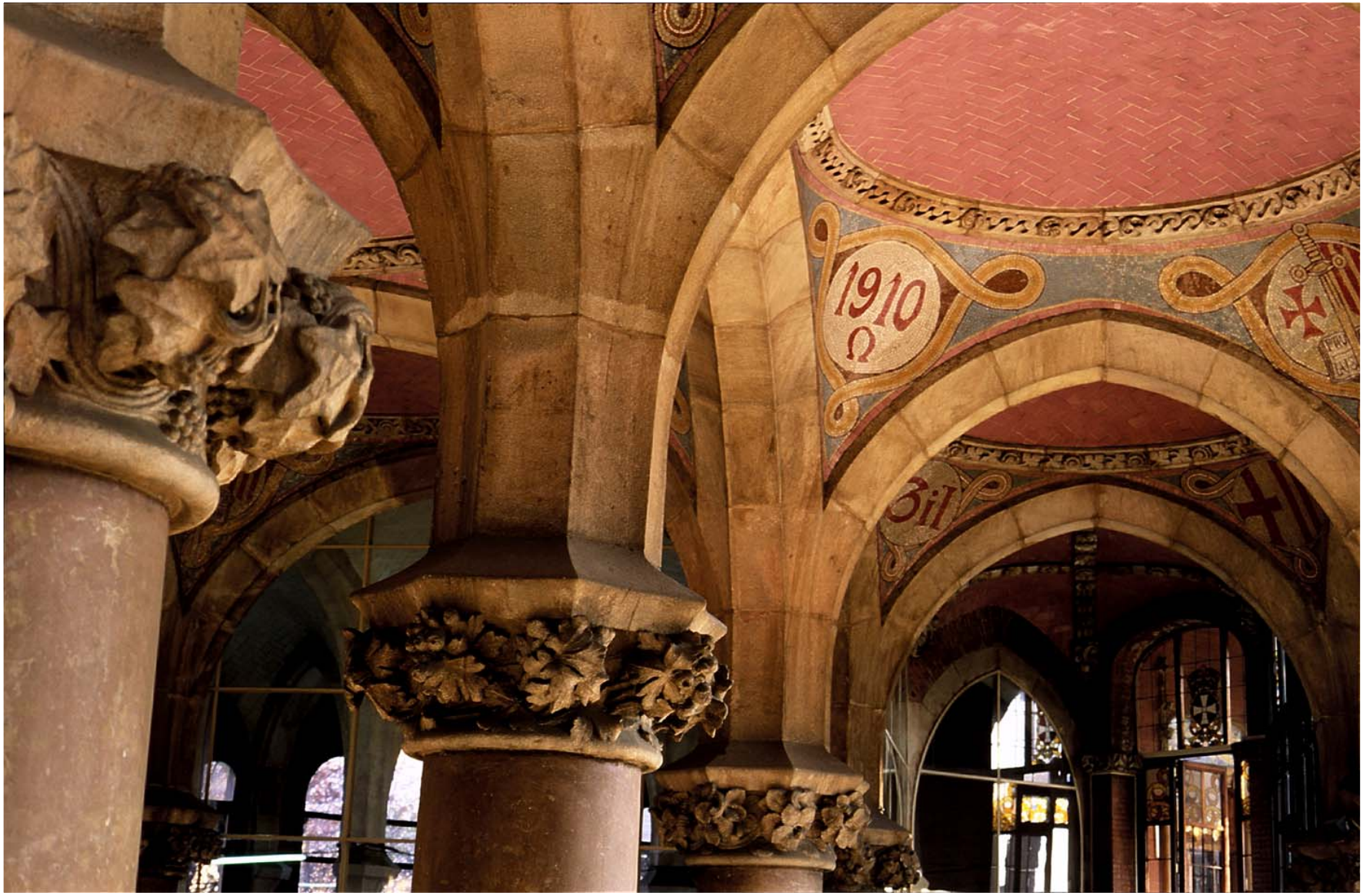
“Simplex AD” (<5%)

“Complex AD” (>95%)

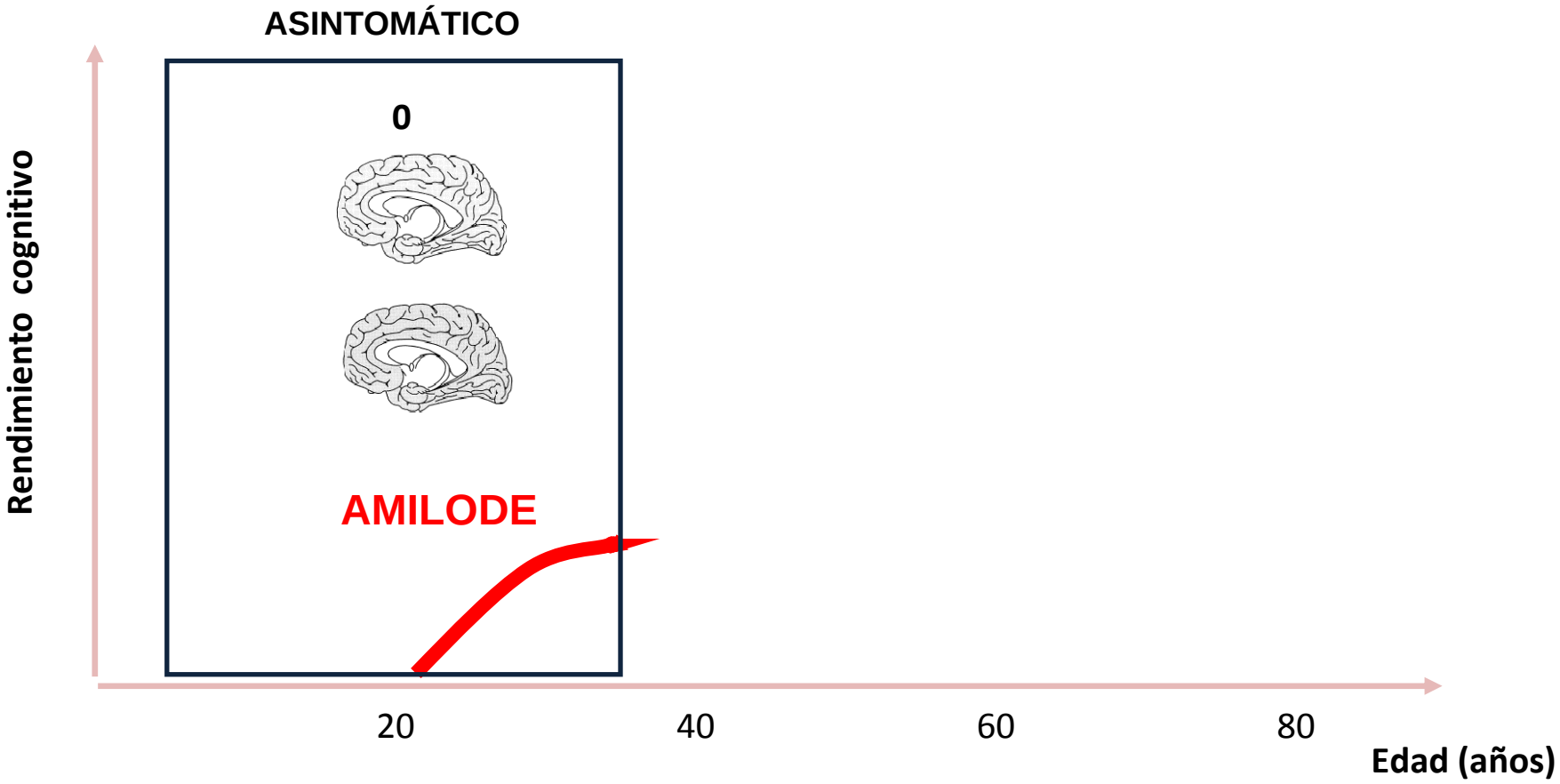
Dubois, B. et al. Lancet Neurology 2010

Enfermedad de Alzheimer (EA)	**EA Preclínica**
•EA típica	Asintomático
•EA prodrómica	Con riesgo de EA
•Demencia de EA	EA presintomática
•EA mixta	Deterioro Cognitivo Leve

TRATAMIENTO: futuro



Tractamiento preventivo



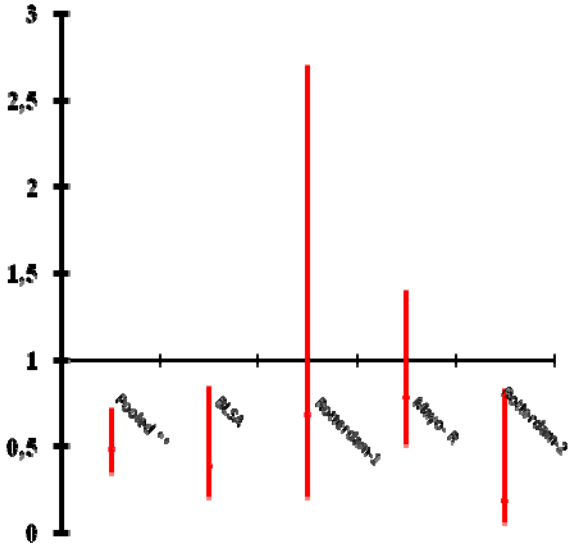
Estrategias para modificar el curso de la enfermedad

No específicas

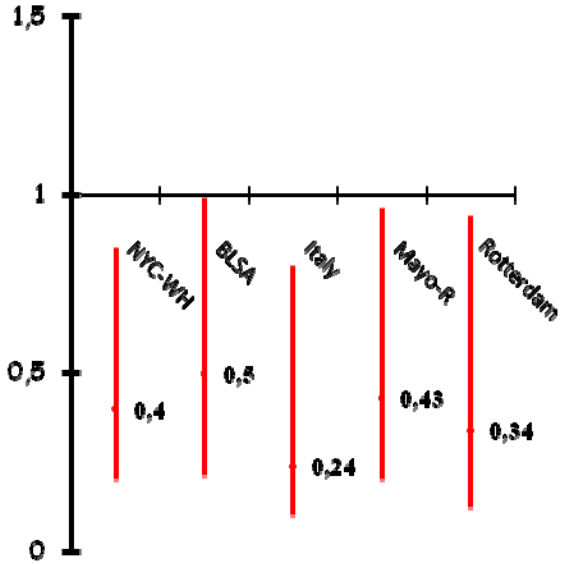
- **Tratamiento hormonal: estrógenos**
- **Anti-inflamatorios**
- **Dieta/ejercicio**
- **Vitaminas y antioxidantes**

- Específicas
  - Anti-amiloide
  - anti- Microtúbulos - asociados a proteína tau

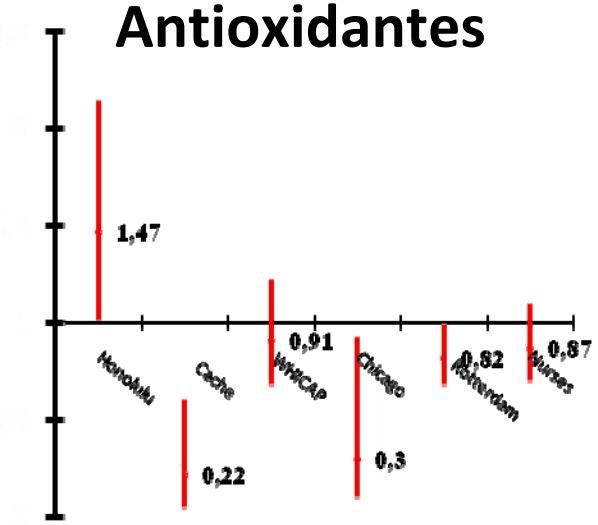
Anti-inflamatorios



Estrógenos



Antioxidantes



Vitamin E for Alzheimer's disease and mild cognitive impairment (Review)

Vitamin E should not be recommended for treatment or prevention of cognitive impairment.

Paul S. Aisen PS, et al.
JAMA. 2008;300(15):1774-1783

High-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD

Estrogen therapy and Alzheimer's dementia

Craig MC et al. **Ann. N.Y. Acad. Sci. 2010**;1205:245–253

- Studies to date suggest that there may be a "critical period" around the time of menopause during which the prescription of ET may reduce the risk of developing AD in later life.

- This effect may be most significant in women under 49 years old, after this point may have a neutral or negative effect, particularly when initiate in women over 60–65 years old.

- Estrogen probably reduces the changes in brain structure and function associated with brain aging.

Dietary Antioxidants and Long-term Risk of Dementia

Devore EE, et al. Arch Neurol. 2010;67(7):819-825

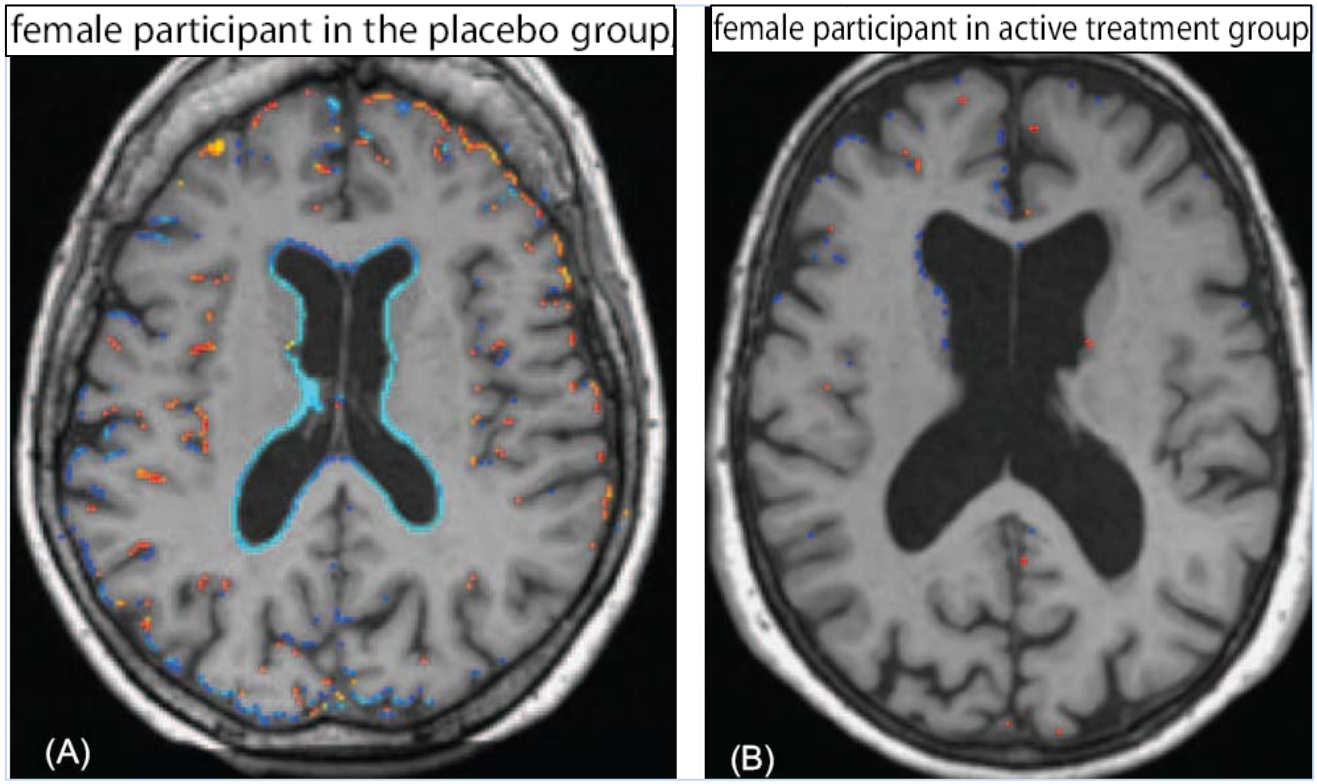
- The Rotterdam Study in the Netherlands: 5395 participants, 55 + years, free of dementia,
- Follow-up period of 9.6 years, dementia developed in 46 (365 AD).
- Higher intake of vitamin E at study baseline was associated with lower long-term risk of dementia (25% less likely) to develop dementia
- Dietary intake levels of vitamin C, beta carotene, and flavonoids were not associated with dementia risk

Conclusion: Higher intake of foods rich in vitamin E may modestly reduce long-term risk of dementia and AD.

Homocysteine-Lowering by B Vitamins Slows the Rate of Accelerated Brain Atrophy in Mild Cognitive Impairment:

A Randomized Controlled Trial.

Smith AD et al. PLoS ONE | 1 September 2010 | Volume 5 | Issue 9 | e12244

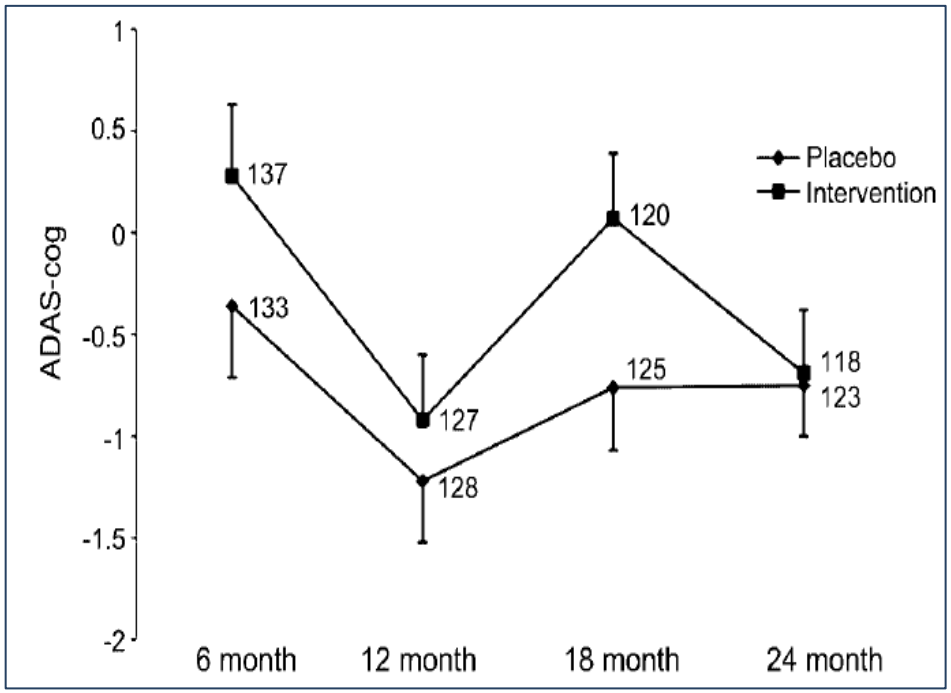


The accelerated rate of brain atrophy in elderly with mild cognitive impairment can be slowed by treatment with homocysteine-lowering B vitamins.

Vitamins B12, B6, and folic acid for cognition in older men

Ford AH, et al. Neurology 2010; 75:on line

- **To investigate whether supplementing older men with vitamins B12, B6, and folic acid** improves cognitive function.
- **299 community-representative hypertensive men 75 years** and older to a randomized, double-blind controlled clinical trial of folic acid, vitamin B6, and B12 supplementation vs placebo over 2 years.

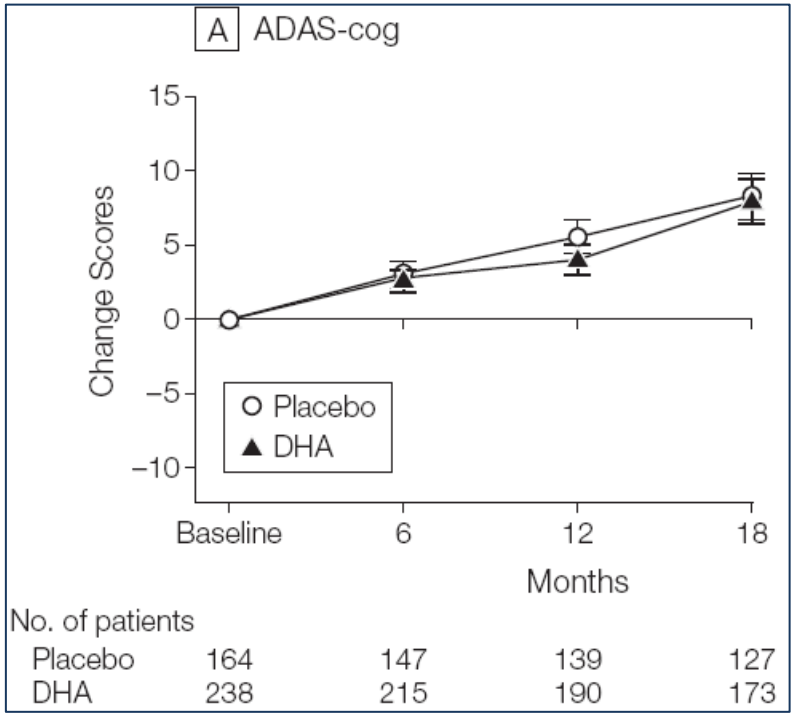


This study provides Class I evidence that vitamin supplementation with daily doses of 400 g of B12, 2 mg of folic acid, and 25 mg of B6 over 2 years does not improve cognitive function in hypertensive men aged 75 and older

Docosahexaenoic Acid Supplementation and Cognitive Decline in Alzheimer Disease

A Randomized Trial

Quinn JF, **JAMA** 2010;304(17):1903-1911



- **Supplementation with DHA the long-chain polyunsaturated fatty acid in the brain, had no beneficial effect on rate of change on ADAS-cog score**
- **Rate of brain atrophy was not affected by treatment with DHA:**
  - **DHA group had 1.32% volume decline per year compared with the placebo group 1.29%**

Supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer disease.

¡Que no estamos tan mal.... al loro!

Alzheimer's Disease International

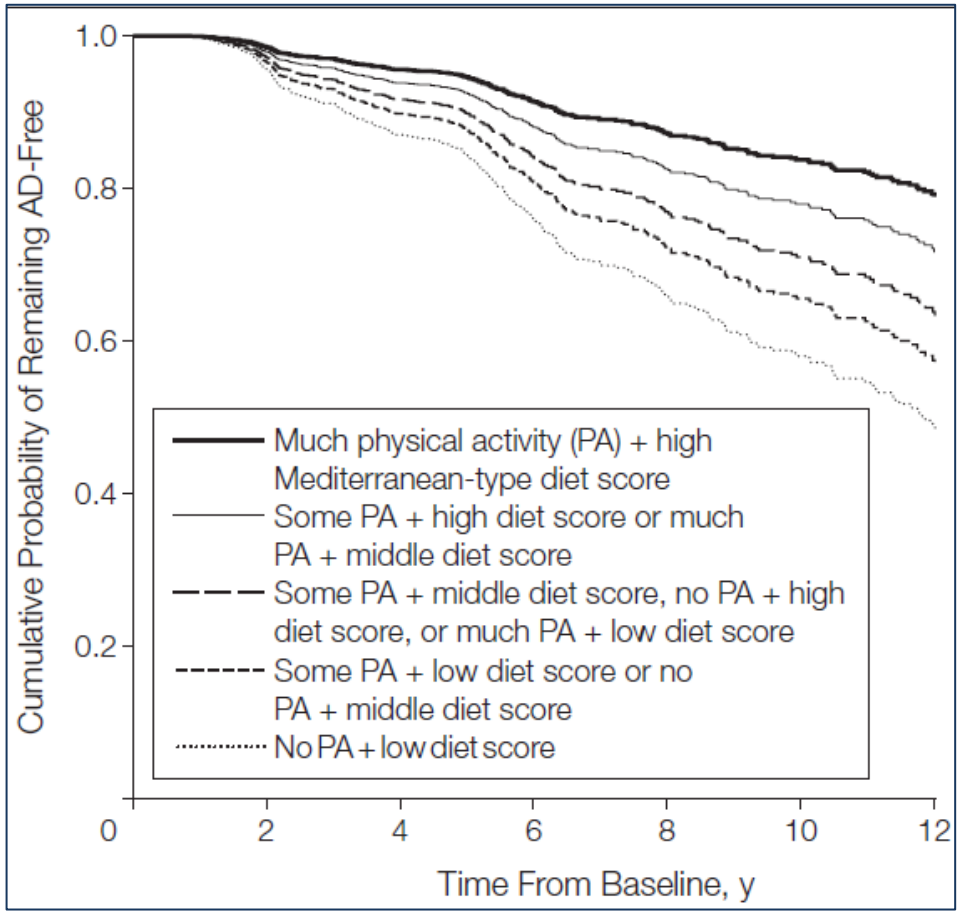
World Alzheimer Report

2009

Executive Summary

Physical Activity, Diet, and Risk of Alzheimer Disease

Scarmeas N, et al. JAMA. 2009;302(6):627-637

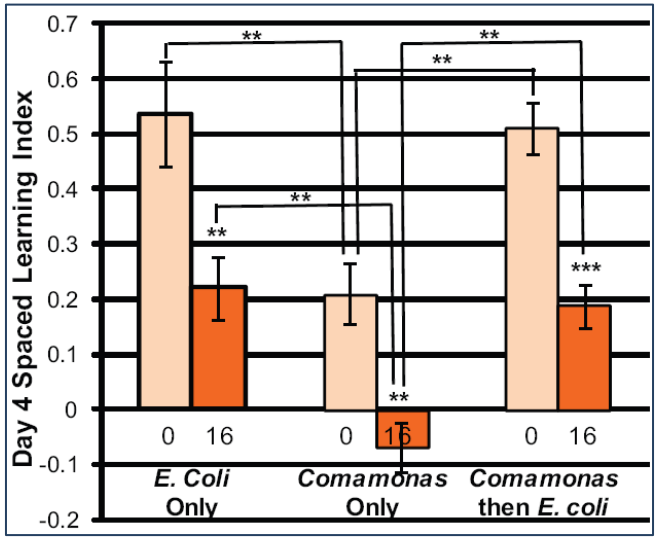


The results support the potentially independent and important role of both physical activity and dietary habits in relation to AD risk.

Insulin Signaling and Dietary Restriction Differentially Influence the Decline of Learning and Memory with Age

Kauffman Al et al. PLoS Biology |1 May 2010 | Volume 8 | Issue 5 | e1000372

Reduced insulin signaling and Dietary Restriction affect maintenance of learning and memory with age differently.

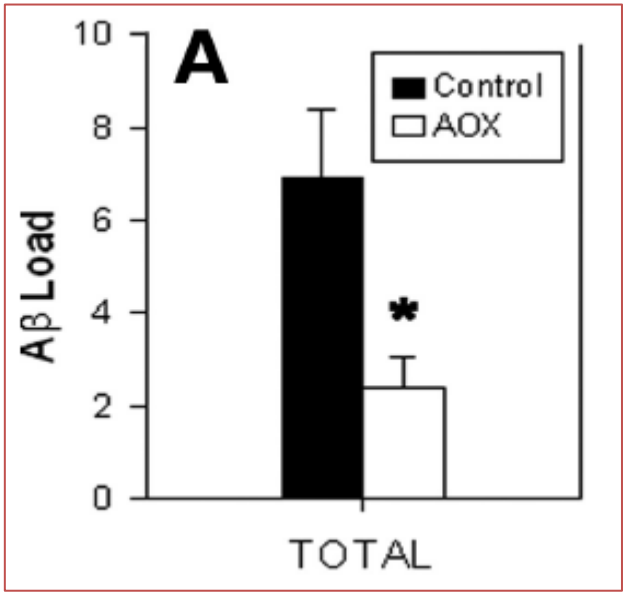


Specific longevity treatments (C. elegans) have acute and long-term effects on cognitive functions that decline with age through their regulation of rate-limiting genes required for learning and memory.

Synergistic Effects of Long-Term Antioxidant Diet and Behavioral Enrichment on Amyloid Load and Non-Amyloidogenic Processing in Aged Canines

Pop V, et al. The Journal of Neuroscience, July 21, 2010 • 30(29):9831–9839

A load pooled according to diet or environment

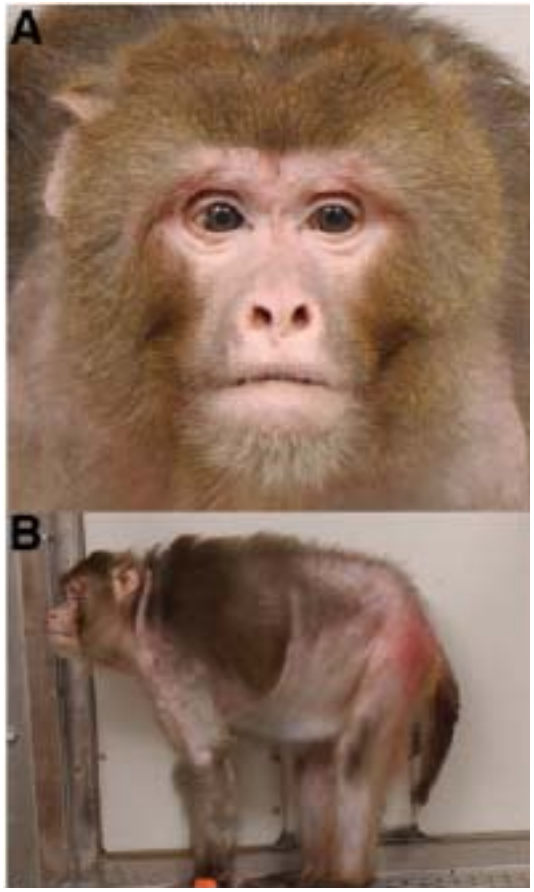


When groups are separated according to diet, significantly lower A load is found in response to antioxidants in the total brain

The strongest and most consistent effects on A pathology were observed in canines receiving the combined EA intervention.
A load was significantly decreased in several brain regions: frontal cortex (soluble A42), and parietal cortex (A56 kDa oligomer)

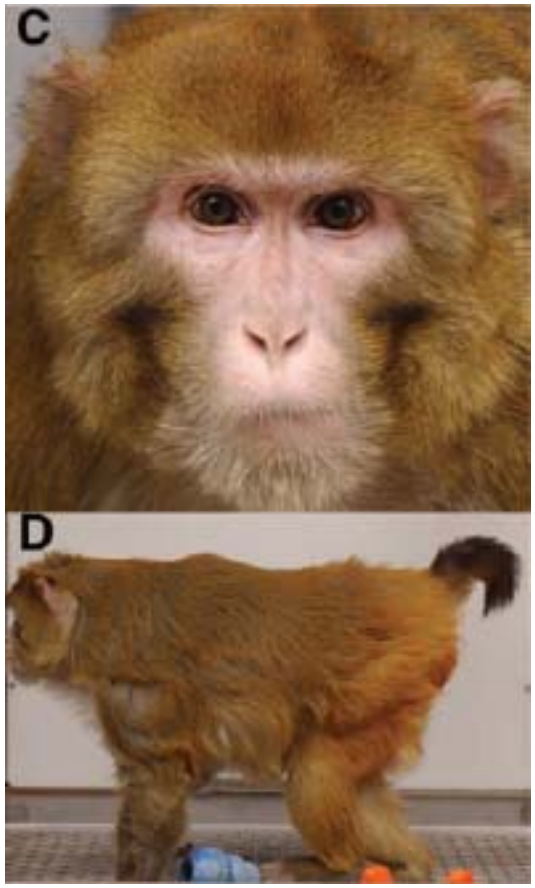
La restricción calórica retarda la aparición de las patologías asociadas a la edad: diabetes, cancer, enfermedades cardiovasculares y atrofia cerebral.

animal control de 27.6 años



50% SUPERVIVENCIA

Misma edad sometido a RC



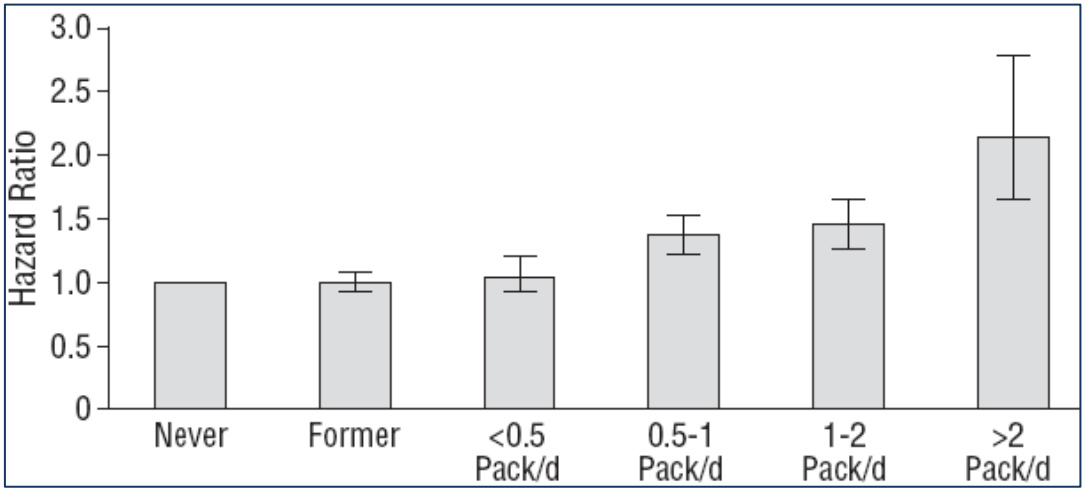
86% SUPERVIVENCIA

Colman RJ, et al. **SCIENCE** 10 JULY 2009 VOL 325 201- 204

Heavy Smoking in Midlife and Long-term Risk of Alzheimer Disease and Vascular Dementia

Rusanen M et al. ***Arch Intern Med****. Published online October 25, 2010.*
doi:10.1001/archinternmed.2010.393

The risk of dementia Alzheimer disease according to smoking amount in midlife.

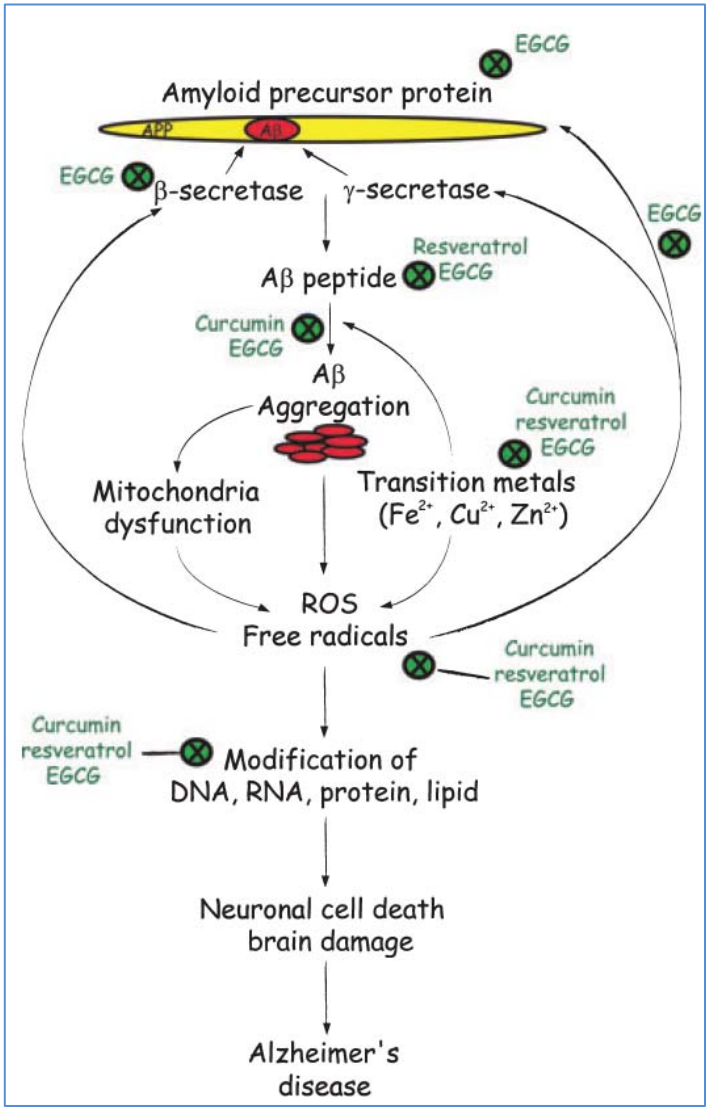


Prospective data from a multiethnic population-based cohort of 21.123 members of a health care system who participated in a survey between 1978 and 1985.

In this large cohort, heavy smoking in midlife was associated with a greater than 100% increase in risk of dementia, AD, and VaD more than 2 decades later. These results suggest that the brain is not immune to long-term consequences of heavy smoking.

Naturally occurring phytochemicals for prevention of Alzheimer's disease.

Kim J et al. JOURNAL OF NEUROCHEMISTRY | 2010 | 112 | 1415–1430



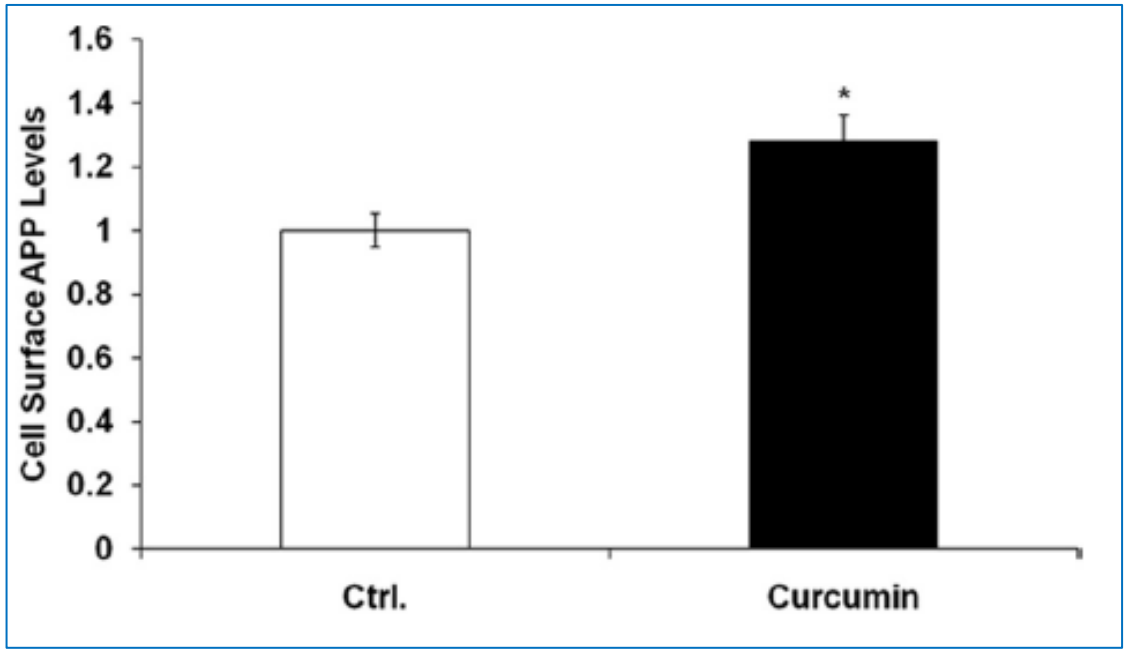
Curcumin, resveratrol, and green tea catechins:

have been suggested to have the potential to prevent AD because of their anti-amyloidogenic, anti-oxidative, and anti-inflammatory properties.

These polyphenolic phytochemicals also activate adaptive cellular stress responses, called 'neurohormesis', and suppress disease processes

Curcumin Decreases Amyloid- Peptide Levels by Attenuating the Maturation of Amyloid- Precursor Protein

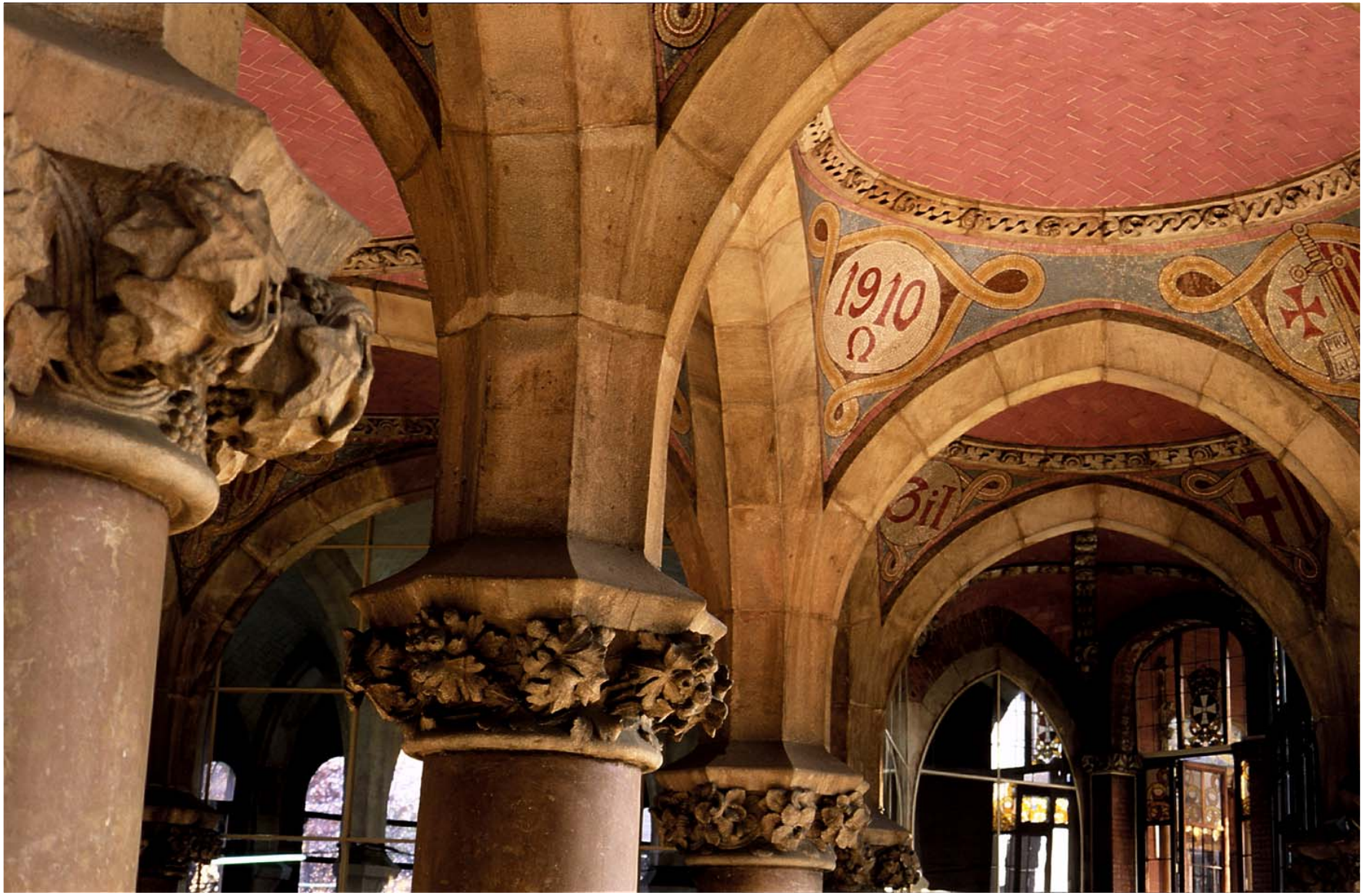
Zhang C et al. **THE JOURNAL OF BIOLOGICAL CHEMISTRY** VOL. 285, NO. 37, pp. 28472–28480, **September 10, 2010**



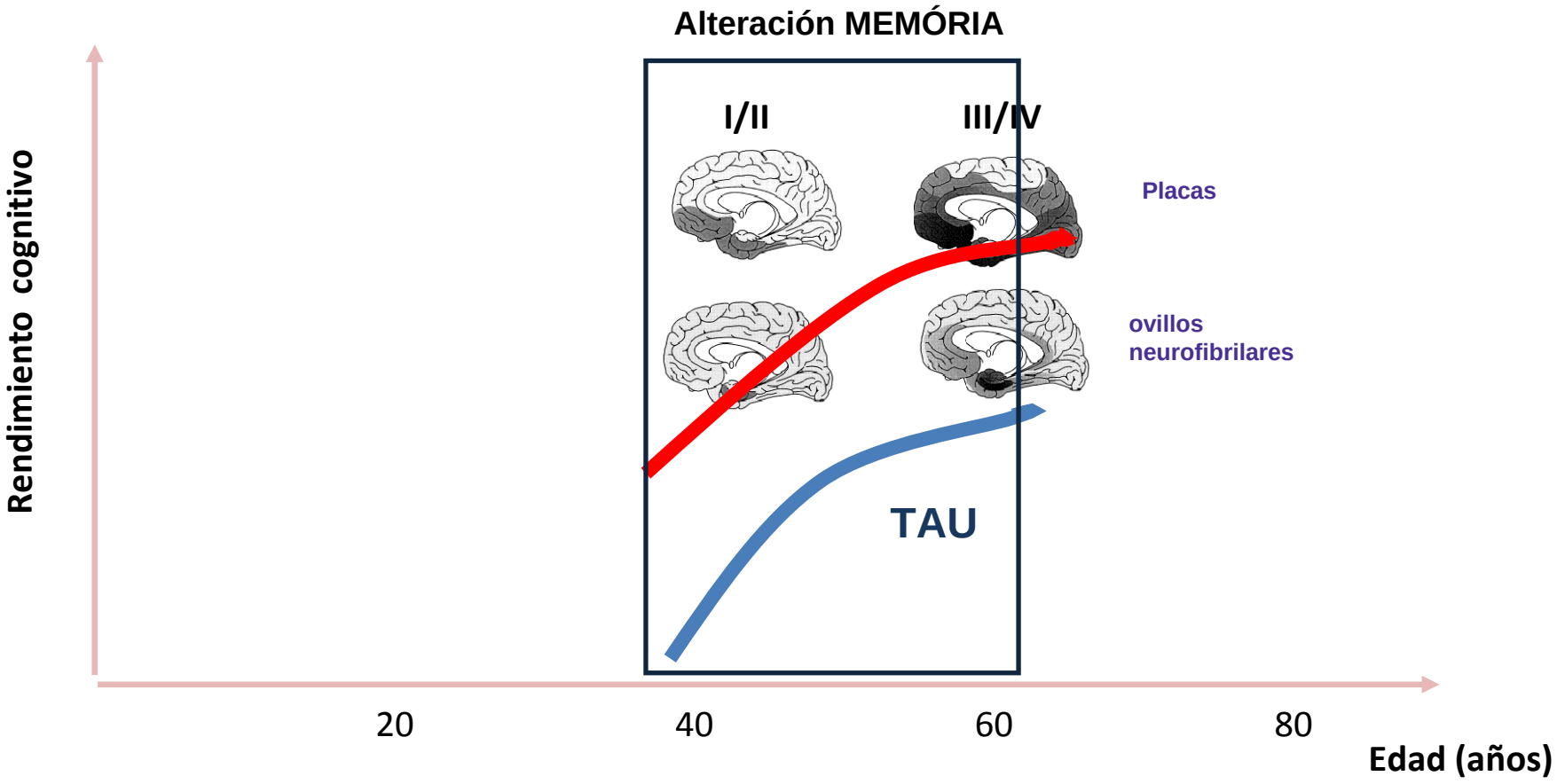
Curcumin treatment significantly increases cell surface APP levels in H4-APP751 cells.

We show for the first time that curcumin potently lowers A levels by attenuating the maturation of APP in the secretory pathway. These data provide a mechanism of action for the ability of curcumin to attenuate amyloid pathology.

TRATAMIENTO



Tratamiento muy inicial



Estrategias que modifican el curso de la EA

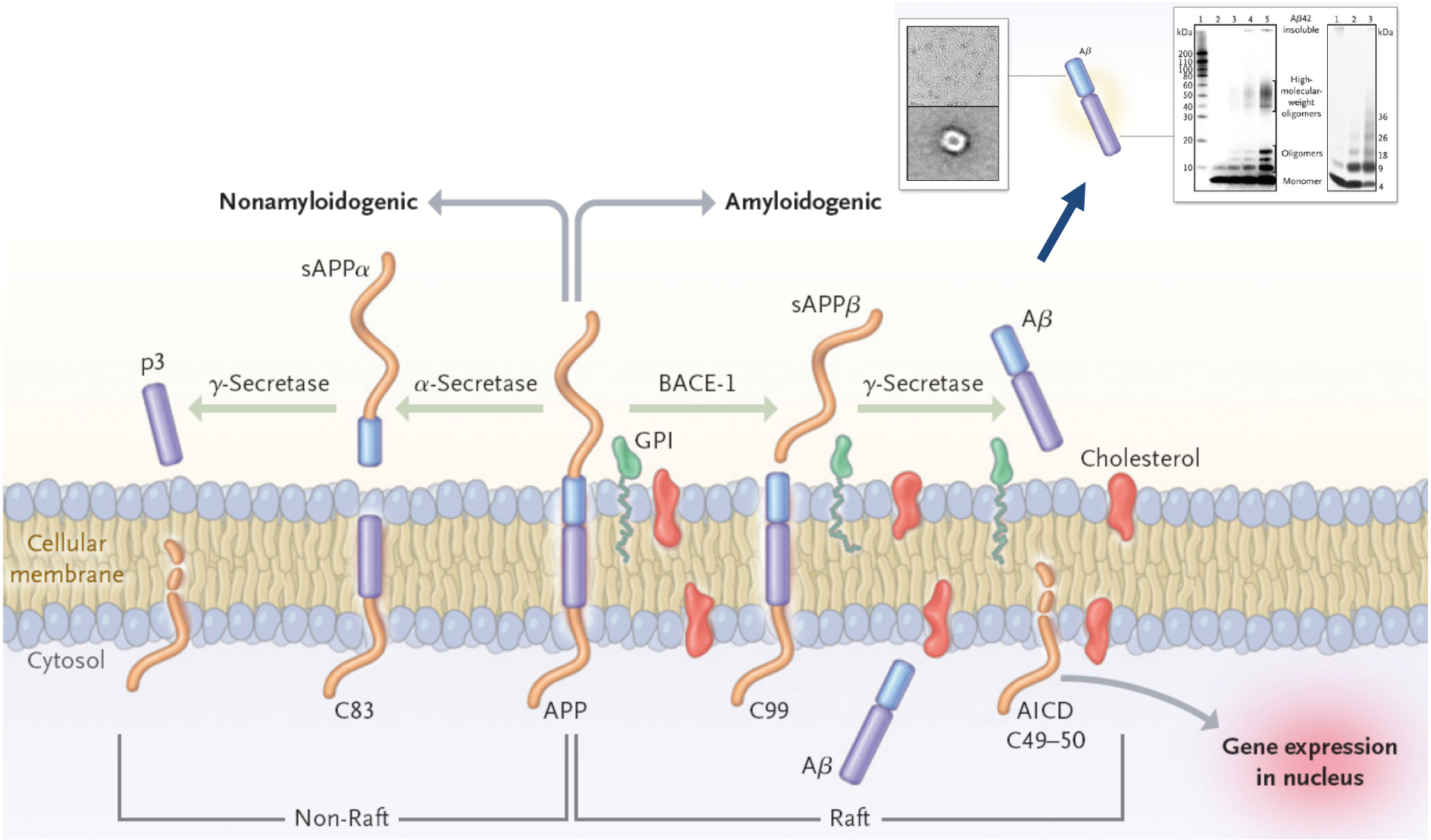
No específiques

- Tractament hormonal: estròg ens
- Anti-inflamatoris
- Dieta/exercici
- Vitamines i antioxidants

- **Específicas**
  - **Anti-amiloide**
  - **anti- Microtúbulos - asociados proteína tau**

Alzheimer's Disease

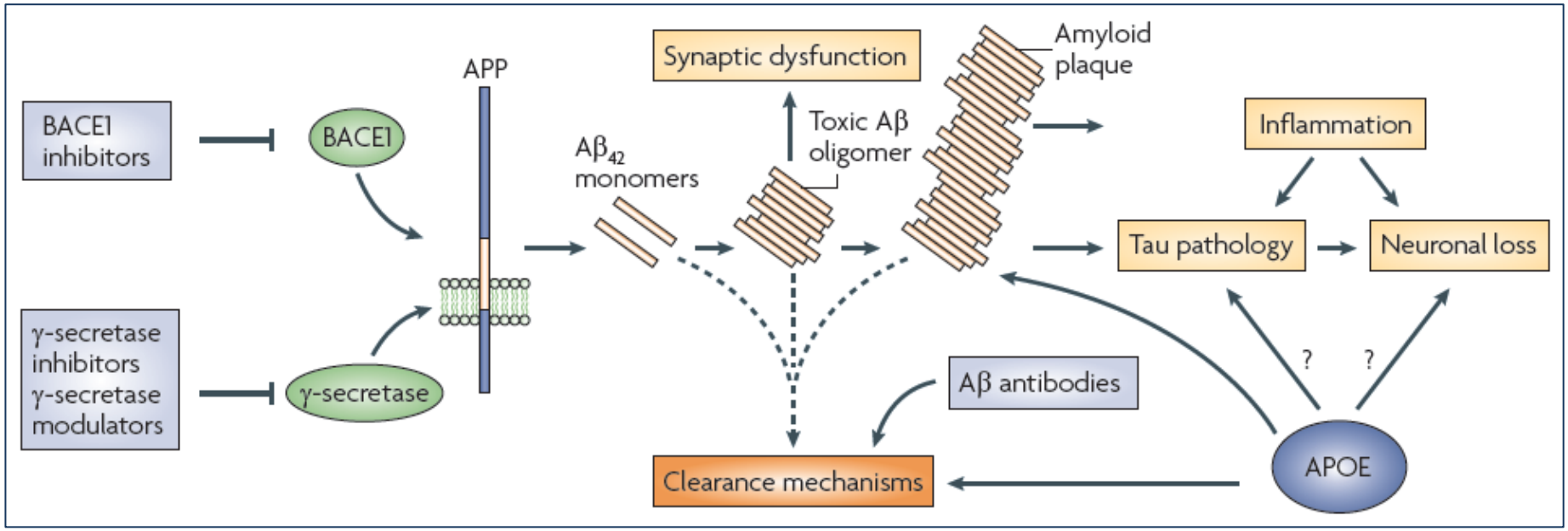
Querfurth HW, LaFerla FM. N Engl J Med 2010;362:329-44.



Alzheimer's disease: strategies for disease modification

Martin Citron Nature Reviews | Drug Discovery vol 9 | May 2010 | 387-398

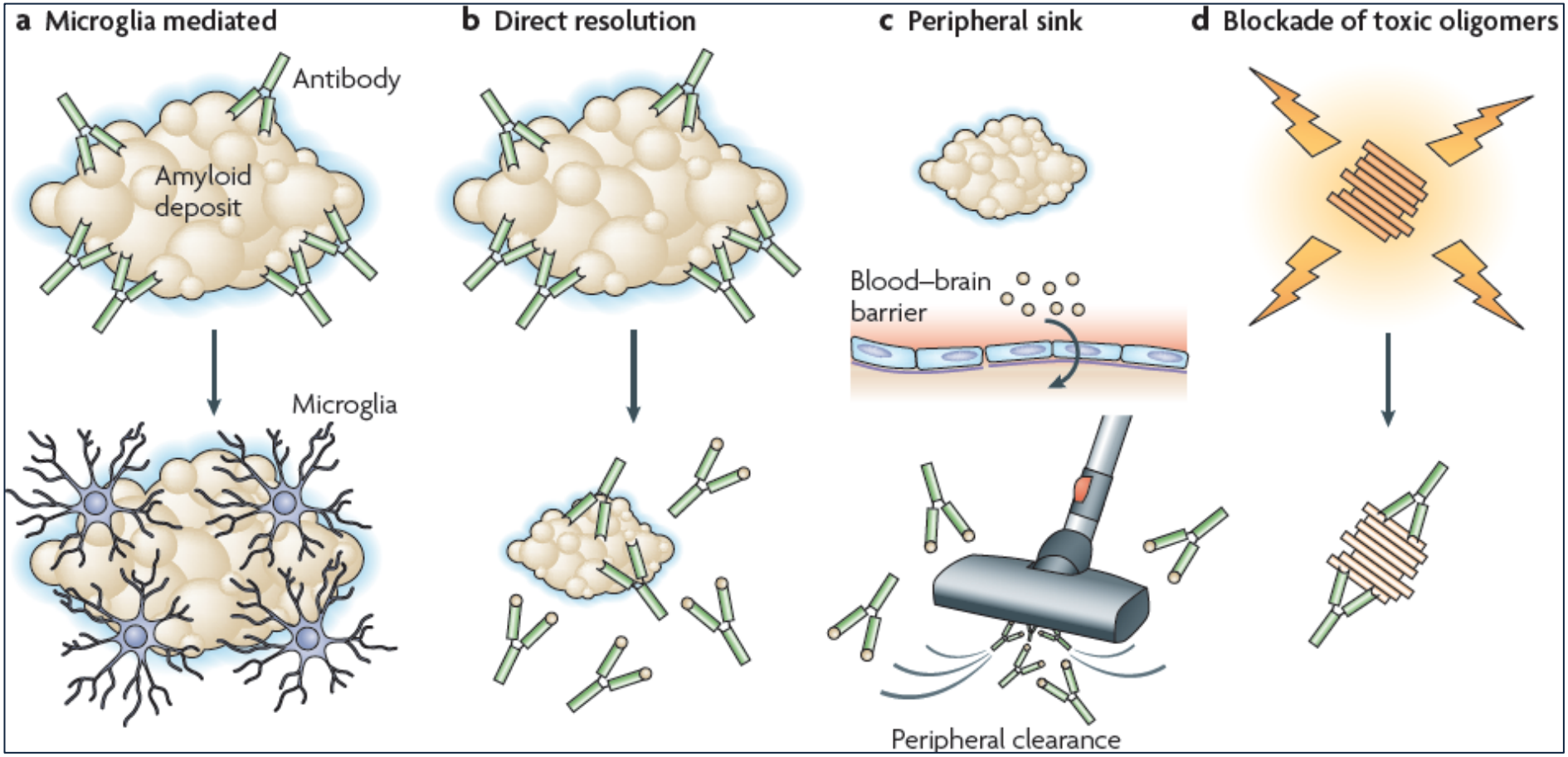
The amyloid cascade and major therapeutic approaches

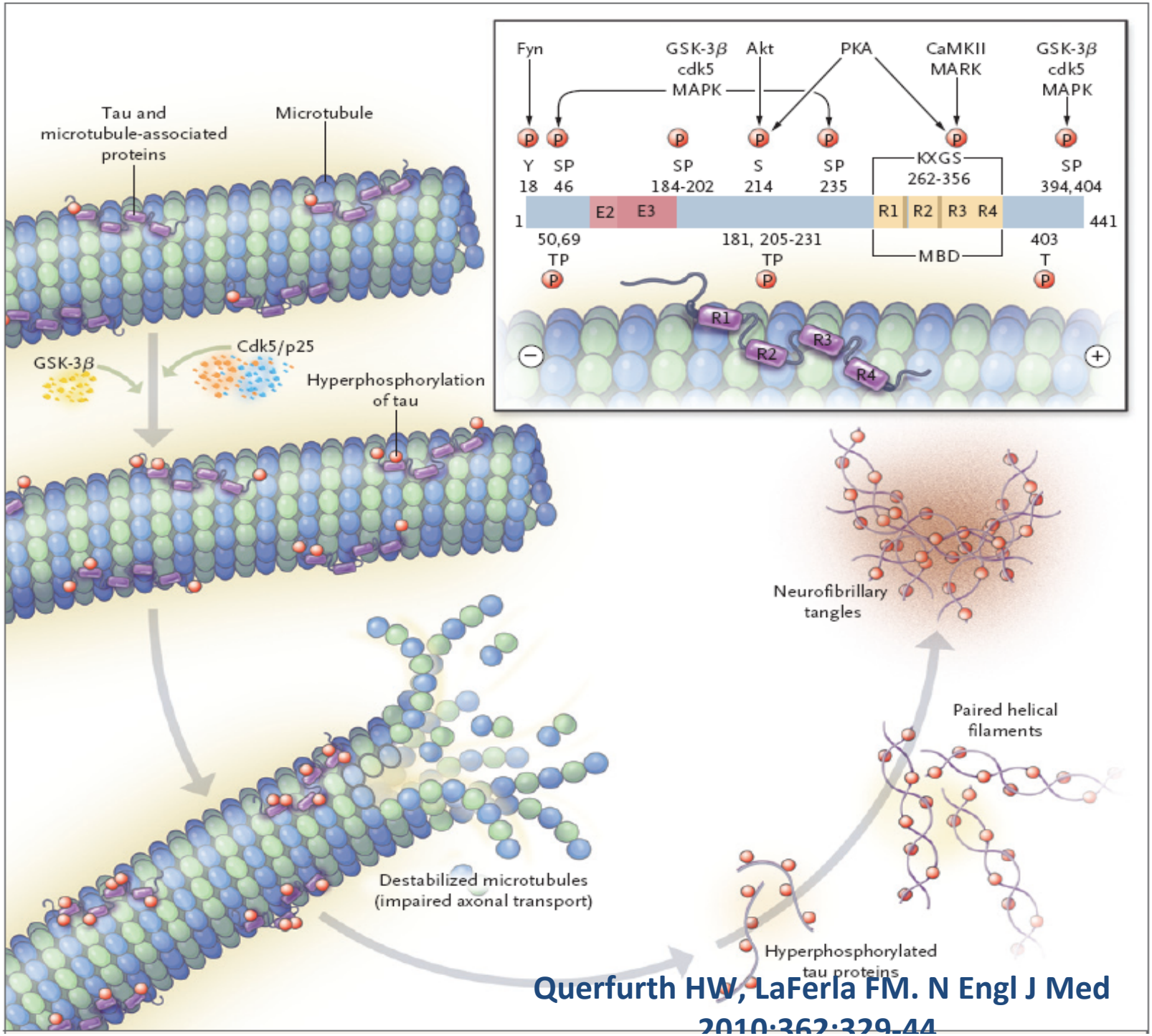


Alzheimer's disease: strategies for disease modification

Martin Citron Nature Reviews | Drug Discovery vol 9 | May 2010 | 387-398

Models of antibody-mediated amyloid clearance



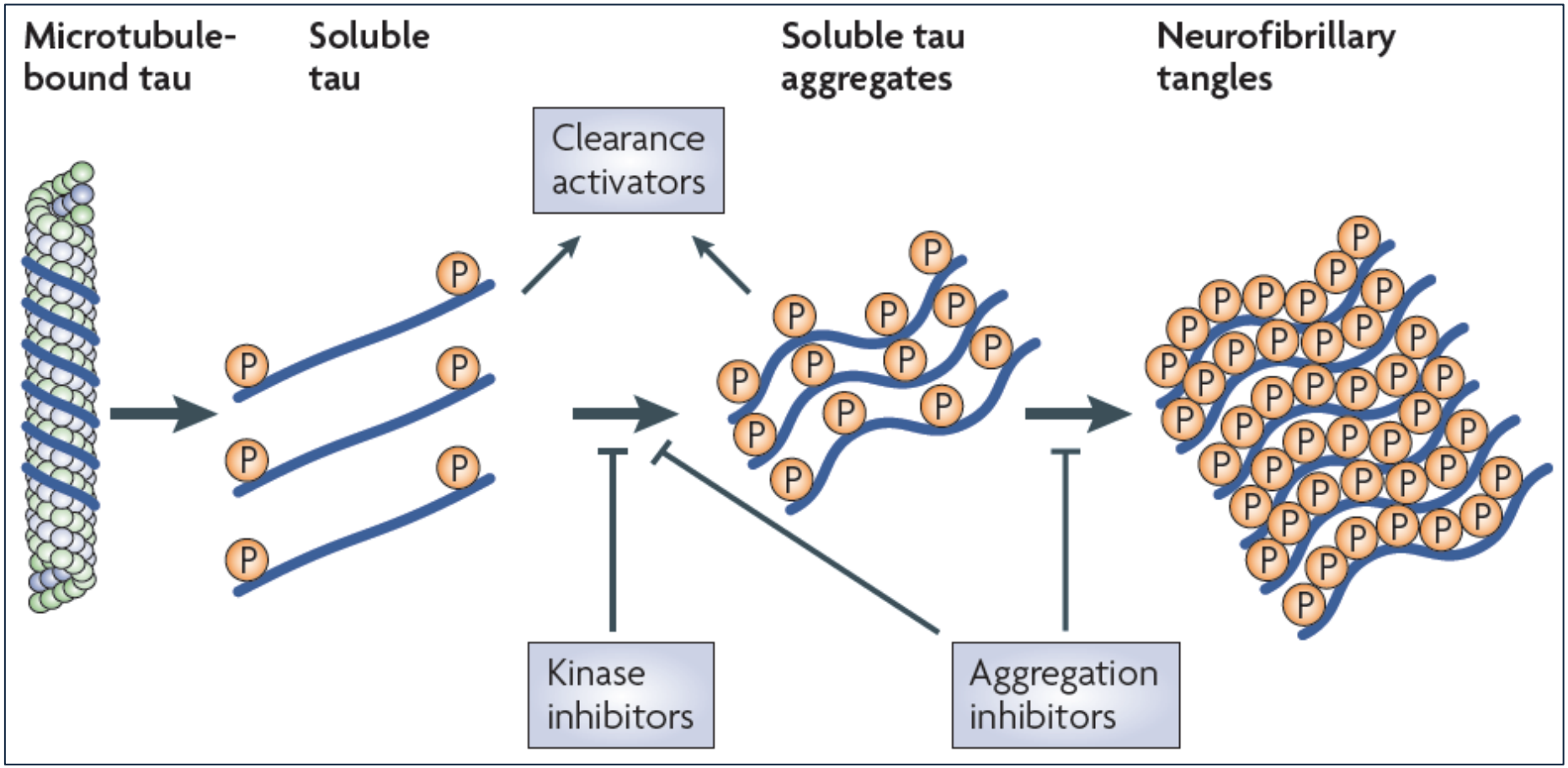


Querfurth HW, LaFerla FM. N Engl J Med 2010;362:329-44

Alzheimer's disease: strategies for disease modification

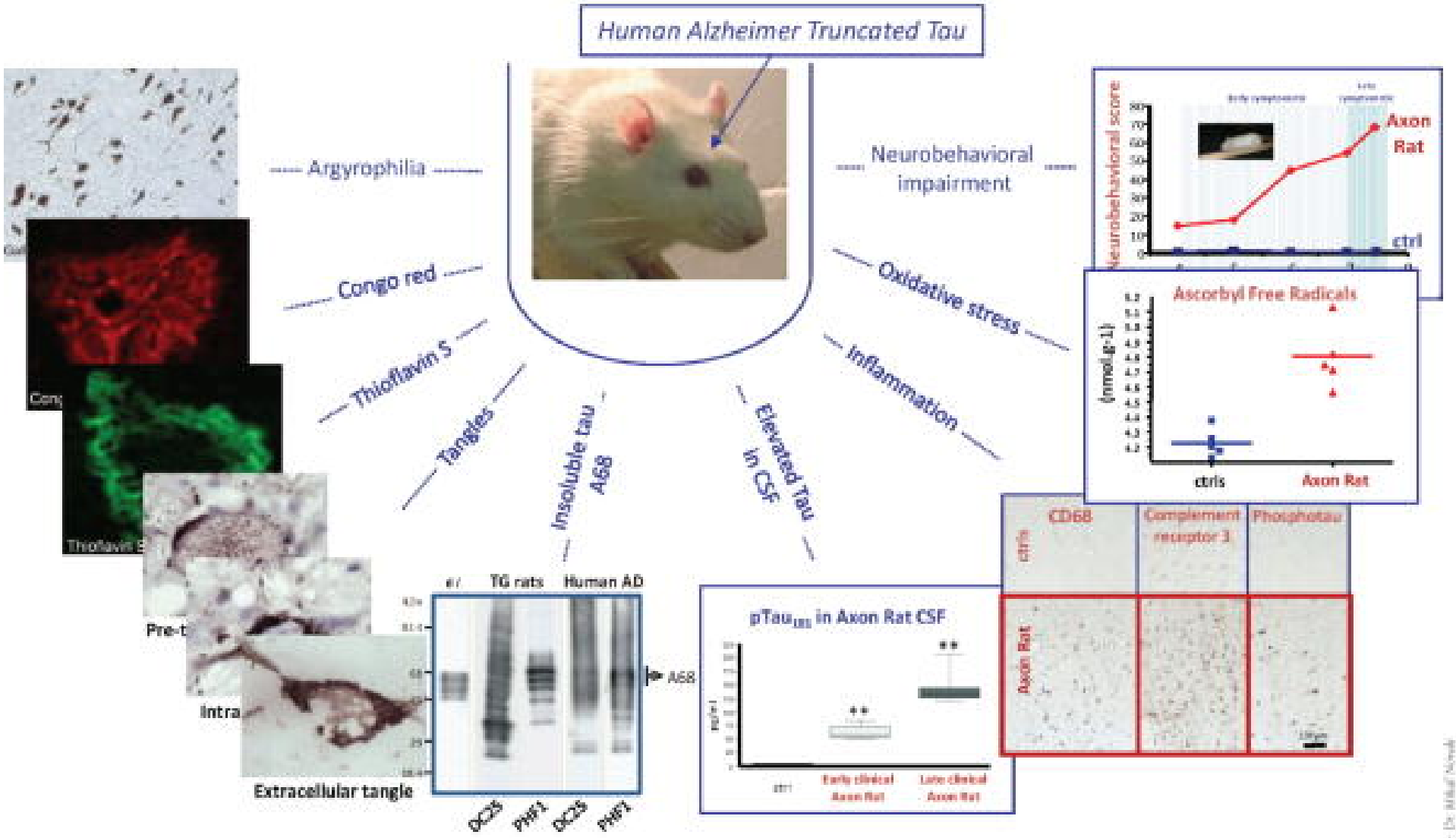
Martin Citron Nature Reviews | Drug Discovery vol 9 | May 2010 | 387-398

Tau pathology and major therapeutic approaches



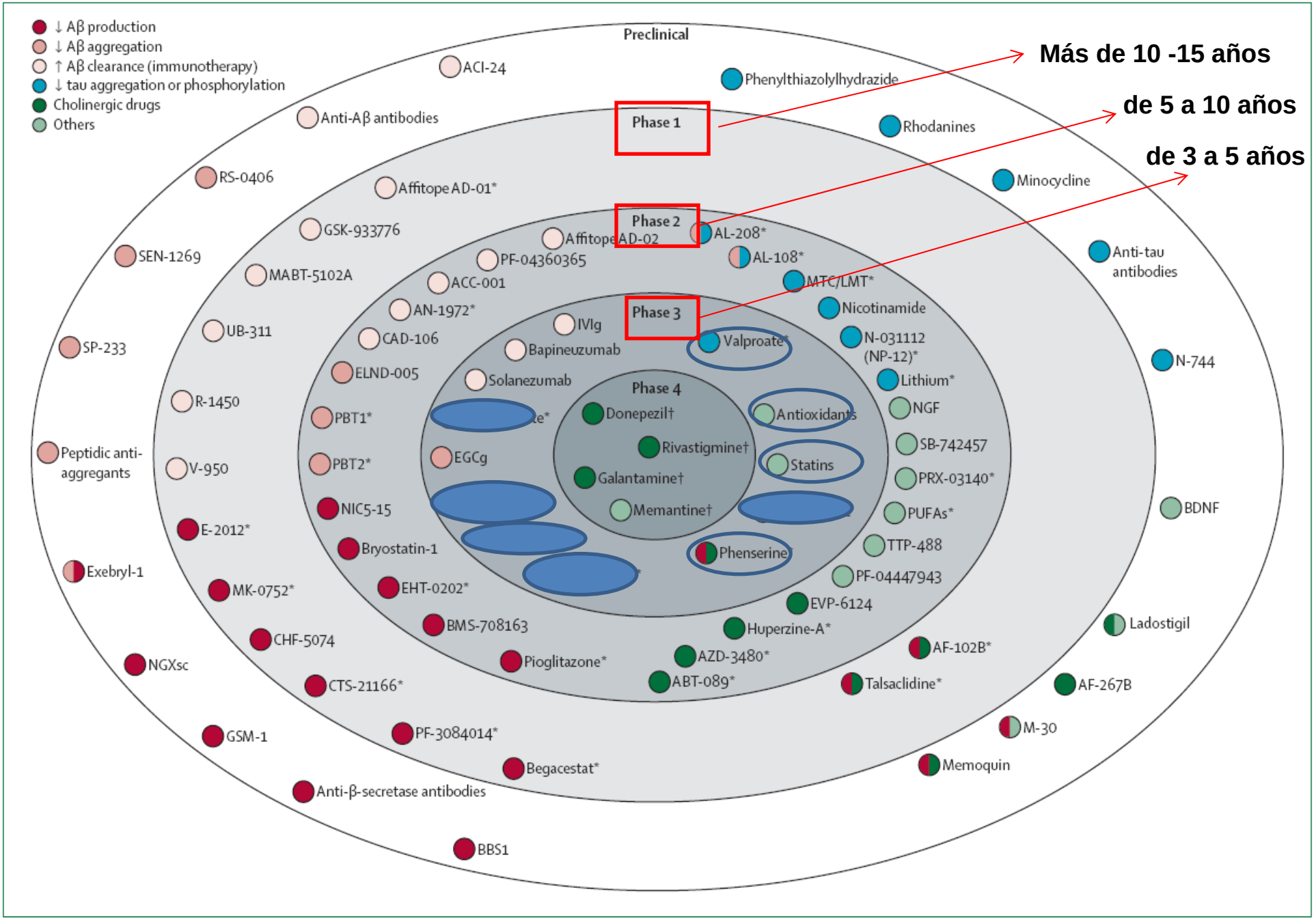
Tau Transgenic Rat Reproduces Human Neurofibrillary Degeneration in Alzheimer's Disease and Therefore Is Essential for the Development of the AD Tau Vaccine

Alzheimer truncated tau *induces and drives* complete neurofibrillary degeneration



Zilka et al, *FEBS Lett* (2006); Cente et al. *Eur J Neurosci.* (2006); Hmkova et al. *Brain Res.* (2007); Kason et al. *Eur J Neurosci.* (2008); Cente et al. *J Alz Dis* (2009).

¿Estemos lejos o cerca de descubrir un fármaco para la prevención o curación del alzheimer?



Mangialasche F et al. **Lancet Neurol 2010**; 9: 702–16

Otros tratamientos y patogenias

Trasplante de células madre en la enfermedades neurodegenerativas

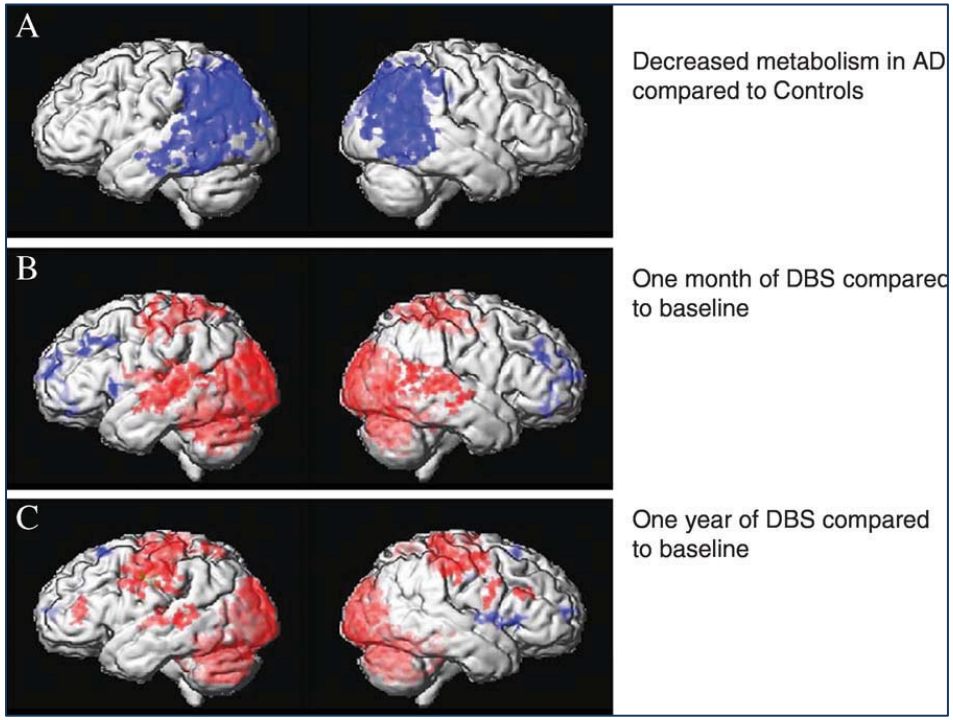
Cell-based therapy for PD and AD: clinical trials.

Disease	Transplanted cells	Functional outcome	References
PD (over 400 patients since the late 1980's)	Human embryonic mesencephalic tissue	*Positive*: can restore dopamine system and ease motor deficits *Negative*: dyskinesias, Lewy bodies in transplanted cells, practical and ethical issues, no net benefit in 3 randomized, double-blind, placebo-controlled studies	Hedlund and Perlmann, 2009; Greene, 2009
PD (recruiting patients)	Autologous mesenchymal stem cells (MSCs)	None to date – recruiting stage	ClinicalTrials.gov NCT00976430
AD (8 patients)	Autologous primary fibroblasts genetically modified to produce NGF	No long-term adverse effects Suggested improvement in the rate of cognitive decline, robust NGF-induced neurite growth	Tuszynski et al., 2005
AD (6 patients)	Human cell line genetically modified to produce NGF contained in a catheter-like capsule	Preliminary data indicated the safety and tolerability of this procedure	Eriksdotter-Jonhagen et al., 2008

Shihabuddin LS et al. **Neuropharmacology** 58 (2010) 845-854

A Phase I Trial of Deep Brain Stimulation of Memory Circuits in Alzheimer's Disease

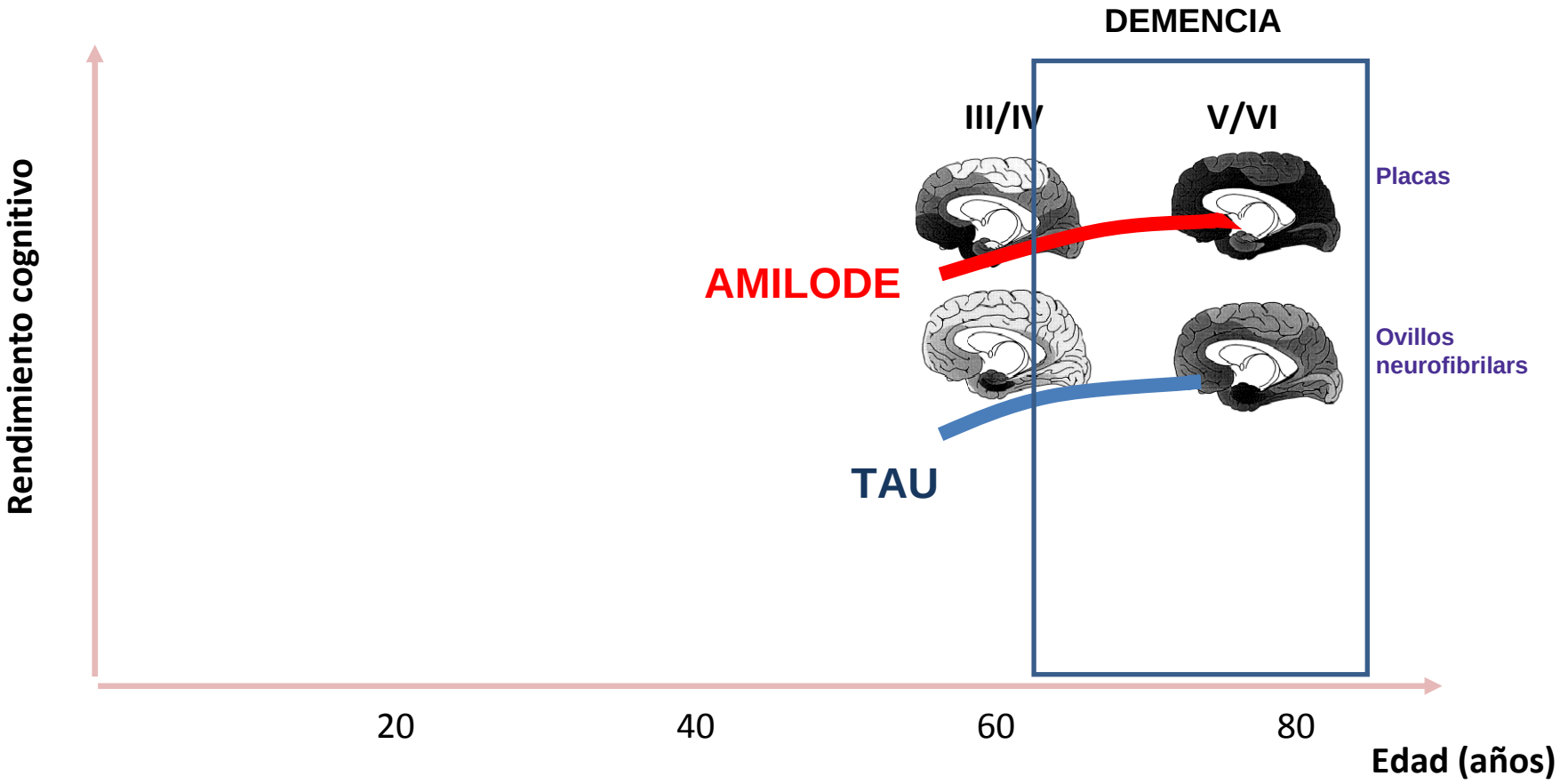
Laxton AW, et al. ANN NEUROL 2010;early edition august 4



- **DBS drove neural activity in the memory circuit (entorhinal, and hippocampal areas)**
- **PET scans showed an early and striking reversal of the impaired glucose utilization in the temporal and parietal lobes that was maintained after 12 months**
- **ADAScog – MMSE suggested possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients.**
- **There were no serious adverse events.**

Tratamiento sintomático

Tratamiento sintomático



Fármacos aprobados para tratamiento de la EA

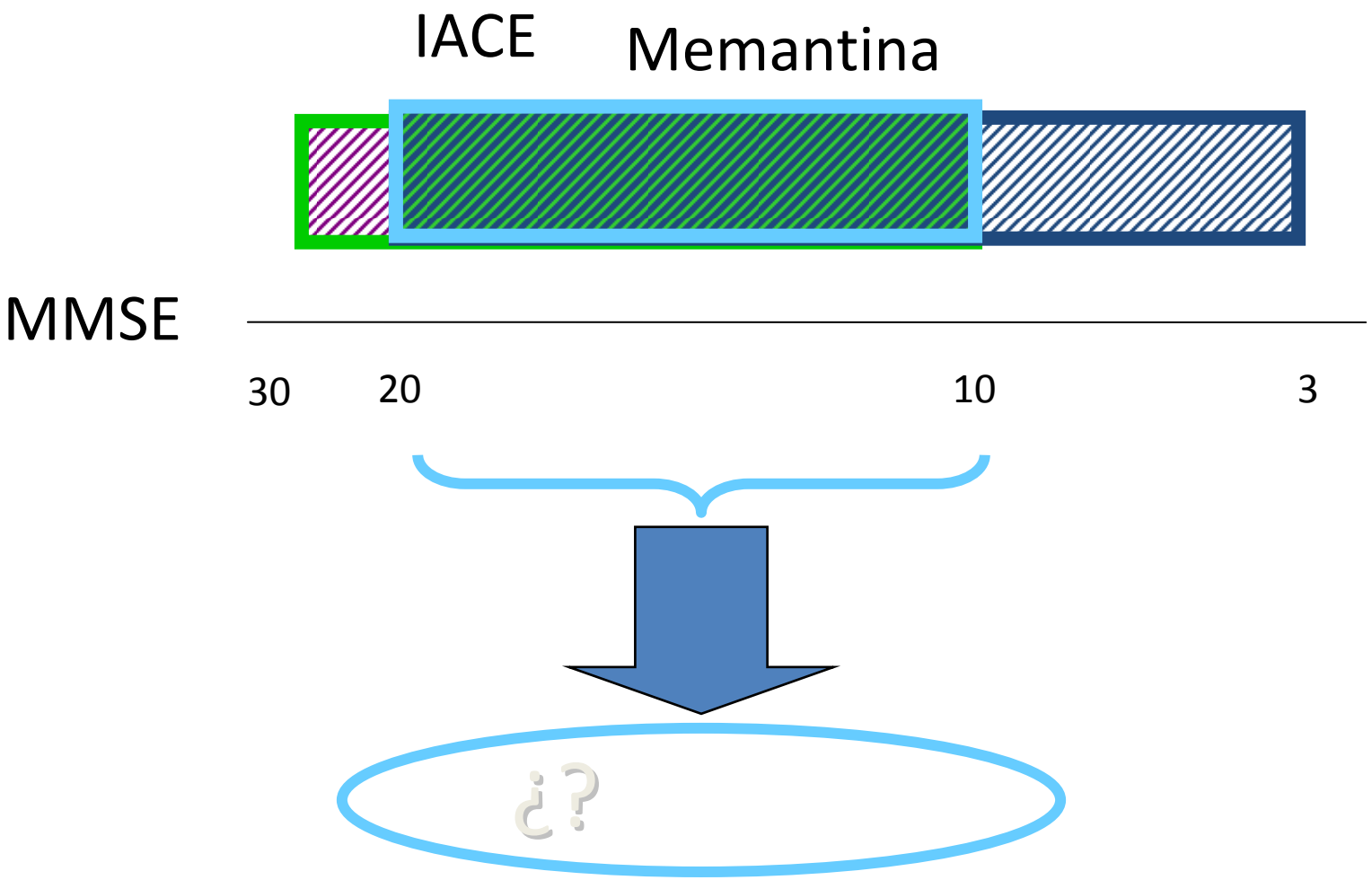
	Disease stage	Symptomatic activity*	Potential neuroprotective activity
AChEIs: improve cognition, behaviour, and functional and global clinical state			
Donepezil†	All stages[3,4,15]	AChEI	Possibly decreases Aβ production and Aβ-induced toxicity; modulates expression of AChE isoforms; increases expression of nicotinic receptors[2]
Rivastigmine	Mild to moderate[3]	AChEI and BChEI	Possibly decreases Aβ production and Aβ-induced toxicity; modulates expression of AChE isoforms; increases expression of nicotinic receptors[2]
Galantamine	Mild to moderate[3]	AChEI (nicotinic receptor modulation)	Possibly decreases Aβ production and Aβ-induced toxicity; modulates expression of AChE isoforms; increases expression of nicotinic receptors[2]
Huperzine-A‡	Approved in China for mild-to-moderate stages; dietary supplement in some countries[5]	AChEI	Modulates APP processing by enhancing soluble APPα secretion; antioxidant, anti-apoptotic effects; mitochondrial protection[2,6]
NMDA receptor antagonists: improve cognition, behaviour, and functional state			
Memantine	Moderate to severe (monotherapy and in combination with AChEI)[10-14]	Uncompetitive, voltage-dependent NMDA receptor antagonist	Decreases Aβ toxicity; prevents hyperphosphorylation of tau; decreases microglia-associated inflammation; increases release of neurotrophic factors from astroglia[7-9]

Mangialasche F et al. **Lancet Neurol** 2010; 9: 702–16

EFNS

- Enfermedad de Alzheimer
  - IACE (rivastigmina, donepezilo, galantamina) en el momento del diagnóstico
  - Memantina sola, o combinada con un IACE, en pacientes con EA moderada a grave
  - Evidencia insuficiente para utilizar: ginkgo biloba, antiinflamatorios, nootrópicos, selegilina, estrógenos, vitamina E o estatinas

- Enfermedad de Parkinson con demencia (EPD)
  - IACE (rivastigmina)
  - Evidencia insuficiente para la indicación de memantina


IACE
Memantina
MMSE
30
20
10
3
¿?

Síntomas conductuales en la EA

- Agitación
- Depresión
- Psicosis
- Alteración del sueño
- Ansiedad
- Desinhibición

Soporte para familiares

Evaluación regular de las necesidades de los cuidadores

Ajutda práctic a
Soporte emocional / asesoramiento

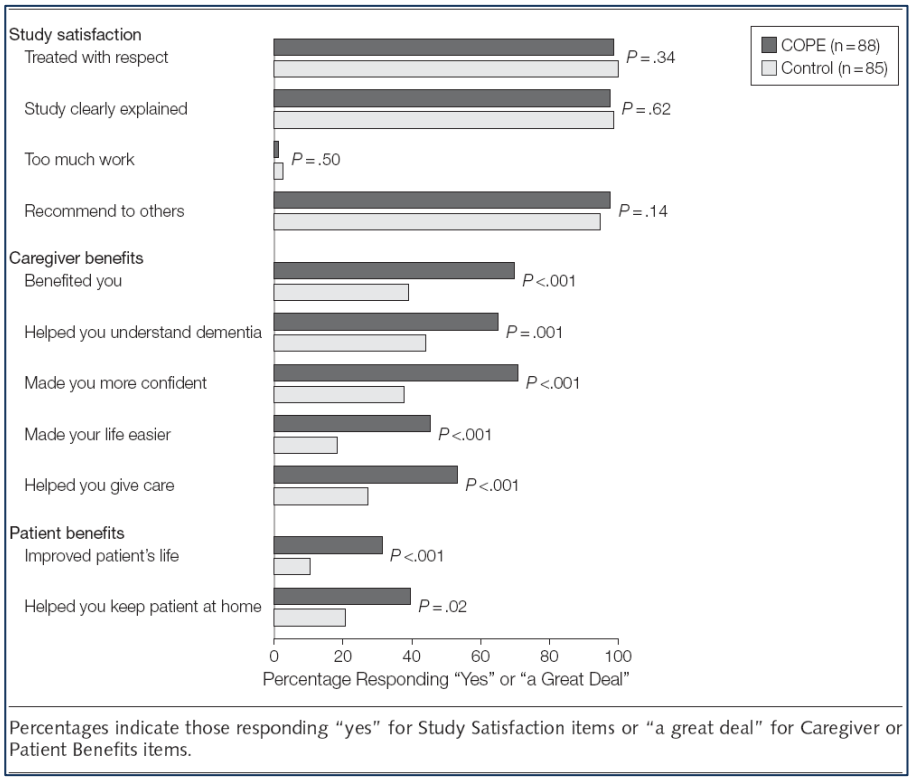
Información

Privilegios Financieros
Legislación
Respiro
Otras fuente de soporte (e.j. Servicios sociales organizaciones de pacients y de familiares)

A Biobehavioral Home-Based Intervention and the Well-being of Patients With Dementia and Their Caregivers: The COPE Randomized Trial.

Gitlin LN et al. JAMA. 2010;304(9):983-991

Perceived Benefits of Intervention and Control Group Caregivers at 9 Months



COPE: Care of Persons with Dementia in their Environments

Among community-living dyads, a nonpharmacologic biobehavioral environmental intervention compared with control resulted in better outcomes for COPE dyads at 4 months.

De los principios a la práctica

Los seis principios del Alzheimer Disease International (ADI)

- Promover el conocimiento y la comprensión de la Enfermedad
- Respeto de los derecho humanos de los enfermos
- Reconocimiento del papel clave de las familias y cuidadores
- Facilitar el acceso a los sistemas de salud y sociales
- Emfatizar la importancia de un tractament óptimo después del diagnóstico
- Tomar medidas para la prevención, mejorando la salud pública

Tema	Reconocimiento	Diagnóstico	Calidad de vida	Implementación
17 objectiivos	***Promover el conocimiento y la Comprensión***	***Apoyo y diagnóstico precoz***	***Vivir bien con demencia***	***Haciendo el cambio***
	1. Campañas de información pública	2. Unidades de Memoria 3. Información para pacientes y cuidadores 4. Continuidad en el apoyo 5. Apoyo supervisado	6. Mejorar el apoyo comunitario 7. Estrategias para los cuidadores 8. Mejorar la atención hospitalaria 9. Mejorar la atención intermedia 10. Ayuda domiciliaria y teleayuda 11. Mejorar la atención en el hogar 12. Mejorar la atención en etapa final	13. Competencia, desarrollo y entrenamento 14. Estrategias de comisiones locales 15. Monitorización i evaluación 16. Investigación 17. Ayuda nacional y regional

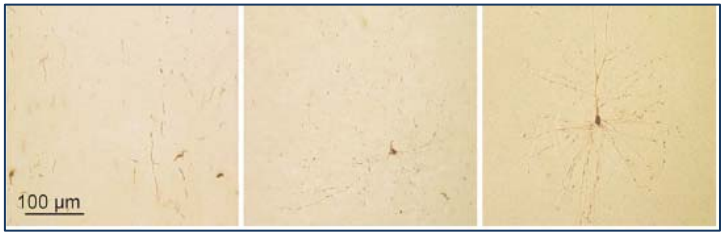
Lindesay J et al. Int J Clin Pract 2010

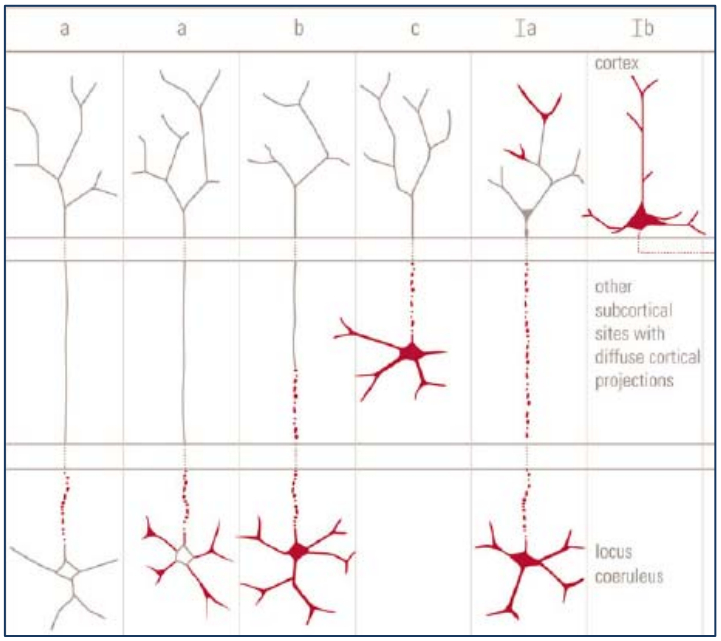
¿Cómo quiero ser de mayor....?

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

Braak H, et al. Acta Neuropathol DOI 10.1007/s00401-010-0789-4
Published online: 15 December 2010

Brains of 42 individuals between the ages of 4 and 29





- 38/42 displayed tau protein (pretangle material)
- 41/42 individuals showed no extracellular amyloid-b protein
- 16/42 cases abnormal tau was found in the transentorhinal region
- 22/26 cases that lacked abnormal tau in the transentorhinal region had subcortical lesions confined to non-thalamic nuclei with diffuse projections to the cerebral cortex
- 19/22 individuals the pretangle material was confined to the noradrenergic coeruleus/subcoeruleus complex.

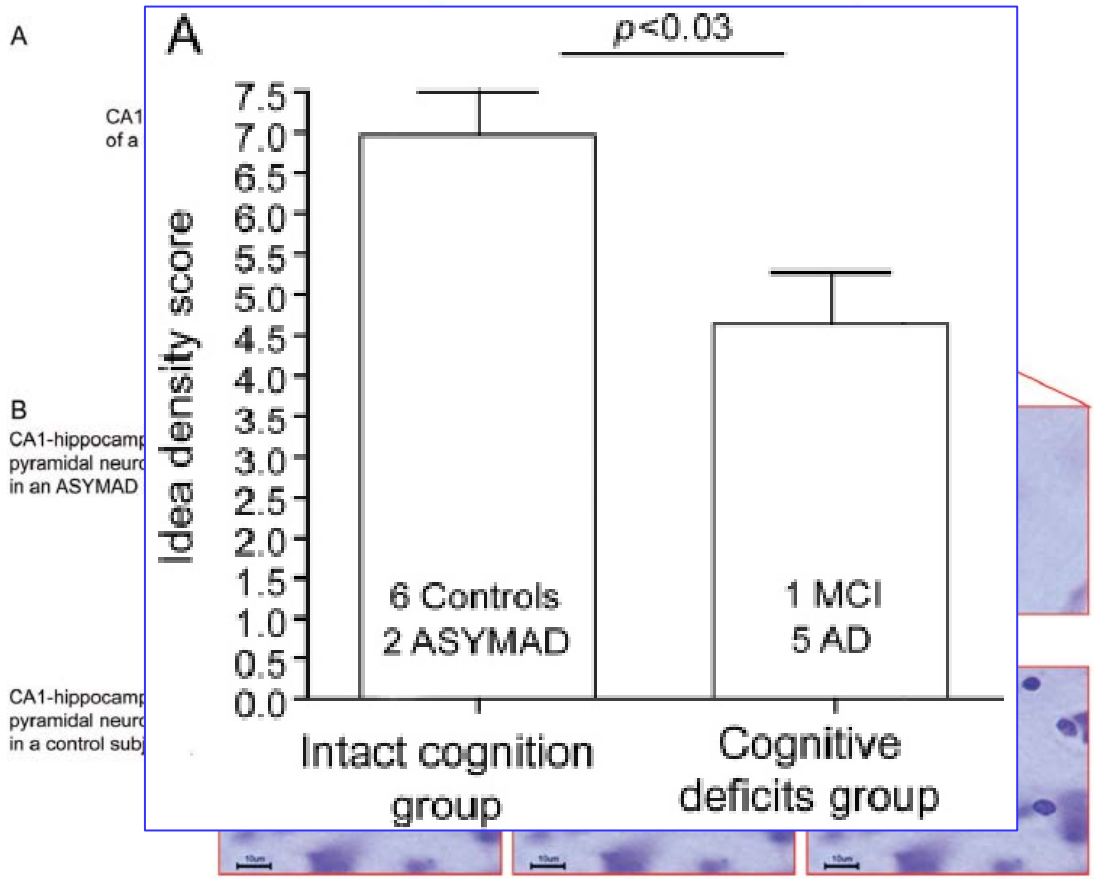
Alzheimer's disease-related pathological process leading to neurofibrillary tangle formation does not begin in the cerebral cortex but, rather, in select subcortical nuclei, and it may start quite early, i.e., before puberty or in early young adulthood.


PARA ABRIR
RTA PULSAR
BOTON

The Nun Study

Clinically silent AD, neuronal hypertrophy, and linguistic skills in early life

Iacono D, et al. ***Neurology*** 2009;73:665–673

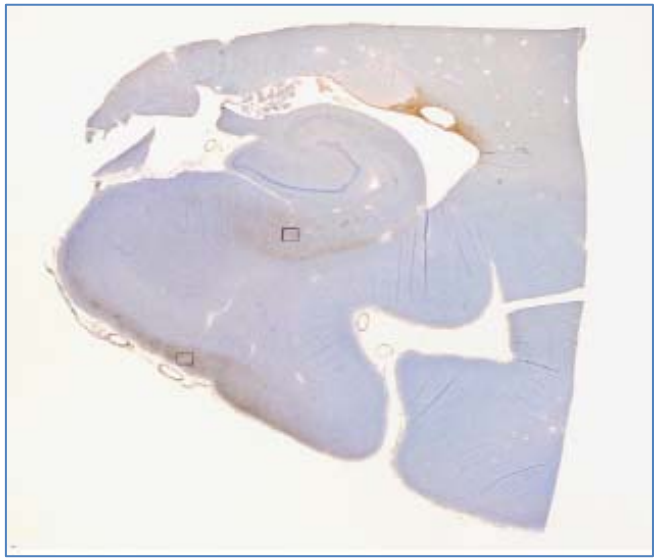


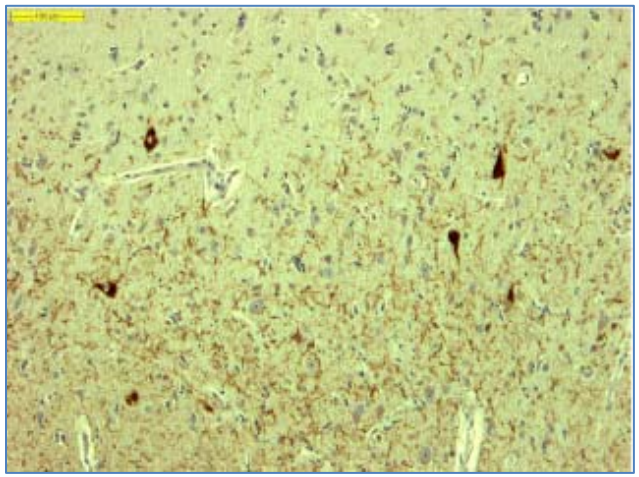
1) **Neuronal hypertrophy may constitute an early cellular response to AD pathology**
2) **higher idea density scores in early life are associated with intact cognition in late life despite the presence of AD lesions.**

No disease in the brain of a 115-year-old woman

Wilfred F.A. den Dunnena et al Neurobiology of Aging 29 (2008) 1127–1132

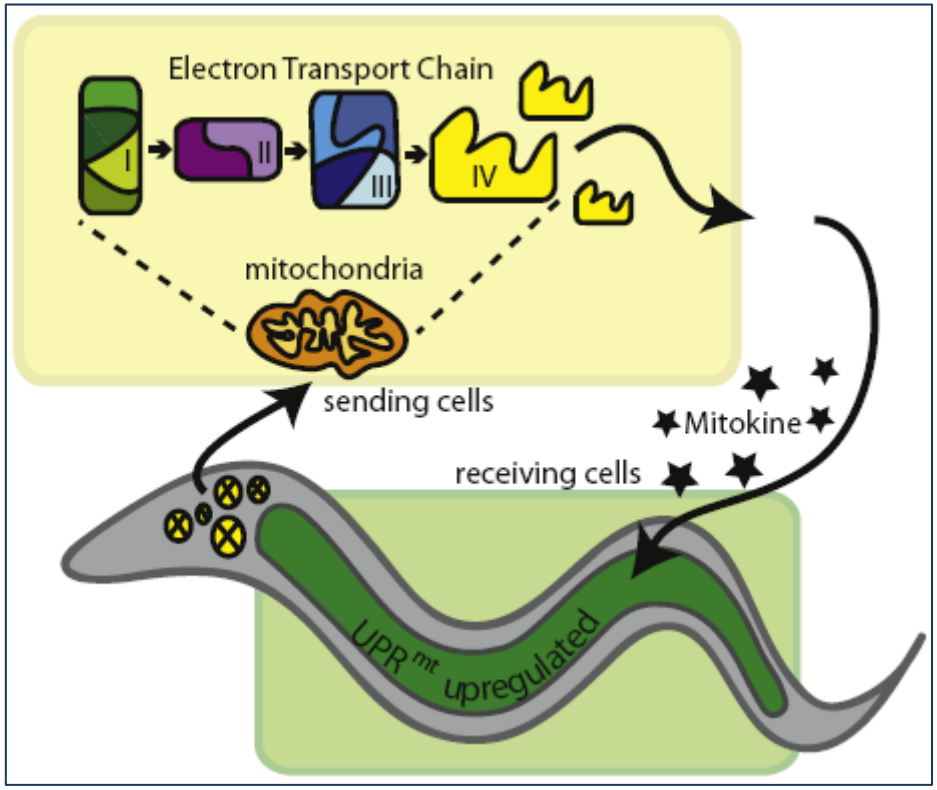
		November 2002	May 2004
Dementia screening	Mini mental state examination[a] (without visual items; max. = 27)	27	26
	Cognitive screening test[b] (max. = 20)	20	20
Attention	Digits forward (WAIS)	Score 6 Span: 5 digits (6th decile 55–65 years)	Score 5 Span: 5 digits
Working memory	Digit backwards (WAIS)[c]	Score: 6 Span: 4 digits (6th decile 55–65 years)	Score 2 Span: 2 digits
	Serial sevens[d]	4 errors (in complete series)	3 errors (stuck halfway; test terminated)
Verbal reasoning	Similarities subtest of the Groninger intelligence test[e]	>16 (7th decile 60–75 years)	not administered
Retrieval from semantic memory	Word fluency (1 min) animals[e]	15 (5th decile 60–75 years)	16 (5th decile 60–75 years)
	Word fluency (1 min) professions[e]	14 (6th decile 60–75 years)	10 (2th decile 60–75 years) (some preservation)





The Cell-Non-Autonomous Nature of Electron Transport Chain-Mediated Longevity

Durieux J, et al. **Cell** January 7, 2011; 144, 79–91



Model for the Cell-Non-Autonomous Nature of the UPRmt Cells experiencing mitochondrial stress, in this scenario neuronal cells (circles) marked within the yellow box, produce a signal that is transmitted from the mitochondria to the nucleus to regulate the expression of genes regulated by UBL-5 and possibly DVE-1. These cells serve as sending cells and produce an extracellular signal (mitokine) that can be transmitted to distal, receiving cells, in this case intestinal cells marked in the green box. Receiving cells perceive the mitokin

The alteration of mitochondrial function in key tissues is essential for establishing and maintaining a prolongevity cue. Mitochondria may establish and perpetuate the rate of aging for the whole organism independent of cell-autonomous functions.

¿pero qué haces para mantenerte tan bien?

- Hago ejercicio. Vigilo las calorías de la dieta (mediterranea o asturiana), siempre con un vaso de vino o sidra.
- No fumo
- Tengo una vida social activa, leo, escucho música, miro la TV (especialmente los partidos de futbol del Barça)

pero tu tampoco recuerdas el nombre de las personas, ¿cómo estás seguro de estar empezando un alzheimer?

- Me han hecho unos test y tengo la memoria semántica bien
- En la RM no tengo atrofia del hipocampo, ni lesiones vasculares
- En el LCR mis valores de b-42 y de P-tau son normales
- En el PET-FDG tengo toda la corteza roja
- En el PET-PIB tengo la corteza verde.....

Hospital de la Sta Creu i Sant Pau