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Cognition, Alzheimer's disease, animal models – F. Collette & E. Salmon

Psychologie & Neuroscience Cognitives
PsyNCog
Psychology & Neuroscience of Cognition

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Quizz : True / False

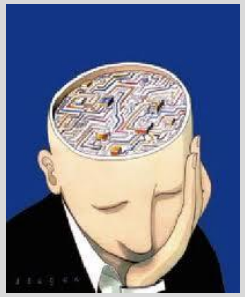
1) All cognitive abilities develop at the same rate during childhood
2) All cognitive abilities decrease during non-pathological aging
3) All brain areas are affected in the same way during non-pathological aging
4) Increased and decreased brain activity can coexist in non-pathological aging
5) Memory deficits are the only symptom of Alzheimer's disease (AD)
6) Biomarkers for AD can be present years before the first clinical signs
7) AD pathology can be easily distinguished from normal aging
8) The occurrence of clinical onset of AD is modulated by life experiences

What is cognition?

- **Refers to mental activities including:**

Executive functions

Problem solving



Attention

Langage

Decision making

Memory

Reading

- **Cognitive psychology : the study of how people perceive, learn remember, and think about information**
- **Cognitive neuroscience: how these mental activities are implemented in the brain (structure and functions)**

Cognition: the example of memory

- **Each cognitive system can be subdivided into sub-systems**
- **Each system includes a series of processes**

Memory systems

- Declarative
  - Long-term memory
    - Episodic memory
    - Semantic memory
    - Autobiographical memory
  - Short-term memory
- Non declarative
  - Procedural memory
  - Implicit memory
  - Classical conditioning
  - Non-associative learning

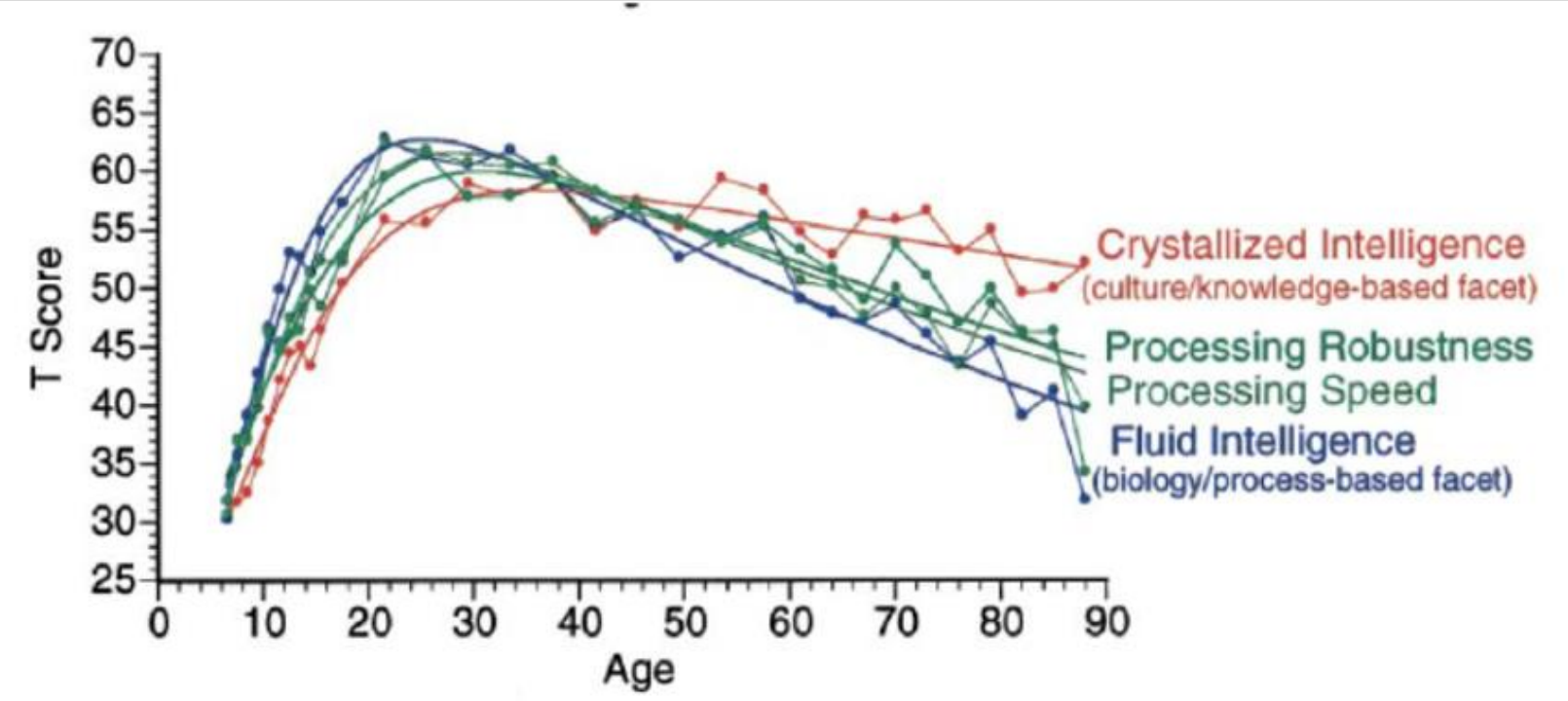
Processes

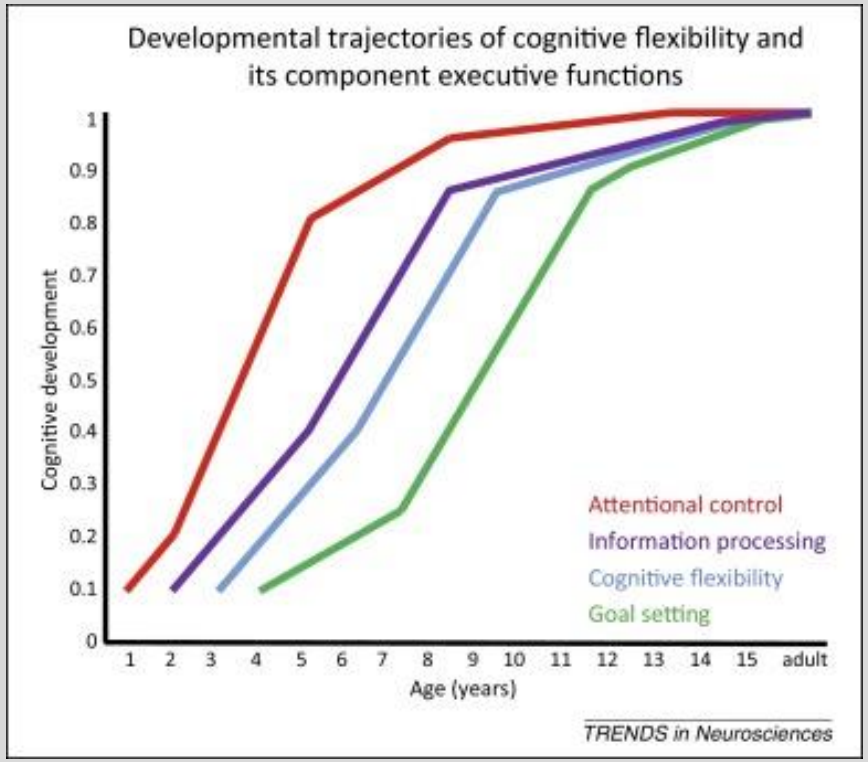
- Encoding
- Storage
- Retrieval

Specific cognitive tasks asses the efficiency of processes associated to each (sub)system

Cognition and life span

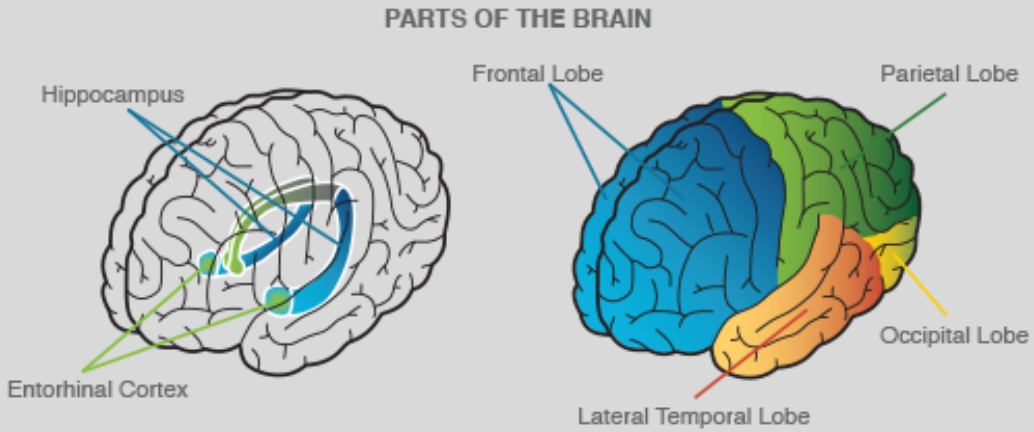
- Cognitive abilities develops at childhood, peak at adulthood and decrease with advanced age.
- Developmental curves are specific to the sub-systems and process





Cognition and pathology

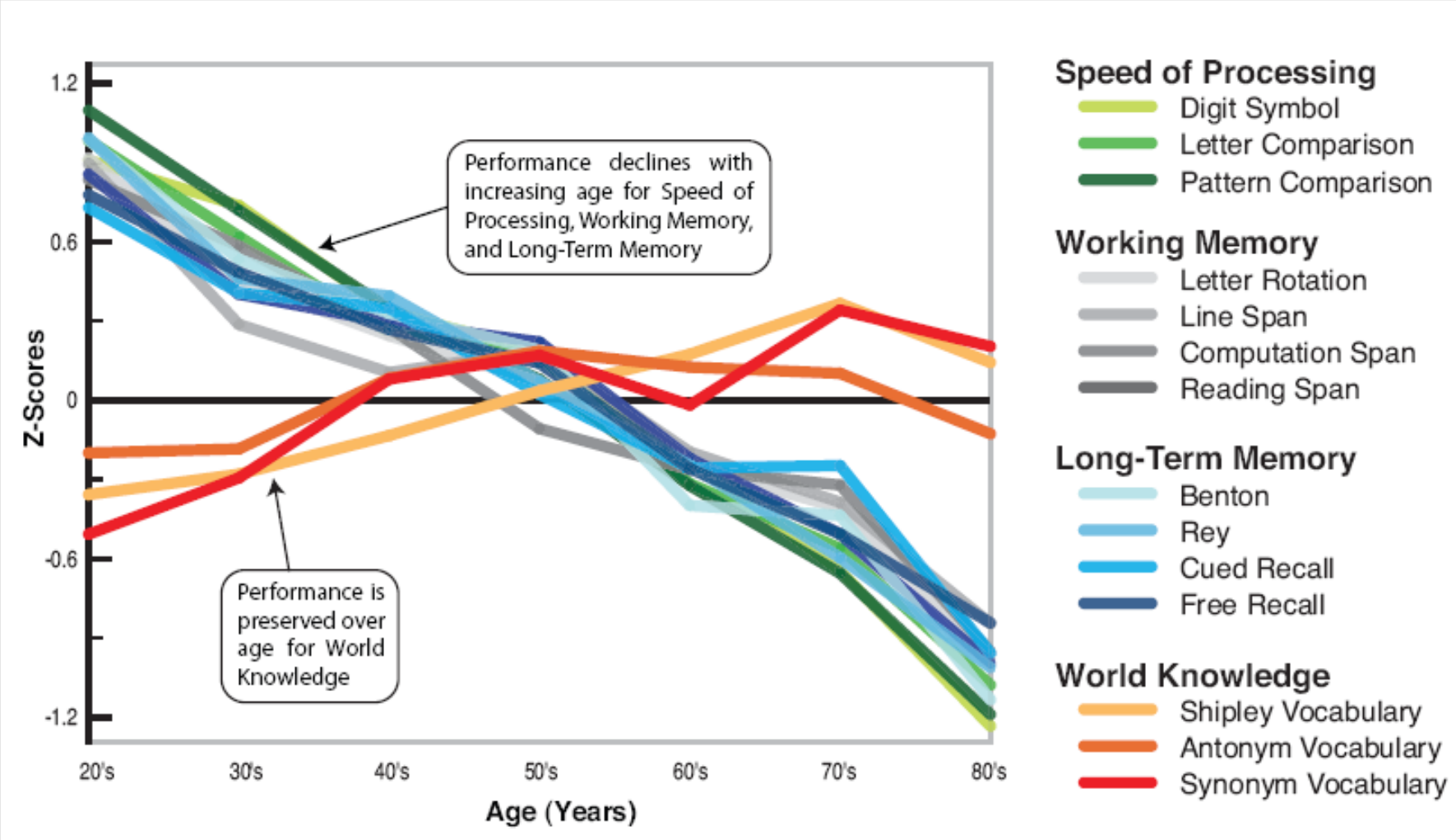
- Cognitive impairments following brain injury:
  traumatic brain injury
  neurodegenerative disease
  stroke
  …



- Most frequent cognitive impairments in the episodic memory and attentional/executive domains
  ➔recruitment of a large network of brain areas

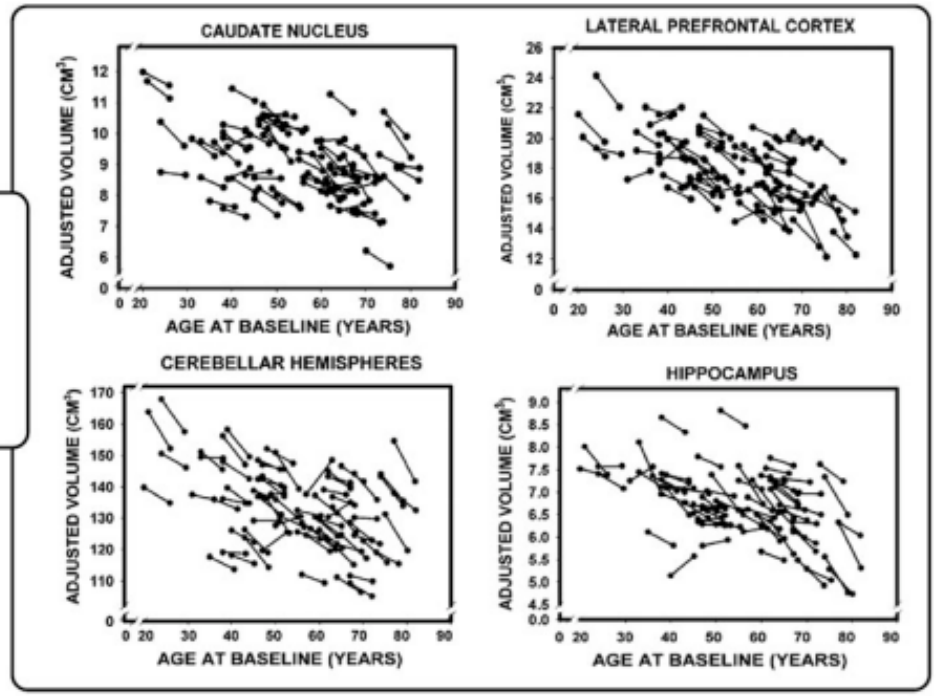
- Cognitive deficits are specific to the localization of brain lesions
  Episodic memory: medial temporal lobe
  Executive processes: frontal areas

Aging, brain and cognition

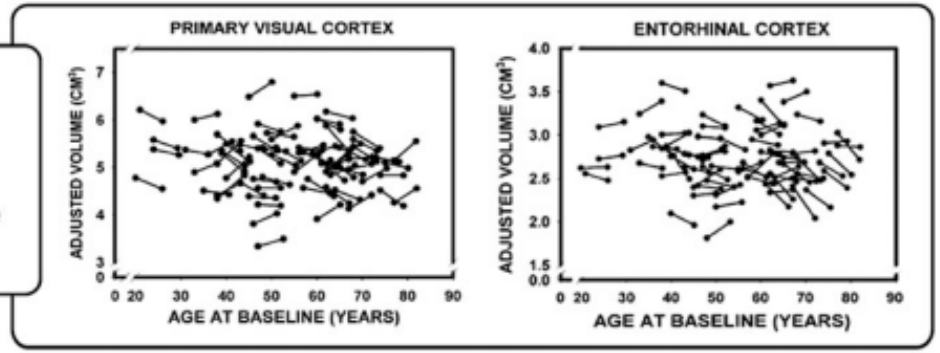


Aging, brain and cognition

Brain regions that reduce in volume with age.

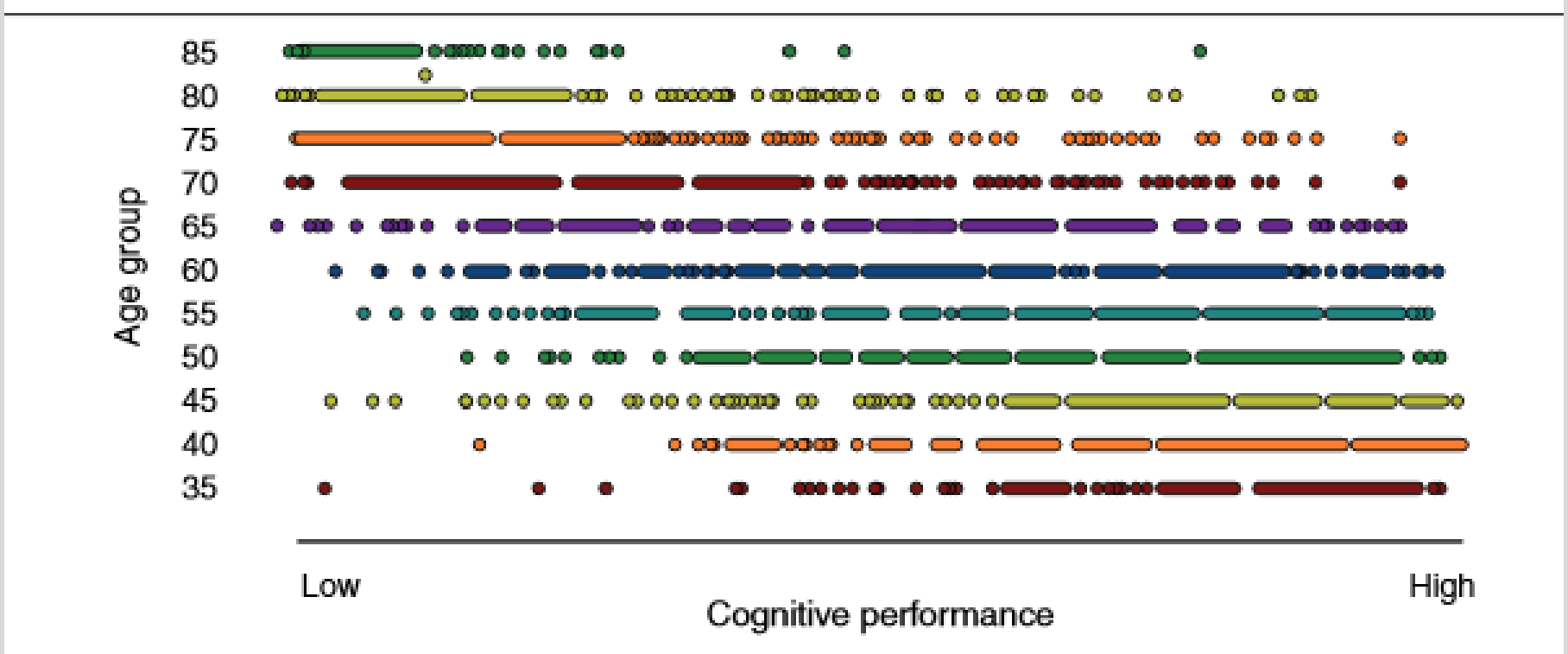


Brain regions with minimal reduction or stable volume with age.



Raz et al., 2005

Aging, brain and cognition



Nyberg, 2012

Aging, brain and cognition

- Several neural mechanisms are associated to age-related cognitive changes

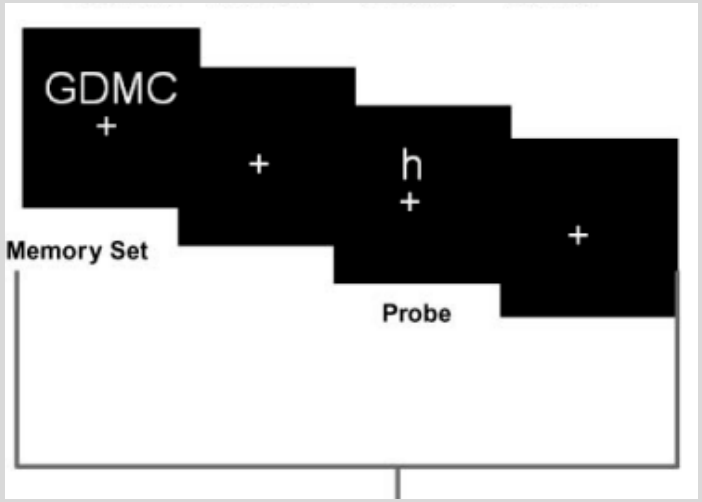
(1) Decrease of brain activity → *Deficit due to resource limitation or inadequate use of cognitive strategies*

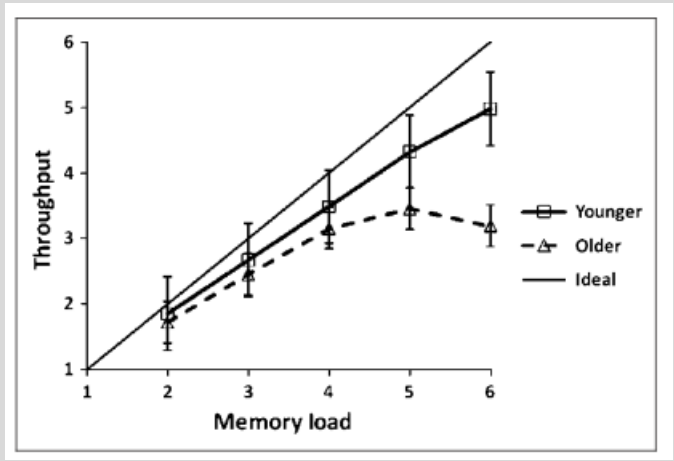
(2) Increase of brain activity
Recruitment of supplementary brain areas

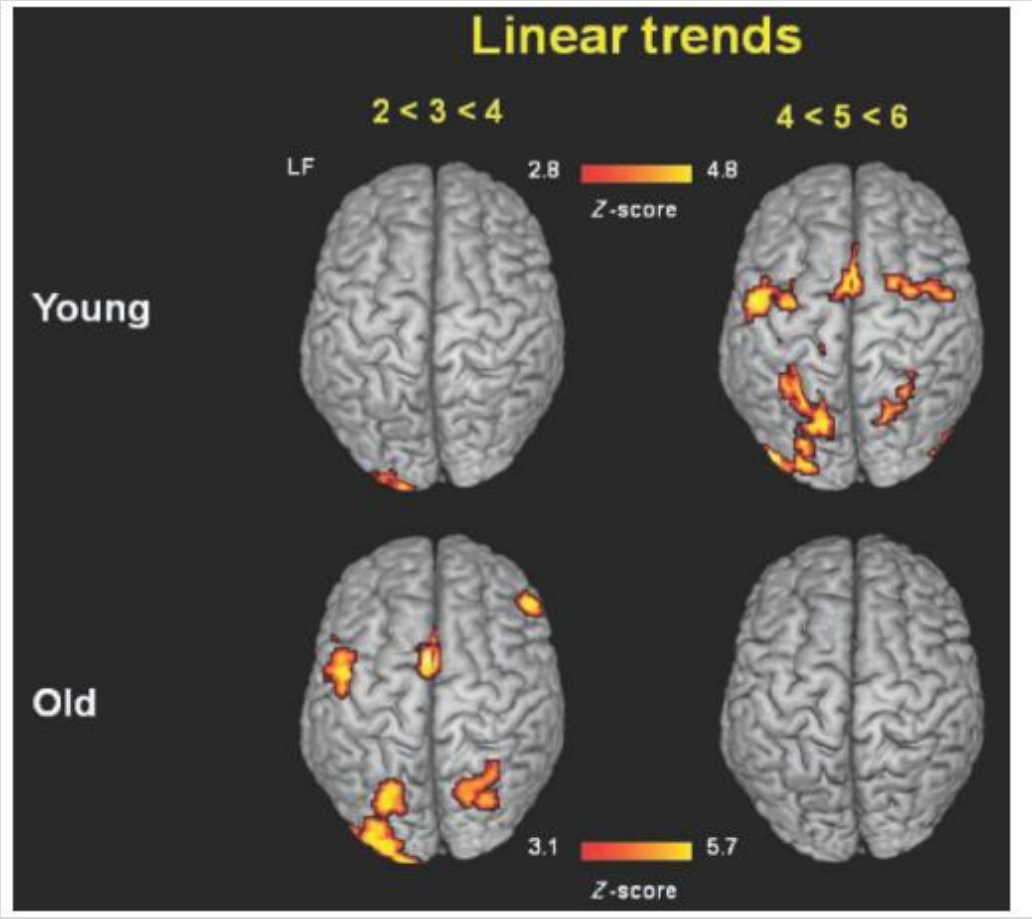
Cognitive performance OK: brain activity compensating for other less efficient areas
Cognitive performance KO: unfocused brain activity not directly related to the ongoing task

- **Patterns of increased and decreased brain activity can coexist within a same task !!!**

Aging, brain and cognition







Schneider-Garces et al. (2010)

Alzheimer's disease (AD)

- the most widespread cause of dementia
- Characterized by a progressive decline in cognitive performance
- Episodic memory deficits are the first and dominant symptoms in the typical form (anterograde amnesia and spatio-temporal disorientation)
- Deficits in other cognitive domains are next observed and also behavioral disorders (apathy,…)
- The expression and evolution of symptoms vary across individuals
- There is an important repercussion of symptoms in daily life activities

- Atypical variant of AD: posterior cortical atrophy, PPA, frontal variant

How to diagnose AD?

- Until 2000: mainly extensive neuropsychological evaluation, and confirmation *post-mortem* via neuropathological examination

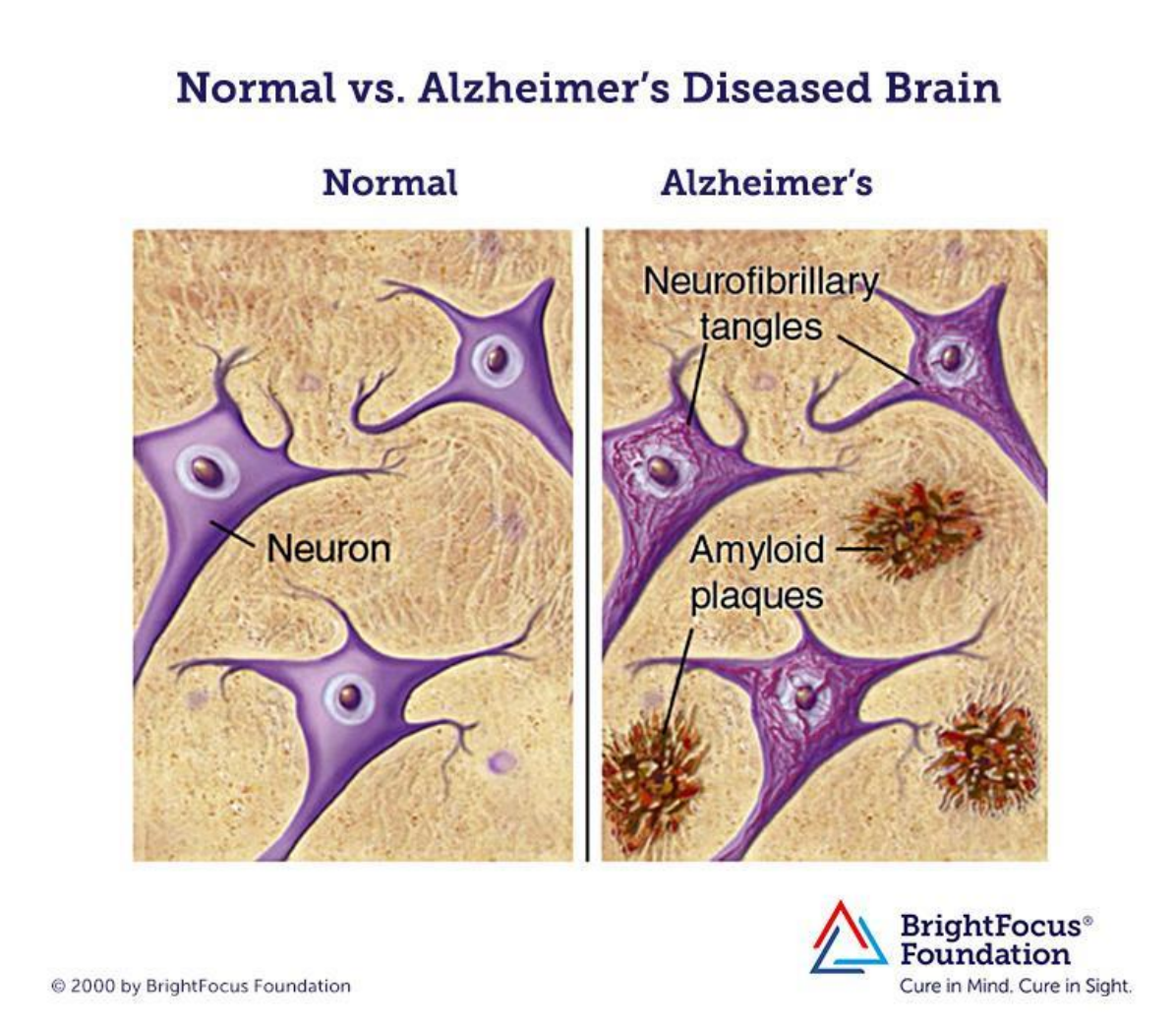
- Now: biomarkers* based on neuroimaging or cerebrospinal fluid
  - Tau neurofibrillary tangles
  - β-amyloid plaques
  - Brain atrophy (predominantly in the hippocampus and neocortex)
  - Brain hypometabolism (mainly in the PCC and temporo-parietal cortex)

* a biological or molecular signature of AD

- Genetic
  - sporadic AD (risk factor APOε), accounts for >99% for all AD cases; late onset (after 65 years)
  - familial AD (mutation in amyloid precursor protein or presenilin), <1% for all AD cases; early age of onset (<65 years)

The pathophysiological process of AD begins years, if not decades, before the diagnosis of clinical dementia

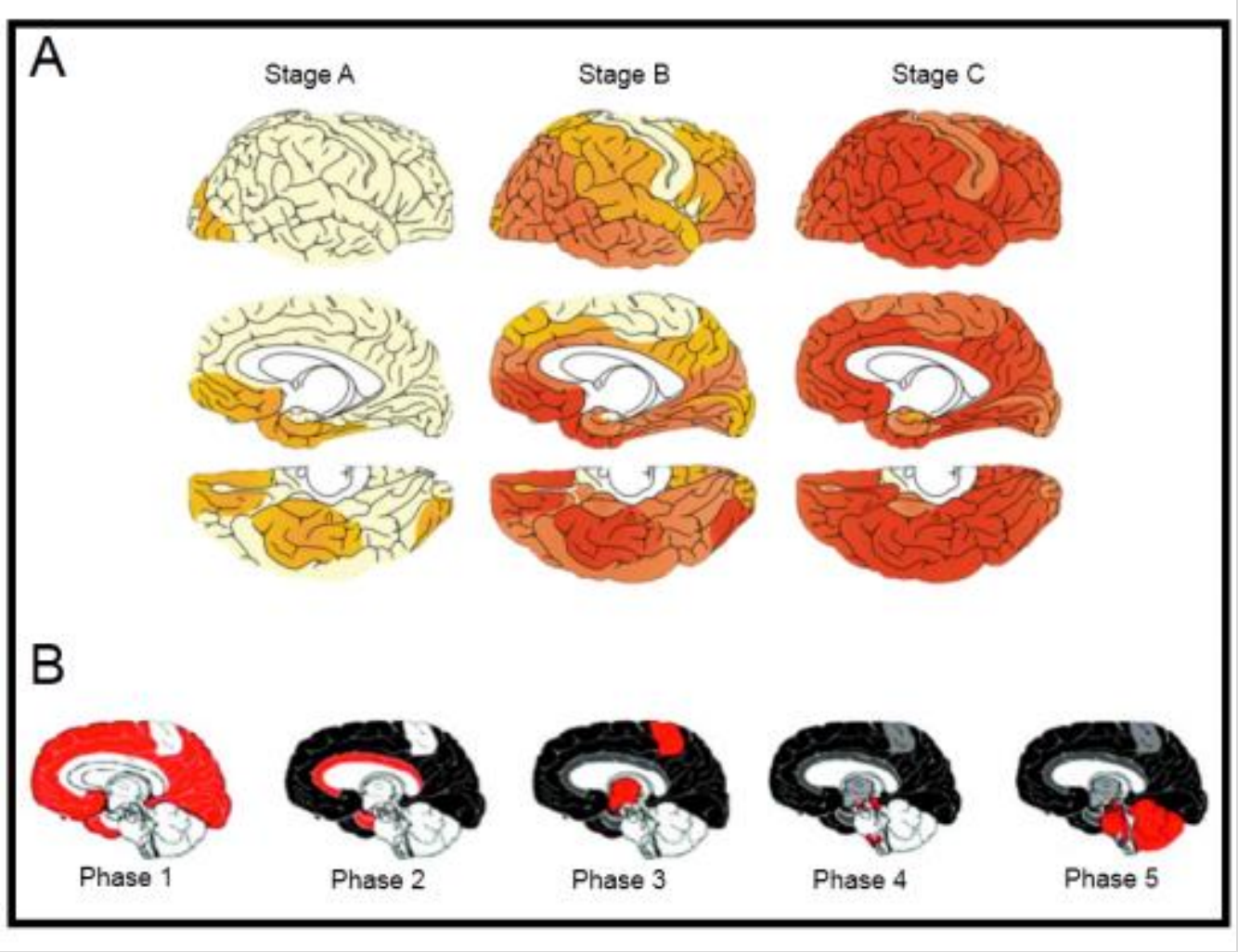
β-amyloid plaques and neurofibrillary tangles



- Beta amyloid is a protein fragment snipped from an amyloid precursor protein (APP). In a healthy brain, these protein fragments are broken down and eliminated. In AD, the fragments accumulate to form hard, insoluble plaques.

- Neurofibrillary tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate, or group, in an insoluble form. In its normal form, the tau protein helps transport nutrients and other important substances from one part of the nerve cell to another

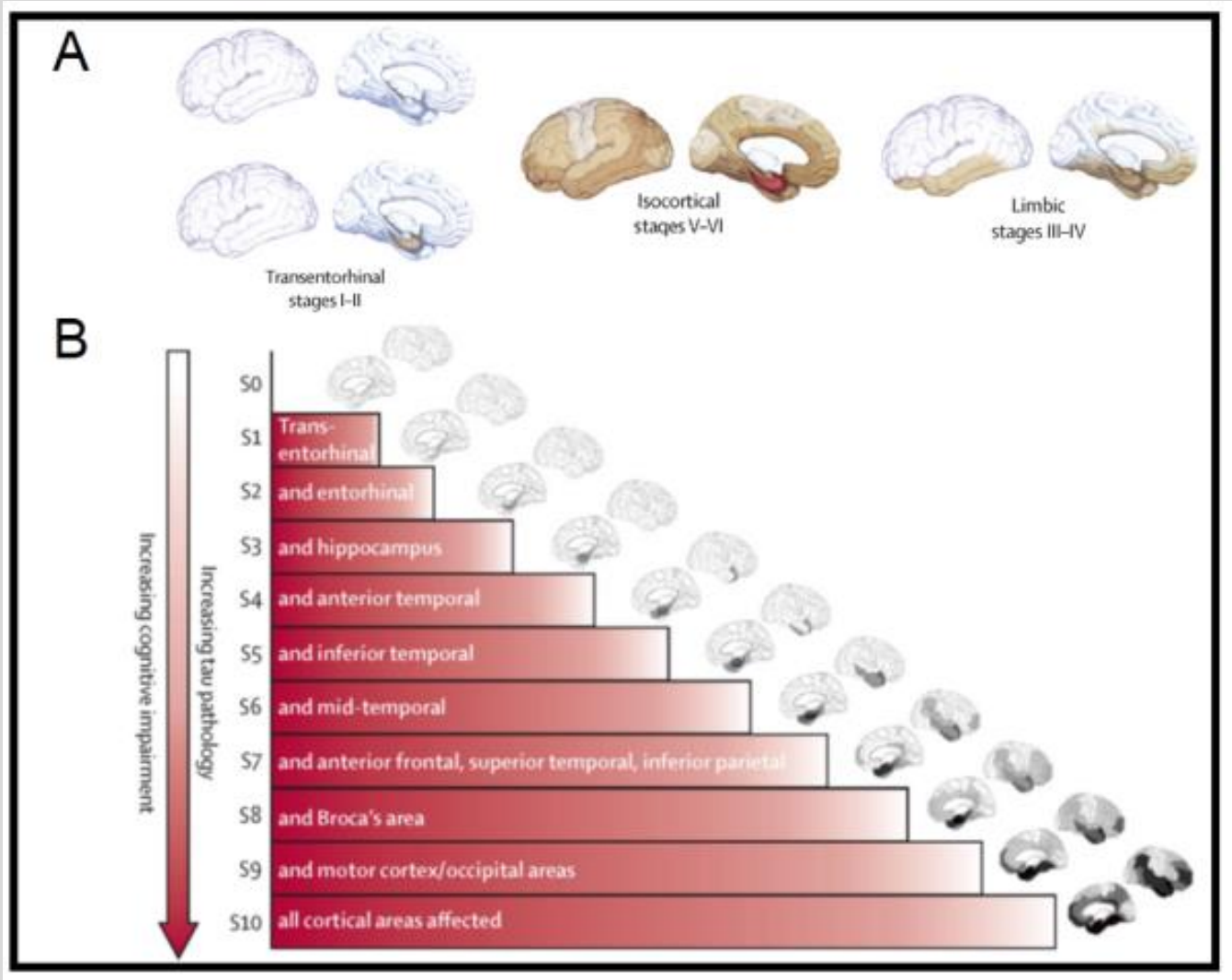
Topography of β-amyloid plaques deposition



(A) Braal & Braak 1991

(B) Thal et al. (2002)

Topography of tau neurofibrillary tangles deposition

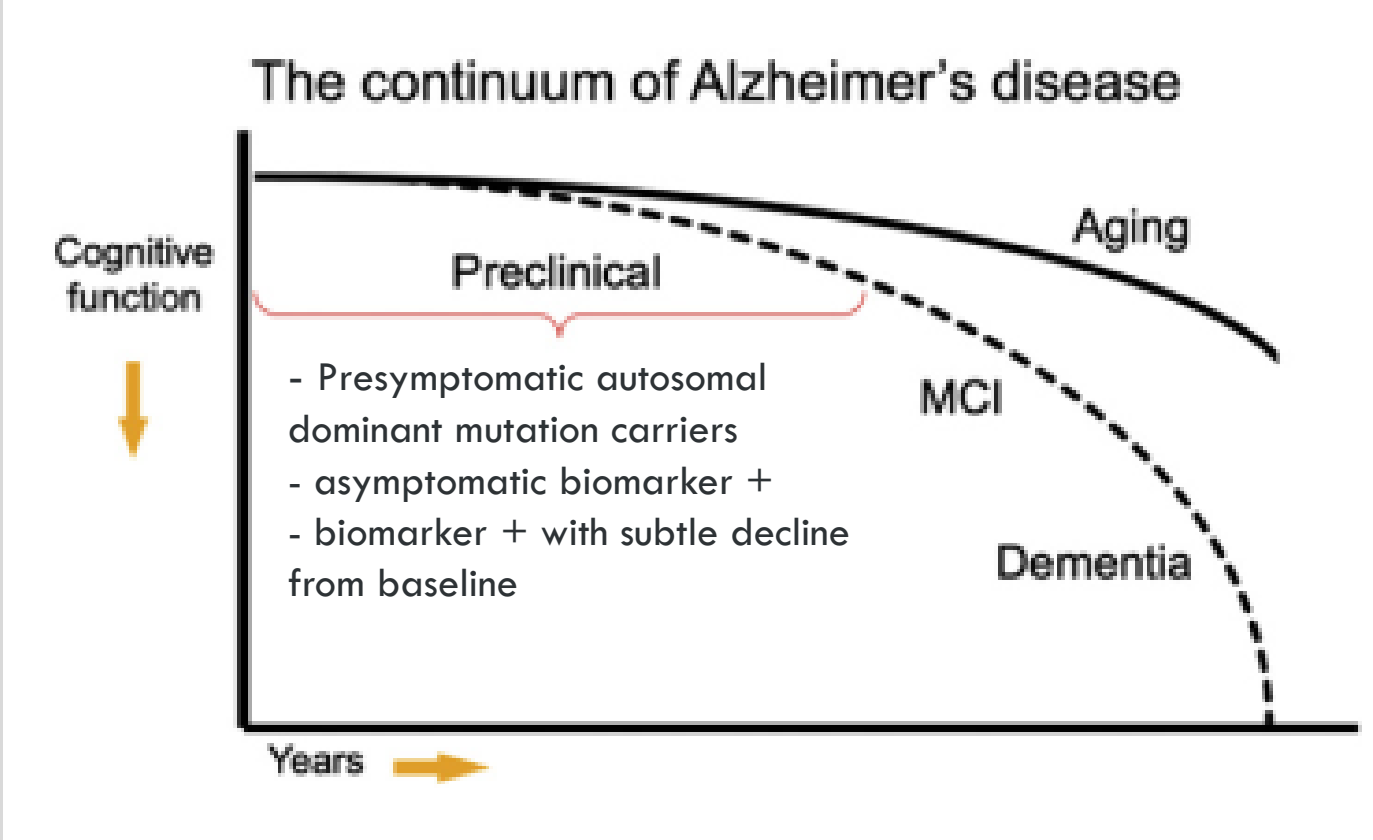


Braak & Braak (1997)

Delacourte (1999)

S1 and S2: asymptomatic
Between S3 and 6: occurrence of cognitive deficits

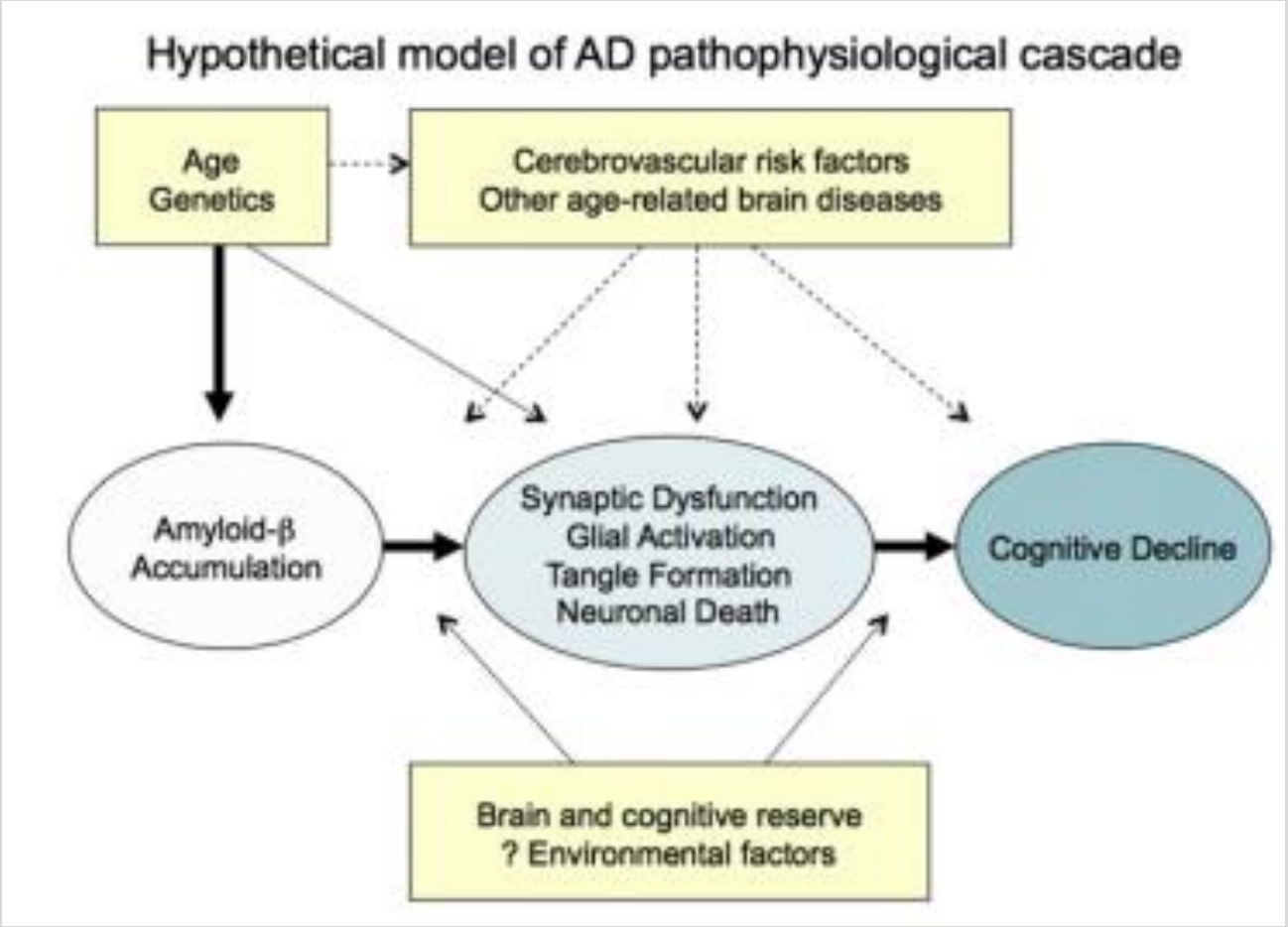
A continuum from normal aging to AD...



Sperling et al. (2011)

A continuum from normal aging to AD…

An hypothetical model of the Alzheimer's disease (AD) pathophysiological sequence leading to cognitive impairment.



Sperling et al. (2011)

A continuum from normal aging to AD...

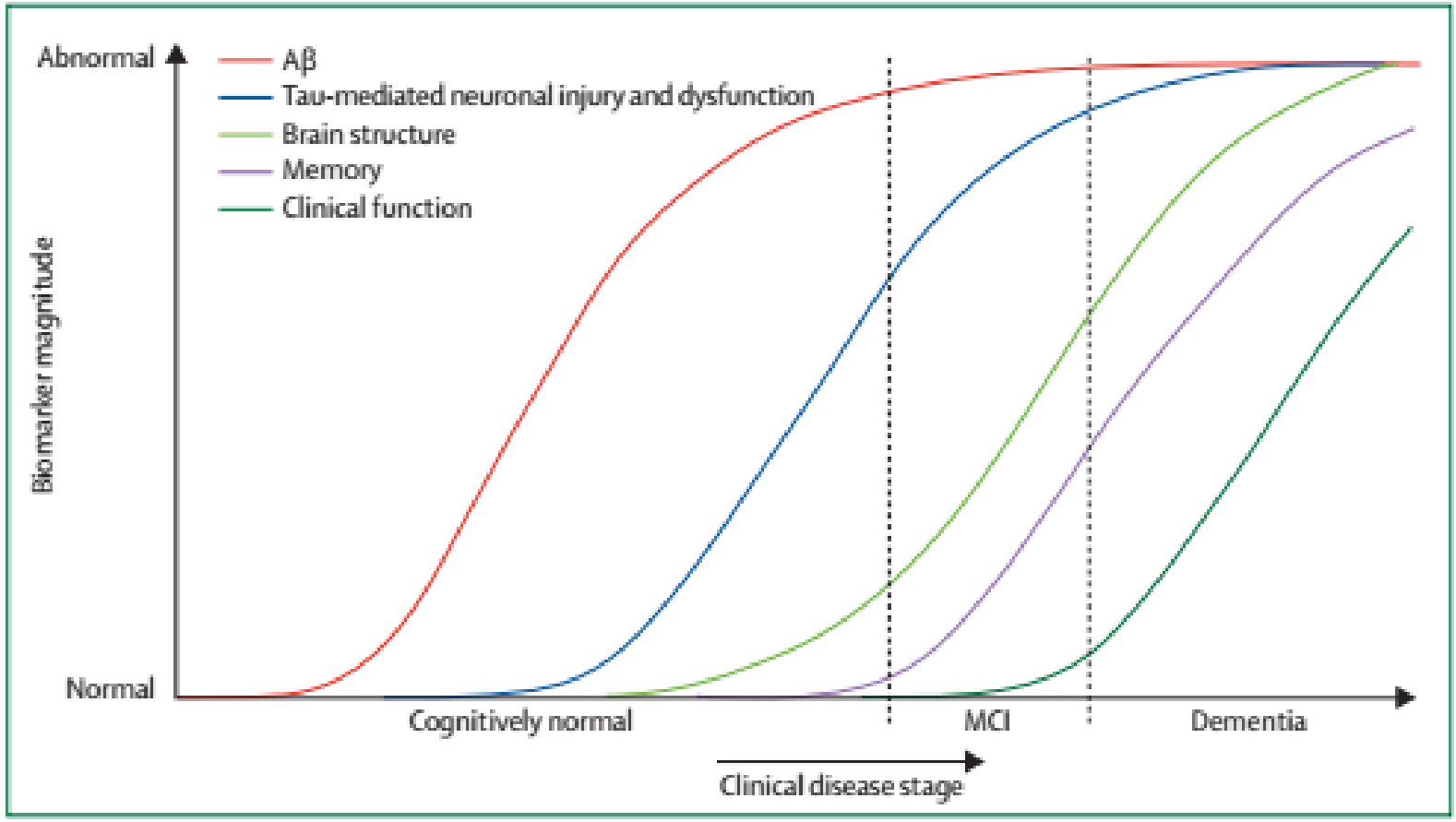
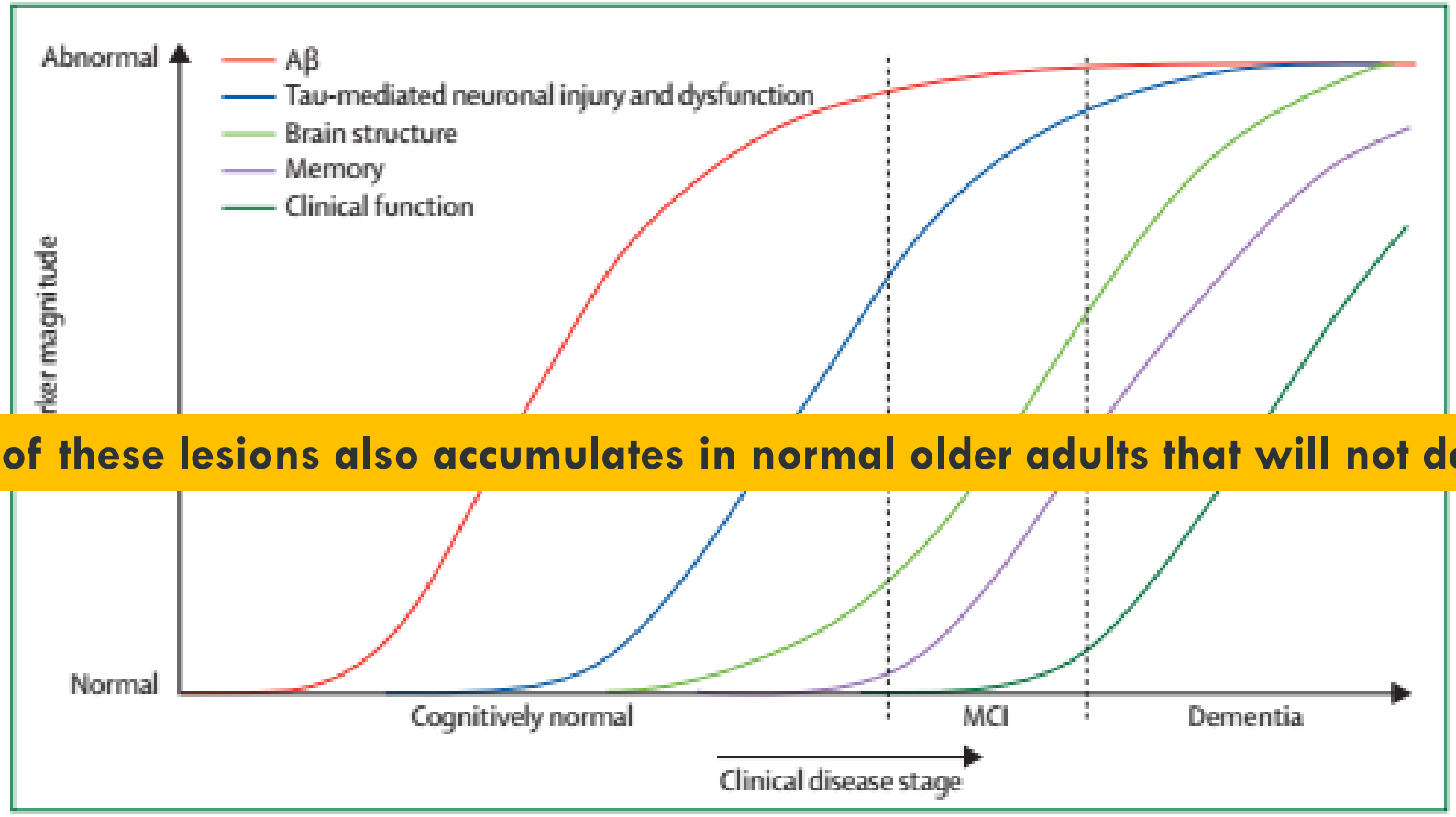


Figure 1: **2010 model of dynamic biomarkers of the Alzheimer's disease pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose PET. Brain structure is measured by structural MRI. Aβ=amyloid β. MCI=mild cognitive impairment. Reproduced from Jack and colleagues,[18] by permission of Elsevier.

A continuum from normal aging to AD…



Some of these lesions also accumulates in normal older adults that will not develop AD

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Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose PET. Brain structure is measured by structural MRI. Aβ=amyloid β. MCI=mild cognitive impairment. Reproduced from Jack and colleagues,[18] by permission of Elsevier.

The preclinical stages of AD

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Alzheimer's & Dementia 12 (2016) 292-323

Alzheimer's & Dementia

Perspective

Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria

Bruno Dubois[a,*,1], Harald Hampel[a,b,1], Howard H. Feldman[c,1], Philip Scheltens[d], Paul Aisen[e], Sandrine Andrieu[f], Hovagim Bakardjian[g], Habib Benali[h], Lars Bertram[i,j], Kaj Blennow[k], Karl Broich[l], Enrica Cavedo[b,m], Sebastian Crutch[n], Jean-François Dartigues[o], Charles Duyckaerts[p], Stéphane Epelbaum[a], Giovanni B. Frisoni[q,r], Serge Gauthier[s], Remy Genthon[t], Alida A. Gouw[f,u], Marie-Odile Habert[v,w], David M. Holtzman[x,y], Miia Kivipelto[z,aa], Simone Lista[b], José-Luis Molinuevo[ab,ac], Sid E. O'Bryant[ad], Gil D. Rabinovici[ae], Christopher Rowe[af], Stephen Salloway[ag,ah,ai], Lon S. Schneider[aj], Reisa Sperling[ak,al], Marc Teichmann[a], Maria C. Carrillo[am], Jeffrey Cummings[an], Cliff R. Jack, Jr,[ao]; from the Proceedings of the Meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The Preclinical State of AD"; July 23, 2015; Washington DC, USA

[a]*Institute of Memory and Alzheimer's Disease (IM2A) and Brain and Spine Institute (ICM) UMR S 1127 Frontlab, Department of Neurology, AP_HP, Pitié-Salpêtrière University Hospital, Sorbonne Universities, Pierre et Marie Curie University, Paris 06, Paris, France*

The preclinical stages of AD

GLOSSARY

Lexicon used in the article.

State versus stage

"State" refers to a given pathophysiological framework (state of asymptomatic at-risk versus state of Alzheimer's disease), whereas "stage" refers to a degree of disease progression within a given state (preclinical, prodromal, and dementia for AD).

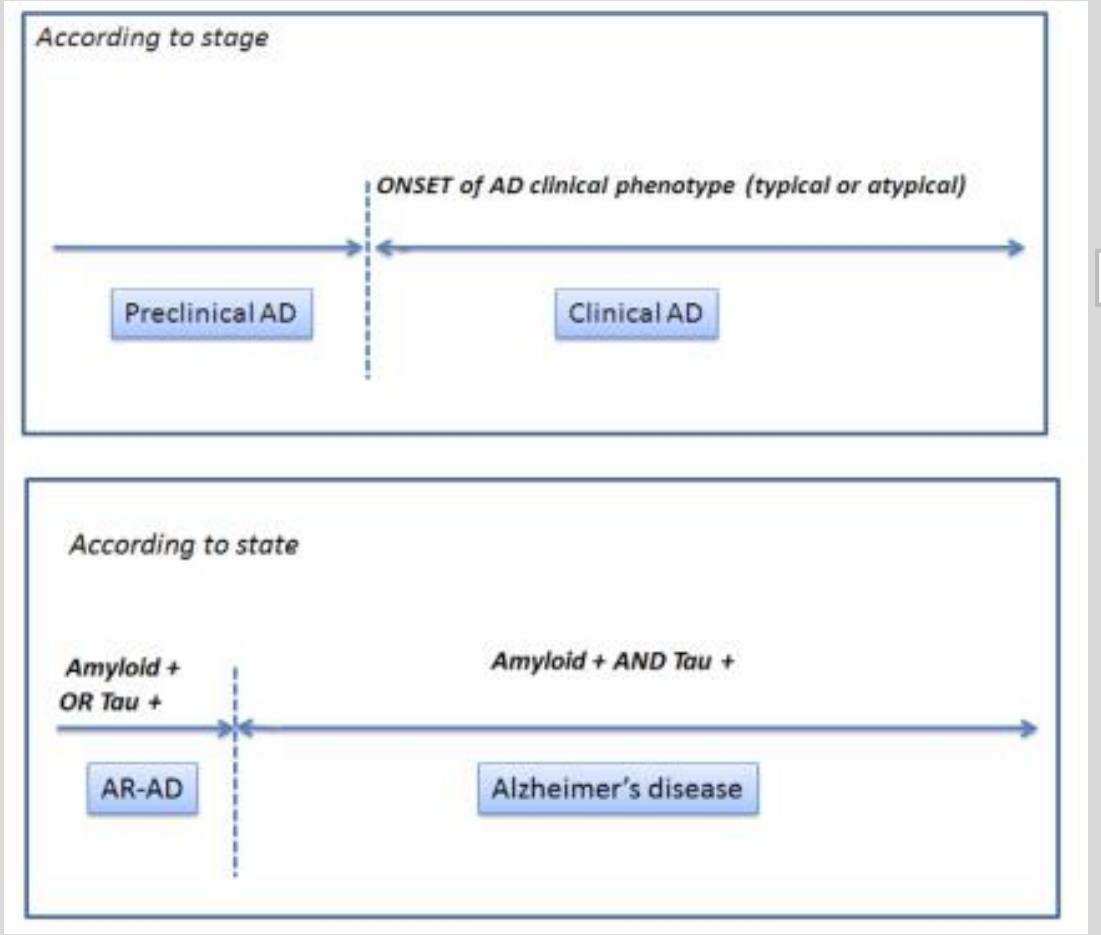
Alzheimer's disease

AD is defined by the positivity of biomarkers of both amyloidopathy (A+) and tauopathy (T+) in line with the pathologic definition of the disease. Therefore, two phases of the disease can be distinguished in the continuum:

- A clinical stage ("clinical AD") defined by the occurrence of the clinical phenotype of AD (either typical or atypical) and which encompasses both the prodromal and the dementia stages;
- A preclinical stage ("preclinical AD") before the onset of the clinical phenotype. The development of biomarkers of Alzheimer pathology makes possible to recognize AD before the onset of the specific clinical phenotype.

Asymptomatic at risk for AD

This state consists of cognitively normal individuals for whom the biomarker pattern is insufficient to reach the above definition of AD. They can be characterized by the positivity of the pathophysiological biomarker (i.e. either "Asymptomatic A+" or "Asymptomatic T+").



The AD disease

Risk factors

Preclinical = when risk factors are high

The preclinical stages of AD

Table 1
Toward a unified conception of preclinical AD

Proposed definition	NIA-AA, 2011	IWG-2, 2014	Proposed criteria, 2016
AD starts			
With the first brain lesion	+		
With the first symptom of AD		+	
When there is evidence of Aß and Tau pathology			+
Preclinical AD can be detected in asymptomatic individuals			
When there is evidence of Aß pathology	+ (stage 1)	+ (PET)	
When there is evidence of Aß and Tau pathology	+ (stage 2)*	+ (CSF)	+
Asymptomatic at risk for AD can be detected in cognitively normal individuals			
When there is evidence of Aß pathology ("Asymptomatic A+") OR evidence of Tau pathology ("Asymptomatic T+")			+

Abbreviations: AD, Alzheimer's disease; NIA-AA, National Institute on Aging/Alzheimer Association; IWG, international working group.

NOTE. The criteria now stipulate that the Aß+ group (A+) is asymptomatic at risk for AD, whereas the Aß+/Tau+ group (A+, T+) is considered as having preclinical AD.

*In the NIA-AA criteria, markers on neurodegeneration (i.e., brain atrophy on MRI or hypo-metabolism on FDG PET) were also considered instead of tau markers to diagnose preclinical AD.

Dubois et al. (2016)

The preclinical stages of AD

Table 1
Staging categories for preclinical AD research

Stage	Description	Aβ (PET or CSF)	Markers of neuronal injury (tau, FDG, sMRI)	Evidence of subtle cognitive change
Stage 1	Asymptomatic cerebral amyloidosis	Positive	Negative	Negative
Stage 2	Asymptomatic amyloidosis + "downstream" neurodegeneration	Positive	Positive	Negative
Stage 3	Amyloidosis + neuronal injury + subtle cognitive/behavioral decline	Positive	Positive	Positive

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose (18F); sMRI, structural magnetic resonance imaging.

Sperling et al. (2011)

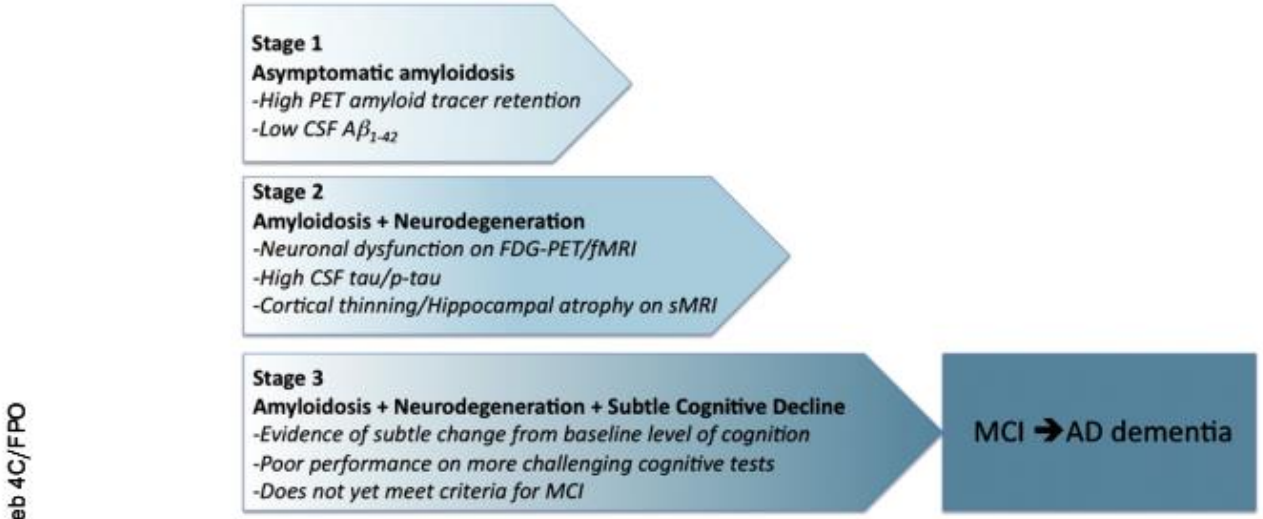


Fig. 5. Graphic representation of the proposed staging framework for preclinical AD. Note that some individuals will not progress beyond Stage 1 or Stage 2. Individuals in Stage 3 are postulated to be more likely to progress to MCI and AD dementia. Abbreviations: AD, Alzheimer's disease; Ab, amyloid beta; PET, position emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose, fMRI, functional magnetic resonance imaging, sMRI, structural magnetic resonance imaging.

The preclinical stages of AD

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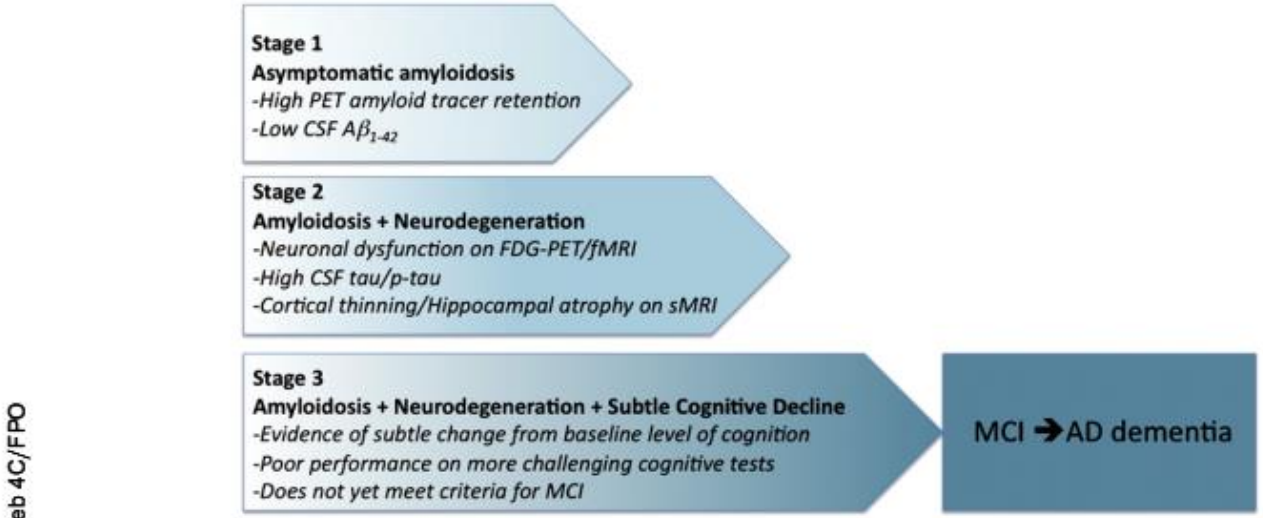
Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose (18F); sMRI, structural magnetic resonance imaging.

Research criteria for AD

Sperling et al. (2011)



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Factors influencing the natural history of preclinical stages

- Some elderly individuals show little if any cognitive disturbances even in presence of high level of pathophysiological biomarkers, suggesting the influence of additional mediators such as cognitive reserve

- On the other hand, the process can be accelerated by several factors affecting the risk and/or the rate of progression

The occurrence of clinical onset of AD is the expression of a complex algorithm where the presence of AD brain lesions play a key role and additional positive and/or negative factors need to be considered as they modulate the effect of brain lesions

Factors influencing the natural history of preclinical stages

- Age and genetic : the prevalence of amyloid pathology increased from 10% (at age 50 years) to 44% (at age 90 years) among participants with normal cognition with a 2 to 3 times higher prevalence estimates in APOE ε4 carriers
- Several lifestyle factors have been identified that may delay the onset of clinical AD.

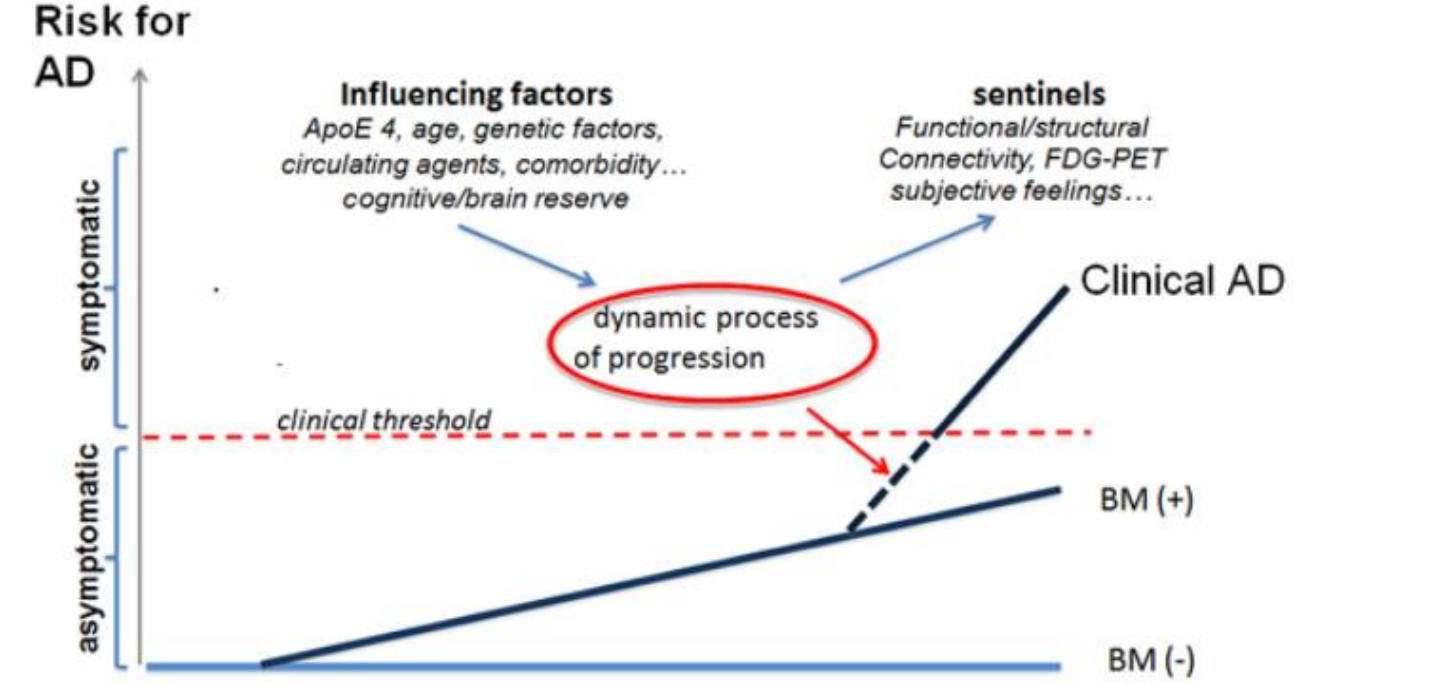

Fig. 2. The risk of clinical AD–hypothetical model. Abbreviation: AD, Alzheimer's disease; BM, pathophysiological biomarkers.

Mild Cognitive Impairment (MCI)

- Individuals at the mild end of the cognitive spectrum spanning normal aging to Alzheimer's disease
- Very subtle decline in cognitive functions
- Some MCI patients regain normal cognitive functioning

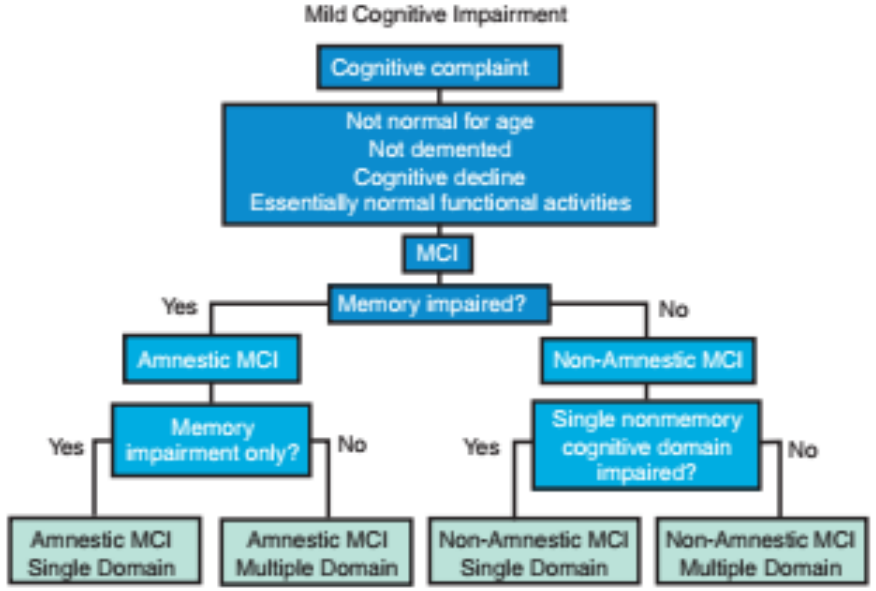

Fig. 5 Flow chart of decision process for making diagnosis of subtypes of mild cognitive impairment (with permission from Ref. [36].

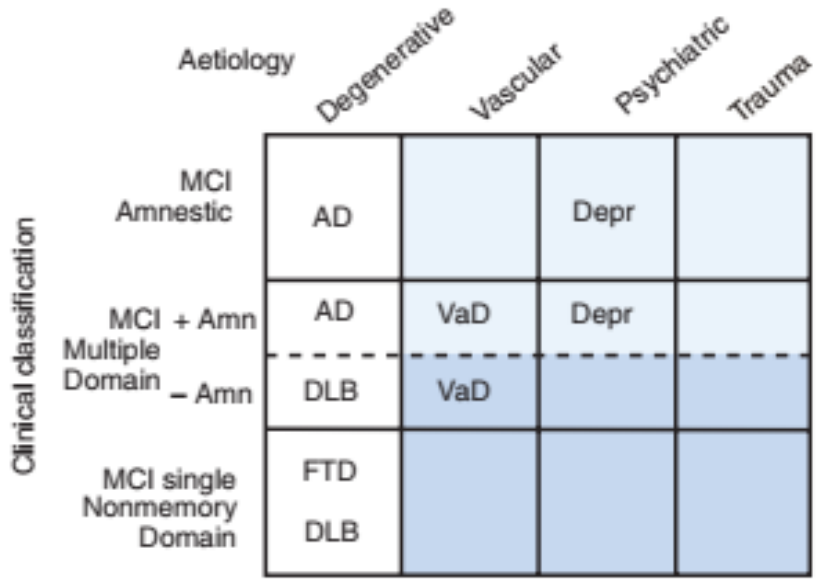

Fig. 4 Classification of clinical subtypes of mild cognitive impairment with presumed aetiology (with permission from Ref. [1].

Subjective cognitive decline

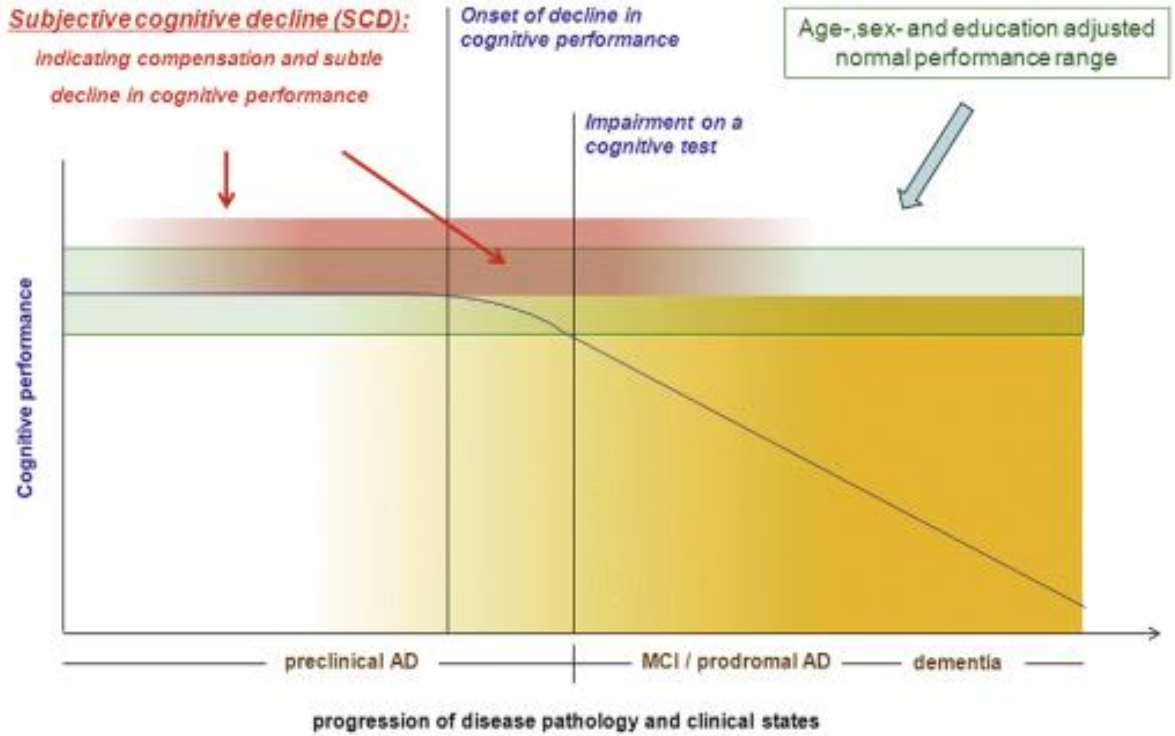

Table 3
Features that increase the likelihood of preclinical AD in individuals with SCD according to current data: SCD *plus* (preclinical AD)

- Subjective decline in memory, rather than other domains of cognition
- Onset of SCD within the last 5 y
- Age at onset of SCD ≥60 y
- Concerns (worries) associated with SCD
- Feeling of worse performance than others of the same age group

If available or possible to obtain in the respective study:

- Confirmation of cognitive decline by an informant
- Presence of the *APOE* ε4 genotype
- Biomarker evidence for AD (defines preclinical AD)

Abbreviations: AD, Alzheimer's disease; SCD, subjective cognitive decline.

Quizz : True / False

1) All cognitive abilities develop at the same rate during childhood
2) Some cognitive abilities are preserved during non-pathological aging
3) All brain areas are affected in the same way during non-pathological aging
4) Increased and decreased brain activity can coexist in non-pathological aging
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