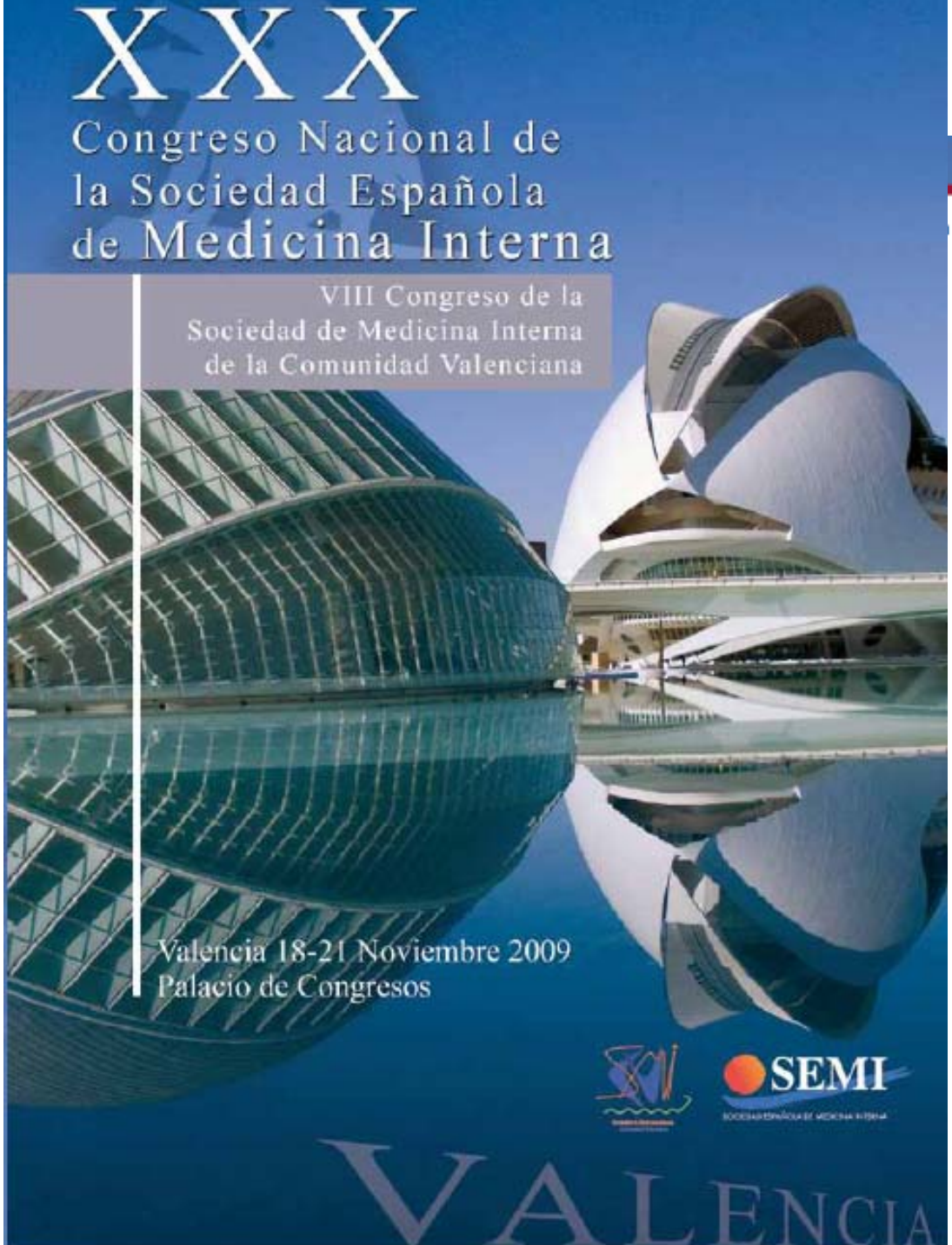


JUEVES, 19 DE NOVIEMBRE

AUDITORIO 1

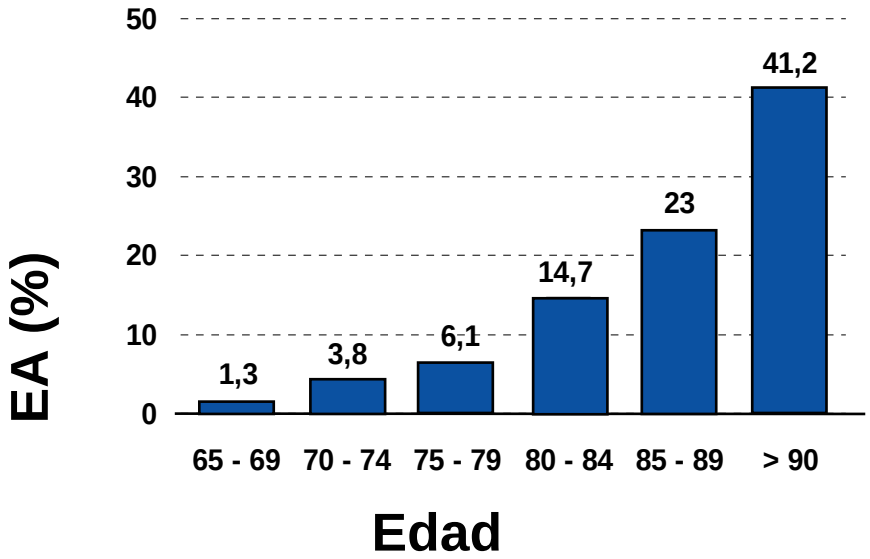
MESA REDONDA 7

AVANCES EN EL TRATAMIENTO DE LAS ENFERMEDADES NEUROLÓGICAS

Demencias

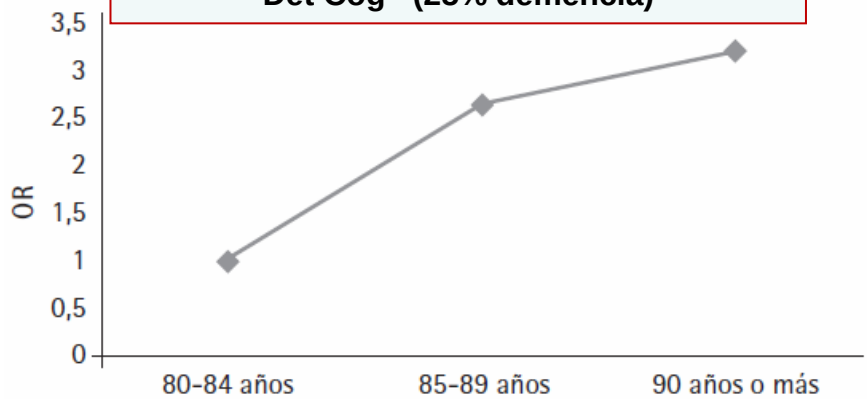
Dr. Rafael Blesa González
Servicio de Neurología
Hospital de la Santa Creu i Sant Pau. Barcelona

Epidemiología



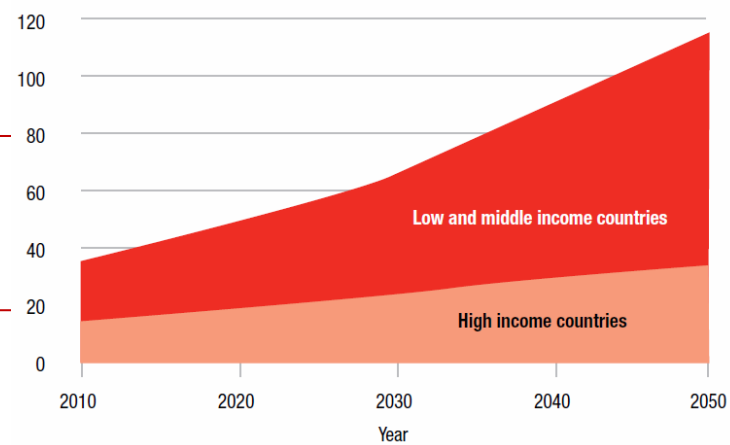
Launer, LJ et al. Neurology, 1999; 52: 78-84

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



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

An estimated 35.6 million people worldwide will be living with dementia in 2010. This number is estimated to nearly double every 20 years, to 65.7 million in 2030, and 115.4 million in 2050.

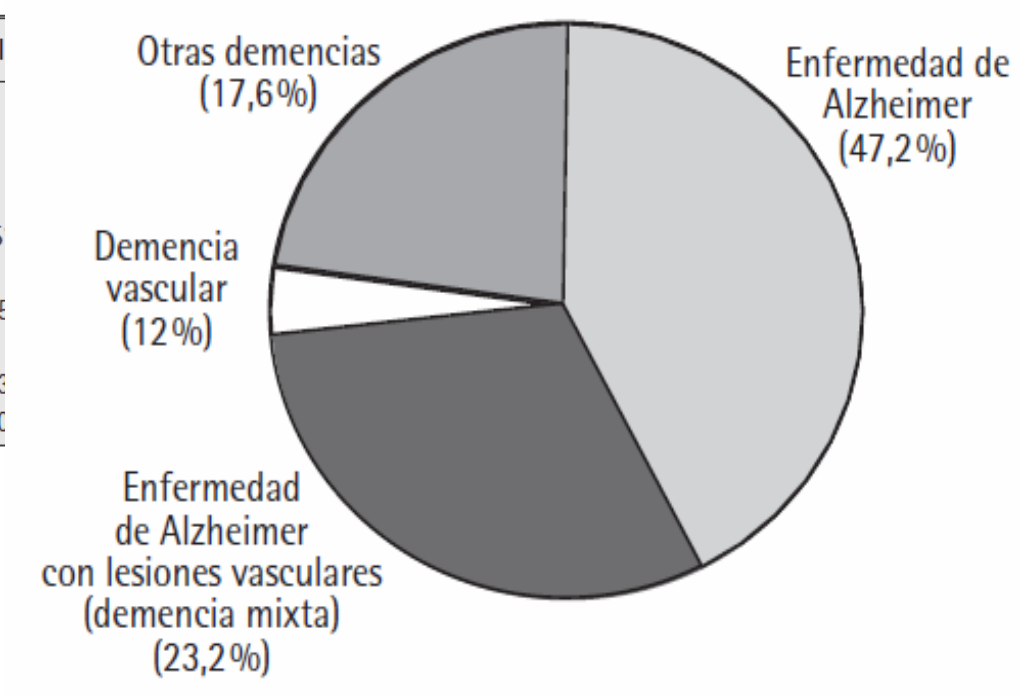


Prevalencia de deterioro cognitivo en personas mayores de 80 años: estudio COGMANLLEU

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

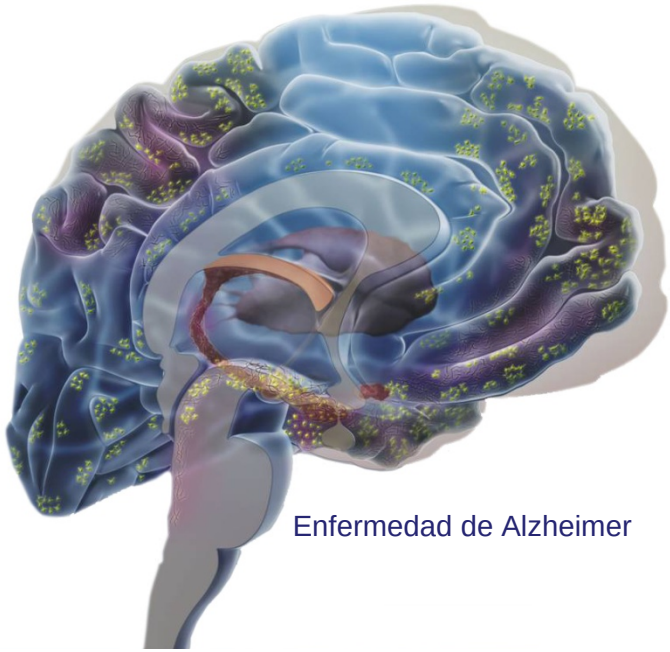
Prevalencia de demencia

	80-84	85-89	90-94	≥95	Total
Total					
Número de sujetos evaluados	206	181	47	6	440
Alzheimer sin lesiones vasculares	5,8 (12)	16 (29)	19,1 (9)	16,7 (1)	11,6 (5
Alzheimer con lesiones vasculares	2,9 (6)	9,4 (17)	4,2 (2)	–	5,7 (25
Demencia vascular	1,9 (4)	3,3 (6)	6,4 (3)	–	2,9 (13
Demencias (todas)	13,1 (27)	33,1 (60)	38,3 (18)	50,0 (3)	24,5 (10

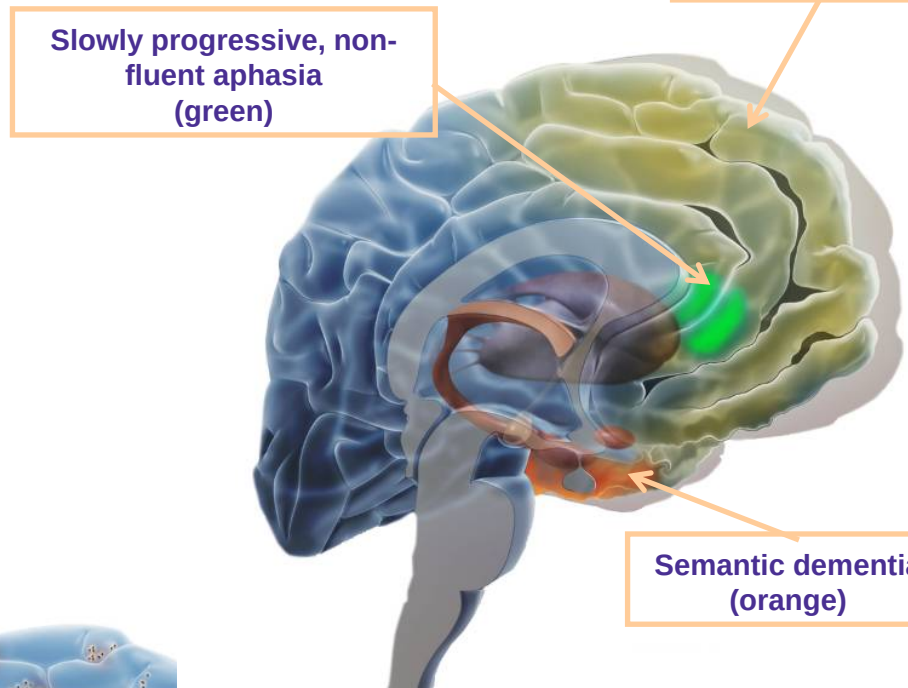


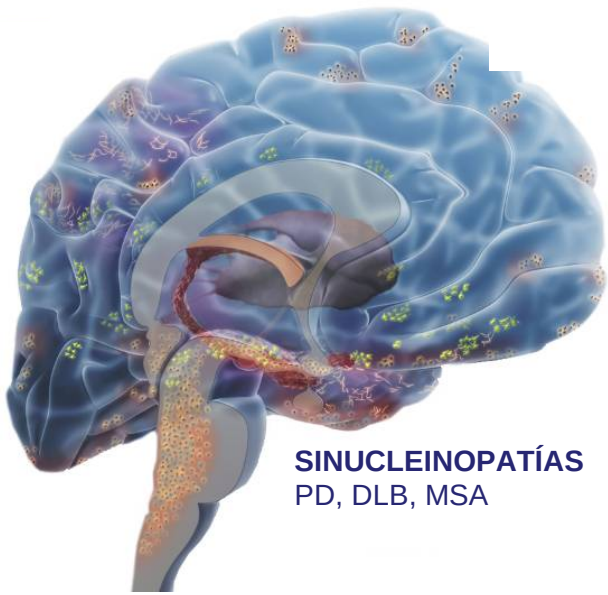
-**EA representaba 70,3 % de las demencias**
- **Demencia vascular 12%**
- **Otras demencias degenerativas y secundarias 17,6%.**
- **Se observó asociación de la demencia con la edad y el género.**

Demencias neurodegenerativas = PROTEINOPATÍAS



Enfermedad de Alzheimer





SINUCLEINOPATÍAS
PD, DLB, MSA

Biochemical classification of degenerative dementias

1.Tauopathies (examples):
- Tangle-dominant dementia (3+4R tau, no/few amyloid deposits)
- Argyrophilic grain disease (4R tau) (+/¡ Alzheimer lesions)
- Progressive supranuclear palsy, Corticobasal degeneration (4R tau)
- Frontotemporal dementia linked to chromosome 17 (FTDP-17)
- Pick's disease (3R tau doublet, no Exon 10)

1a. Alzheimer disease (3+4R tau triplet + amyloid) – probably a specific entity

2. -Synucleinopathies
- Dementia with Lewy bodies
- Parkinson's disease with dementia (PDD)

3. TDP-43 proteinopathies
- ALS-dementia (uibiquitin/TDP-43 + inclusions)
- Familial FTLD with Ubi + , Tau-negative inclusions FTD + MND) [progranulin]

4. Polyglutamine repeat (CAG) disorders
- Huntington's disease (CAG triplet repeat)

5. Neuro Filmentopathies
- *Intermediate filament inclusion disease (NIFID)*

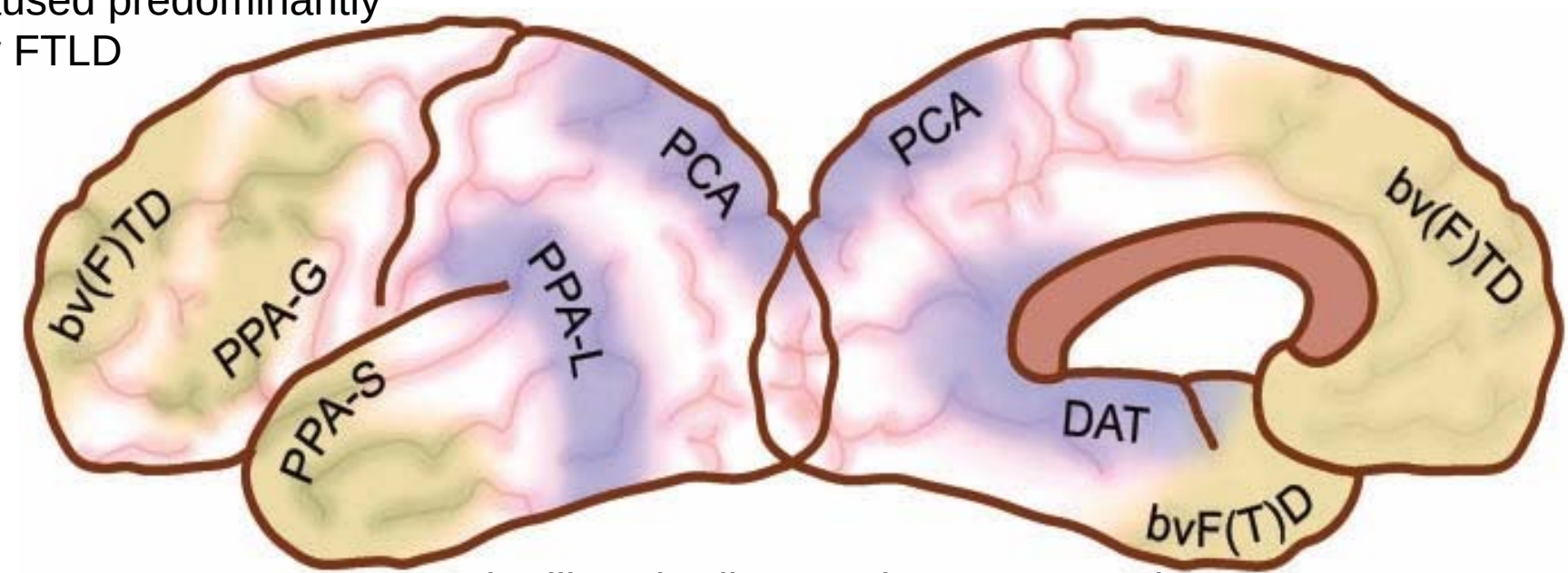
6. Neuroserpinopathies
-Dementia + myoclonus epilepsy (neuroserpin gene mutation)

7. Prion diseases

8. Lysosomal disorders
- Niemann-Pick type C disease. Ceroid lipofuscinosis, etc.

Frontotemporal lobar degeneration

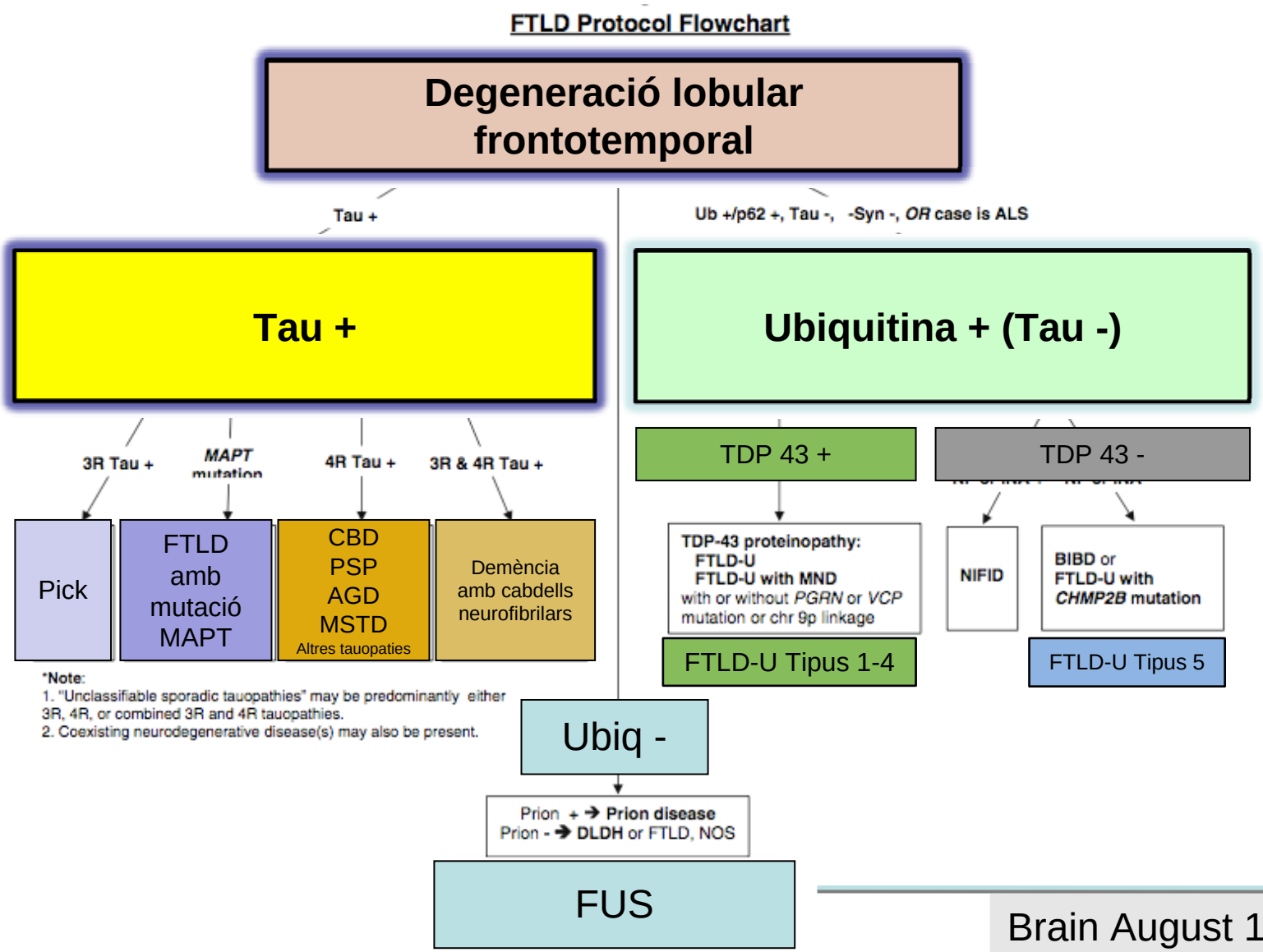
The tan shading indicates syndromes caused predominantly by FTLD



The lilac shading syndromes caused predominantly by Alzheimer's disease: DAT = amnestic dementia of the Alzheimer type; PCA = posterior cortical atrophy syndrome.

Weintraub S, Mesulam M. **Brain 2009:** 132; 2906–2908

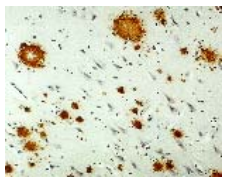
Classificació anatomopatològica



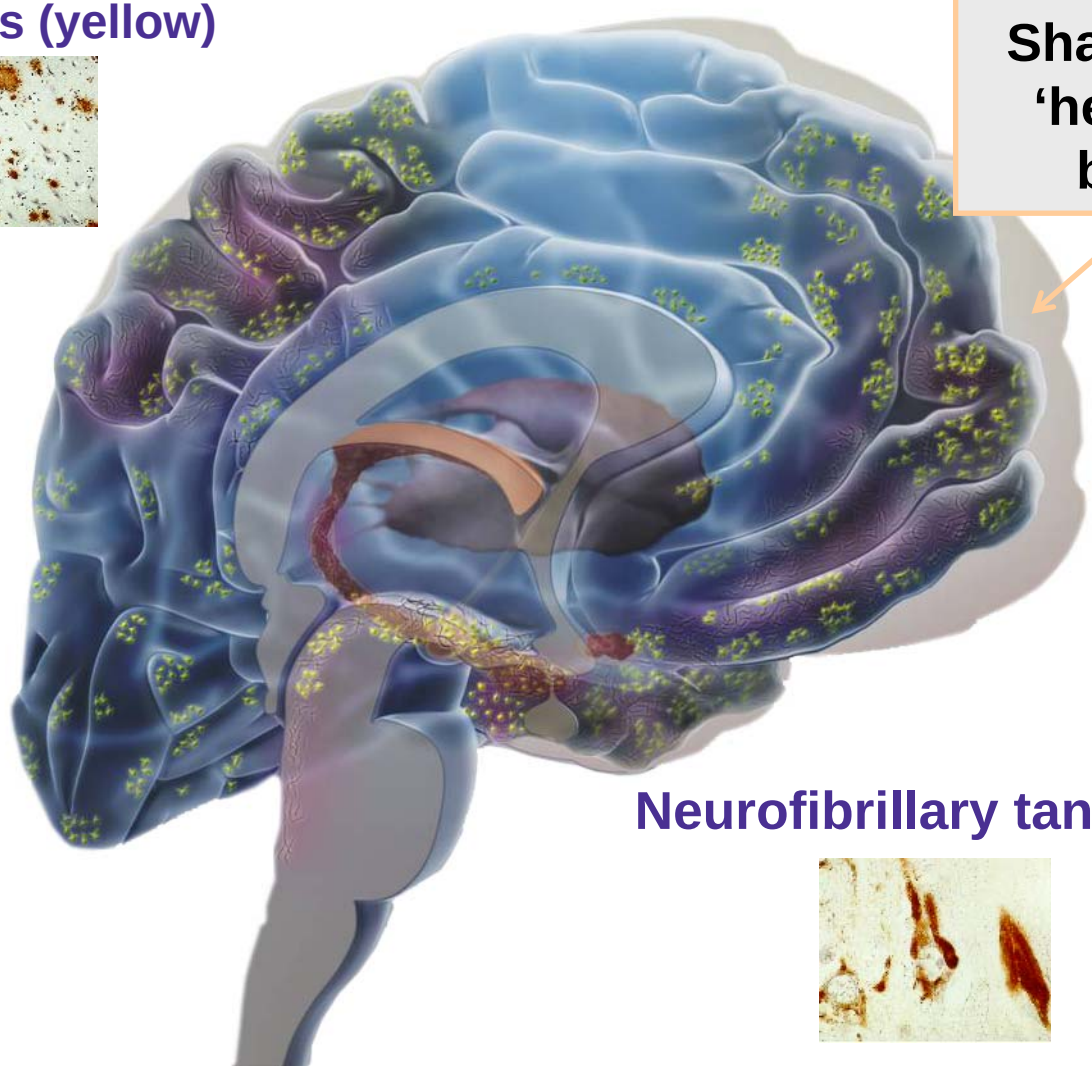
Brain August 11, 2009

AD pathology: brain atrophy and distribution of plaques and neurofibrillary tangles

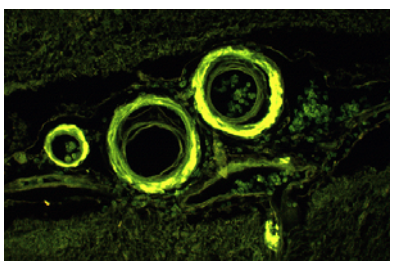
Plaques (yellow)



Shadow of 'healthy' brain

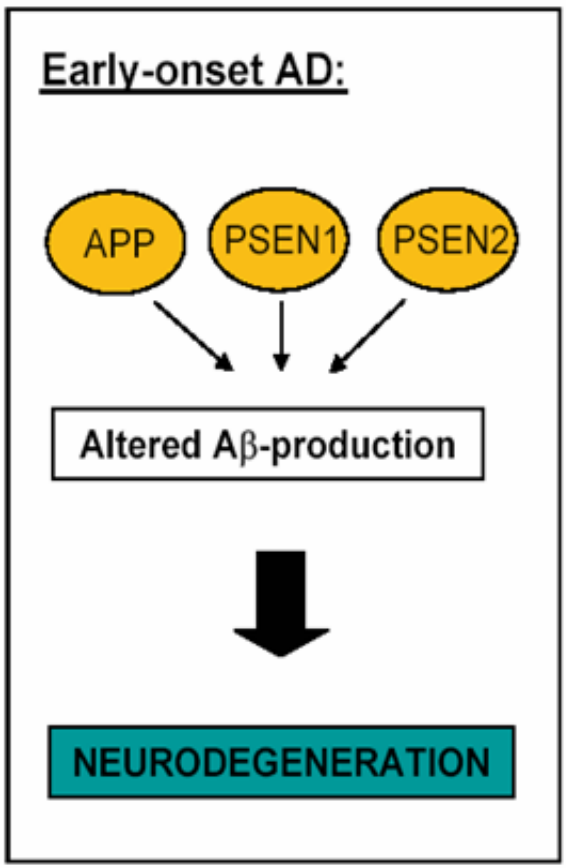


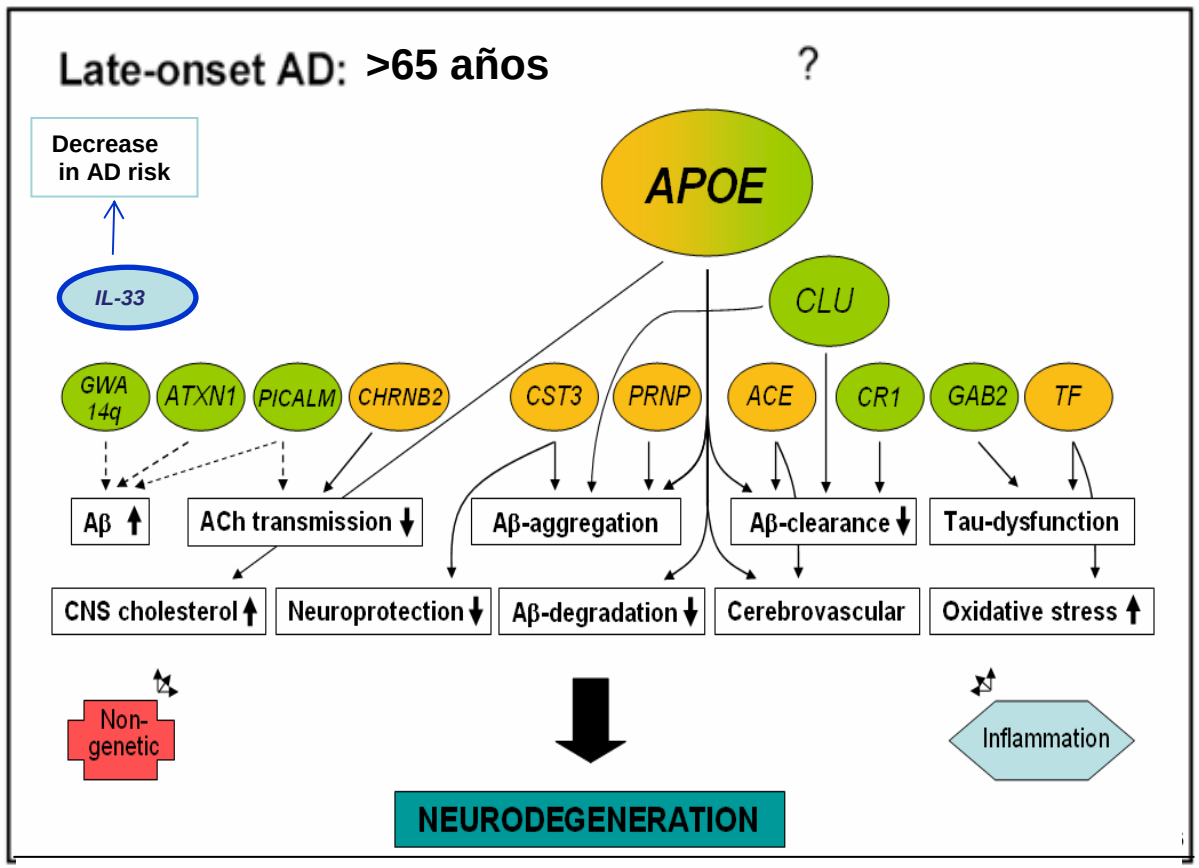
Angiopatía amiloide



Neurofibrillary tangles (pink)

The dichotomy of AD genetics





“Simplex AD” (<5%)

“Complex AD” (>95%)

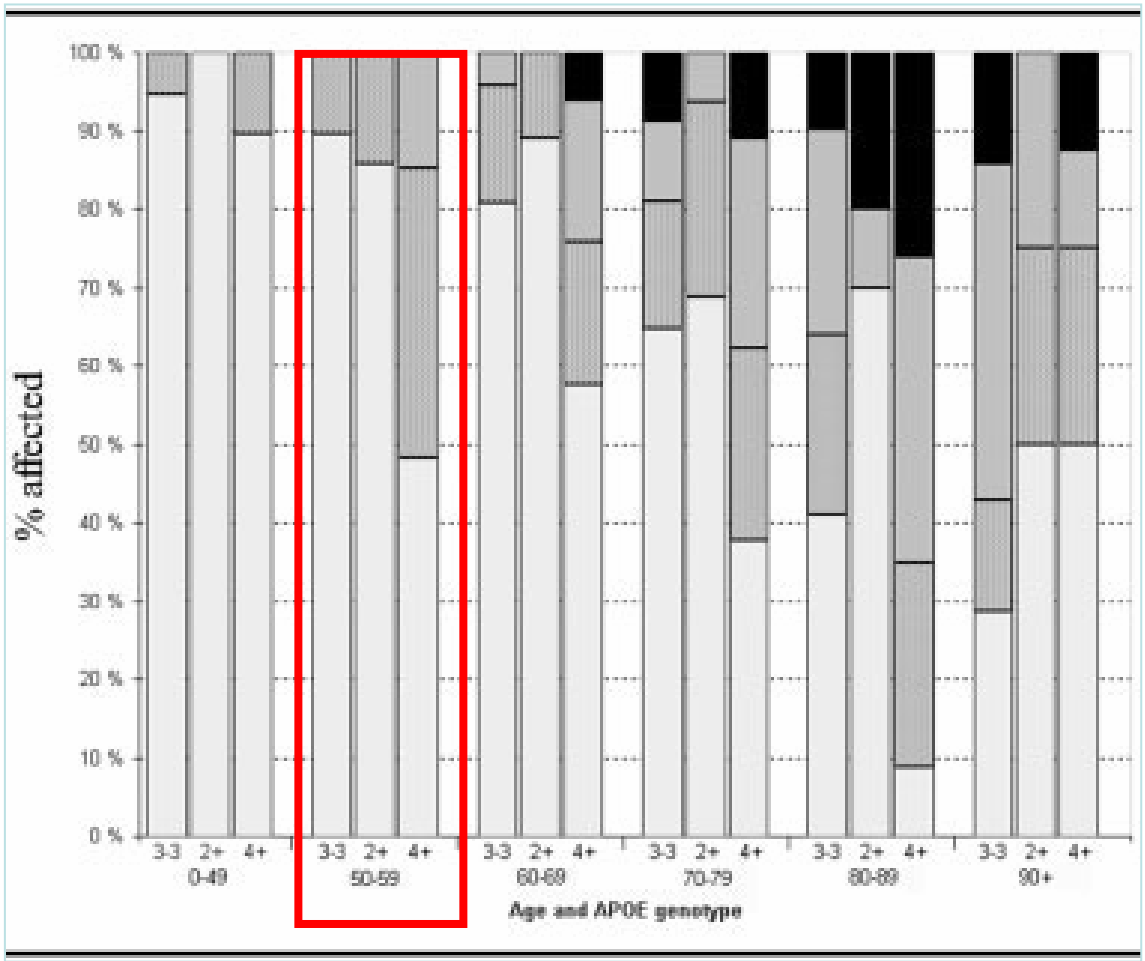
Factores genéticos y ambientales que pueden influir en la forma senil de la enfermedad de Alzheimer: estudio de casos y controles anidado
Bufill E et al. *Neurología 2009;24(2):108-112*

Variable	β estimado	*Odds ratio* ajustada	IC 95% OR	p (Test Wald)
Edad				
86 años y más	1,88	6,54	2,06-20,82	0,001
Sexo				
Mujer	1,15	3,17	0,80-12,50	0,099
Hipertensión	-1,01	0,37	0,10-1,32	0,123
Anestesia general	1,17	3,23	1,03-10,09	0,044
Antecedentes de demencia	0,65	1,91	0,60-6,04	0,271
Presencia de ApoE4	1,23	3,44	0,67-17,62	0,139

La edad es el principal factor asociado a la EA.
Otros factores: sexo femenino, haber estado expuestos a anestesia general y ApoE4

Apolipoprotein E–Dependent Accumulation of Alzheimer Disease–Related Lesions Begins in Middle Age

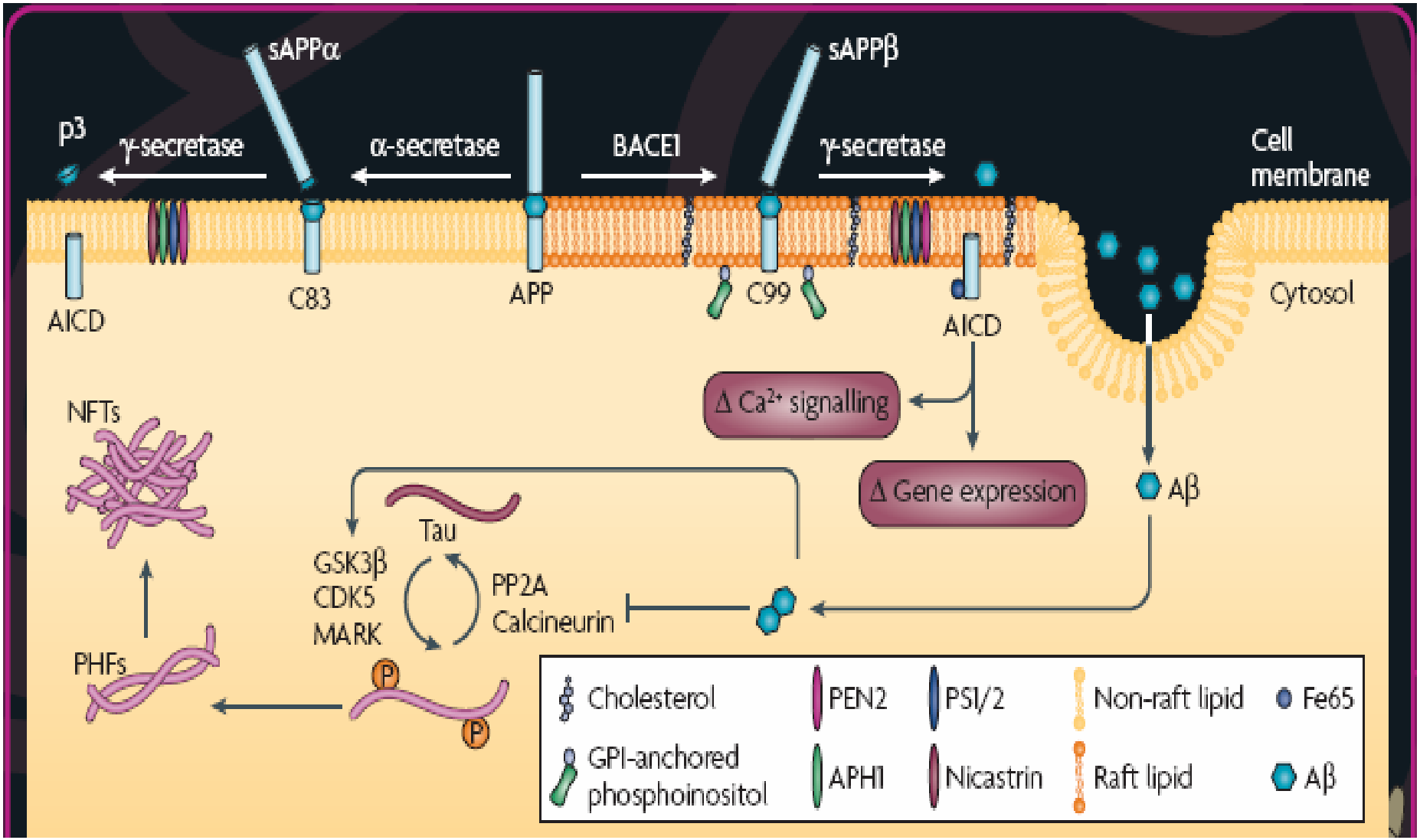
Kok E, et al**. Ann Neurol 2009;**65:650–657



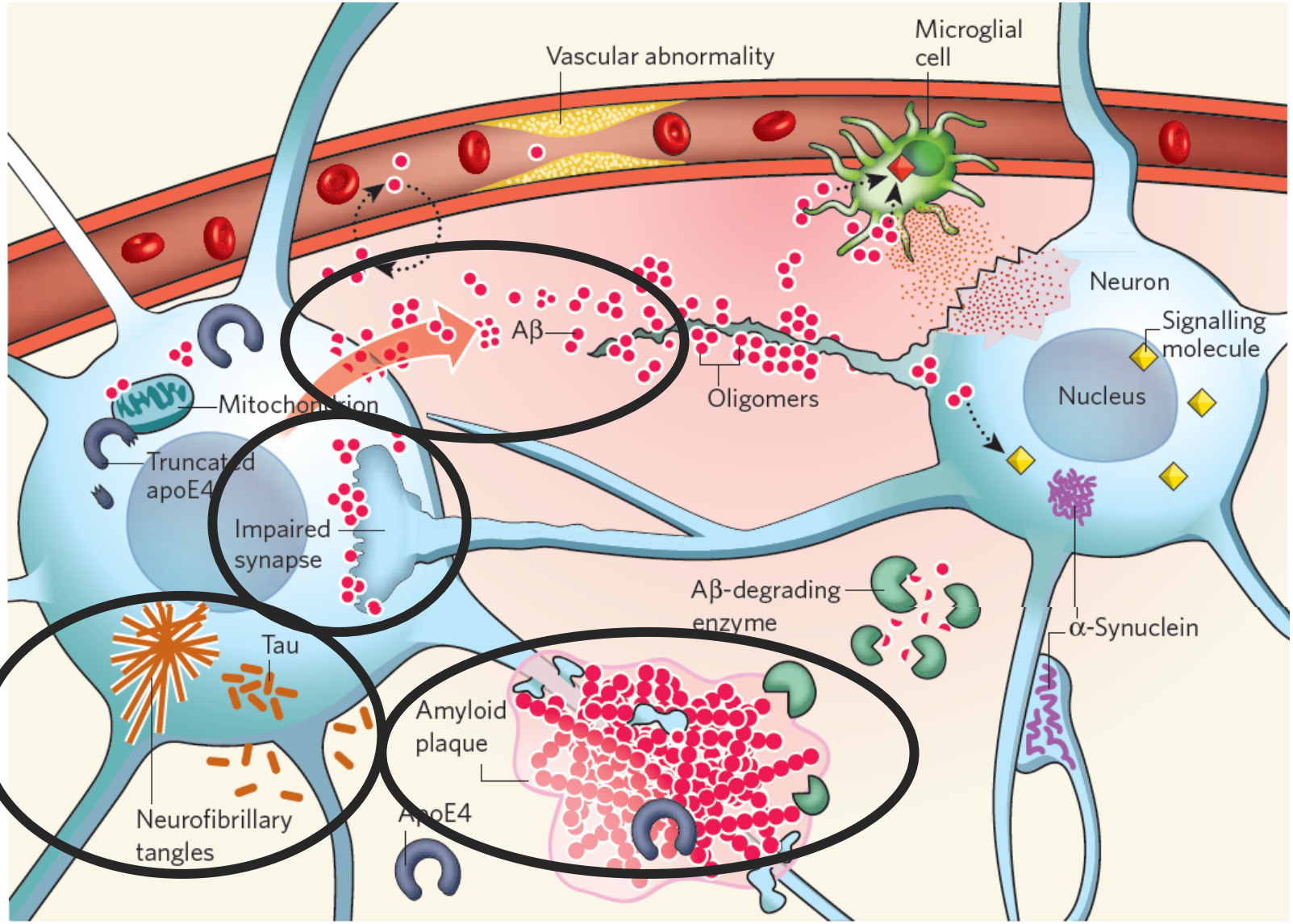
Appeared at around 30 years of age, reaching almost 100% in the oldest.

Interpretation: The brain changes associated with AD may already begin developing early in middle age, especially among APOE ε4 carriers.

APP and tau processing in neurons



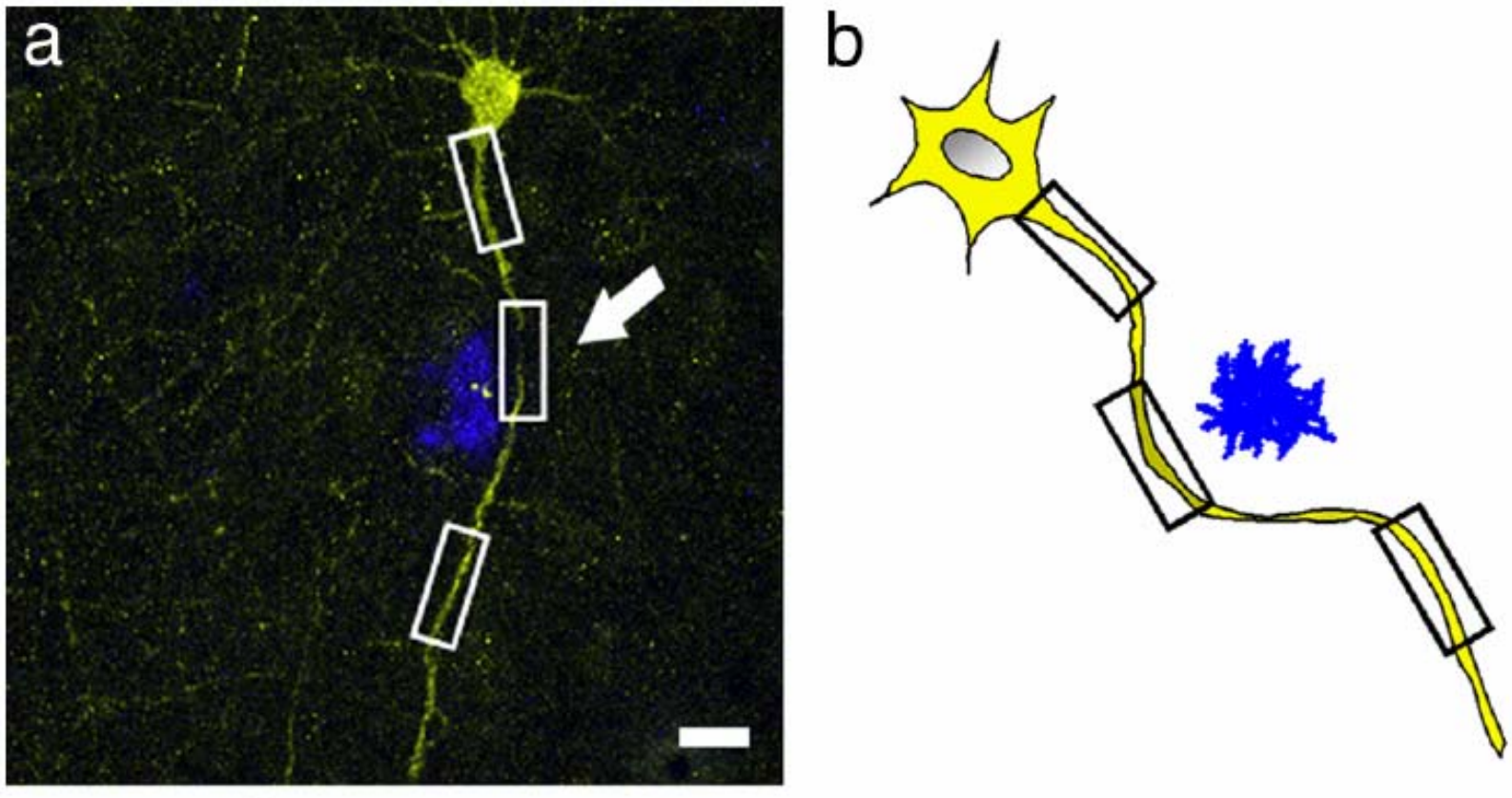
LaFerla FM. Nature Review Neuroscience, 2008



Lennart Mucke, **NATURE Vol 461|15 October 2009**

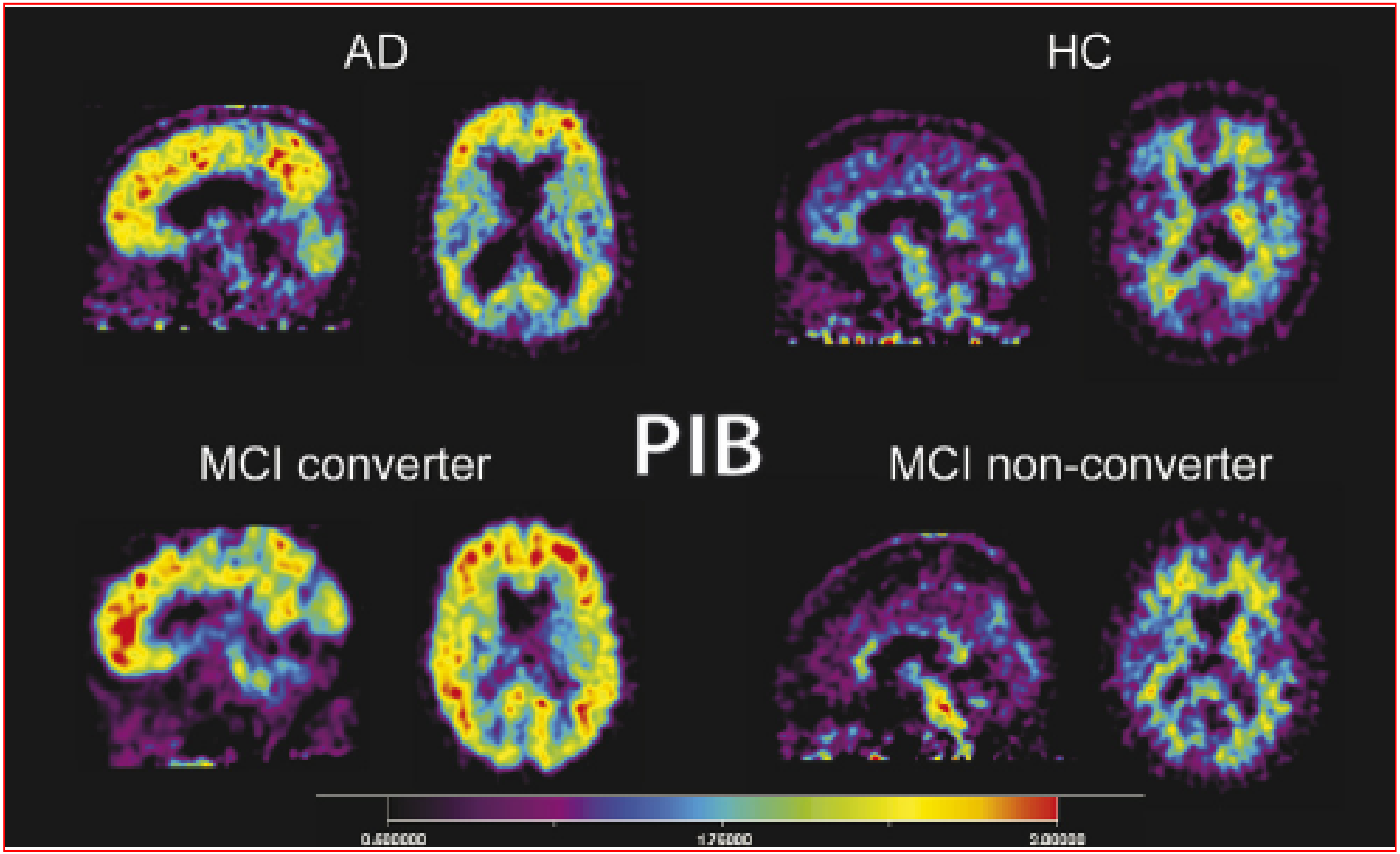
A Reporter of Local Dendritic Translocation Shows Plaque – Related Loss of Neural System Function in APP-Transgenic Mice

Meyer-Luehmann M, et al. The Journal of Neuroscience, October 7, 2009 • 29(40):12636 –12640

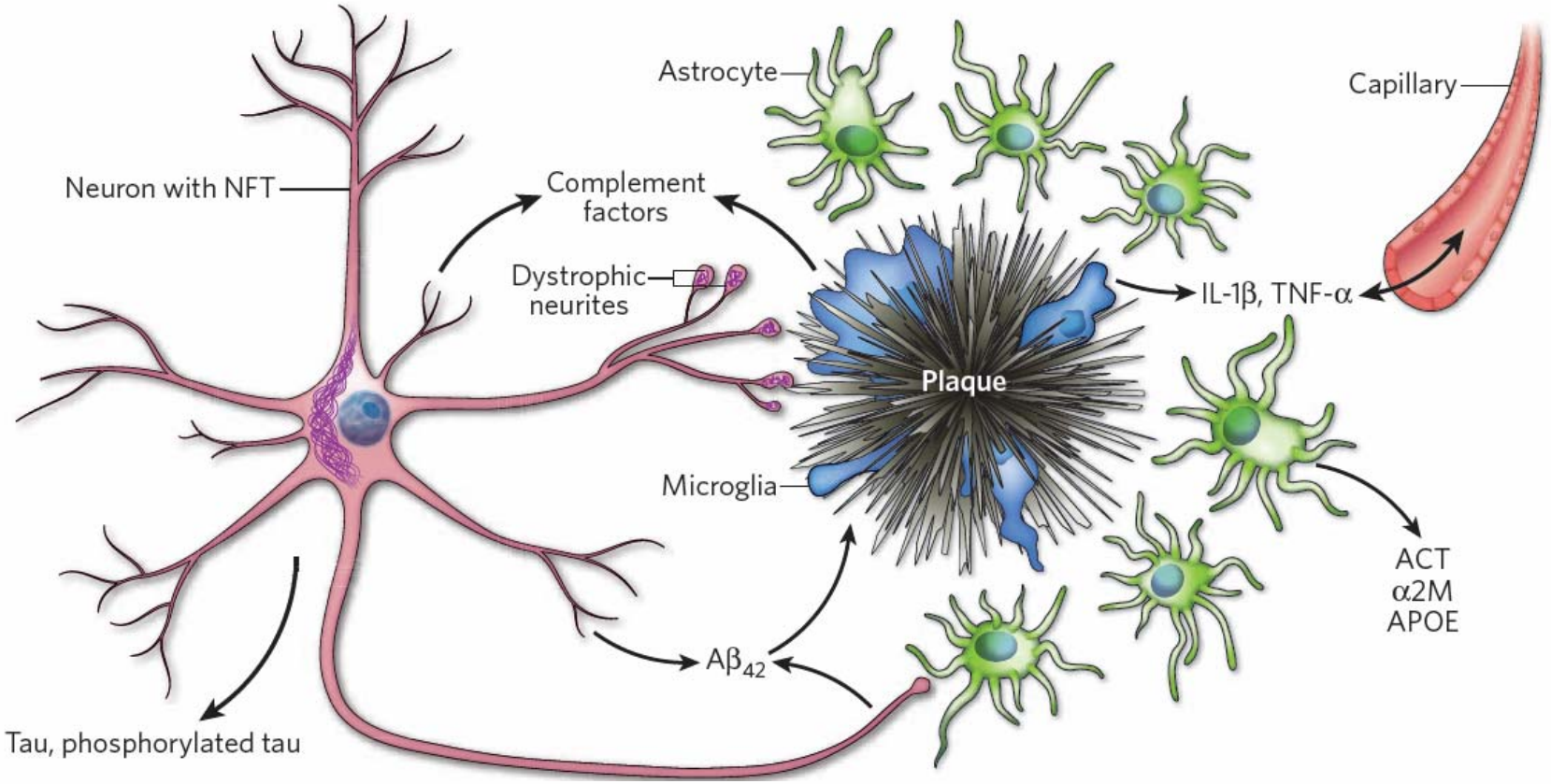


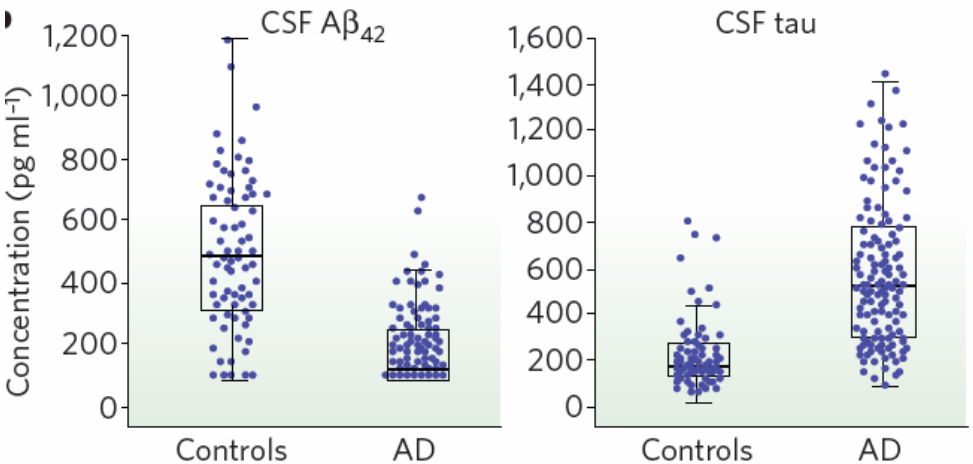
In APP/PS1 mice, neurons close to plaques, and dendritic segments close to plaques, both showed diminished fluorescent intensity and therefore neuronal activity.

Plaques are a focal lesion leading to impaired neural system function

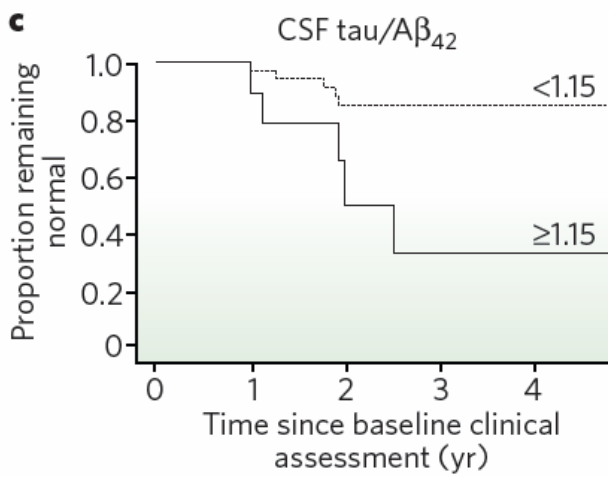


Forsberg A et al. Neurobiology of Aging 29 (2008) 1456–1465


Astrocyte
Capillary
Neuron with NFT
Complement factors
Dystrophic neurites
IL-1β, TNF-α
Plaque
Microglia
ACT
α2M
APOE
Aβ42
Tau, phosphorylated tau

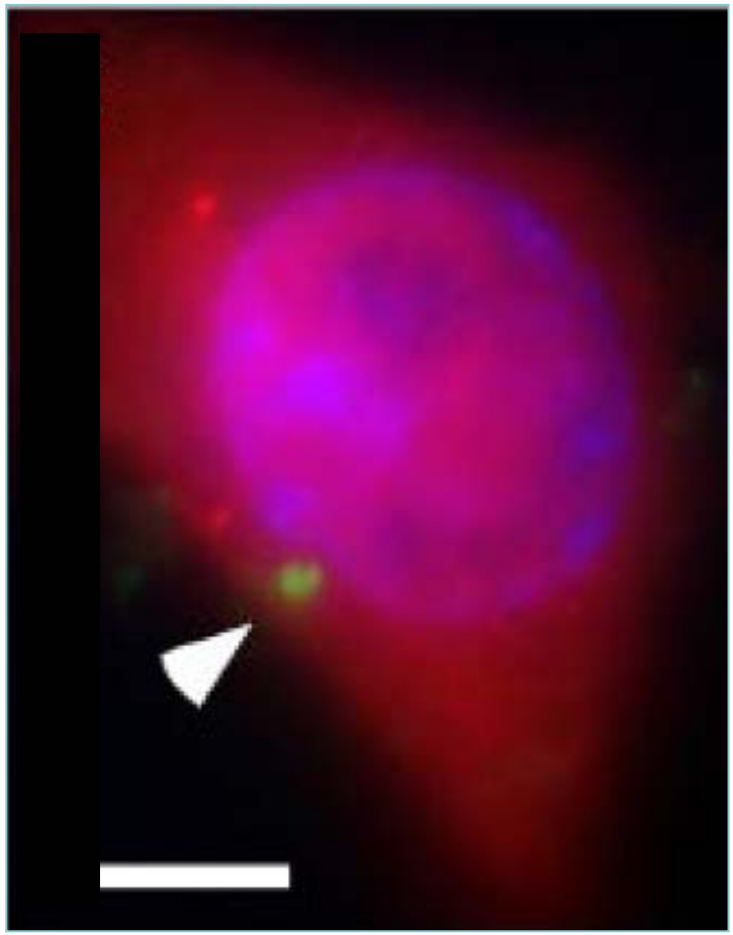

CSF Aβ42
Concentration (pg ml-1)
1,200
1,000
800
600
400
200
0
Controls
AD

CSF tau
1,600
1,400
1,200
1,000
800
600
400
200
0
Controls
AD


c
CSF tau/Aβ42
Proportion remaining normal
1.0
0.8
0.6
0.4
0.2
0
<1.15
≥1.15
0
1
2
3
4
Time since baseline clinical assessment (yr)

Propagation of Tau Misfolding from the Outside to the Inside of a Cell

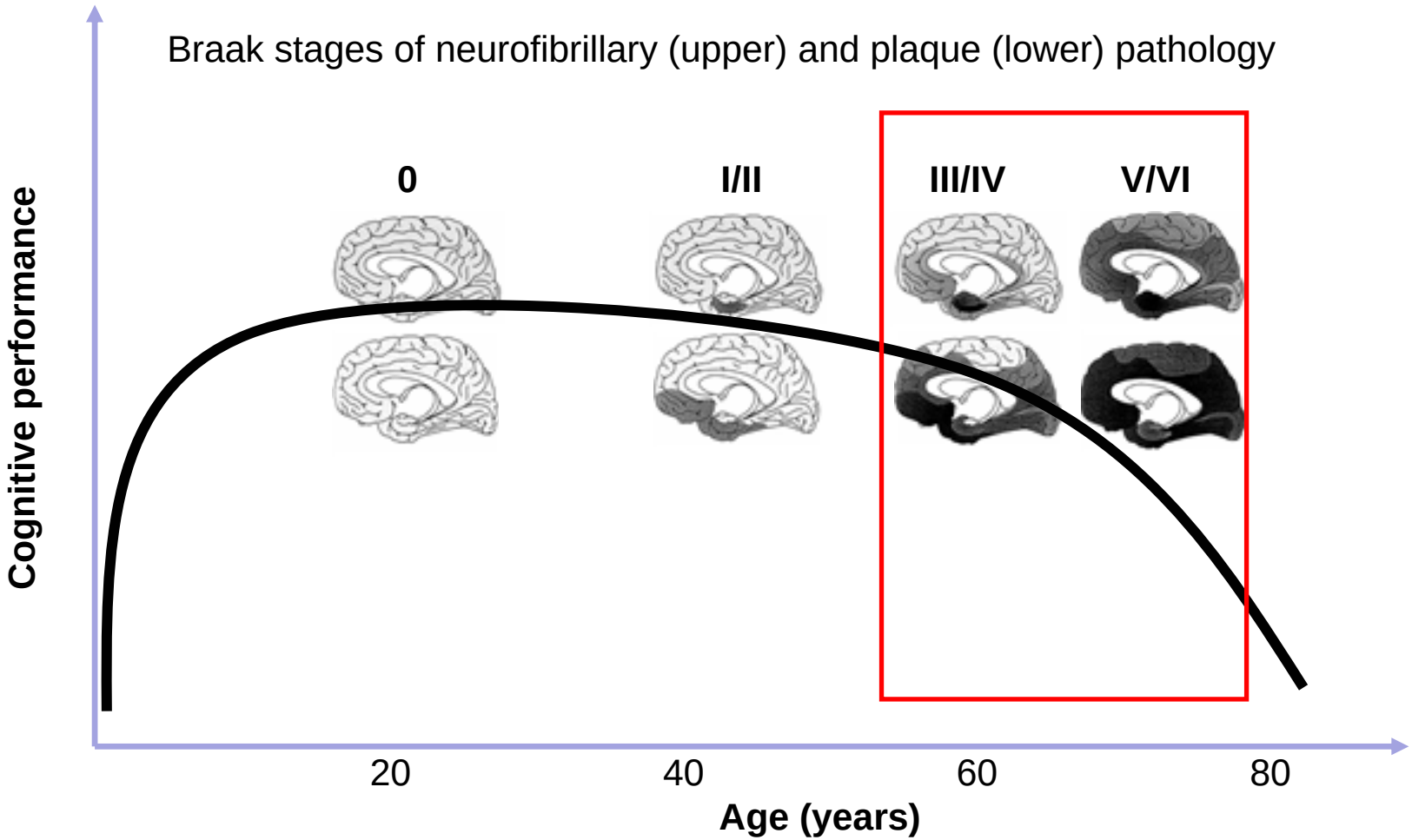
Bess Frost B, et al. THE JOURNAL OF BIOLOGICAL CHEMISTRY
VOL. 284, NO. 19, pp. 12845–12852, May 8, 2009



Direct visualization indicates a Tau-YFP inclusion (*white arrowhead*) within an mCherry-expressing cell

Tau aggregates can propagate a fibrillar, misfolded state from the outside to the inside of a cell.

Tratamiento



Hans Förstl for Neuronet, Novartis

EFNS recommendations for the treatment of dementia

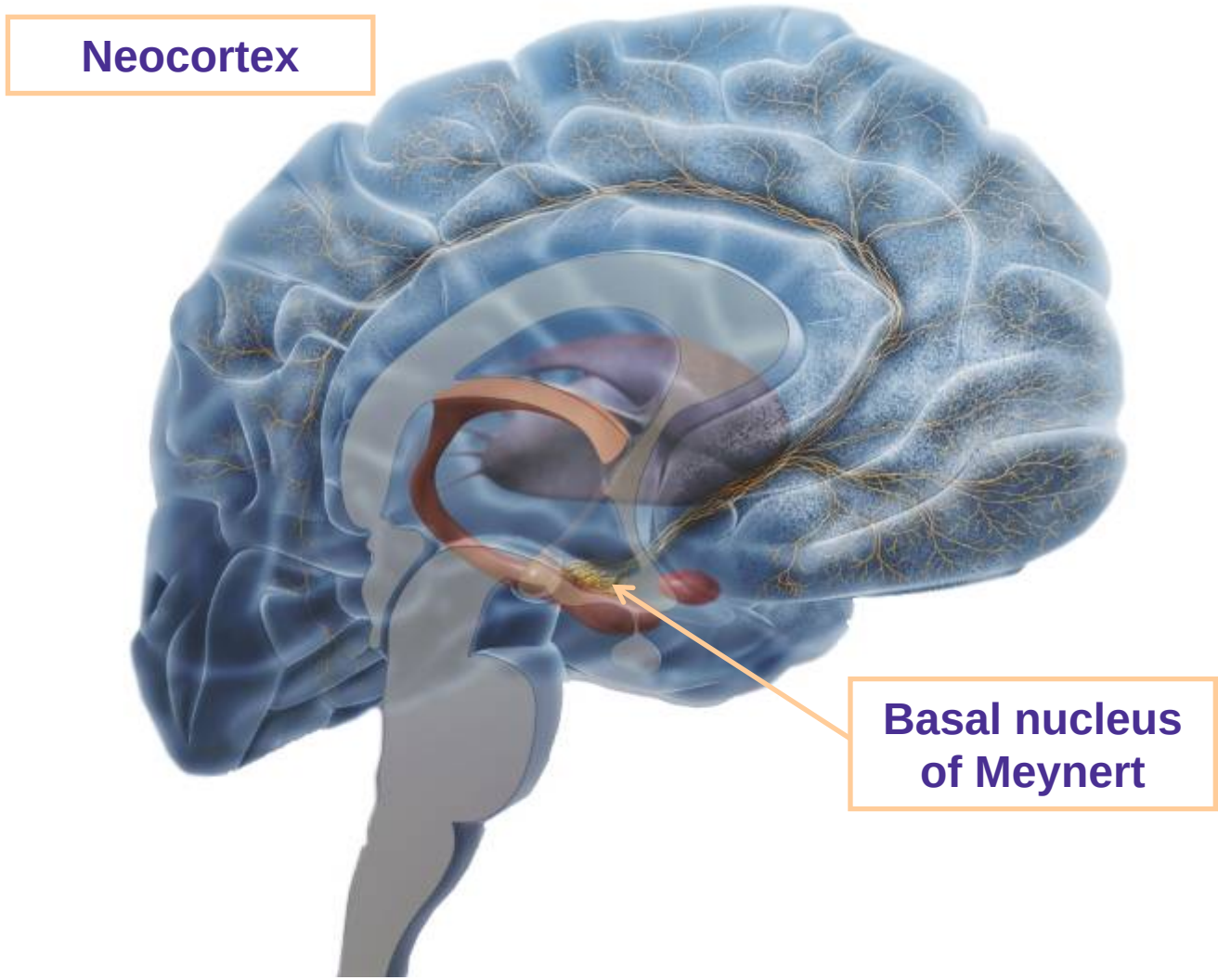
Alzheimer's disease

- ChEIs (rivastigmine, donepezil, galantamine, tacrine) at diagnosis
- Memantine alone, or in combination with a ChEI, in patients with moderate to severe Alzheimer's disease
- Insufficient evidence for the use of ginkgo biloba, anti-inflammatory drugs, nootropics, selegiline, oestrogens, vitamin E or statins

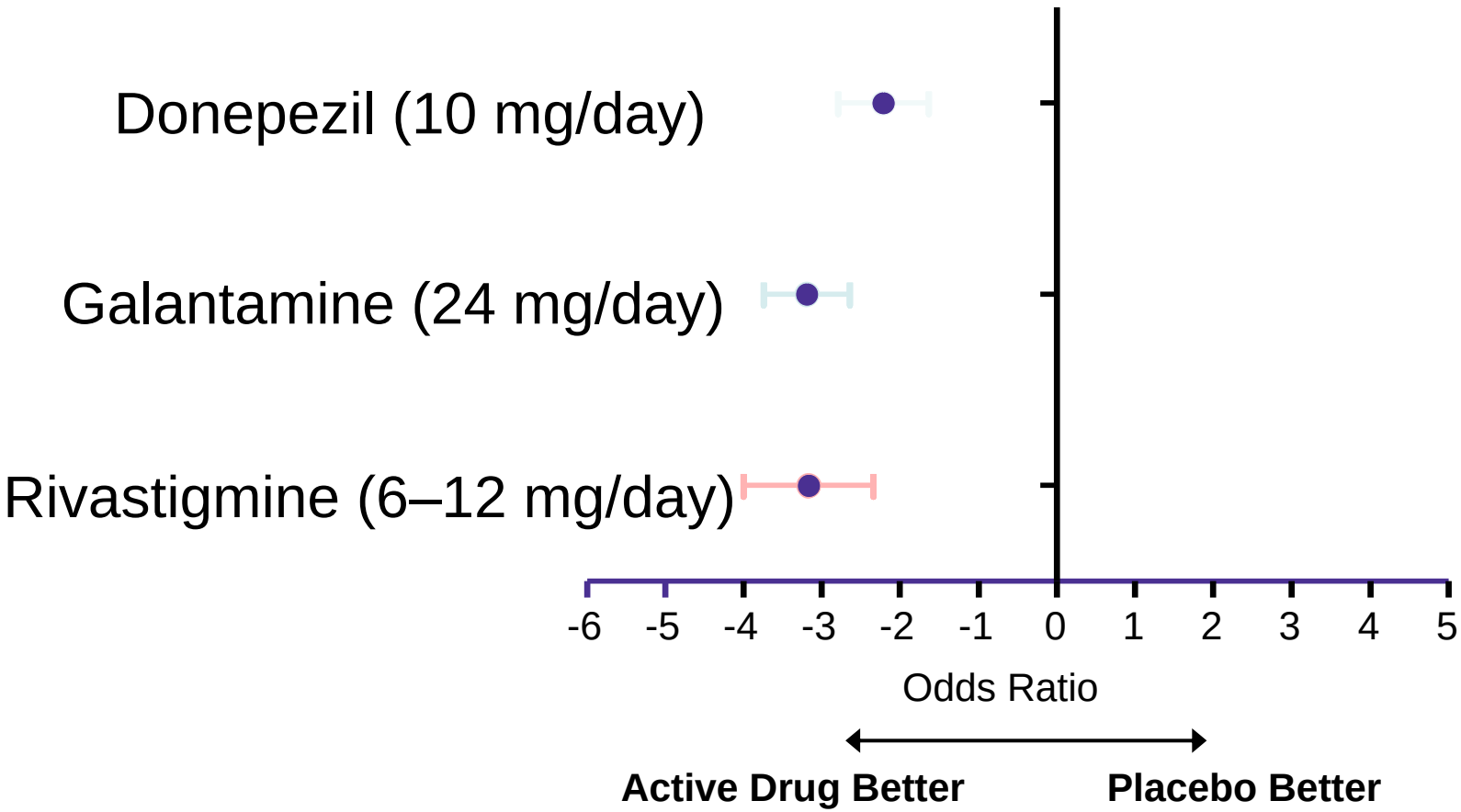
Parkinson's disease dementia

- ChEIs (rivastigmine is the only ChEI approved for PDD)
- Insufficient evidence for the use of memantine

Neocortical cholinergic projections from the basal nucleus of Meynert to the neocortex



Effects of oral ChEIs on cognition: Meta-analysis of pivotal trials



Ritchie CW, et al. *Am J Geriatr Psychiatry* 2004:12:358–69

Most common side effects of ChEIs

	Prescribing information (older oral meds)[1]				Patch study[2]	
	Placebo	Donepezil 10 mg/day	Galantamine 16–24 mg/day	Rivastigmine 6–12 mg/day	Placebo	Rivastigmine 9.5 mg/24 h
Nausea	6–12%	11%	24%	47%	5%	7%
Vomiting	3–6%	5%	13%	31%	3%	6%
Diarrhoea	5–11%	10%	9%	19%	3%	6%

1. Prescribing information for oral donepezil (2007), galantamine (2007) and rivastigmine (2006)
2. Winblad B, et al. *Int J Geriatr Psychiatry* 2007;22:456–67

Cholinesterase Inhibitors and Hospitalization for Bradycardia: A Population-Based Study

Park-Wyllie LY et al. PLoS Medicine, September 2009 | Volume 6 | Issue 9 | e1000157

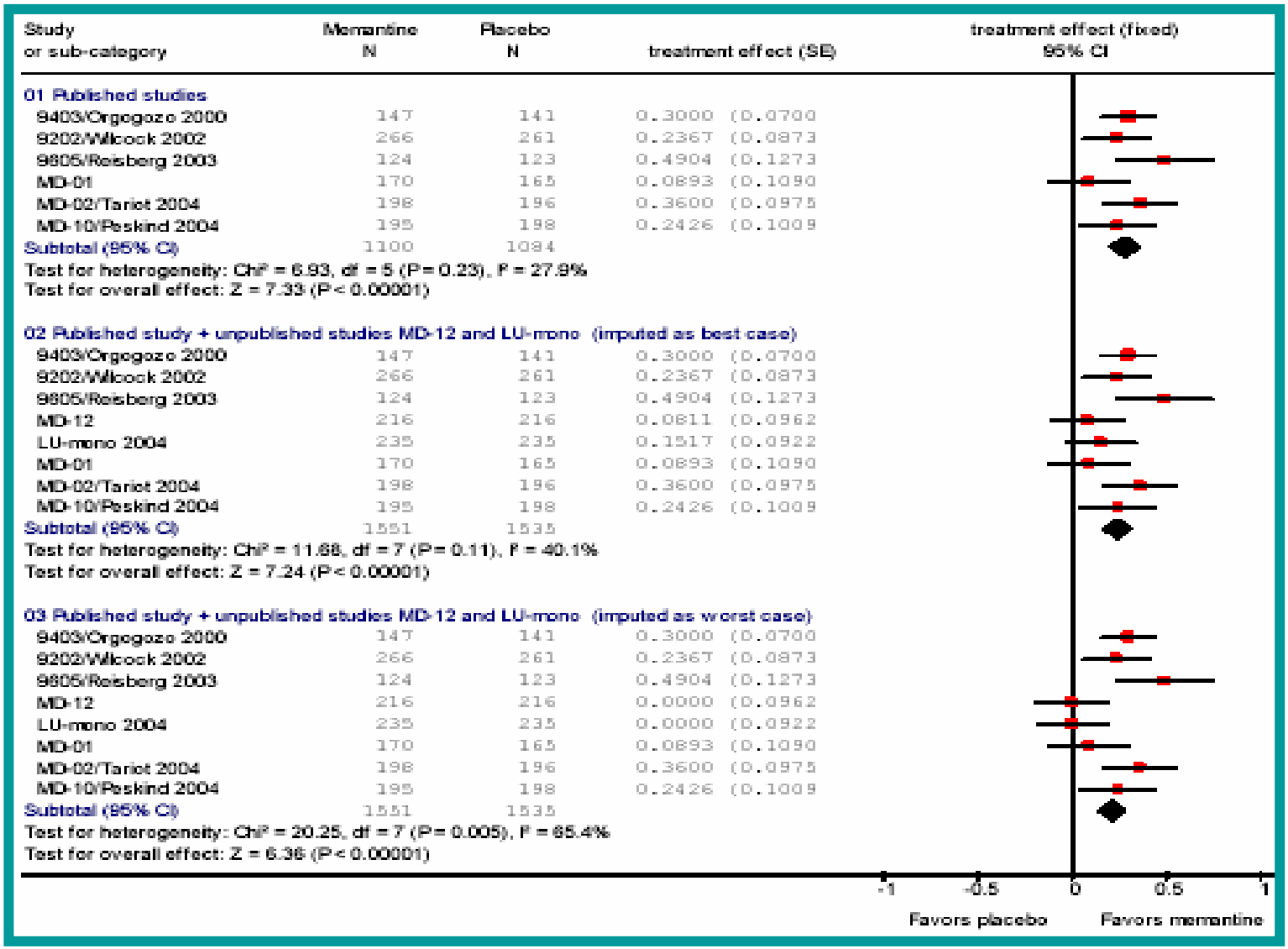
Table 2. Risk of bradycardia-related hospital admissions and recent cholinesterase inhibitor use.

Overall and Subgroup Analyses	Exposure in Risk Interval	Exposure in Reference Interval	Adjusted OR[a] (95% CI)
Full population			
Overall			2.13 (1.29–3.51)
Cases ($n=161$)	139	22	$p=0.003$
Control ($n=466$)	349	117	
I. Subgroup with cardiac comorbidity			
Overall			2.25 (1.18–4.28)
Cases ($n=97$)	84	13	$p=0.014$
Control ($n=274$)	202	72	
II. Subgroup using negative chronotropes			
Overall			2.34 (1.16–4.71)
Cases ($n=80$)	69	11	$p=0.017$
Control ($n=220$)	158	62	

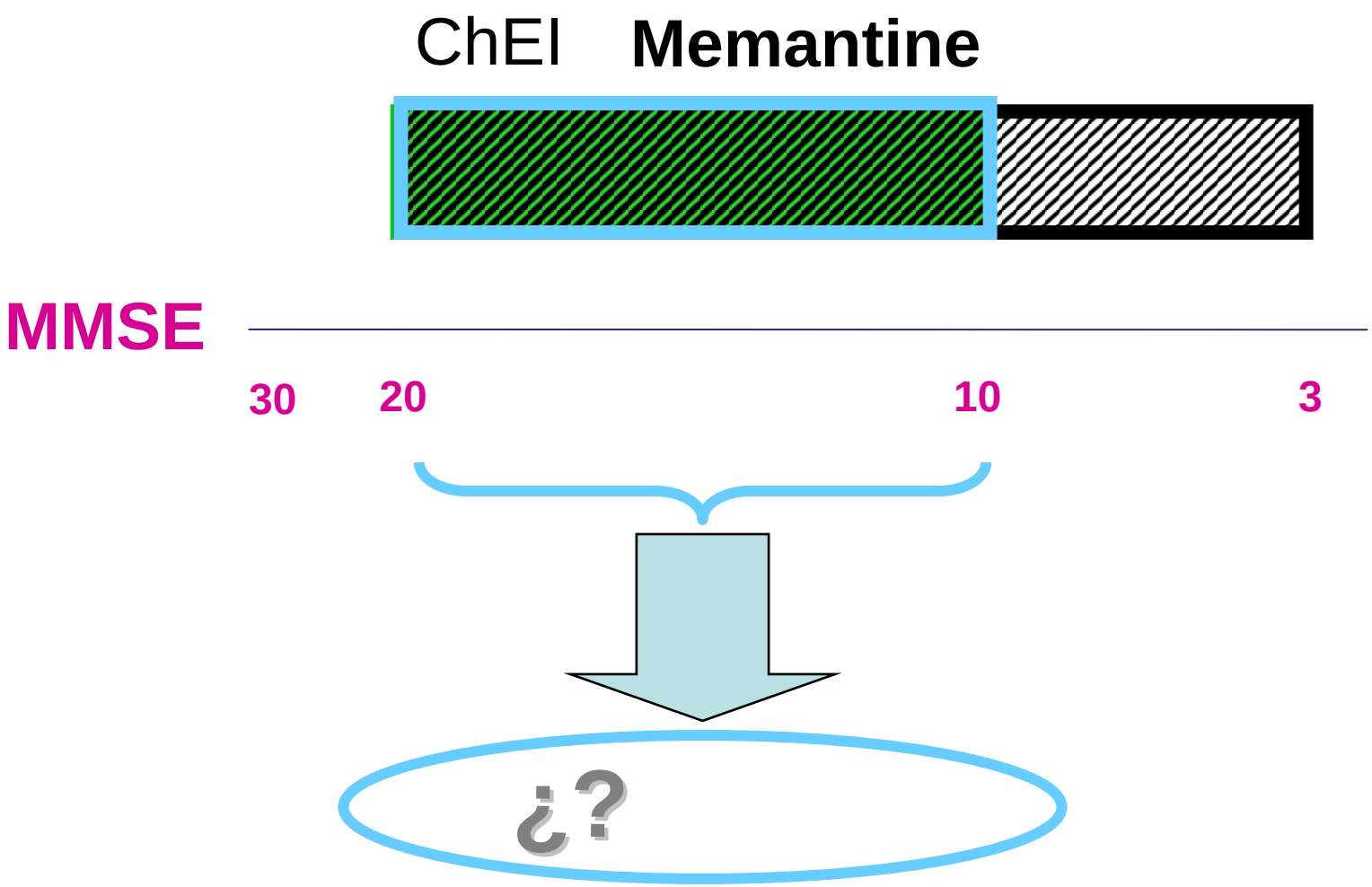
Among older patients, initiation of cholinesterase inhibitor therapy was associated with a more than doubling of the risk of hospitalization for bradycardia. Resumption of therapy following discharge was common, suggesting that the cardiovascular toxicity of cholinesterase inhibitors is underappreciated by clinicians.

Meta-analysis of memantine: Summary and commentary on the Cochrane Collaboration's systematic review

McShanea R,et al Alzheimer's & Dementia 1 (2005) 67–71



ChEI + Memantine:
Can they be associated?

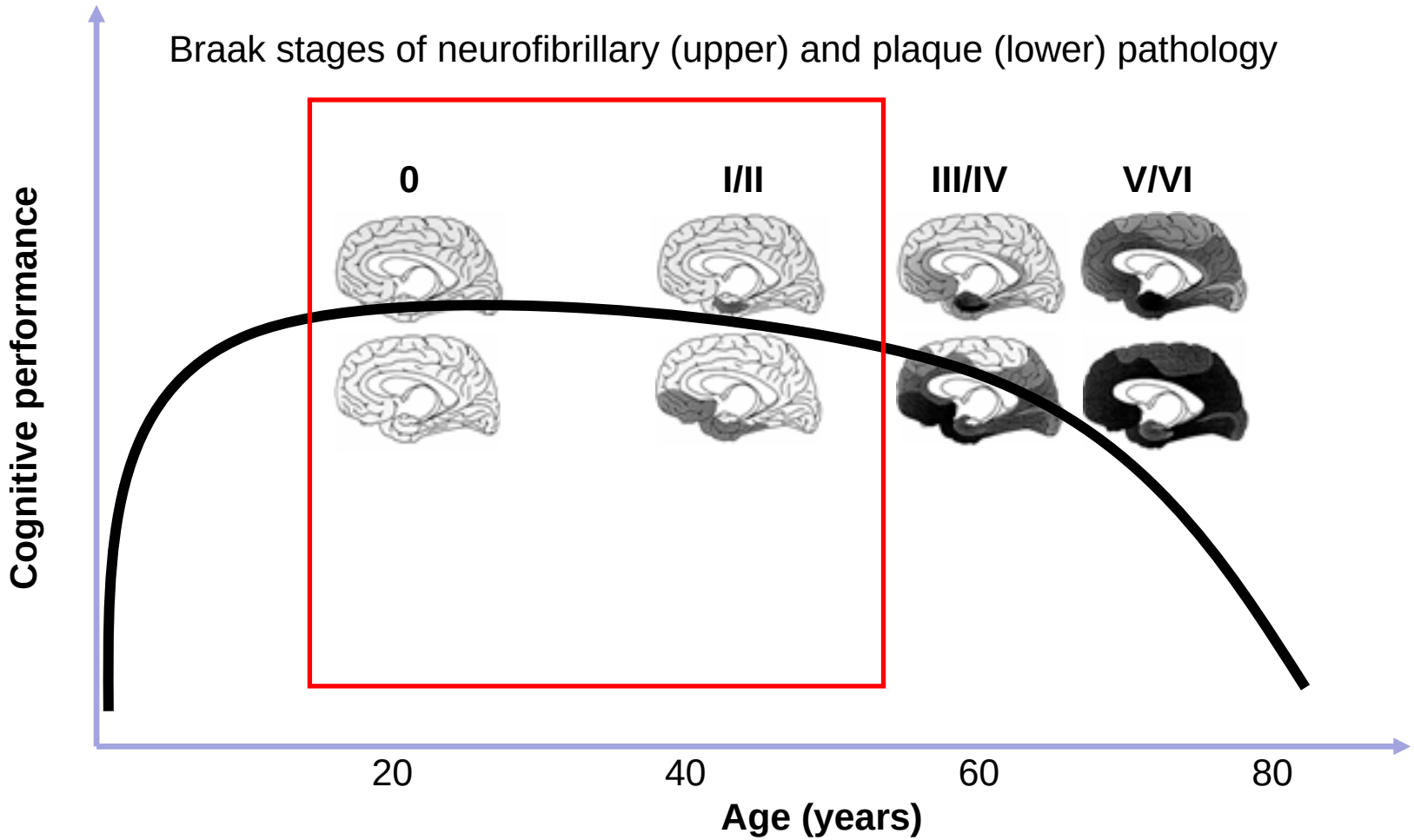


Behavioural symptoms of AD

- Agitation
  - Inappropriate verbal, vocal or motor activity. Symptoms: physical aggression; verbal aggression, wandering
- Depression
  - Self-pity, rejection sensitivity, anhedonia and psychomotor disturbance
- Psychosis
  - Visual or auditory hallucinations, delusions
- Sleep disorders
  - Disturbances of sleep and day-night reversals
- Anxiety
  - Pacing, wringing of hands, fidgeting, Godot syndrome (anxiety regarding upcoming events), fear of being left alone
- Disinhibition
  - Inappropriate behaviour, emotionally unstable,poor insight and judgement

Support for caregivers

- Regular assessment of the carers' needs:
  - Practical help
  - Emotional support / counselling
- Information
  - Financial entitlements
  - Advocacy
  - Respite
  - Other sources of support (e.g. social services, patient organizations)



Hans Förstl for Neuronet, Novartis

Disease's modifying strategies

Non specific

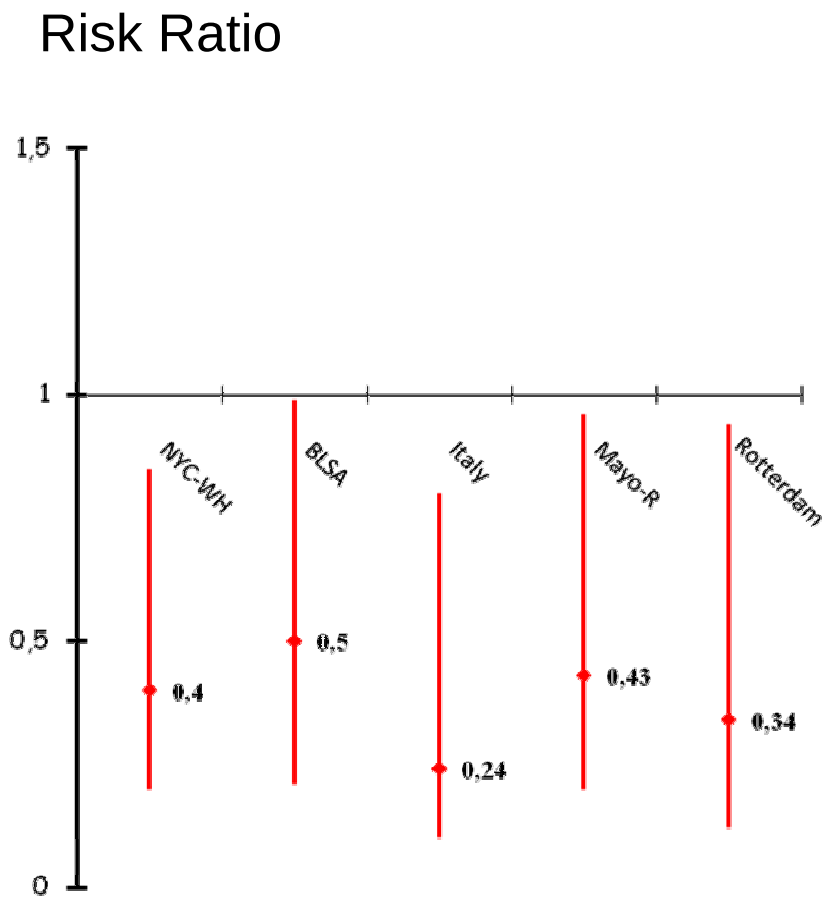
- Hormone replacement
- Nonsteroidal anti-inflammatory drugs
- Diet/cholesterol/statins
- Vitamine and antioxidantes

Specific

- antiamyloid
- anti- microtubule-associated protein tau
- Metal protein attenuating compounds

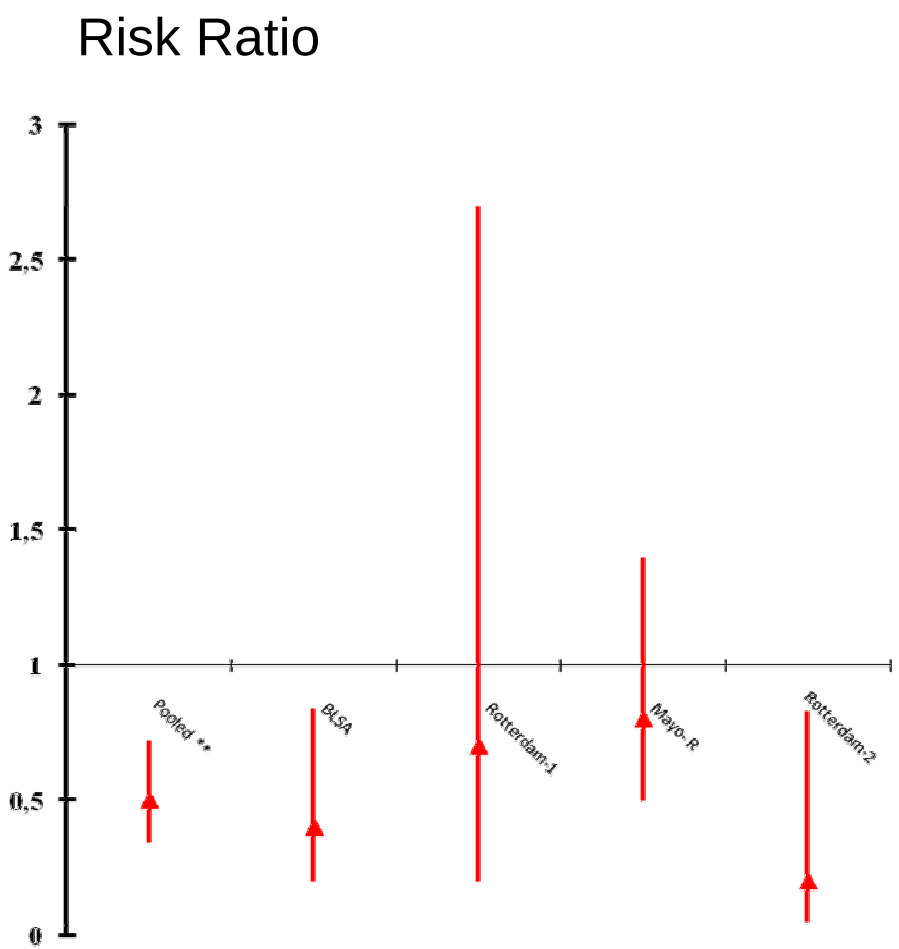
Estrogen Use

- Several cohort studies showed a reduced risk.
- Randomized clinical trials show no effect on either symptoms or progression.
- Increased risk of dementia and cognitive impairment among post menopausal women.



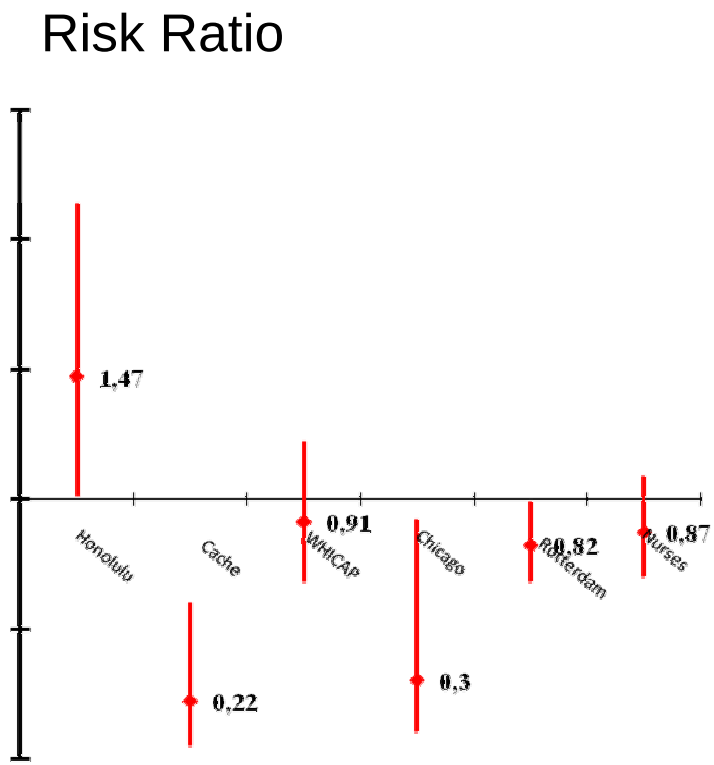
Anti-inflammatory drugs

- Inflammation around Aβ deposit and NFT.
- Aβ activates complement.
- Activated microglia produce oxygen free radicals and proteases and may cause neuronal death.
- NSAIDs reduce amyloid burden in Tg mice.
- Clinical trials are thus far disappointing.



Antioxidants

- Several cohort studies showed a marginal reduction in risk.
- Randomized clinical trial show no effect on progression from MCI to AD.



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

The Cochrane Library 2008, Issue 4

Isaac MGEKN, Quinn R, Tabet N

Implications for practice

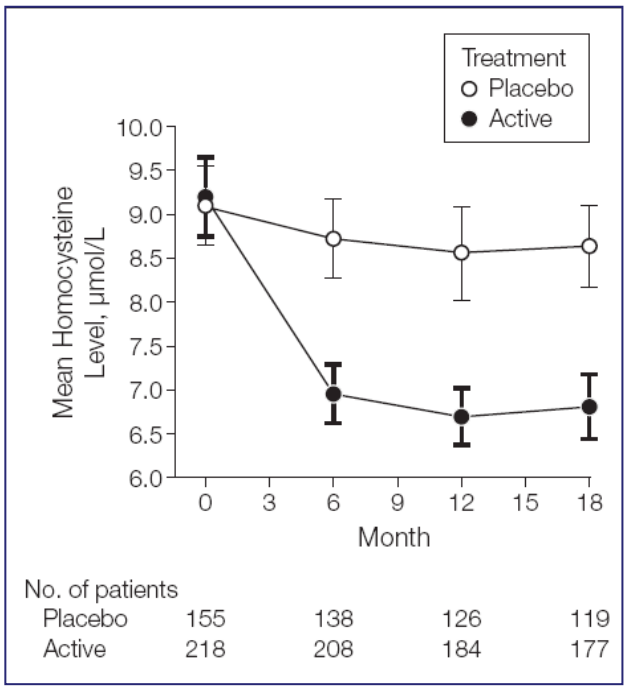
- **As the current evidence stands, Vitamin E should not be recommended for treatment or prevention of cognitive impairment.**

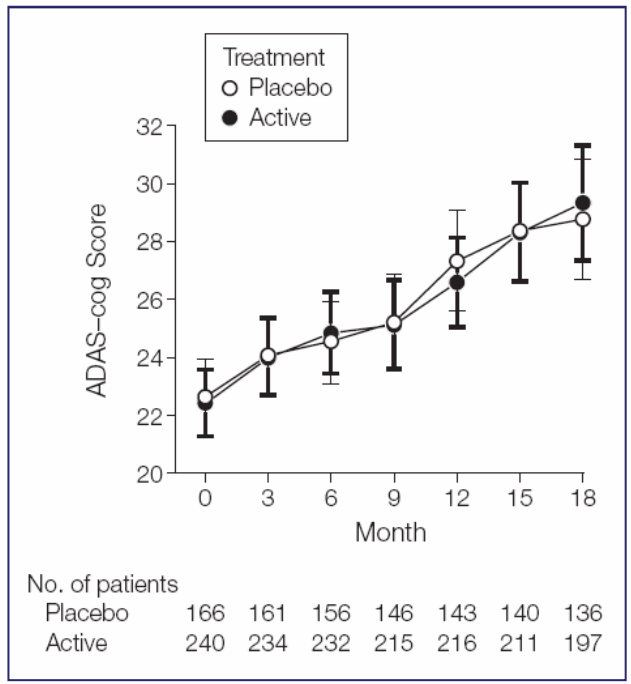
Implications for research

- **Overall, there is insufficient evidence to confirm efficacy. There is a need for more randomized double-blind placebo controlled trials to confirm or contradict the little available evidence.**

Trial Decline in Alzheimer Disease: A Randomized Controlled High - Dose B Vitamin Supplementation and Cognitive

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





The vitamin supplement was effective in reducing homocysteine levels it had no beneficial effect on the primary cognitive measure

This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD

ICAD Chicago 2008
Phase 2

- **Therapeutic Breakfast Food?**

- A proof-of-concept human trial of a nutrient drink (Souvenaid). In plasma at 12 weeks, Souvenaid increased the concentration of the omega-3 fatty acid DHA, and reduced that of homocysteine, improved performance of the WMS-r memory test (effect size larger in MMSE > 23 mild AD

Disease's modifying strategies

Non specific

- Hormone replacement
- Nonsteroidal anti-inflammatory drugs
- Diet/cholesterol/statins
- Vitamine and antioxidantes

Specific

- antiamyloid
- anti- microtubule-associated protein tau
- Metal protein attenuating compounds

Amyloid-β immunisation for Alzheimer's disease

Wisniewski T, et al. Lancet Neurol 2008; 7: 805–11

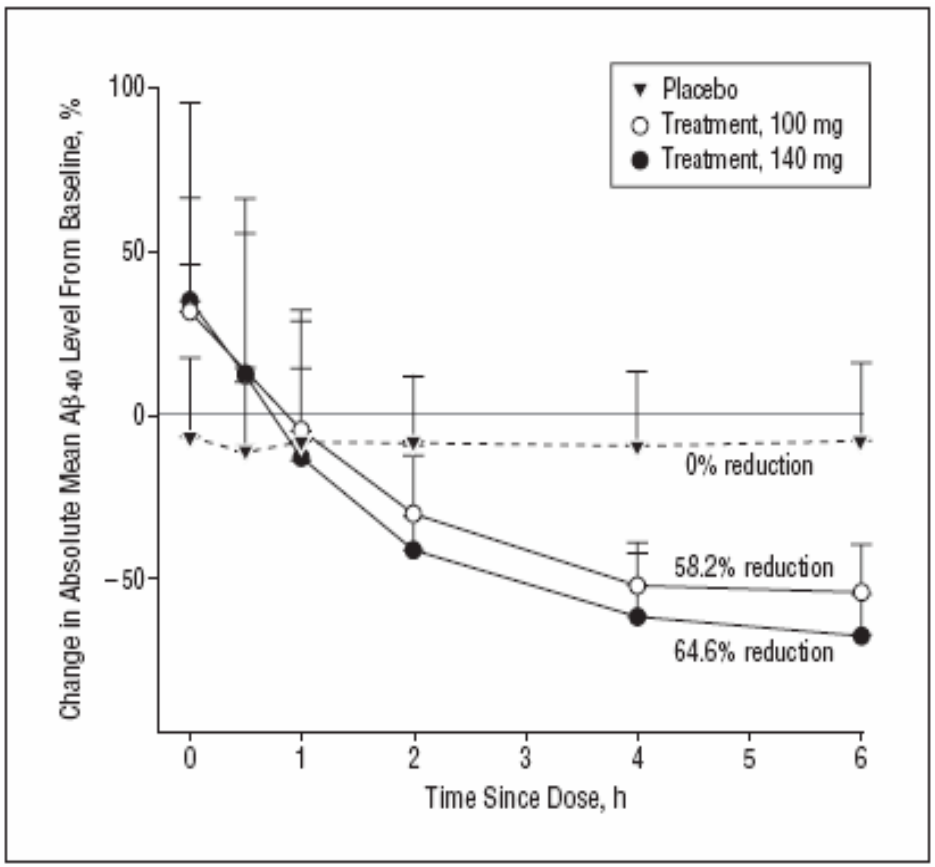
	Phase	Intervention	Primary outcomes	Size	Duration
Active immunisation					
NCT00498602	Phase II	ACC-001+QS21 vs ACC-001 vs placebo	Safety, tolerability	228	Nov, 2007, to March, 2012
NCT00411580	Phase I	CAD106	Safety, tolerability	60	June, 2005, to April, 2008
NCT00464334	Phase I	V950	Safety	70	April, 2007, to Sept, 2011
Passive immunisation					
NCT00575055	Phase III	Bapineuzumab	Cognitive, functional	800	Dec, 2007, to Dec, 2010
NCT00329082	Phase II	LY2062430	Safety, tolerability	25	May, 2006, to May, 2008
NCT00299988	Phase II	Intravenous immunoglobulin	ADAS-cog, ADAS-CGIC	24	Start Feb, 2006; ongoing but recruitment complete
NCT00455000	Phase I	PF-04360365	Safety, tolerability, pharmacokinetics	36	March, 2007, to June, 2008
NCT00531804	Phase I	R1450	Adverse events, laboratory measures, vital signs	80	Dec, 2006, to Jan, 2009

ADAS-cog/CGIC=Alzheimer's disease assessment score cognitive scale/clinician's global impression of change.

Table: Current randomised, double-blind, parallel-assignment studies of immunotherapy in Alzheimer's disease

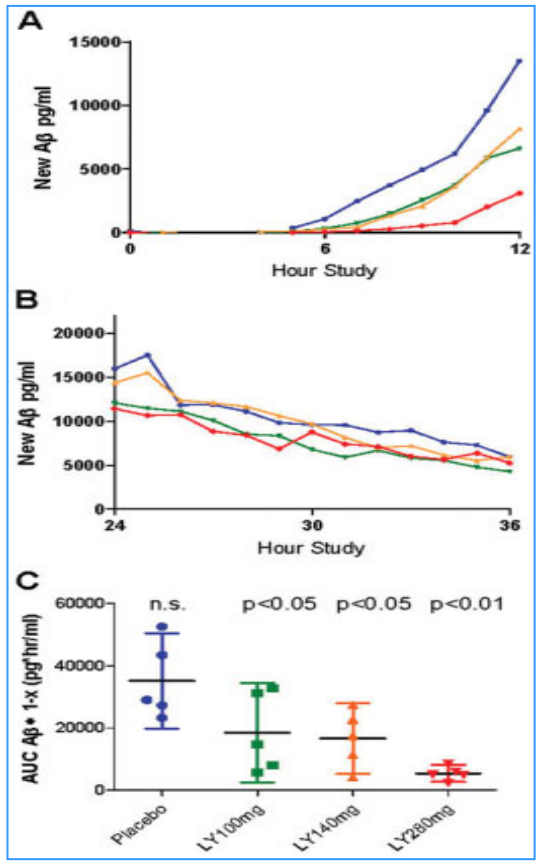
Phase 2 Safety Trial Targeting Amyloid Production With γ-Secretase Inhibitor in Alzheimer Disease

Fleisher AS, et al. Arch Neurol. 2008;65(8):1031-1038



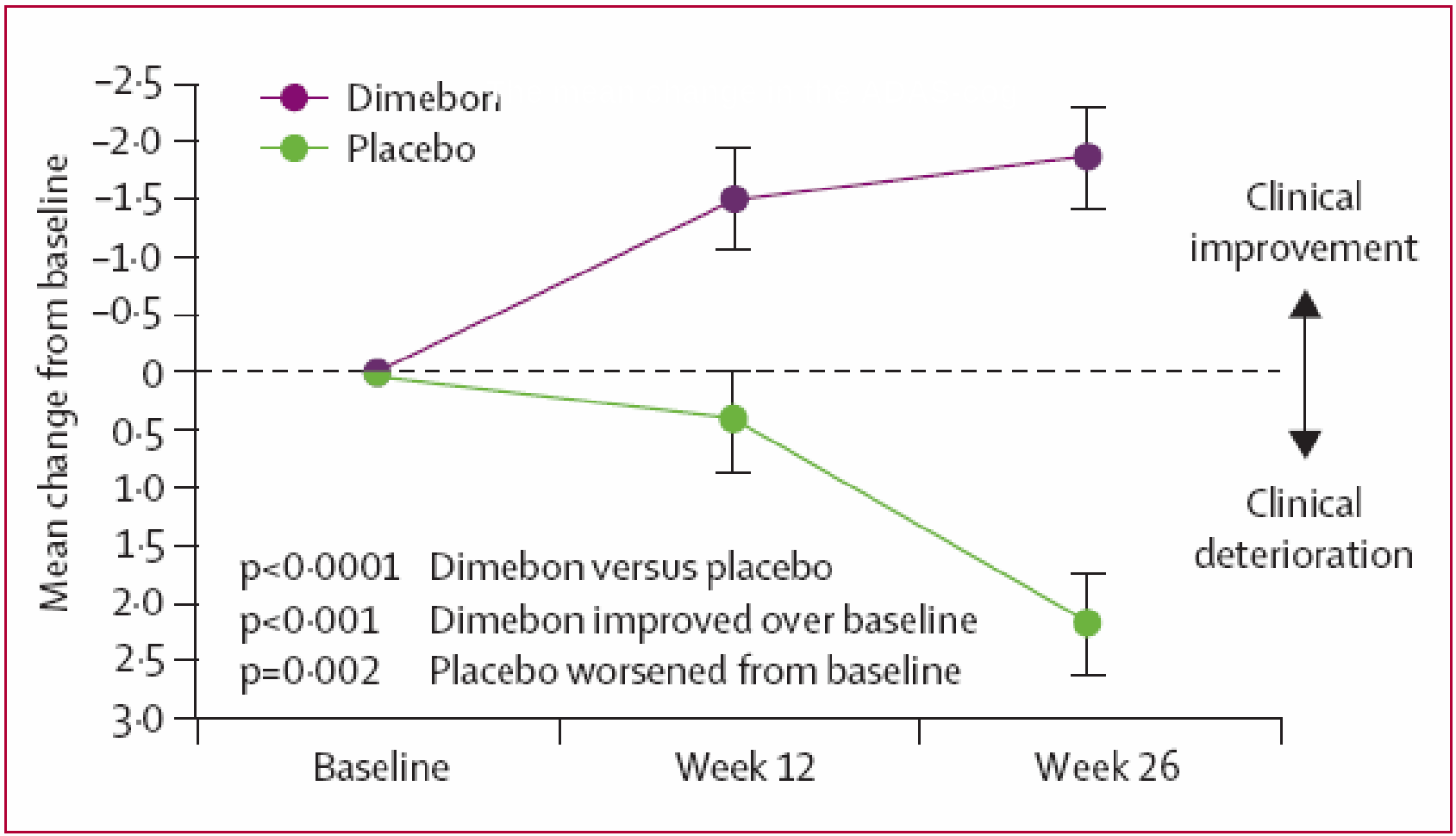
Ag-Secretase Inhibitor Decreases Amyloid- Production in the Central Nervous System

Bateman RJ, et al. Ann Neurol 2009;66:48–54



Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo controlled study

Doody RS, et al. Lancet 2008; 372: 207–15



ONGOING CLINICAL TRIALS FOR TREATING ALZHEIMER'S DISEASE

Approach or drug	Proposed mechanism of action	Phase
β-Secretase inhibition	Decreases formation of Aβ from amyloid precursor protein	II
γ-Secretase inhibition	Decreases formation of Aβ from amyloid precursor protein	II/III
Active immunization with Aβ peptides	Generates anti-Aβ antibodies that interact with Aβ and remove it from the brain by uncertain downstream mechanisms	II
Passive immunization with anti-Aβ antibodies	The antibodies interact with Aβ and remove it from the brain by uncertain downstream mechanisms	III
Intravenous pooled immunoglobulins	May enhance clearance of Aβ and other harmful proteins from the brain; may decrease harmful inflammatory processes	III
Scyllo-inositol	Decreases formation and stability of pathogenic Aβ assemblies	II
Latrepirdine	Prevents mitochondrial dysfunction	III
Inhibition of receptor for advanced glycation end products (RAGE)	Blocks stimulation of the cell-surface receptor RAGE, which binds Aβ, decreasing Aβ levels in the brain and preventing Aβ from activating pathogenic pathways	II
Stimulation of insulin signalling	Prevents hyperglycaemia; may overcome insulin resistance in the brain	II
Selective oestrogen-receptor modulator	Promotes neuroprotective effects of oestrogen without eliciting its harmful effects	II
Neurotrophic and neuroprotective agents	Stimulate neurotrophic and antioxidant pathways or pathways that protect against excitotoxicity	II

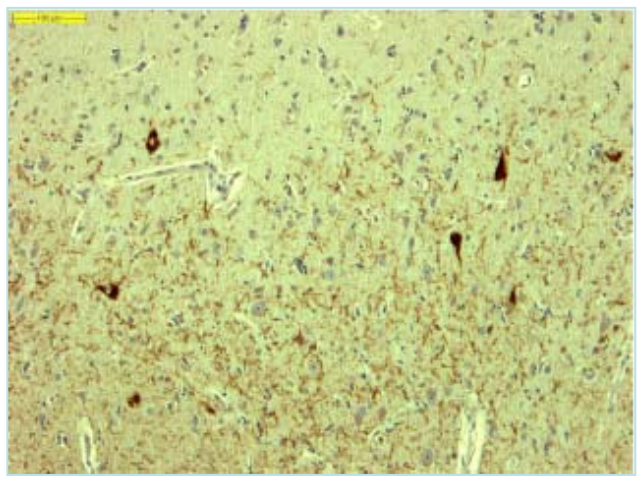
Lennart Mucke, **NATURE Vol 461|15 October 2009**

Longer … and better life

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

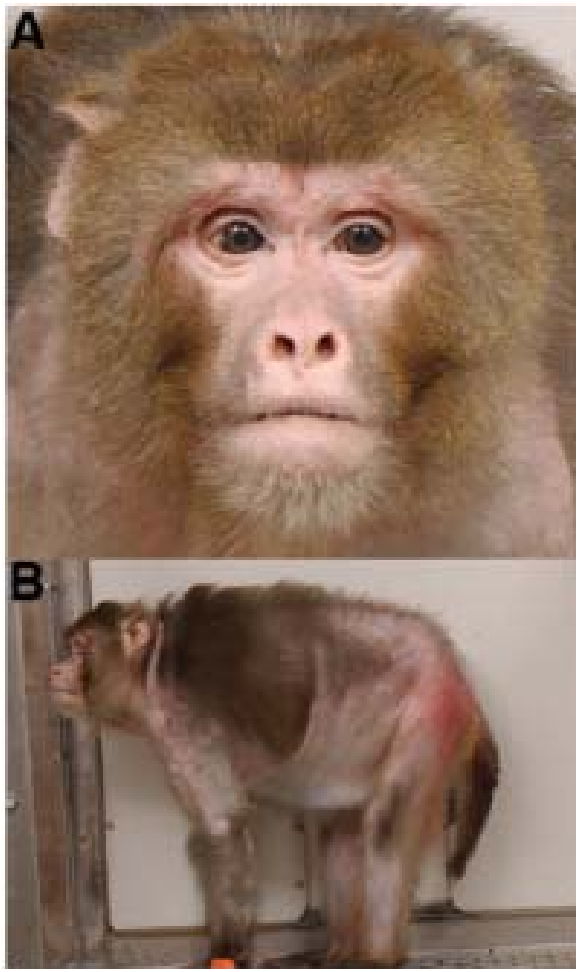
		November 2002	May 2004
Dementia screening	Mini mental state examination[a] (without visual items; max. = 27)	27	26
	Cognitive screening test[b] (max. = 20)	20	20
Attention	Digits forward (WAIS)	Score 6 Span: 5 digits (6th decile 55–65 years)	Score 5 Span: 5 digits
Working memory	Digit backwards (WAIS)[c]	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)



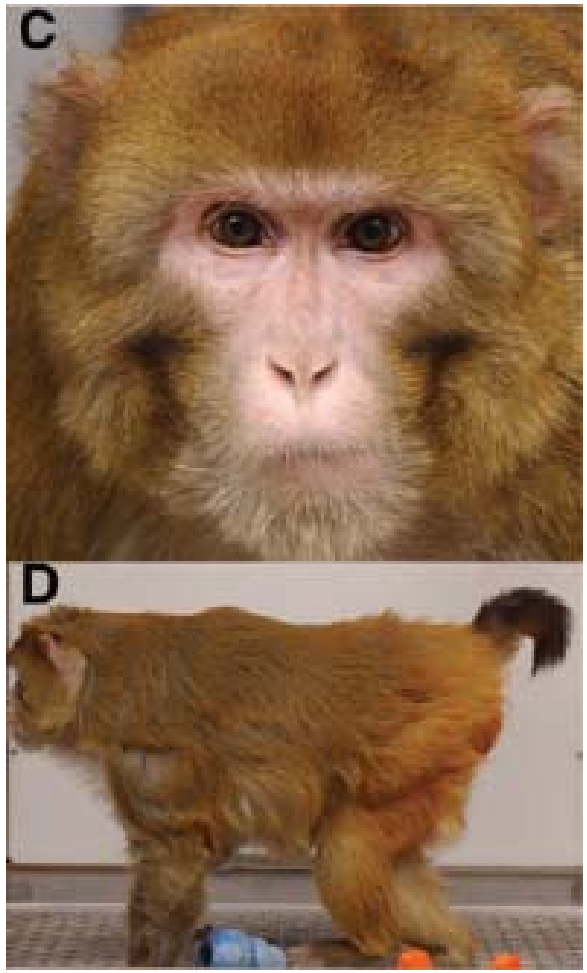
Caloric Restriction Delays Disease. Onset and Mortality in Rhesus Monkeys

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

Photographs of a typical control animal at 27.6 years of age



Photographs of an age-matched animal on CR.



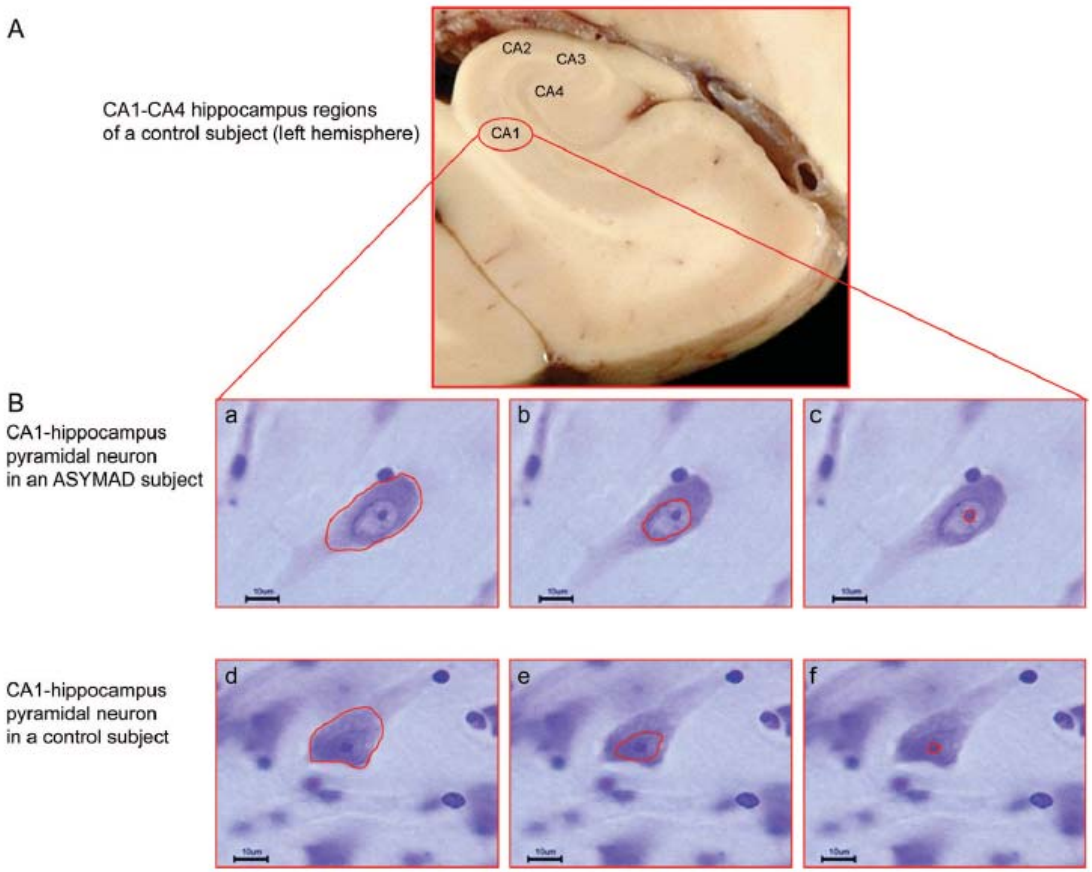
50% of control fed animals survived as compared with 80% of the CR animals.

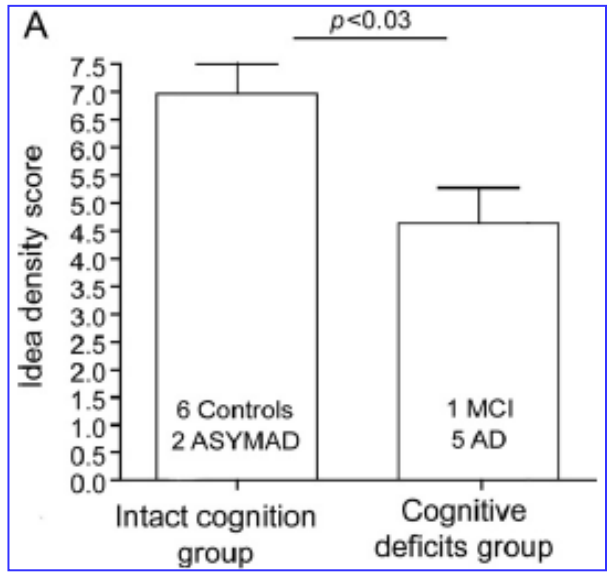
CR delayed the onset of age-associated pathologies: diabetes, cancer, cardiovascular disease, and brain atrophy.

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.

Caffeine Reverses Cognitive Impairment and Decreases Brain Amyloid-beta Levels in Aged Alzheimer's Disease Mice.
Arendash GW, et al. J Alzheimers Dis. 2009 Jul;17(3):661-80.

- **AD transgenic mice given a moderate level of caffeine intake (the human equivalent of 5 cups of coffee per day) are protected from development of cognitive impairment and have decreased hippocampal Abeta levels due to suppression of both BACE1 and PS1)**

Phosphodiesterase 5 Inhibition Improves Synaptic Function, Memory, and Amyloid- Load in an Alzheimer's Disease Mouse Model
Puzzo P, The Journal of Neuroscience, June 24, 2009 • 29(25):8075– 8086

- **The phosphodiesterase 5 inhibitor (PDE5) sildenafil, a molecule that enhances phosphorylation of CREB, a molecule involved in memory, through elevation of cGMP levels, is beneficial against the AD phenotype in a mouse model of amyloid deposition.**

Pascual Maragall declaró en Octubre del 2007, en el salón de actos del Hospital de St Pau, que le habían diagnosticado un “principio” de la enfermedad de Alzheimer.

Ha creado la Fundación Pascual Maragall para la investigación de la enfermedad de Alzheimer

Hospital de la Santa Creu i Sant Pau

2009

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