I nuovi criteri nella diagnosi di demenza.

Camillo Marra

Clinica della Memoria

Fondazione Policlinico Gemelli- IRCCS

Convegno SINDEM Regione Emilia Romagna
Bologna 25 Ottobre 2019

Dalla Malattia Clinica alla Malattia Biologica

……1997 Fase preterapeutica

1997-2007 La malattia clinica e la diagnosi precoce

2007-2010 La terra di mezzo

2010-2018 L’entità clinico biologica

>2018…….La malattia Biologica

views &reviews

Article abstract—Clinical criteria for the diagnosis of Alzheimer's disease include insidious onset and progressive impairment of memory and other cognitive functions. There are no motor, sensory, or coordination deficits early in the disease. The diagnosis cannot be determined by laboratory tests. These tests are important primarily in identifying other possible causes of dementia that must be excluded before the diagnosis of Alzheimer's disease may be made with confidence. Neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy. The criteria proposed are intended to serve as a guide for the diagnosis of probable, possible, and definite Alzheimer's disease; these criteria will be revised as more definitive information becomes available.

Clinical diagnosis of Alzheimer's disease:

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

La Malattia è definita sulla base della presentazione fenotipica e di uno specifico pattern di presentazione neuropsicologica

Viene effettuata una distinzione tra sindrome demenziale e demenza di Alzheimer

La malattia è definita come entità clinica sulla base di caratteristiche di comparsa, progressione e associazione con eventuali altre patologie

Vengono descritti decorsi e possibili evoluzioni

Divisione in
AD probabile
AD possibile
Ad certa

La certezza è possibile solo in presenza di Markers Neuropatologici di malattia

Table 2. Neuropsychological evaluation

The major cognitive processes that are impaired in Alzheimer's disease, with examples of the kinds of tests used to assess these functions, include:

orientation to place and time, graded by a test such as the Mini-Mental State Examination[1];

memory evaluated by tests such as a free-recall test[7] of concrete nouns, a 3-4 paired-associate learning test (verbal and nonverbal) by use of a recognition paradigm, the Recognition Span Test,[8] and the Brown-Peterson Distractor Test[9,10] (stopping the task when the patient fails or begins to produce the distractor instead of the stimulus trigrams);

language skills tested by examination of verbal fluency of the semantic or category type, with the examiner writing responses, and by other tests such as the Boston Naming Test[11] (preferably one of the abbreviated forms), the Boston Diagnostic Aphasia Examination,[12] the Western Aphasia Test,[13] and the Token Test[14-16] with Reporter's Test[17];

praxis evaluated by tests[18] such as those in which the patient copies a drawing (cube, daisy, clock, or house) or performs the block design subtest of the Wechsler Adult Intelligence Scale[19];

attention monitored by tests such as a reaction-time task[20] or by the Continuous-Performance Test[21];

visual perception studied by use of a variety of tasks, such as the Gollin Incomplete-Pictures Test[22] and the Hooper Test[23];

problem-solving skills determined by tests such as the Wisconsin Card Sorting Test[24,25] or The Poisoned Food Problem Task of Arenberg[26,27]; and

social function, activities of daily living,[28,29] and instrumental activity of daily living,[30] assessed by methods similar to those described in the Philadelphia Geriatrics Center Forms.[31]

DSM-5 criteria of major neurocognitive disorder (dementia)

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

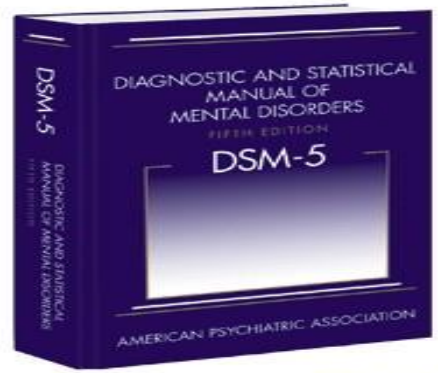
C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

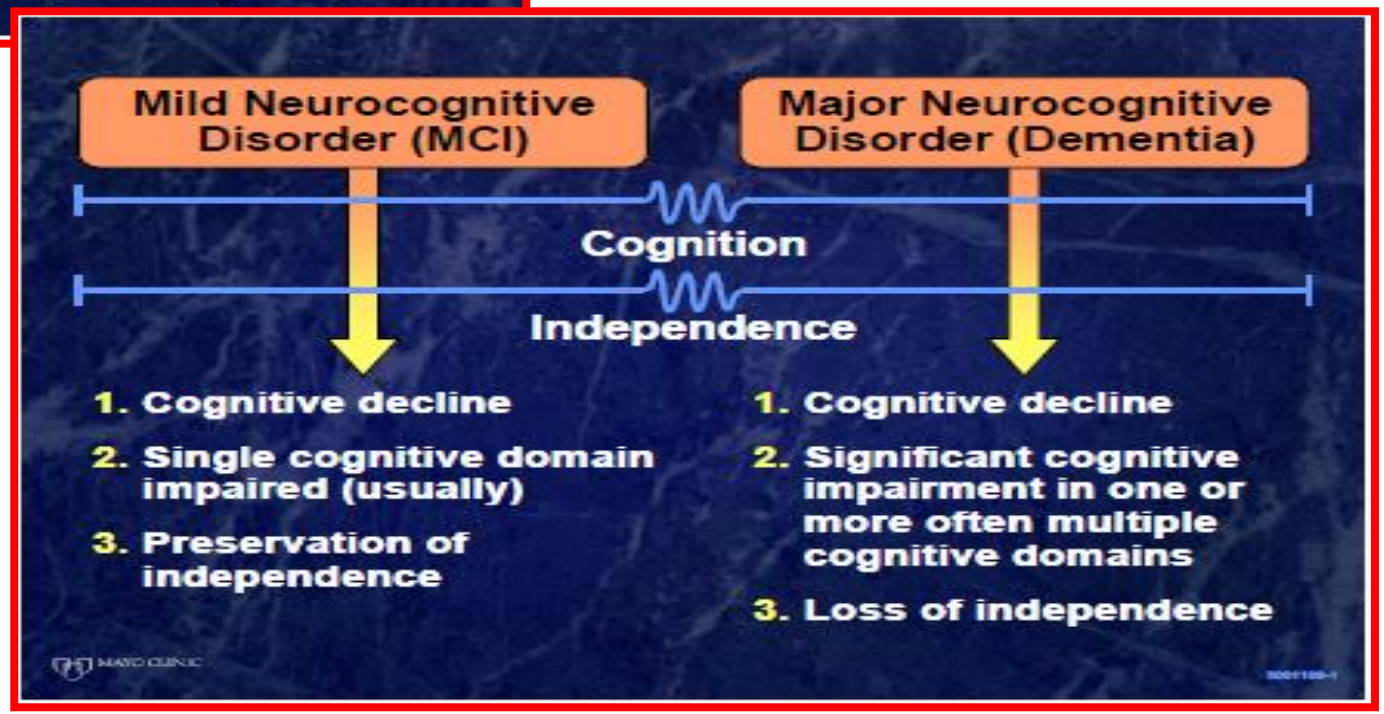
Neurocognitive Disorders
Domains

Domain	Tasks
Complex attention	Major: diminished, multiple stimuli Mild: takes longer
Executive abilities	Major: abandon complex activities Mild: ↑ effort, multi-tasking
Learning/memory	Major: repeat self in conversation Mild: recent events, occas repeat
Language	Major: anomia, paraphasias Mild: ↓ naming, word finding
Visuoconstruction Visuoperception	Major: not driving, ↓ navigation Mild: maps, effort
Social cognition	Major: insensitivity social contexts Mild: subtle personality, ↓ empathy

MAYO CLINIC



DSM-5
2013



Journal of Internal Medicine 2004; 256: 240–246

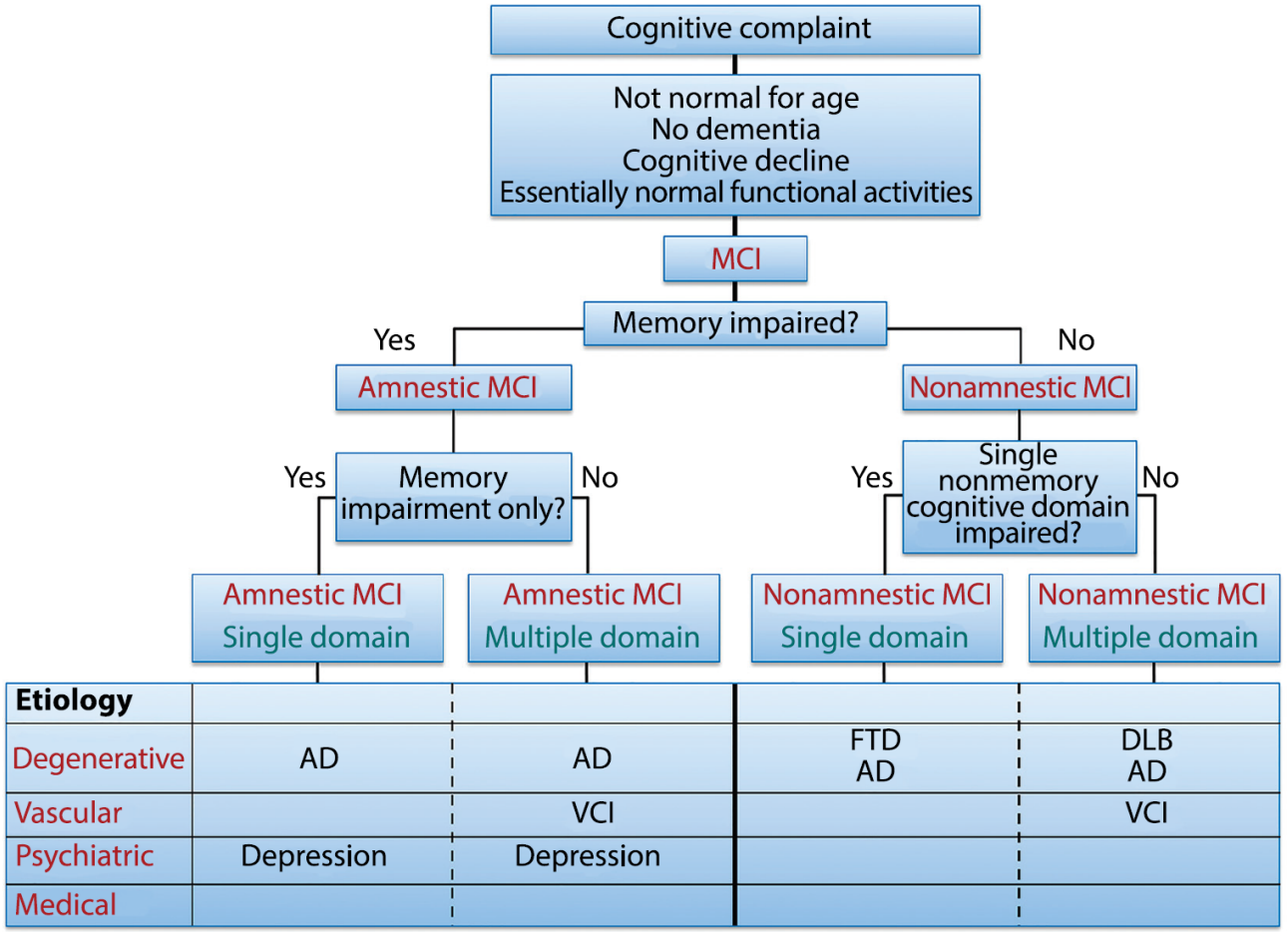
KEY SYMPOSIUM

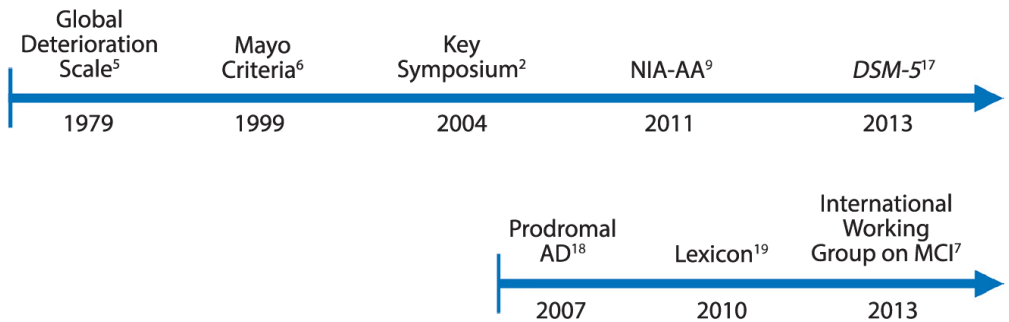
Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment

B. WINBLAD[1], K. PALMER[2], M. KIVIPELTO[2], V. JELIC[1], L. FRATIGLIONI[2], L.-O. WAHLUND[1], A. NORDBERG[3], L. BÄCKMAN[2], M. ALBERT[4], O. ALMKVIST[1], H. ARAI[5], H. BASUN[6], K. BLENNOW[7], M. DE LEON[8], C. DECARLI[9], T. ERKINJUNTTI[10], E. GIACOBINI[11], C. GRAFF[12], J. HARDY[13], C. JACK[14], A. JORM[15], K. RITCHIE[16], C. VAN DUIJN[17], P. VISSER[18] & R.C. PETERSEN[19]

2004-2013

Passaggio da un fase clinico diagnostica ad una fase di definizione di una entità clinica associata a biomarkers ed esami strumentali





ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–7

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may **increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process**. However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time. There are several reasons for this limitation: (1) the core clinical criteria provide very good diagnostic accuracy and utility in most patients; (2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed, (3) there is limited standardization of biomarkers from one locale to another, and (4) access to biomarkers is limited to varying degrees in community settings. Presently, the use of biomarkers to enhance

I CRITERI NIA (NATIONAL INSTITUTE ON AGING)

Diagnosi Clinica AD probabile: inclusione del concetto di forme atipiche

AD con livelli crescenti di certezza

- Dimostrata progressione di un disturbo cognitivo
- Indipendenza della diagnosi dalla disponibilità di biomarkers
- Portatori di un gene causativo di malattia

AD con evidenza di processo patofisiologico di AD

-indicatori di stato: Presenza di Beta amiloide

-indicatori di neurodegenerazione:

phosfotau

PET ipometabolismo TP

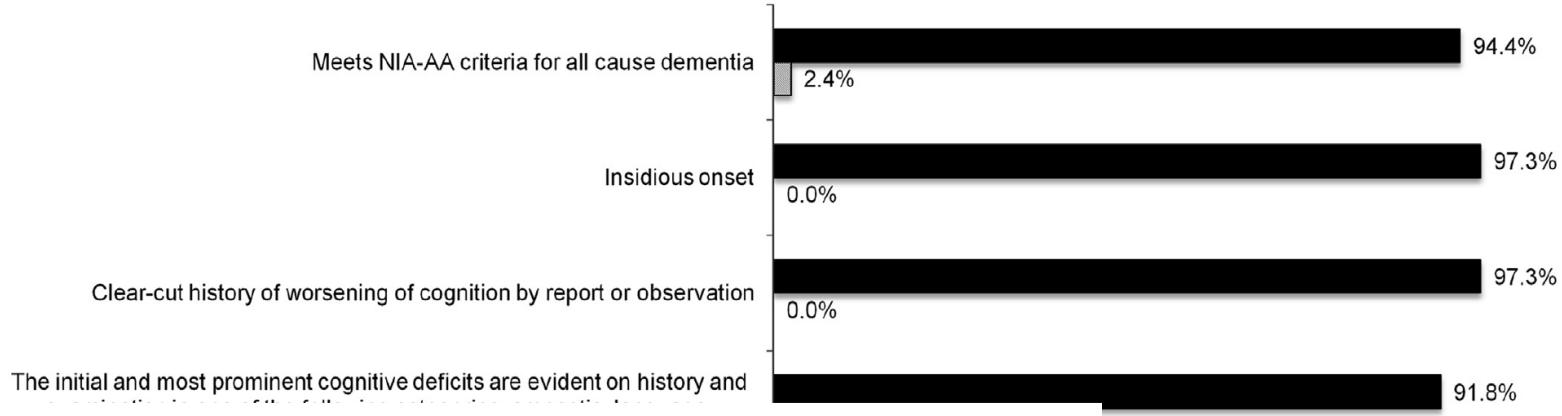
RM con atrofia Temporo mesiale o ippocampale

Possibile demenza di AD: Presenza di markers ma quadro fenotipico non corrispondente ad AD ma ad altre forme di demenza

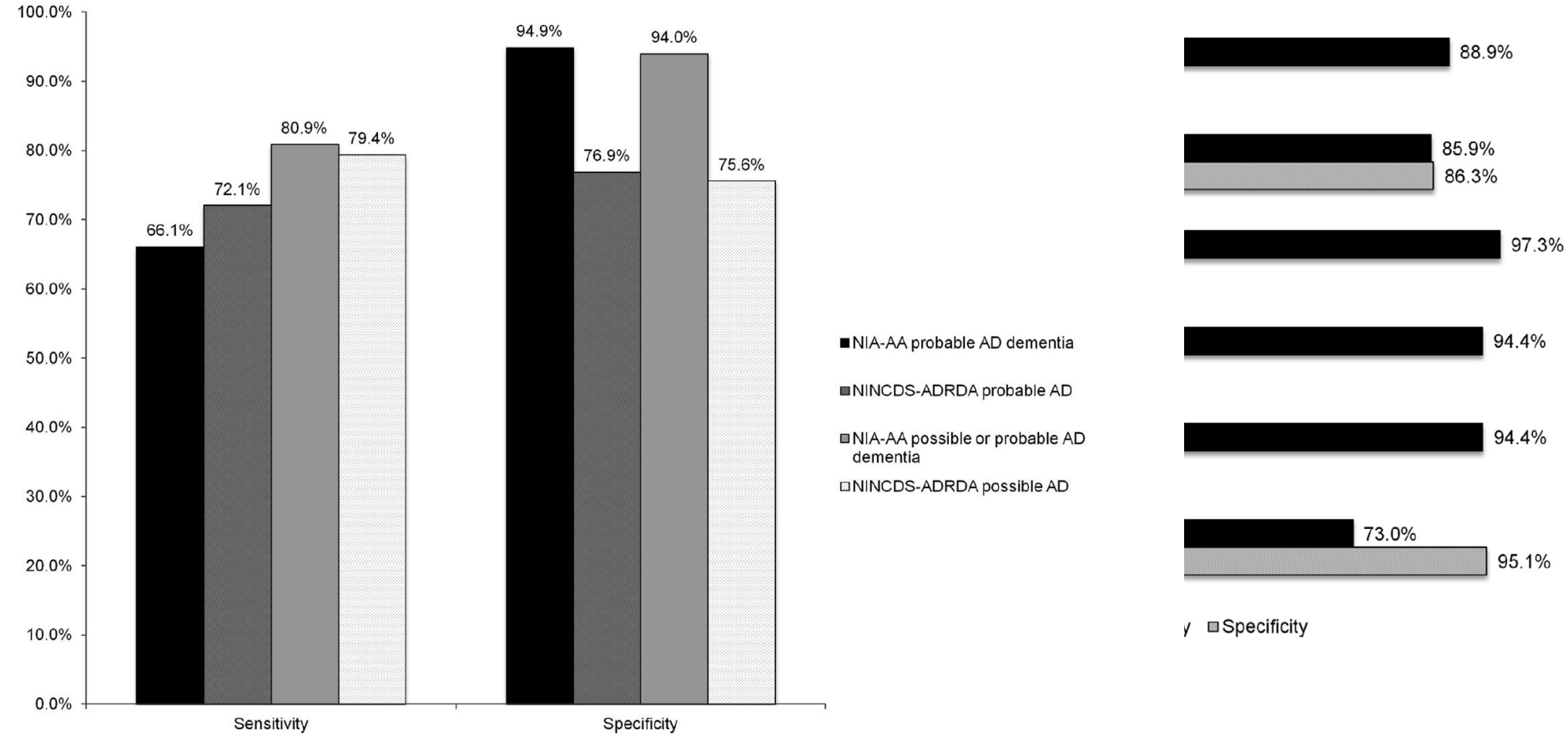
ELSEVIER
CrossMark
Alzheimer's & Dementia 11 (2015) 207-215
Alzheime & Dementi

Do NIA-AA criteria distinguish Alzheimer's disease from frontotemporal dementia?

Jennifer M. Harris[a,b], Jennifer C. Thompson[a], Claire Gall[a], Anna M. T. Richardson[a,b], David Neary[a,b], Daniel du Plessis[a], Piyali Pal[a], David M. A. Mann[a,b], Julie S. Snowden[a,b], Matthew Jones[a,b,*]



NIA-AA AD dementia	AD patholo
Met probable criteria	A = 42 (tru positives
Did not meet probable criteria	C = 22 (fal negatives
Met possible or probable criteria	E = 58 (tru positives
Did not meet possible or probable criteria	G = 15 (fal negatives



Key Symposium

Journal of INTERNAL MEDICINE

Click here for more articles from the symposium

doi: 10.1111/joim.12190

Watch Guest Editor Professor Mila Kivipelto talk about the 9th Key Symposium: Updating Alzheimer's Disease Diagnosis here.

Mild cognitive impairment: a concept in evolution

R. C. Petersen[1], B. Caracciolo[2,3], C. Brayne[4], S. Gauthier[5], V. Jelic[6] & L. Fratiglioni[2,7]

a consensus: report of the International Working Group on Mild Cognitive Impairment

B. WINBLAD[1], K. PALMER[2], M. KIVIPELTO[2], V. JELIC[1], L. FRATIGLIONI[2], L.-O. WAHLUND[1], A. NORDBERG[3], L. BÄCKMAN[2], M. ALBERT[4], O. ALMKVIST[1], H. ARAI[5], H. BASUN[6], K. BLENNOW[7], M. DE LEON[8], C. DECARLI[9], T. ERKINJUNTTI[10], E. GIACOBINI[11], C. GRAFF[12], J. HARDY[13], C. JACK[14], A. JORM[15], K. RITCHIE[16], C. VAN DUIJN[17], P. VISSER[18] & R.C. PETERSEN[19]

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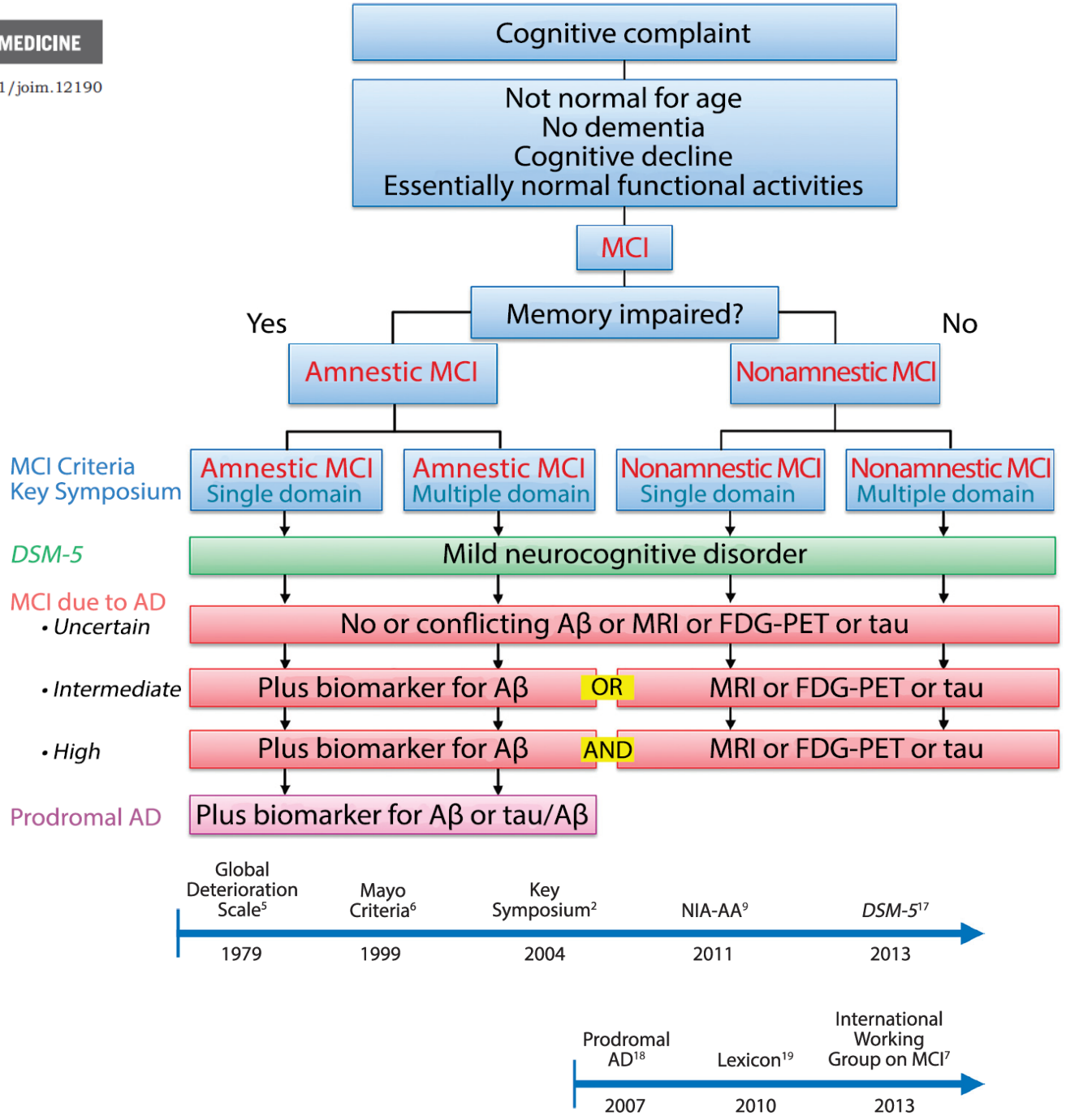

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

Necessità di uno specifico inquadramento neuropsicologico con test specifici

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

Necessità di uno specifico inquadramento Neuropatologico

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

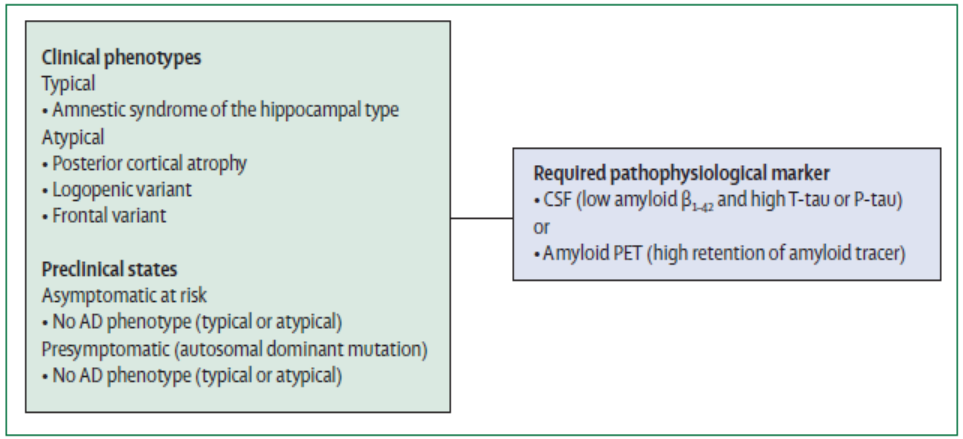

Figure: **AD is defined as a clinicobiological entity**
A simplified algorithm is proposed: in any condition and at any stage of the disease, the diagnosis of AD relies on the presence of a pathophysiological marker. AD=Alzheimer's disease.

Ruolo della presentazione fenotipica

Quale tipo di prova?

Major criterion
Presence of an early and significant episodic memory impairment that includes the following features:
1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly, or does not normalize with cueing or recognition testing and after effective encoding of information has been previously assessed
3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances.

- Free and cued reminding selective test(FCRST) sec. paradigma di Grober e Buschke

Dubois et al, 2007, 2010

Amnestic syndrome of the medial temporal type identifies prodromal AD

A longitudinal study

Neurology® 2007;69:1859-1867

M. Sarazin, PhD*
C. Berr, PhD*
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S. Legrain, MD
B. Michel, MD
M. Puel, MD
M. Volteau, PhD
J. Touchon, MD
M. Verny, PhD
B. Dubois, MD

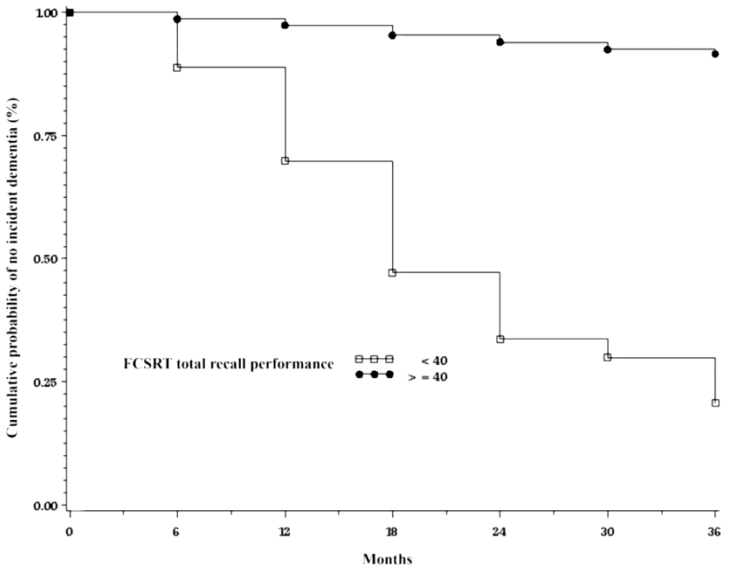
Table 1 Inclusion criteria of the MCI population at baseline (n = 217)

	% (n)
Memory complaint	100 (217)
Objective memory impairment	
Impairment in both MMSE word recall* and IST	48 (104)
Impairment in IST	12.4 (27)
Impairment in MMSE word recall	39.6 (86)
IADL	
No IADL change	87.1 (189)
Minor IADL change†	12.9 (28)

Table 3 Receiver operating characteristic analysis: Demographic factors and neuropsychological tests associated with incident AD dementia

	AUC	CI (AUC)	*p* Value	Cutoff	Se	Sp
Age	0.72	(0.65, 0.79)				
Age + gender	0.72	(0.65, 0.79)	0.21			
Age + education	0.72	(0.65, 0.79)	0.79			
Age + gender + education	0.73	(0.66, 0.80)	0.49			
FCSRT total recall*	0.94	(0.91, 0.97)	<0.0001	40	79.7	89.9
FCSRT index of cueing*	0.93	(0.89, 0.96)	<0.0001	71	78.0	84.8
FCSRT free recall*	0.92	(0.88, 0.96)	<0.0001	17	71.2	91.8
FCSRT delayed free recall*	0.92	(0.89, 0.96)	<0.0001	6	76.3	90.5
FCSFT delayed total recall*	0.89	(0.85, 0.94)	<0.0001	14	69.5	88.6
FCSRT number of intrusions*	0.87	(0.81, 0.92)	<0.0001	2	64.4	85.4
Verbal fluency (category)*	0.80	(0.74, 0.87)	0.003	13	55.9	82.3
WAIS similarities*	0.78	(0.72, 0.85)	0.04	11	49.2	72.2
FCSRT false recognition*	0.78	(0.71, 0.84)	0.002	1	20.3	98.1
Serial digit learning test*	0.77	(0.7, 0.84)	0.04	80	57.6	67.7
DENO 100*	0.76	(0.7, 0.83)	0.07	89	55.9	67.7
Benton Visual Retention Test*	0.76	(0.69, 0.83)	0.07	11	42.4	77.2
Trail Making test B*	0.75	(0.68, 0.82)	0.09	138	62.7	67.1
WAIS digit symbol test*	0.74	(0.67, 0.81)	0.15	10	37.3	71.5
Stroop test (inhibition condition)*	0.74	(0.67, 0.81)	0.22	59	52.5	58.2
Verbal fluency (letter S)*	0.74	(0.67, 0.81)	0.19	17	57.6	56.3
Trail Making test A*	0.73	(0.66, 0.8)	0.36	53	62.7	58.9
Double task of Baddeley*	0.72	(0.65, 0.79)	1.00	94	50.8	56.3

Figure Kaplan-Meyer survival curves for the development of Alzheimer disease (AD) dementia in patients with mild cognitive impairment for subjects with or without amnestic syndrome of the medial temporal type



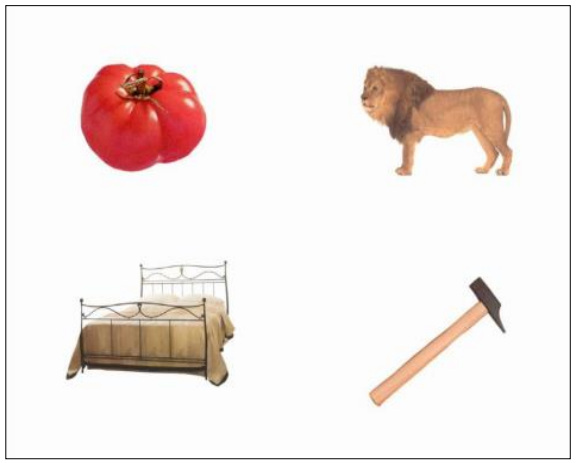
Neurol Sci (2011) 32:1057–1062
DOI 10.1007/s10072-011-0607-3

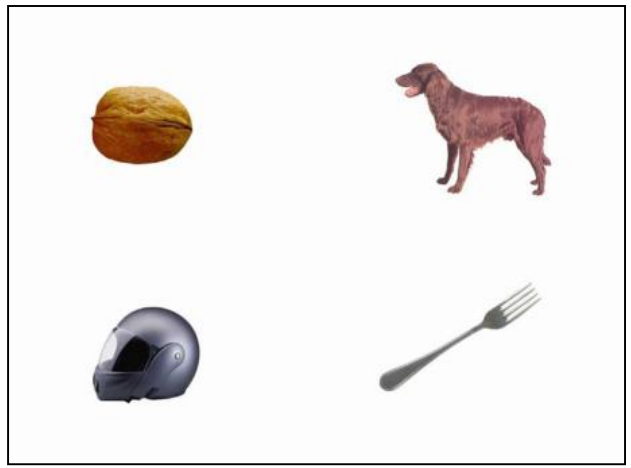
ORIGINAL ARTICLE

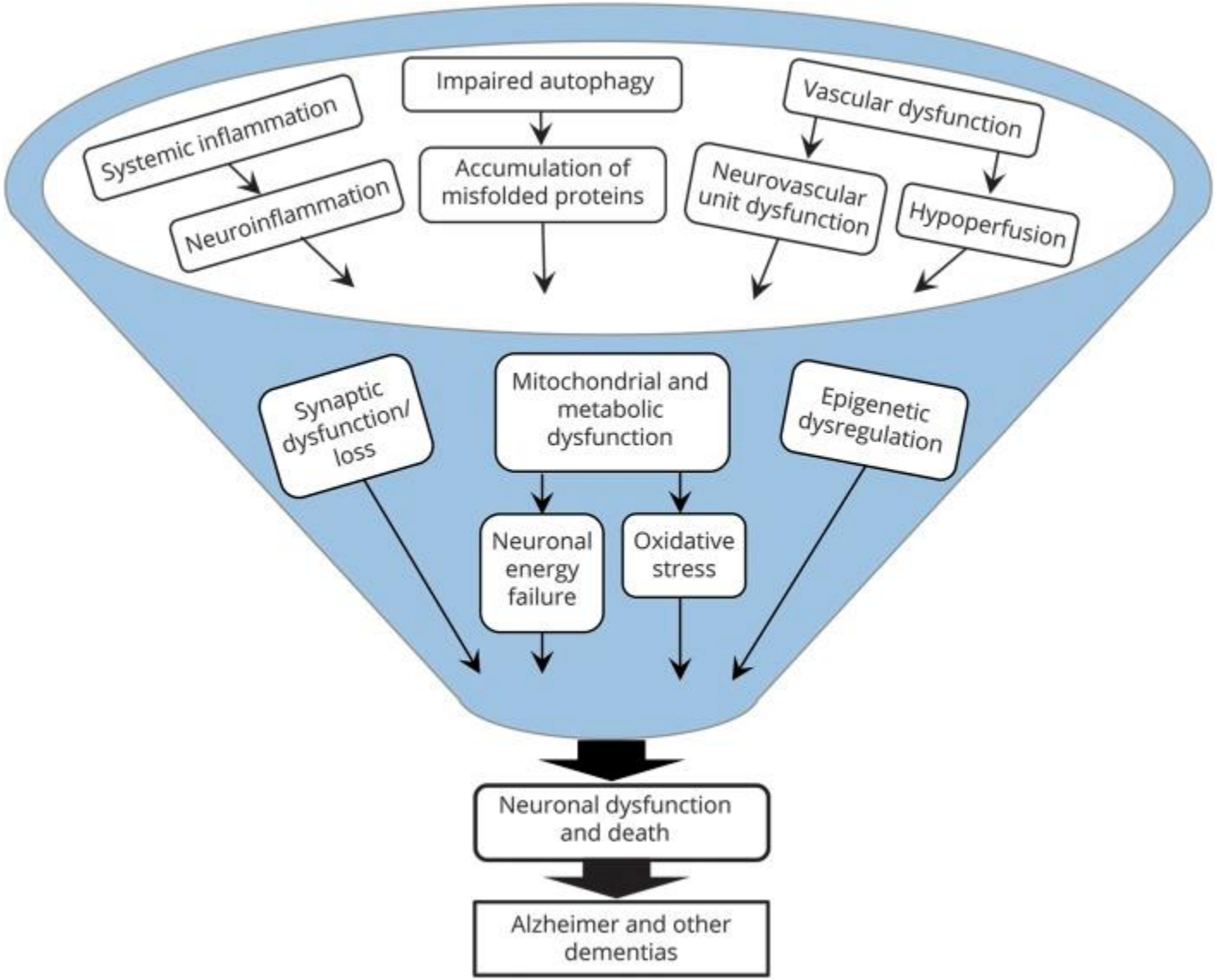
Free and cued selective reminding test: an Italian normative study

P. Frasson · R. Ghiretti · E. Catricalà · S. Pomati · A. Marcone · L. Parisi · P. M. Rossini · S. F. Cappa · C. Mariani · N. Vanacore · F. Clerici

Apprendimento codificato di 12 figure
-Free recall
-Cued recall
Ripetuto tre volte
-Delayed free recall
-Delayed cued recall







……forse non abbastanza presto

Alzheimer's & Dementia 11 (2015) 1191-1201

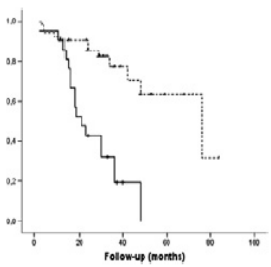
Featured Article

Prediction of AD dementia by biomarkers following the NIA-AA and IWG diagnostic criteria in MCI patients from three European memory clinics

Annapaola Prestia[a], Anna Caroli[b], Sara K. Wade[c,d], Wiesjie M. van der Flier[e,f], Rik Ossenkoppele[e,g], Bart Van Berckel[g], Frederik Barkhof[g], Charlotte E. Teunissen[h], Anders Wall[i], Stephen F. Carter[j], Michael Schöll[j], Il Han Choo[j,k], Agneta Nordberg[j,l], Philip Scheltens[e], Giovanni B. Frisoni[a,m,*]

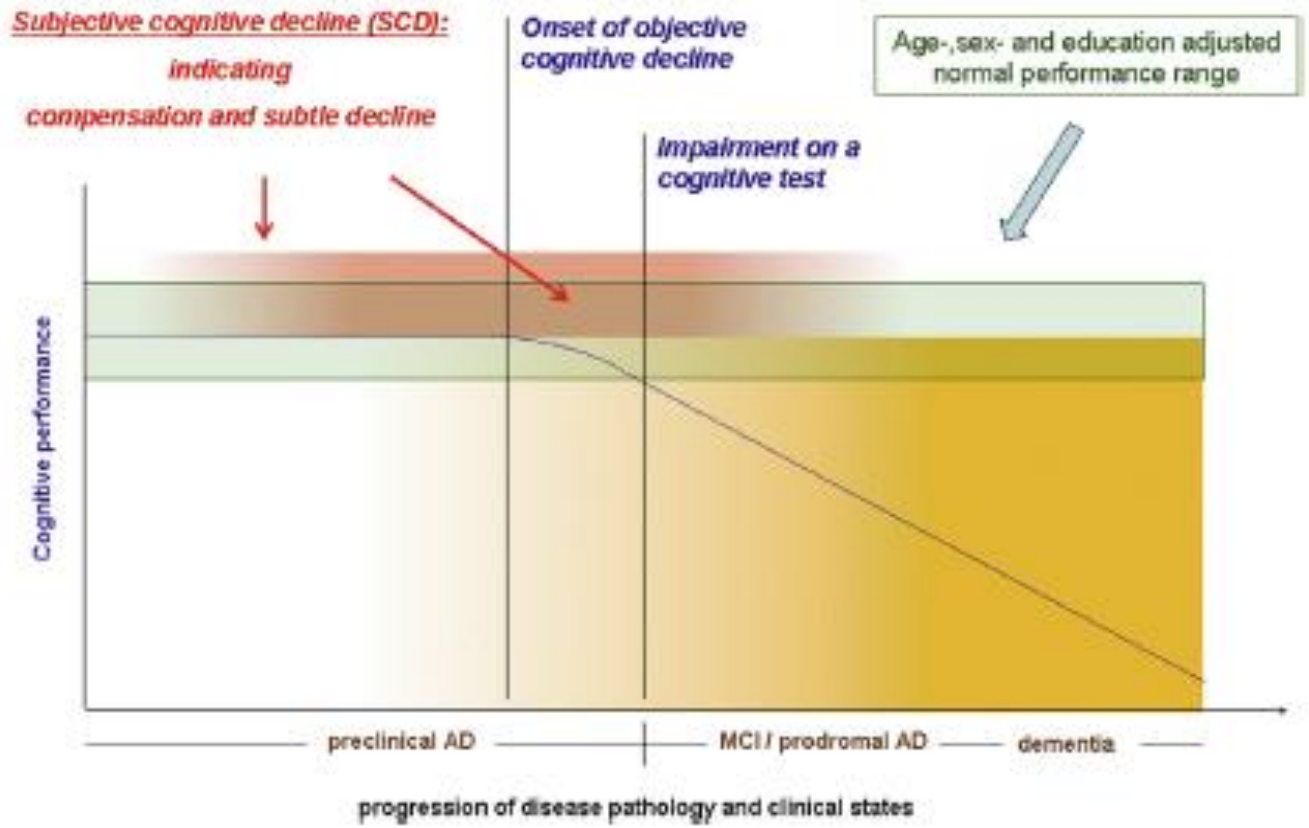
Table 1
Sociodemographic and clinical features and neurodegeneration and amyloidosis markers in MCI patients by progression at follow-up

	pMCI	sMCI	*P*
N	29	44	
Age (yrs) [range]	67.6 ± 8.9 [52÷83]	65.3 ± 9.4 [50÷85]	.31
Gender (females)	18 (62%)	23 (52%)	.41
Follow-up time (months) [range]	23.3 ± 16.3 [2÷76]	31.8 ± 16.5 [12÷84]	.033
Baseline MMSE [range]	26.7 ± 1.6 [24÷29]	27.5 ± 1.8 [24÷30]	.053
Last follow-up MMSE* [range]	22.3 ± 2.7 [17÷27]	27.8 ± 2.0 [24÷30]	<.0001
MMSE yearly change* [quartiles]	−4.6 ± 5.4 [−4.9, −2.9, −1.5]	0.1 ± 0.8 [−0.5,0.0,0.6]	<.0001
APOE genotype (ε4 carriers)†	15 (58%)	21 (51%)	.61
CSF Aβ42 [range]	429 ± 122 [230÷768]	688 ± 293 [288÷1404]	<.0001
CSF τ [range]	645 ± 330 [215÷1423]	399 ± 196 [96÷889]	<.0001
FDG-PET AD t-sum score [range]	35,093 ± 27,008 [6837÷116,026]	8945 ± 11,250 [954÷65,292]	<.0001
Age-adjusted hippocampal atrophy (W scores) [range]	−2.6 ± 2.2 [−6.5÷1.9]	−1.1 ± 2.6 [−7.2÷4.5]	.013

	IWG	NIA-AA	Unadjusted				Adjusted				
				95% CI				95% CI			
	Prodromal AD	Likelihood of MCI due to AD	HR	Lower	Upper	*P*	HR	Lower	Upper	*P*	Survival curves
Aβ42 + AND FDG-PET +	NA	High	4.50	2.30	10.87	<.001	4.87	2.16	10.97	<.001	

F. Jessen et al. / Alzheimer's & Dementia ■ (2014) 1–9

Course of cognitive symtomes in AD



Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

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Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Entità clinico-biologica

Gli MCI che sono inquadrabili come 'Prodromal Alzheimer' Disease' presentano sia un pattern di danno amnesico con caratteristiche mesio-temporali e markers liquorali di patologia amiloidea e neurodegenerazione

Ruolo della Neuropsicologia: identificare attraverso l'identificazione di tali pattern quadri di MCI amnesico che sono suscettibili di evoluzione a demenza di Alzheimer

Passaggio da un costrutto sindromico ad uno biologico di Malattia di Alzheimer

La malattia di Alzheimer è caratterizzata come un continuum sindromico dalla fase in cui i sintomi sono assenti a quella in cui è presente il disturbo cognitivo

Il lessico non è più quello della divisione in classi sindromiche cliniche (SCD, MCI, MCI due to AD) ma in classi di danno biologico A-T-N

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

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AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Biomarker Profile	Cognitive stage: Cognitively Unimpaired	Mild Cognitive Impairment	Dementia
$A^- T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
$A^+ T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
$A^+ T^+(N)^+$			
$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
$A^- T^+(N)^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
$A^- T^-(N)^+$			
$A^-T^+(N)^+$			

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Second, we determined that these recommendations should be cast as a "research framework," not as diagnostic criteria or guidelines. Unlike the 2011 NIA-AA criteria for MCI or AD dementia based on clinical criteria (i.e., without biomarkers) [2,3], the 2018 research framework is not intended for general clinical practice. It is called a

addition, AD neuropathologic changes are often present without signs or symptoms, especially in older persons. Thirty to forty percent of cognitively unimpaired (CU) elderly persons have AD neuropathologic changes at autopsy [67–69], and a similar proportion has abnormal amyloid biomarkers [33,53–55,60,70–73]. The fact that an

Identificazione tra individui sani A+T+/- coloro che non evolveranno in una sindrome clinica
-resilienza individuale acquisita e su base multigenetica
-diverse caratteristiche del burden di danno amiloideo
-età di osservazione

Indicatori funzionali, di connettività e clinico-neuropsicologici
Ruolo Nuovo della neuropsicologia

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Featured Article

The effect of diagnostic criteria on outcome measures in preclinical and prodromal Alzheimer's disease: Implications for trial design

Daniela Bertens[a,*], Betty M. Tijms[a], Lisa Vermunt[a], Niels D. Prins[a,b], Philip Scheltens[a], Pieter Jelle Visser[a,c,1], for the Alzheimer's Disease Neuroimaging Initiative

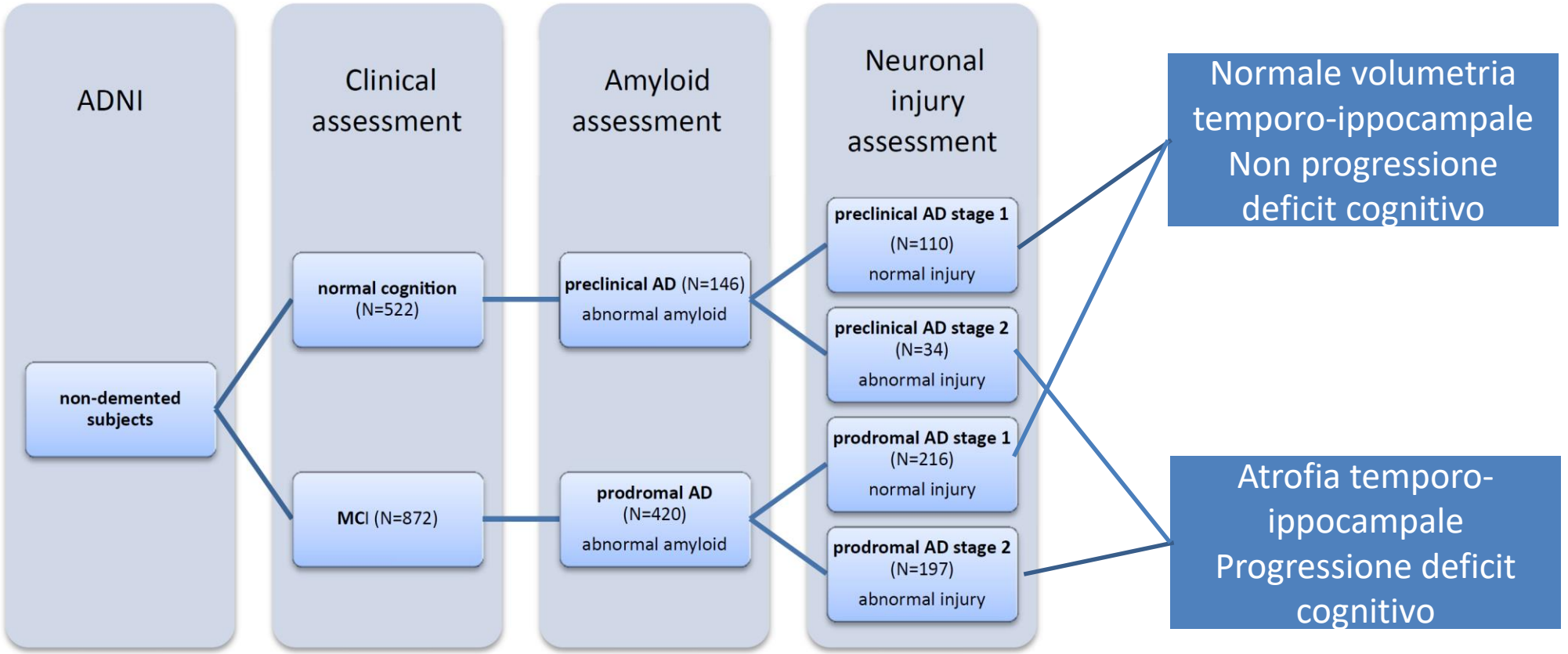

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Table 2 Mean and standard deviation of variables at baseline for subjects who remained normal versus subjects who developed clinical symptoms and were diagnosed with MCI or Alzheimer's disease dementia

Table 5 Increment in prediction of progression from normal cognition to MCI for variables added in order of potential application in a clinical trial

Variable	HR of model (95% CI)	HR: *P*-value	AUC of model (95% CI)	Time to outcome for model	Model sensitivity	Model specificity	Change in AUC versus prior step in model: *P*-value
APOE4			0.703 (0.627, 0.798)	5 years	0.629	0.660	-
			0.699 (0.628, 0.784)	7 years	0.613	0.671	-
			0.685 (0.617, 0.764)	10 years	0.618	0.644	-
APOE4[a]	1.862 (1.013, 3.424)	0.045					
APOE4 + Cognitive			0.777 (0.730, 0.850)	5 years	0.708	0.710	0.021
			0.785 (0.738, 0.852)	7 years	0.696	0.735	0.006
			0.772 (0.716, 0.842)	10 years	0.680	0.724	0.010
APOE4[a]	1.931 (1.042, 3.580)	0.037					
Paired Associates Immediate	0.629 (0.484, 0.816)	<0.001					
Digit Symbol Substitution	0.553 (0.384, 0.796)	0.001					
APOE4 + Cognitive + MRI			0.811 (0.769, 0.880)	5 years	0.723	0.750	0.052
			0.811 (0.769, 0.871)	7 years	0.723	0.747	0.062
			0.787 (0.733, 0.861)	10 years	0.680	0.759	0.223
APOE4[a]	2.036 (1.108, 3.740)	0.022					
Paired Associates Immediate	0.695 (0.534, 0.905)	0.007					
Digit Symbol Substitution	0.500 (0.347, 0.719)	<0.001					
R. Hippocampus volume	0.712 (0.539, 0.939)	0.016					
R. entorhinal cortex thickness	0.705 (0.522, 0.952)	0.022					
APOE4 + Cognitive + MRI + CSF p-tau			0.849 (0.802, 0.910)	5 years	0.799	0.745	0.015
			0.843 (0.798, 0.897)	7 years	0.803	0.735	0.014
			0.822 (0.769, 0.886)	10 years	0.737	0.770	0.024
APOE4[a]	2.068 (1.124, 3.805)	0.020					
Paired Associates Immediate	0.625 (0.476, 0.821)	0.001					
Digit Symbol Substitution	0.445 (0.306, 0.648)	<0.001					
R. Hippocampus volume	0.667 (0.503, 0.884)	0.005					
R. entorhinal cortex thickness	0.588 (0.424, 0.815)	0.001					
CSF p-tau	1.912 (1.490, 2.454)	<0.001					

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The Clinical Use of Cerebrospinal Fluid Biomarkers for Alzheimer's Disease Diagnosis: The Italian Selfie

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Table 2
Range of normality of CSF biomarkers $A\beta_{42}$, t-tau, and p-tau

Biomarker	Normal value (ng/L)	Laboratories (n)
$A\beta_{42}$	>450	2
	>500	10
	>550	4
	567–1022	1
	>600 ($n=1$)	1
	790 ± 228	1
T tau	<300	4
	<350	3
	<375	2
	<400	1
	<450	4
	<500	1
	170–512	2
	243 ± 127	1
p-tau181	<35	1
	33–66	1
	<52	2
	<61	11
	<65	1
	<67	1

n, number of laboratories; values are expressed in ng/L.

Table 1
Laboratories of CSF biomarkers

Laboratories of CSF biomarkers	Centralized laboratories	Internal laboratories	Hospitals sending
	15	10	15
Laboratories supporting Memory and Dementia Regional Centers (Dem-RC)§	Yes 32.50%	No 67.5%	
Number of analysis per month§	Less than 10 41.66%	Less than 20 45.83%	More than 20 12.50%
Standardization of pre-analytical procedures*	Yes 62.02%	No 37.98%	
External Quality control§	Yes 56%	No 44%	

Centralized laboratories provide biomarkers analysis for a network of neighboring hospitals; Internal laboratories perform CSF biomarkers analysis for own inpatients independently. Results are reported as percentage of collected questionnaires (*) or percentage of laboratories using CSF biomarkers ($n=40$)(§).

Fig. 1. Distribution of laboratories of CSF biomarkers.

CDCD – Servizi offerti per area geografica

Descrizione	n CDCD	%	nord (n=219)	%	centro (n=87)	%	sud-isole (n=195)	%
Valutazione clinica	481	96	212	97	84	97	185	95
Valutazione neuropsicologica	467	93	209	95	83	95	175	90
Esami ematochimici	380	76	174	79	65	75	141	72
ECG e visita cardiologica	374	75	166	76	61	70	147	75
RM cerebrale	350	70	162	74	63	72	125	64
TAC	368	73	171	78	64	74	133	68
EEG computerizzato	235	47	122	56	36	41	77	39
SPECT/PET cerebrale	258	51	137	63	35	40	86	44
Indagini genetiche (APOE, PS1, PS2)	149	30	85	39	25	29	39	20
Neuroimaging funzionale	121	24	58	26	22	25	41	21
Risonanza volumetrica	89	18	42	19	19	22	28	14
Markers liquorali (A-beta 1-42, prot. TAU)	165	33	107	49	27	31	31	16
Comunicazione della diagnosi	405	81	198	90	69	79	138	71
Ricovero in Day Hospital	178	36	91	42	36	41	51	26
Ricovero ordinario (degenza ordinaria)	233	47	127	58	40	46	66	34
Pianificazione visite periodiche e verifica eventuali nuove necessità assistenziali	438	87	204	93	74	85	160	82
Prescrizione del trattamento farmacologico	467	93	210	96	82	94	175	90
Monitoraggio del trattamento farmacologico	461	92	208	95	83	95	170	87
Counselling individuale con il paziente	367	73	174	79	62	71	131	67
Counselling con paziente e familiari	391	78	182	83	74	85	135	69
Counselling per familiari e caregiver	369	74	178	81	63	72	128	66
Attività informativa per familiari e caregivers	395	79	186	85	69	79	140	72
Trattamenti psico-sociali	177	35	95	43	29	33	53	27
Riabilitazione cognitiva	225	45	111	51	42	48	72	37
Riabilitazione motoria	176	35	82	37	33	38	61	31
Riabilitazione logopedica	130	26	66	30	21	24	43	22
Riabilitazione occupazionale	130	26	53	24	31	36	46	24
Assistenza domiciliare Integrata	247	49	114	52	38	44	95	49
Servizi diurni (CDI, CDD, CDA, etc.)	205	41	113	52	41	47	51	26
Servizio residenziale (RSA; RS, etc.)	247	49	127	58	40	46	80	41
Ricovero di sollievo	195	39	114	52	29	33	52	27
Servizio di trasporto	88	18	54	25	16	18	18	9
Servizio di telesoccorso	52	10	36	16	5	6	11	6
Pratiche legali e invalidità civile	222	44	110	50	42	48	70	36
Attività di ricerca clinico-epidemiologica	192	38	94	43	37	43	61	31
Attività di formazione e aggiornamento professionale	304	61	151	69	57	66	96	49
Contatti con le Associazioni dei familiari dei pazienti	291	58	155	71	51	59	85	44

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SIN DOCUMENT

Position paper of the Italian Society for the study of Dementias (Sindem) on the proposal of a new Lexicon on Alzheimer disease

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The proposed new diagnostic criteria and the new proposed lexicon for AD are conceptually attractive. However, the evidence about the instrumental and laboratory markers for the diagnosis of the preclinical and asymptomatic states of the disease are, until to now, insufficient to support the routine clinical use of these investigations.

Prodromal AD

Prodromal AD (also called "predementia stage of AD")

This term refers to the early symptomatic, predementia phase of AD in which (1) clinical symptoms including episodic memory loss of the hippocampal type (characterised by a free recall deficit on testing not normalised with cueing) are present, but not sufficiently severe to affect instrumental activities of daily living and do not warrant a diagnosis of dementia; and in which (2) biomarker evidence from CSF or imaging is supportive of the presence of AD pathological changes. This phase is now included in the new definition of AD. The term of prodromal AD might disappear in the future if AD is considered to encompass both the predementia and dementia stages

Panel 2. Prodromal AD according to Dubois et al. [1]

Preclinical states of AD

Preclinical states of AD (including both "asymptomatic at-risk state for AD" and "presymptomatic AD")

These terms refer to the long asymptomatic stage between the earliest pathogenic events/brain lesions of AD and the first appearance of specific cognitive changes. Traditionally, a preclinical or asymptomatic phase was recognised post mortem by the evidence of histological changes typical of Alzheimer's pathology in individuals considered as cognitively normal before death. Today, two preclinical states can be isolated in vivo:

- *Asymptomatic at-risk state for AD*: this state can be identified in vivo by evidence of amyloidosis in the brain (with retention of specific PET amyloid tracers) or in the CSF (with changes in amyloid β, tau, and phospho-tau concentrations). In the absence of knowledge about the value of these biological changes to predict the further development of the disease, the asymptomatic phase of AD should still be referred to as an "at-risk state for AD"
- *Presymptomatic AD*: this state applies to individuals who will develop AD. This can be ascertained only in families that are affected by rare autosomal dominant monogenic AD mutations (monogenic AD)"

Panel 1. Preclinical states of AD according to Dubois et al. [1]

Diagnosis and management of dementia with Lewy bodies

Third report of the DLB consortium

1. *Central feature* (essential for a diagnosis of possible or probable DLB)

   Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

2. *Core* features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)

   Fluctuating cognition with pronounced variations in attention and alertness

   Recurrent visual hallucinations that are typically well formed and detailed

   Spontaneous features of parkinsonism

3. *Suggestive features* (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)

   REM sleep behavior disorder

   Severe neuroleptic sensitivity

   Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

4. *Supportive features* (commonly present but not proven to have diagnostic specificity)

   Repeated falls and syncope

   Transient, unexplained loss of consciousness

   Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence

   Hallucinations in other modalities

   Systematized delusions

   Depression

   Relative preservation of medial temporal lobe structures on CT/MRI scan

   Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity

   Abnormal (low uptake) MIBG myocardial scintigraphy

   Prominent slow wave activity on EEG with temporal lobe transient sharp waves

McKeith IG et al. 2005

Table 1 Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

McKeith IG et al. 2017

I criteri diagnostici di Lund e Manchester

Table 57.3 *Consensus diagnostic criteria for frontotemporal dementia (Neary* et al.*, 1998)*

Core diagnostic features
Insidious onset and gradual progression
Early decline in social interpersonal conduct
Early impairment in regulation of personal conduct
Early emotional blunting
Early loss of insight

Supportive diagnostic features
Behavioural disorder
- Decline in personal hygiene and grooming
- Mental rigidity and inflexibility
- Distractibility and impersistence
- Hyperorality and dietary changes
- Perseverative and stereotyped behaviour
- Utilization behaviour

Speech and language
- Altered speech output
  - Aspontaneity and economy of speech
  - Press of speech
- Stereotypy of speech
- Echolalia
- Perseveration
- Mutism

Physical signs
- Primitive reflexes
- Incontinence
- Akinesia, rigidity, and tremor
- Low and labile blood pressure

Investigations
- Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
- Electroencephalography: normal on conventional EEG despite clinically evident dementia
- Brain imaging (structural and/or functional): predominant frontal and/or temporal abnormality

Supportive features
Onset before 65 years: positive family history of similar disorder in first-degree relative
Bulbar palsy, muscular weakness and wasting, fasciculations (associated motor neurone disease present in a minority of patients)

Diagnostic exclusion features
Historical and clinical
- Abrupt onset with ictal events
- Head trauma related to onset
- Early, severe amnesia
- Spatial disorientation
- Logoclonic, festinant speech with loss of train of thought
- Myoclonus
- Corticospinal weakness
- Cerebellar ataxia
- Choreoathetosis

Investigations
- Brain imagining: predominant postcentral structural or functional deficit; multifocal lesions on CT or MRI
- Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as MS, syphilis, AIDS, and herpes simplex encephalitis

Relative diagnostic exclusion features
Typical history of chronic alcoholism
Sustained hypertension
History of vascular disease (e.g. angina, claudication)

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Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

Katya Rascovsky,[1] John R. Hodges,[2] David Knopman,[3] Mario F. Mendez,[4,5] Joel H. Kramer,[6]

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

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III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
   C.1. Frontal and/or anterior temporal atrophy on MRI or CT
   C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD
B. Histopathological evidence of FTLD on biopsy or at post-mortem
C. Presence of a known pathogenic mutation

Demenza Frontotemporale variante comportamentale

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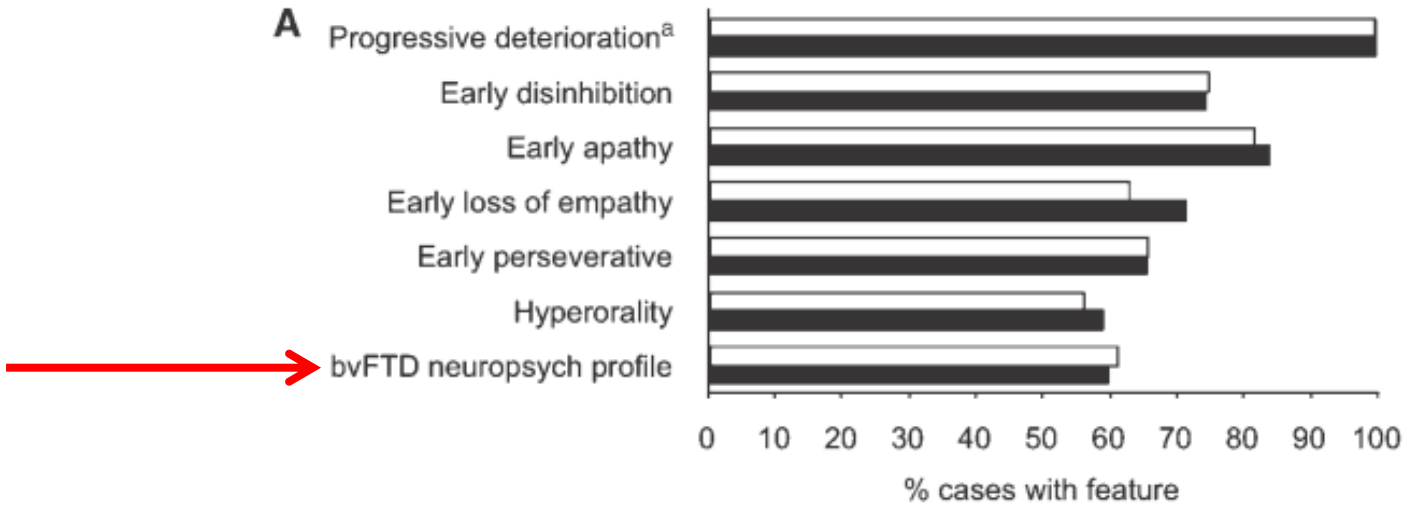

Demenza Frontotemporale variante comportamentale

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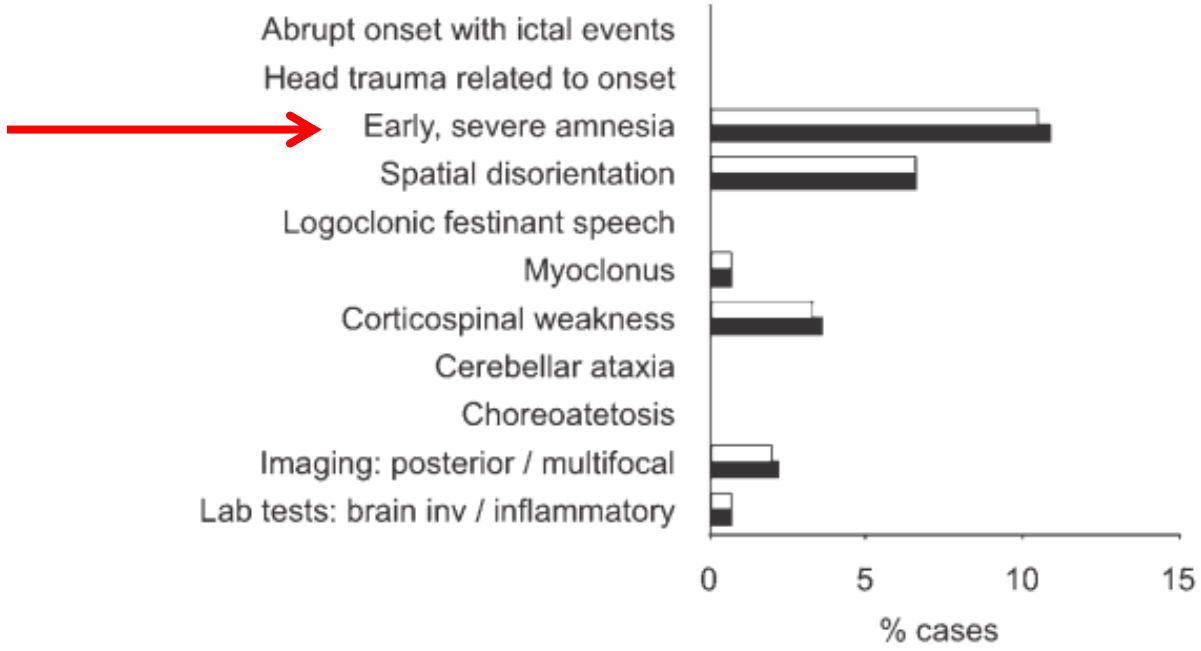

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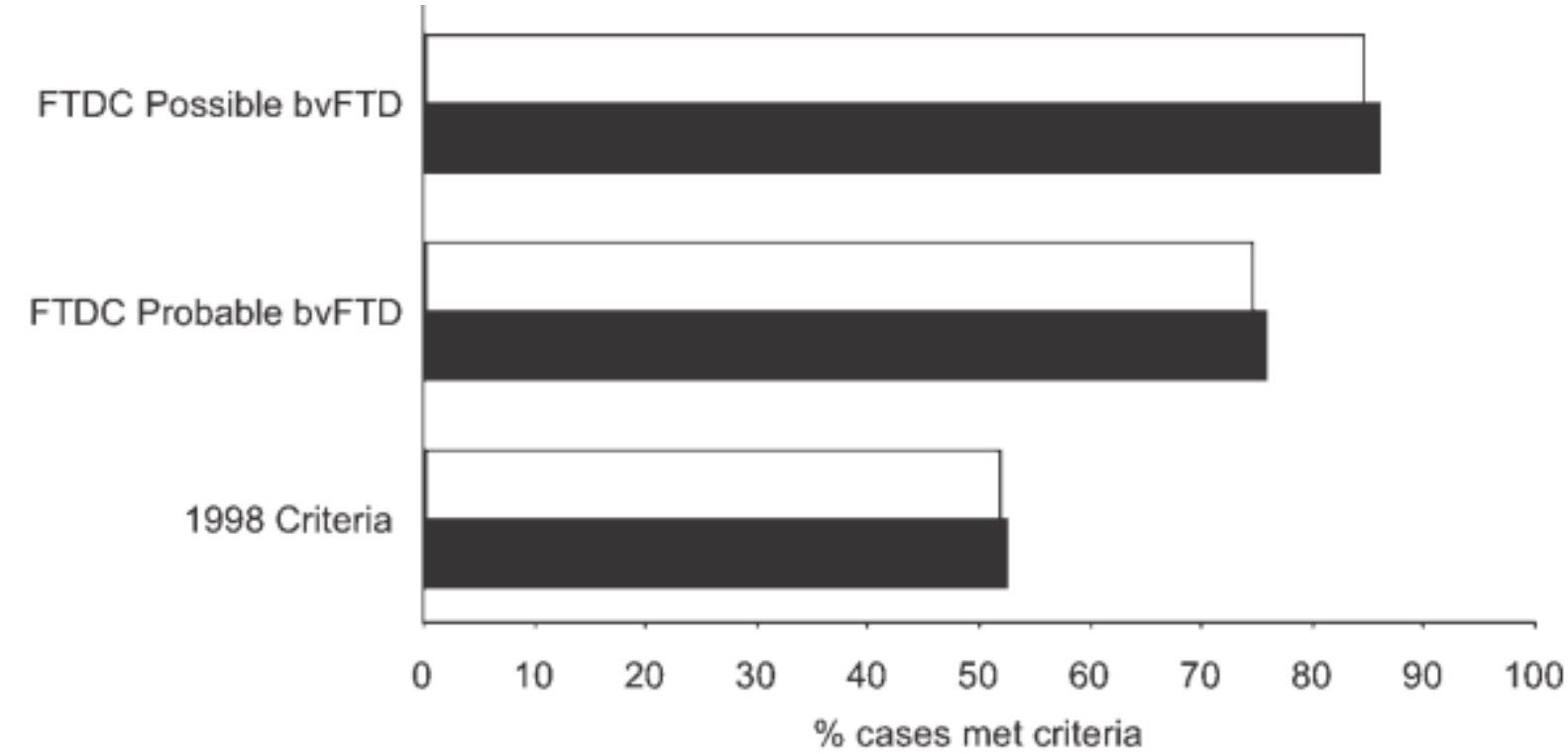

……take home messages

I criteri diagnostici per le demenze e per la demenza di Alzheimer in particolare hanno avuto negli ultimi 40 anni una progressiva modificazione legata al venire incontri a bisogni inizialmente solo diagnostici ma poi anche di prospettiva terapeutica

Il percorso seguito ha previsto nell'ordine:

-affinare la diagnostica tra le varie forme di demenza

-raggiungere una diagnosi precoce

-integrare nella diagnosi i progressi legati allo sviluppo delle neuroimmagini e dello studio sui biomarkers.

-includere nella diagnosi specifici pattern neuropsicologici e markers biologici della diagnosi allo scopo di definire criteri per l'identificazione dei soggetti da sottoporre ad un intervento disease modifying.

In assenza di terapie disease modifying:

Al momento la definizione operativa di demenza e perfettamente definita nei criteri DSM V. Si ritiene che in una prospettiva non terapeutica la diagnostica proposta dal Position paper della SINDEM abbia ancora una sostanziale validità

La diagnostica delle fasi prodromiche e atipiche necessita di una definizione attraverso biomarkers per la scelta di eventuali indagini genetiche e per definire anche pattern e staging di progressione e le condizioni di comorbilità

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Prof. Guido Gainotti
Dr. Davide Quaranta
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Dr.ssa Laura Serra

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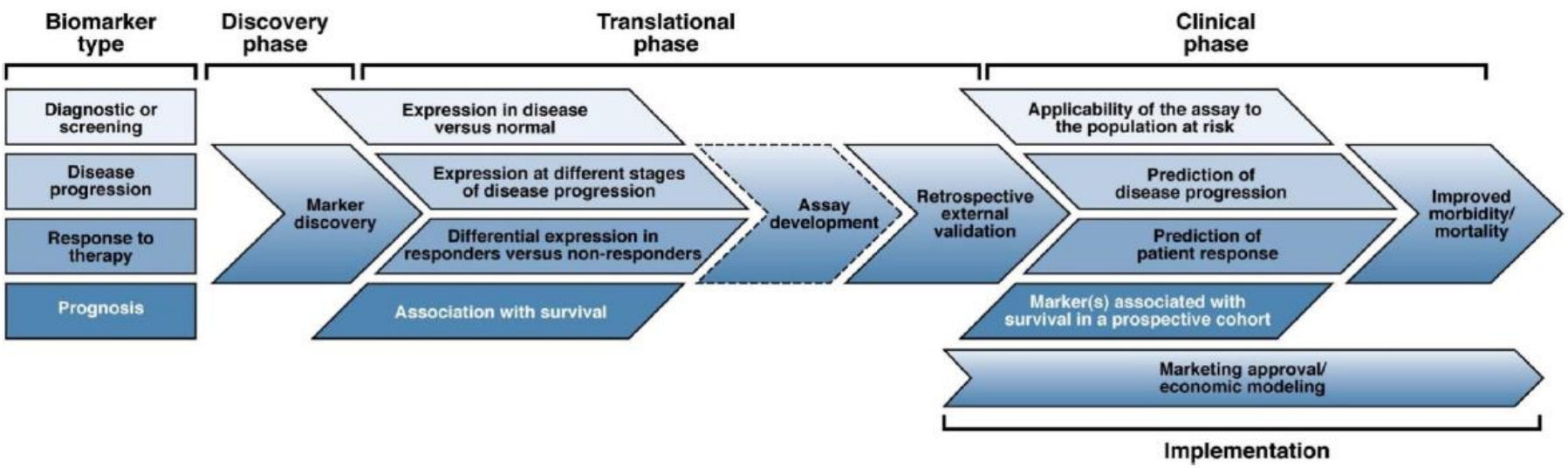
Grazie dell’attenzione

The Biomarker pipeline paradigm



Ruolo della Neuropsicologia nella diagnostica del MCI

- Dall'introduzione del concetto di MCI il ruolo della valutazione NPS consiste nel distinguere i tipi di profilo neuropsicologico del MCI (amnesico/non amnesico – singolo/multiplo dominio

- Identificare le possibili evoluzioni del MCI in relazione al pattern di presentazione

- Descrivere markers neuropsicologici in grado di distinguere i pazienti con MCI con rischio di progressione a demenza rispetto a soggetti che rimarranno stabili o ritorneranno a una condizione di normalità

Modifica della prospettiva in un'ottica di terapia disease modifying specifica dell'AD

Identificazione di markers neuropsicologici capaci di distinguere il disturbo mnesico della AD rispetto a quello delle altre forme di demenza

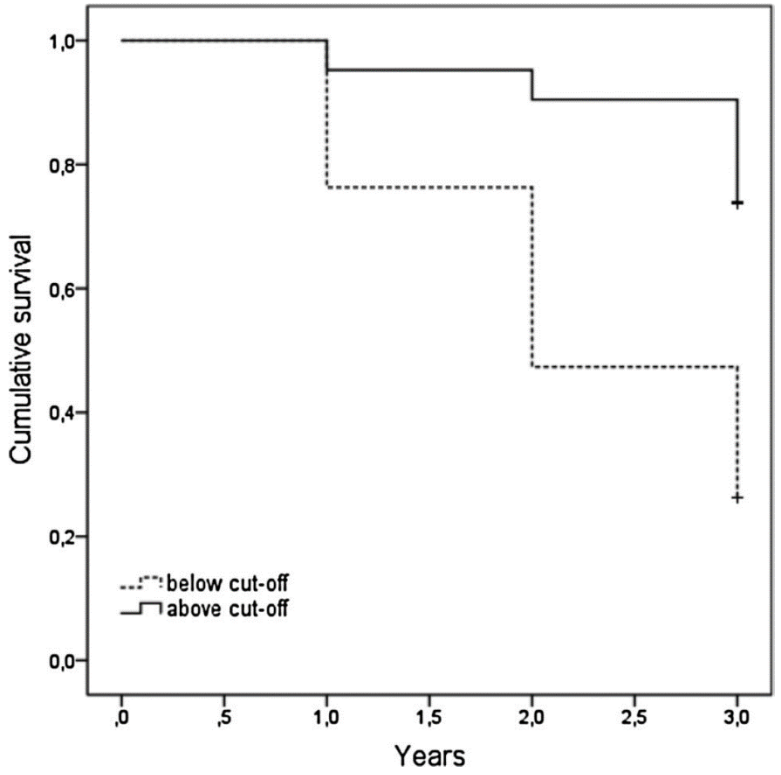
Journal of Neurology (2019) 266:102–111
https://doi.org/10.1007/s00415-018-9108-0

ORIGINAL COMMUNICATION

Predicting progression to Alzheimer's disease in subjects with amnestic mild cognitive impairment using performance on recall and recognition tests

Maria Stefania De Simone[1] · Roberta Perri[1] · Lucia Fadda[1,2] · Carlo Caltagirone[1,2] · Giovanni Augusto Carlesimo[1,2]

Misura del forgetting in compiti di richiamo differito e Facilitazione al riconoscimento può distinguere MCI converters e non converters e identificare i soggetti che convertiranno in AD



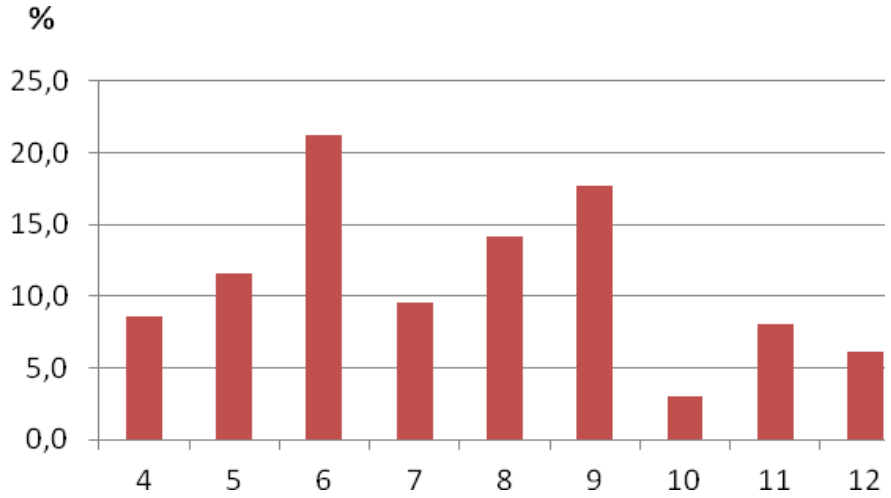
	Immediate	Delayed	Forgetting (%)	*d′*	*C*	ISR (%)
HC	9.8 (2)	7.8 (2.6)	−13	3.7 (1.3)	−0.16 (0.6)	+86
s-MCI	7 (2.2)^{a***}	4.1 (2.4)^{a***}	−19 ^{a***}	2.6 (0.9)^{a**}	−0.41 (0.6)	+81
c-MCI	5.8 (1.4)$^{a*** b**}$	2.3 (1.7)^{a***b***}	−24 ^{a***}	1.8 (1.1)$^{a*** b***}$	−0.26 (0.7)	+72 $^{a*** b***}$

Episodic Memory Quotient- EMQ

- Suddivisione in terzili dei punteggi grezzi ottenuti in quattro sub test di memoria

	RAVLT richiamo immediato		RAVLT richiamo differito		RAVLT accuratezza		ROCF riproduzione differita	
Terzile	Min	Max	Min	Max	Min	Max	Min	Max
1	10	22	0	1	0.5	0.7	0	3.2
2	23	27	2	3	0.71	0.78	3.5	5
3	28	44	4	7	0.8	0.97	5.6	19

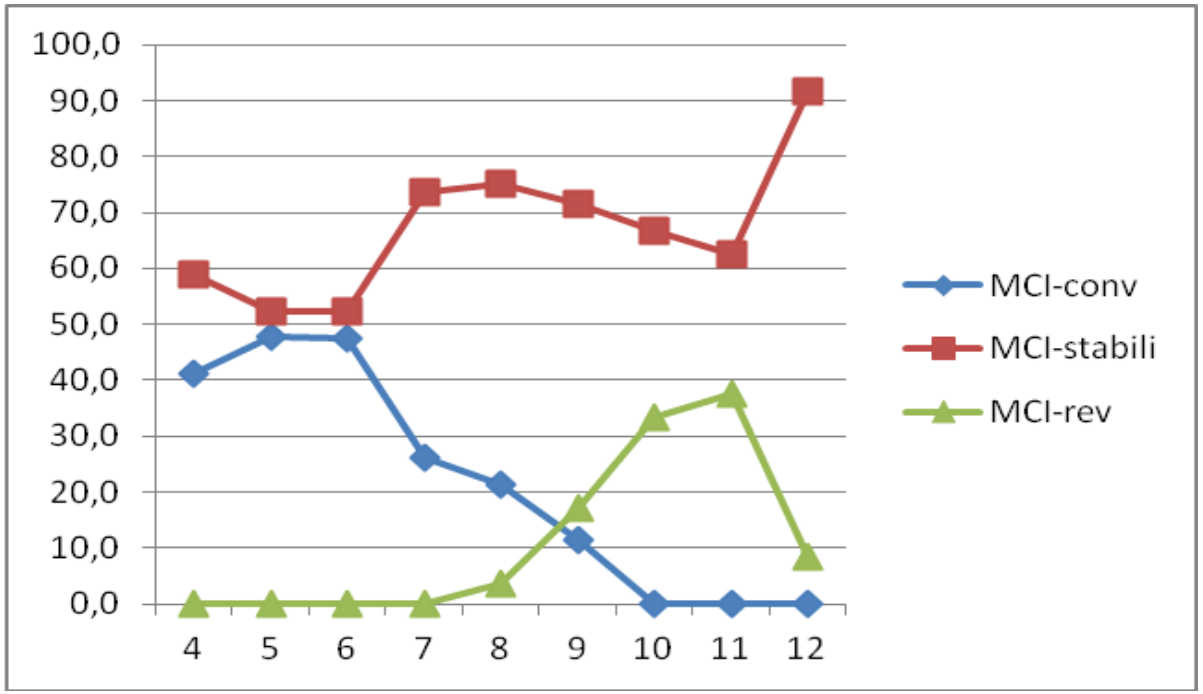
- Distribuzione dei punteggi EMQ nell'intero campione.



Marra C. et al, 2016 JAD

Episodic Memory Quotient- EMQ

Distribuzione percentuale dei pazienti MCI-conv, MCI-stabili e MCI-rev rispetto ai punteggi EMQ.



MCI-stabili: 7.80 ± 2.293; MCI-conv: 6.08 ± 1.412; MCI-rev: 9.76 ± 1.480; $F_{2,195}$=24,97; p<0,001

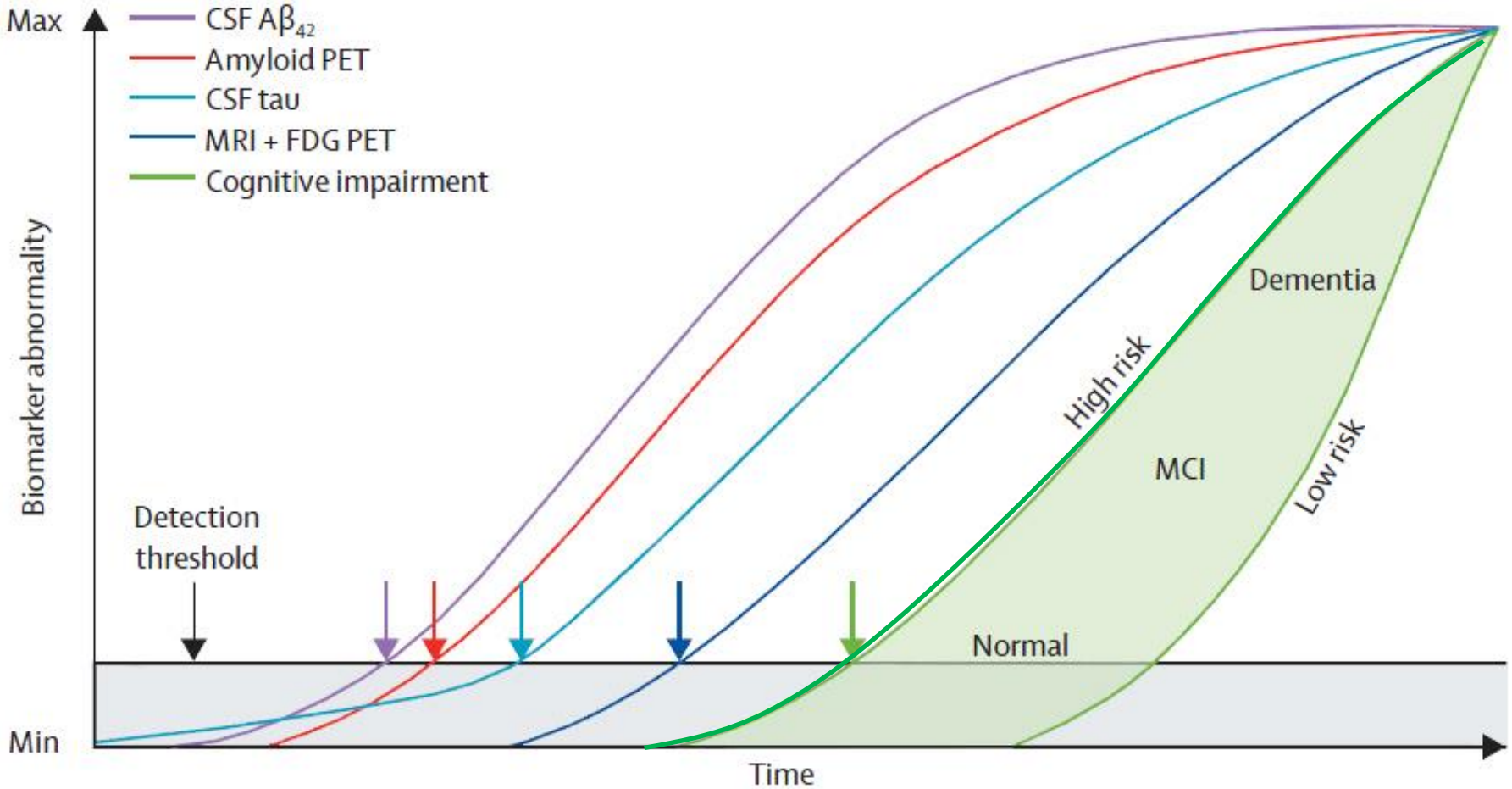
Marra C. et al, 2016 JAD

Episodic Memory Quotient- EMQ

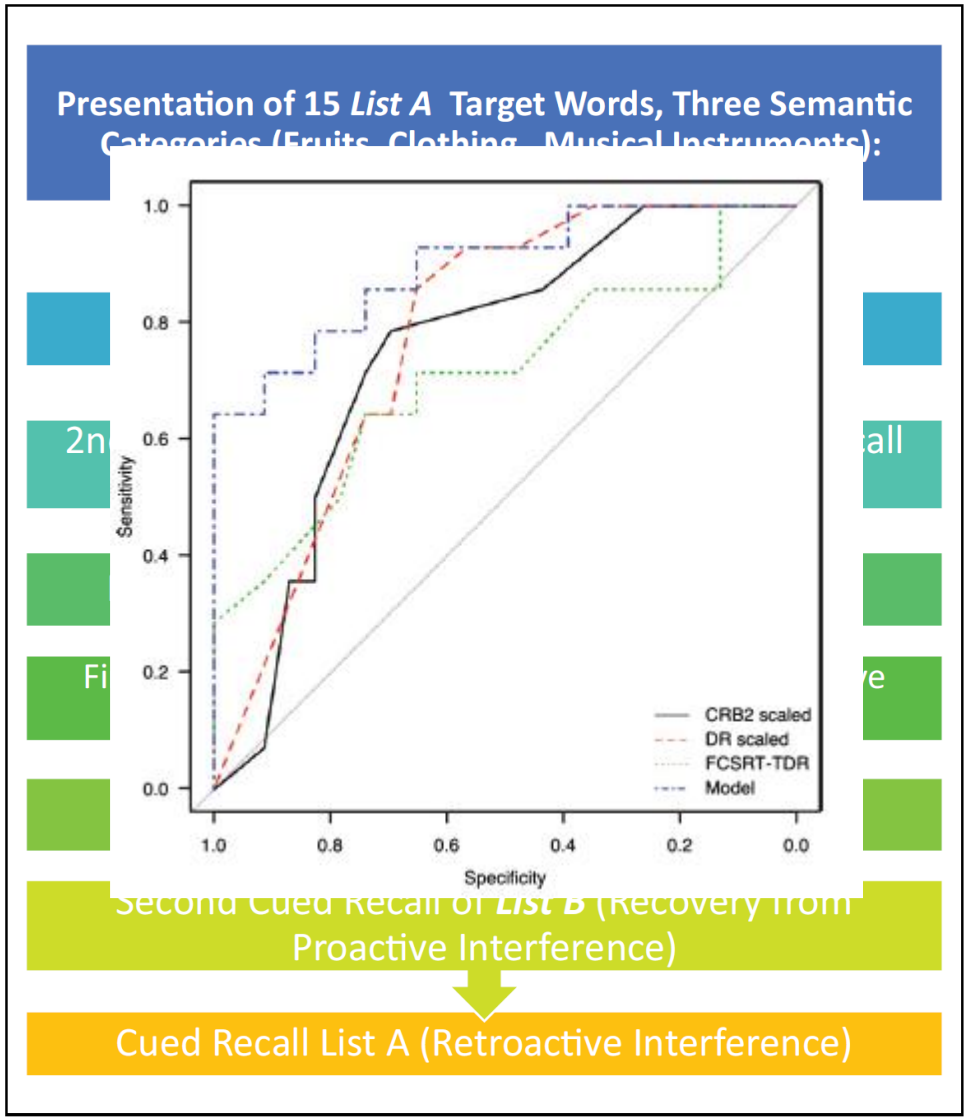
Affidabilità del punteggio EMQ rispetto alle altre prove di memoria

Test	AUC
MMSE	0.7701
RAVLT: richiamo immediato	0.6706
RAVLT: richiamo differito	0.7728
RAVLT: accuratezza nel riconoscimento	0.6950
ROCF: riproduzione differita	0.7643
EMQ	0.8298

Marra C. et al, 2016 JAD


Max
Min
Biomarker abnormality
CSF Aβ42
Amyloid PET
CSF tau
MRI + FDG PET
Cognitive impairment
Detection threshold
Normal
MCI
Dementia
High risk
Low risk
Time

Paradigmi di interferenza proattiva



Identifica MCI rispetto a controlli

Il punteggio correla con il burden globale di amiloide e con il deposito di amiloide nel precuneo, nel cingolo posteriore e anteriore

Misura più efficace della FCSRT nell'identificare MCI che progrediranno a demenza

Journal of Alzheimer's Disease 61 (2018) 103–111
DOI 10.3233/JAD-170604
IOS Press

Comparison between FCSRT and LASSI-L to Detect Early Stage Alzheimer's Disease

Jordi A. Matias-Guiu[a,*], María Nieves Cabrera-Martín[b], Rosie E. Curiel[c], María Valles-Salgado[a], Teresa Rognoni[a], Teresa Moreno-Ramos[a], José Luis Carreras[b], David A. Loewenstein[c] and Jorge Matías-Guiu[a]

(Lowestein-Acevedo scale of semantic interference and Learning LASSI-L)

International Psychogeriatrics: page 1 of 10 © International Psychogeriatric Association 2017
doi:10.1017/S1041610217000102

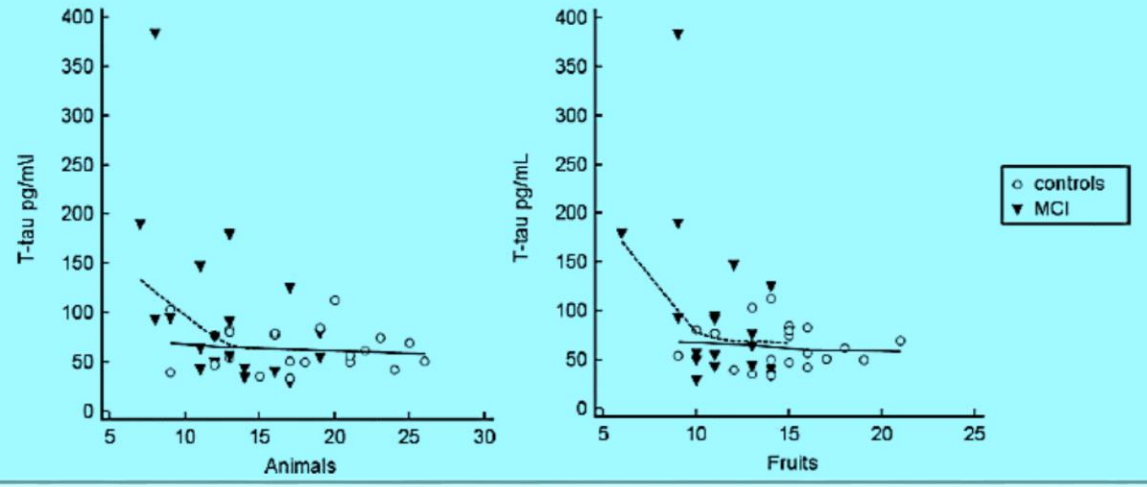
Multiple category verbal fluency in mild cognitive impairment and correlation with CSF biomarkers for Alzheimer's disease

Roberta M. Mirandez, Ivan Aprahamian, Leda L. Talib, Orestes V. Forlenza and Marcia Radanovic

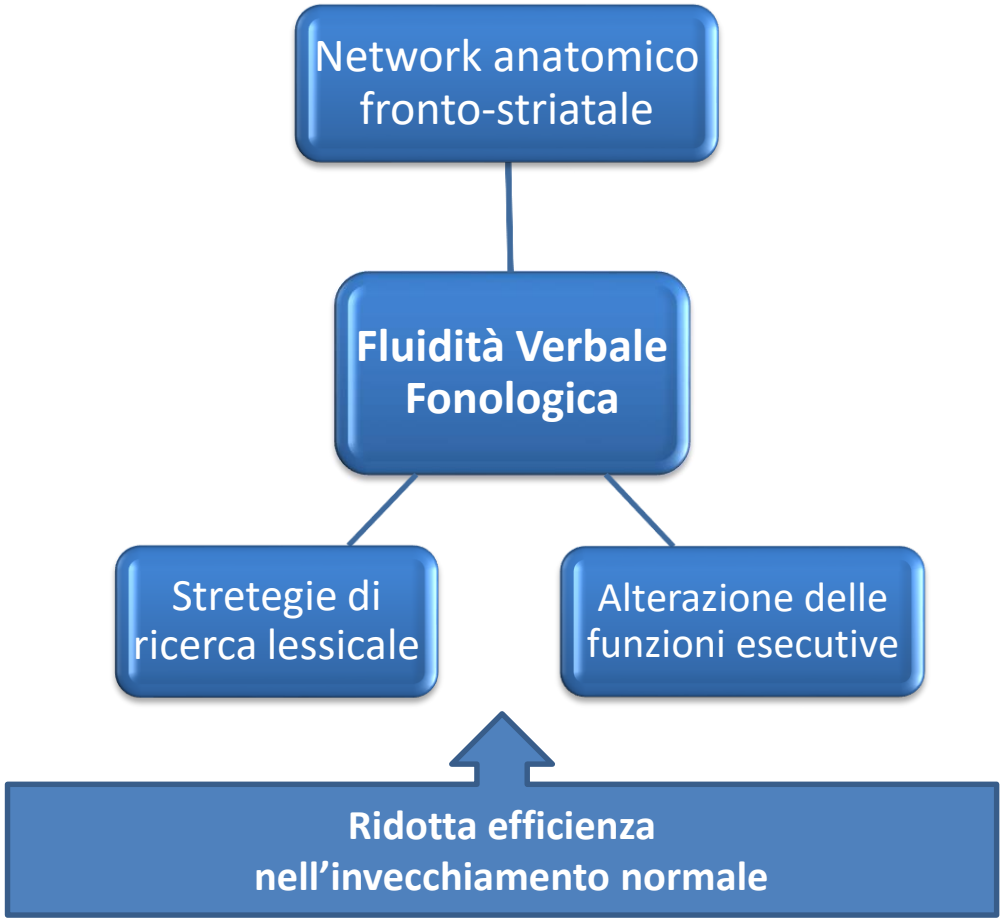
Popolazione di 30 soggetti MCI e 37 soggetti di controllo. Valutate le capacità discriminative dei test e le correlazioni con T-tau

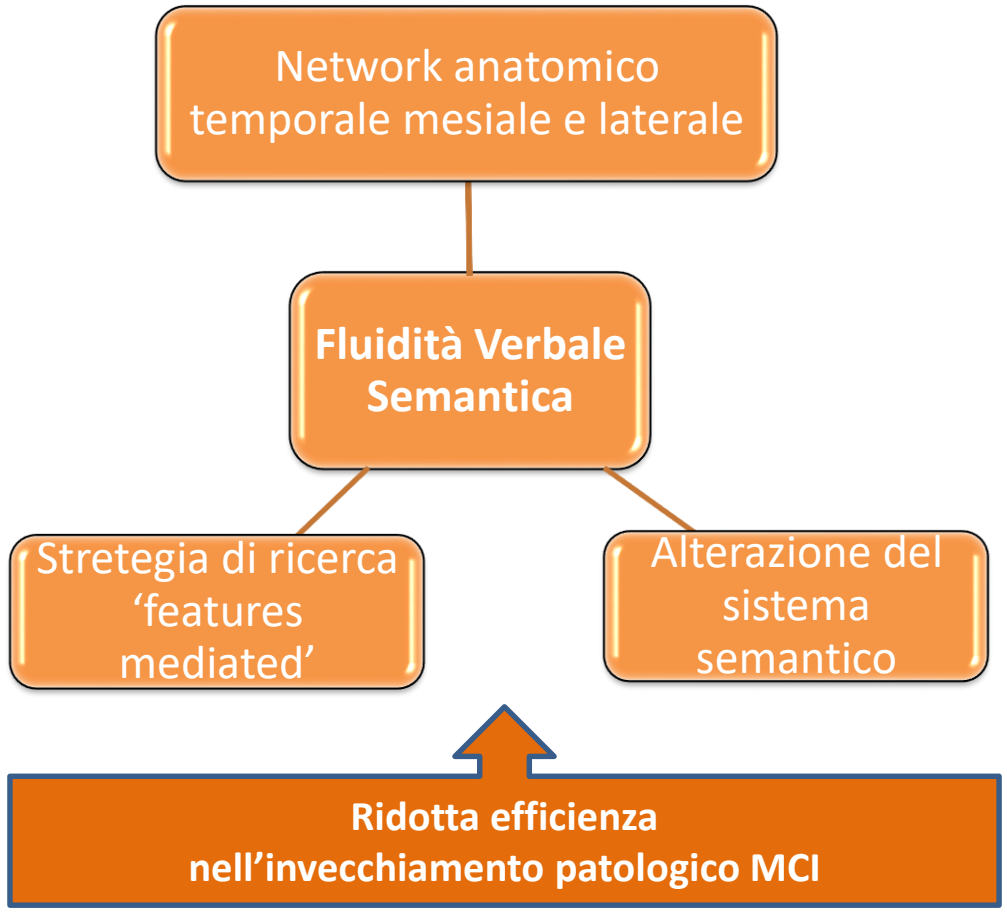
CATEGORY	CUT-OFF SCORE	AUC (CI 95%)	SENSITIVITY	SPECIFICITY	+PV	−PV	*P*-VALUE
Animals	14	0.794 (0.780–0.883)	73.3%	72.9%	39.5	93.5	<0.0001
Fruits	12	0.740 (0.618–0.839)	53.3%	81.0%	41.4	89.4	0.001
Means of transportation	12	0.719 (0.596–0.822)	76.7%	62.2%	30.3	91.3	0.0005
Verbs	11	0.700 (0.576–0.806)	53.3%	81.0%	44.6	91.0	0.0022
FAS-COWA	41	0.744 (0.622–0.843)	86.6%	54.0%	27.7	94.0	0.0001
Animal*FAS-COWA		0.833 (0.722–0.913)	70.0%	75.6%			0.0029

Notes: AUC: area under the curve; CI: confidence interval; PV: predictive value; FAS-COWA-FAS controlled oral word association.



Discrepancy score Phonological/Semantic





Discrepanza tra Fluenza categoriale e per Fluenza fonologica

Nei soggetti di controllo la Fluenza verbale categoriale mantiene un vantaggio rispetto alla Fluenza verbale fonologica indipendentemente da
-età
-scolarità
-sesso

Journal of the International Neuropsychological Society (2016), **22**, 570–576.

doi:10.1017/S1355617716000291

Preservation of the Semantic Verbal Fluency Advantage in a Large Population-Based Sample: Normative Data from the TILDA Study

Roisin M. Vaughan,[1] Robert F. Coen,[2] Rose Anne Kenny,[3] AND Brian A. Lawlor[2]
[1]St. Ita's Hospital, Portrane, Co. Dublin, Ireland
[2]Mercer's Institute of Research on Ageing, St. James's Hospital, Dublin 8, Ireland
[3]The Irish Longitudinal Study on Ageing (TILDA), Trinity College, Dublin, Ireland

Discrepancy score	Frequency (%)
<−16	0
−13–15	0.1
−10–12	0.3
−7–9	0.6
−4–6	1.9
−1–3	4.3
0	2.6
1–3	11.7
4–6	16.0
7–9	17.9
10–12	16.4
13–15	11.5
16–18	8.3
19–21	4.0
22–25	2.2
26–29	1.2
>30	0.7

7.2%

90.2%

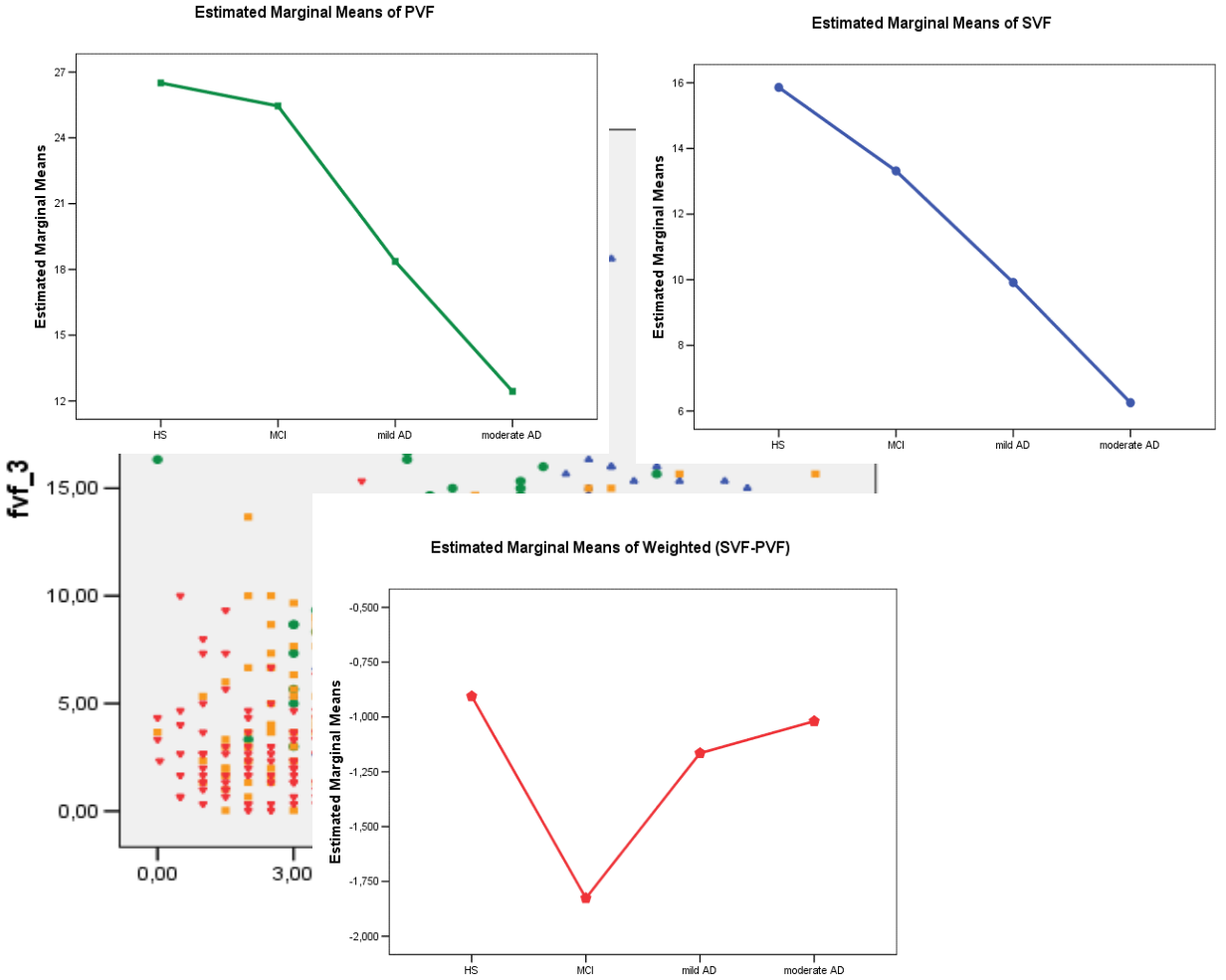
5780 community-dwelling older adults were included in this prospective, longitudinal study. Discrepancy scores were calculated by subtracting phonemic fluency score from semantic fluency score for each participant

Il delta tra Fluenza categoriale e per Fluenza fonologica

la discrepanza tra FVF e FVC permette di disembricare nella prova di fluenza categoria la componente esecutiva dal deficit della memoria semantica per se

Confronto tra 251 MCI amnesici confrontati con 262 soggetti di controllo e 178 pazienti affetti da AD lieve e 143 affetti da AD moderato

Il Δ tra Fluidità verbale fonologica e semantica mostra che il disturbo semantico precede quello esecutivo nel MCI



Marra et al. Submitted 2019

Criteri di identificazione di altri markers cognitivi di precoce disturbo cognitivo nella Malattia di Alzheimer

Basi teoriche

- markers neuropsicologici derivanti dalle conoscenze sulla progressione del danno funzionale potrebbero essere più precoci di quelli che derivano dal classico impegno anatomopatologico precoce ippocampale

Coinvolgimento precoce delle aree associative nella AD → interessamento del precuneo e delle aree associative nella AD precedente al danno morfologico (studi PET/SPET)

Perdita dei meccanismi di connettività e di plasticità sinaptica → alterazioni evidenziabili nei paradigmi di tipo EEG in cui si osserva una netta riduzione dei sistemi 'small world' in fase preclinica di malattia

Progressione del danno cognitivo nelle aree temporo ippocampali → impegno neuropatologico temporalmente diverso nelle aree entorinali, peririnali, ippocampali e paraippocampali.

Il pattern di progressione della malattia di Alzheimer vede il coinvolgimento precoce di aree cerebrali che sono substrato funzionale e anatomico di altre abilità cognitive ,oltre quelle di memoria episodica a lungo termine, non ancora operativamente definite

Neurobiology of Aging 38 (2016) 188–196

Contents lists available at ScienceDirect

Neurobiology of Aging

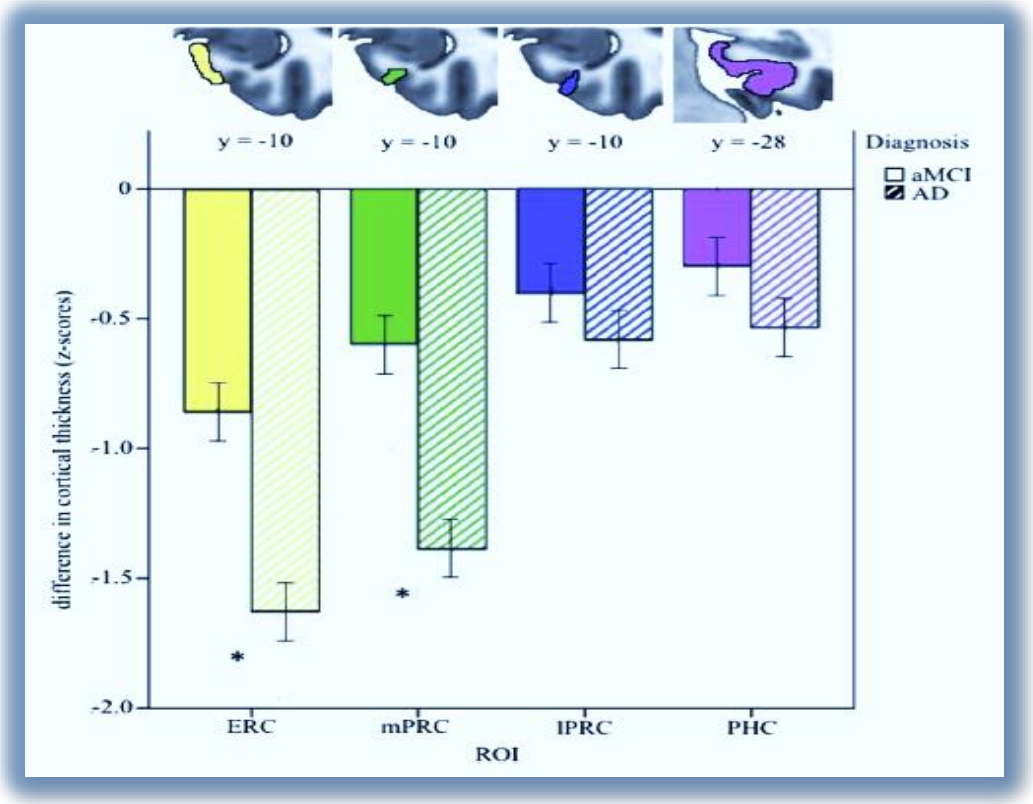
journal homepage: www.elsevier.com/locate/neuaging

Cortical thinning of parahippocampal subregions in very early Alzheimer's disease

Sabine Krumm [a,b,*], Sasa L. Kivisaari [c], Alphonse Probst [a,d], Andreas U. Monsch [a,b], Julia Reinhardt [e], Stephan Ulmer [f,g], Christoph Stippich [b,e], Reto W. Kressig [a,h], Kirsten I. Taylor [a,b,i,1]

Pazienti con MCI prodromico con MMSE >26
Pazienti con AD lieve con MMSE >22

La riduzione di volume della corteccia entorinale e della corteccia mediale peririnale è più severa e più precoce di quella della corteccia laterale peririnale e della corteccia paraippocampale



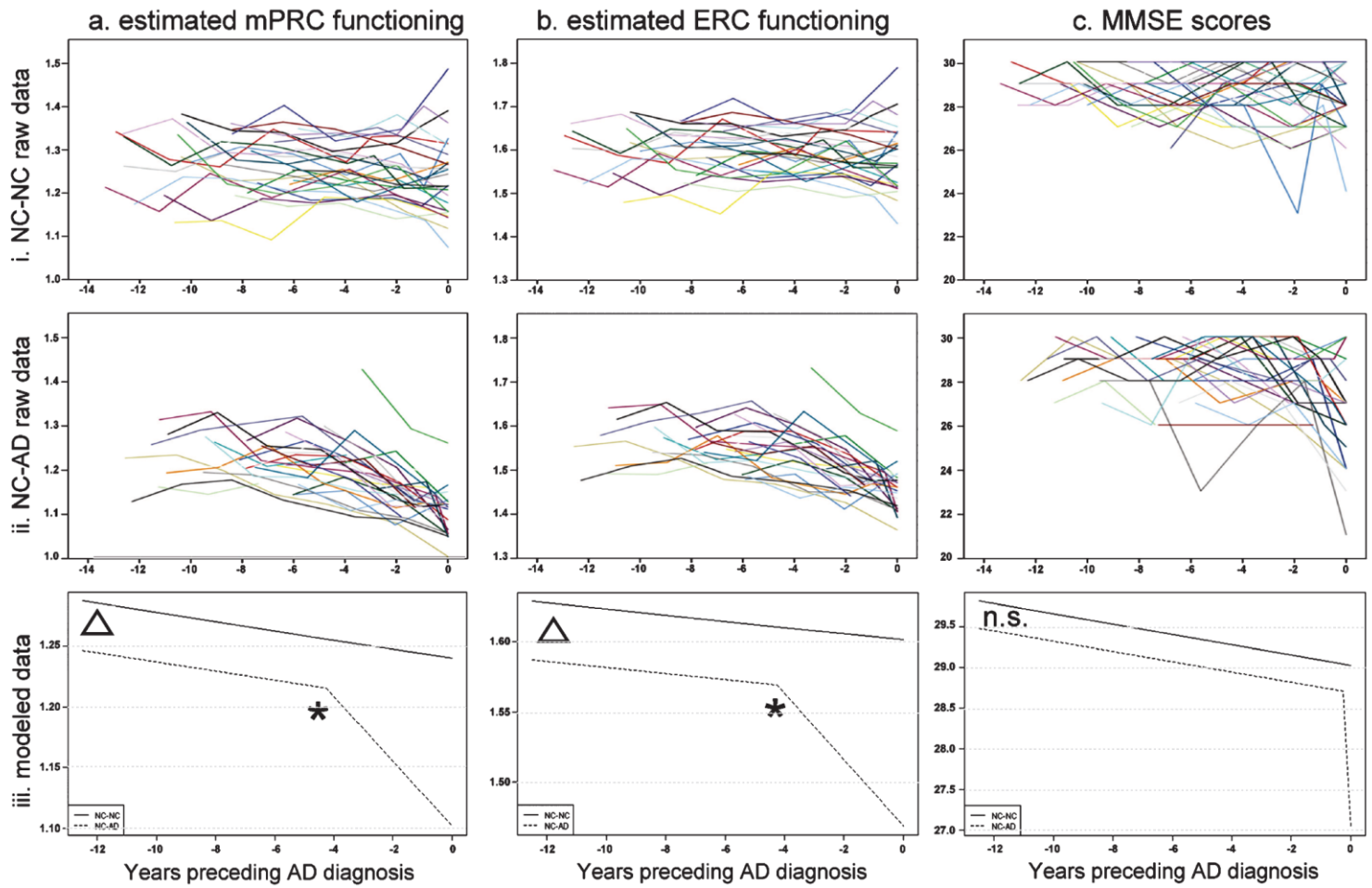
La compromissione della memoria semantica dovrebbe precedere quella della memoria episodica

QUALE MISURA?

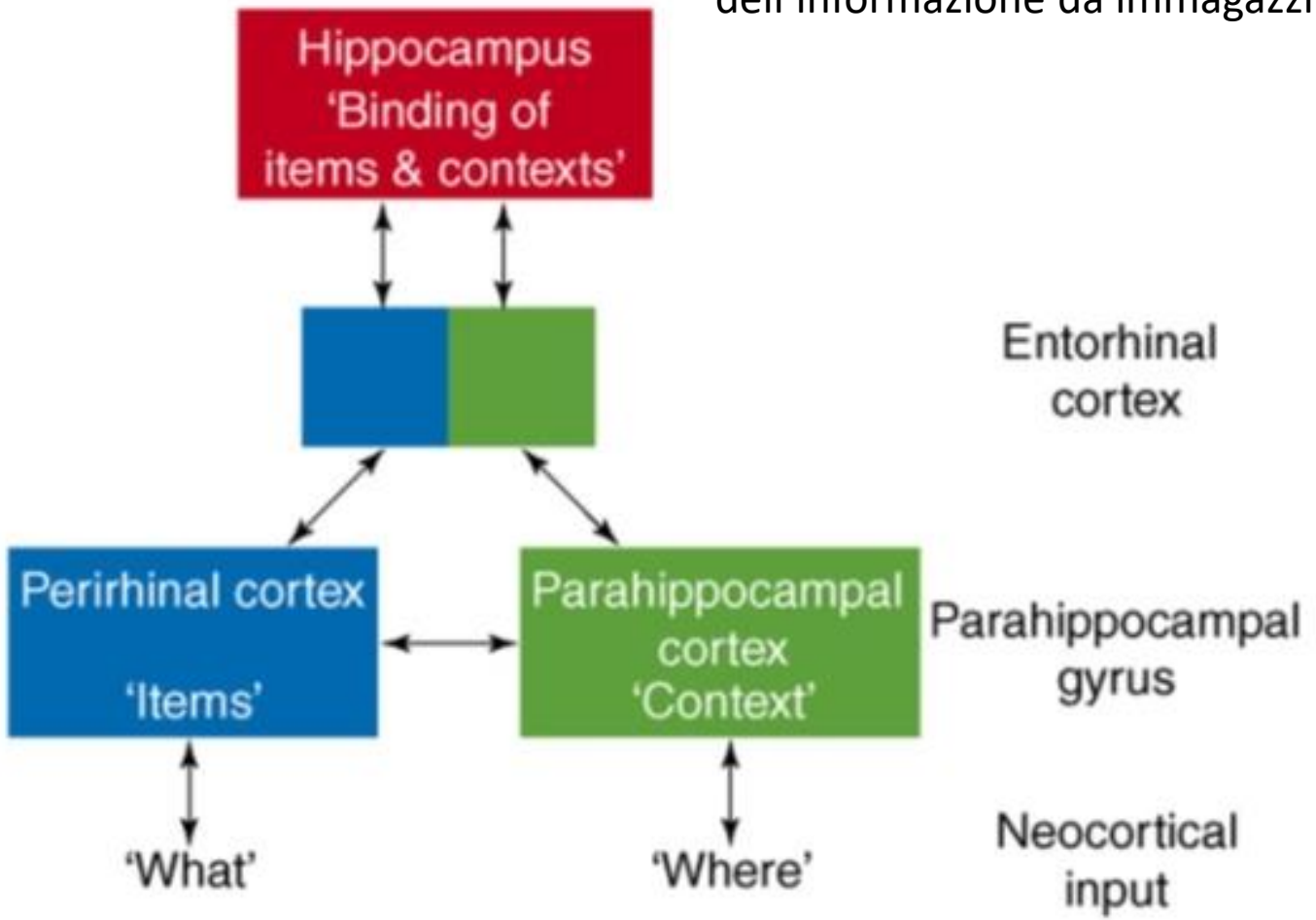
Journal of Alzheimer's Disease 52 (2016) 573–580
DOI 10.3233/JAD-150158
IOS Press

Neuropsychological Markers of Medial Perirhinal and Entorhinal Cortex Functioning are Impaired Twelve Years Preceding Diagnosis of Alzheimer's Dementia

Daniela I. Hirni[a,b], Sasa L. Kivisaari[c], Sabine Krumm[a,b], Andreas U. Monsch[a,b], Manfred Berres[d], Fatma Oeksuez[a], Julia Reinhardt[e], Stephan Ulmer[f,g], Reto W. Kressig[a,b], Christoph Stippich[b,e] and Kirsten I. Taylor[a,b,h,*,1]



Ipotesi su un ruolo delle strutture ippocampali non solo nella funzione di immagazzinamento di informazione ma punto di convergenza e di binding tra le diverse caratteristiche dell'informazione da immagazzinare



Test di working Memory Binding

Figure 2(a)

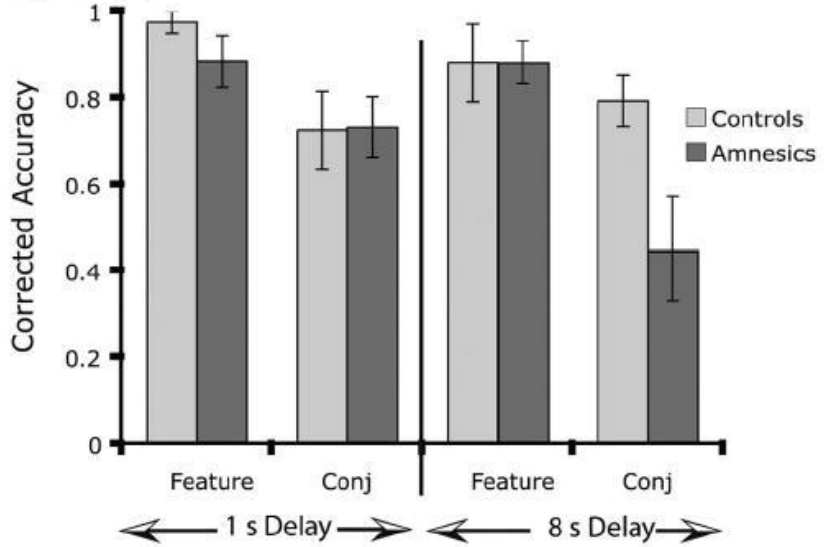
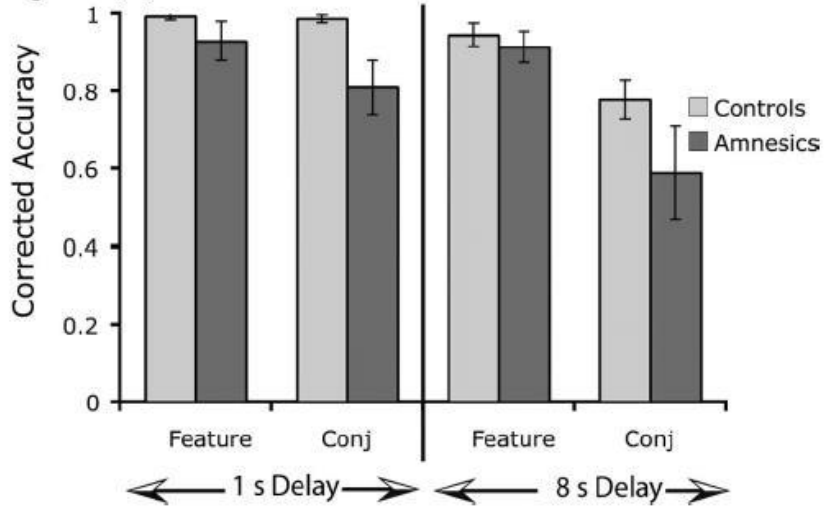
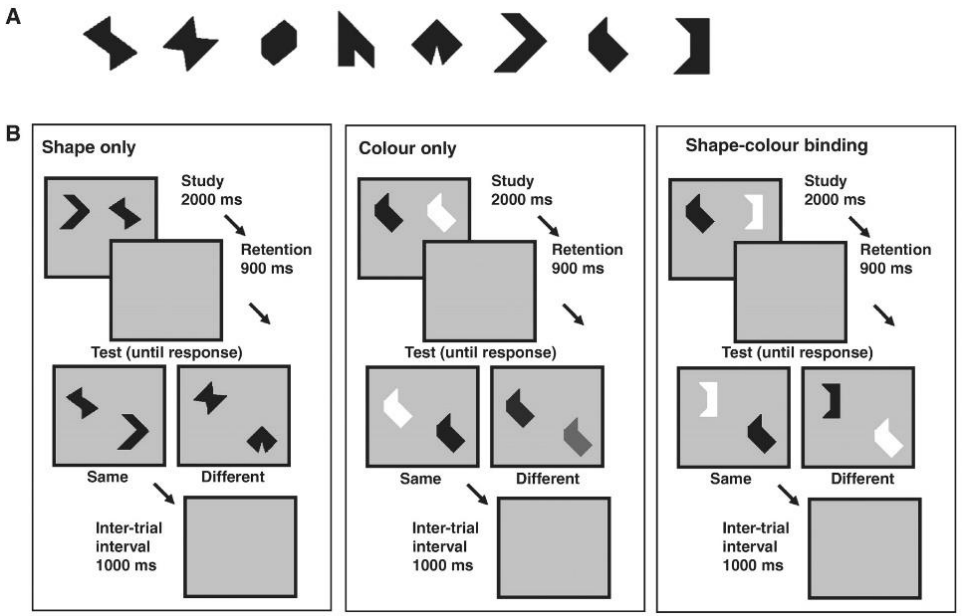


Figure 2(b)





4596 • The Journal of Neuroscience, April 26, 2006 • 26(17):4596 – 4601

Brief Communications

Working Memory for Conjunctions Relies on the Medial Temporal Lobe

Ingrid R. Olson,[1] Katie Page,[3] Katherine Sledge Moore,[1] Anjan Chatterjee,[1,2] and Mieke Verfaellie[3]
[1]The Center for Cognitive Neuroscience, University of Pennsylvania and [2]Department of Neurology, University of Pennsylvania Medical School, Philadelphia, PA 19104, and [3]Boston University School of Medicine and VA Boston Healthcare System, Boston, MA 02130

Quali Marker di fluenza categoriale ?

Review

For reprint orders, please contact: reprints@futuremedicine.com

Biomarkers in Medicine

Diagnostic and prognostic role of semantic processing in preclinical Alzheimer's disease

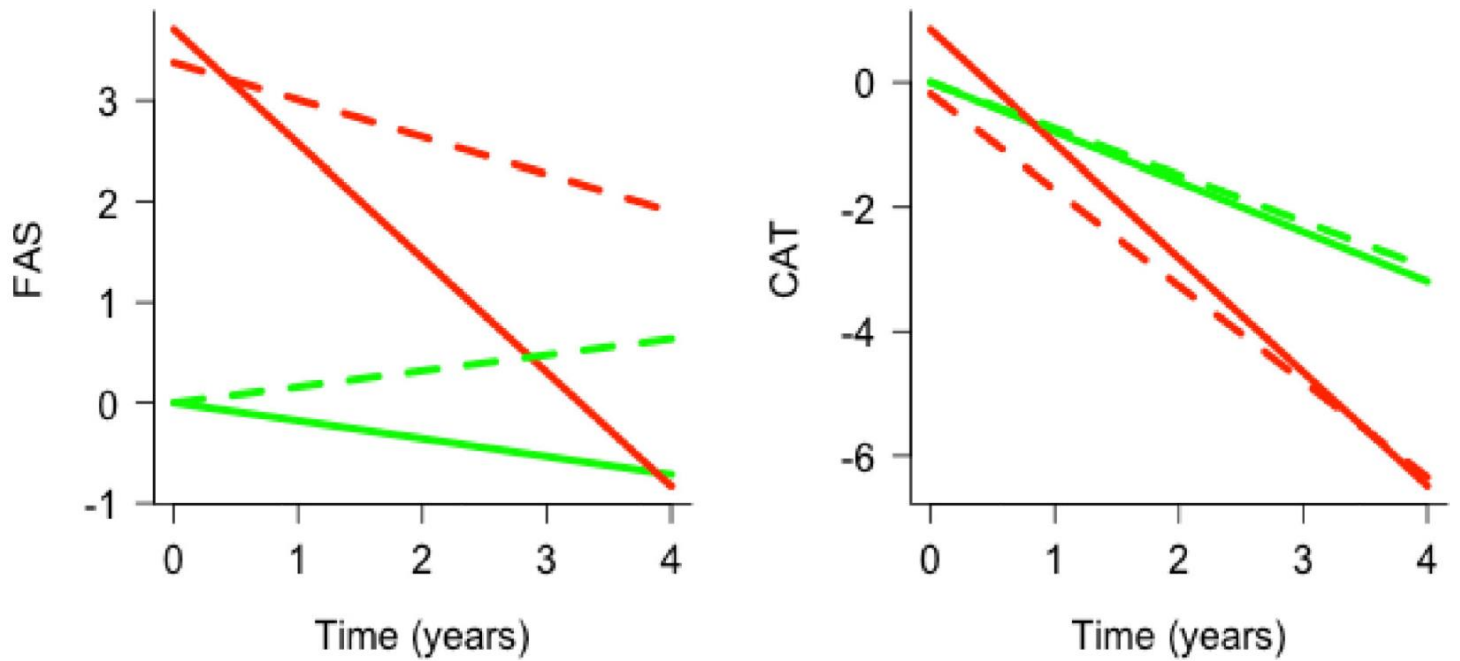
Annalena Venneri*[,‡,1], Caroline Jahn-Carta[‡,1], Matteo De Marco[1], Davide Quaranta[2] & Camillo Marra[3]

- Effetti di classe grammaticale
- Effetti di classe categoriale
- Impoverimento del Sistema semantico
  - Tipicalità
  - Sequenze e prossimità semantica delle parole prodotte
  - Riduzioni dei campi semantici
- Discrepanze tra Test di fluidità fonologica e semantica

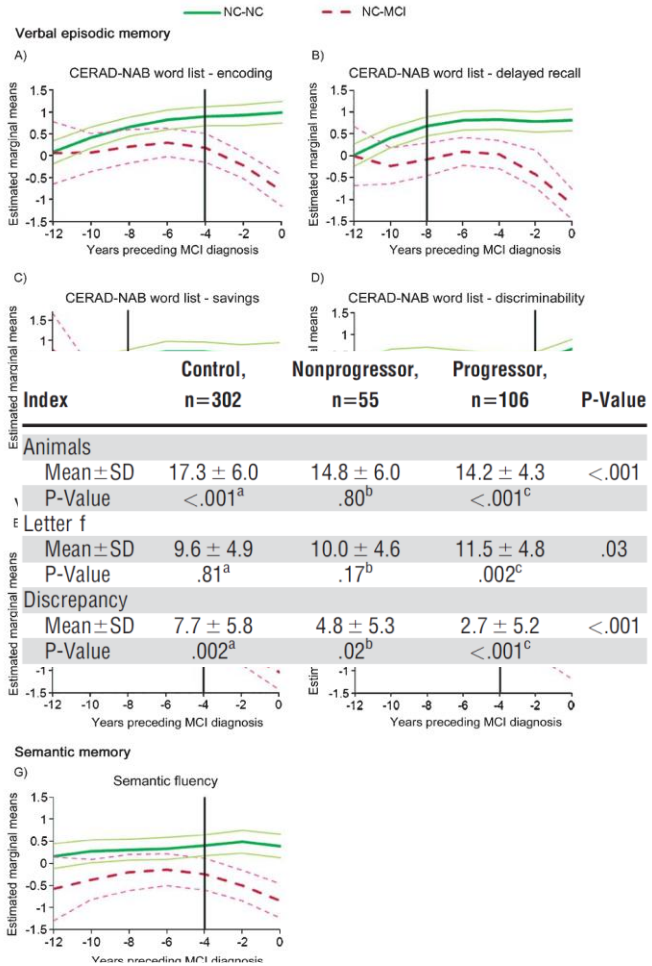
Neuropsychology. 2016 July ; 30(5): 624–630. doi:10.1037/neu0000246.

Biomarker Validation of a Decline in Semantic Processing in Preclinical Alzheimer's Disease

Kathryn V. Papp[1], **Elizabeth C. Mormino**[2], **Rebecca E. Amariglio**[1,2], **Catherine Munro**[2], **Alex Dagley**[2], **Aaron P. Schultz**[2], **Keith A. Johnson**[1,2,4], **Reisa A. Sperling**[1,2,3], and **Dorene M. Rentz**[1,2]



Discrepanza tra Fluenza categoriale e per Fluenza fonologica



Index	Control, n=302	Nonprogressor, n=55	Progressor, n=106	P-Value
Animals				
Mean±SD	17.3 ± 6.0	14.8 ± 6.0	14.2 ± 4.3	<.001
P-Value	<.001[a]	.80[b]	<.001[c]	
Letter f				
Mean±SD	9.6 ± 4.9	10.0 ± 4.6	11.5 ± 4.8	.03
P-Value	.81[a]	.17[b]	.002[c]	
Discrepancy				
Mean±SD	7.7 ± 5.8	4.8 ± 5.3	2.7 ± 5.2	<.001
P-Value	.002[a]	.02[b]	<.001[c]	

Journal of Alzheimer's Disease 48 (2015) 1095–1107
DOI 10.3233/JAD-150137
IOS Press

The 12 Years Preceding Mild Cognitive Impairment Due to Alzheimer's Disease: The Temporal Emergence of Cognitive Decline

Panagiota Mistridis[a,b], Sabine Krumm[a,b], Andreas U. Monsch[a,b,*], Manfred Berres[c] and Kirsten I. Taylor[a,b,d,1]
[a]*Memory Clinic, University Center for Medicine of Aging Basel, Felix Platter Hospital, Basel, Switzerland*
[b]*University of Basel, Basel, Switzerland*
[c]*Department of Mathematics and Technology, University of Applied Sciences Koblenz, Koblenz, Germany*
[d]*Centre for Speech, Language and the Brain, Department of Experimental Psychology, University of Cambridge, Cambridge, UK*

BRIEF REPORT

Semantic and Phonemic Verbal Fluency Discrepancy in Mild Cognitive Impairment: Potential Predictor of Progression to Alzheimer's Disease

Roisin M. Vaughan, MB, Robert F. Coen, PhD,* RoseAnne Kenny, MD,† and Brian A. Lawlor, MD**

J Am Geriatr Soc 2018.

ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 64-75

Alzheimer's & Dementia

Perspective

Measuring cognition and function in the preclinical stage of Alzheimer's disease

Sandra Weintraub[a,b], Maria C. Carrillo[c], Sarah Tomaszewski Farias[d], Terry E. Goldberg[e], James A. Hendrix[c,*], Judith Jaeger[f,g], David S. Knopman[h], Jessica B. Langbaum[i], Denise C. Park[j], Michael T. Ropacki[k], Sietske A. M. Sikkes[l,m], Kathleen A. Welsh-Bohmer[n], Lisa J. Bain[o], Robert Brashear[p], Kumar Budur[q], Ana Graf[r], Ferenc Martenyi[s], Marta Segardahl Storck[t], Christopher Randolph[u,v]

Dimostrazione che la presenza di Beta amiloide determina modificazioni del comportamento in diversi test anche 10 anni prima dell'insorgenza del MCI con impegno della:

- Attenzione
- Processing speed
- Memoria episodica e semantica

Difficile definizione del pattern patologico a livello di singolo paziente

Uso di 'composite score' nei prevention trial allo scopo di misurare longitudinalmente la progressione

Difficile distinzione operativa dell'invecchiamento nel soggetto con AD preclinico rispetto al soggetto normale

Diversi meccanismi di riserva cognitiva secondo età , intelligenza premorboso momento della progressione clinica

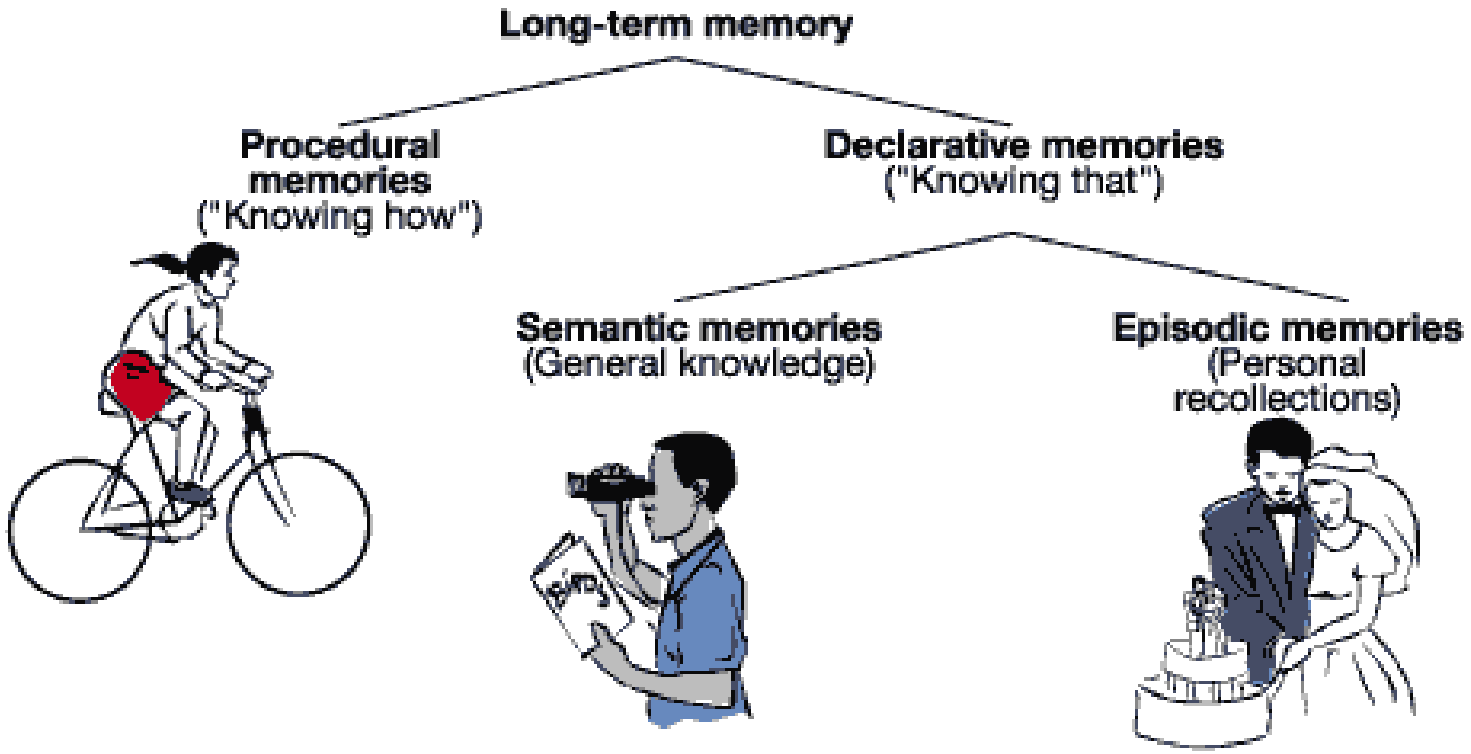
Table 2
EPAD-ENE: Measures and cognitive domains

Cognitive domains	Measures
Primary	
Verbal episodic memory	List learning and story memory (RBANS)
Visual episodic memory	Figure recall (RBANS)
Visuospatial/constructional	Figure copy and line orientation (RBANS)
Language	Picture naming (RBANS)
Attention/executive functioning	Semantic fluency (RBANS)
	Digit span (RBANS)
	Coding (RBANS)
Secondary	
Working memory	Dot counting (NIH examiner/ toolbox)
Choice reaction time and set-shifting	Flanker (NIH examiner/toolbox)
Paired associate learning	Name/face pairs (NIH examiner/ toolbox)
Exploratory	
Allocentric space	Four mountains task
Egocentric space	Supermarket trolley virtual reality

Abbreviations: EPAD-ENE, EPAD Neuropsychological Evaluation; RBANS, Repeatable Battery for Neuropsychological Status; NIH, National Institute of Health.

Table 1
Comparison of cognitive composites used in prevention trials

Domain	Test	TOMM	API ADAD	APCC	PACC	PACC-A4
Global functioning and mental status	MMSE				■	■
Attention	WAIS-III Digit Span, forward	■				
	Trails A			2		
Perceptual speed	Symbol digit modalities					
Executive function	Trails B	■				
	WAIS-III Digit Span, backward					
	WAIS-R Digit Symbol Substitution Test				■	■ 6
	Ravens Progressive Matrices (subset)			■		
Orientation	MMSE orientation to place			■		
	MMSE orientation to time		■			
Language	Multilingual Naming Test	■				
	Semantic fluency (animals)					
	Lexical/phonemic fluency (FAS)					
	Boston Naming Test		1			
Visuospatial	Clock drawing	■				
	Copy of BVMT-R figures					
	Judgment of line orientation			3		
	CERAD–constructional praxis		■			
	Ravens Progressive Matrices (subset)		■	■		
Episodic memory	CVLT	■				
	Brief Visuospatial Memory Test					
	CERAD Word List–delayed recall		■	4		
	Logical Memory–delayed recall			5	■	
	FCSRT				■	■
	Paragraph Recall					



what

where/when

Confrontation Naming
Visual matching
Verbal Matching
Category Fluency

RAVLT IR and DR
FCSRT
Rey's Figure
Prose memory
Paired learning

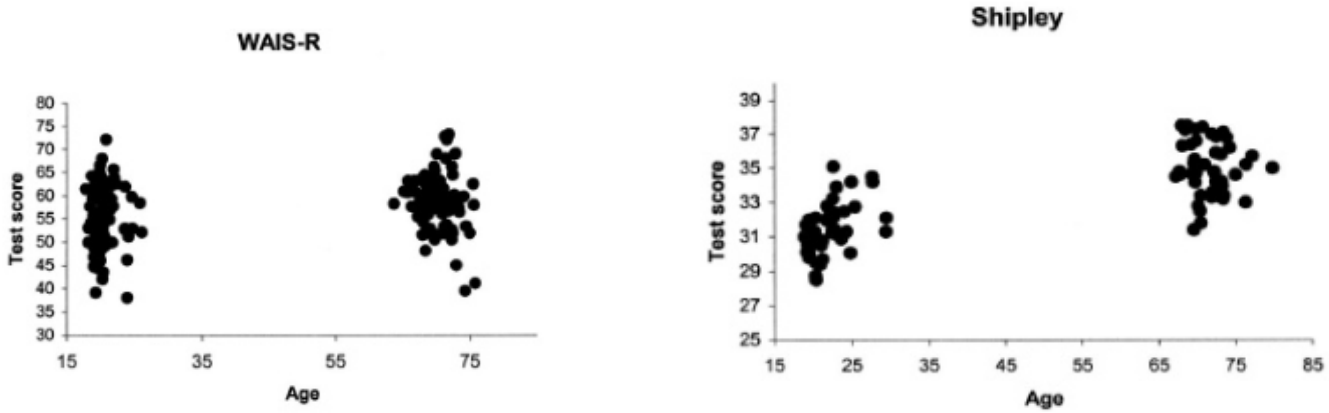
Il vocabolario si arricchisce con l'età

Psychology and Aging
2003, Vol. 18, No. 2, 332–339

0882-7974/03/$12.00 DOI: 10.1037/0882-7974.18.2.332

Aging and Vocabulary Scores: A Meta-Analysis

Paul Verhaeghen
Syracuse University



L'invecchiamento normale non determina modificazioni sostanziali dell'elaborazione degli attributi semantici delle parole.

Il vocabolario non decresce con l'età ma sembra più ricco.

La riduzione della capacità di generare liste di parole su criterio categoriale è spesso dovuta al concomitante disturbo disesecutivo

Fluenza Categoriale

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY
2008, 30 (5), 501–556

Psychology Press
Taylor & Francis Group

Language performance in Alzheimer's disease and mild cognitive impairment: A comparative review

Vanessa Taler and Natalie A. Phillips

Department of Psychology/Centre for Research in Human Development, Concordia University, Montréal, Québec, Canada, and Bloomfield Centre for Research on Aging, Montréal, Québec, Canada

TABLE 1
Summary statistics for the studies presented in Appendices A and B

	Test		
	Category fluency	*Letter fluency*	*Naming*
Studies reporting difference between NE and MCI/QD/preclinical dementia/miminal AD	29	8	22
Studies reporting no difference between NE and MCI/QD/preclinical dementia/minimal AD	3	8	13
Studies reporting difference between MCI/QD preclinical dementia/minimal AD and mild AD	17	4	12
Studies reporting no difference between MCI/QD and AD	0	5	5
Studies reporting predictive value for AD	21	9	12
Studies reporting no predictive value for AD	6	7	12

Note. AD = Alzheimer's disease. NE = normal elderly. MCI = mild cognitive impairment. QD = questionable dementia.

Deficit semantici
accesso ai lessici - effetto categoriale

Effetti categoriali descritti per l'AD indipendenti dal genere e dal dato esperienziale

Neuropsychology
2007, Vol. 21, No. 2, 207–211

0894-4105/07/$12.00 DOI: 10.1037/0894-4105.21.2.207

Gender-Related Dissociations of Categorical Fluency in Normal Subjects and in Subjects With Alzheimer's Disease

Camillo Marra, Monica Ferraccioli, and Guido Gainotti
Neuropsychology Service, Catholic University of Rome

Mean Number of Birds *and* Furniture *Items Produced by Male and Female Normal Subjects and Patients With AD on the Semantic Fluency Task*

Group	Gender	Category: *Birds*	Category: *Furniture*	*p*	Average
Normal controls	Women	6.53 (3.07)	8.47 (2.60)	.0004	7.50 (2.46)
Normal controls	Men	8.59 (2.60)	6.80 (2.19)	.0001	7.70 (1.99)
Average		7.61 (2.11)	7.69 (1.90)	*ns*	
Patients with AD	Women	3.17 (2.45)	4.86 (2.81)	.003	4.02 (2.63)
Patients with AD	Men	4.58 (2.62)	4.59 (2.19)	*ns*	4.59 (2.34)
Average		3.64 (2.2)	4.77 (2.24)	.001	

Nei soggetti di controllo è presente un diverso effetto 'Gender' su due classi semantiche

Nell'AD si osserva la perdita prevalente della categoria 'Birds' rispetto alla categoria 'Furniture'

Nei maschi questo effetto è mascherato dall'iniziale maggiore familiarità

La perdita categoriale per i 'Birds' non è correlata alla gravità dell'AD

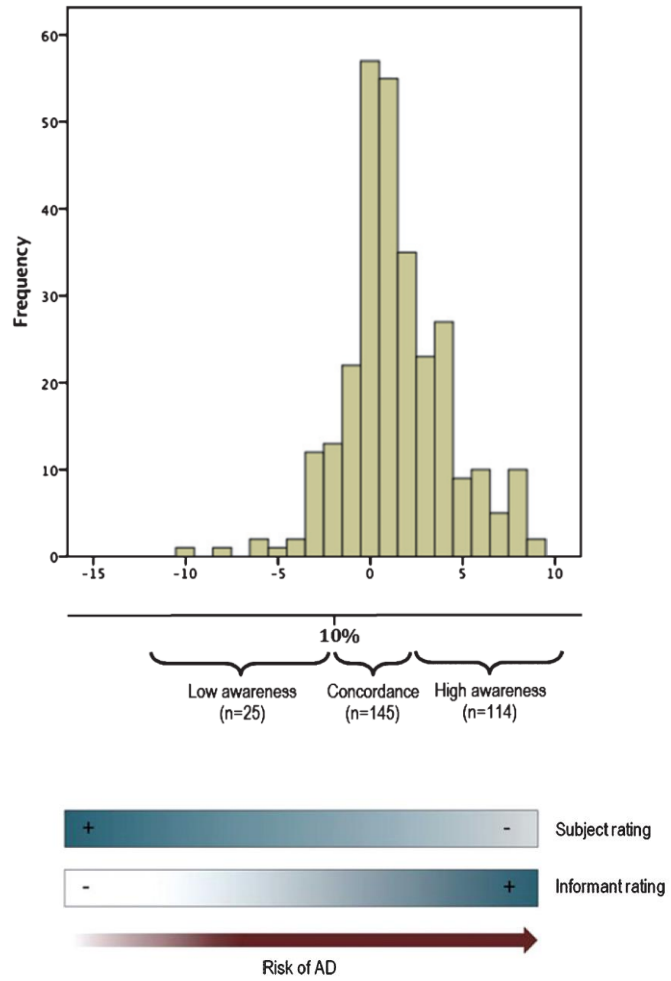
Table 2
Test, amyloid PET, and MRI results of subjects with high and low cognitive awareness

	High awareness ($n = 86$)		Low awareness ($n = 19$)		Group comparison				
	Range	*M* (*SEM*)	Range	*M* (*SEM*)	*df*	Error	*F*	*p*	*d*
Subjective Cognitive Decline									
IQCD	1–14	6.34 (0.36)	0–14	4.47 (0.85)	1	103	4.709	0.032*	0.552
AC									
Physical condition	0–8	2.43 (0.24)	0–4	1.11 (0.33)	1	99	5.838	0.018*	0.630
Attention	0–9	3.61 (0.22)	0–9	2.39 (0.59)	1	99	5.000	0.028*	0.578
Memory	0–9	3.95 (0.22)	0–8	2.17 (0.57)	1	99	10.868	0.001*	0.857
Language	0–8	2.96 (0.20)	0–6	2.00 (0.42)	1	99	4.197	0.043*	0.534
Mood	0–8	2.65 (0.25)	0–7	1.67 (0.52)	1	99	2.722	0.102	0.428
Health state	0–10	3.08 (0.25)	0–6	2.33 (0.40)	1	99	1.741	0.190	0.346
Life stress	0–9	3.85 (0.28)	0–8	2.89 (0.66)	1	99	2.022	0.158	0.370
Senses	0–10	3.75 (0.26)	0–7	2.22 (0.52)	1	99	6.387	0.013*	0.658
Total	4–61	26.28 (1.29)	0–48	16.78 (2.89)	1	99	9.110	0.003*	0.791
ASC	0–65	25.44 (2.05)	0–52	13.21 (4.70)	1	103	6.268	0.014*	0.635
McNair	4–37	15.30 (0.68)	2–32	10.61 (1.60)	1	102	8.078	0.005*	0.737
AD-NOS	6–60	27.20 (1.17)	9–37	26.06 (2.32)	1	93	0.165	0.686	0.111
Neuropsychiatric symptoms									
NPI									
Anxiety	0–4	0.17 (0.08)	0–12	0.67 (0.67)	1	100	2.063	0.154	0.372
Dysphoria/depression	0–3	0.07 (0.04)	0–1	0.06 (0.06)	1	100	0.026	0.873	0.026
Irritability	0–1	0.04 (0.02)	0-0	0.00 (0.00)	1	100	0.581	0.448	0.229
Sleep disorders	0–6	0.36 (0.13)	0–4	0.33 (0.24)	1	100	0.006	0.936	0.026
STAI-B	11–61	41.71 (2.10)	30–60	44.67 (8.67)	1	29	0.181	0.673	0.259
GDS	0–11	2.72 (0.53)	0–4	2.67 (1.33)	1	30	0.001	0.973	0.018
Autonomy and quality of life									
Bristol ADL	0–5	0.21 (0.07)	0–2	0.47 (0.19)	1	99	1.901	0.171	0.371
EQ-5D-3L	5–10	6.56 (0.12)	5–7	6.16 (0.18)	1	103	2.383	0.126	0.391
Cognitive functioning									
MMSE	27–30	28.64 (0.10)	28–30	28.53 (0.18)	1	103	0.237	0.627	0.121
FCSRT	41–48	46.00 (0.22)	42–48	46.16 (0.42)	1	103	0.095	0.758	0.079
AIBL Episodic Memory									
Immediate	–4.71–1.24	0.00 (0.08)	–0.81–0.85	–0.04 (0.10)	1	103	0.047	0.829	0.055
Delayed	–1.30–1.21	–0.01 (0.07)	–0.72–0.86	0.05 (0.10)	1	103	0.171	0.680	0.100
ZAVEN-like	–1.40–1.31	0.03 (0.06)	–1.12–1.48	–0.12 (0.14)	1	103	0.976	0.325	0.255
ADCS-PACC-like	–2.89–0.98	–0.06 (0.07)	–0.61–0.59	–0.03 (0.07)	1	103	0.028	0.868	0.047
Amyloid PET imaging									
^{18}F-AV45-SUVr	0.54–1.52	0.77 (0.02)	0.61–1.58	0.90 (0.06)	1	103	6.782	0.011*,¥	0.680

Journal of Alzheimer's Disease 59 (2017) 753–762
DOI 10.3233/JAD-170399
IOS Press

Low Cognitive Awareness, but Not Complaint, is a Good Marker of Preclinical Alzheimer's Disease

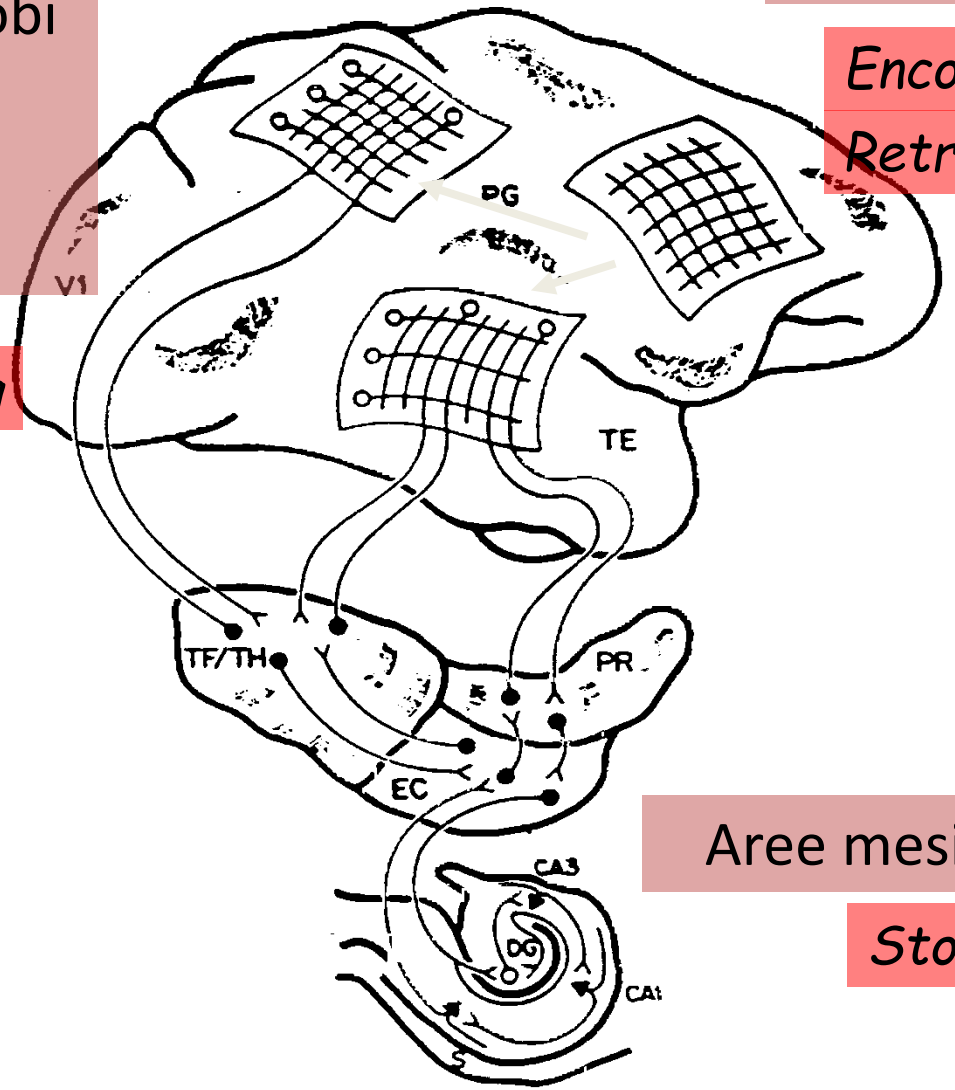
Federica Cacciamani[a], Caroline Tandetnik[a,b], Geoffroy Gagliardi[a], Hugo Bertin[c,d], Marie-Odile Habert[c,d], Harald Hampel[a,e,f,g], Laurie Boukadida[a], Marie Révillon[a], Stéphane Epelbaum[a,e,g,1,*] and Bruno Dubois[a,e,g,1], on behalf of the INSIGHT-PreAD study group[2]



Cerebral cortical areas involved in long-term declarative memory functioning

Aree sensoriali associative dei lobi parietale, temporale e occipitale

Encoding



Lobi frontali

Encoding elaborativo

Retrieval strategico

Aree mesio-temporali

Storage

Courtesy by GA. Carlesimo

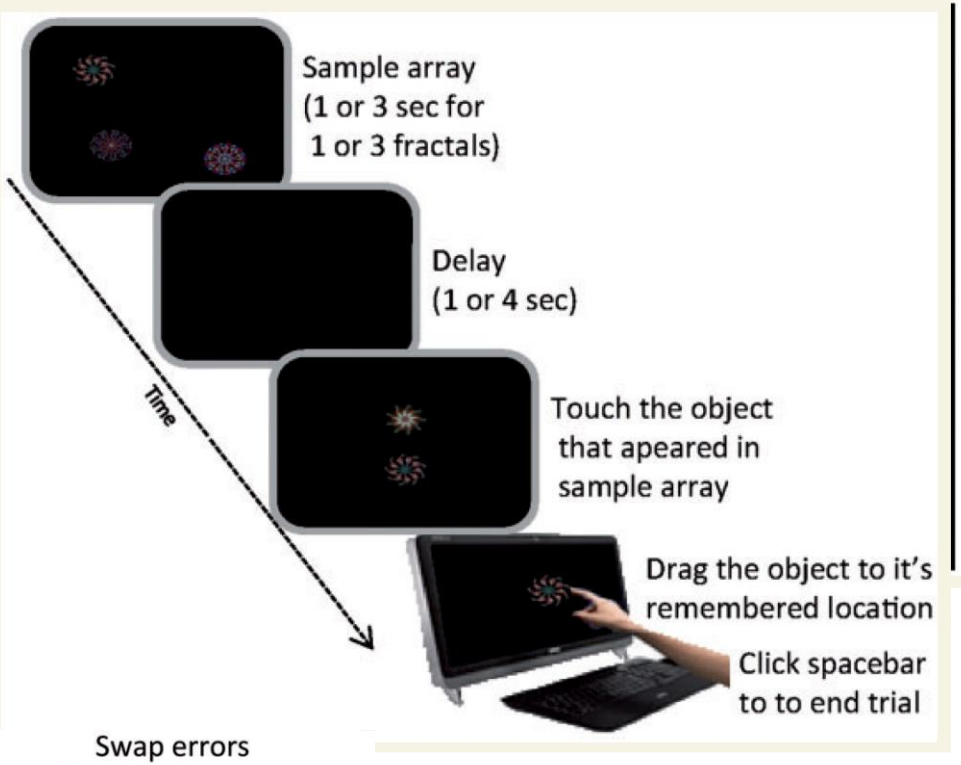
doi:10.1093/brain/awt129 Brain 2013: 136; 2474–2485 | 2474

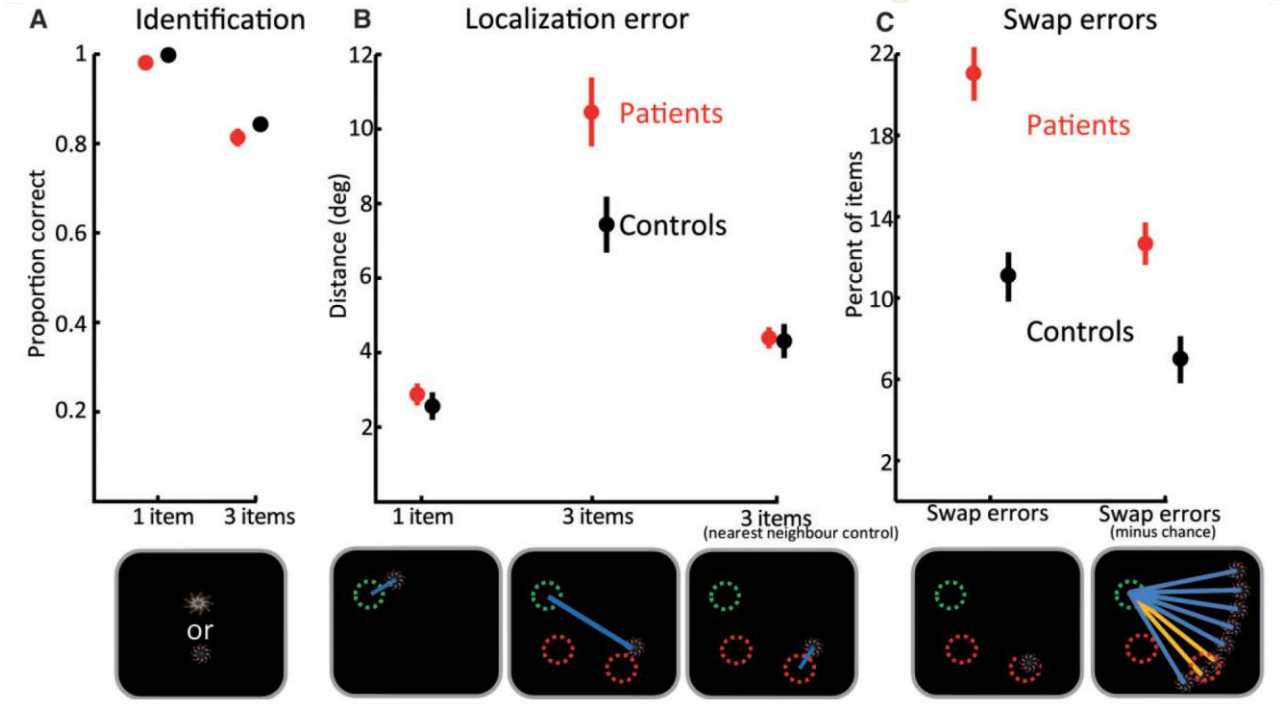
BRAIN
A JOURNAL OF NEUROLOGY

Binding deficits in memory following medial temporal lobe damage in patients with voltage-gated potassium channel complex antibody-associated limbic encephalitis

Yoni Pertzov,[1] Thomas D. Miller,[2] Nikos Gorgoraptis,[1] Diana Caine,[1] Jonathan M. Schott,[1] Chris Butler[2] and Masud Husain[2]

Da un campione originario di 16 pazienti sono stati esaminati 7 pazienti affetti da encefalite LG1 che erano risultati normali in compiti di memoria visiva per singoli items





CORTEX 78 (2016) 150–164

Available online at www.sciencedirect.com

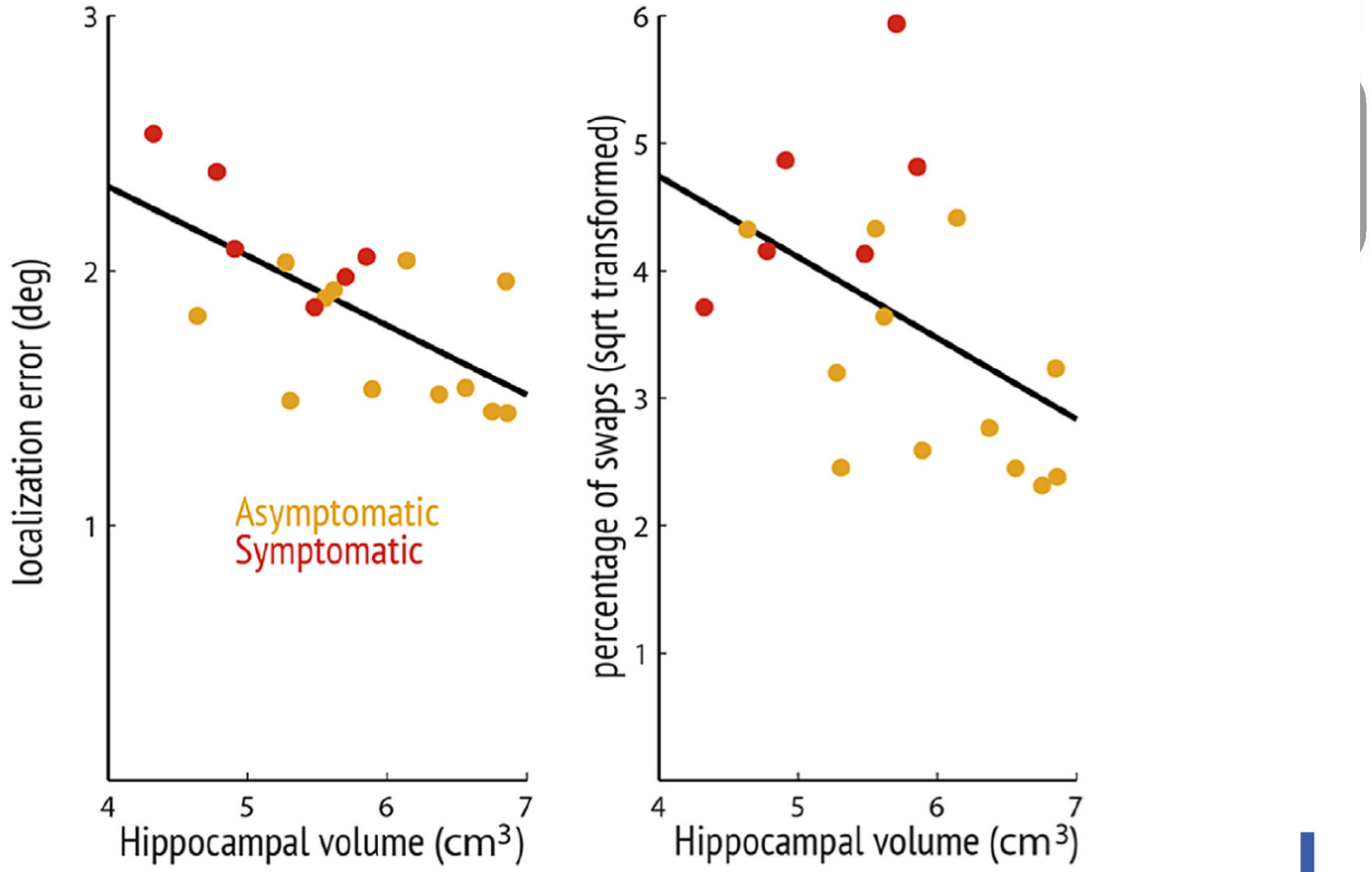
ScienceDirect

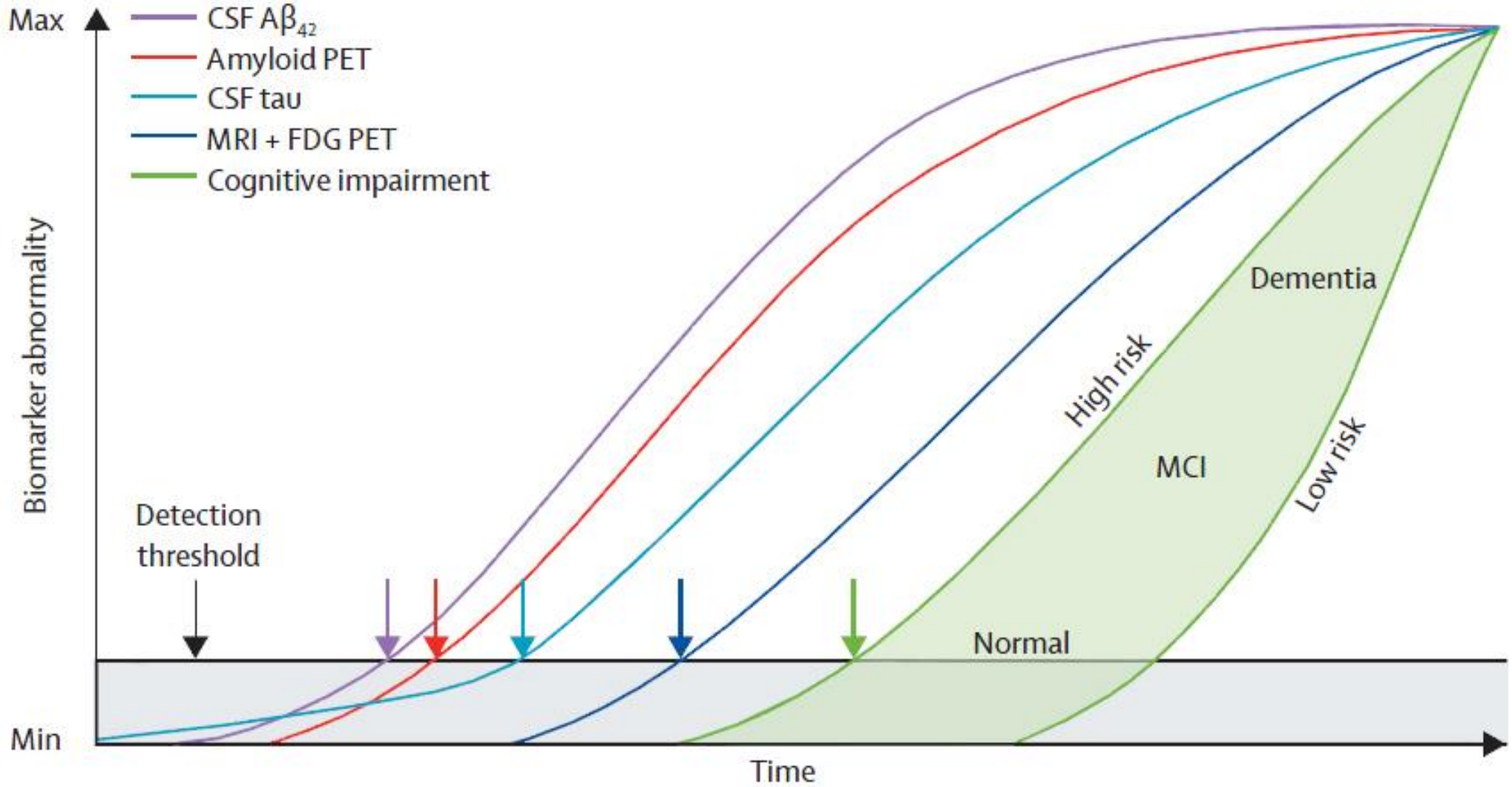
Journal homepage: www.elsevier.com/locate/cortex

Visual short-term memory binding deficit in familial Alzheimer's disease

Yuying Liang [a,1], Yoni Pertzov [b,1], Jennifer M. Nicholas [a,c], Susie M.D. Henley [a], Sebastian Crutch [a], Felix Woodward [a], Kelvin Leung [a], Nick C. Fox [a] and Masud Husain [d,e,*]

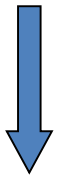
A B C




Max
Min
Biomarker abnormality
CSF Aβ42
Amyloid PET
CSF tau
MRI + FDG PET
Cognitive impairment
Detection threshold
Normal
High risk
MCI
Dementia
Low risk
Time

Un solo test o molti test nella diagnosi precoce di Demenza di Alzheimer?

Quale grado di test e quale sensibilità?



Diagnosi di MCI dipendente dal
Tipo di test + Livello del cut-off

Validità dei punteggi compositi mnesici