Valutazione clinica

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IL CERVELLO CHE CAMBIA 9

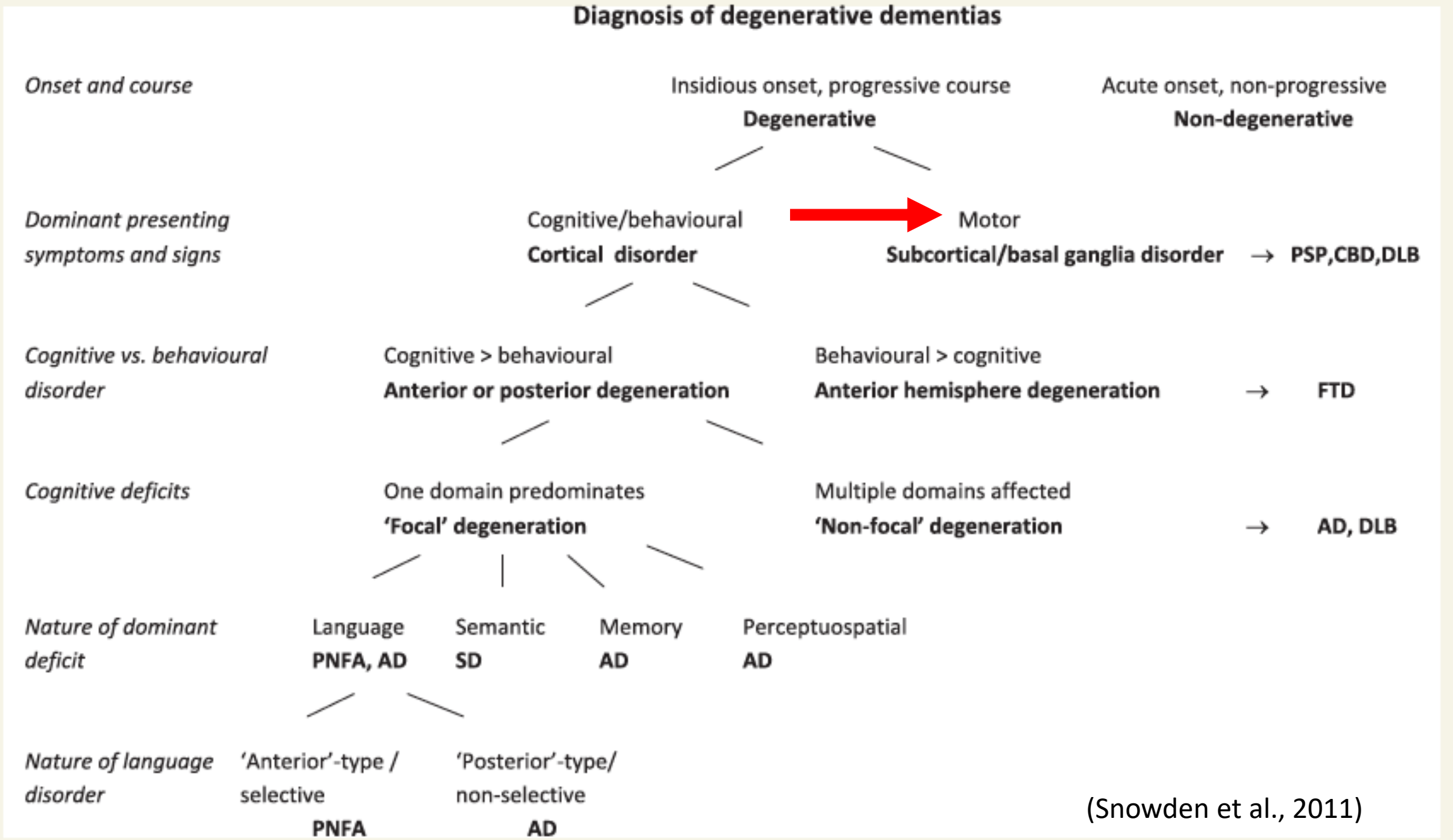
DISORDINI COGNITIVI E DEMENZE:
RECENTI AVANZAMENTI E FRONTIERE
DI RICERCA

Il clinico e i disturbi cognitivi

Esame obiettivo (oltre la cognitività)?

Come restituisco i risultati?

Che fare?



(Snowden et al., 2011)

Figure 1 Algorithm for diagnosis of degenerative dementias. AD = Alzheimer's disease; CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; PNFA = progressive supranuclear palsy; PSP = progressive supranuclear palsy; SD = semantic dementia.

Neurobiology of Aging
Volume 76, April 2019, Pages 9-17

Regular article

Neuroimaging findings and clinical trajectories of Lewy body disease in patients with MCI

Federico Massa [a], Dario Arnaldi [a, b], Francesca De Cesari [a], Nicola Girtler [a, c], Andrea Brugnolo [a, c], Matteo Grazzini [a], Matteo Bauckneht [d, e], Riccardo Meli [a], Silvia Morbelli [d, e], Matteo Pardini [a, b], Gianmario Sambuceti [d, e], Fabrizio De Carli [f], Pietro Tiraboschi [g], Flavio Nobili [a, b]

***Table 3** Relation of specific cognitive function measures to global parkinsonism among individuals with MCI**

	Effect on global parkinsonism			
Cognitive domain	Estimate	SE	*p* Value	R^2 change†
Episodic memory	−0.24	0.11	0.034	0.01
Semantic memory	−0.35	0.12	0.003	0.02
Working memory	−0.10	0.11	0.358	0.00
Perceptual speed	−0.42	0.08	0.001	0.08
Visuospatial ability	−0.16	0.09	0.080	0.00

Parkinsonian signs in subjects with mild cognitive impairment

P. A. Boyle, R. S. Wilson, N. T. Aggarwal, et al.

Neurology 2005;65;1901-1906
DOI 10.1212/01.wnl.0000188878.81385.73

Research Report

Early detection of subtle motor dysfunction in cognitively normal subjects with amyloid-β positivity

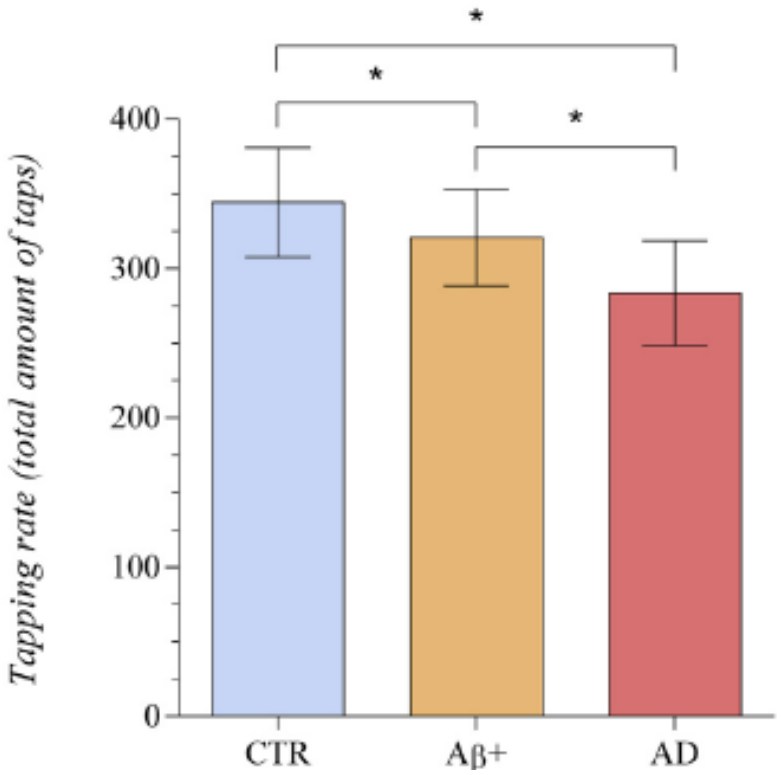
Maria A. Mollica [a,1], Adrià Tort-Merino [a,1], Jordi Navarra [b,c], Irune Fernández-Prieto [b,c,d], Natalia Valech [a], Jaume Olives [a], María León [a], Alberto Lleó [f,g], Pablo Martínez-Lage [h], Raquel Sánchez-Valle [a,e], José L. Molinuevo [a,e] and Lorena Rami [a,e,*]

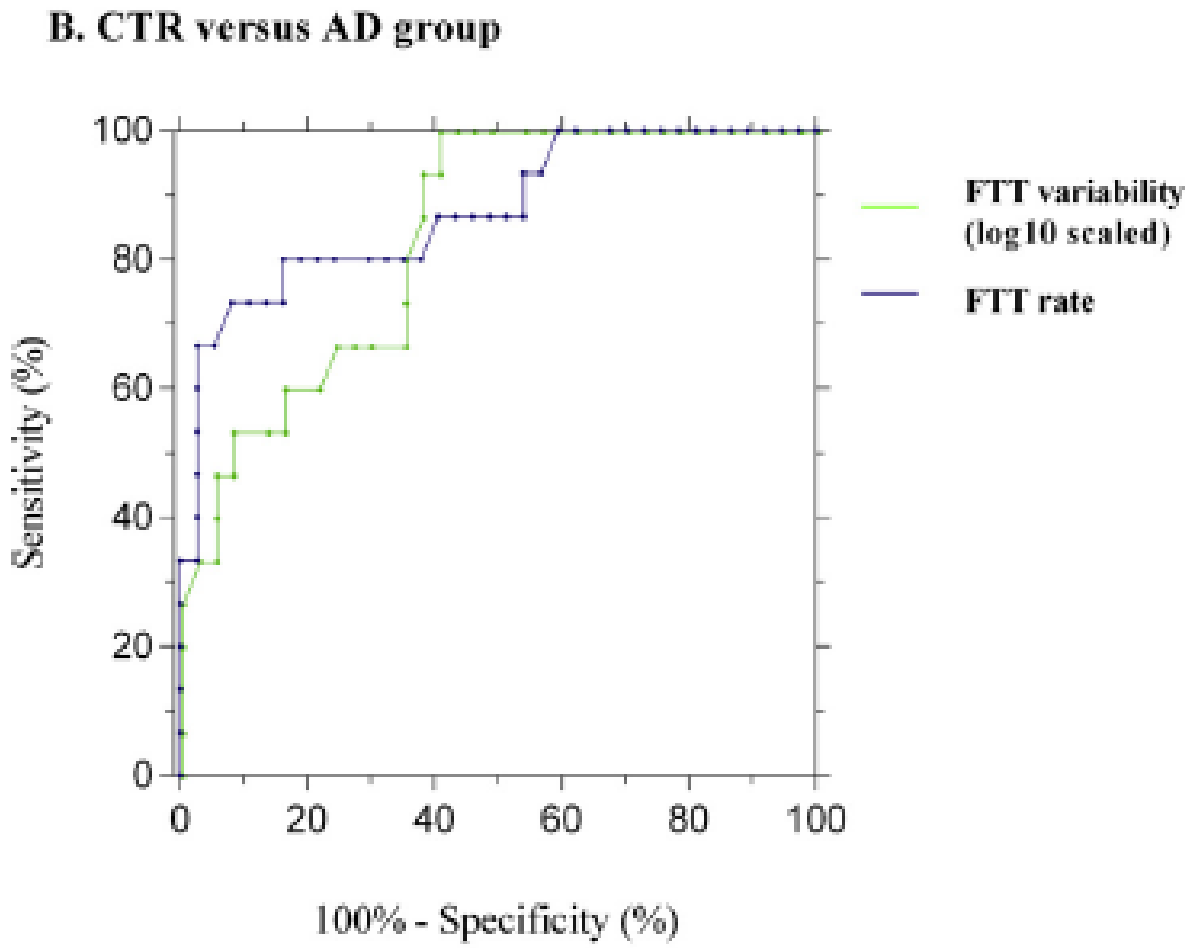
CORTEX 121 (2019) 117–124

Parameter	CTR (n = 37)	Aβ+ (n = 20)	AD (n = 15)
Age	64.7 (6.4)	66.5 (7.7)	67.3 (8.5)
Education (years)	11.7 (4.3)	11.2 (4.3)	10.8 (5.1)
% female	64.8% (24/37)	70.0% (14/20)	60.0% (9/15)
$A\beta_{42}$ (pg/ml)	822.9 (177.8)	442.9 (103.9)	368.6 (109.2)
tau (pg/ml)	232.1 (76.0)	232.7 (115.9)	624.1 (217.1)
p-tau (pg/ml)	52.6 (12.7)	47.8 (20.2)	94.3 (26.4)
% APOEε4	11.7% (4/37)	40.0% (8/20)	57.1% (8/14)[c]

E-Prime 2.0 (Psychology Software Tools Inc., Pittsburgh, PA) was used to create a modified computerized version of the standard (and manually-administered) FTT. Participants were instructed to tap repeatedly and as fast as they could on the computer keyboard's spacebar with their index finger while looking at a fixation point, until a STOP sign appeared on the screen. Instructions were given verbally by the experimenter and also displayed on the monitor. The participants sat in

Early detection of subtle motor dysfunction in cognitively normal subjects with amyloid-β positivity





FTT measures	CTR (n = 37)	Aβ+ (n = 20)	AD (n = 15)	F	Effect size	p[a]
Tapping speed	344.37 (36.6)	320.70 (32.3)	283.53 (35.1)	19.37	.370*	.001
Tapping variability[b]	−.75 (.21)	−.57 (.19)	−.46 (.19)	11.40	.257*	.001

The Diagnostic and Prognostic Value of a Dual-Tasking Paradigm in a Memory Clinic

Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-161310
IOS Press

Malene Schjønning Nielsen[a,*], Anja Hviid Simonsen[b], Volkert Siersma[c], Steen Gregers Hasselbalch[b] and Peter Hoegh[a]

Table 1
Characteristics of the study population baseline

	MCI	AD	HC
N (%)	29 (33.3)	17 (19.5)	41 (47.1)
Age (y)	72.0 (66.5–77–5)*	69.0 (63.5–74.5)	65.0 (62.0–71.5)
Gender (M:F, %)	79.3 : 20.7	47.1 : 52.9	53.7 : 46.3
Education (y)	10.0 (8.5–14.0)*	10.0 (7.0–15.5)	13.5 (10.3–16.0)
Follow-up (months)	29.0 (20.25–35.0)*	19.0 (12.0–33.5)*	35.0 (34.5–36.0)
MMSE score	28.0 (26.5–29.0)*	27 (22.5–29)*	29.0 (28.0–30.0)
ACE score	85.5 (81.3–90.0)*	81.0 (64.5–87.5)*	95 (93.0–97.0)
TUG (s)	8.3 (7.4–9.3)	8.6 (7.4–11.3)	7.6 (6.9–8.6)
TUG-DT (s)	9.5 (8.9–13.7)**	14.1 (10.3–20.3)**	8.1 (7.2–9.7)**
Performance TUG-DT (%)****			
Normal	18 (62)	6 (35)	40 (98)
Moderate deviation	11 (38)	6 (35)	1 (2)
Severe deviation	0	5 (30)	0
DT-cost (%)	29.21 (16.3–48.6)*	32.84 (13.3–99.9)*	5.95 (–2.3–15.4)
CSF $A\beta_{42}$ (pg/ml)	681.0 (539.0–1037.0)	583.0 (401.0–676.5)*	920.5 (807.3–1167.3)
CSF P-tau (pg/ml)	58.0 (39.0–74.0)	85.0 (65.5–93.5)***	47.5 (37.3–64.3)
CSF T-tau (pg/ml)	394.0 (233.5–542.5)	573.0 (501.5–892.5)***	283.0 (202.6–382.6)
CSF $A\beta_{42}$/P-tau ratio	12.2 (8.6–23.5)	6.5 (4.3–9.5)***	21.8 (14.2–28.0)

Box 1
Explanation of the categories for performance on the Timed Up and Go Dual Task

Performance categories	Observations
Normal	No notable changes in either: * gait velocity or performance * performance of the cognitive task
Moderate Deviation	Dual tasking imply changes in either: * gait velocity or performance * performance of the cognitive task
Severe Deviation	Dual tasking imply either: * stops walking, when engaging in the cognitive task * incapability of performing the cognitive task, when walking

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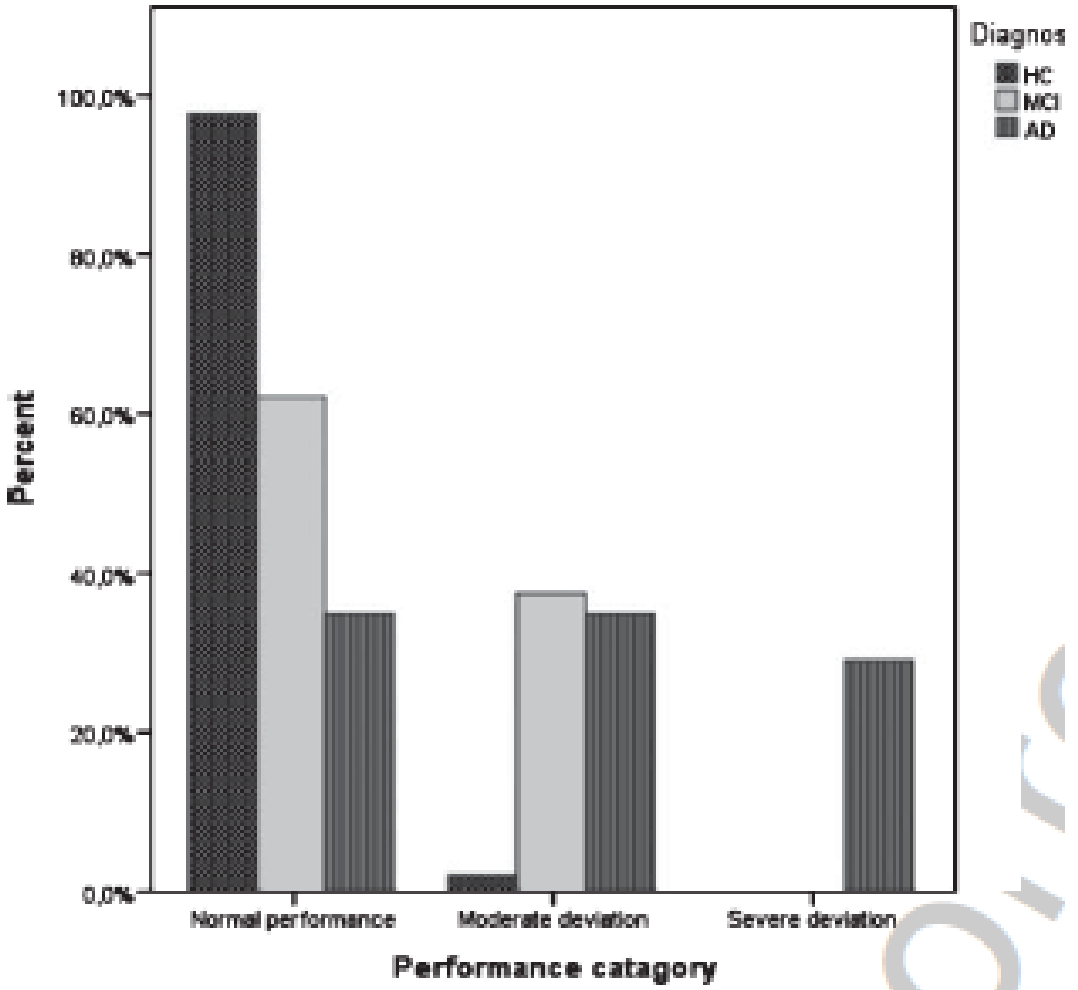

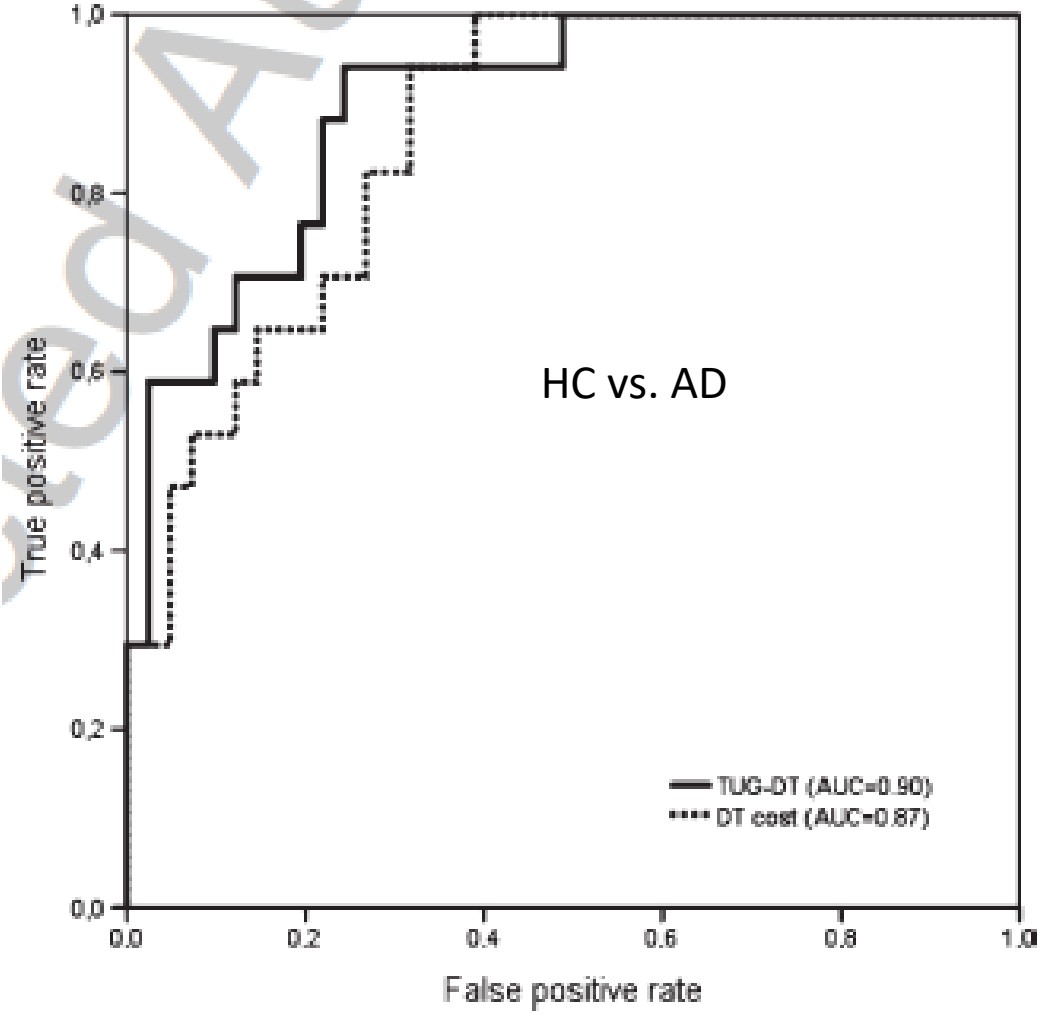

HC vs. AD

Review Article

At the interface of sensory and motor dysfunctions and Alzheimer's disease

M.W. Albers et al. / Alzheimer's & Dementia ■ (2014) 1-29

5. Motor systems in aging and AD

5.1. Summary of key findings

1. Motor impairment is highly prevalent in older adults.
2. Many pyramidal and extrapyramidal (or parkinsonian) motor impairments affect a substantial portion of AD
3. AD pathology can be found in motor neurons of the pyramidal motor pathways and in extrapyramidal motor pathways in AD patients, as well as in some cognitively intact older adults; the presence of AD pathology in monoaminergic nuclei, including the locus coeruleus (LC) and substantia nigra (SN), correlates with the presence of some motor signs.
4. A number of genes (*p16*, interleukin-18 [IL-18], and *COMT*) have been associated with alterations in motor function in nondemented older adults, and the AD risk genes, *PS1* and *APOE* ε4, have been associated with several motor symptoms in AD.
5. In healthy older adults, the primary motor cortex exhibits hypoexcitability, whereas in AD patients, the primary motor cortex exhibits hyperexcitability.

Cognitive And Metabolic Correlates of Mild Motor Impairment In Alzheimer's Disease.

M. *Pardini, A. Signori, D. Arnaldi, R. Meli, L. Filippi, S. Bianchin, M. Baucknhet, L. Carmisciano, S. Morbelli, G. Mancardi, M. Sormani, F. Nobili*
University of Genoa, Genoa, Italy

AIM: To evaluate the presence and neural bases of subtle motor deficit during finger tapping task in Alzheimer's Disease (AD)

TAKE HOME MESSAGE: Fine motor testing could represent a culture-independent surrogate measure of cognition in AD.

BACKGROUND: Recent years have seen an increase in the clinical awareness of the potential relevance of mild motor impairment (MMI) in subjects with AD. Here, we quantitatively evaluated finger opposition movements and correlated the kinematic parameters with cognitive performance and brain metabolism, assessed with FDG-PET, in a group of subjects with AD.

METHODS: 58 subjects affected by AD in the MCI or dementia stages, undergoing brain FDG-PET and standardized cognitive testing for diagnostic purposes, were enrolled (Table). Hand motor function was quantitatively assessed during thumb-to-fingers opposition movements (Figure). Movement speed, expressed in Hertz (i.e., with higher values representing a better performance), was compared with healthy controls normative data and correlated with brain metabolism and cognitive variables.

DISEASE STAGE	
MCI due to AD	44
AD-dementia	14
AGE mean (SD); range	78(5); 67-88
N. OF FEMALES	36
MMSE, mean (SD)	25.6 (4.2)
BABCOCK STORY, DELAYED RECALL, mean (SD)	5.1(3.7)

RESULTS: On finger tapping, patients performed significantly ($p<0.001$) worse than the age-matched normative reference population (1.49±0.62 vs 2.8±0.4). FDG-PET voxelwise analysis (SPM-12; p (uncorrected) <0.001) showed a direct correlation between movement speed and left superior parietal lobe metabolism, taking into account differences in MMSE score and age. A significant correlation was observed between movement speed and both MMSE score (rho=0.45;p=0.02) and Babcock's delayed recall score (rho=0.69;p=0.012).

KEY-POINT: In AD, finger tapping is slower compared to controls and correlates with parietal metabolism, MMSE and memory.

CONCLUSION: Fine hand motor skills are impaired in subjects with AD. The correlation between cortical metabolism, overall cognition, memory and motor impairment suggests that fine motor testing could represent a culture-independent surrogate measure of cognitive difficulties in AD.

Take home message

Non solo MCI: il costrutto del mild motor impairment

Il clinico e i disturbi cognitivi

Esame obiettivo (oltre la cognitività)?

Come restituisco i risultati?

Che fare?

Personalized risk for clinical progression in cognitively normal subjects—the ABIDE project

van Maurik *et al. Alzheimer's Research & Therapy* (2019) 11:33
https://doi.org/10.1186/s13195-019-0487-y

Table 2 Regression coefficient of the final model

	MCI/dementia		
	Coëfficient	Standard error	*p* value
Demographic ($n = 481$)			
Age	0.0854	0.0147	< .001
MMSE	− 0.2497	0.0639	< .001
CSF ($n = 344$)			
Aβ	− 1.0462	0.3668	< .01
Tau	1.2785	0.3384	< .001
Age	0.0704	0.0251	< .01
Gender	− 0.6360	0.3345	< .10
MMSE	− 0.25503	0.0815	< .01
Tau* age	− 0.1393	0.0467	< .01

Table 1 Baseline characteristics

	SCD individuals$n = 481$
No. (%) with clinical progression	70 (15%)
Progression to MCI	49 (10%)
Progression to AD dementia	10 (2%)
Progression to non-AD dementia	11 (2%)
Age	62 ± 9
Gender, no. (%) females	211 (44%)
MMSE	28 ± 1.6
Follow-up duration	3 ± 2
Medial temporal lobe atrophy	0.4 ± 0.5
Global cortical atrophy	0.4 ± 0.6
Hippocampal volume (cm3)	7.2 ± 1
Normalized whole brain volume (cm^3)	1453 ± 100
Amyloid β1–42	879 ± 260
Total Tau	298 ± 196
p-tau	49 ± 22

Data are mean ± standard deviation, unless otherwise specified. *MMSE* mini-mental state examination, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid

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Methods: We included 481 individuals with subjective cognitive decline (SCD) from the Amsterdam Dementia Cohort.

				Demographics only	CSF			
	Age	Sex	MMSE		Normal	AB abnormal	Tau abnormal	Both abnormal
1 year	55	m	30	2% [0–2]	0% [0–1]	0% [0–2]	12% [3–38]	26% [7–71]
			27	3% [2–5]	0% [0–2]	0% [1–5]	26% [8–65]	51% [18–92]
		f	30	2% [0–2]	0% [0–1]	0% [0–1]	6% [2–23]	15% [4–48]
			27	3% [2–5]	0% [0–1]	0% [1–3]	15% [4–44]	32% [9–77]
	70	m	30	5% [3–9]	5% [2–15]	13% [5–34]	4% [1–11]	8% [3–20]
			27	11% [7–16]	12% [5–30]	29% [11–64]	9% [3–21]	19% [9–36]
		f	30	5% [3–9]	3% [1–9]	7% [2–22]	3% [1–6]	5% [2–12]
			27	11% [7–16]	7% [2–22]	16% [5–46]	5% [2–12]	10% [4–24]
5 years	55	m	30	6% [3–11]	1% [0–3]	1% [0–8]	43% [13–89]	73% [27–98]
			27	12% [8–20]	1% [1–7]	4% [1–17]	73% [30–99]	96% [56–100]

Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): a modelling study

Ingrid S van Maurik, Stephanie J Vos, Isabelle Bos, Femke H Bouwman, Charlotte E Teunissen, Philip Scheltens, Frederik Barkhof, Lutz Frolich, Johannes Kornhuber, Jens Wiltfang, Wolfgang Maier, Oliver Peters, Eckart Rüther, Flavio Nobili, Giovanni B Frisoni, Luiza Spiru, Yvonne Freund-Levi, Asa K Wallin, Harald Hampel, Hilkka Soininen, Magda Tsolaki, Frans Verhey, Iwona Kłoszewska, Patrizia Mecocci, Bruno Vellas, Simon Lovestone, Samantha Galluzzi, Sanna-Kaisa Herukka, Isabel Santana, Ines Baldeiras, Alexandre de Mendonça, Dina Silva, Gael Chetelat, Stephanie Egret, Sebastian Palmqvist, Oskar Hansson, Pieter Jelle Visser, Johannes Berkhof, Wiesje M van der Flier, for the Alzheimer's Disease Neuroimaging Initiative

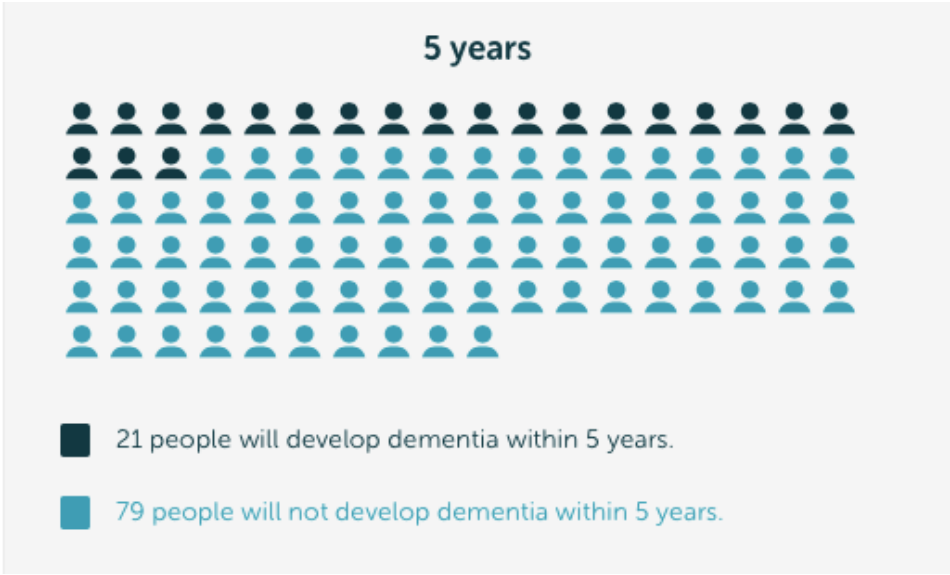
www.thelancet.com/neurology **Published online September 13, 2019**

	ADC (n=666)	ADNI (n=829)	EMIF-AD (n=883)	BioFINDER (n=233)
Baseline data collection period	1995–2014	2004–14	Varied per substudy*	2010–15
Study design	Single-centre longitudinal cohort study	Multicentre longitudinal cohort study	Multicentre longitudinal cohort study	Multicentre longitudinal cohort study
Setting	Tertiary memory clinic	Research	Memory clinics	Memory clinics
Inclusion criteria	Referred to memory clinic, does not fulfil criteria for dementia	Memory complaints verified by study partner, abnormal memory functioning, MMSE of 24–30, clinical dementia rating scale of 0·5, does not fulfil criteria for dementia	Varied per substudy*	Referred to memory clinic, age 60–80 years, baseline MMSE of 24–30, does not fulfil criteria for dementia
Participants who developed dementia	288 (43%)	319 (38%)	272 (31%)	128 (55%)
Follow-up	Clinical follow-up every 12 months	3–12-month interval	Varied per substudy*	Every 12 months for at least 6 years
MRI available	539 (81%)	705 (85%)	727 (82%)	233 (100%)
MRI quantification method	FSL-FIRST, Freesurfer version 5.3	Freesurfer version 5.3	Varied per substudy*	Freesurfer version 5.3
CSF biomarkers available	485 (73%)	558 (67%)	366 (41%)	221 (95%)
CSF platform	Innotest	Luminex and Elecsys	Innotest	Innotest

ADC=Amsterdam Dementia Cohort. ADNI=Alzheimer's Disease Neuroimaging Initiative. EMIF-AD=European Medical Information Framework for Alzheimer's Disease. MMSE=Mini-Mental State Examination. *For substudy details, see appendix pp 2–3.

Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): a modelling study

By contrast, a 62-year-old man with MCI and an MMSE of 29, without knowledge of biomarker results, has progression probabilities to dementia of 7% (95% CI 6–8) in 1 year, 26% (23–29) in 3 years, and 40% (44–35) in 5 years. With normal biomarkers (amyloid β =1264, phosphorylated tau = 12 [measured with Elecsys], and hippocampal volume = 9·8 [calculated with Freesurfer]), he would have progression probabilities of 1% [1–2] in 1 year, 5% (4–7) in 3 years, and 8% (6–11) in 5 years.



https://adappt.health/en/tool

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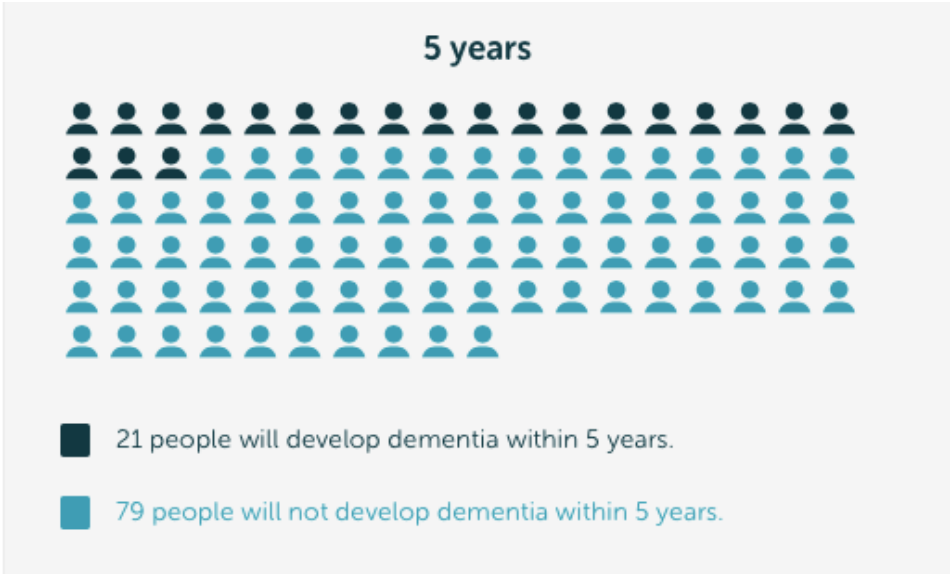

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Take home message

Non solo MCI: il costrutto del mild motor impairment

La restituzione in modo quantitativo della rilevanza clinica dei biomarcatori

Il clinico e i disturbi cognitivi

Esame obiettivo (oltre la cognitività)?

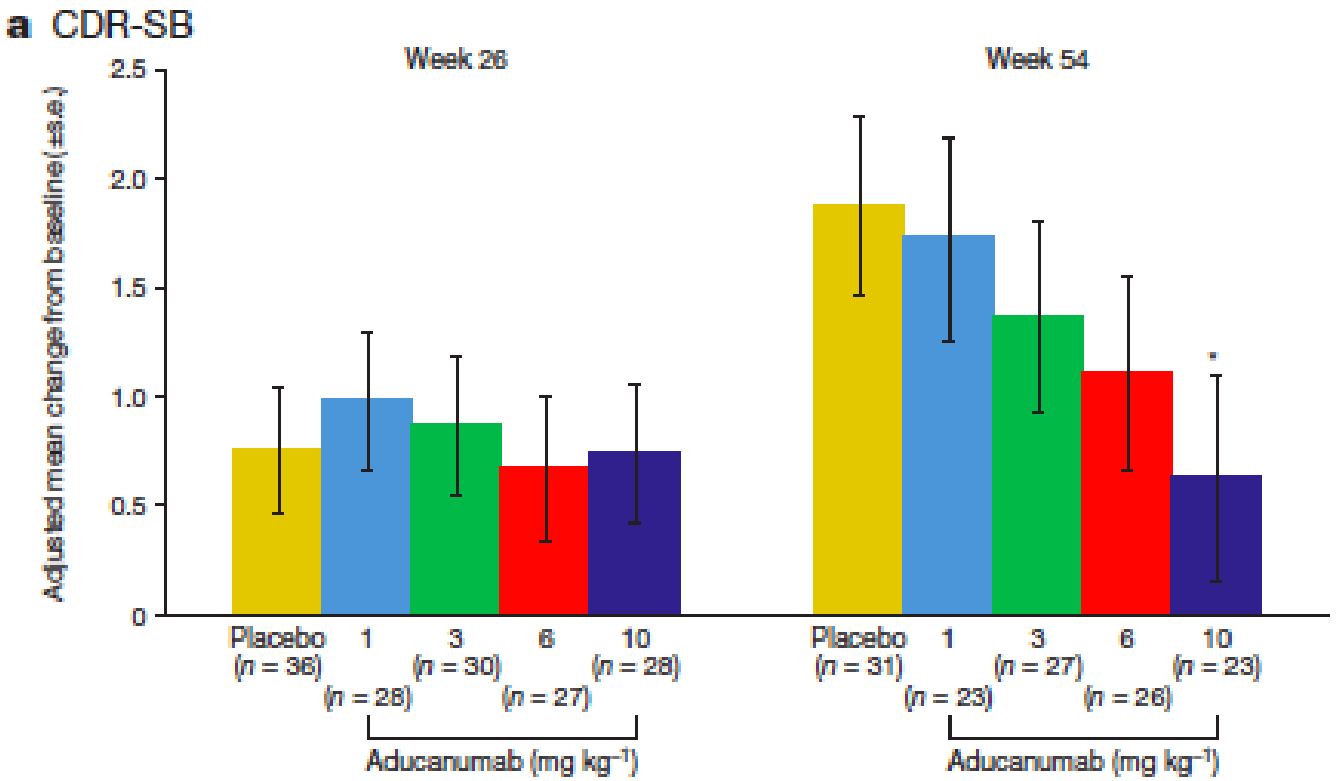
Come restituisco i risultati?

Che fare?

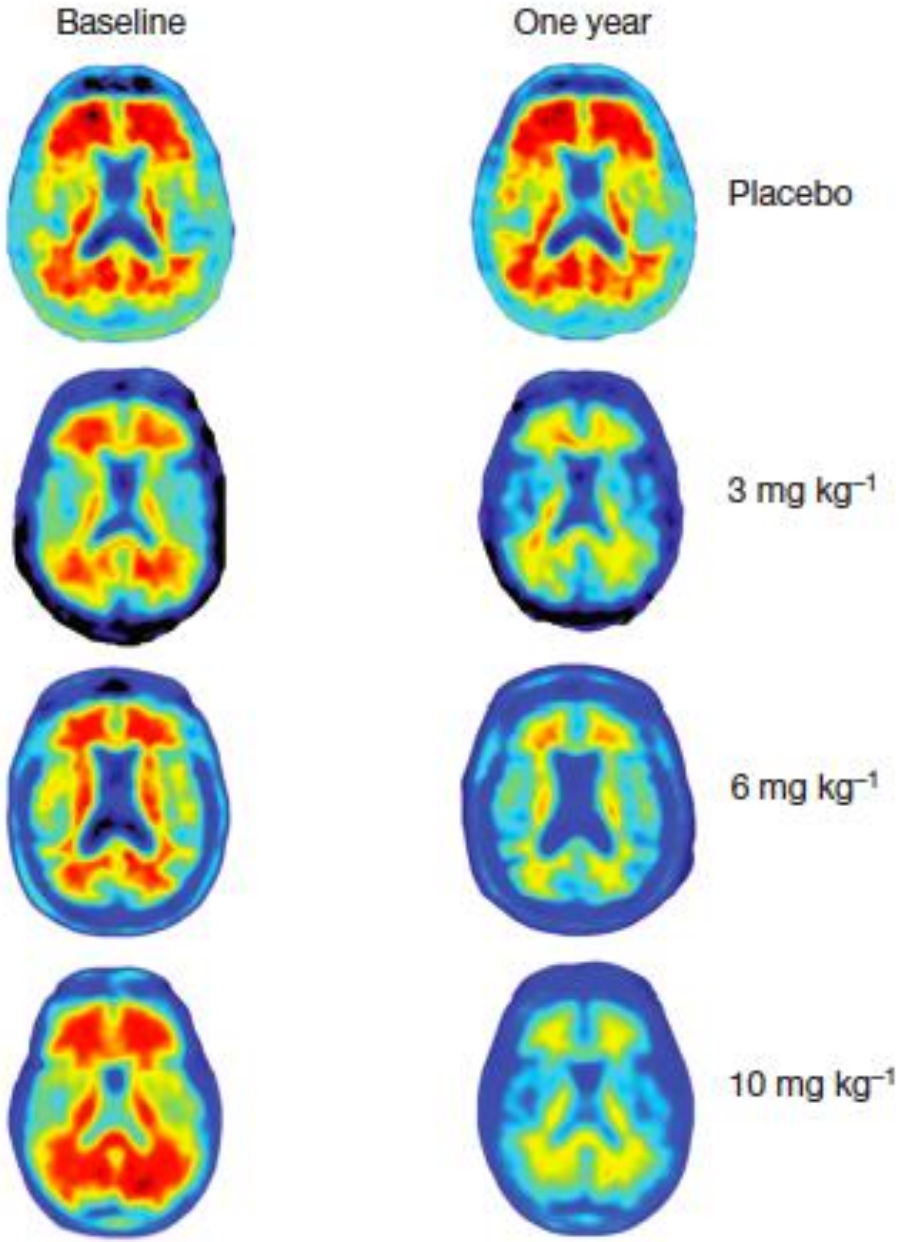
The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1] James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

NATURE | VOL 537 | 1 SEPTEMBER 2016



Dose-response $P < 0.05$ at week 54 based on a linear contrast test



Alzheimer disease and aducanumab: adjusting our approach

Dennis J. Selkoe

In the march towards disease-modifying treatments for Alzheimer disease, immunotherapy with antibodies against amyloid-β protein is furthest along in human trials. The news that Biogen's aducanumab showed no cognitive benefit in phase III trials requires careful analysis of what went wrong and how to position anti-amyloid agents among other therapeutic approaches.

Biogen Plans Regulatory Filing for Aducanumab in Alzheimer's Disease Based on New Analysis of Larger Dataset from Phase 3 Studies

CAMBRIDGE, Mass. and TOKYO, Oct. 22, 2019 (GLOBE NEWSWIRE) -- Biogen (Nasdaq: BIIB) and Eisai,

EMERGE, which met its pre-specified primary endpoint in the new analysis, patients treated with high dose aducanumab showed a significant reduction of clinical decline from baseline in CDR-SB scores at 78 weeks (23% versus placebo, P=0.01). In EMERGE, patients treated with high dose aducanumab also showed a consistent reduction of clinical decline as measured by the pre-specified secondary endpoints: the Mini-Mental State Examination (MMSE; 15% versus placebo, P=0.06), the AD Assessment Scale-Cognitive Subscale 13 Items (ADAS-Cog 13; 27% versus placebo, P=0.01), and the AD Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version (ADCS-ADL-MCI; 40% versus placebo, P=0.001).

Take home message

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La restituzione in modo quantitativo della rilevanza clinica dei biomarcatori

Speranze terapeutiche e rischi comunicativi