The societal and scientific challenges of Alzheimer's disease

SCOR Foundation For Science, March 2023

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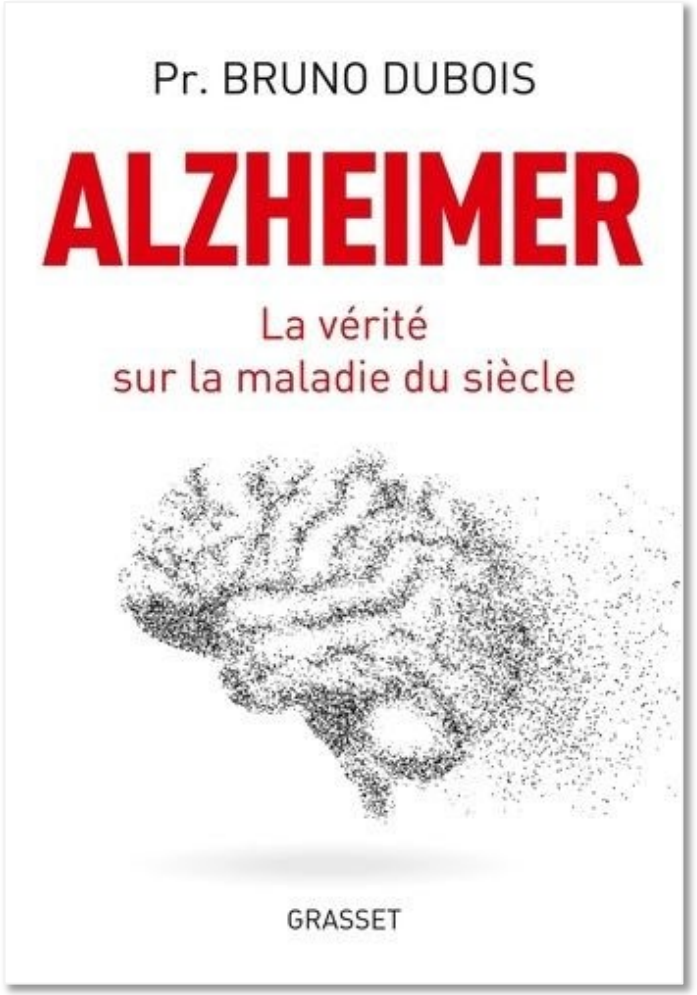
The disease of the century: Why?

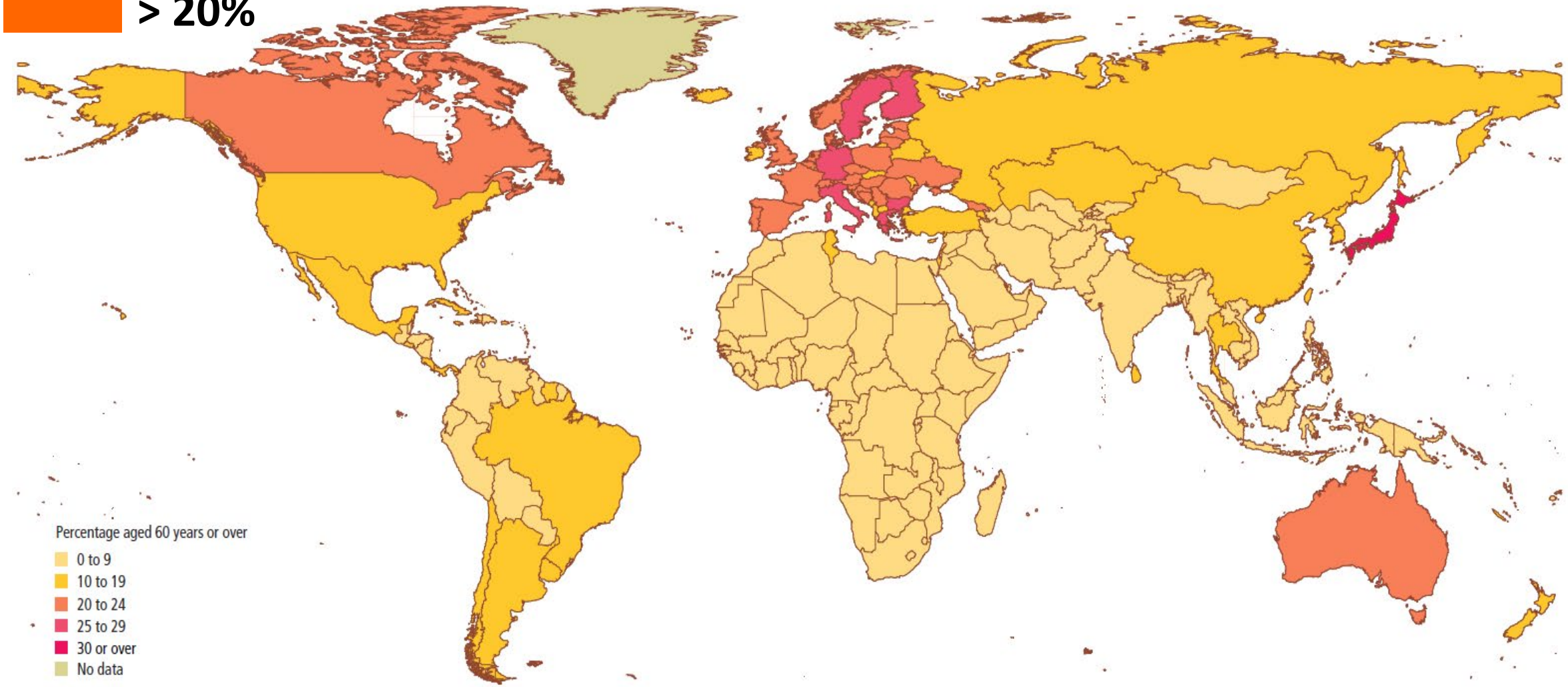


- a disease described in 1906 in the presenium and combined in 1976 with senile dementia
- a disease of the person, the family and the society
- whose frequency increases exponentially with age,
- which has become a public health issue in the last 20 years due to the aging of the population in developed countries

Percentage of population aged over 60

2012

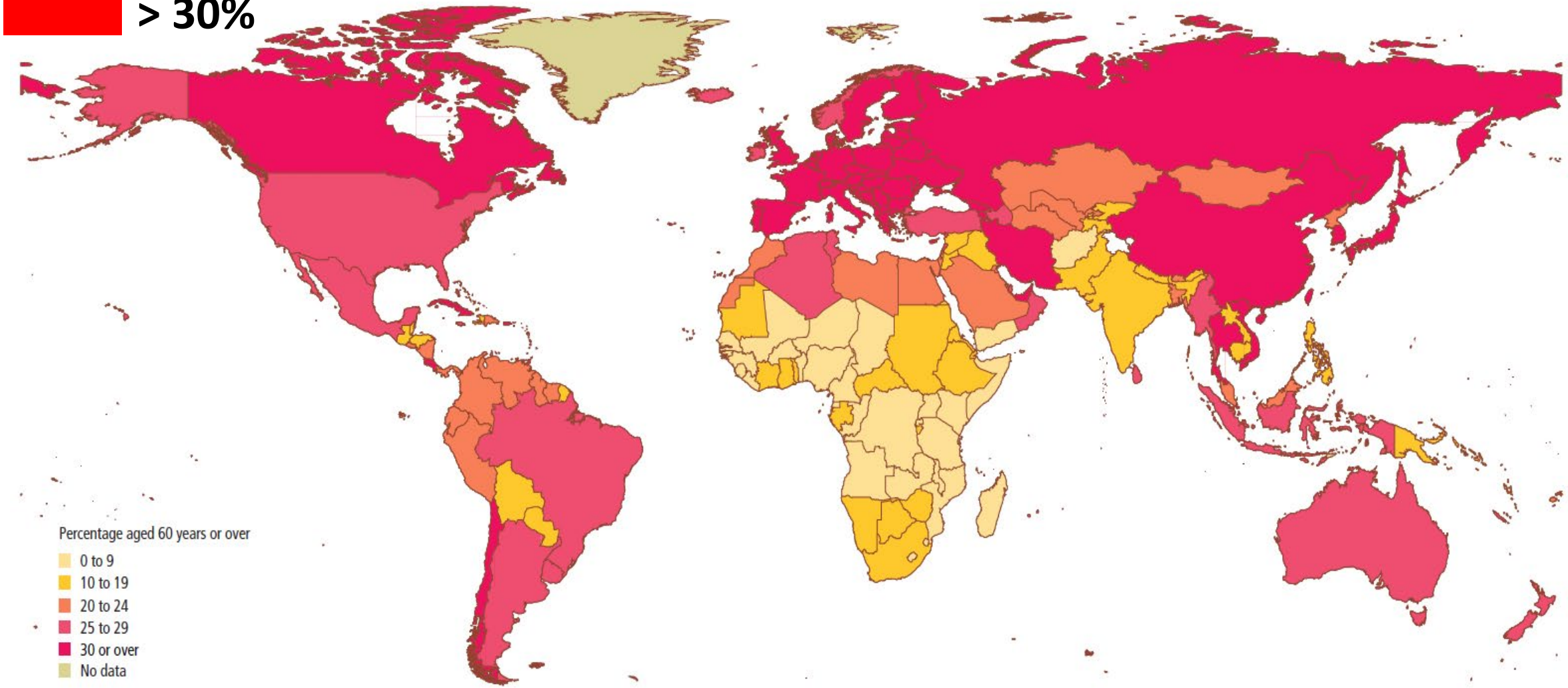
> 20%



Percentage of population aged over 60

2050

> 30%



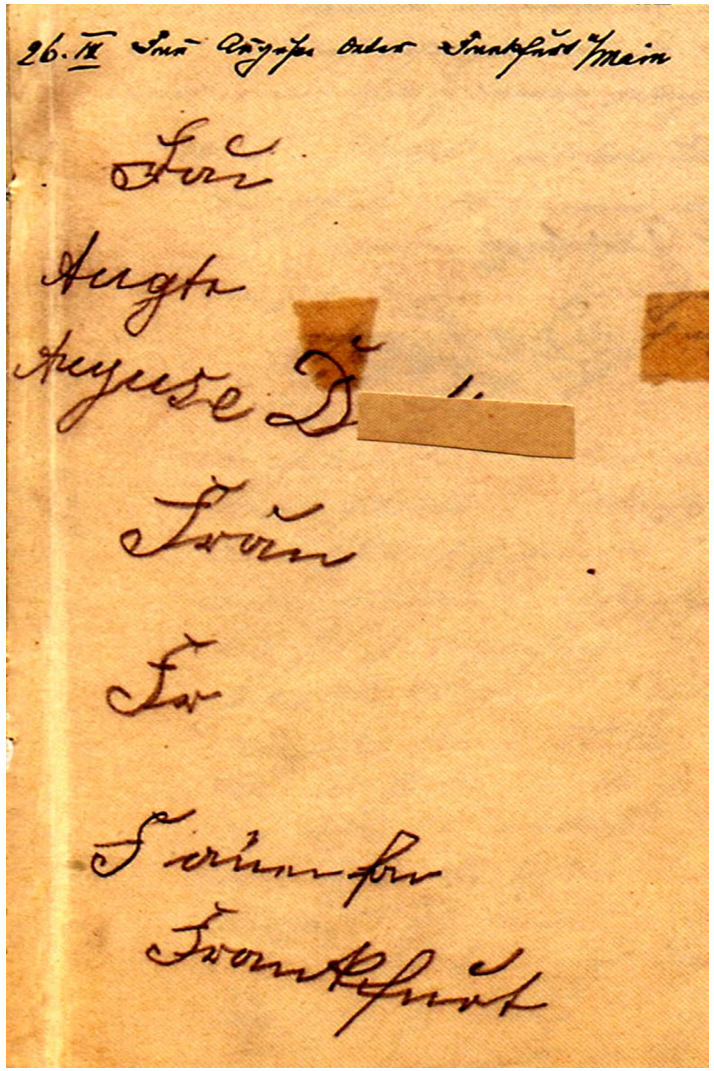
Alzheimer: a disease of the brain

A network of more than 100 Billions of neurons

Different modules involved in specific intellectual functions

Auguste D

Alzheimer's disease

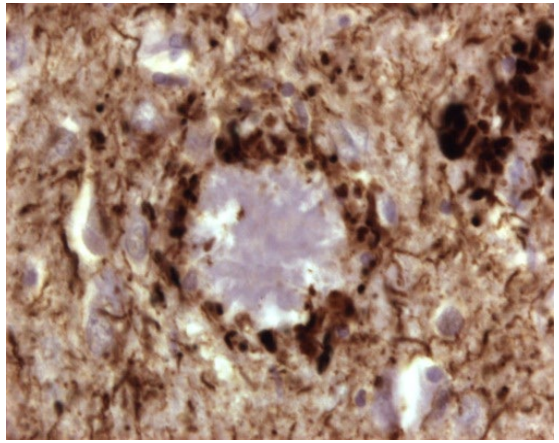


A. Alzheimer

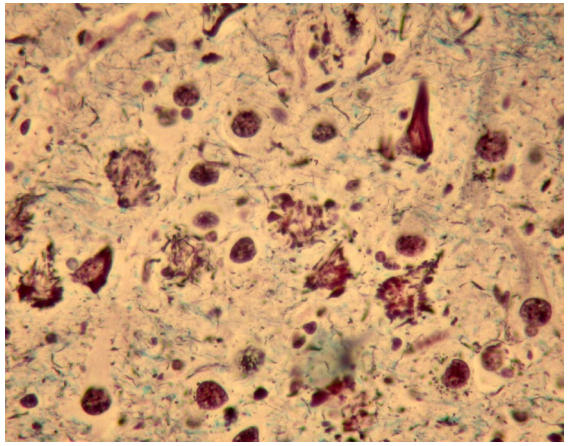
4 NOV 1906

Psychiatry Meeting (Tübingen)

- Memory disorders
- Disorientation
- Comprehension deficits
- Language disorders
- Behavioral changes
- agitation/agressivity
- Paranoïa
- Hallucinations



Amyloid plaques



TNFT (tau lesions)

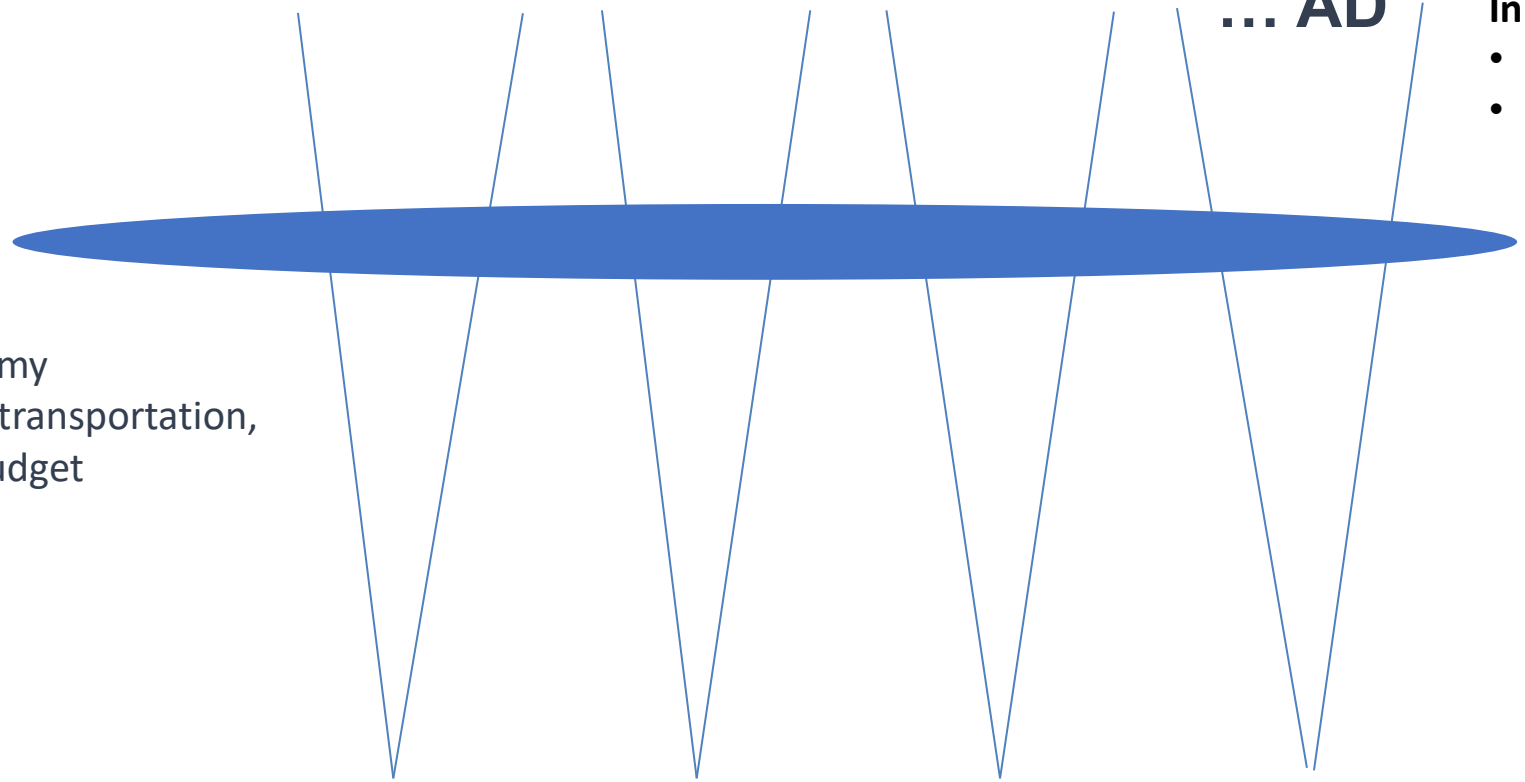
1984

1) The NINCDS-ADRDA Criteria : a 2-Step Process

→ Dementia of the Alzheimer type

… AD

In favor:
- Cognitive assessment
- MRI



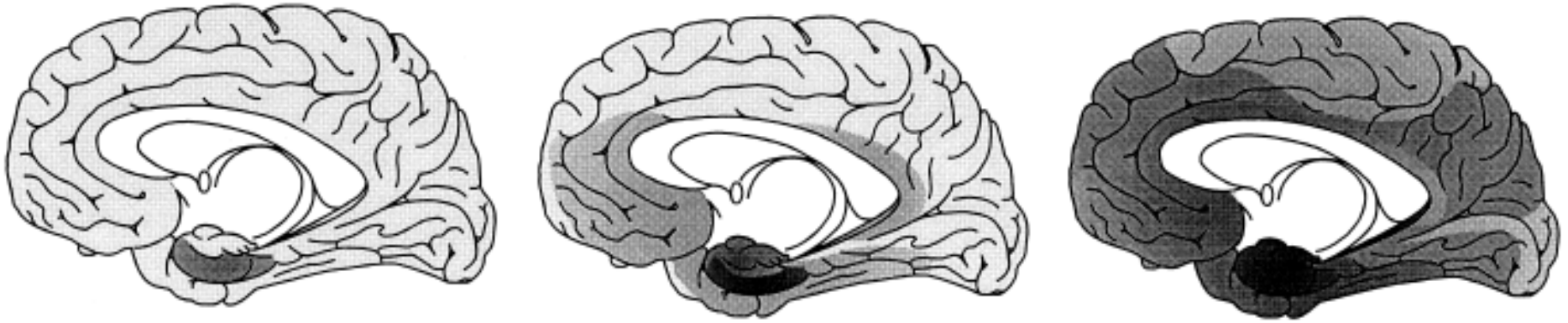
Threshold of dementia

In favor:
- Loss of autonomy
- Impaired ADL: transportation, phone, pills, budget

McKhann et al, 1984

2) AD is a rather homogeneous disease

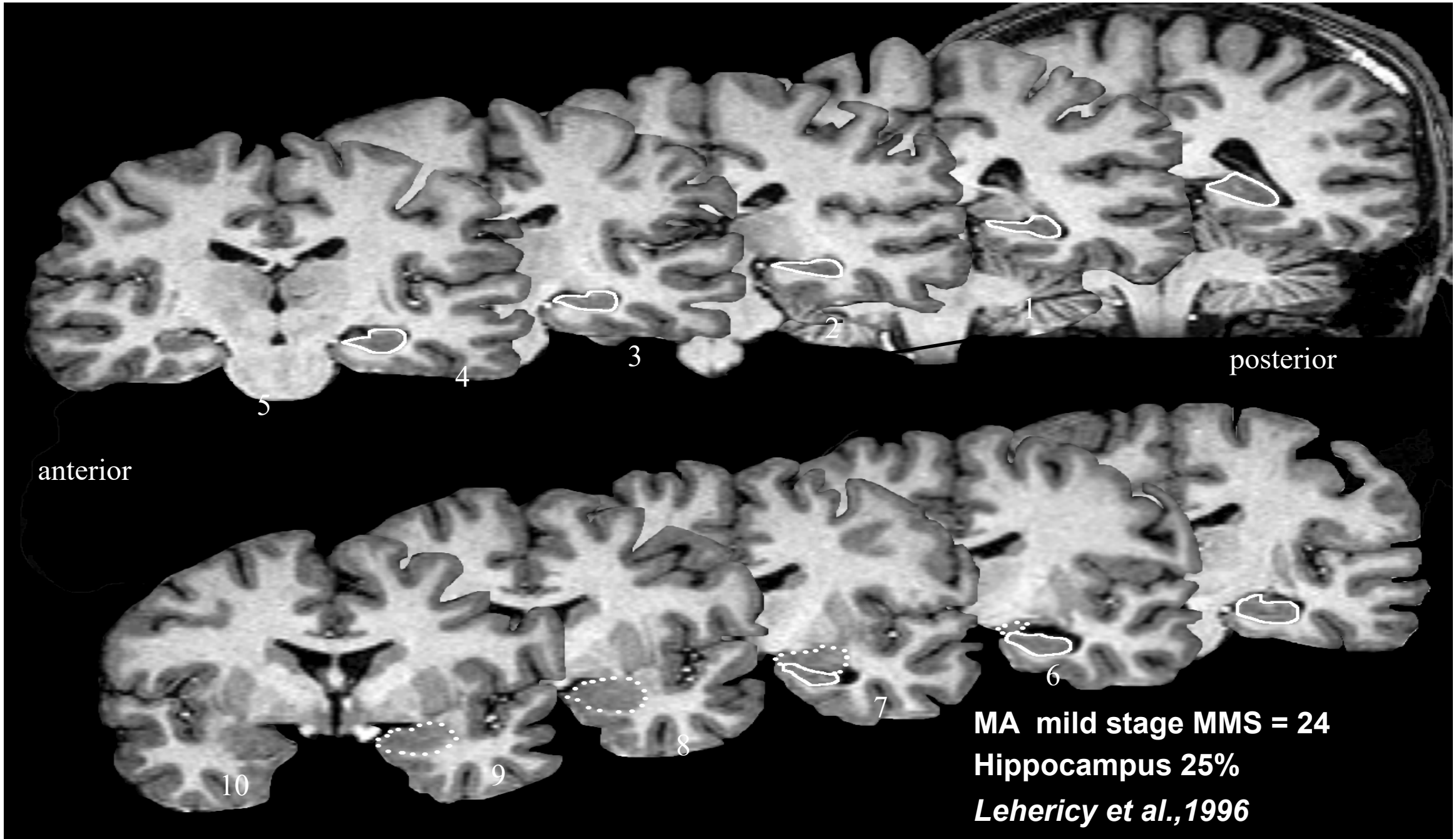
- Typical AD starts as a progressive amnesic disorder, in relation with an early involvement of the hippocampus
  = prodromal stage



Braak et Braak Neurobiol Aging 1997

- secondarily associated with other cognitive (language, gestures, orientation, visual recognition…) /behavioral (apathy, aggressivity…) changes in relation with the diffusion of lesions to neocortical areas
  = dementia stage

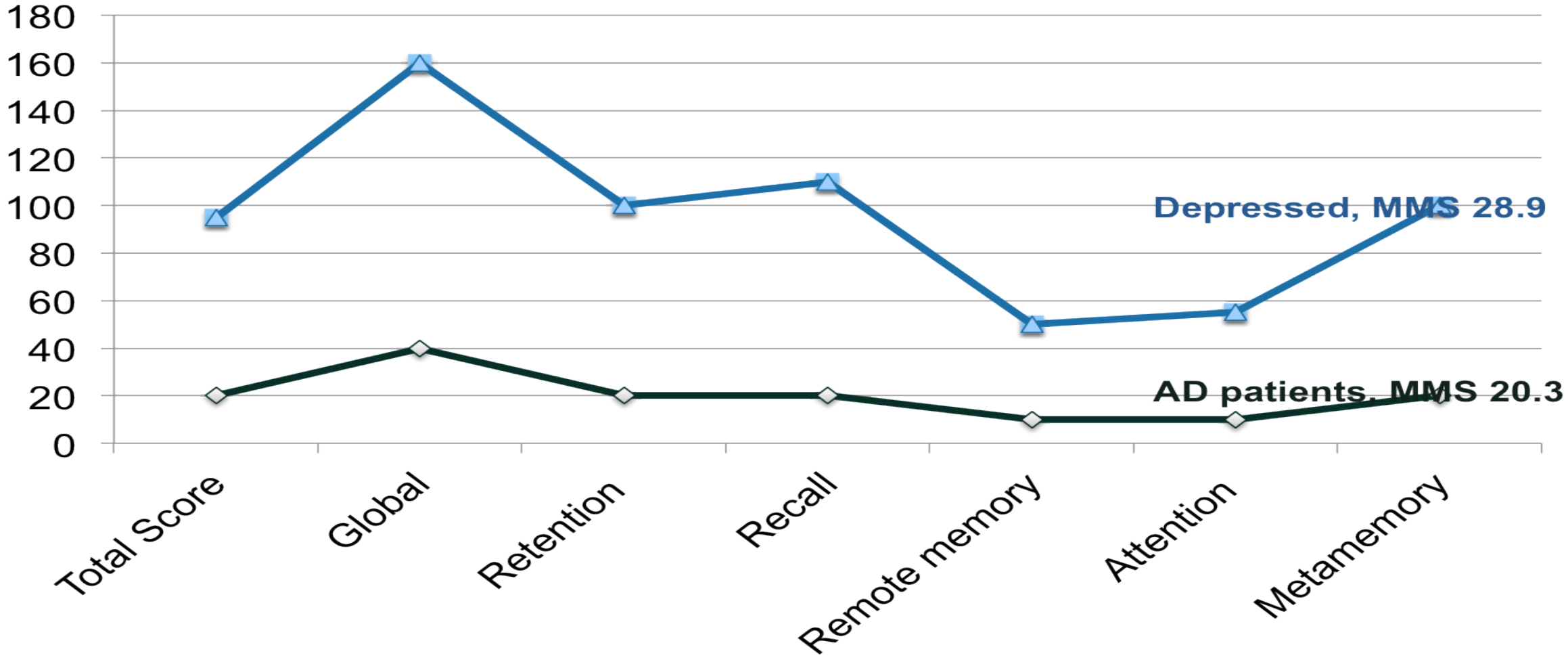
3) Early hippocampal atrophy



Memory complaints do not always mean AD

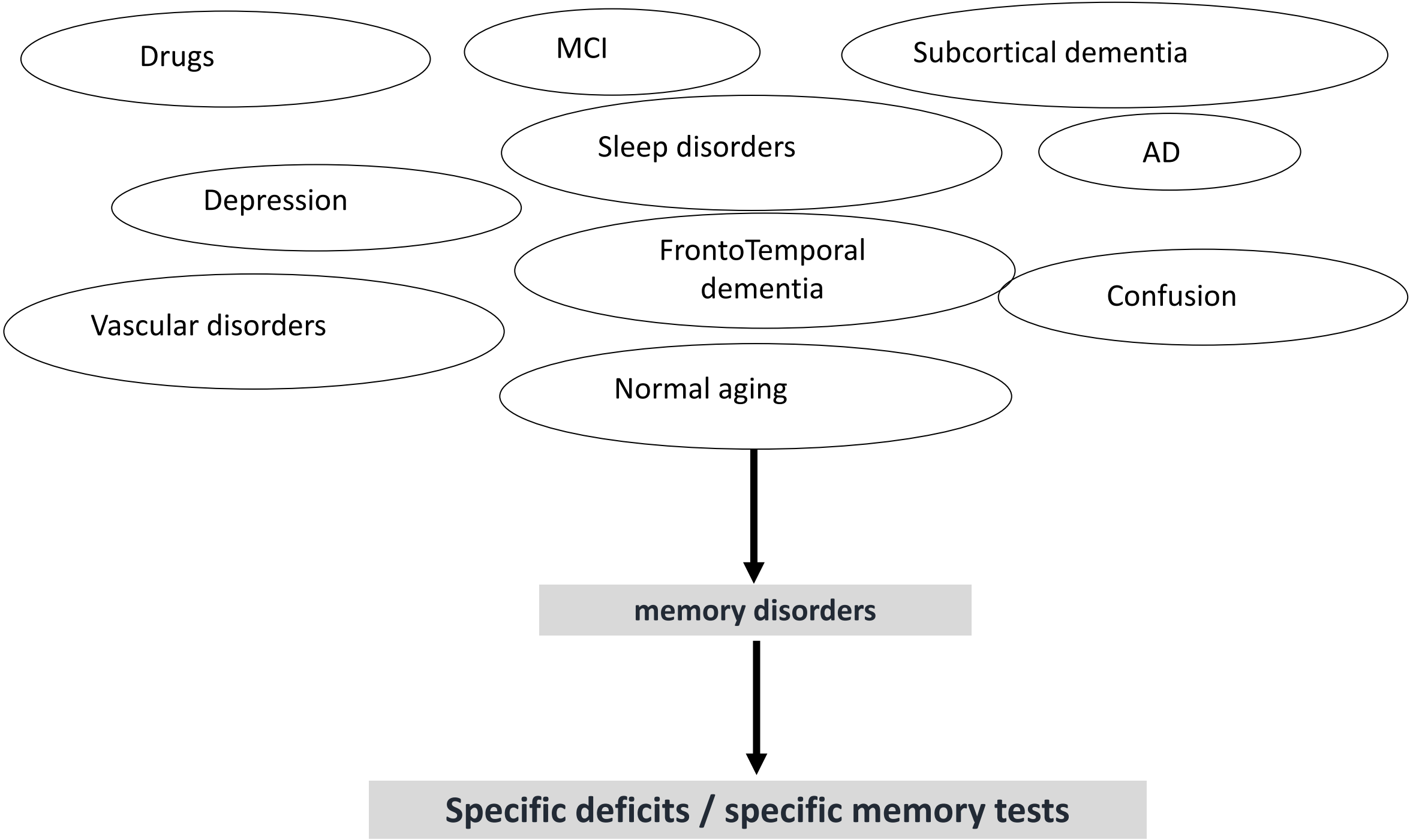
Self-rating of memory functions

Michon et al., 1994



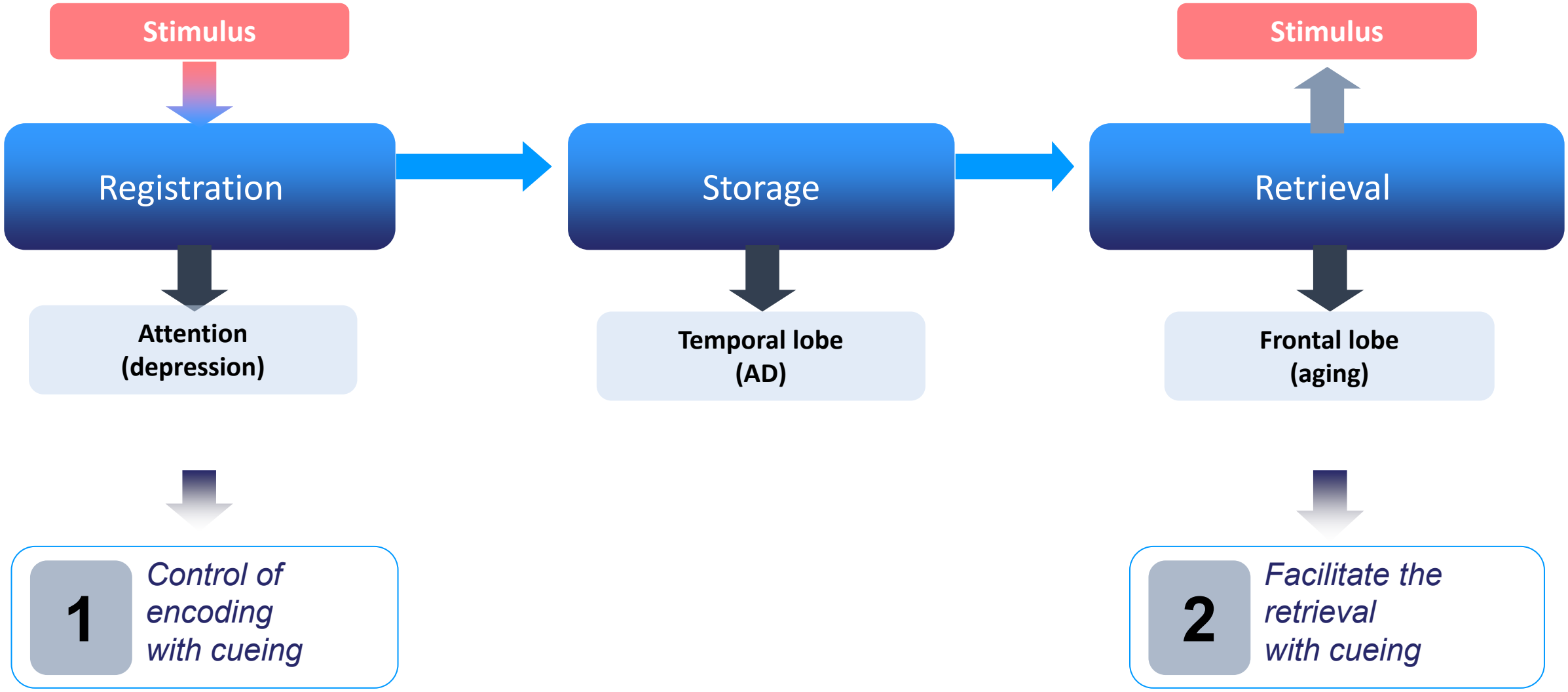
Memory complaints do not always mean AD

- memory complaints: a very **frequent** symptom in general population
- memory complaints: **not correlated** with performance in tests
- memory complaints: often result from **attention disorders**, as in:
  - depression
  - anxiety
  - professional stress
  - drugs
  - sleep disorders ans sleep apnea
  - normal aging
- memory complaints may also be related to a **neurodegenerative disease**


Drugs
MCI
Subcortical dementia
Sleep disorders
AD
Depression
FrontoTemporal dementia
Confusion
Vascular disorders
Normal aging
memory disorders
Specific deficits / specific memory tests

Distinguishing memory disorders from attention disorders

Dubois and Albert, Lancet Neurology, 2004



The specific pattern of AD memory disorders can be identified with cueing

- **Very poor free recall**

Cueing

- **total recall is not normalized**

= hippocampal involvement

(storage deficit)

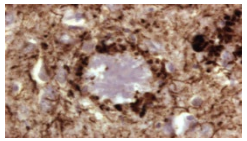
- **Very poor free recall**

- **total recall is normalized**

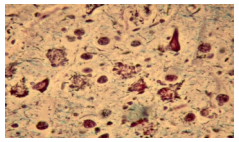
= no hippocampal involvement

(retrieval deficit)

4) Discovery of biomarkers of AD

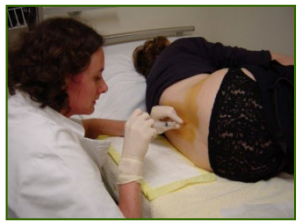


Amyloid plaques

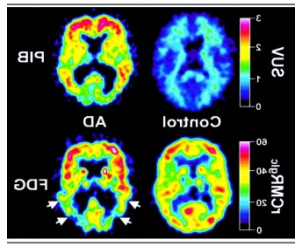


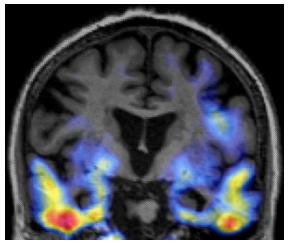
Tau protein

CSF:
- Abeta
- tau levels



Molecular N-I:
- amyloid-PET
- tau-PET

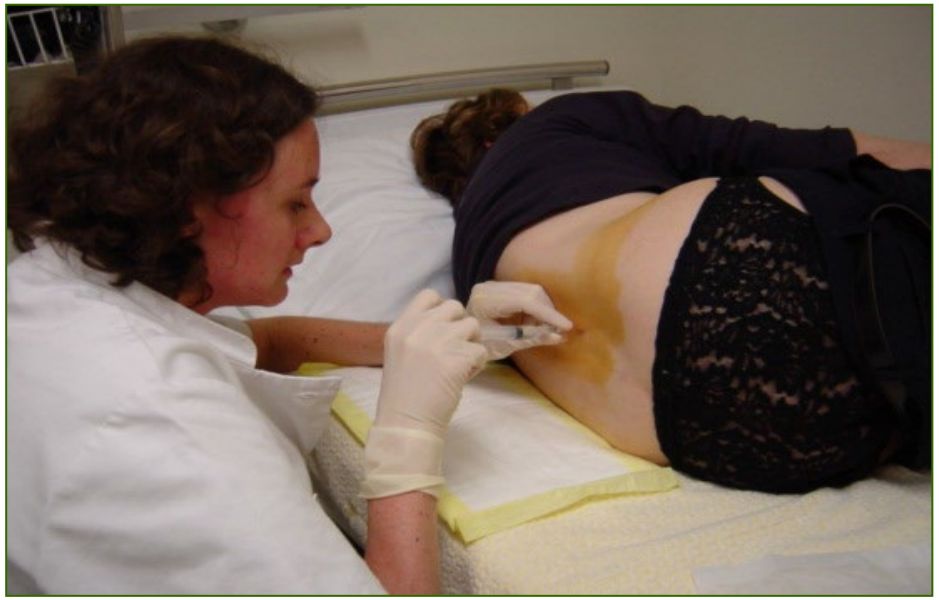




Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

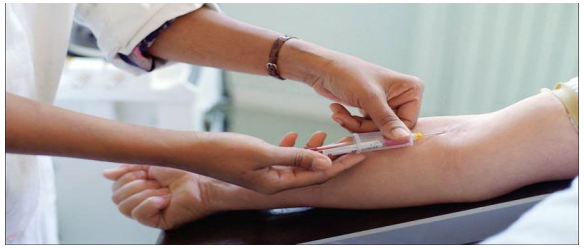
Bruno Dubois, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens*

Biological signature in the CSF



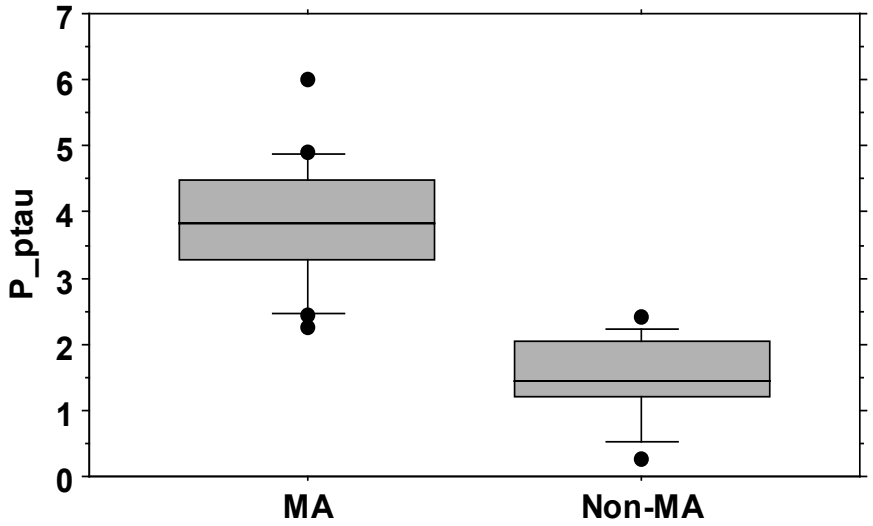
Decrease A beta
Increase Tau et P-Tau
(invasive)

Soon in the blood ?



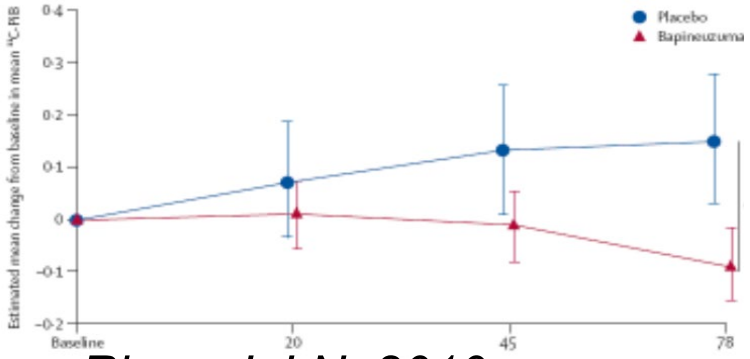
Plasma biomarkers:

- 20 X lower concentrations
- Need for ultra-sensitive technologies:
  - Mass spectrometry
  - Elisa digital (Simoa-Quanterix)
  - Immunomagnetic reduction



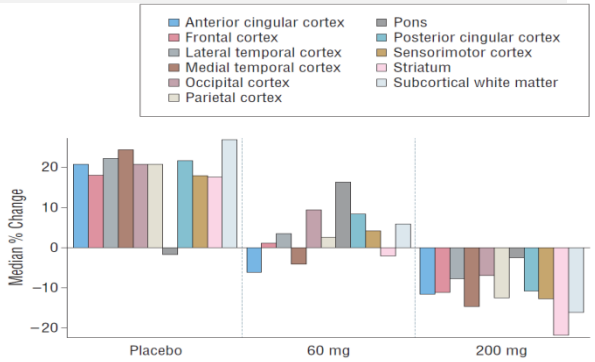
5) DM drugs are active on the brain amyloid load

Bapineuzumab



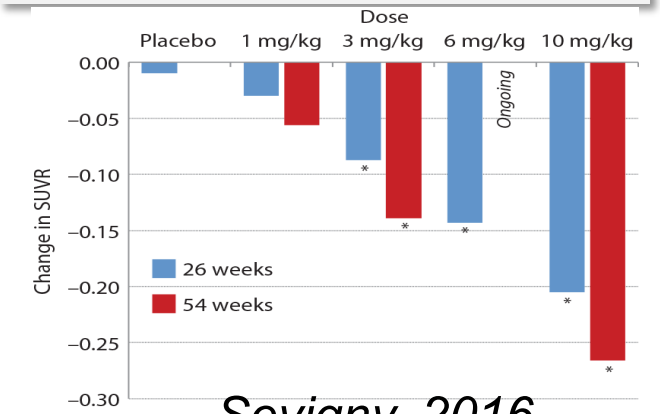
Rinne J. LN, 2010

Gantenerumab



Ostrowitzki, 2012

Aducanumab



Sevigny, 2016

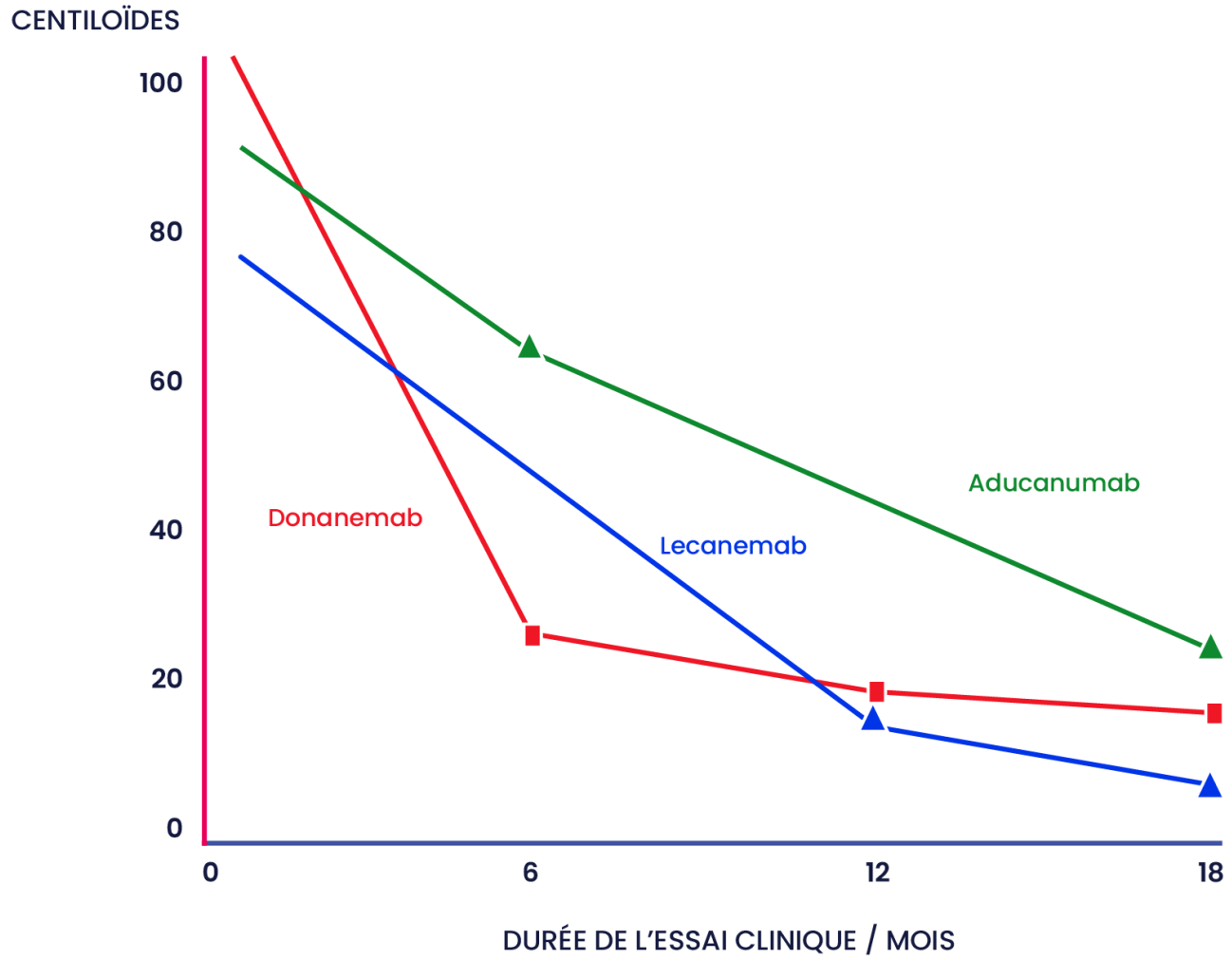
…not on symptoms in demented patients!

The conceptual shift

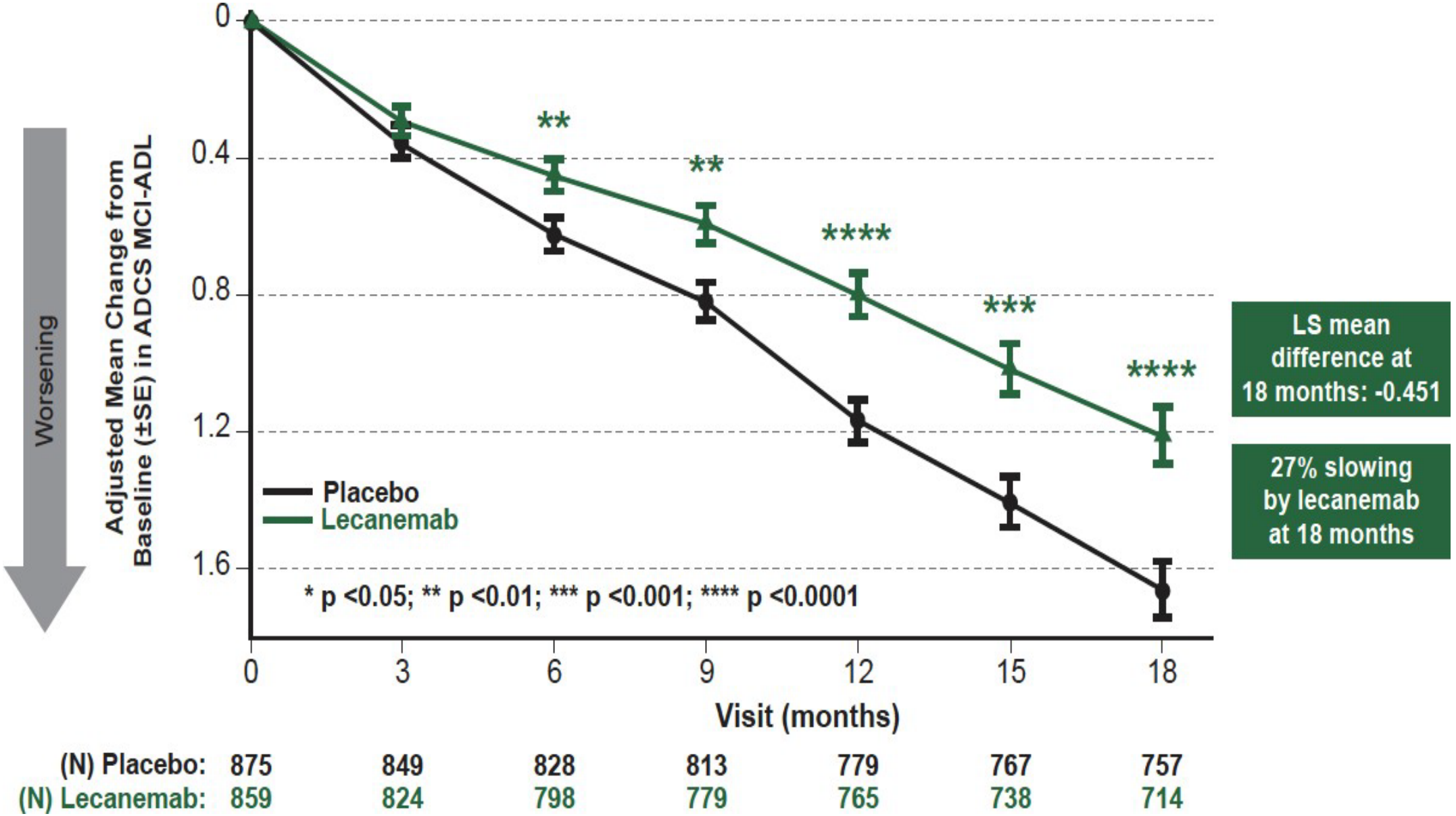
To treat as early as possible…

To treat at a preclinical stage of the disease…

DMTs clear brain amyloid plaques



Slowing down disease progression with Lecanemab



(N) Placebo:	875	849	828	813	779	767	757
(N) Lecanemab:	859	824	798	779	765	738	714

6) Identification of AD patients at early stages

- By introducing the concept of prodromal AD and preclinical AD
- By introducing the concept of « amnestic syndrome of hippocampal type »
- By proposing the 5W test
- By developing a digital application for screening memory in real life
- By including biomarkers in the definition/diagnosis of the disease

The « 5-Word » test

- a 2 mn test
- with 2 stages :
  - learning phase : learning score (/ 5)
  - memory assessment : memory score (/ 5)

Museum

Lemonade

Grashopper

Sieve

Lorry

Sensitivity and specificity

	« 5 word » score	
	<10	=10
AD (n=86)	78	8
« functional » (n=126)	16	110

Sensitivity = 91 %

Specificity = 87 %

Dubois B et al, NPM, 2002

Development of a digital tool for testing cognition at distance

- Elaboration of « santé-cerveau » by Mindmaze
- Available on Tablet or computer
- CE certification, using a secure Web platform (www.curapy.com)
- Consisting of:
  - Short questionnaires
    - Memory complaints
    - Mood
  - 3 short tests:
    - Episodic memory: 5Word Test
    - Tail Making Test A&B
    - DSST

Validation Study

- **64 patients:**
  - 49 with AD : Prodromal 24 and Mild AD 25
  - 15 with other degenerative diseases

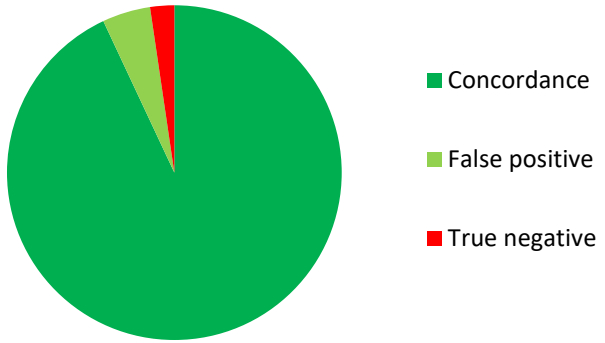
- **65 cognitively normal controls :**
  - with no complain (31)
  - with memory complain and BM(-) (32)
  - with memory complain and biomarkers (+) (2)

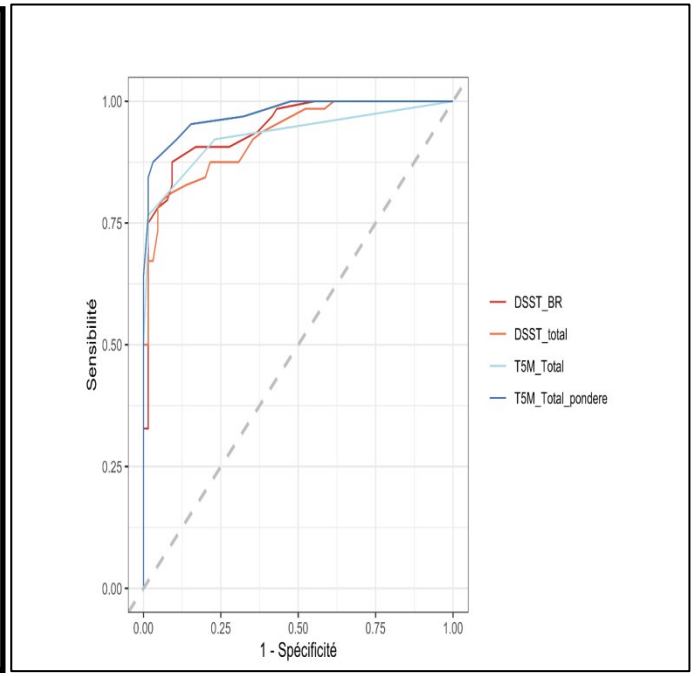
- **All 129 subjects underwent both the Digital tool and a comprehensive neuropsychological battery at the IM2A**

Results

Diagnostic concordance

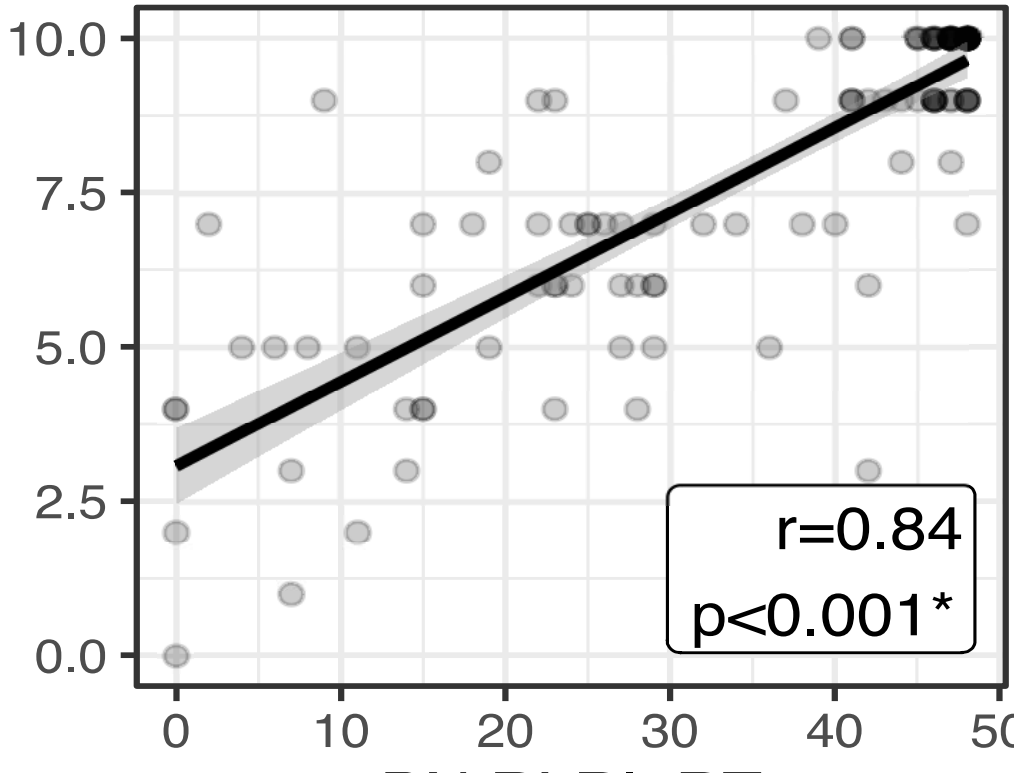
Sensibilité	95,3%
Spécificité	90,8%
VPP	91,0%
VPN	95,2%





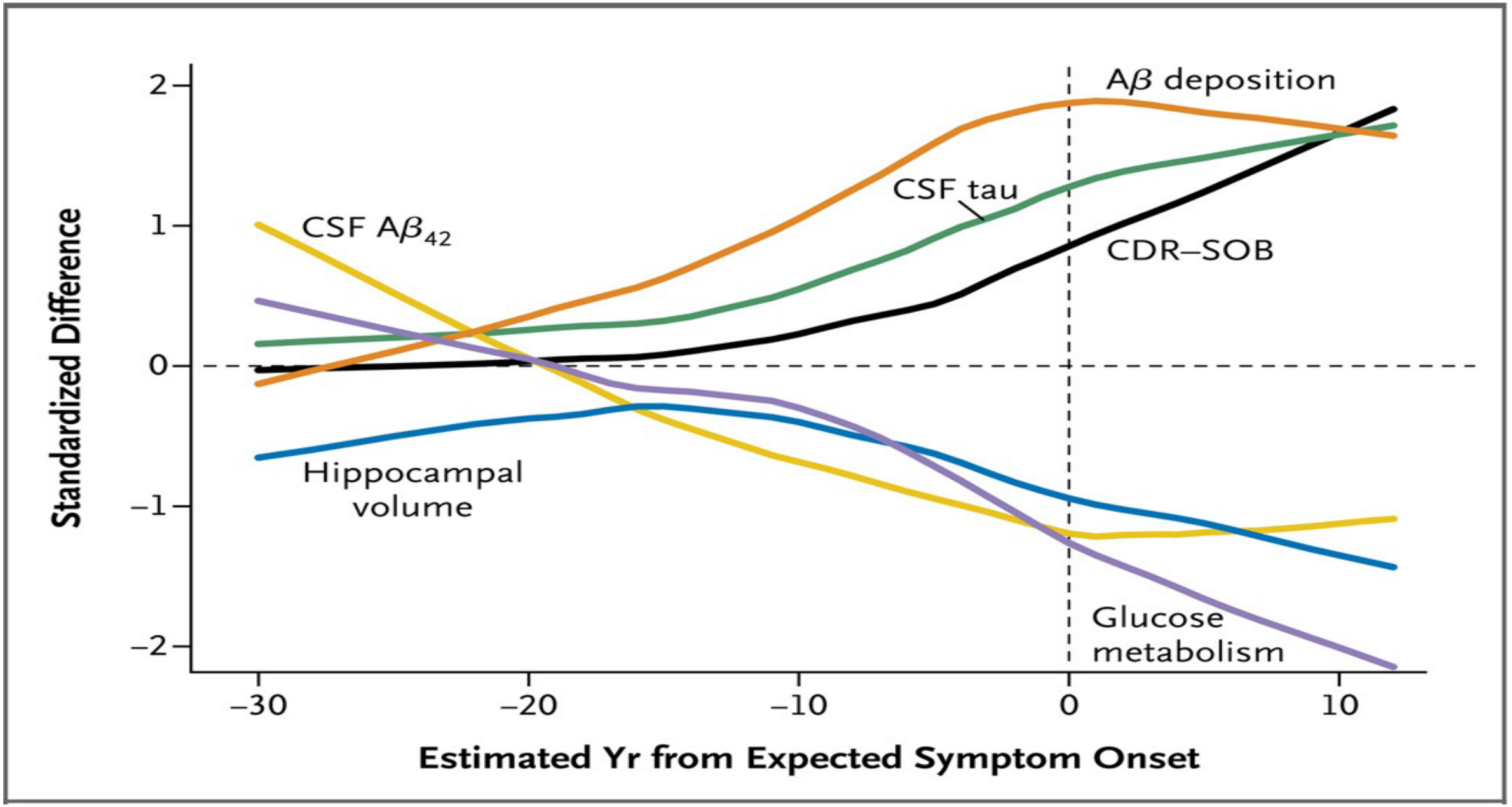
Correlations

5 Word Test / FCSRT

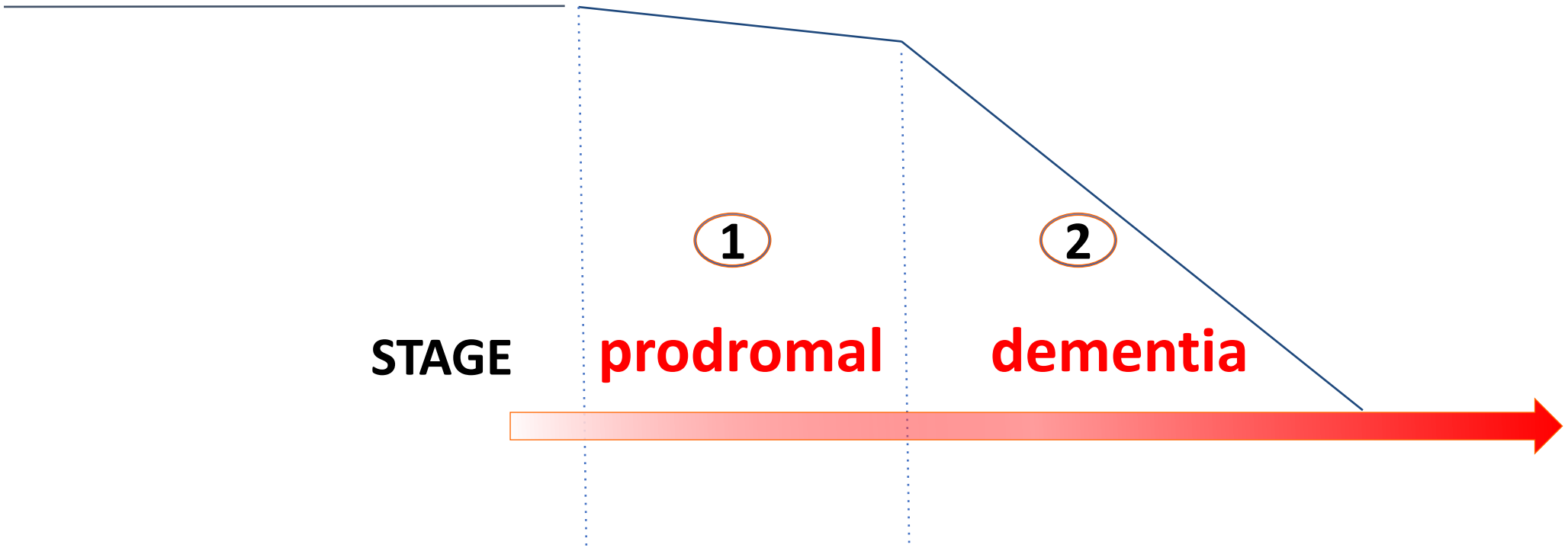


…And in the future?

AD lesions precede the clinical symptoms



The Continuum of AD



The Continuum of AD: the concept of preclinical stage

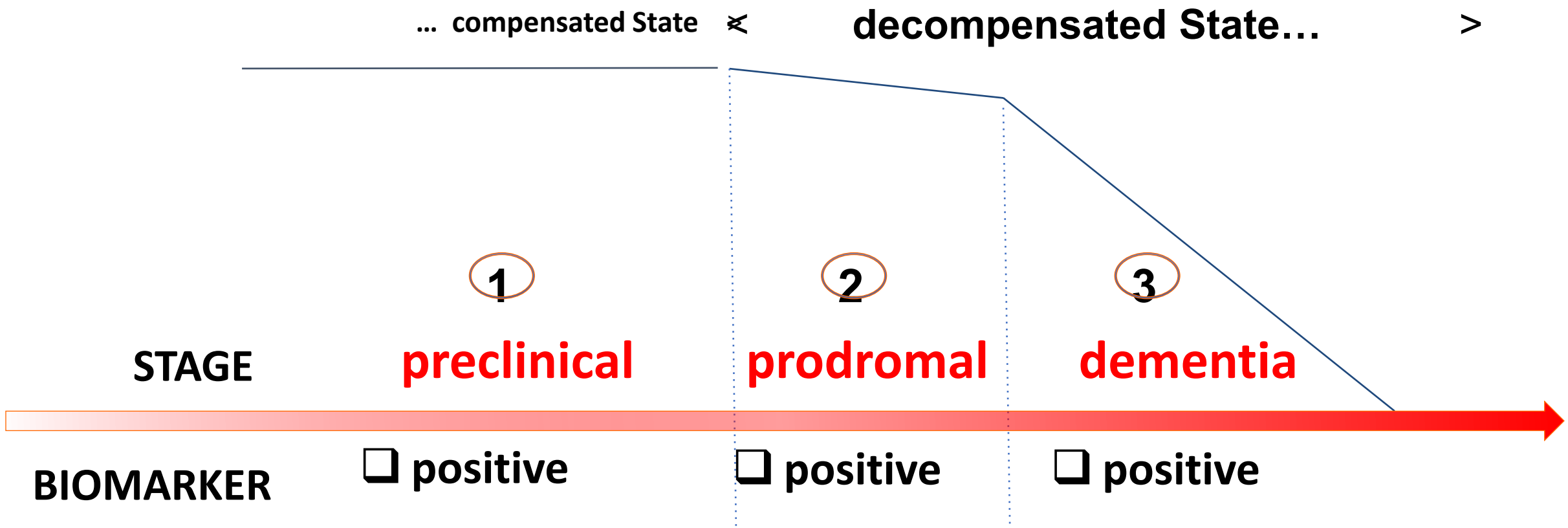
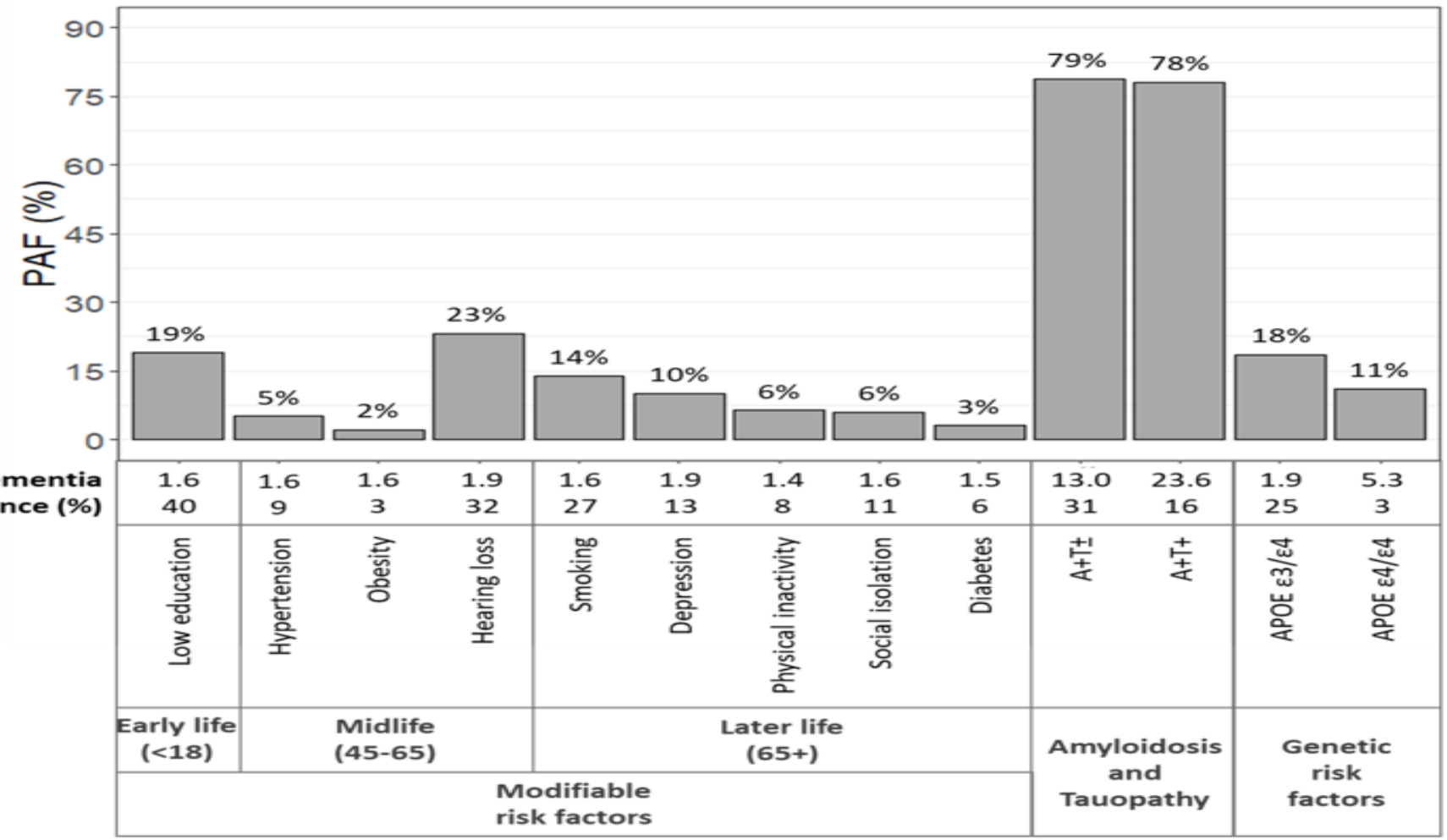
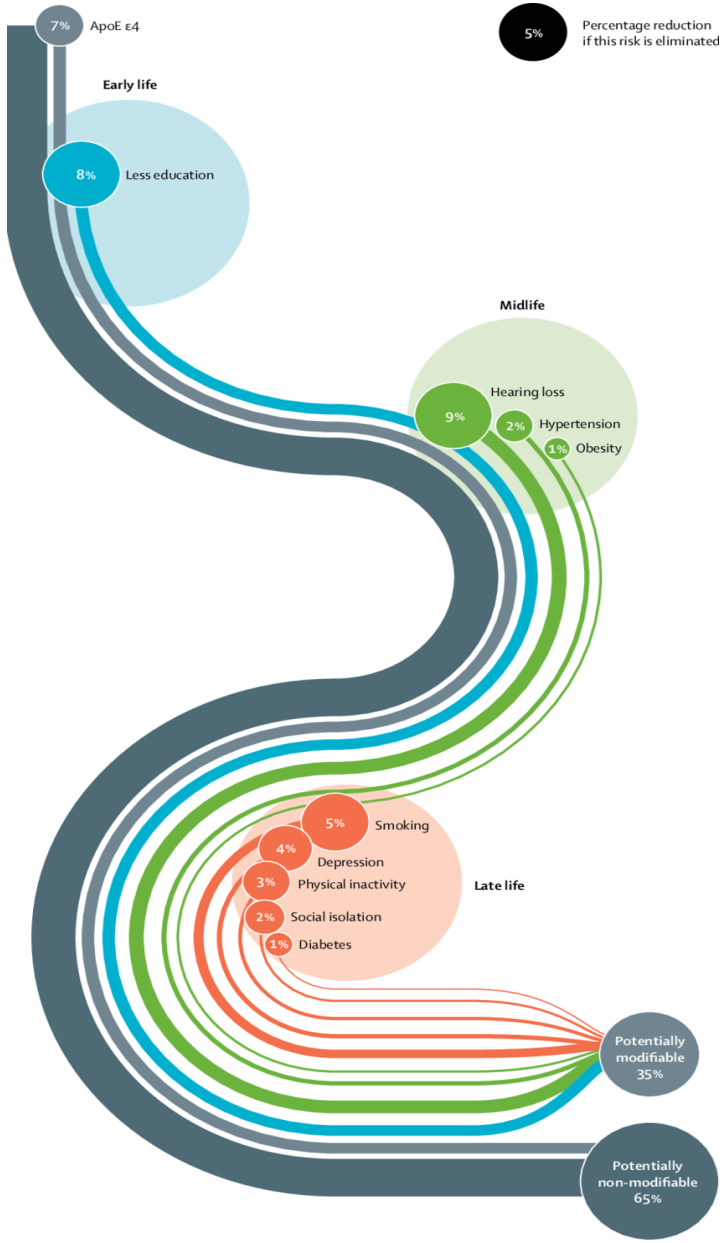


Figure 2. Risk factors for dementia and Alzheimer's disease and their corresponding population attributable fraction (PAF, the proportion of cases that might be spared by full control of the risk factor). PAF figures are unadjusted for communality (the variance in observed variables accounted for by common factors) for a fair comparison among risk factors based on available literature data.

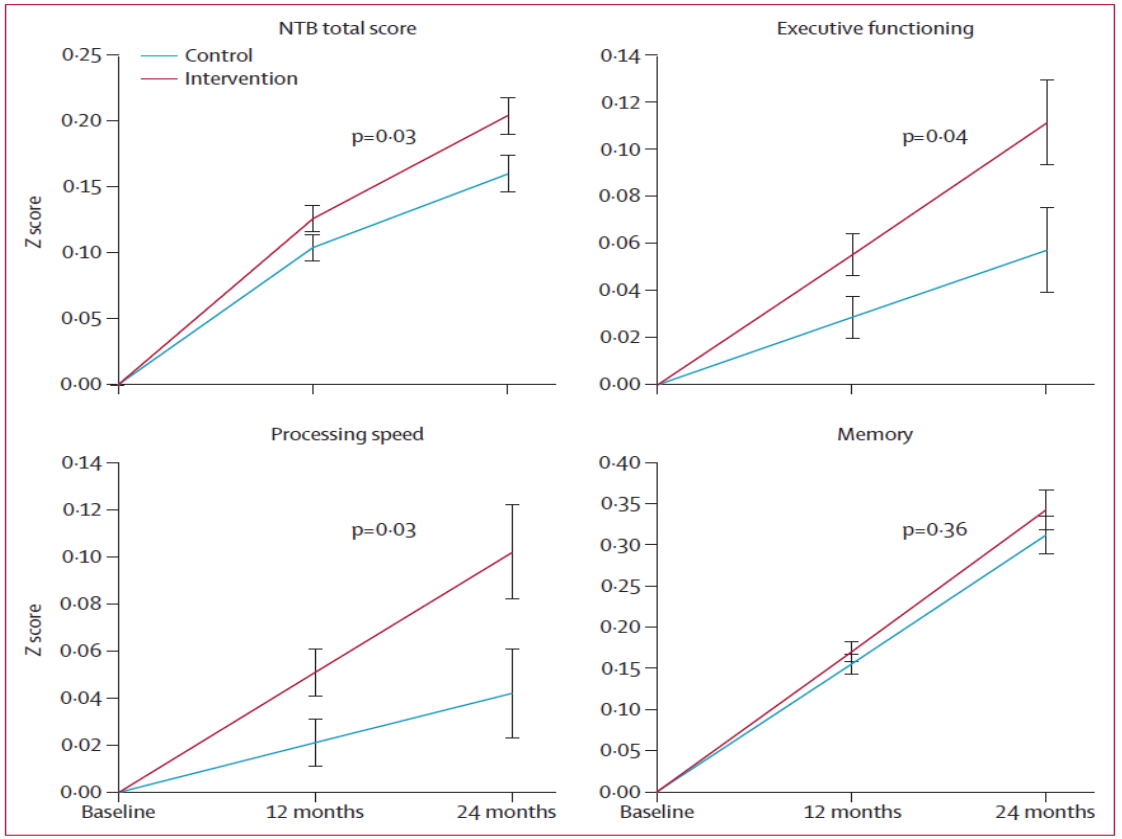


Risk factors of dementia



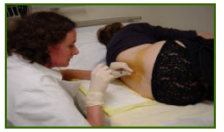
Prevention is possible

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

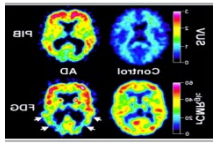


Prevention centers for Cognitive Decline

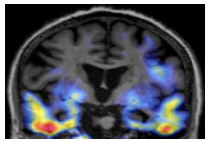
- Public Health problem: 2M; 130M en 2050
- Diagnostic markers
- Prevention possible

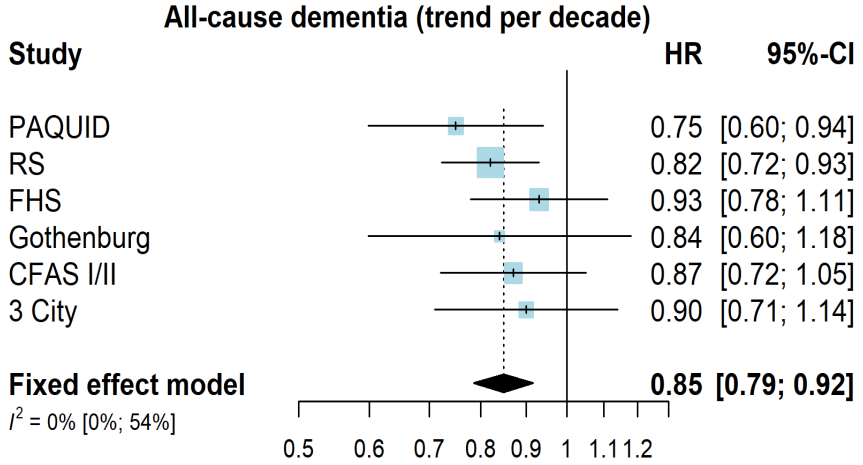


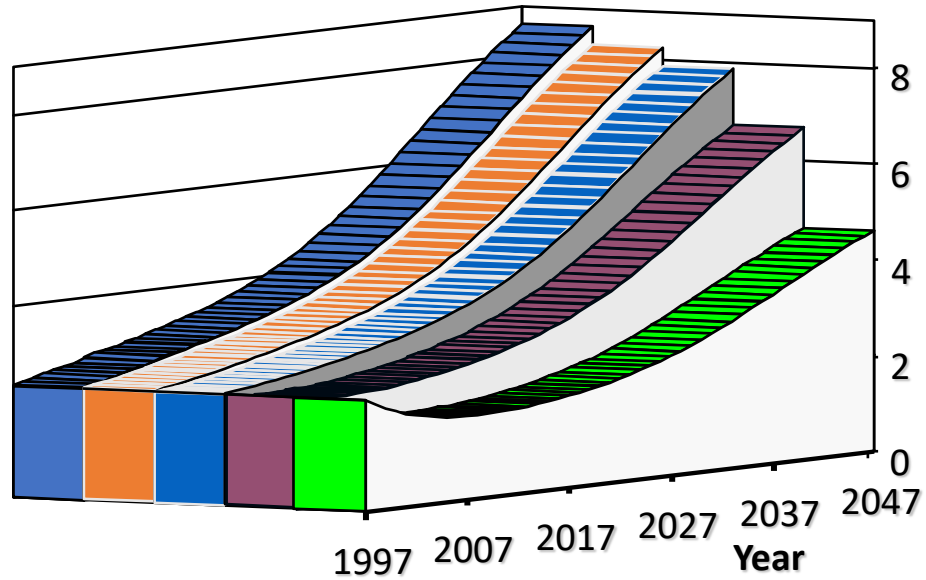
CSF: -
Abeta -
tau levels



Molecular N-I
- amyloid-PET
- tau-PET







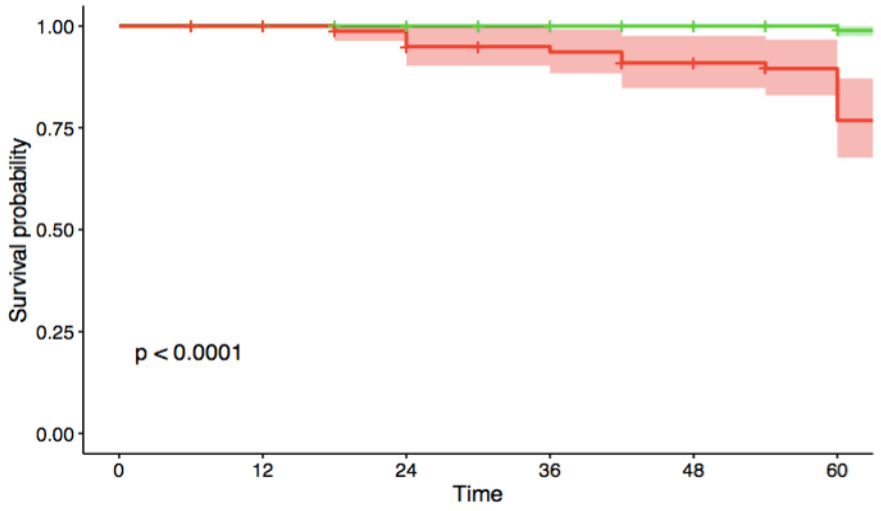
Delaying dementia by 5 years would reduce projected health care costs related to AD by nearly 50%

- DMTs

Cognitive and neuroimaging features and brain β-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study

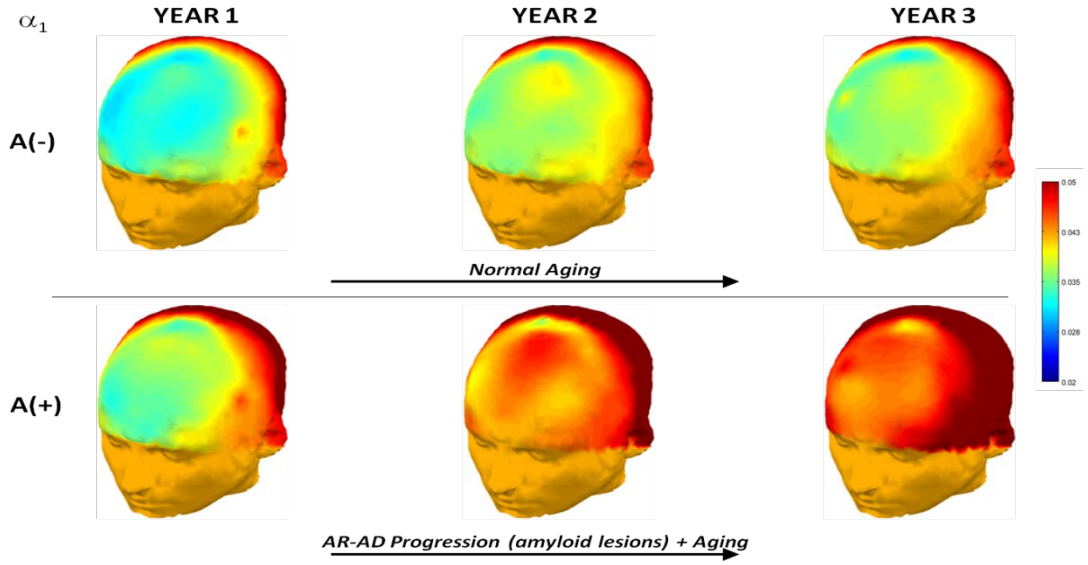
Bruno Dubois, Stephane Epelbaum, Francis Nyasse, Hovagim Bakardjian, Geoffroy Gagliardi, Olga Uspenskaya, Marion Houot, Simone Lista, Federica Cacciamani, Marie-Claude Potier, Anne Bertrand, Foudil Lamari, Habib Benali, Jean-François Mangin, Olivier Colliot, Remy Genthon, Marie-Odile Habert, Harald Hampel, for the INSIGHT-preAD study group

Lancet Neurol 2018; 17: 335–46



A-

A+



ONLY 15 SUBJECTS PROGRESSED TO PRODROMAL AD

LONGITUDINAL α/θ POWER RATIO CHANGES (rEEG)

At M0, M12 and M24 in the (A-) and (A+) groups

Towards a personalised Alzheimer's disease risk profile in asymptomatic at-risk people

Factors that can increase the risk of progression to Alzheimer's disease

- Increased age
- Frailty
- Female sex
- Low education level
- Heterozygous *APOE* ε4 status
- Polygenic risk factors beyond *APOE*
- Family history of Alzheimer's disease
- Memory complaint or subjective cognitive decline
- Magnitude of brain lesions, inferred from pathophysiological biomarker results especially if searched with PET
- Presence of markers of neurodegeneration (ie, isolated hippocampal atrophy on MRI, ^{18}F-fluorodeoxyglucose-PET hypometabolism, or elevated CSF neurofilament light chain)
- Copathology

Factors that could decrease the risk of progression to Alzheimer's disease

- Protective genes, such as the presence of the *APOE* ε2 allele, the *APOE* ε3 Christchurch mutation, or the *A673T APP* Icelandic mutation
- Higher cognitive reserve

Factors that need further confirmation

- Pattern of neuroinflammation
- Functional brain marker of cognitive reserve (eg, connectivity on functional MRI)
- Lifestyle factors (eg, physical activity, sleep, social activity)
- Psychiatric diseases (eg, depression)

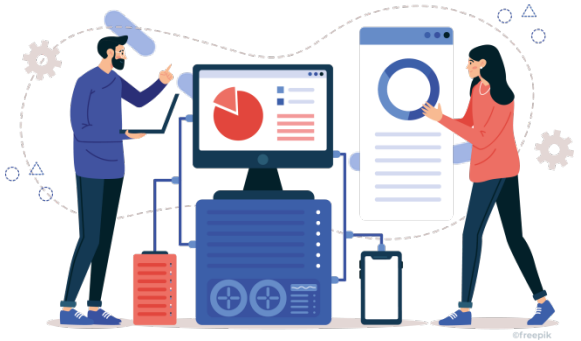
THE FUTURE

Subject

Patient at risk
Control subject

cohorts

databases



Prediction algorithms

Prevention Center for Cognitive Decline

Evaluation of personalized risk

Subject

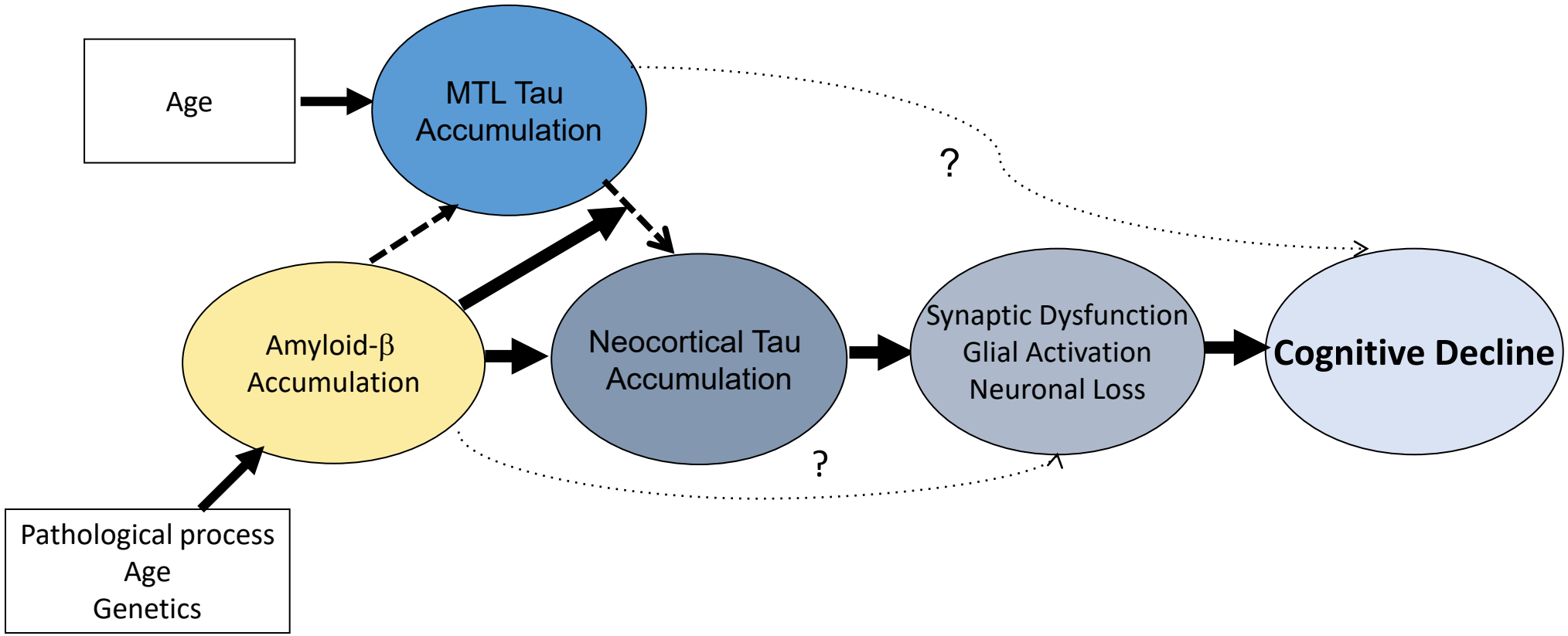
Targeted interventions :

- …on modifiable risk factors

- …with new therapies (DMT)

Thank you for your attention…

Validation of Amyloid Cascade in AD



Modified from Sperling, Mormino, Johnson Neuron 2014