VERSO LA DIAGNOSI DI MALATTIA DI ALZHEIMER SENZA DEMENZA

Quale ruolo dei biomarcatori per l'anziano con decadimento cognitivo?

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Alzheimer's pipeline

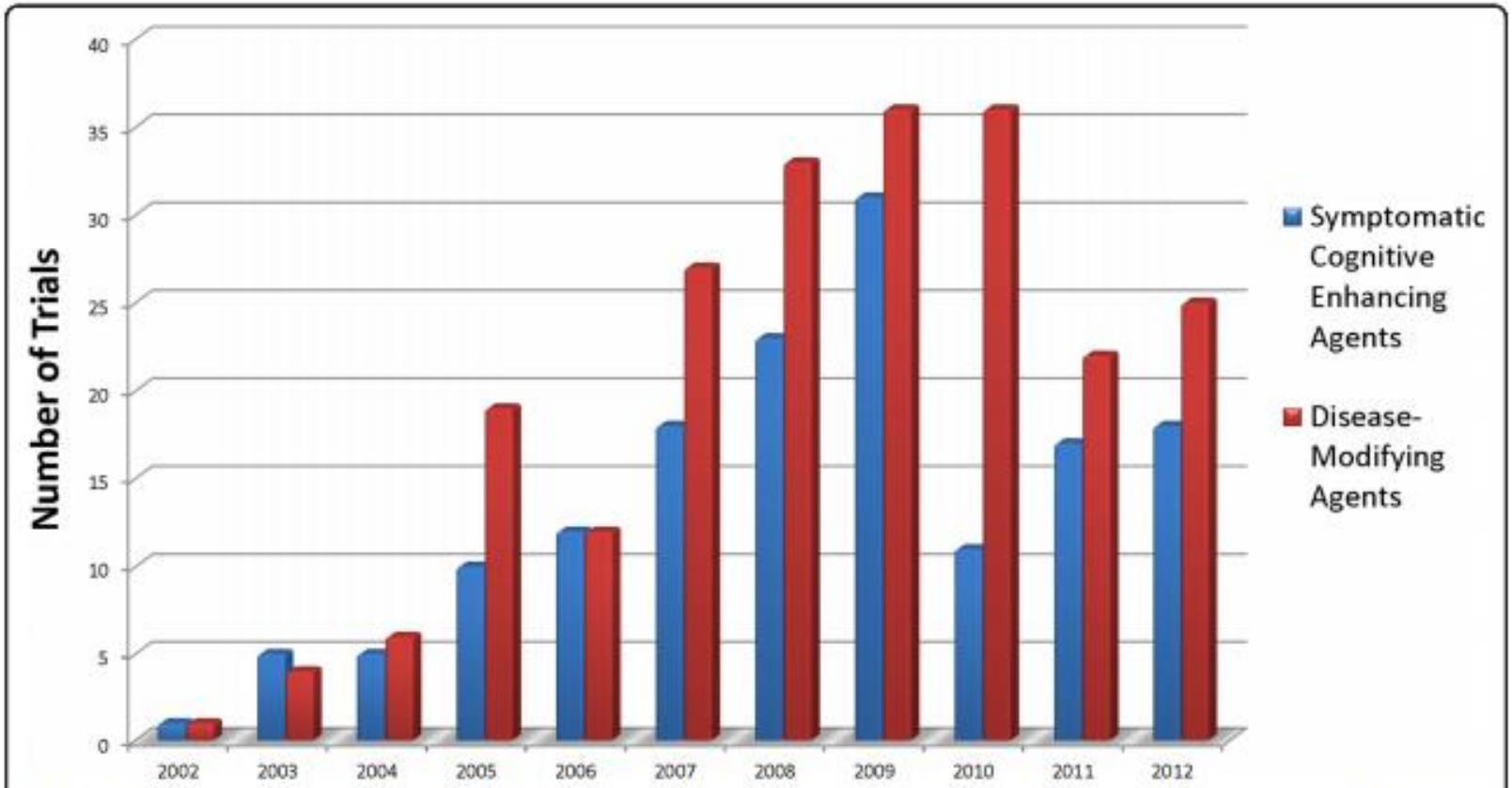
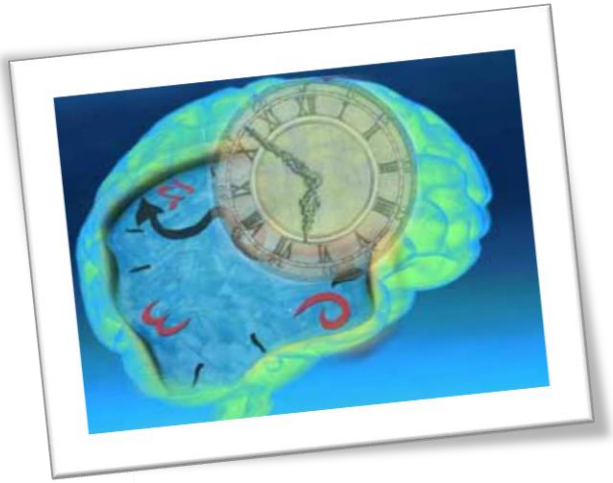


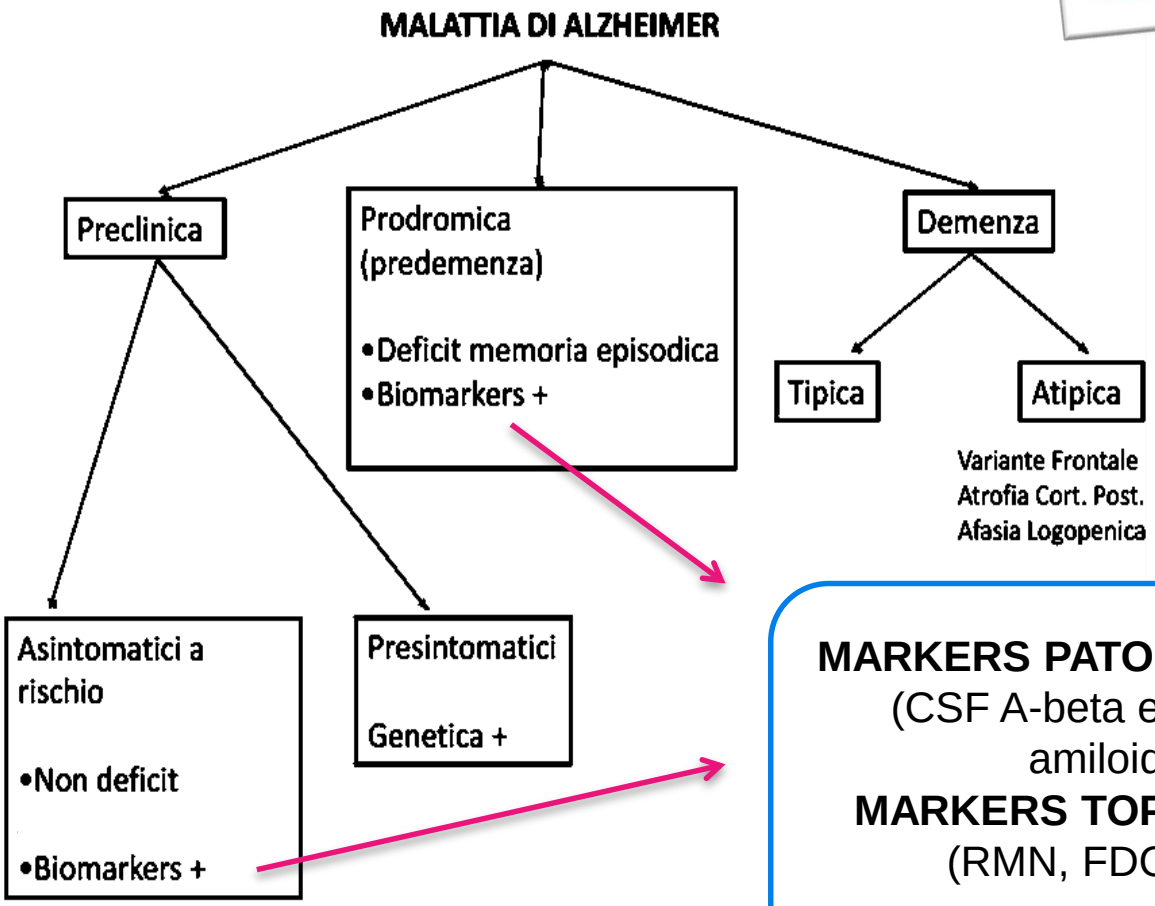
Figure 1 Comparison of number of trials of symptomatic cognitive-enhancing agents and of disease-modifying agents in the 2002 through 2012 period.

Most drugs entering the AD drug-development pipeline have failed; only one agent has been approved since 2004 (memantine). The failure rate since 2002 (excluding agents currently in Phase 3) is 99.6%.

Cummings et al., Alzheimers Res Therapy, 2014

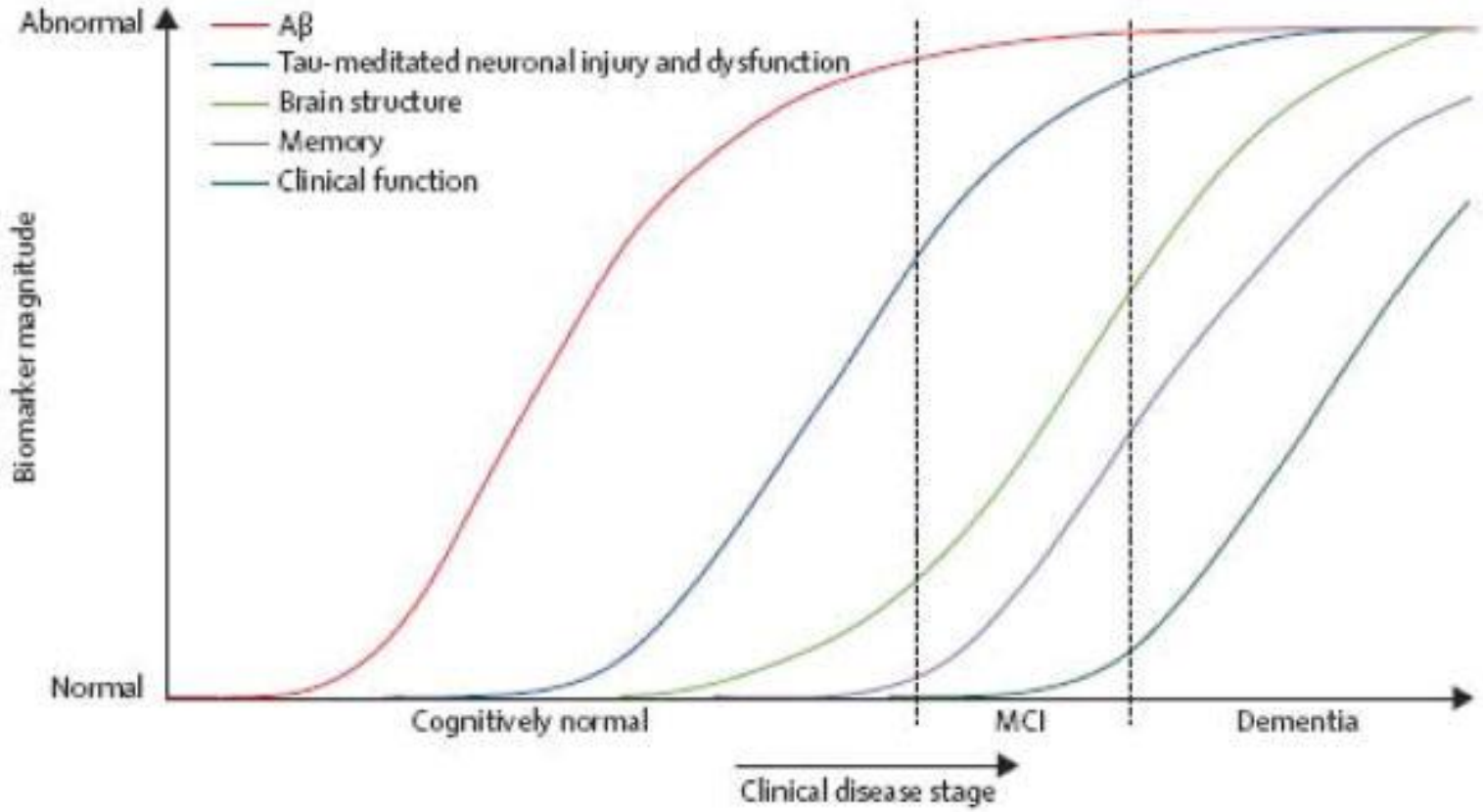
Poichè i trattamenti proposti hanno maggior efficacia nello stadio precoce di malattia, l'obiettivo principale è quello di diagnosticare la malattia di Alzheimer prima che la compromissione delle funzioni cognitive raggiunga lo stadio di demenza.





MARKERS PATOFISIOLOGICI
(CSF A-beta e tau, PET amiloide)
MARKERS TOPOGRAFICI
(RMN, FDG-PET)

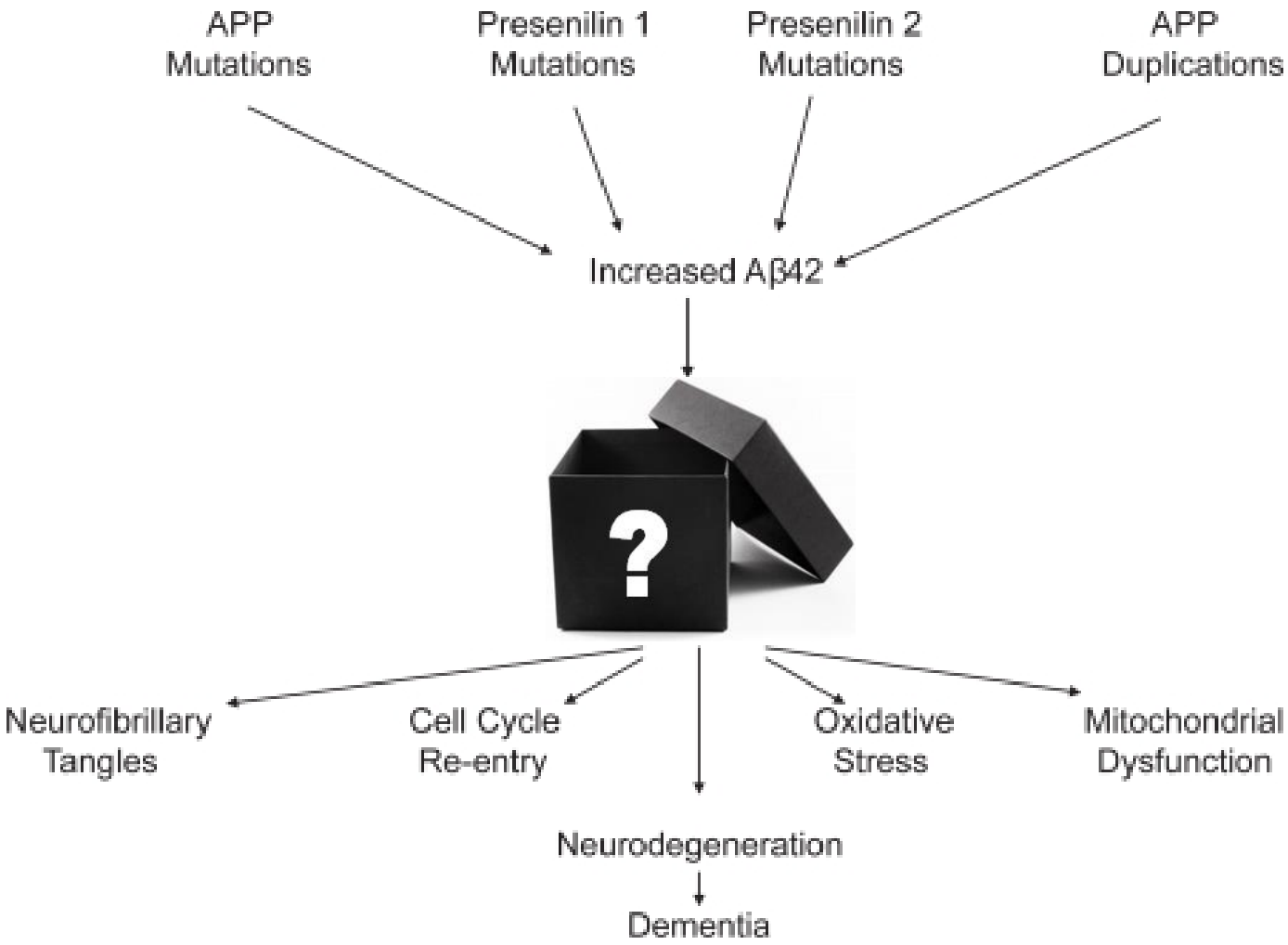
Il ruolo dei biomarcatori



Jack et al. Lancet Neurol, 2013

«Ogni qualvolta una teoria ti sembra essere l'unica possibile, prendilo come un segno che non hai capito né la teoria né il problema che si intendeva risolvere»

(Karl Popper, Conoscenza oggettiva: un punto di vista evoluzionistico)



Swerdlow , Neurobiol Aging, 2007

Amiloide
Proteina tau
?
AD
Stress ossidativo
?
?
Danno neuro-vascolare
Infiam-mazione

CSF

Combining biological markers: toward preclinical diagnosis of AD

Markers	Authors	Marker Combination	Accuracy	Reference
Amyloid cascade	Di Luca M, 2005	Platelet APP forms, ADAM10, BACE	ACC 97.0%	[53]
Plama Abeta	Breteler M, 2006	Plasma Abeta 40 and Plasma Abeta 42	-	[60]
CSF	Andreasen N, 1999	CSF Abeta 42 and CSF Tau	SEN 88%	[70]
	Riemenschneider M, 2002	CSF Abeta 42 and CSF Tau	SEN 90.0%, SPE 90.0%	[71]
	Hansson O, 2006	CSF Abeta 42 and CSF Tau	SEN 95.0%, SPE 83.0%	[77]
	Parnetti L, 2006	CSF Abeta 42, CSF Tau, and CSF phospho Tau	SEN 90% SPE 88%	[78]
	De Leon MJ, 2006	CSF phosphor Tau and CSF isoprostane	ACC 90.0%	[79]
NPS and neuroimaging	Huang C, 2003	NPS (Mini-Mental State Examination, Block Design, Word Recognition test) and SPECT hypoperfusion	ACC 84.0%	[86]
	Borroni B, 2006	NPS (Short Story, Rey Figure Recall, Rey List Delayed Recall) and SPECT hypoperfusion	SEN 77.8%, SPE 77.8%	[91]
	Anchisi D, 2005	NPS (California Verbal Leraning Test) and PET	SEN 85.7%, SPE 97.1%	[92]
Biolomarkers and neuroimaging	Okamura N, 2002	CSF Tau and SPECT hypoperfusion	SEN 88.5%, SPE 90.0%	[93]
	Borroni B, 2005	APP forms and SPECT hypoperfusion	SEN 95.2%, SPE 75.0%	[94]
	Bouwman FH, 2006	CSF Abeta 42, CSF Tau, MRI (medial temporal atrophy)	SEN 94.0%, SPE 70.0%	[95]
Neuroimaging	Small GW, 2006	Cerebral Abeta and Tau (FDDNP-PET and PIB-PET)		

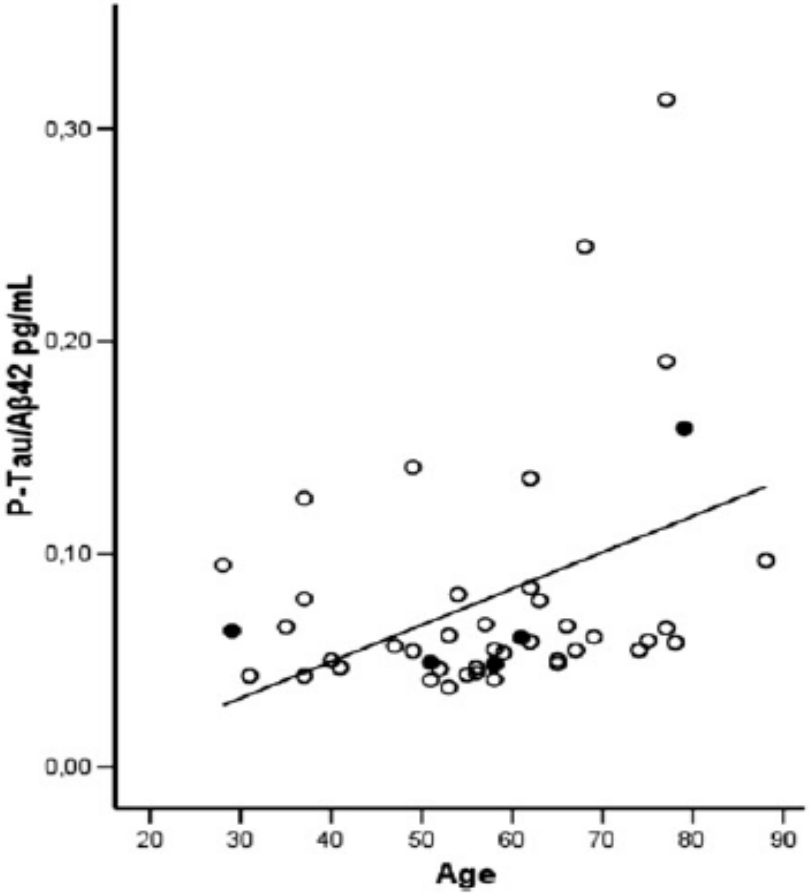
CSF: Cerebrospinal Fluid; NPS: Neuropsychological assessment; APP: Amyloid Precursor Protein; ADAM10: APP disintegrine and metalloprotease 10; BACE: Beta APP Cleaving Enzyme; SPECT: Single Positron Emission Tomography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; SEN: Sensitivity; SPE: Specificity; ACC: Accuracy.

Borroni et al., Curr Med Chem 2007

ELSEVIER

Alzheimer's & Dementia

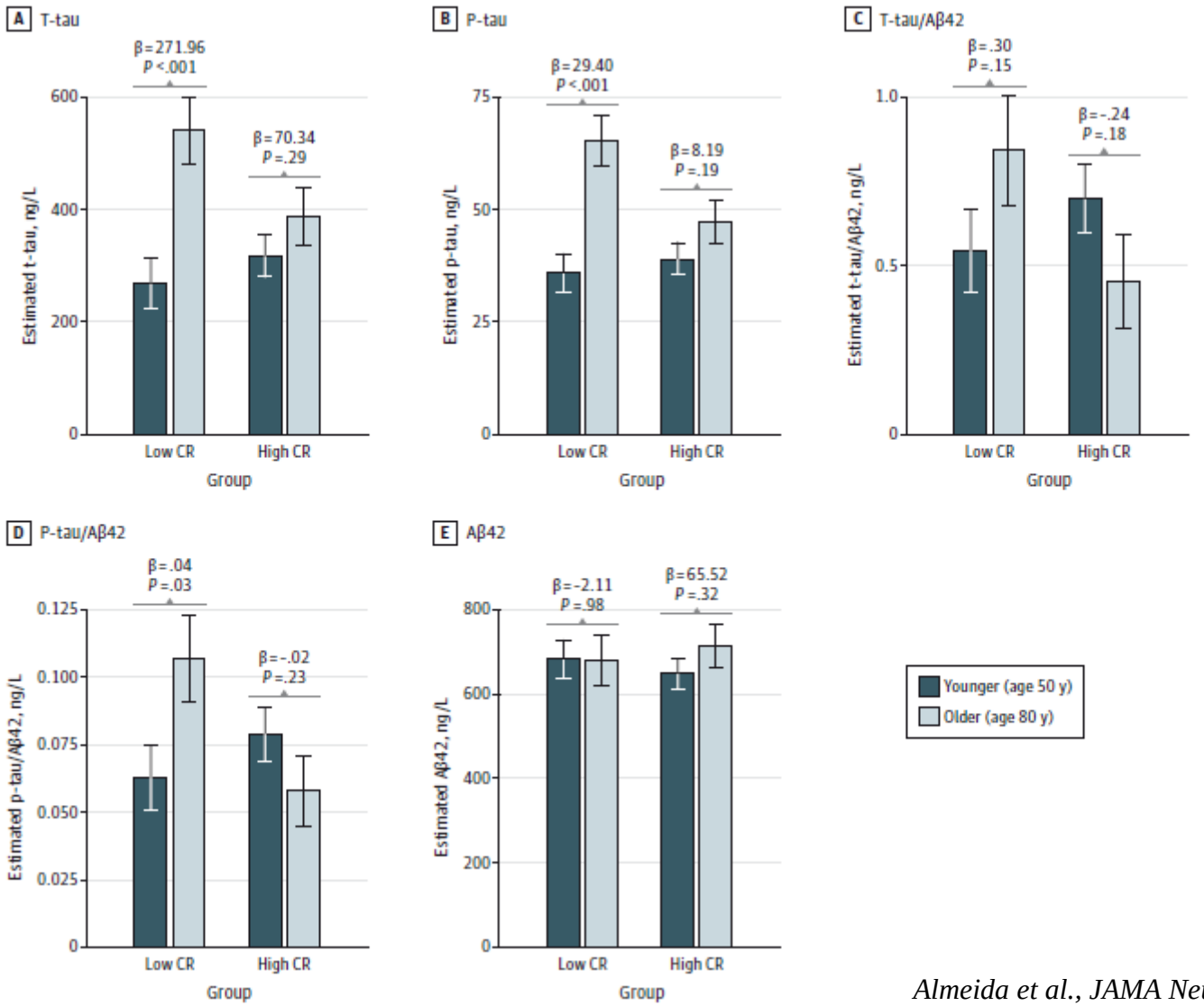
Cerebrospinal fluid markers for Alzheimer's disease in a cognitively healthy cohort of young and old adults



Paternicò et al., Alzheimers Dementia 2012

Original Investigation

Effect of Cognitive Reserve on Age-Related Changes in Cerebrospinal Fluid Biomarkers of Alzheimer Disease



Almeida et al., JAMA Neurol 2015

PET-AMILOIDE

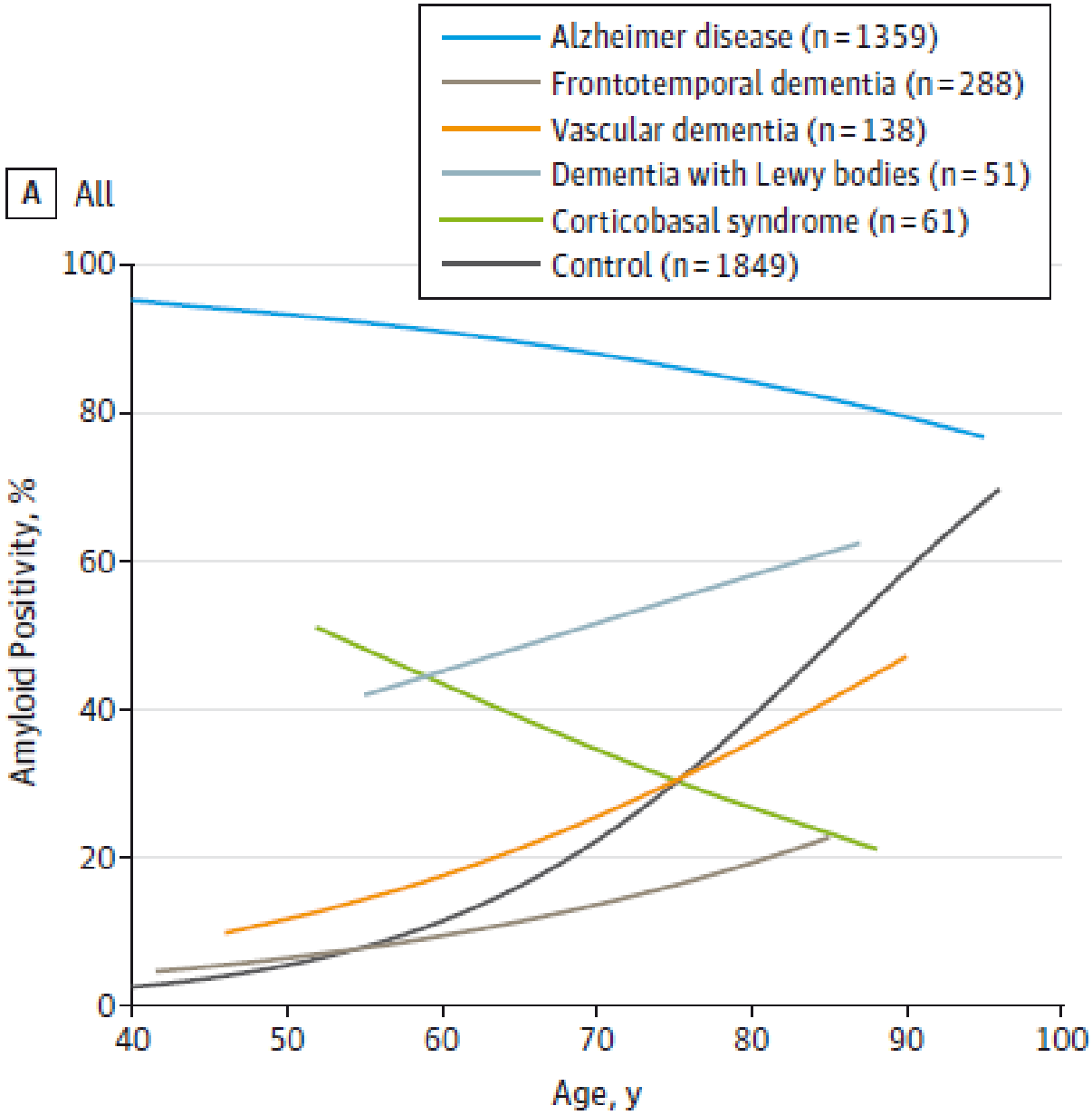
Original Investigation

Prevalence of Amyloid PET Positivity in Dementia Syndromes
A Meta-analysis

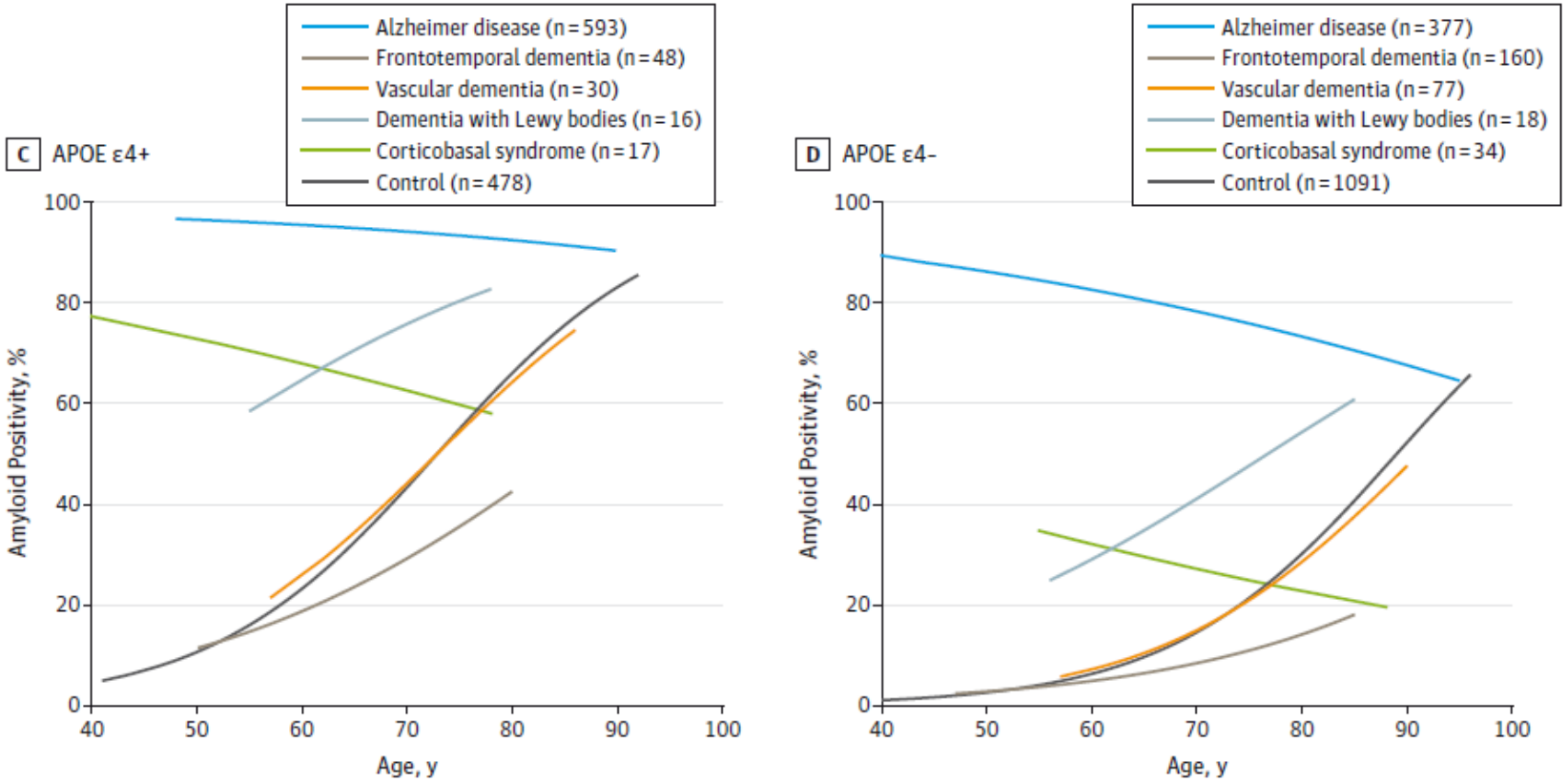
Rik Ossenkoppele, PhD; Willemijn J. Jansen, MSc; Gil D. Rabinovici, MD; Dirk L. Knol, PhD; Wiesje M. van der Flier, PhD; Bart N. M. van Berckel, MD, PhD; Philip Scheltens, MD, PhD; Pieter Jelle Visser, MD, PhD; and the Amyloid PET Study Group

- 29 Cohorts included in the analysis (185 articles)
- 1897 Patients
- 1359 Alzheimer disease
- 288 Frontotemporal dementia
- 138 Vascular dementia
- 51 Dementia with Lewy bodies
- 61 Corticobasal syndrome

Ossenkoppele et al., JAMA 2015



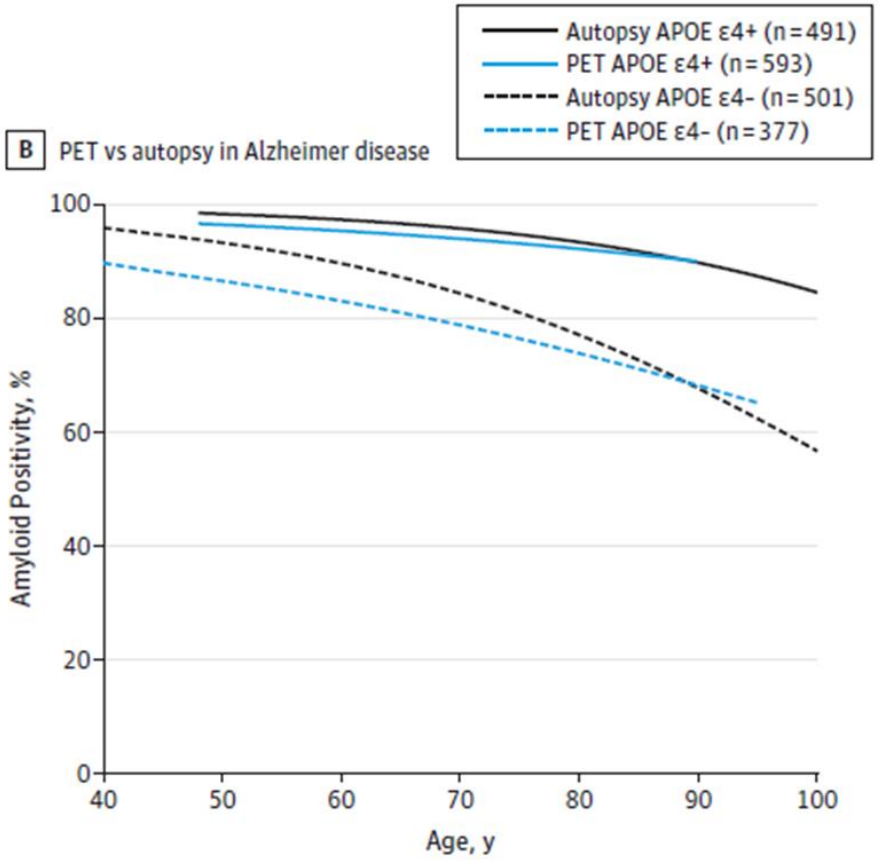
Ossenkoppele et al., JAMA 2015



A negative amyloid PET scan was observed in 12% of clinically diagnosed AD dementia participants and was most common in older APOE ε4 noncarriers.

Ossenkoppele, et al., JAMA 2015

Risultati falsi negativi alla PET possono riflettere una scarsa sensibilità nel riscontrare una patologia amiloidea avanzata, probabilmente a causa di:



- ✓ **diversa conformazione delle placche amiloidee**
- ✓ **deposizione di amiloide nelle aree di riferimento**
- ✓ **severa neurodegenerazione;**

Questa è soltanto una spiegazione parziale poiché, anche se con qualche eccezione, il risultato di PET e neuropatologia corrispondono.

Ossenkoppele et al., JAMA 2015

Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia:

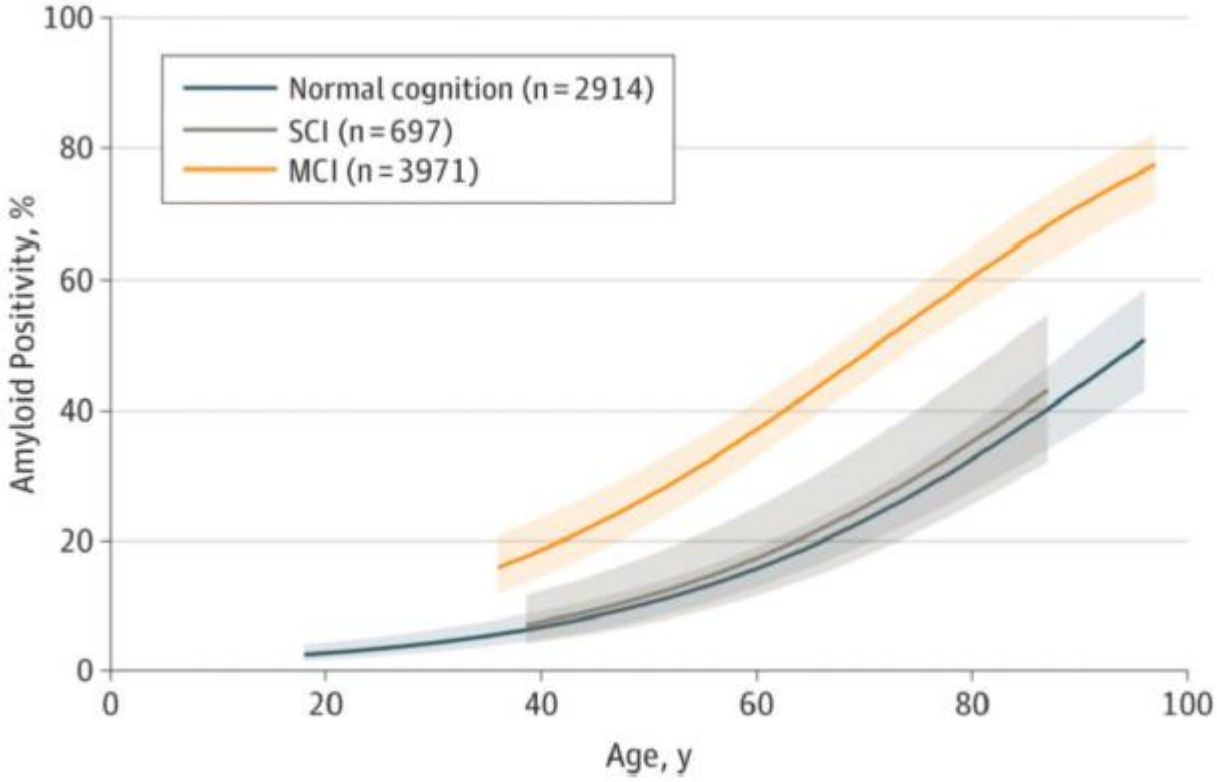
A Meta-analysis

- 2914 participants with normal cognition
- 697 with SCI
- 3972 with MCI
- aged 18 to 100 years
- from 55 studies

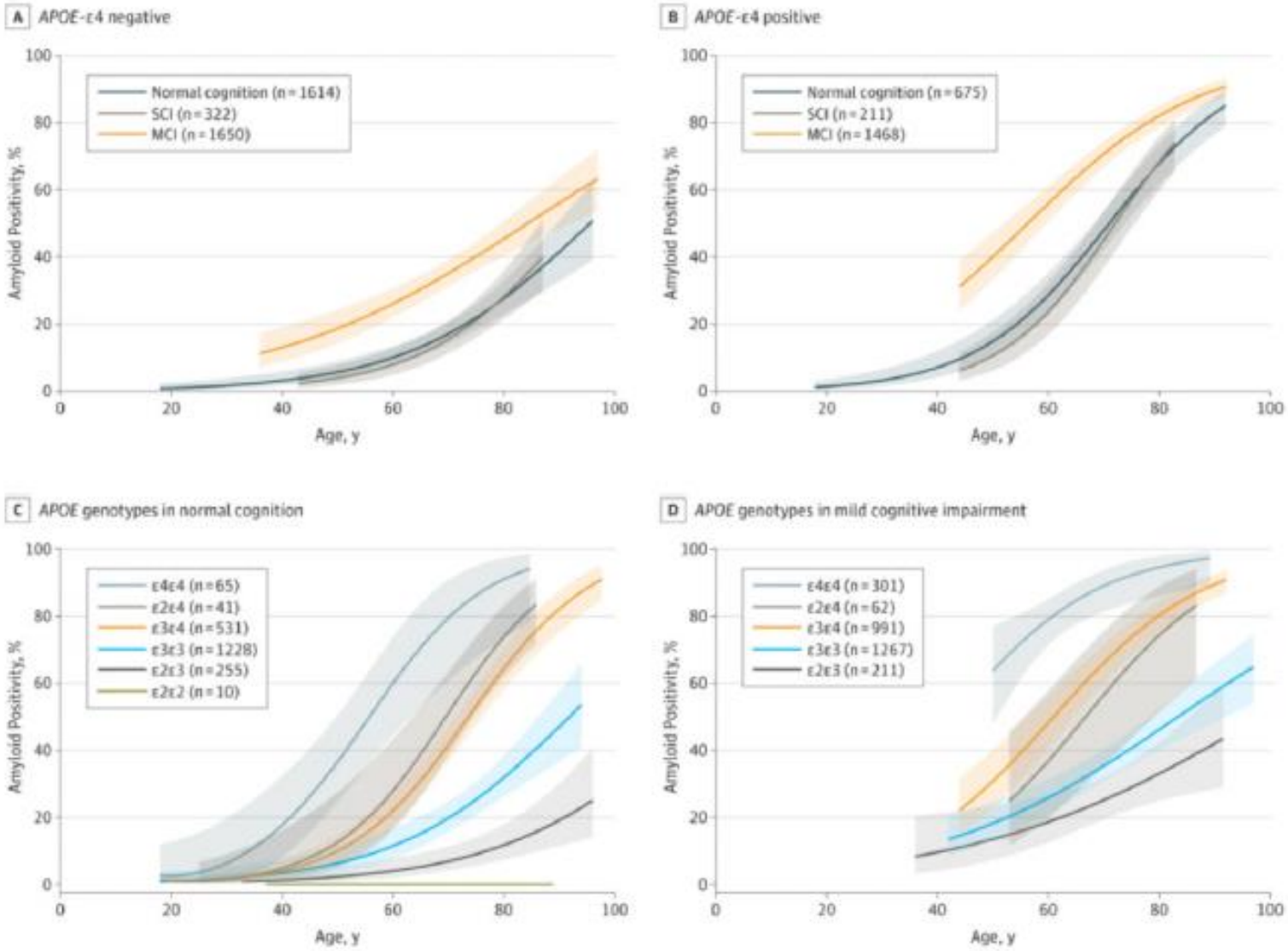
Jansen et al., JAMA 2015

Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia:

A Meta-analysis



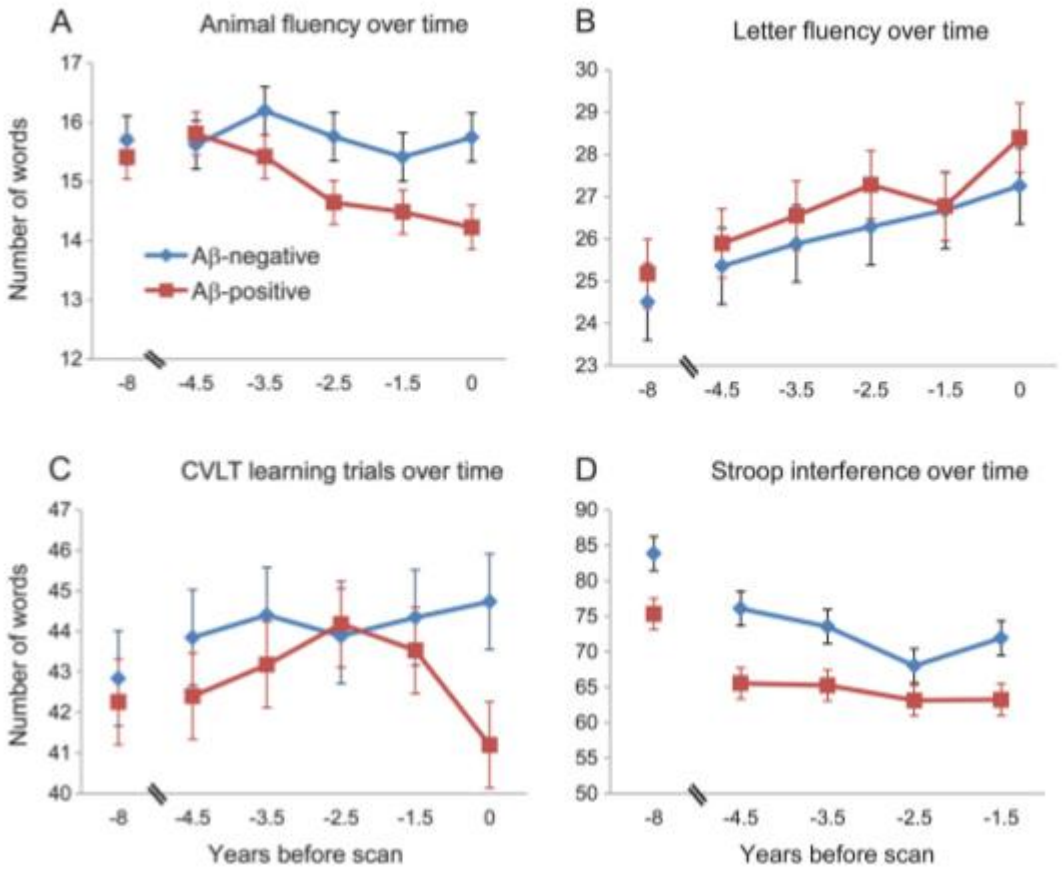
Jansen et al., JAMA 2015



Jansen et al., JAMA 2015

Cognitive trajectories associated with β-amyloid deposition in the oldest-old without dementia

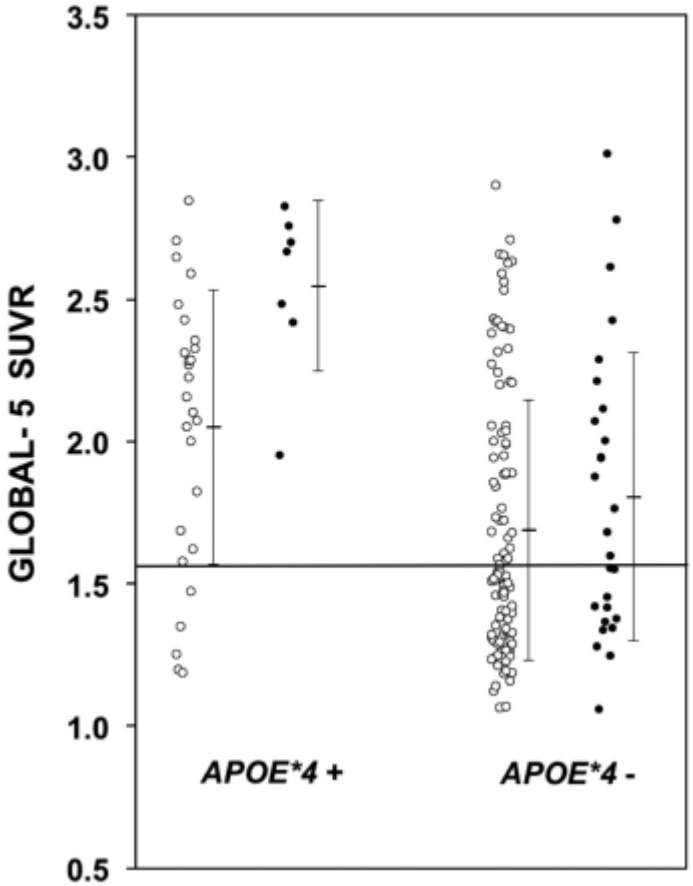
Figure 1 Different patterns of cognitive change over time by Aβ-status group and by test



n.194
mean age 85.5
range 82-95

Snitz et al., Neurology 2013

In Vivo Assessment of Amyloid-β Deposition in Nondemented Very Elderly Subjects



OBJECTIVE:
This study examined amyloid-β (Aβ) deposition in 190 non demented subjects aged ≥82 years to determine the proportion of Aβ-positive scans and associations with cognition, apolipoprotein E (APOE) status, brain volume, and Ginkgo biloba (Gb) treatment.

INTERPRETATION:
The data revealed a 55% prevalence of PiB positivity in non demented subjects age >80 years and 85% PiB positivity in the APOE*4 non demented elderly subjects.

Mathis et al., Ann Neurol 2013

Quale ruolo del Geriatra?

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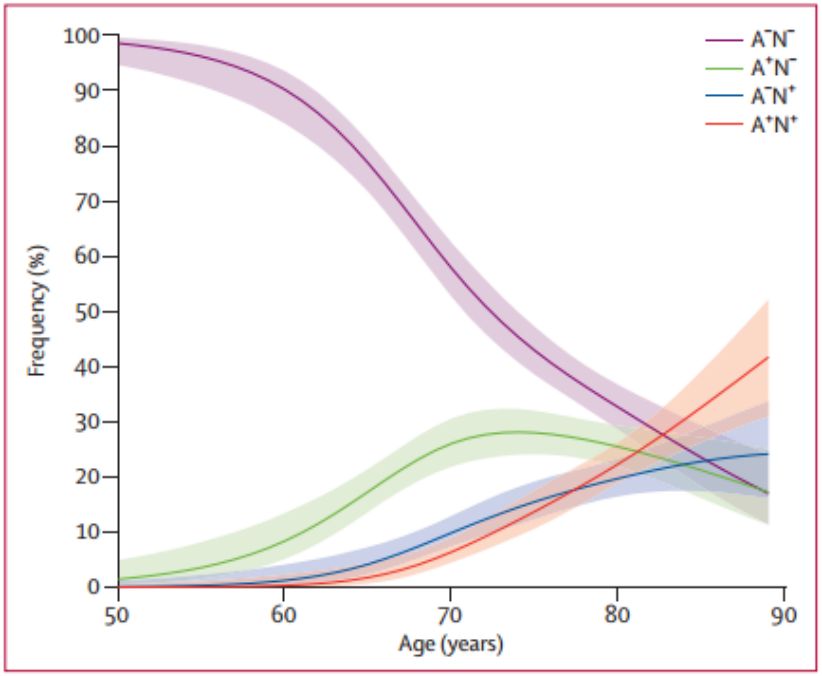
Quale ruolo dei biomarcatori per l'anziano SENZA decadimento cognitivo?

	Amyloid negative, neurodegeneration negative (A^-N^-; n=503)	Amyloid positive, neurodegeneration negative (A^+N^-; n=213)	Amyloid negative, neurodegeneration positive (A^-N^+; n=130)	Amyloid positive, neurodegeneration positive (A^+N^+; n=139)
50–54 years	35 (100%)	0	0	0
55–59 years	37 (100%)	0	0	0
60–64 years	93 (85%)	13 (12%)	3 (3%)	1 (1%)
65–69 years	80 (61%)	37 (28%)	10 (8%)	5 (4%)
70–74 years	110 (52%)	58 (27%)	28 (13%)	16 (8%)
75–79 years	91 (43%)	44 (21%)	36 (17%)	40 (19%)
80–84 years	40 (24%)	45 (27%)	33 (20%)	50 (30%)
85–89 years	17 (21%)	16 (20%)	20 (25%)	27 (34%)

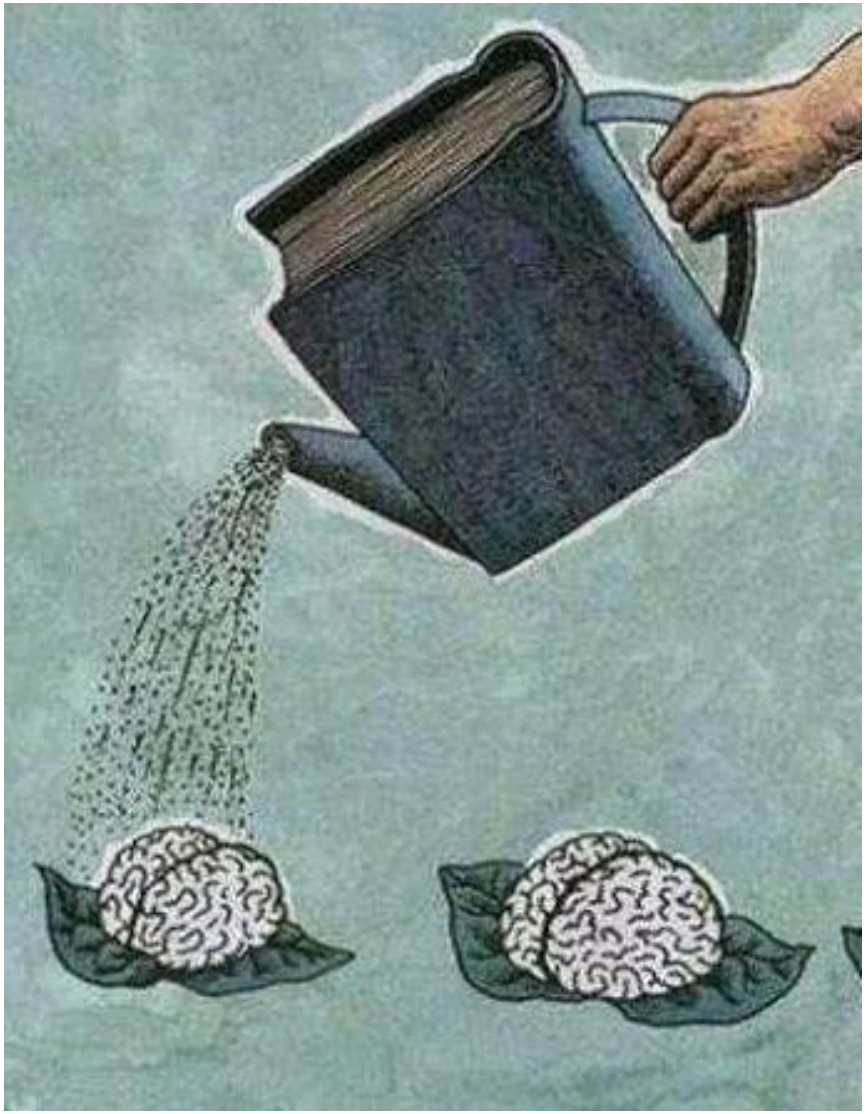
Data are n (%).

Table 2: Numbers of participants in each biomarker group by 5-year age stratum

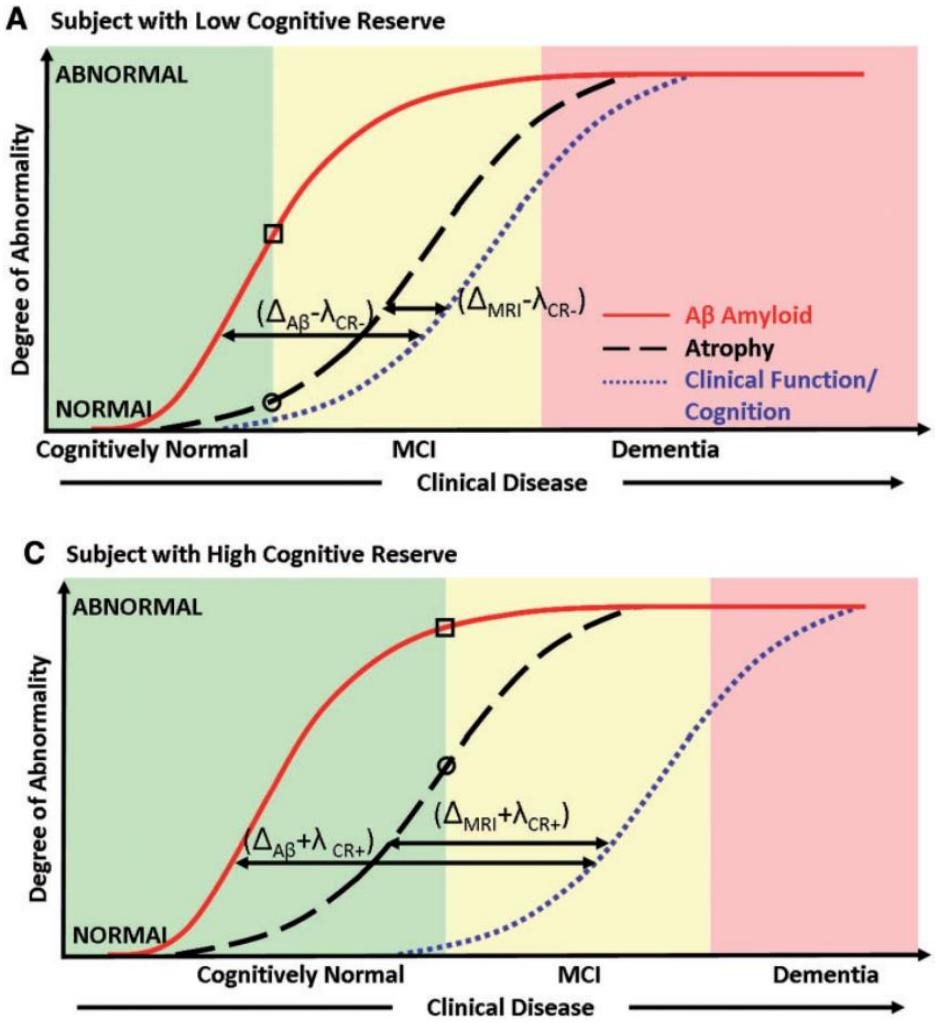


Jack et al., Lancet Neurol 2014

RISERVA COGNITIVA



Cognitive reserve and Alzheimer's disease biomarkers are independent determinants of cognition



Vemuri et al., Brain 2011

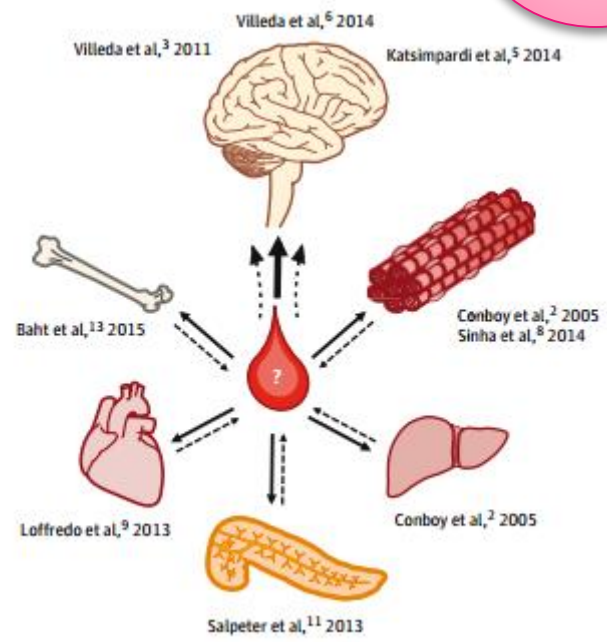
Il ringiovanimento cerebrale: è possibile?

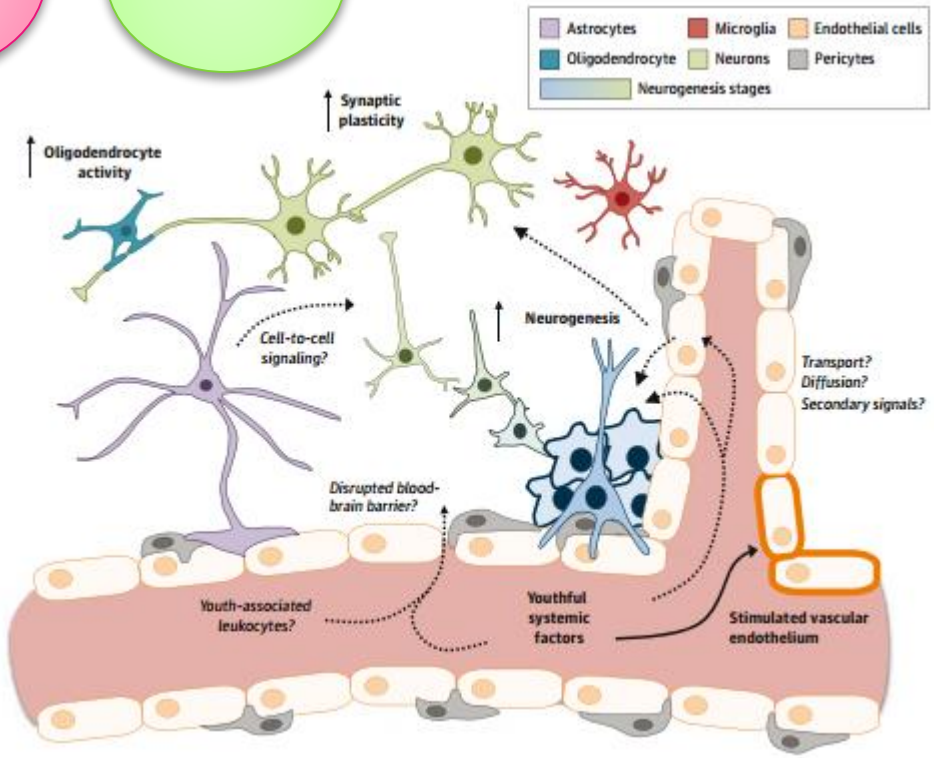
"...c'è molta più neurogenesi nel cervello umano adulto di quanto si potesse pensare in precedenza...anche un piccolo numero di neuroni appena formati possono integrarsi in reti neuronali portando a conseguenze sulle funzioni cognitive..."

Aimone et al., Physiol Rev, 2014

CCL11

GDF 11





Castellano et al., JAMA Neurol 2015

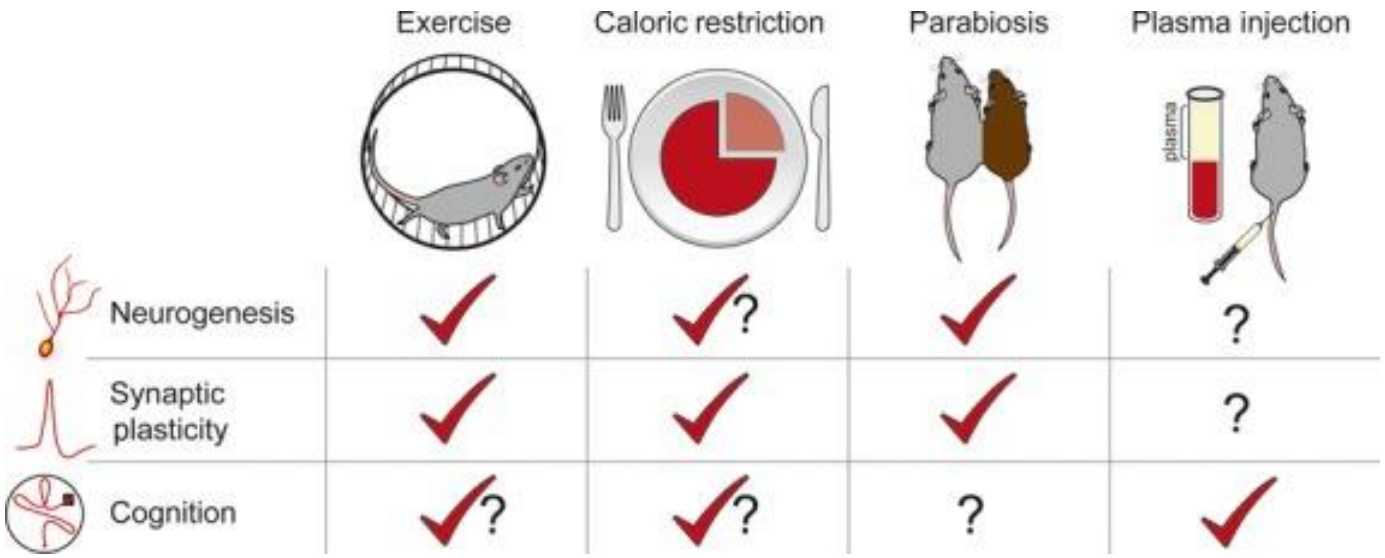
Journal of Neurochemistry JNC

JOURNAL OF NEUROCHEMISTRY | 2015 | 132 | 5–19 doi: 10.1111/jnc.12969

REVIEW

Aging and brain rejuvenation as systemic events

Jill Bouchard*,† and Saul A. Villeda*,†,‡



CONCLUSIONI

- Dei biomarcatori patofisiologici finora studiati, quelli che stimano il carico amiloideo sembrano essere i più significativi, specialmente nell'early onset AD.
- Nel soggetto più anziano, vi è molta probabilità di avere dei falsi positivi (per riserva cognitiva) o negativi (per la concomitanza di molteplici cause di degenerazione neuronale).
- Lo studio dei biomarcatori classici va pertanto riservato ai «casi difficili» come ausilio alla valutazione clinica, neuropsicologica e di imaging strutturale e funzionale, ed a scopo di ricerca, per poter verificare l'utilità dei nuovi farmaci *disease modifying.*
- È necessario intraprendere anche altre strade per ricercare marcatori specifici e sensibili nel paziente anziano e molto anziano.

“**Non ti arrendere mai.** Di solito e' l’ultima chiave del mazzo quella che apre la porta.”

Paolo Coelho

Grazie
per l’attenzione