Roma, 20 novembre 2008
Biostatistica per la ricerca e la pratica clinica

Stato dell'arte e sfide future per la biostatistica nella ricerca clinica: la prospettiva del neurologo

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IRCCS
CENTRO SAN GIOVANNI DI DIO FATEBENEFRATELLI – BRESCIA
Centro Nazionale per lo Studio e la Cura
della Malattia di Alzheimer e Malattie Mentali

Background

Alzheimer: storia naturale, selettività topografica, i nuovi farmaci

Marcatori per monitorare la malattia

Imaging unimodale per monitorare la progressione

Modellare atrofia globale e atrofia locale

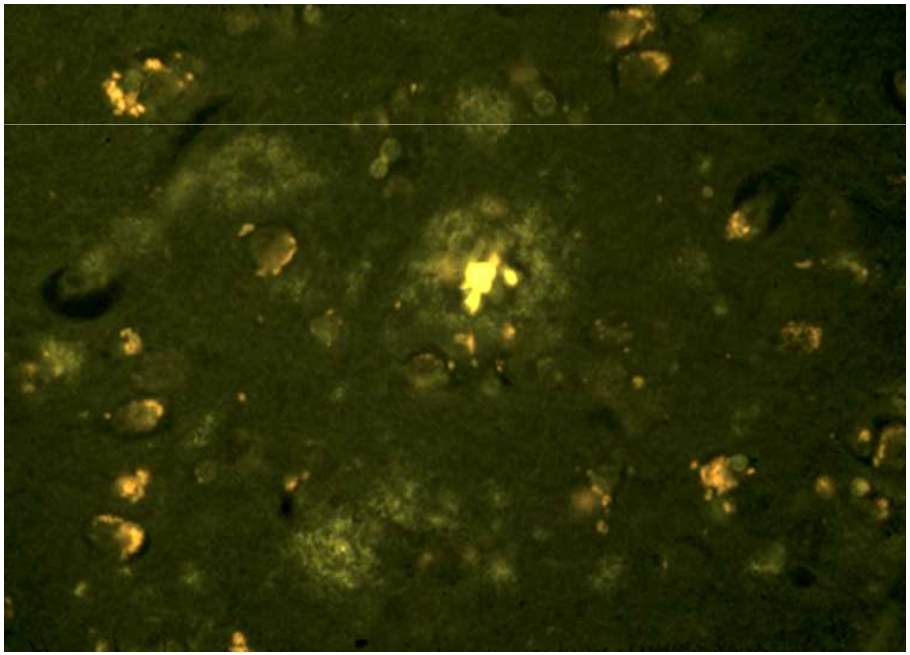
Modellare la topografia della progressione dell'atrofia

Imaging multimodale

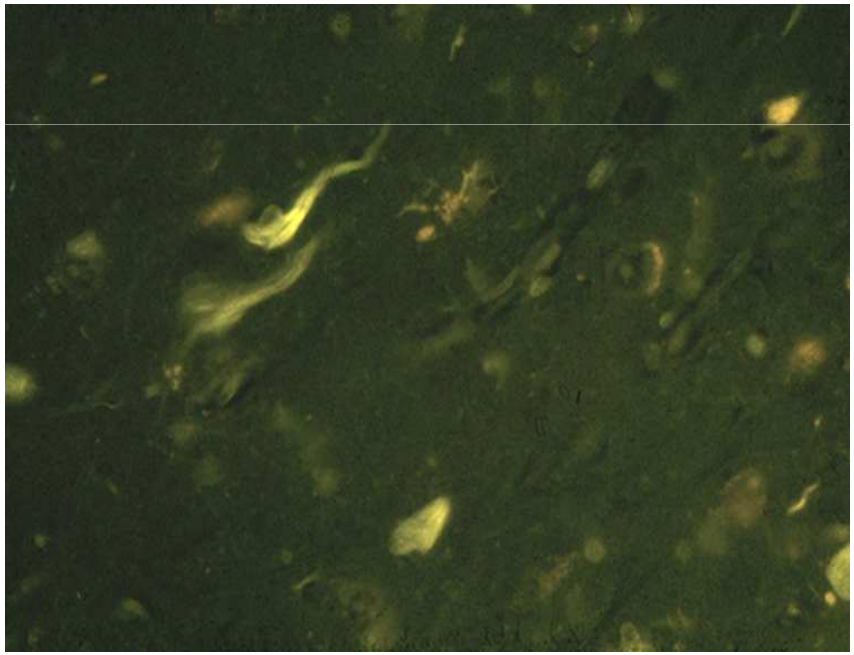
Modellare progressione di atrofia + progressione di altri fenomeni biologici

LA FISIOPATOLOGIA DELLA MALATTIA DI ALZHEIMER

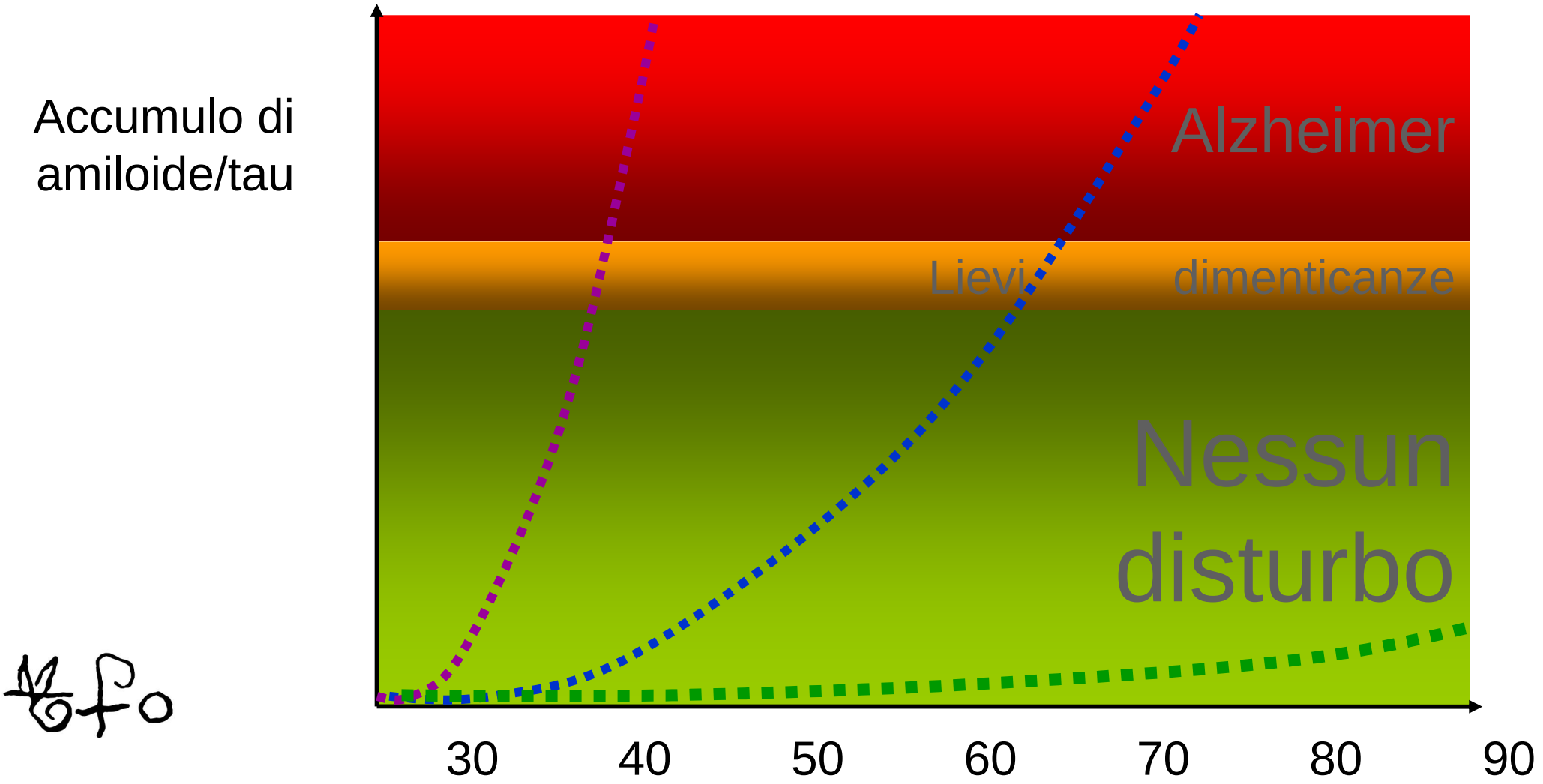
Placche di amiloide



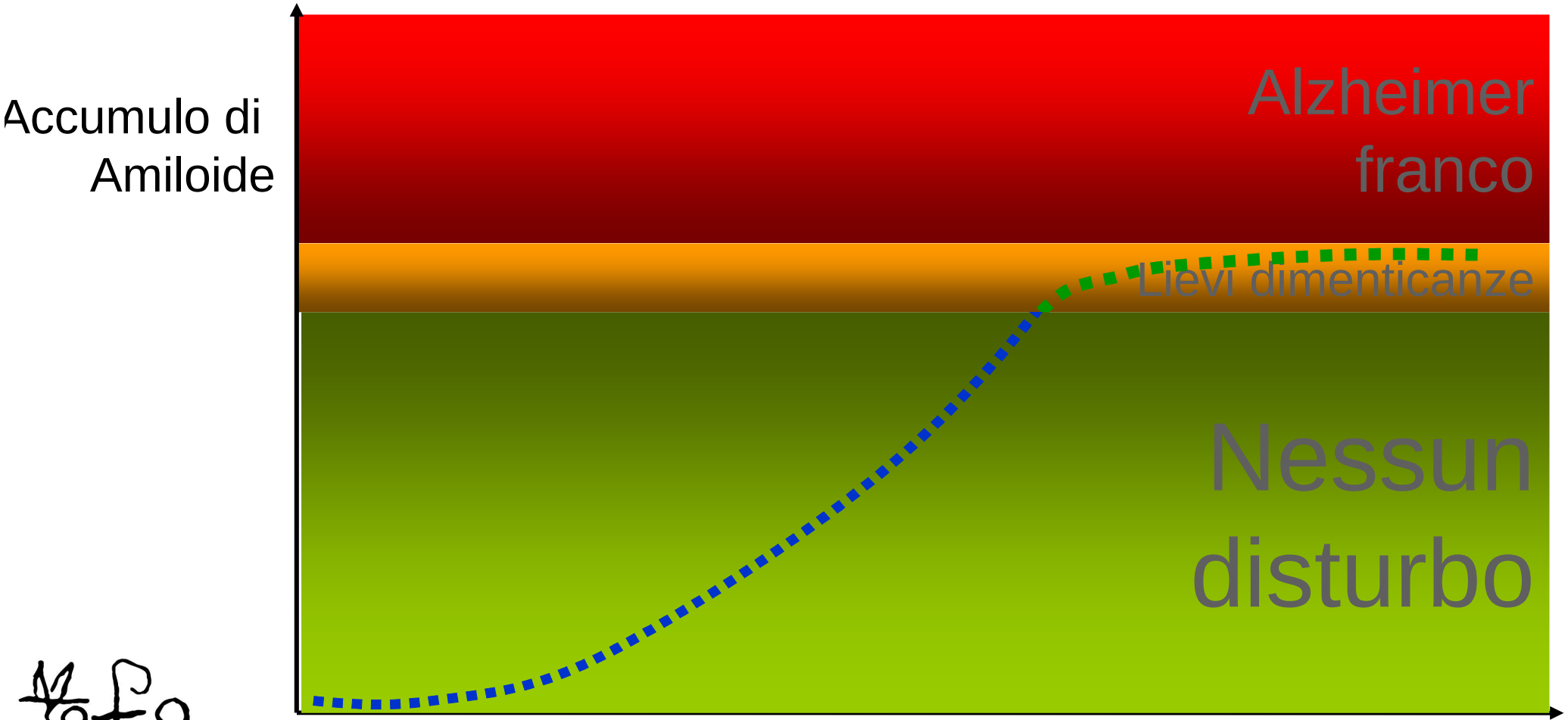
Gomitoli di tau HP



PERCHE' CI SI AMMALA DI ALZHEIMER

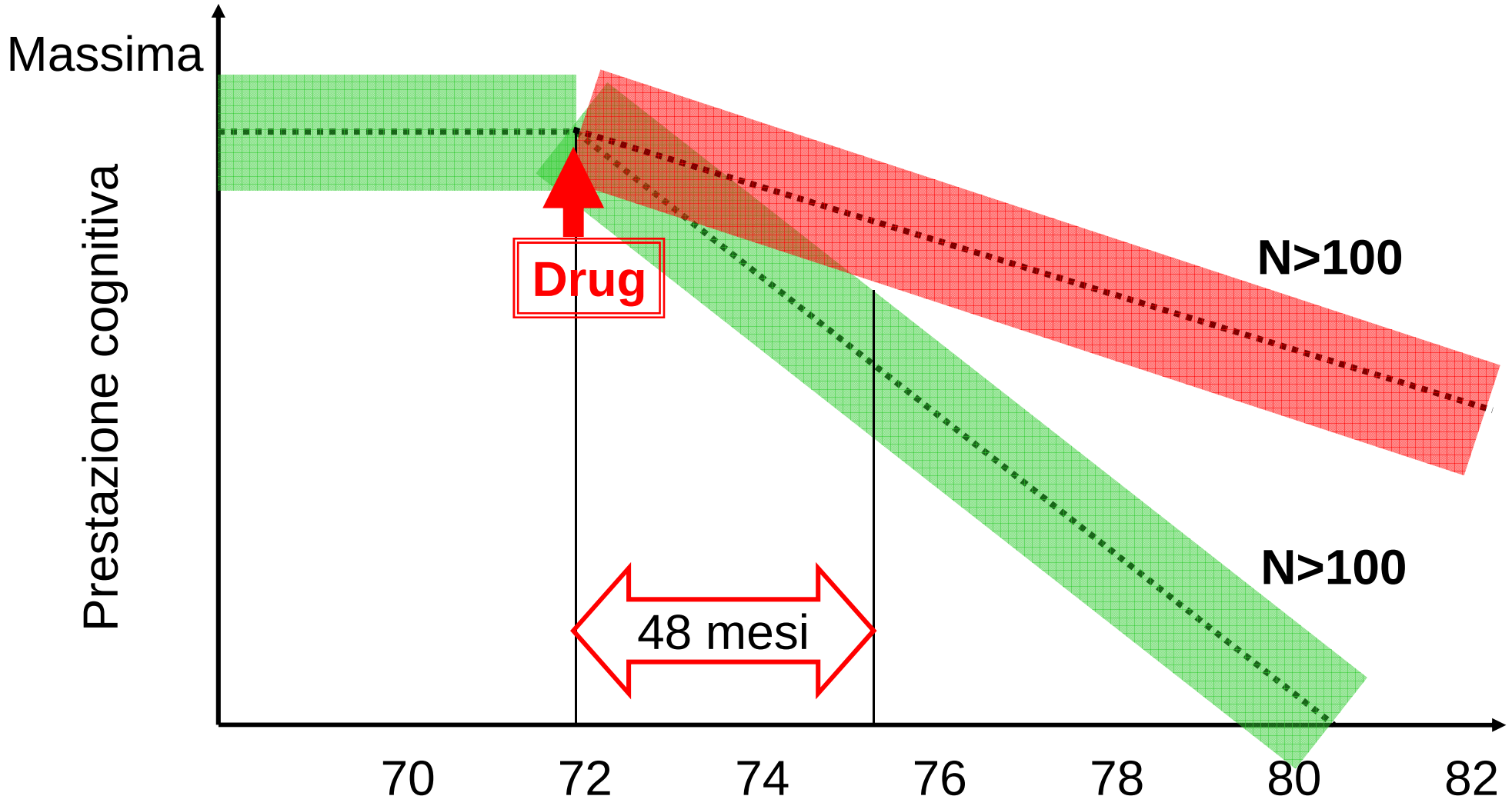


DIAGNOSI PRECOCE + FARMACI ANTIAMILOIDE



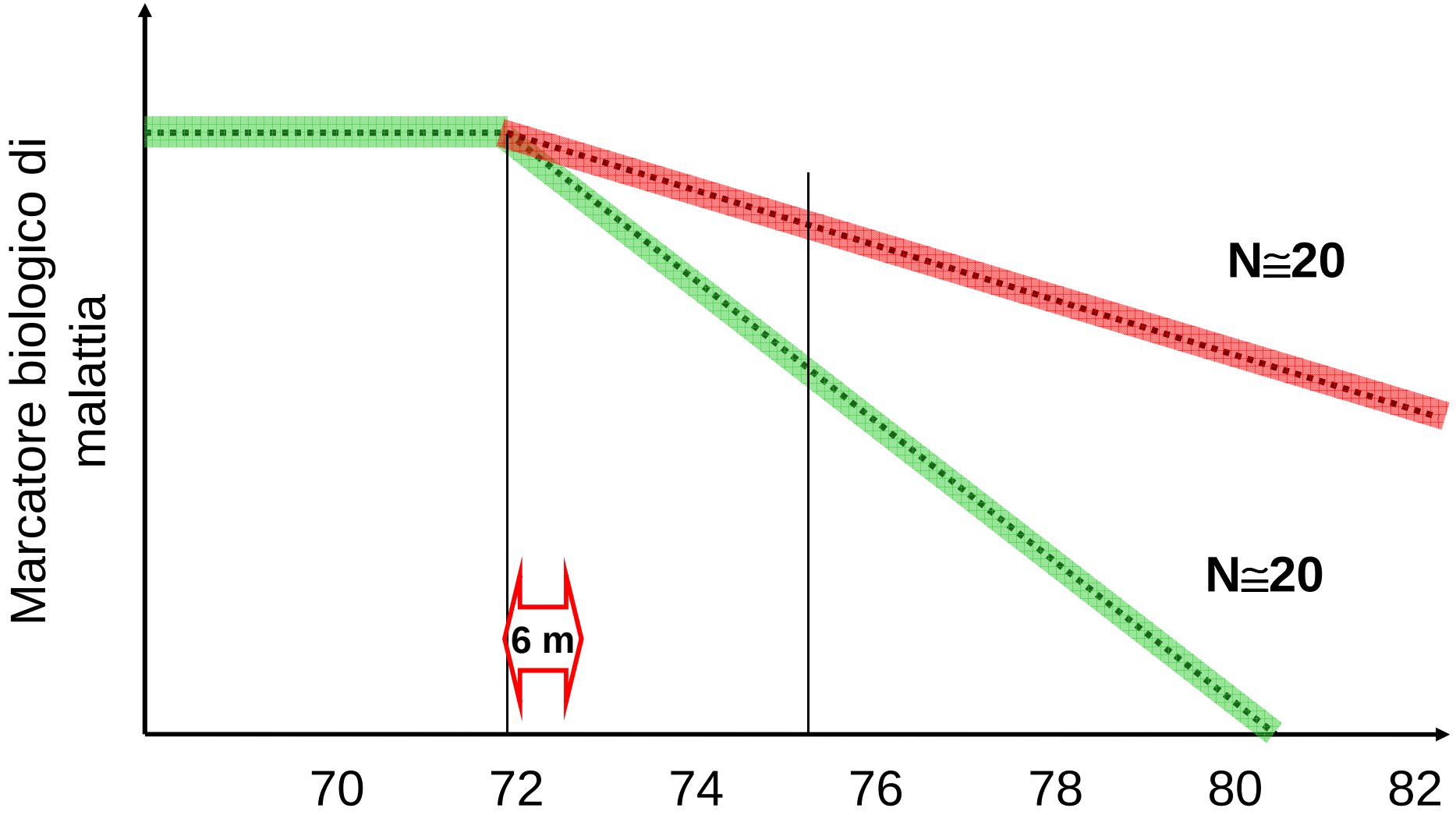
TERAPIA PER ALZHEIMER

Efficacia dei farmaci sperimentali su parametri cognitivi



TERAPIA PER ALZHEIMER

Efficacia dei farmaci sperimentali su marcatori biologici di malattia



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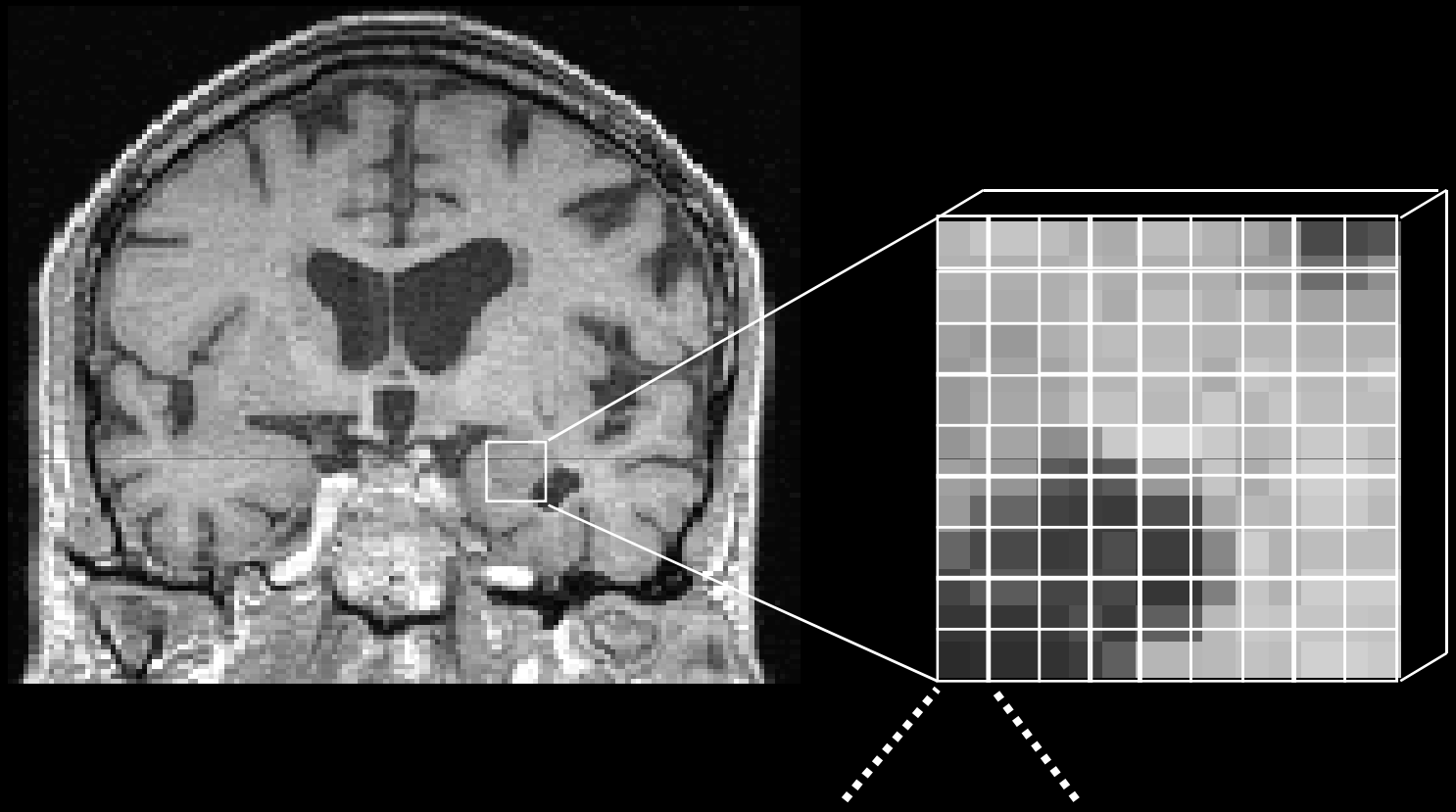
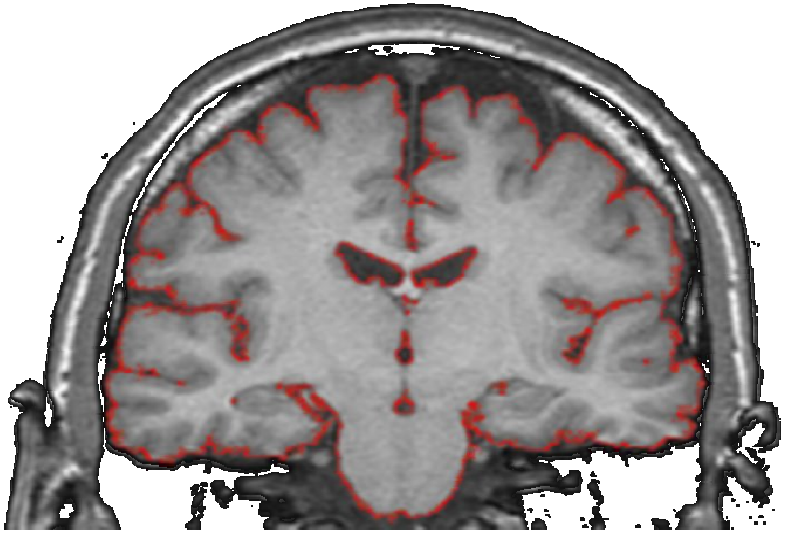


4 M voxels, 2^{16} gray shades

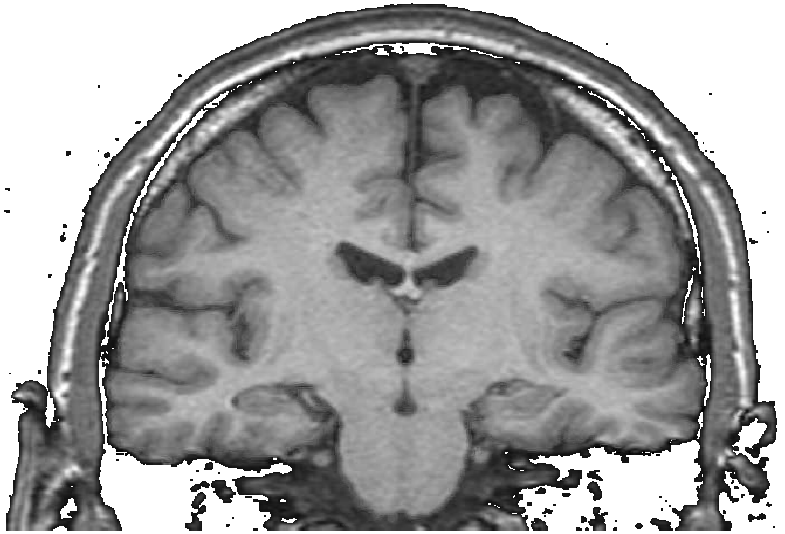
WHOLE BRAIN ATROPHY RATES

The brain-boundary shift integral

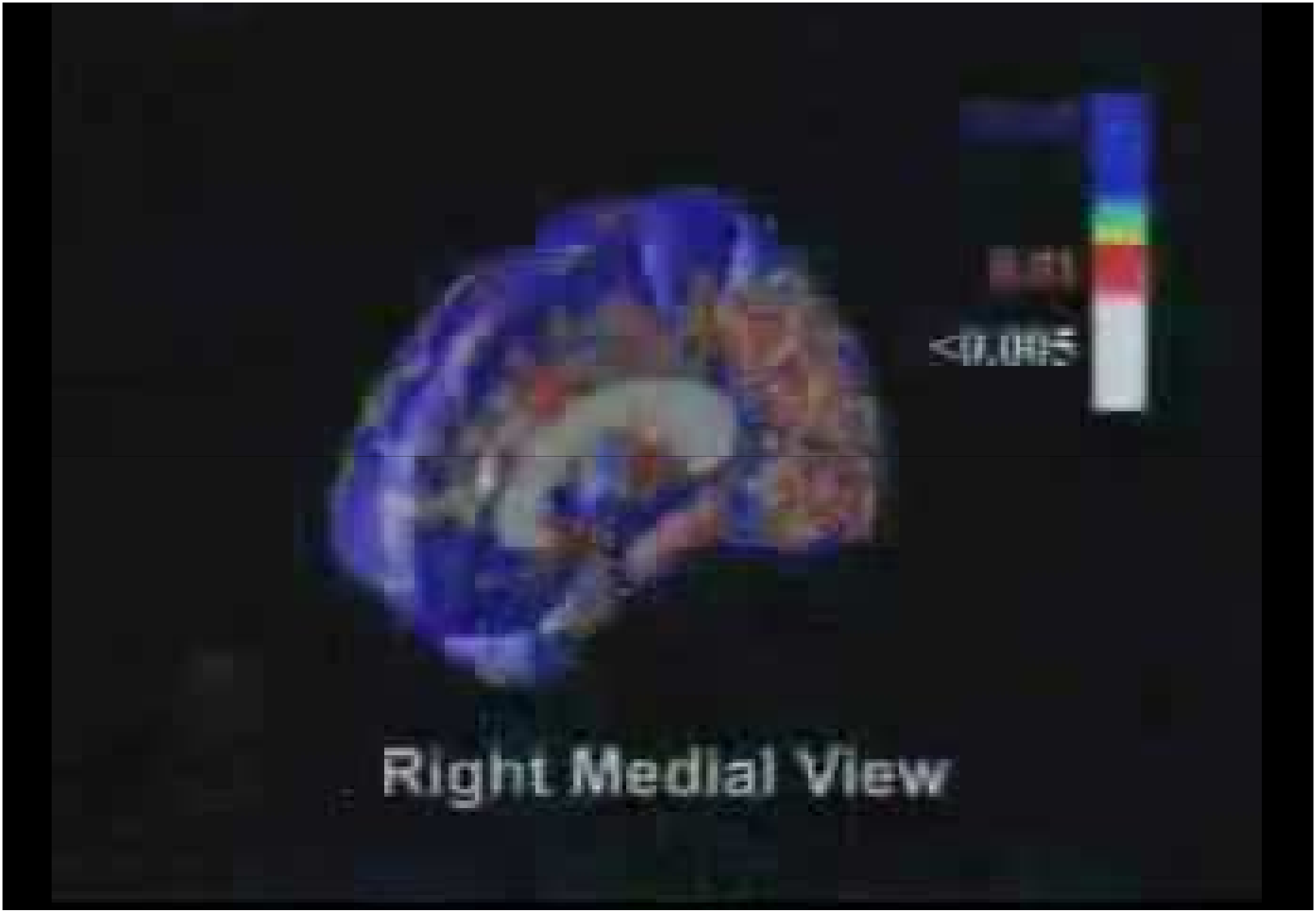
Baseline scan

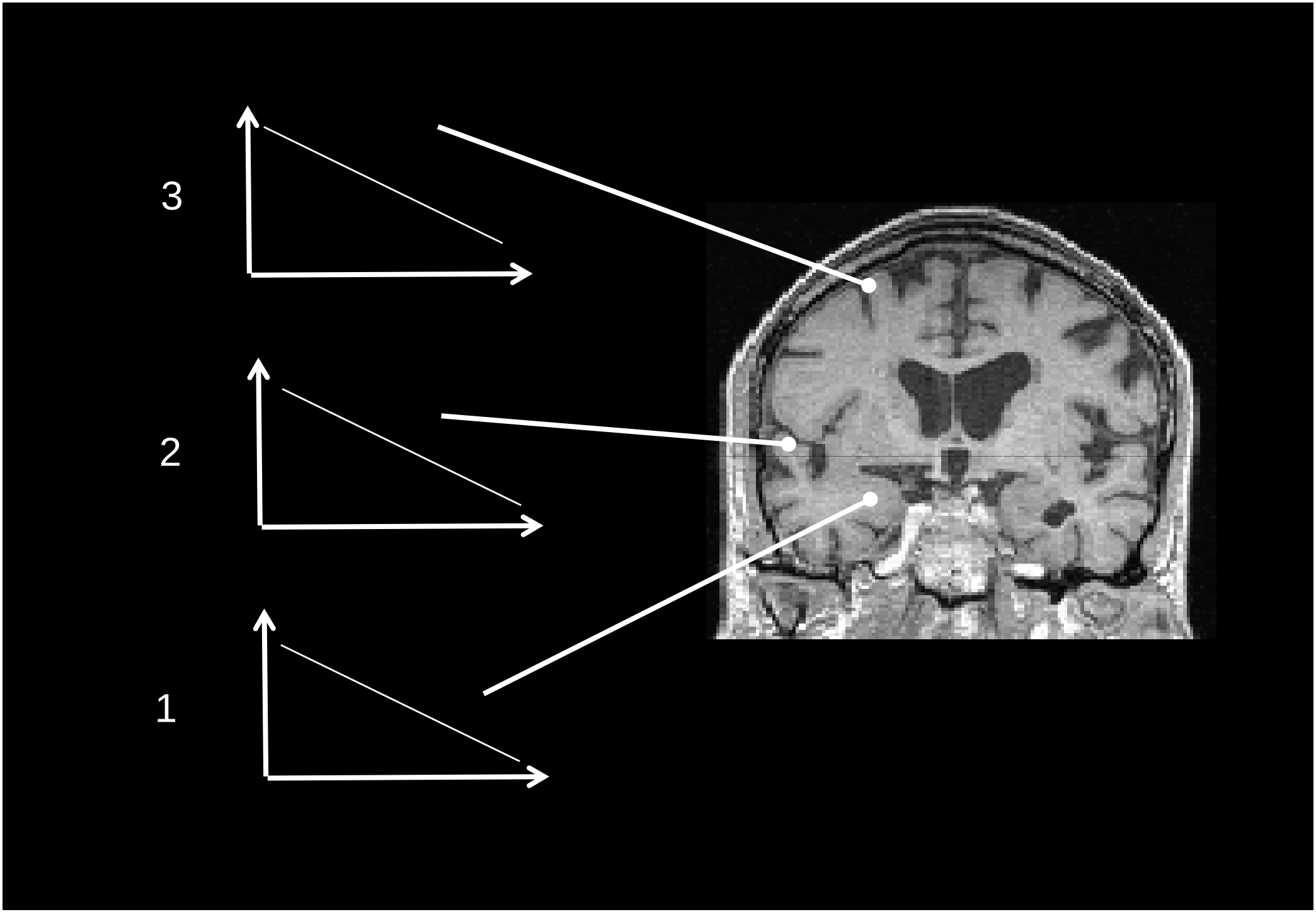


Follow-up scan
(1 year later)




0.005
Left Oblique View


Right Medial View


3
2
1

CORTICAL PATTERN MATCH.
Mappaggio progressione della malattia

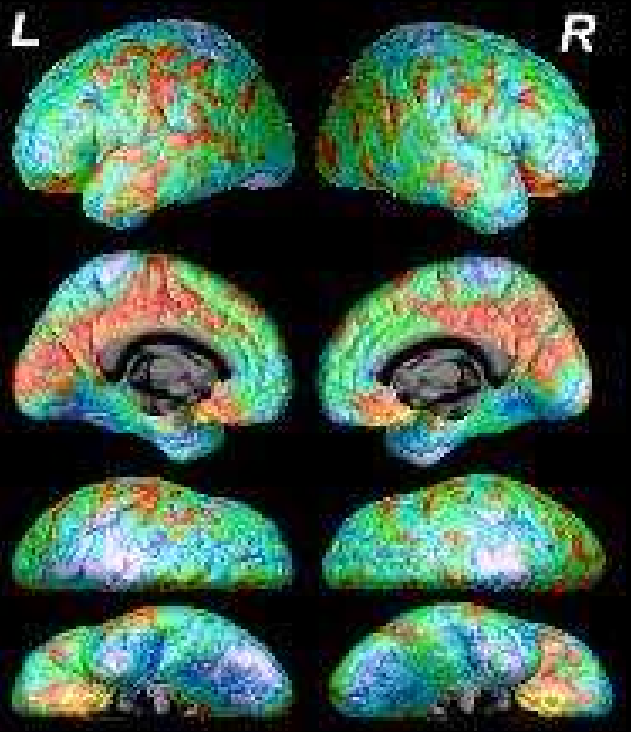
Table 1. Sociodemographic, cognitive, and genetic features of the study groups.

	Older healthy (N=20)	Incipient AD (N=11)	Mild AD (N=15)	Moderate AD (N=15)
Age, years	**73.9 ± 7.9**	**77.6 ± 5.6**	**72.7 ± 8.9**	**73.4 ±9.5**
Gender, female (%)	**14 (70%)**	**3 (27%)**	**10 (67%)**	**13 (87%)**
Education, years	**9.0 ± 4.5**	**8.5 ± 4.5**	**7.1 ± 5.6**	**5.2 ± 2.1**
Mini Mental State Exam	**29.1 ± 1.0**	**26.5 ± 2.0**	**23.5 ± 2.2**	**16.5 ± 2.0**
[range]	**[30-27]**	**[29-24]**	**[27-20]**	**[19-13]**
ApoE ε4 carriers, n (%)	**4/20 (20%)**	**5/11 (45%)**	**5/15 (33%)**	**7/13 (54%)**

MAPPAGGIO PROGRESSIONE DELLA MALATTIA

Perdita di sost grigia corticale

Incipient AD vs older healthy



Posterior cing & retrospl cx
Entorhinal cx
Subgenual/orbitofr cx

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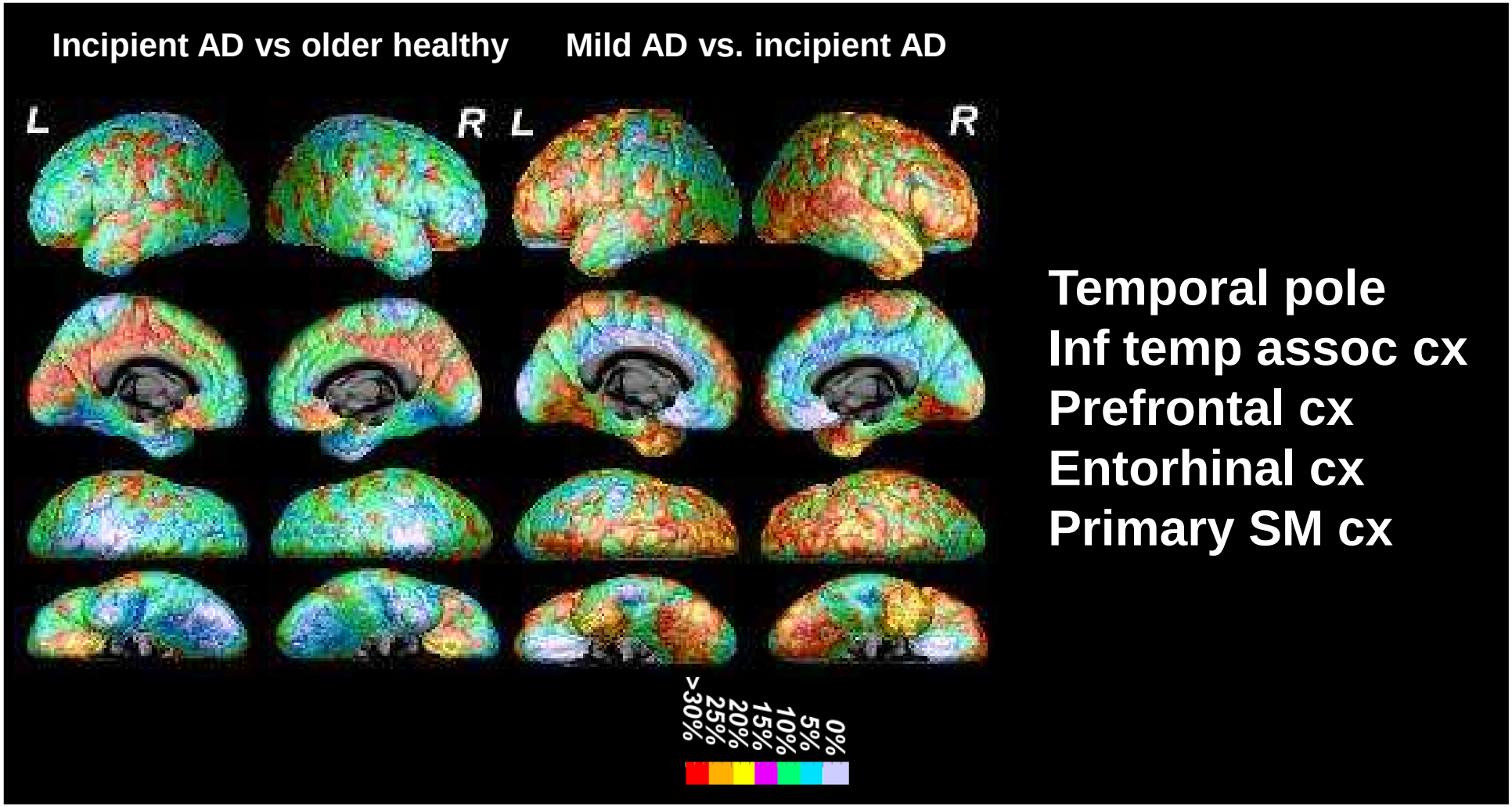
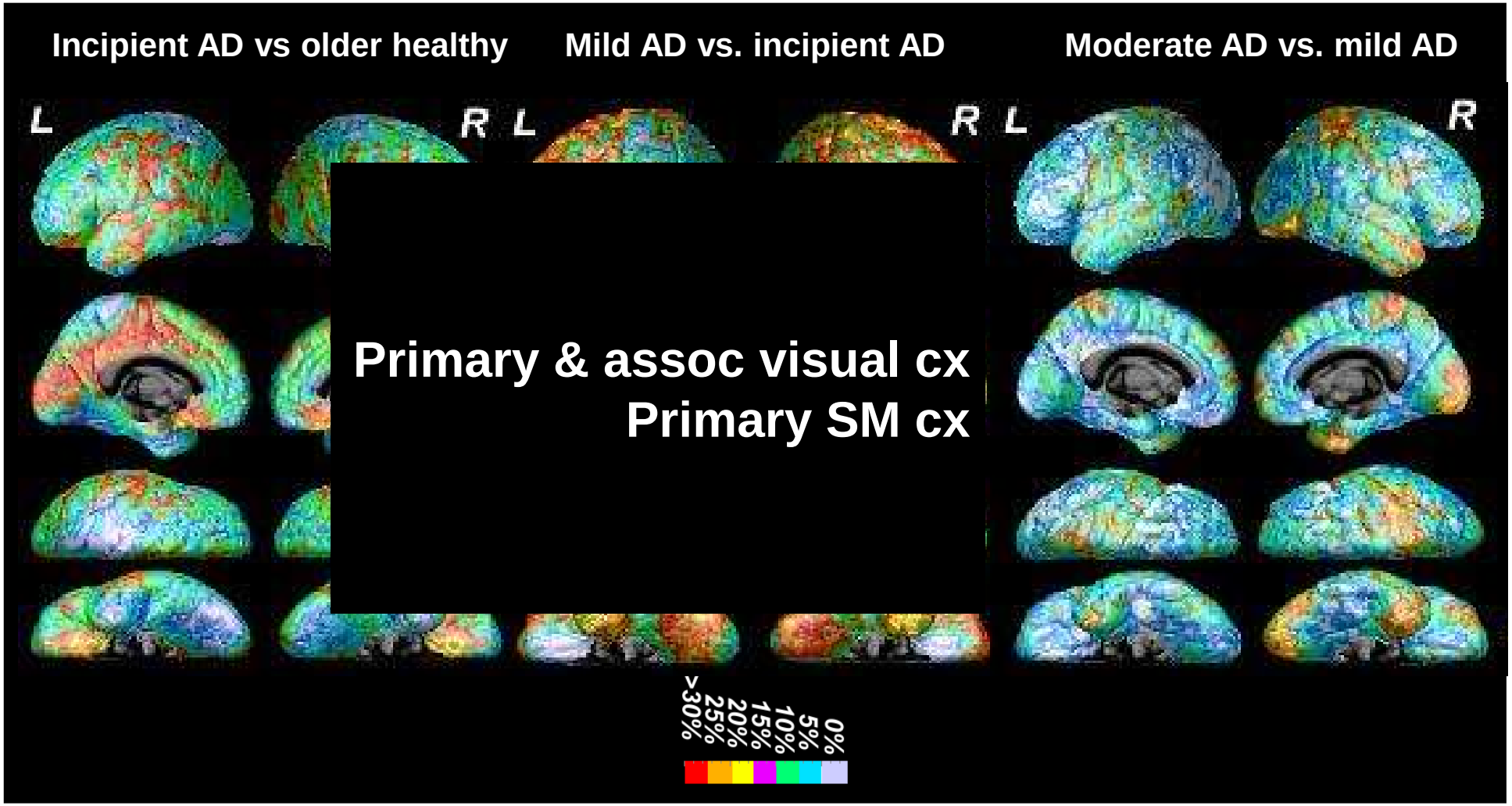
Perdita di sost grigia corticale

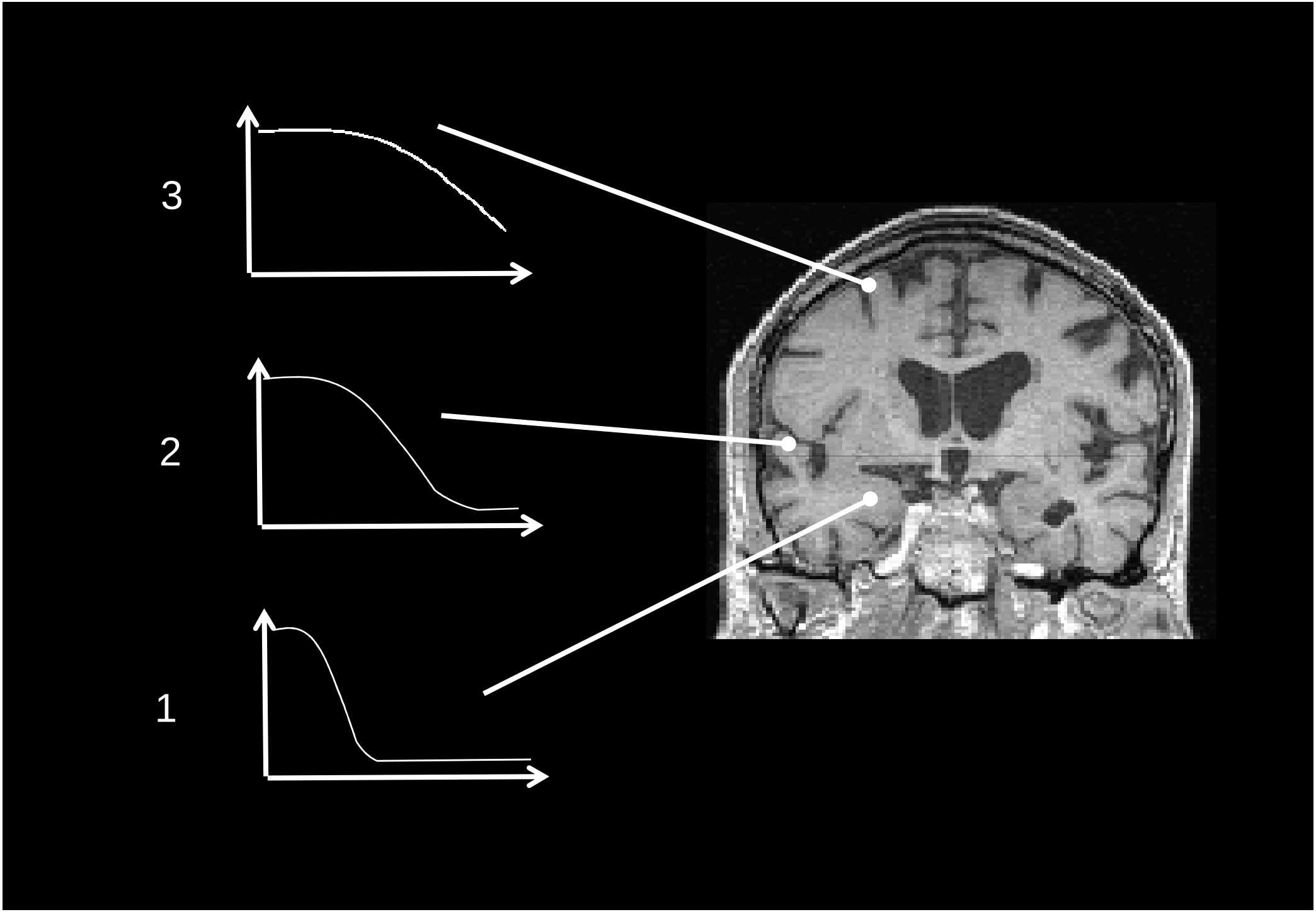


- Temporal pole
- Inf temp assoc cx
- Prefrontal cx
- Entorhinal cx
- Primary SM cx

MAPPAGGIO PROGRESSIONE DELLA MALATTIA

Perdita di sost grigia corticale




3
2
1

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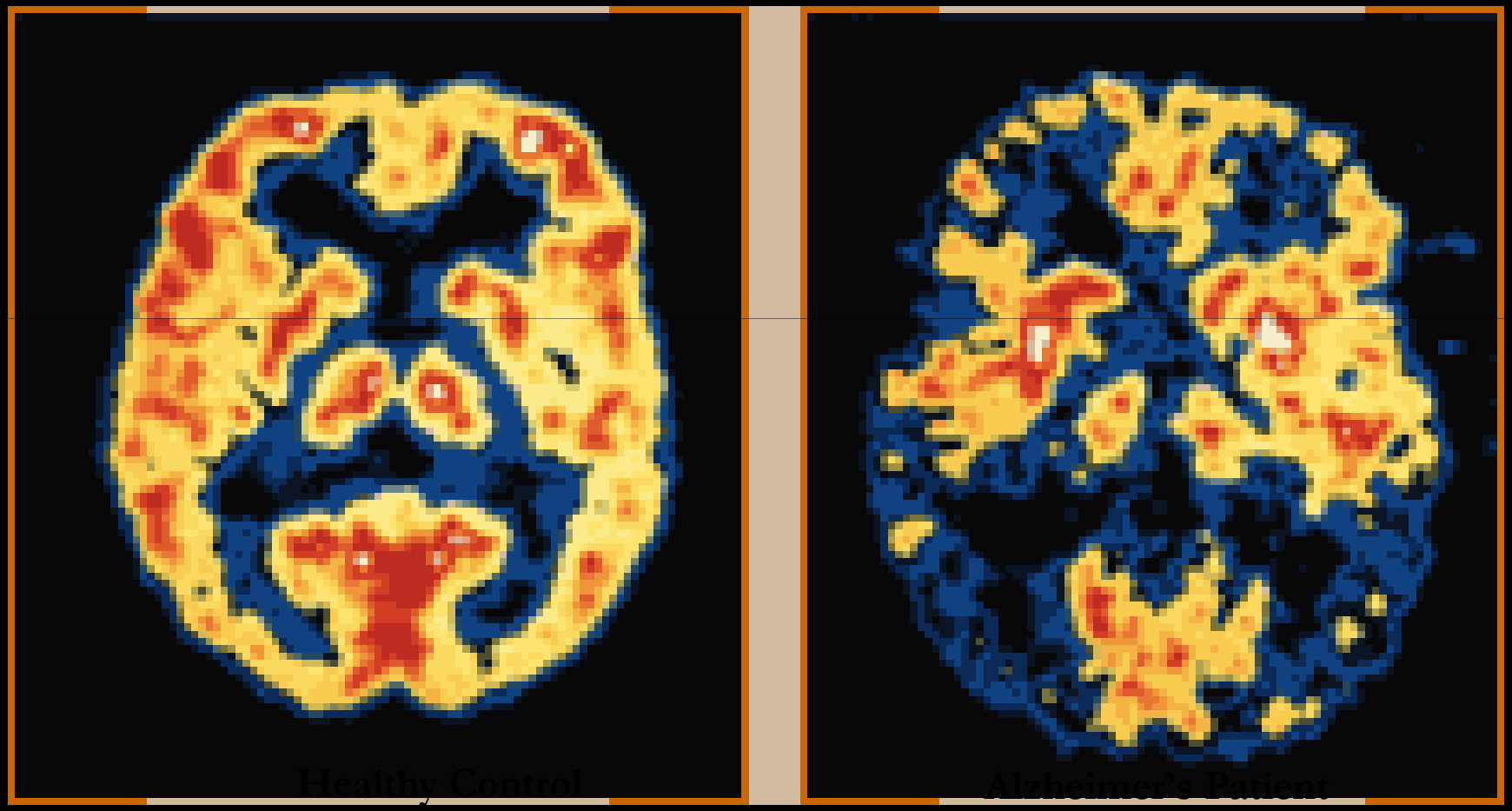
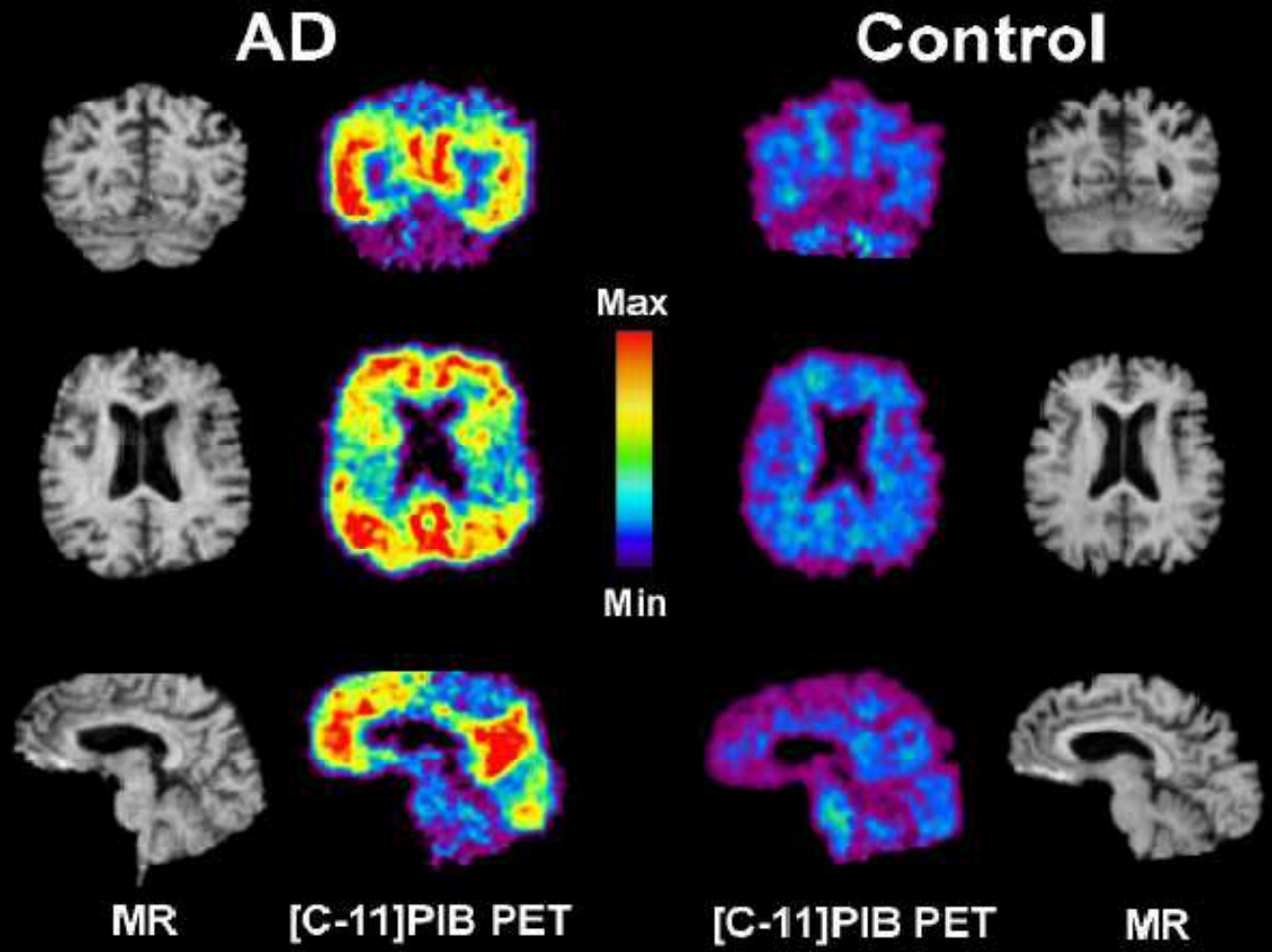
Positron Emission Tomography
Glucose metabolism deficits in Alzheimer's



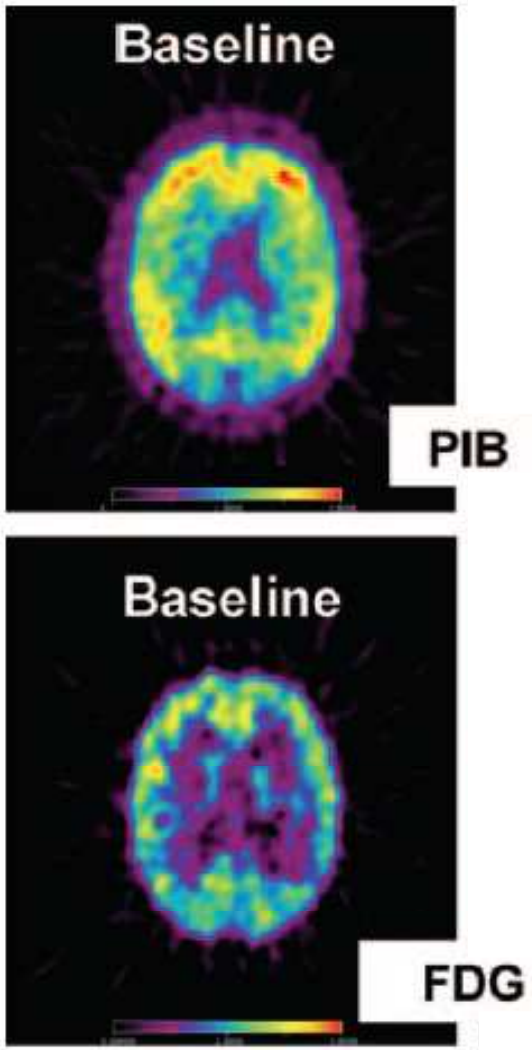


University of Pittsburgh
PET Amyloid Imaging Group

Klunk et al., Annals of Neurology 2004

AMYLOID IMAGING WITH [^{11}C] PIB

Little sensitivity to change



An AD patient showed deterioration in cognition after 2 years follow-up (7 points in MMSE). The images show only slightly increased PIB retention (upper) but a pronounced decrease in glucose uptake (lower).

Engler et al., Brain 2006;29:2856

AMYLOID IMAGING WITH C^{11} PIB

Little sensitivity to change

	Stable (<3 MMSE points)		Progressing (≥3 points)	
	AD-S (*n*= 10)		AD-P (*n*= 5)	
	Baseline	Follow-up (*P*-value)	Baseline	Follow-up (*P*-value)
Fr ctx	1.86 ± 0.74	1.90 ± 0.72 (0.346)	2.38 ± 0.35	2.32 ± 0.25 (0.684)
Par ctx	1.81 ± 0.55	1.85 ± 0.55 (0.344)	2.21 ± 0.27	2.18 ± 0.26 (0.790)
Temp ctx	1.51 ± 0.55	1.52 ± 0.37 (0.740)	1.82 ± 0.22	1.78 ± 0.19 (0.737)
Cing post	1.84 ± 0.65*	1.88 ± 0.63 (0.480)	2.43 ± 0.33*	2.29 ± 0.32 (0.441)
Occ ctx	1.49 ± 0.41	1.54 ± 0.45 (0.291)	1.89 ± 0.33	2.02 ± 0.39 (0.057)
Striatum	1.97 ± 0.69	1.92 ± 0.69 (0.292)	2.23 ± 0.30	2.35 ± 0.34 (0.271)
Pons	1.81 ± 0.24	1.83 ± 0.32 (0.828)	1.64 ± 0.22	1.65 ± 0.22 (0.940)
SWM	1.73 ± 0.31	1.69 ± 0.26 (0.642)	1.72 ± 0.29	1.71 ± 0.21 (0.923)
Cb ctx	1.09 ± 0.08	1.07 ± 0.12 (0.668)	1.06 ± 0.08	1.08 ± 0.08 (0.051)

Follow up of 2.0+0.5 years

Engler et al., Brain 2006;29:2856

METABOLIC IMAGING WITH FDG PET

Good sensitivity to change

	AD-stable (AD-S) $n = 9$		AD-progressive (AD-P) $n = 4$	
	Baseline	Follow-up (*P*-value)	Baseline	Follow-up (*P*-value)
Cing post dx	38.29 ± 9.50	31.30 ± 10.27 (**0.0145**)	24.29 ± 4.56**	19.44 ± 3.42** (**0.0448**)
Cing post sin	40.05 ± 10.63	33.25 ± 9.27 (0.0556)	25.81 ± 2.70**	20.69 ± 3.10** (0.0564)
Fr ctx dx	37.75 ± 12.09	30.85 ± 7.32 (**0.0500**)	30.36 ± 4.78	23.91 ± 7.23 (0.0700)
Fr ctx sin	38.42 ± 9.30	33.18 ± 4.25 (0.0614	31.67 ± 2.11*	24.02 ± 6.87 (0.0592)
Par ctx dx	35.31 ± 6.43	29.26 ± 8.22 (**0.0486**)	22.90 ± 7.38*	17.61 ± 3.09** (0.0964)
Par ctx sin	36.65 ± 6.48	30.65 ± 7.66 (**0.0430**)	26.96 ± 4.36**	20.11 ± 1.83** (0.0964)
Par temp dx	32.81 ± 6.11	27.77 ± 8.75 (0.0720)	25.09 ± 3.54*	16.90 ± 2.81** (**0.0273**)
Par temp sin	35.08 ± 7.56	29.29 ± 8.71 (0.0503)	27.78 ± 2.06*	18.62 ± 4.12** (**0.0356**)
Caudate nucleus dx	43.47 ± 9.59	37.36 ± 5.87 (0.1417)	37.25 ± 2.50	34.58 ± 7.34 (0.5180)
Caudate nucleus sin	43.92 ± 7.75	35.05 ± 7.69 (**0.0320**)	38.95 ± 2.66	31.41 ± 1.90 (**0.0342**)
Whole brain	35.42 ± 4.96	28.31 ± 5.01 (**0.0453**)	30.34 ± 3.04	24.85 ± 2.93 (**0.0400**)
Pons	24.63 ± 4.66	22.16 ± 3.90 (0.2138)	23.26 ± 2.30	23.41 ± 1.85 (0.9030)

Follow up of 2.0+0.5 years

Engler et al., Brain 2006;29:2856

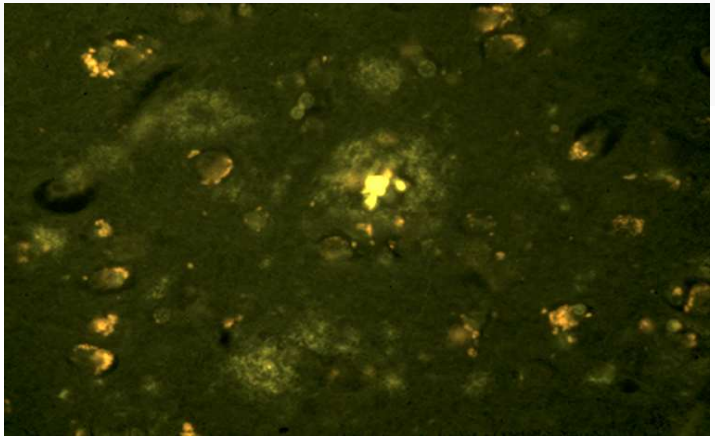
CONCLUSIONI

I modelli statistici attuali sono inadatti a descrivere i fenomeni neurobiologici delle malattie neurodegenerative

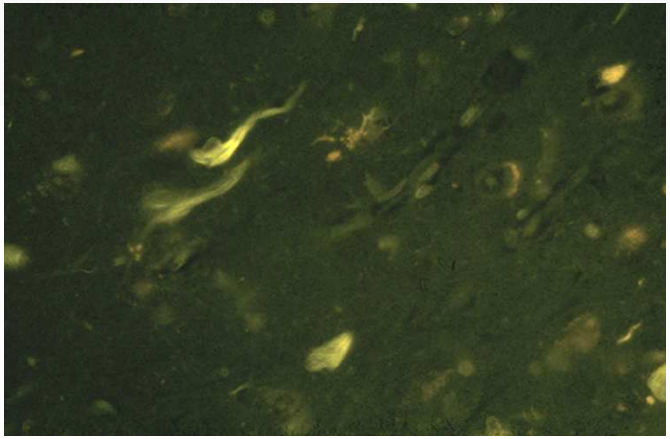
E' indispensabile sviluppare modelli in grado di accomodare:
- la specificità topografica delle relazioni temporali
- la multispettralità della neurobiologia cerebrale

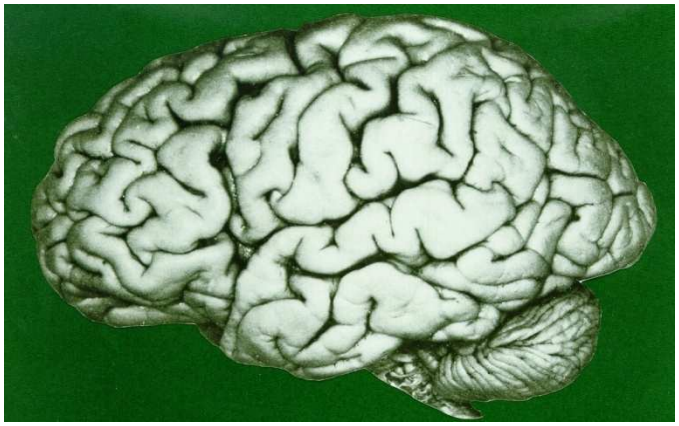
IL CERVELLO NELL'ALZHEIMER

Placche di amiloide

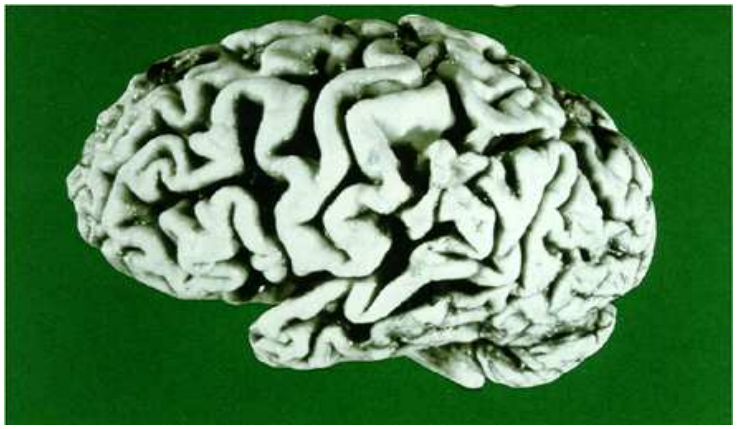


Gomitoli di tau HP



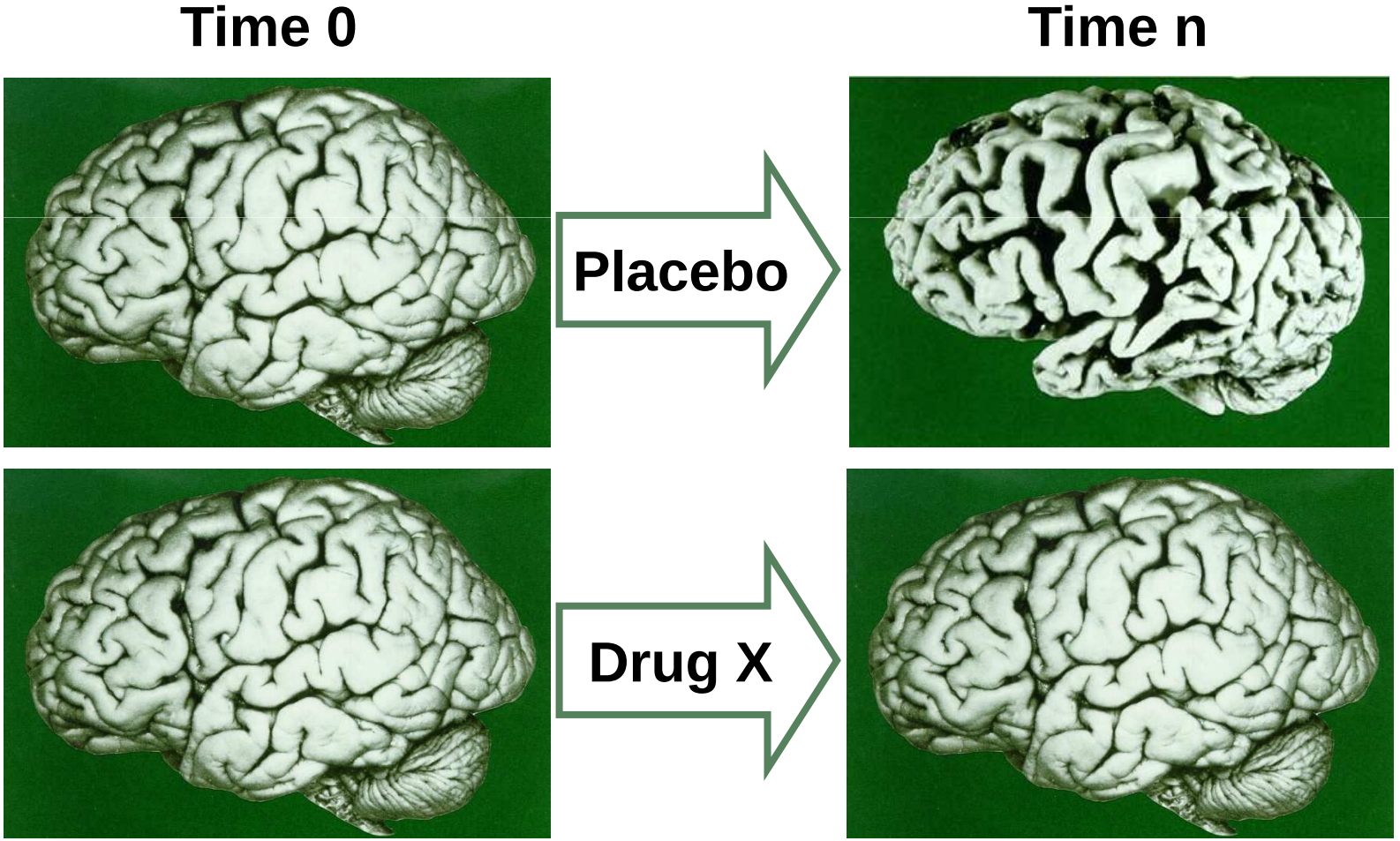


Cervello normale



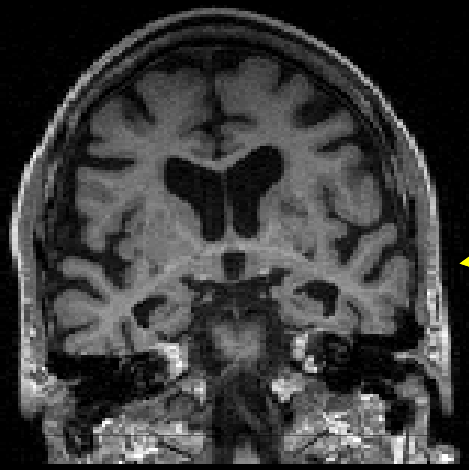
Cervello Alzheimer

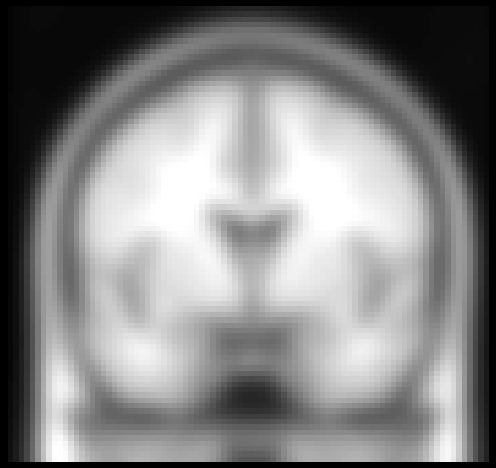
FACE VALIDITY OF PROGRESSION OF ATROPHY AS A DISEASE MARKER IN ALZHEIMER'S

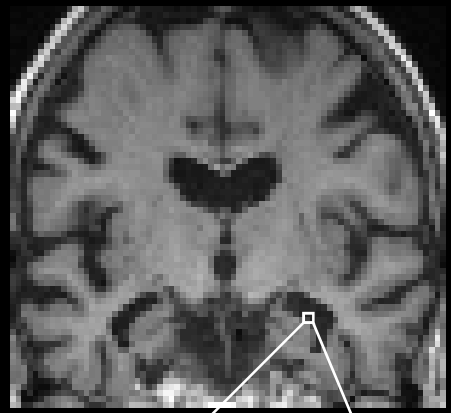


Template

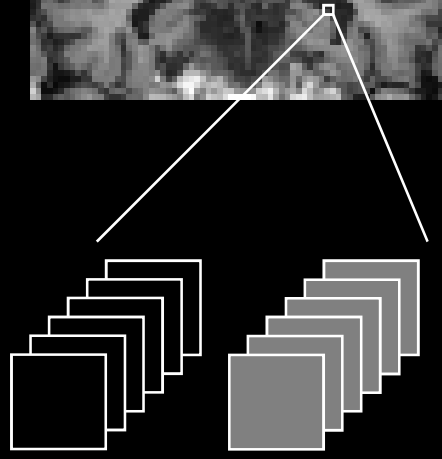
Image in stereotactic space

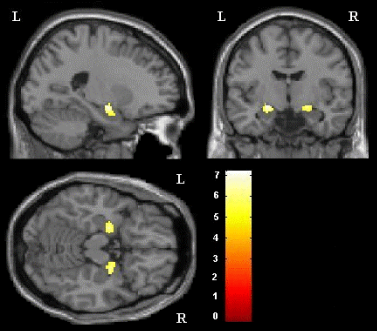


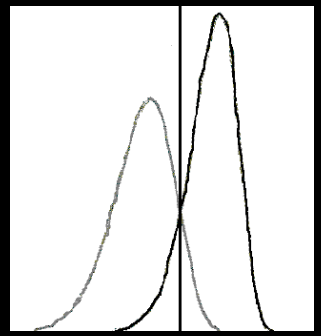




Patient's image







T-test

Change in brain volume over time in a woman with familial Alzheimer's disease (voxel-compression method)

(Fox et al, Lancet 2001)