Grand Round
October 9 2014

Clinical approach to cognitive disorders

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Outline

History
Biology of AD
Diagnostic criteria
DSM 5
Vascular Dementia
BPSD
MCI
Neuropsychological tests
Imaging
Therapy


Hugon Finn

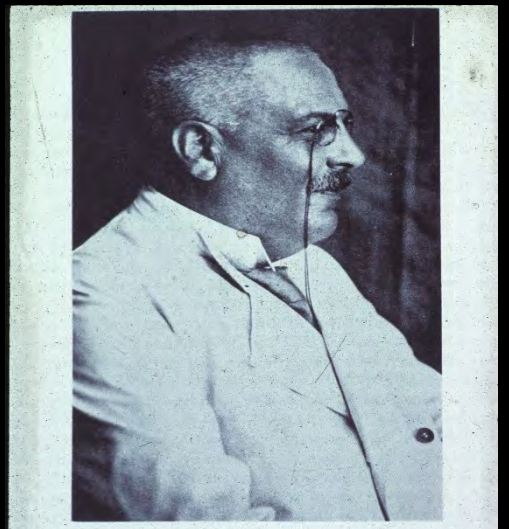
LOEB CLASSICAL LIBRARY

CICERO

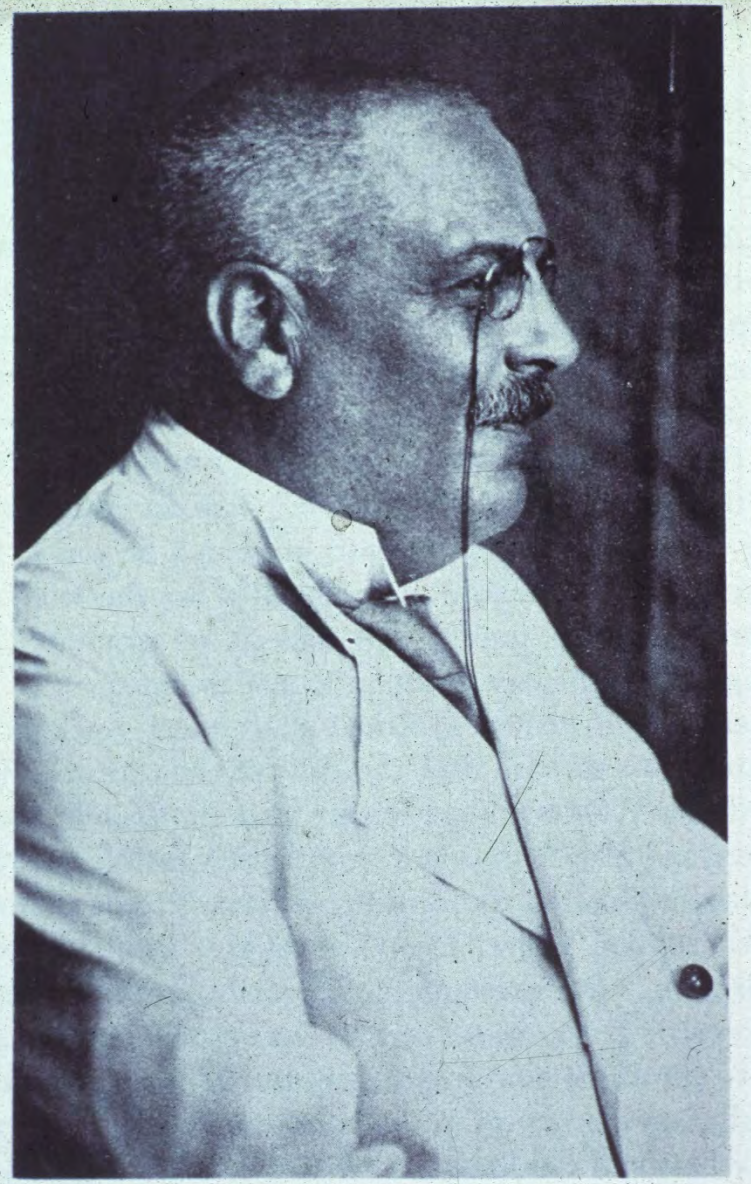
DE SENECTUTE
DE AMICITIA
DE DIVINATIONE

Translated by

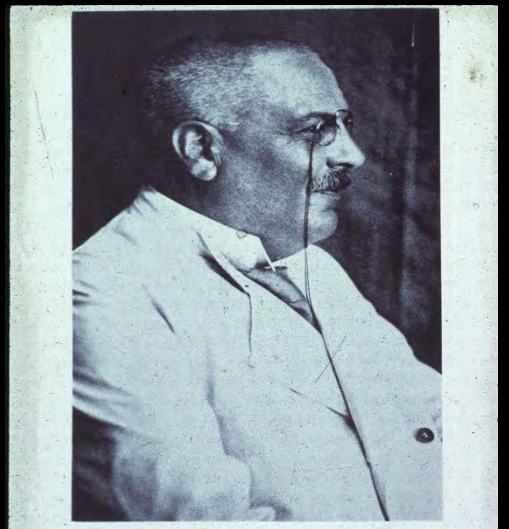
W. A. FALCONER



Alzheimer



Agleimer



Alzheimer

Fig. 2 e 3 - Foto di gruppo dei frequentatori del laboratorio di istopatologia del sistema nervoso di Alois Alzheimer nei primi anni di questo secolo (per gentile concessione della Sig.ra Coccinella, figlia del Professor Ugo Cerletti).


What we know about the pathogenesis of AD

Alzheimer's Disease: 100 years and beyond

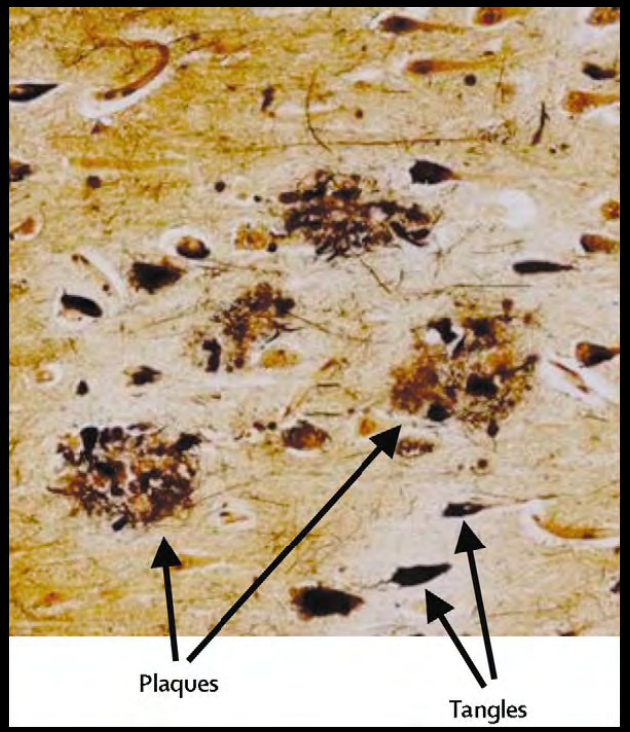
γ-secretase complex
1998

1906

1984
Aβ
sequence

BACE

Case closed. Plaques and tangles in the brain of Auguste D.



Amyloid

So named by Virchow because thought to resemble starch

The cleavage of a large, transmembrane-spanning protein the amyloid precursor protein (APP) forms the Aβ peptide

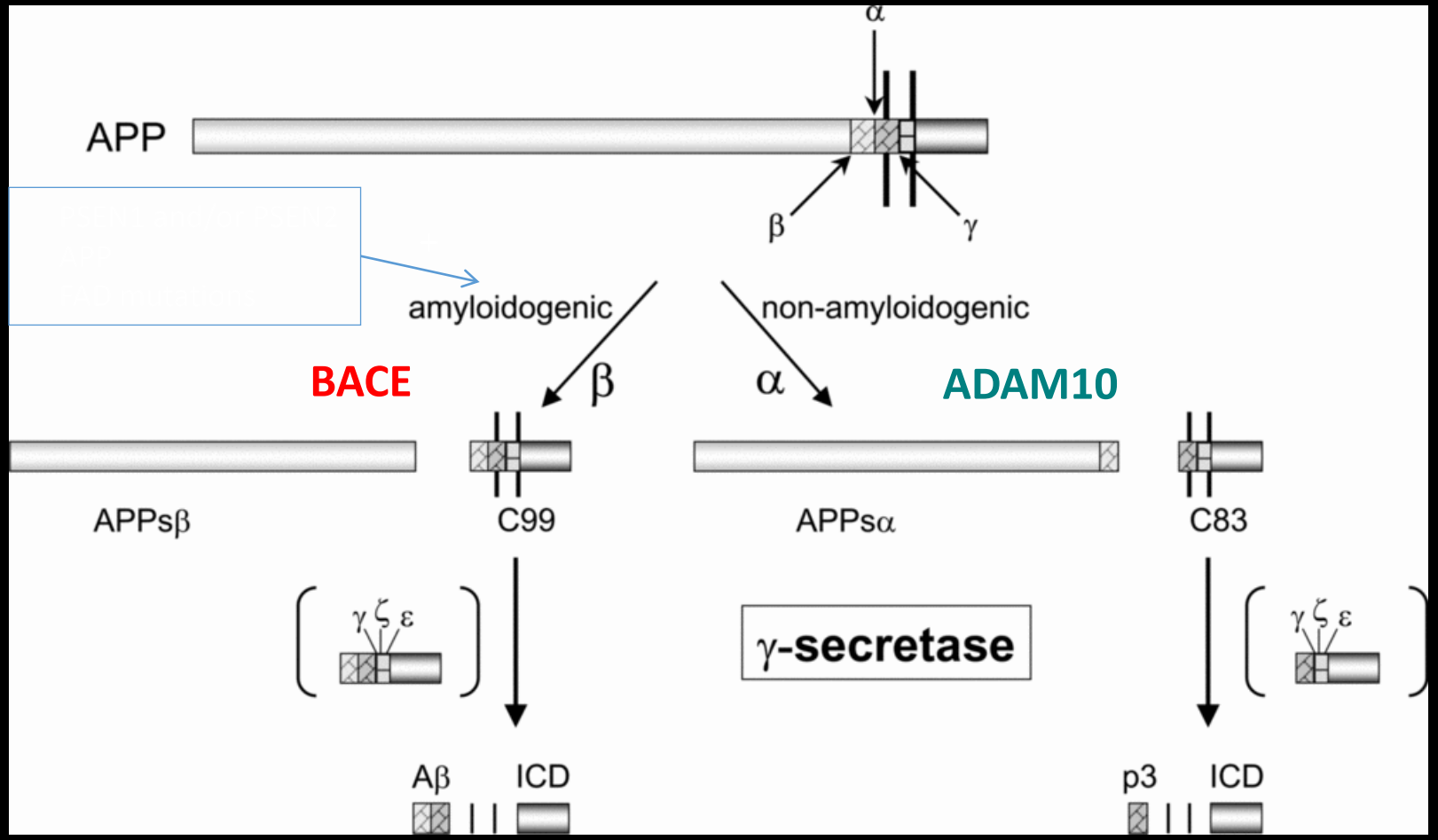
There are 2 pathways for cleaving APP into smaller fragments: amyloidogenic and nonamyloidogenic pathways

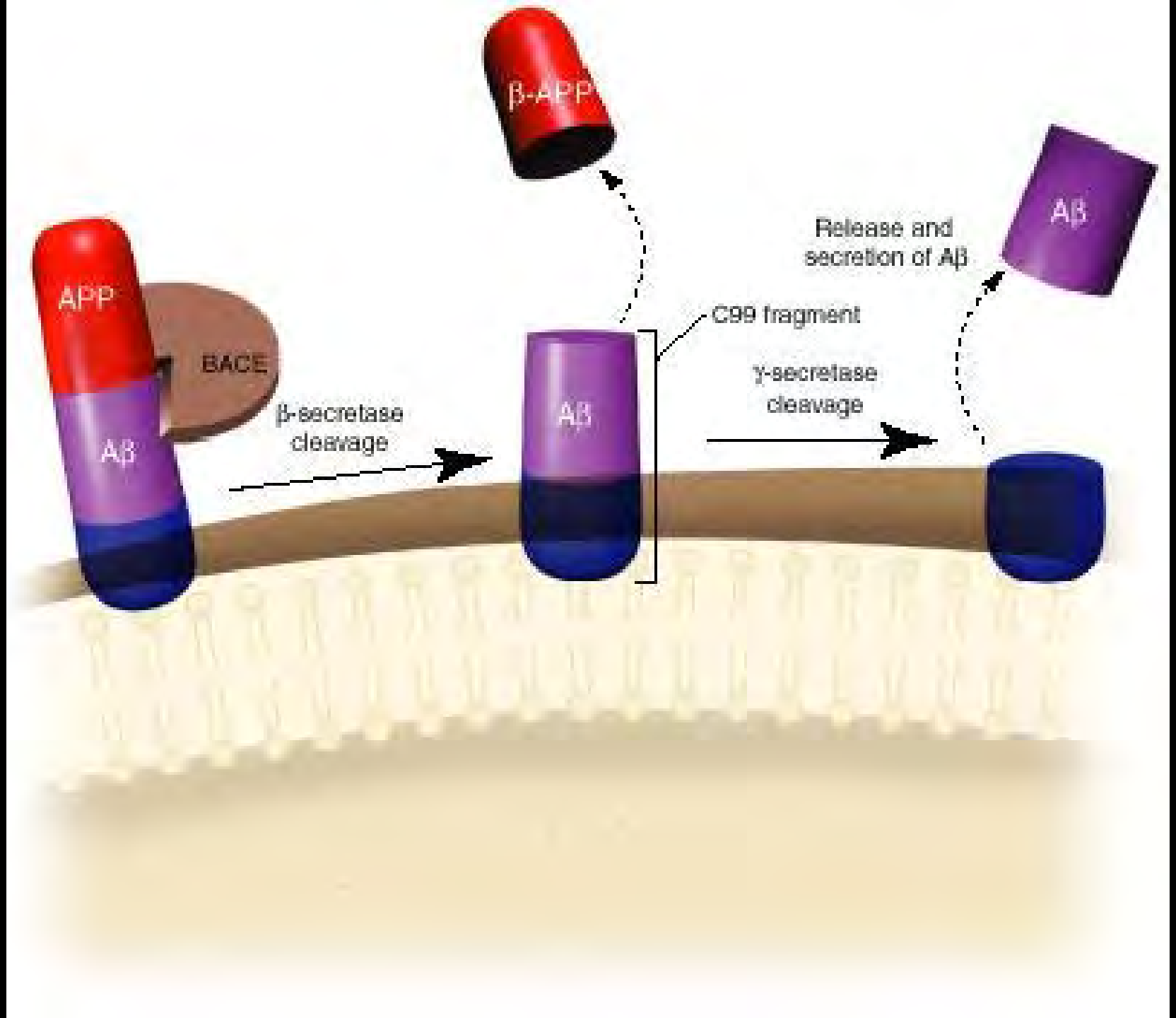
The amyloidogenic pathway involves the action of 2 enzymes: β secretase (BACE), which cleaves APP into a soluble fragment and a larger, membrane-bound fragment called C99, and γ secretase, which cleaves C99 into Aβ peptide and a smaller, membrane-bound fragment called C59

The nonamyloidogenic pathway involves cleavage by the enzyme α secretase

Promotion of the non-amyloidogenic alpha-secretase cleavage of amyloid precursor protein (APP) to release soluble APP is a plausible mechanism for AD treatment

APP metabolism: a mutually exclusive dance between alpha- and beta-secretase




β-APP
APP
BACE
Aβ
β-secretase
cleavage
Aβ
C99 fragment
γ-secretase
cleavage
Release and
secretion of Aβ
Aβ

Tau protein

The subunit protein of one of the major hallmarks of AD, the neurofibrillary tangles

τ?

Tau was one of the first microtubule-associated proteins (MAPs) to be characterized. Its role is to promote the self-assembly of tubulin into microtubules (hence Tau = Tubulin Associated Unit).

Tau protein

The subunit protein of one of the major hallmarks of AD, the neurofibrillary tangles

It was only in the mid 80’s that its presence in the tangles was confirmed

The tau protein

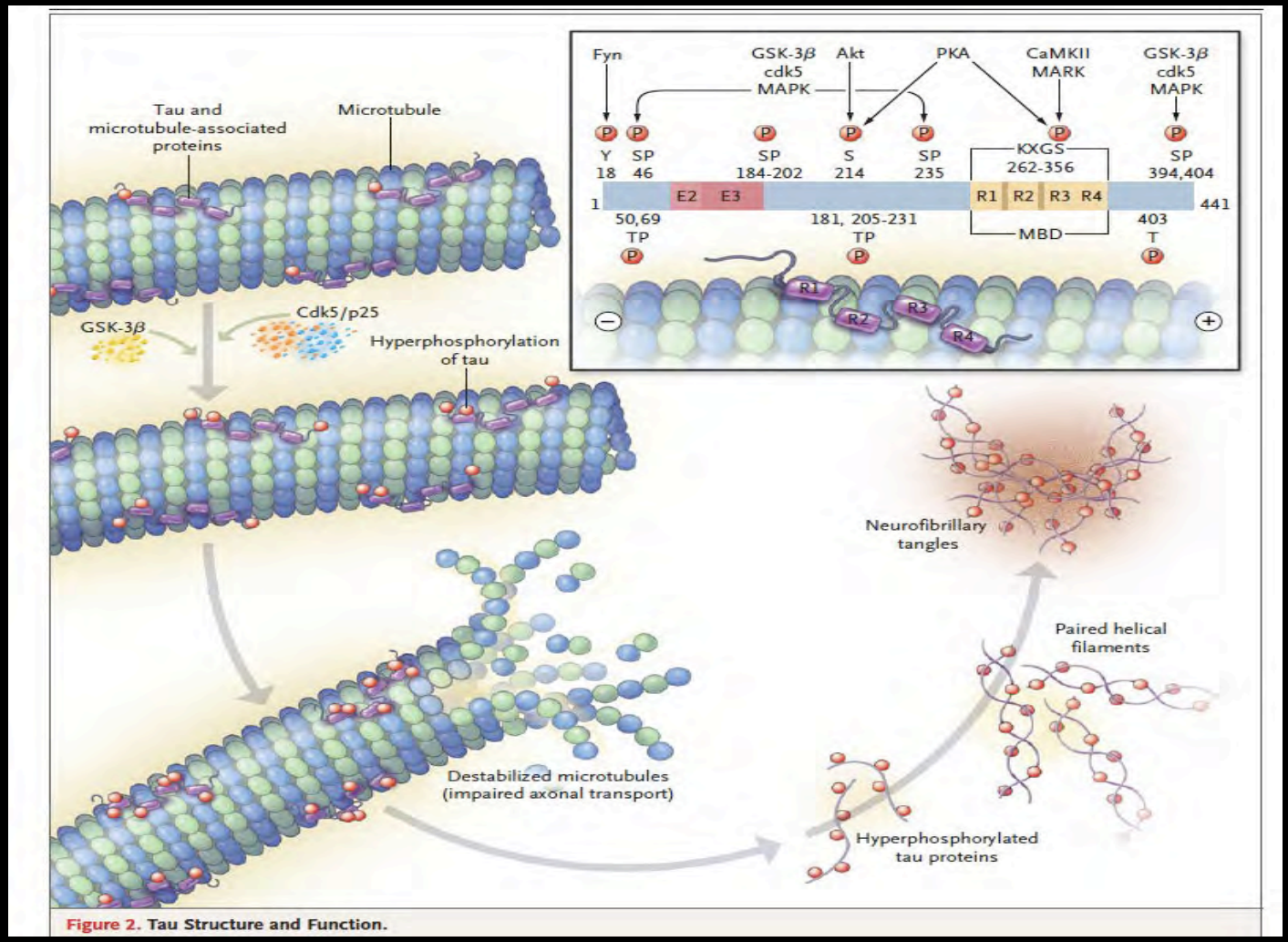


Figure 2. Tau Structure and Function.

G.S. Zubenko, M. Wusylko, B.M. Cohen, F. Boller, I. Teply

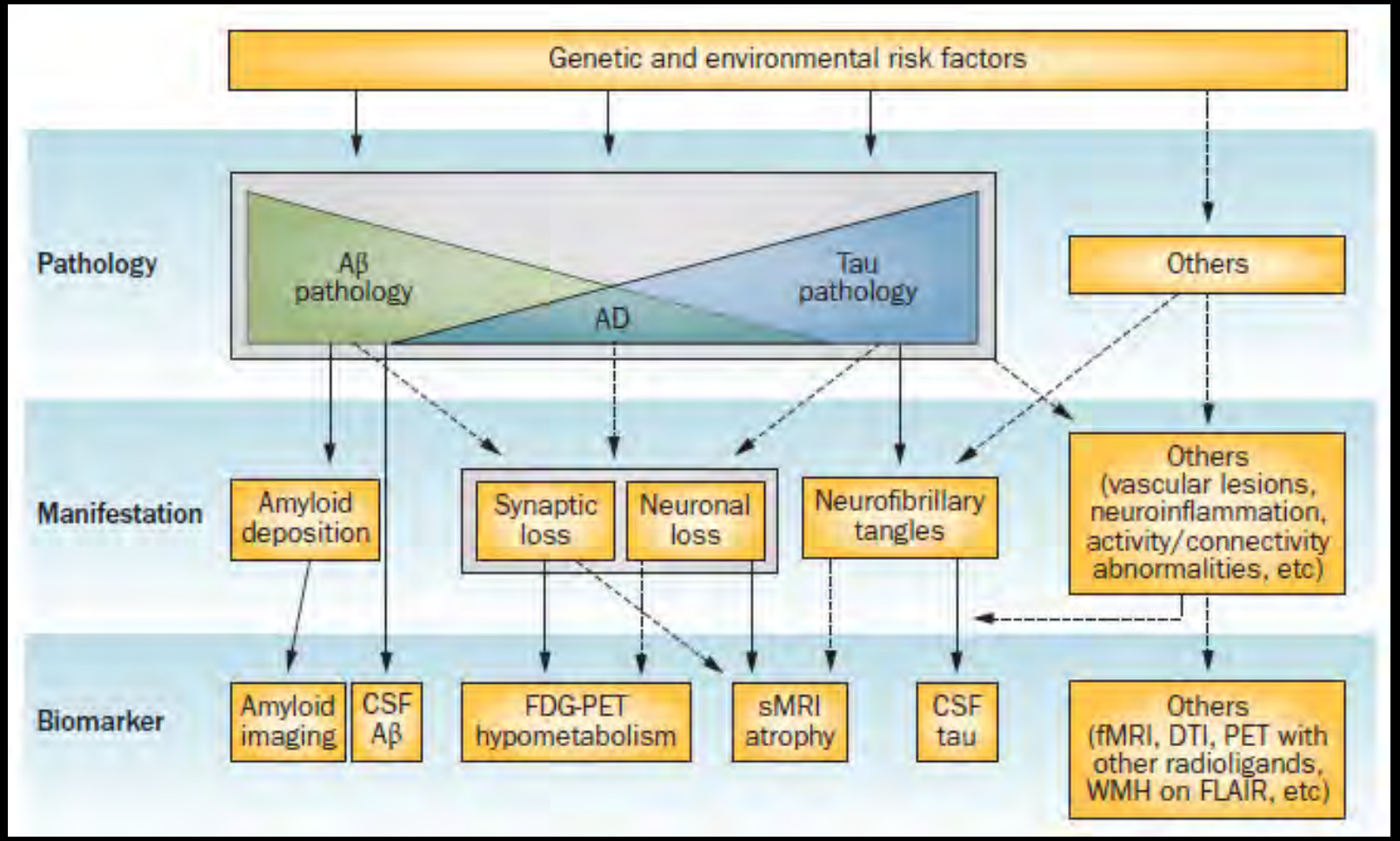
Family study of platelet membrane fluidity in Alzheimer's disease

Science, 238 (1987), pp. 539–542

DiLuca et al have reported that patients affected by Alzheimer disease show a differential level of platelet APP forms

This observation has several implications: APP processing abnormalities do occur in extraneuronal tissues, such as platelets, thus, suggesting that Alzheimer disease is a systemic disorder

Neuronal injury could be caused by different factors (with various possible sequences): Aβ and tau pathologies may be partly independent, each under the influence of common and independent risk factors, and interacting with each others to promote the AD neuropathological cascade → consider each biomarker at the same level with an additive effect on the risk of AD



Chételat, Nat Rev Neurol, 2013

Aβ-independent processes—rethinking preclinical AD

Gaël Chételat

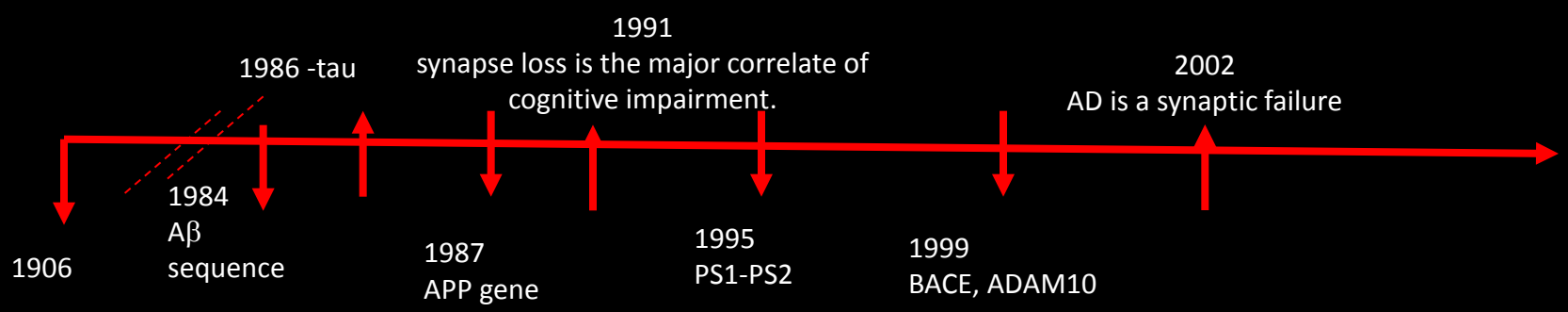
The amyloid cascade hypothesis, which posits that amyloid-β accumulation is the key event in Alzheimer disease neurodegeneration, has dominated the field for 20 years. Recent findings, however, show that neuronal-injury biomarkers are independent of amyloid-β, calling for reconsideration of the pathological cascade and assessment of alternative therapeutic strategies.

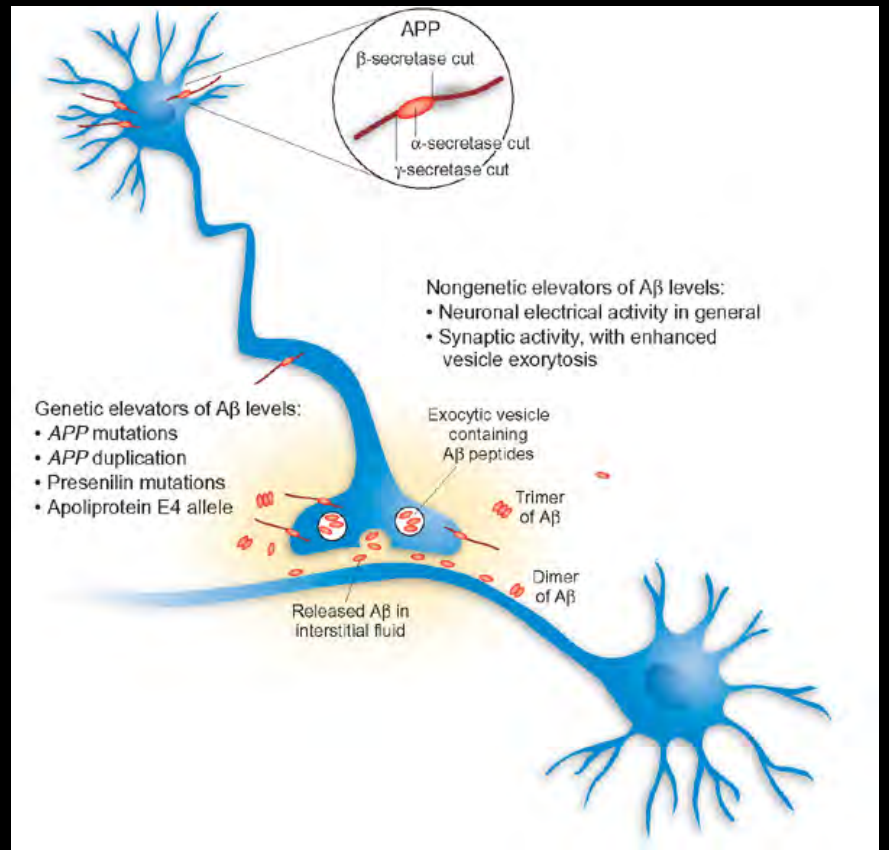
Chételat, G. *Nat. Rev. Neurol.* **9**, 123–124 (2013); published online 12 February 2013; doi:10.1038/nrneurol.2013.21

This conclusion has major implications for AD research and treatment. It contradicts not only earlier statements that SNAP represents non-AD pathology and that Aβ initiates preclinical AD, but also the sequential biomarker model of AD and—perhaps of greatest consequence—the amyloid cascade hypothesis.

We are entering an era in which the unitary view of AD as a disease with a single sequential pathological pathway—with Aβ considered as the only initial and causal event—is likely to be progressively replaced by a more complex picture in which AD is considered as a multiparameter pathology that is subtended by several partly independent pathological processes.

Complexity of AD molecular pathogenesis → Several molecular pathways are involved

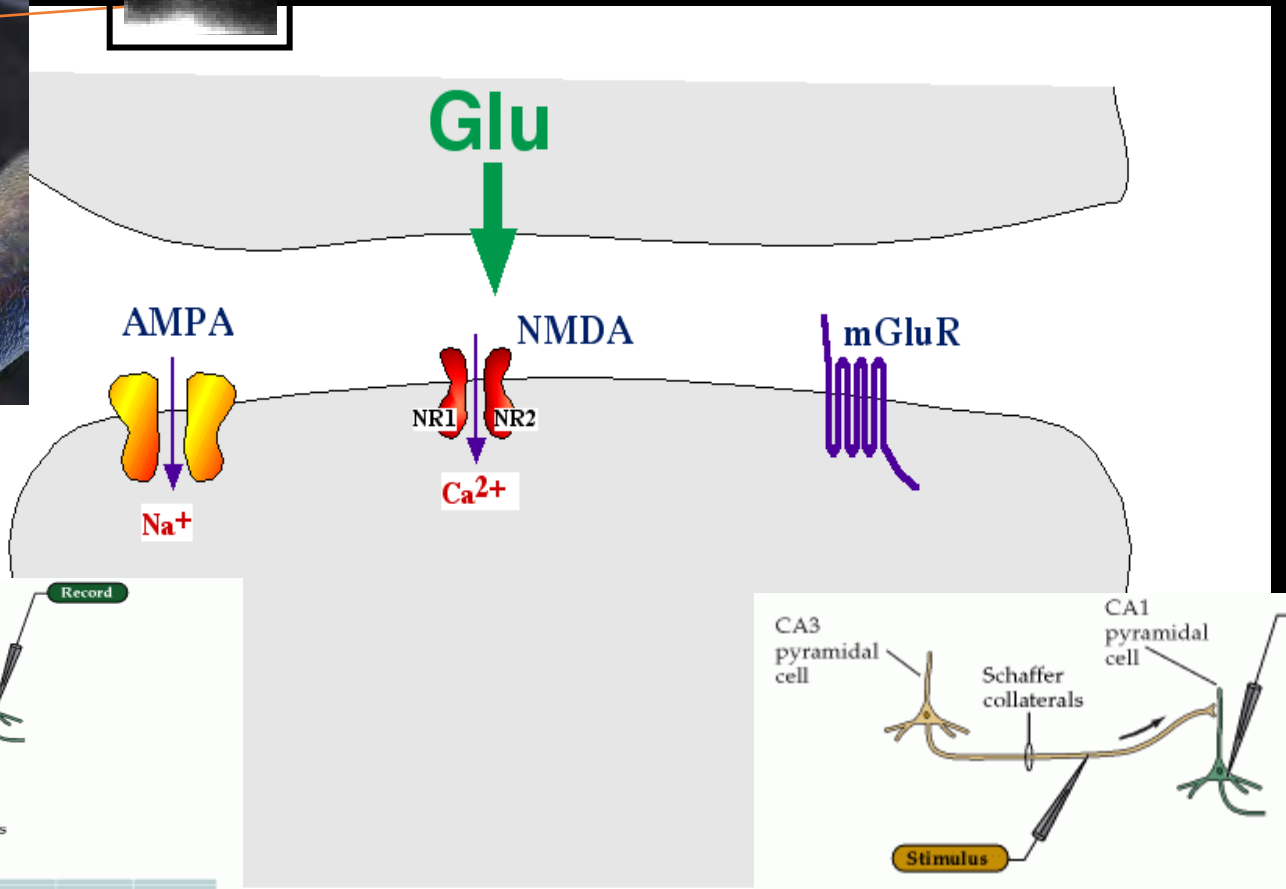


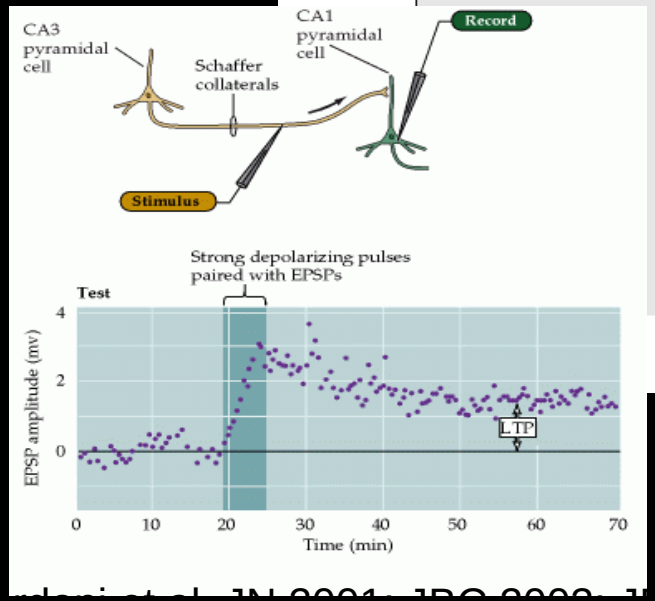


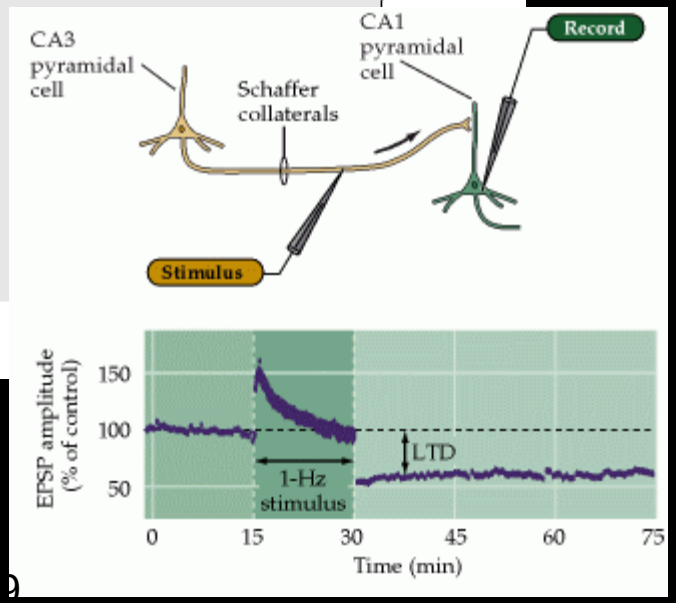
Alzheimer disease as a synaptopathy

The ups and downs of Aβ
Dennis J Selkoe, Nat Med 2006

The glutamatergic synapse

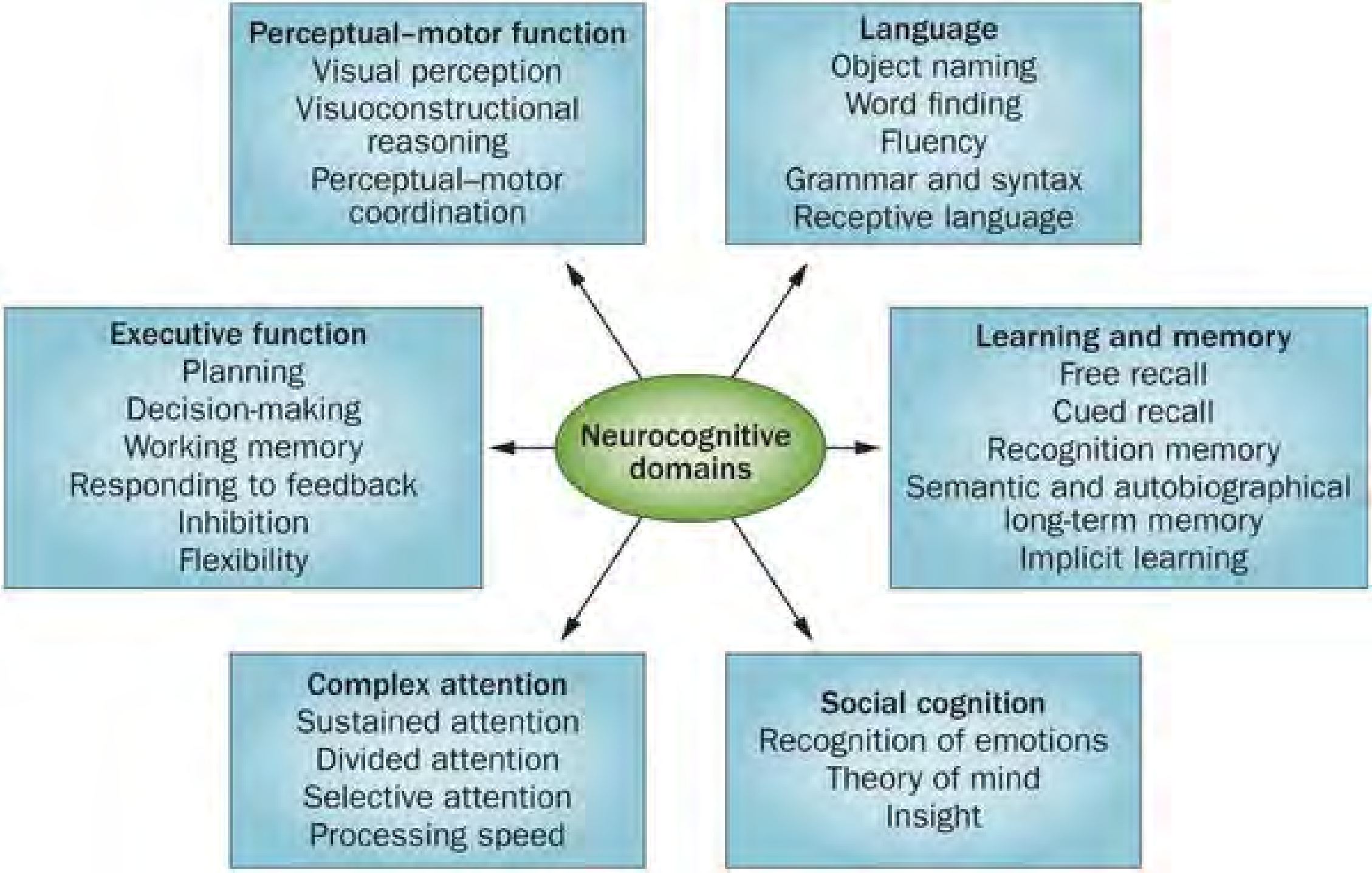






DSM II

It classified the brain syndromes according to reversibility. Acute brain syndrome (“delirium') was defined as a reversible condition and chronic brain syndrome (“dementia”) was defined as an irreversible syndrome.


Perceptual–motor function
Visual perception
Visuoconstructional reasoning
Perceptual–motor coordination
Language
Object naming
Word finding
Fluency
Grammar and syntax
Receptive language
Executive function
Planning
Decision-making
Working memory
Responding to feedback
Inhibition
Flexibility
Neurocognitive domains
Learning and memory
Free recall
Cued recall
Recognition memory
Semantic and autobiographical long-term memory
Implicit learning
Complex attention
Sustained attention
Divided attention
Selective attention
Processing speed
Social cognition
Recognition of emotions
Theory of mind
Insight

DSM 5 Major cognitive 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 (that is, 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.

BPSD’s

Some of the behavioral and psychological symptoms of dementia (BPSD), specifically agitation, aggression, and psychosis, can be even more troubling or disabling for patients, and can significantly burden family members and caregivers.

Subtypes with diagnostic criteria in DSM-5

- Alzheimer disease
- Frontotemporal lobar degeneration
- HIV infection
- Huntington disease
- Lewy body disease
- Parkinson disease
- Prion disease
- Substance and/or medication use
- Traumatic brain injury
- Vascular disease

Neurocognitive disorder with Lewy bodies

- Cognitive impairment of insidious onset and gradual progression
- Early changes are in complex attention and executive function rather than in learning and memory.
- Core features:
- Fluctuating cognition with pronounced variations in attention and alertness,
- Recurrent visual hallucinations that are well formed and detailed, and spontaneous features of Parkinsonism subsequent to the development of cognitive decline.
- Further suggestive features are rapid eye movement (REM) sleep behaviour disorder and severe neuroleptic sensitivity.

Frontotemporal neurocognitive disorder

- Insidious and gradual onset of impairment in behavior, personality and/or language
- Prominent decline and/or executive abilities
- Relative preservation of memory and perceptual motor functions
- Imaging suggests frontal and/or temporal involvement

In familiar cases a number of causative mutations have ben identified

Overlaps with PSP, CBD and motor neuron disease

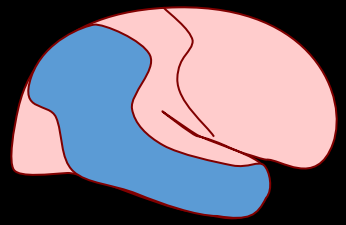
Corticobasal degeneration (corticodentatonigral degeneration)

- Progressive apraxia
- Extrapyramidal features (asymmetrical)
- Myoclonus
- Gaze palsies
- Alien hand syndrome

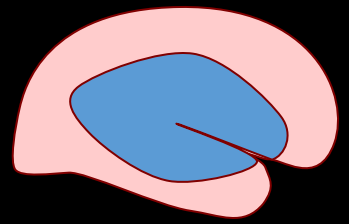
Primary Progressive Aphasia

- A language deficit initially arises as the only consequential impairment and remains predominant throughout most of the course of the disease.
- 3 subtypes: Agrammatic; logopenic; semantic.
- The underlying neuropathology of PPA is, most commonly, frontotemporal lobar degeneration in the agrammatic and semantic forms, and Alzheimer disease (AD) pathology in the logopenic form.

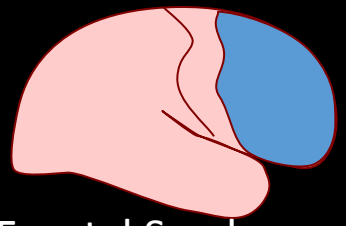
Topographie et symptomes



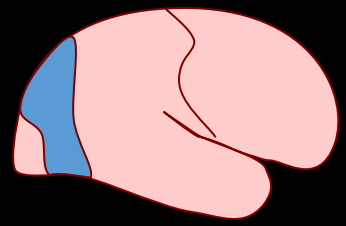
Aphaso-apraxo-agnosic S.(AD)



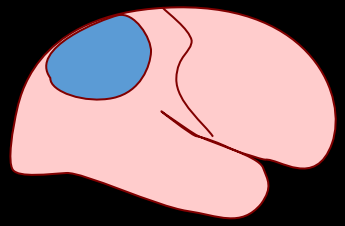
Progressive Aphasia



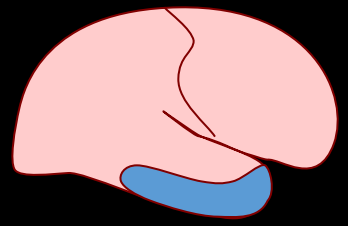
Frontal Syndrome



Progressive Agnosia



Progressive Apraxia



Semantic Dementia

Chronic Traumatic Encephalopathy and Tau Deposition

45-year old retired NFL football player with wistory of more than 10 concussions during his career

FIGURE 1. Case A. Whole-mount 50-μm coronal sections immunostained for tau with monoclonal antibody AT8 and counterstained with cresyl violet showing irregular patchy deposition of phosphorylated tau protein in frontal, subcallosal, insular, temporal, and parietal cortices and the medial temporal lobe.

McKee et al, J Neuropathol Exp Neurol 2009;68:709-735

Synucleinopathies

- Disorders sharing a common pathologic lesion composed of aggregates of insoluble α-synuclein protein in selectively vulnerable populations of neurons and glia.
- 4 types : α, β, γ and Synoretin
- Mainly PD, but also LBD and MS Atrophy

Vascular Dementia
NINDS AIREN criteria
Roman et al., 1993 revised 2002

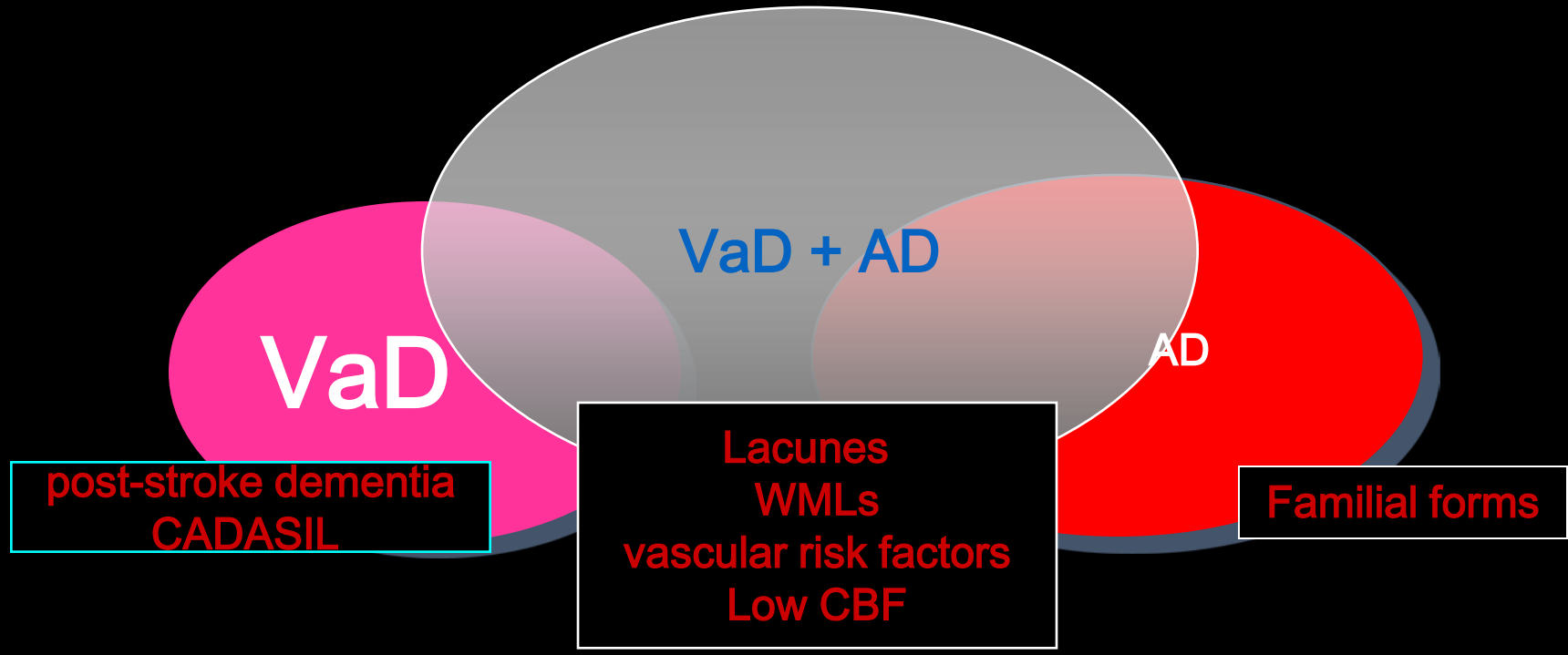
- Cognitive loss (often mainly “subcortical‘”
- Vascular brain lesions demonstrated by imaging
- Exclusion of other causes of dementia, such as AD

It may be caused by multiple strokes (MID or poststroke dementia) but also by single strategic strokes, multiple lacunes, and lesions such as border zone infarcts and ischemic periventricular leukoencephalopathy (Binswanger's disease).

Microvascular Function and Dementia

- Ischemic brain injury is a cause of cognitive impairment
- Extensive interaction between ischemic stroke and AD progression
- Diffuse white matter lesions currently provide the main neuroimaging marker of cerebrovascular impairment
- In the absence of large vessel disease, ASL MRI should provide a direct measure of microvascular integrity

Interactions Between VaD and AD



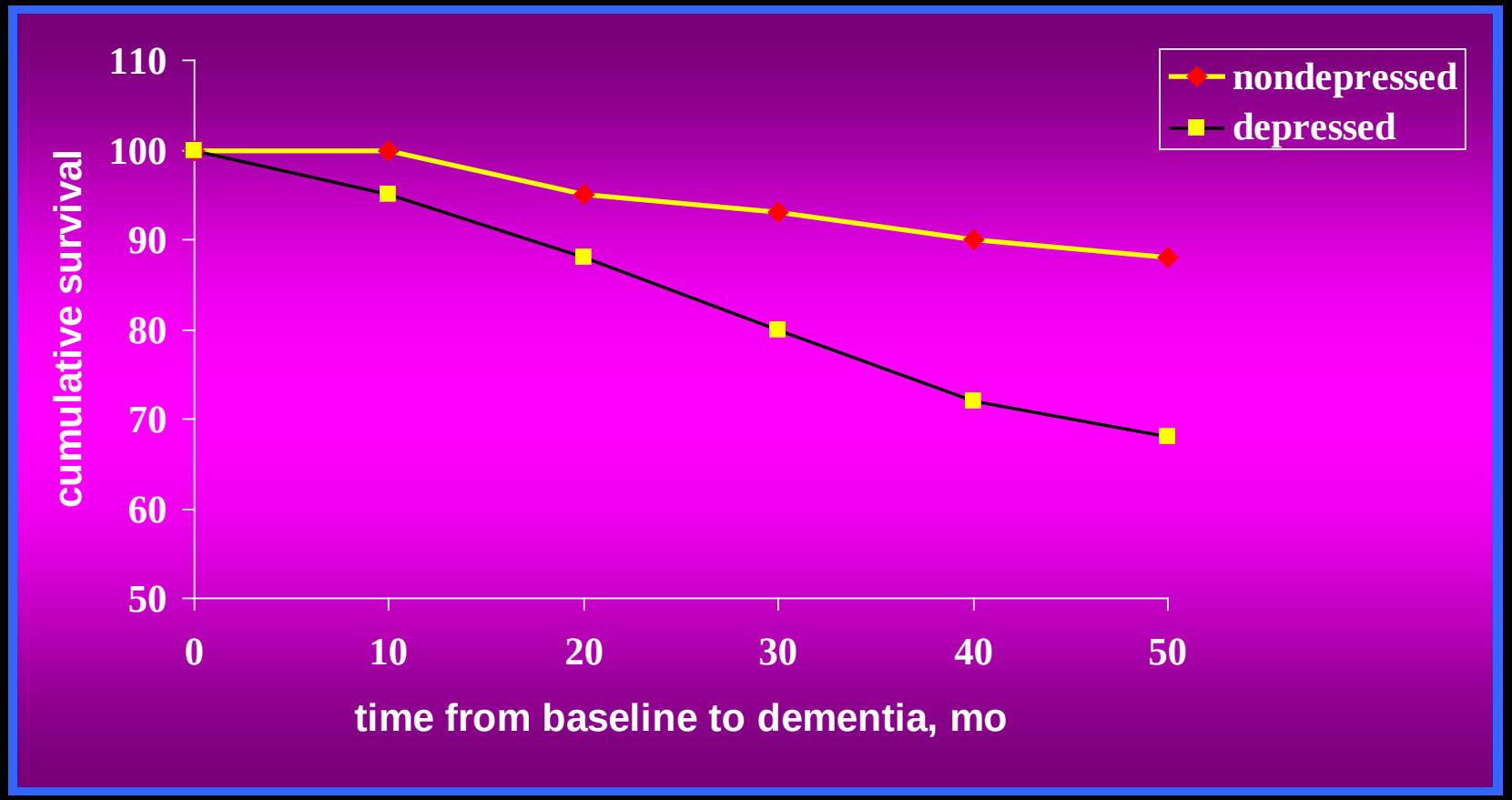
Source: T. Erkinjuntti modified by Roman

Case-control and prospective epidemiological studies illustrating the high co-morbidity and risk incidence between neuropsychiatric disorders and AD

Psychiatric diagnosis	Co-morbidity with MCI/dementia	Studies reporting associated risk towards dementia progression
Major depressive disorders	15–17% prevalence in AD patients [255, 256]; 20–63% prevalence in MCI patients (reviewed in [257])	Meta-analysis show an estimated doubling of incidence risk of AD in MCI patients with MDD [258, 259]. Late-life depression increases risk of dementia up to three times [260]
Anxiety	70% co-morbidity (54% together with depression) in AD patients [261]. 25–36% prevalence in MCI patients [262, 263]	83% risk for developing AD in MCI patients with anxiety symptoms [262]
Apathy	55% prevalence in AD patients [264]; 20% prevalence alone and 29% prevalence together with depression in AD patients [265]. 50% prevalence in MCI patients [266]	Depression (67 vs. 31%) and apathy (50 vs. 18%) more common in MCI subjects later diagnosed with AD [266]. Apathy, but not depression predicted conversion to AD in MCI patients [23].

Aznar & Knudsen, J Alz Dis, 2011

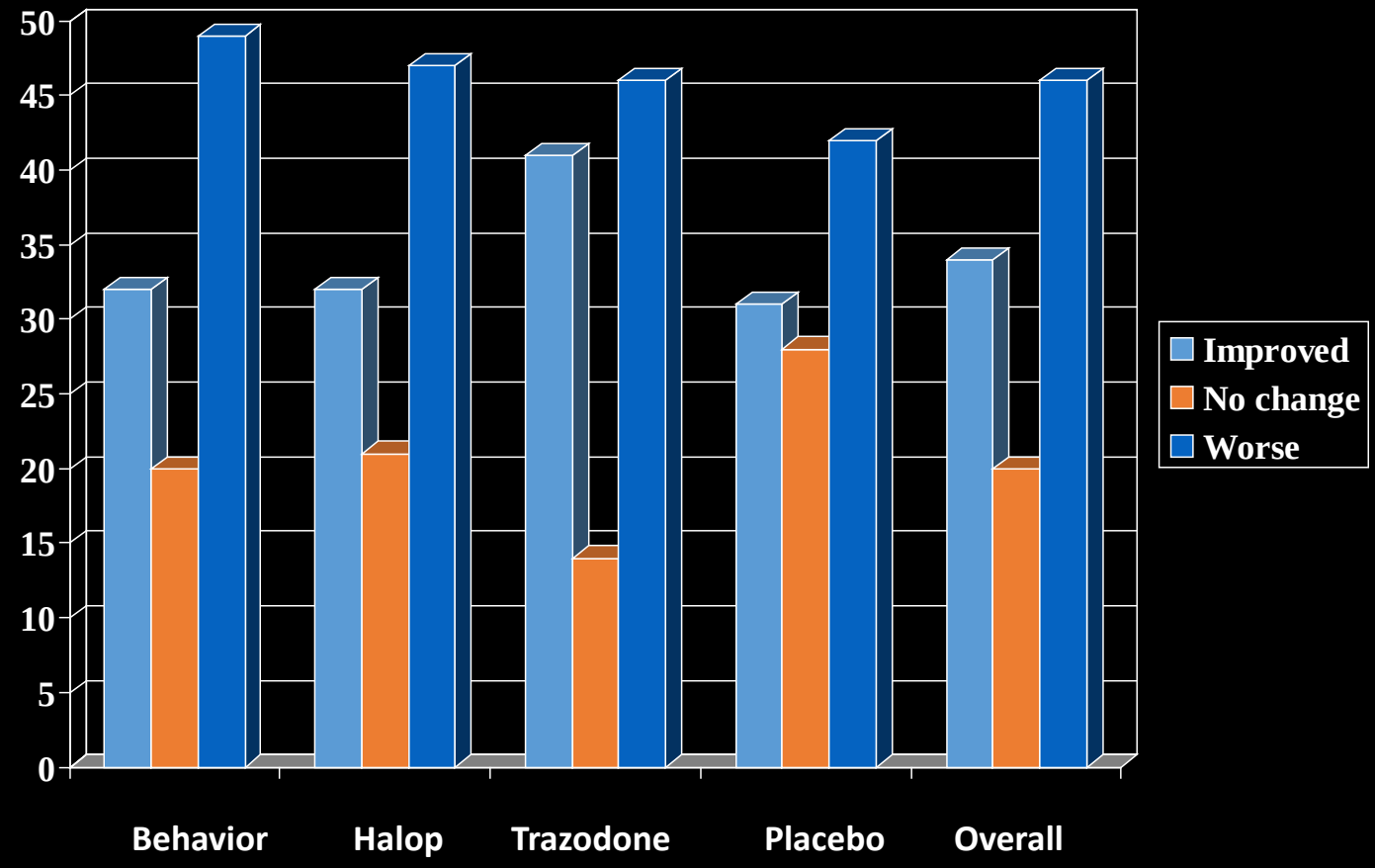

F. Netter
© CIBA



Cumulative survival for subjects with and without depressed mood at baseline evaluation , as function of time from baseline evaluation to the diagnosis of dementia during follow-up

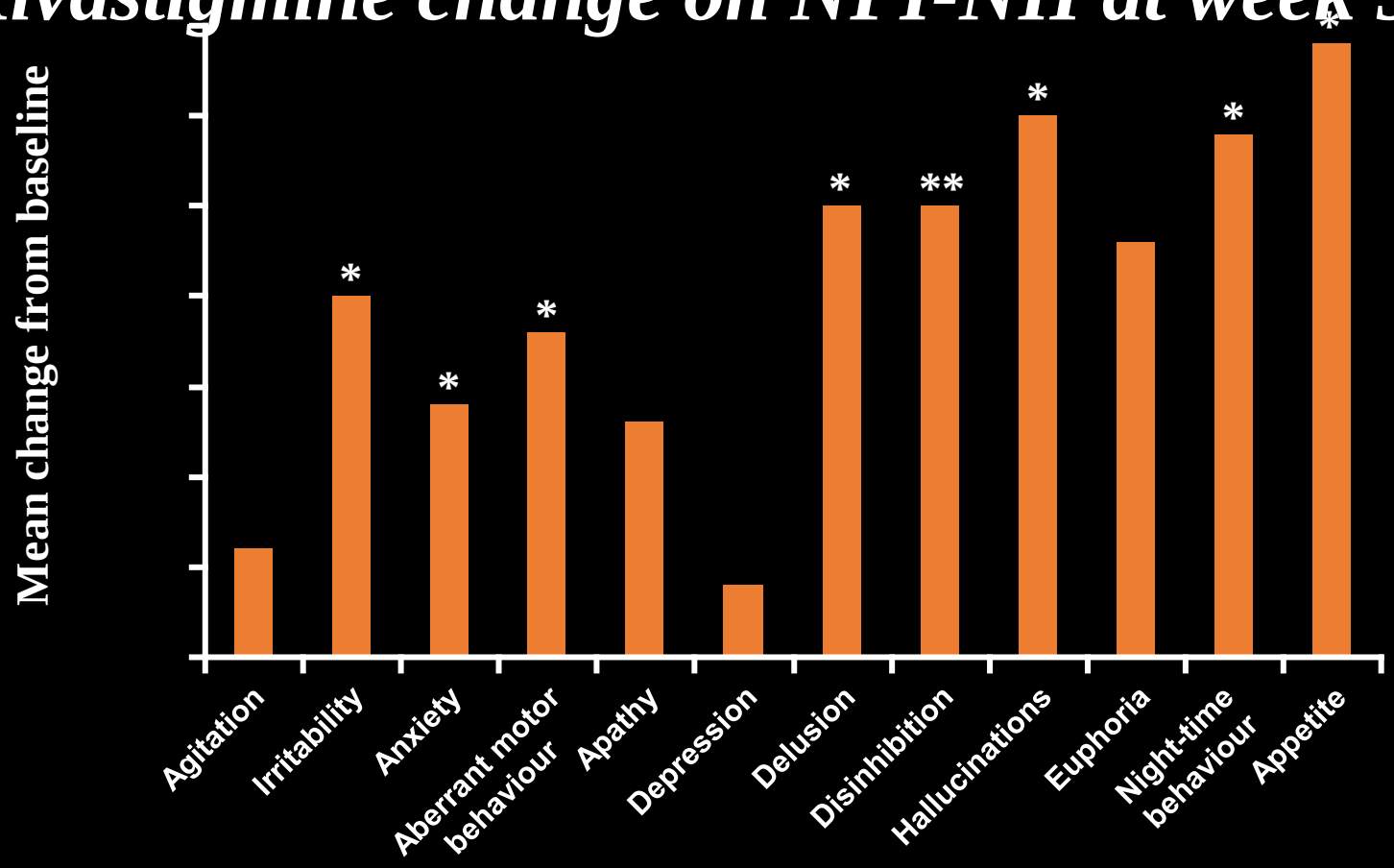
Devanand et al. Arch Gen Psychiatry 1996;53:175-182

Rx of Agitation
Teri et al., 2000



Mean change in scores in patients symptomatic at baseline

Rivastigmine change on NPI-NH at week 52



*p<0.05 vs baseline; **p<0.001 vs baseline; OC analysis
NPI-NH=Neuropsychiatric Inventory Nursing Home Version

Summary

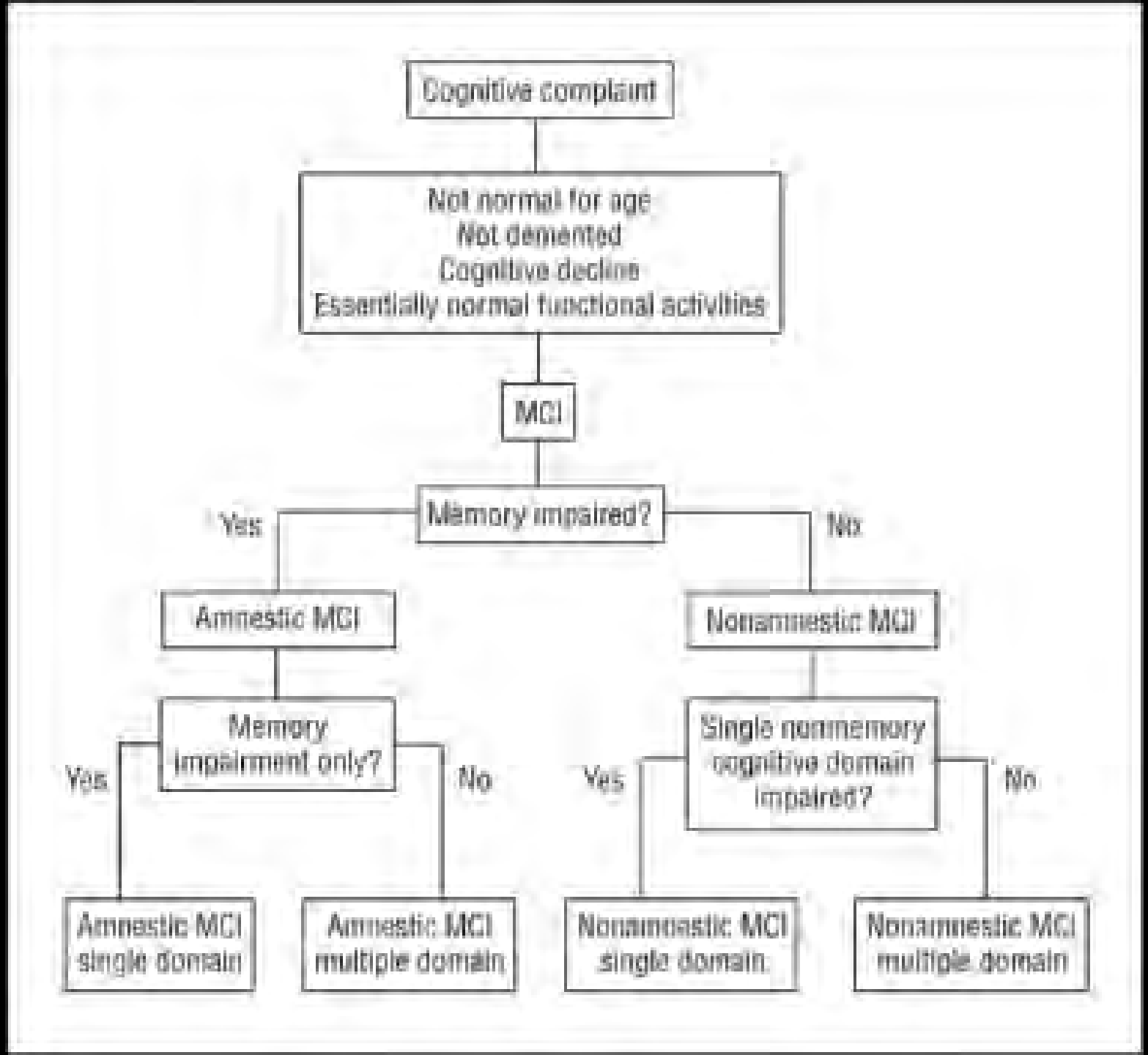
- BPSD direct expression of the brain disease process
- Cholinesterase inhibitors induce behavioral changes and reduce use of psychotropic medications
- Association of non pharmacological & pharmacological interventions

Mild Cognitive Impairment (MCI)

- Patient's complaint of memory loss (entourage).
- Performance is abnormal at memory tests.
- ADL intact,
- IQ normal (vocabolary); no dementia

Petersen, 2003

- Amnestic MCI
- Multiple domain MCI
- Single non memory domain MCI (executive, language…)

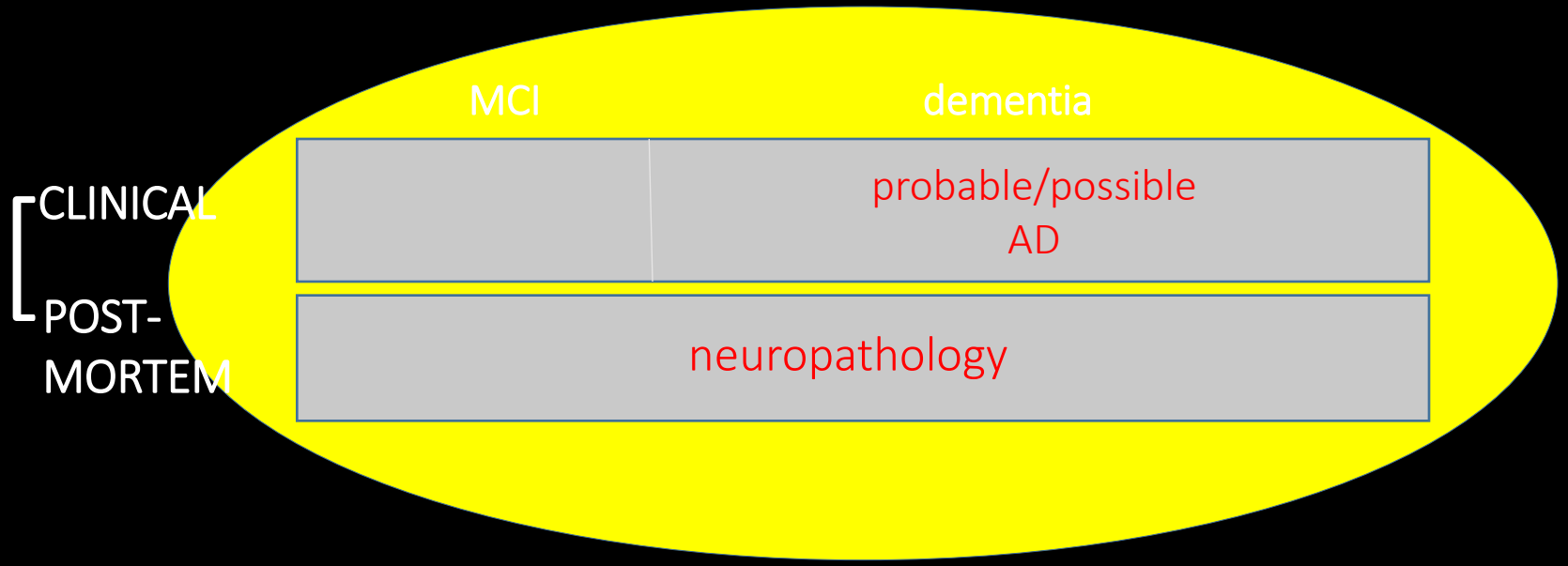

Cognitive complaint
Not normal for age
Not demented
Cognitive decline
Essentially normal functional activities
MCI
Memory impaired?
Yes
No
Amnestic MCI
Nonamnestic MCI
Memory impairment only?
Single nonmemory cognitive domain impaired?
Yes
No
Yes
No
Amnestic MCI single domain
Amnestic MCI multiple domain
Nonamnestic MCI single domain
Nonamnestic MCI multiple domain

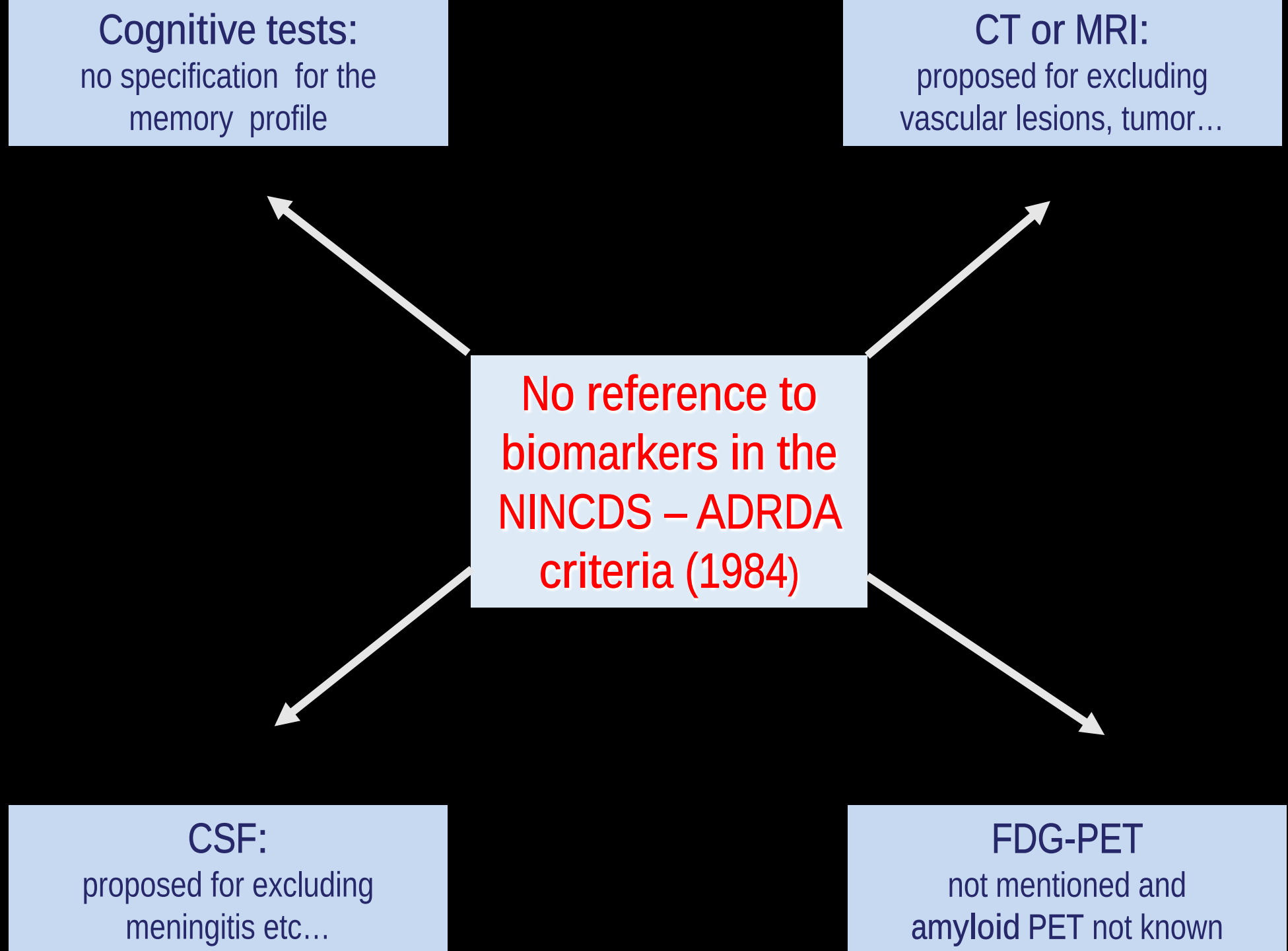
MCI ten years later
Petersen et al. Arch Neurology
66: 1447-1445, 2009

1984 The NINCDS-ADRDA criteria

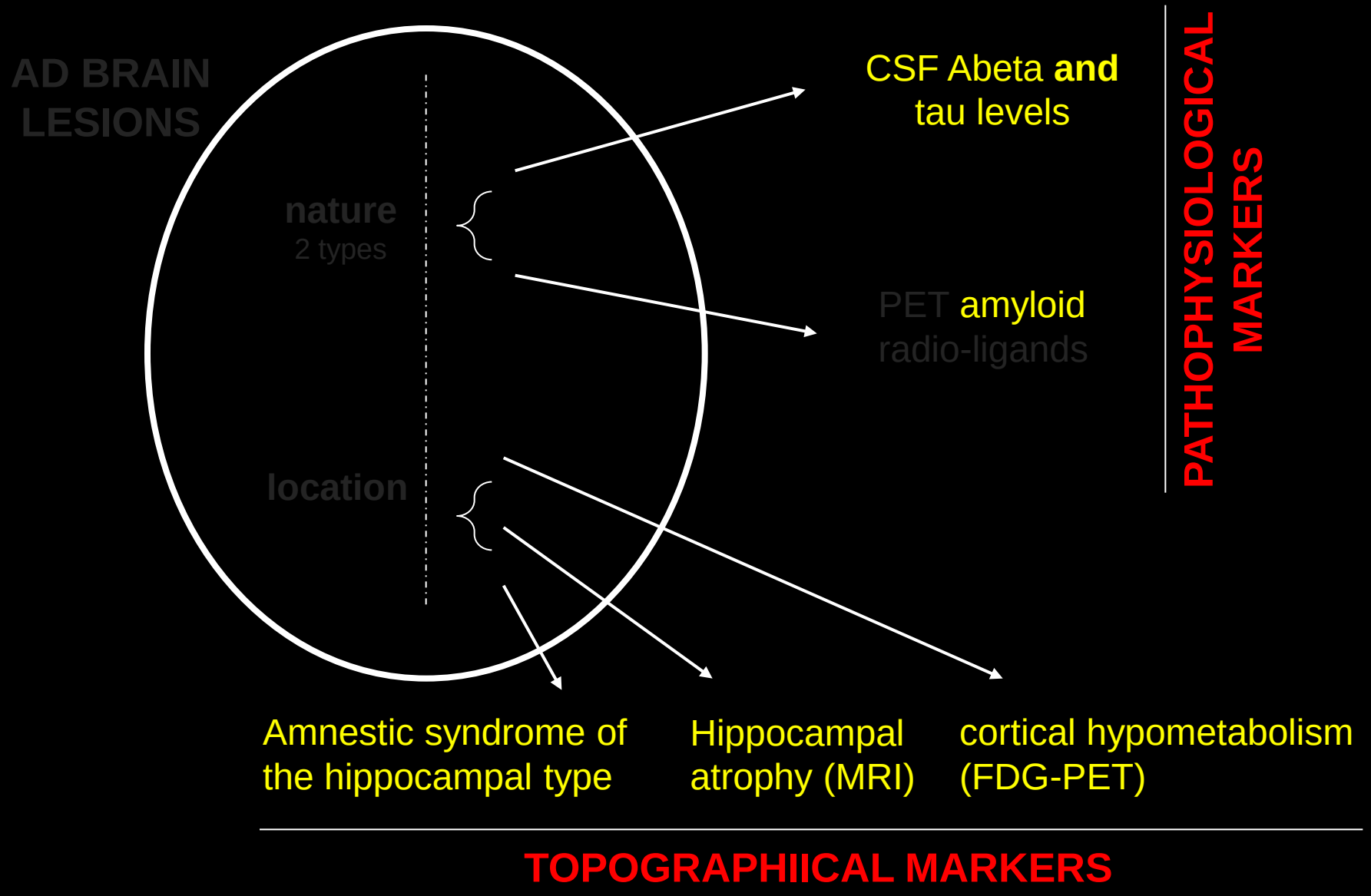
The rules

1) **The clinical diagnosis** of AD cannot be certified and needs a post-mortem confirmation to be ascertained
2) **The clinical diagnosis** of AD can only be ‘probable’
3) **The clinical diagnosis** of AD can only be made when the disease is advanced and reaches the threshold of dementia




Cognitive tests:
no specification for the memory profile
CT or MRI:
proposed for excluding vascular lesions, tumor…
No reference to biomarkers in the NINCDS – ADRDA criteria (1984)
CSF:
proposed for excluding meningitis etc…
FDG-PET
not mentioned and amyloid PET not known

(2) Discovery of biomarkers of AD



Being more specific even at the prodromal stage of AD

	memory	CSF	MRI	PET-FDG	PET-ligand
NINCDS - ADRDA	not specified	exclusion	exclusion	not specified	not known
New criteria	amnestic no cues MC help	↘ Abeta ↗ T- P tau	MTL atrophy	P–T hypo metabolism	PiB retention
Specificity for Prodromal AD	>90% *Sarazin 2007*	>90% *Hanson 2006*	>85% *Colliot 2008*	>80% *Mosconi 2004*	>95% *Rowe 2007*

Sarazin et al. *Neurology.* 2007;69:1859-2016. Hansson et al. *Lancet Neurol*. 2006;5:228–234. Colliot et al. *Psychiatr Sci Hum Neurosci*. 2008;6:68-75. Mosconi et al. *Neurology*. 2004;63:2332-2340. Rowe et al. *Alzheimers Dement*. 2007;3.

IWG research criteria for the diagnosis of AD: revising the NINCDS-ADRDA criteria

Dubois et al., Lancet Neurol., 2007

1 major clinical criterion

Amnestic syndrome of the 'hippocampal type'

(that can be isolated or associated to other cognitive / behavioral changes)

+ 1 or more biomarker present

Structural: atrophy of medial temporal lobe (MRI)

Biological: changes in biomarkers (CSF)

Functional: temporo-parietal hypometabolism on FDG-PET

Molecular: ligand retention on amyloid-PET

Applicability of the New Criteria: When?

1) In research settings: A high diagnostic accuracy is needed for:

- study of **specific outcomes**: requires well phenotyped cohorts
- academic **research projects**: not on heterogeneous population with a low/intermediate likelihood of diagnostic accuracy
- inclusion in **clinical trials** : most of ongoing trials are based on the New Criteria: *BMS (γ secretase inhibitor); Affiris (immunotherapy): Roche (immunotherapy); Lilly (BACE inhibitor); Nutricia (Medical food-Souvenaid); Sanofi (immunotherapy) …*

2) In specific clinical conditions: BMs increase diagnostic accuracy that may be required in case of:

- young onset AD
- complex cases: PCA, PPA…

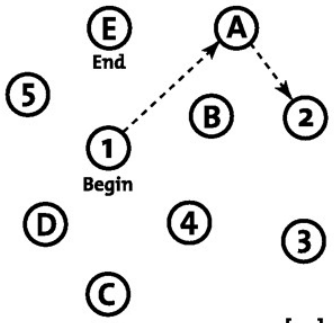
Neuropsychological tests (NACC)

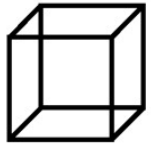
MoCA	Logical Memory Immediate
Word List Learning	Digit Span forward
Rey Figure copy/immediate recall	Digit Span backwards
Block Design	Categories
Stroop	Trails A
Fluency Tasks	Trails B
Abstract Reasoning/Similarities	WAIS R Digit Symbol
Serial 7's	Logical Memory recall

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE





Copy cube [ ]

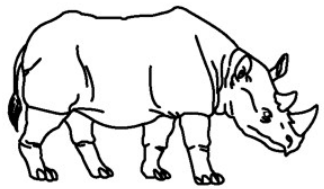
Draw CLOCK (Ten past eleven) (3 points) [ ]

[ ] Contour [ ] Numbers [ ] Hands

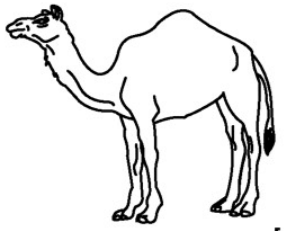
POINTS __/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

 Version 7.0 www.mocatest.org

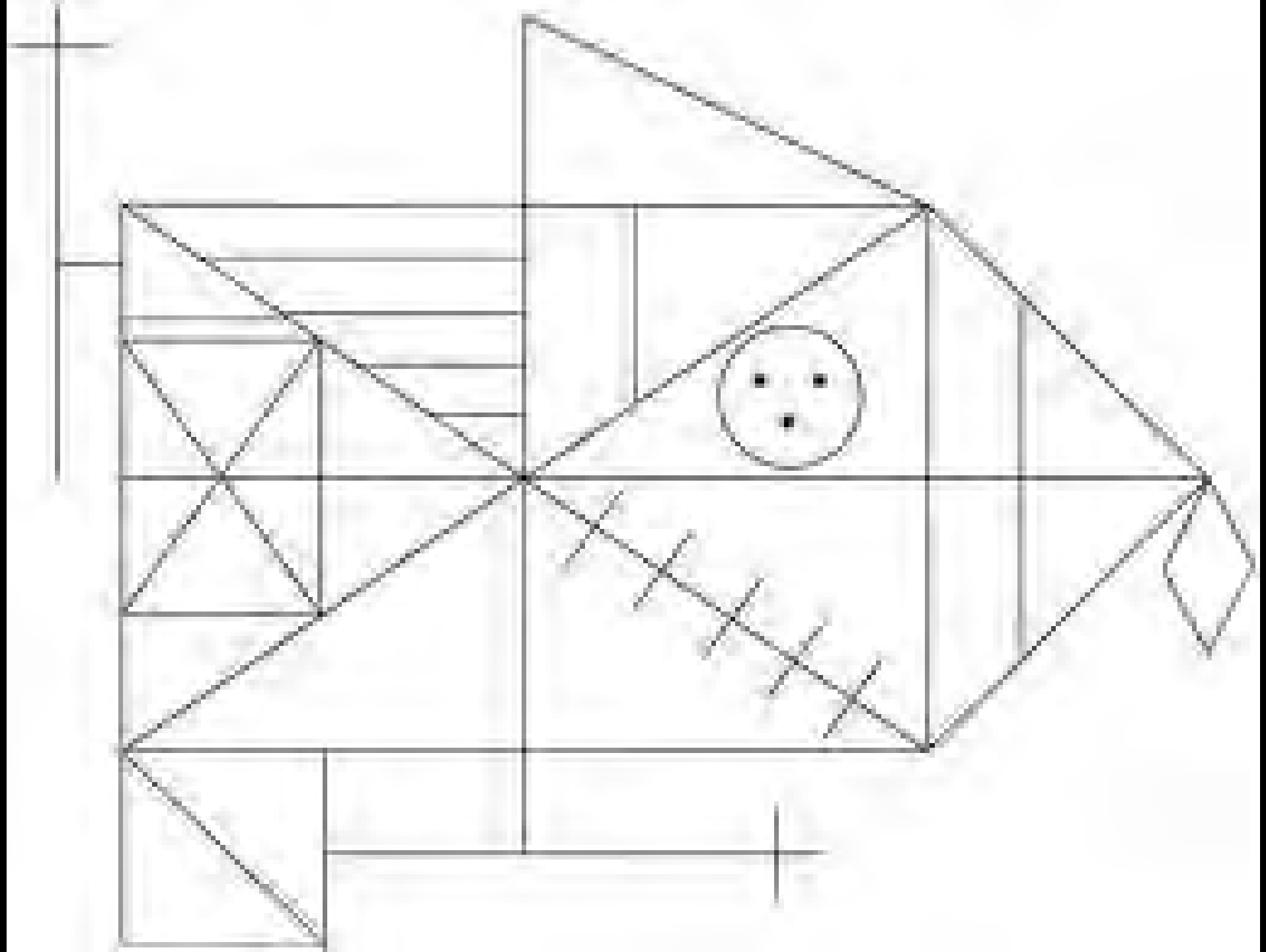
Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

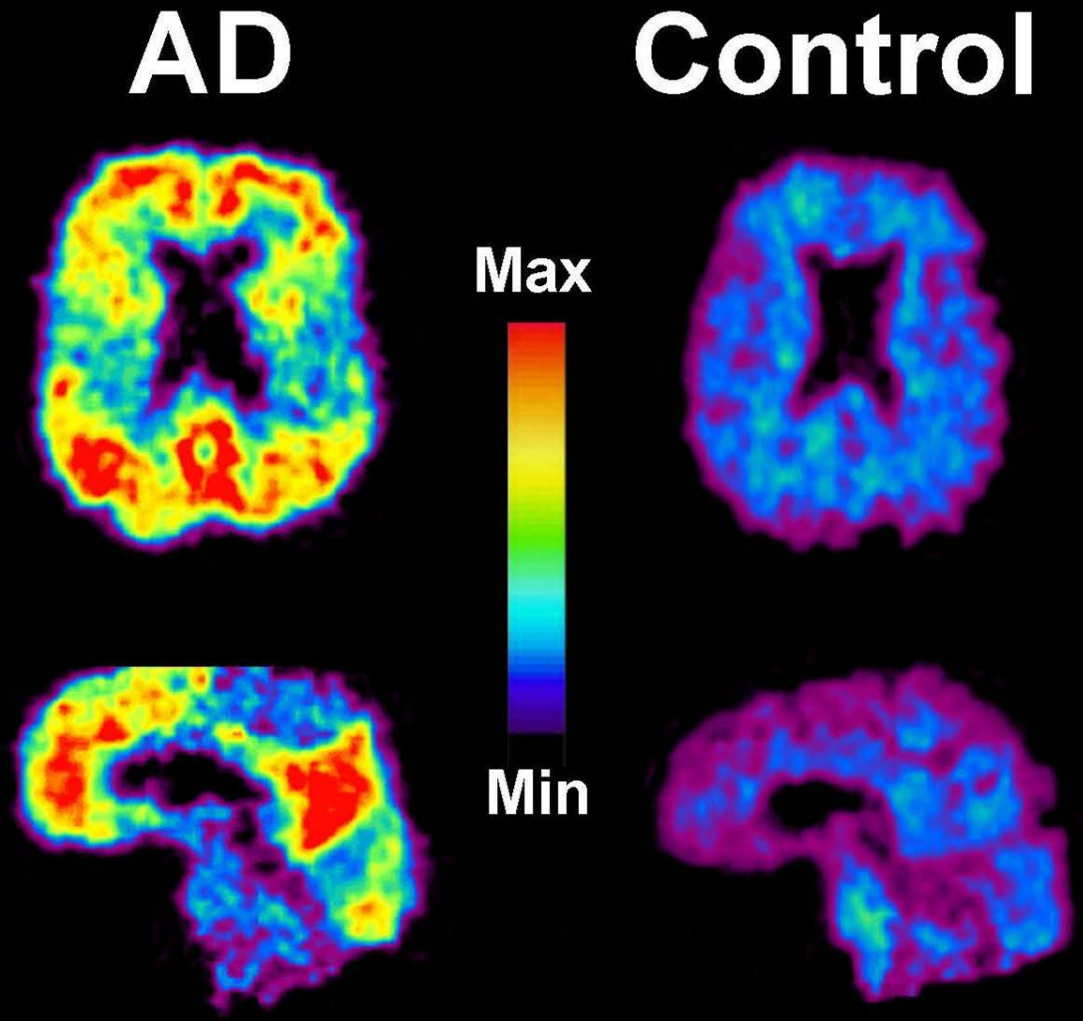
Administered by: _____

BLUE	RED	YELLOW	ORANGE
GREEN	BLUE	PURPLE	RED
PURPLE	YELLOW	RED	BLUE
ORANGE	BLUE	YELLOW	RED
RED	GREEN	ORANGE	BLUE
PURPLE	YELLOW	BLUE	ORANGE



Imaging

In 2004, a breakthrough in the clinical evaluation of AD emerged with the development of ^{11}C-Pittsburgh compound B (PiB), an analog of thioflavin-T, the fluorescent dye used to visualize Aβ plaques in postmortem samples of AD brain.



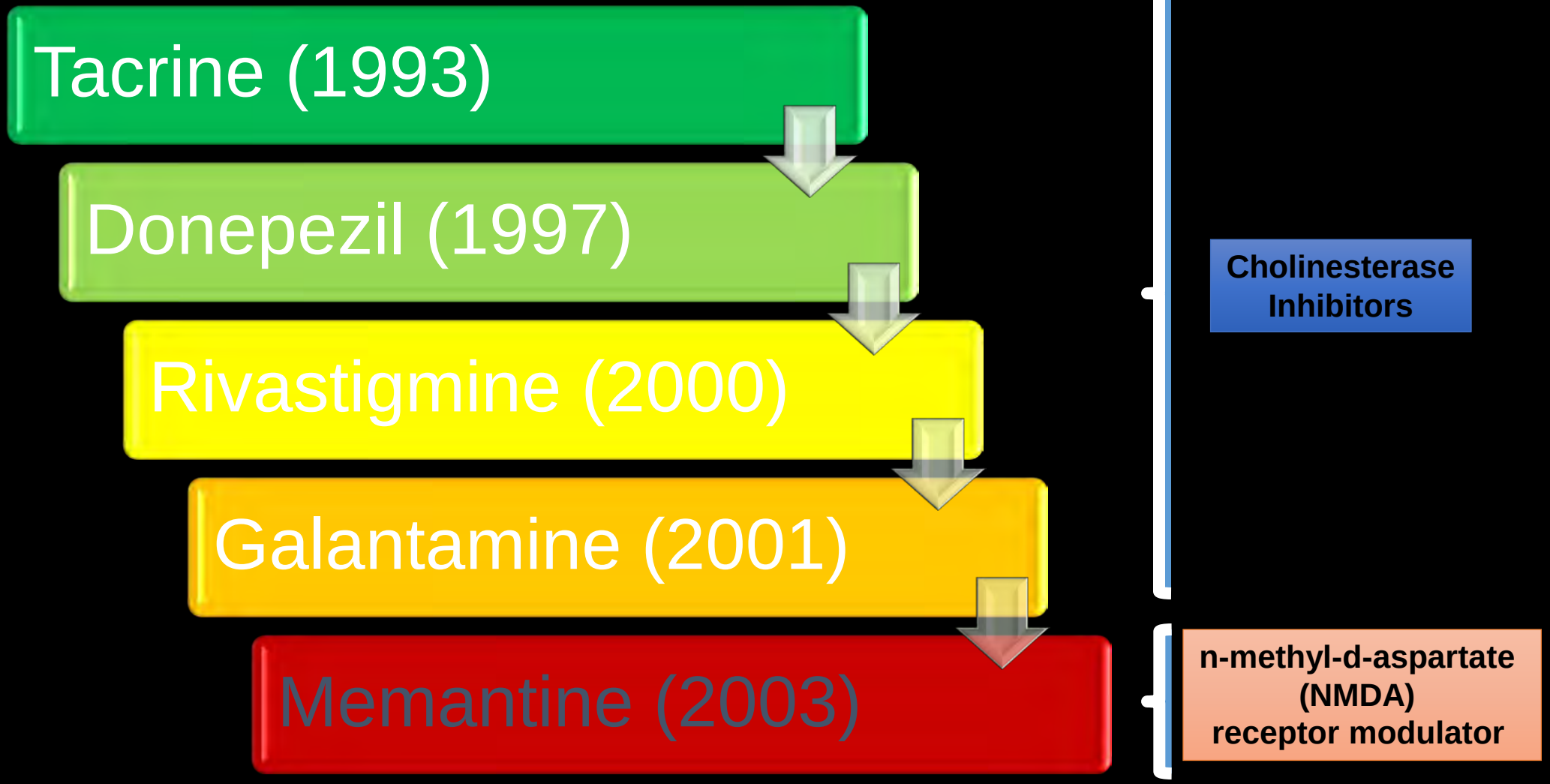
PiB PET SCANS

University of Pittsburgh
PET Amyloid Imaging Group

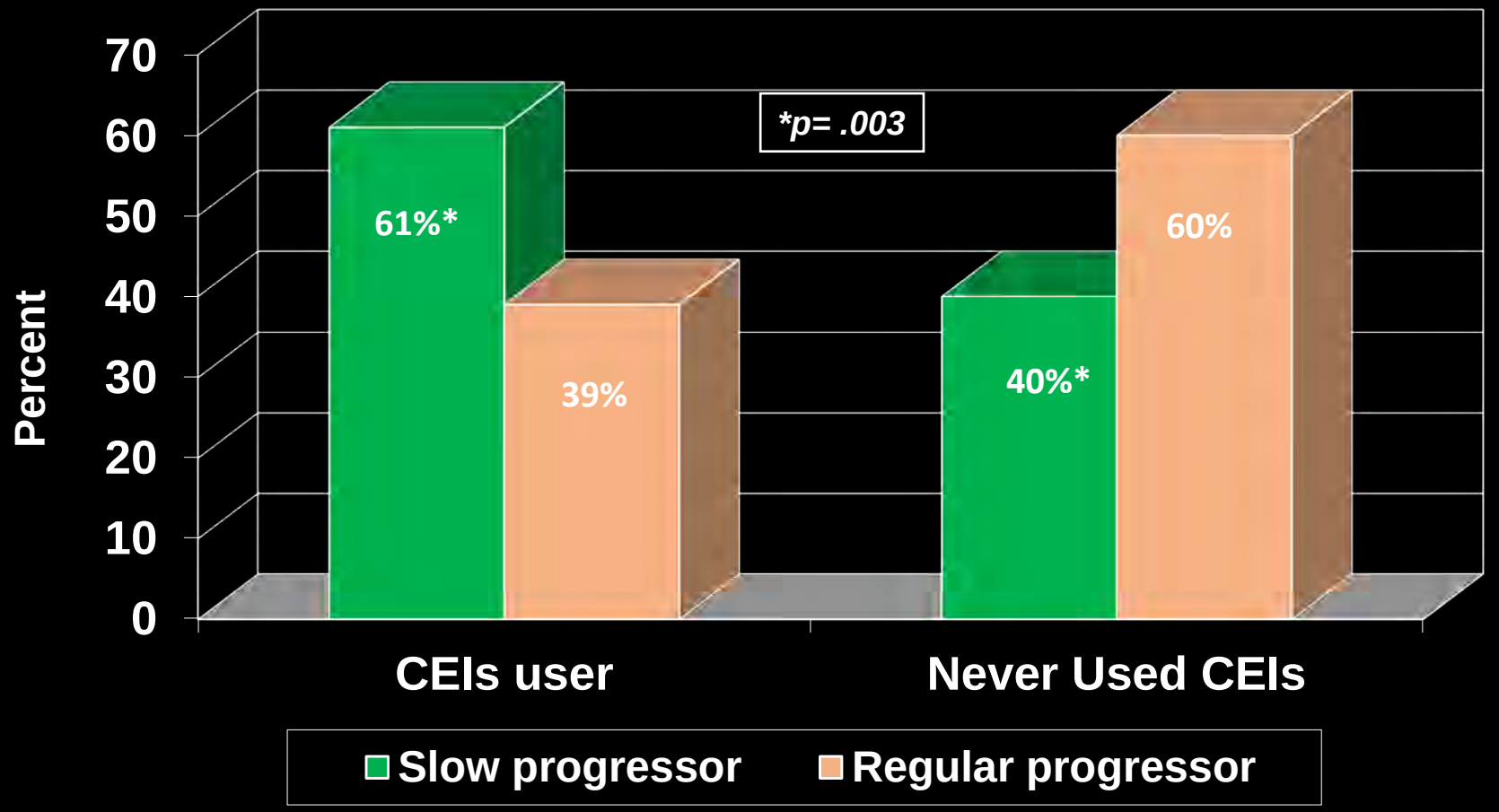
Imaging

More recent advances include the development of PET radiotracers for imaging aggregates of hyperphosphorylated tau protein in neurofibrillary tangles.

Approved Medications for Alzheimer's disease



Rate of progression in “slow” and “regular” progressors in patients with and without cholinesterase inhibitors (CEIs)

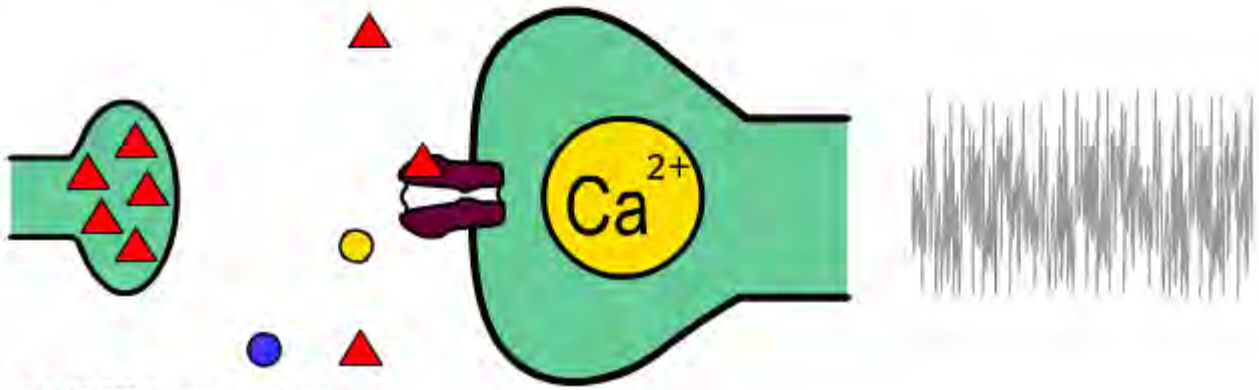


Likelihood that a patient would have a MMSE score change of 2 or less after one-year follow-up (Logistic regression analysis):
-Sedative/hypnotics use (OR= .38, 95% CI: .15 – .98)
-Cholinesterase inhibitors (OR= 2.32, 95% CI: 1.4 – 3.7)

Lopez et al. JAGS, 2005

Memantine M and dementia

Memantine protects the neuron from elevated prolonged calcium influx



NMDA receptor

magnesium

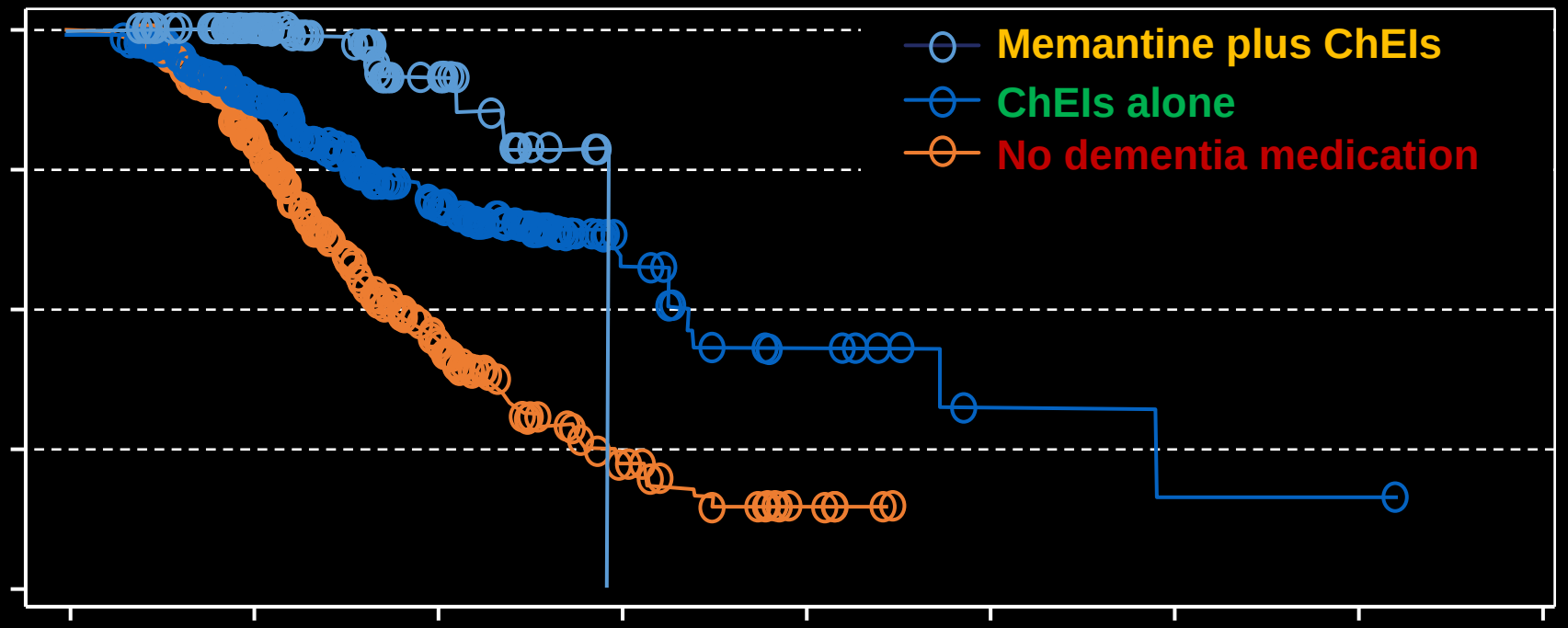
glutamate

calcium

MERZ

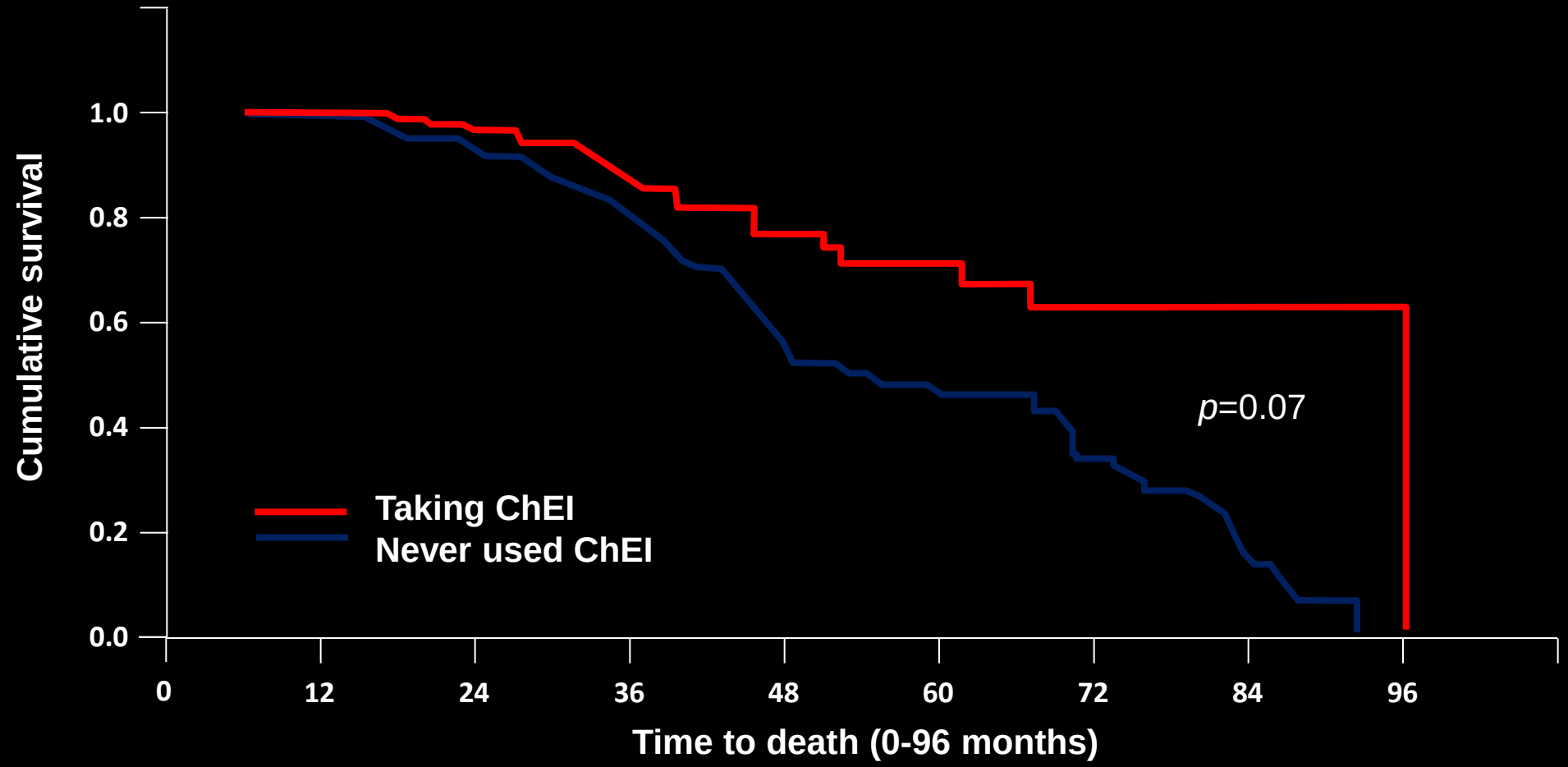
Memantine in combination with Cholinesterase inhibitors delays nursing home admission

(N= 949 Probable AD Patients)



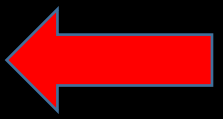
Lopez et al. J Neurol Neurosurg Psychiatry 2009; 80: 600–607

There is no association between cholinesterase inhibitors use and time to death



Primary Prevention Trials
Ginkgo Evaluation for Memory Study (GEMS)
All Dementia and Subtypes of Dementia comparing *Ginkgo* to placebo

Outcome	All Participants (N=3069)		
	# of Events	HR (95% CI)	P value
All Dementia	523	1.12 (0.94, 1.33)	0.21
Alzheimer's* without vascular dementia**	353	1.18 (0.97, 1.46)	0.11
Alzheimer's with vascular dementia	124	1.09 (0.77, 1.55)	0.63
Total Alzheimer's Dementia	477	1.16 (0.97, 1.39)	0.11
Vascular dementia without Alzheimer's	24	0.41 (0.17, 0.98)	0.05

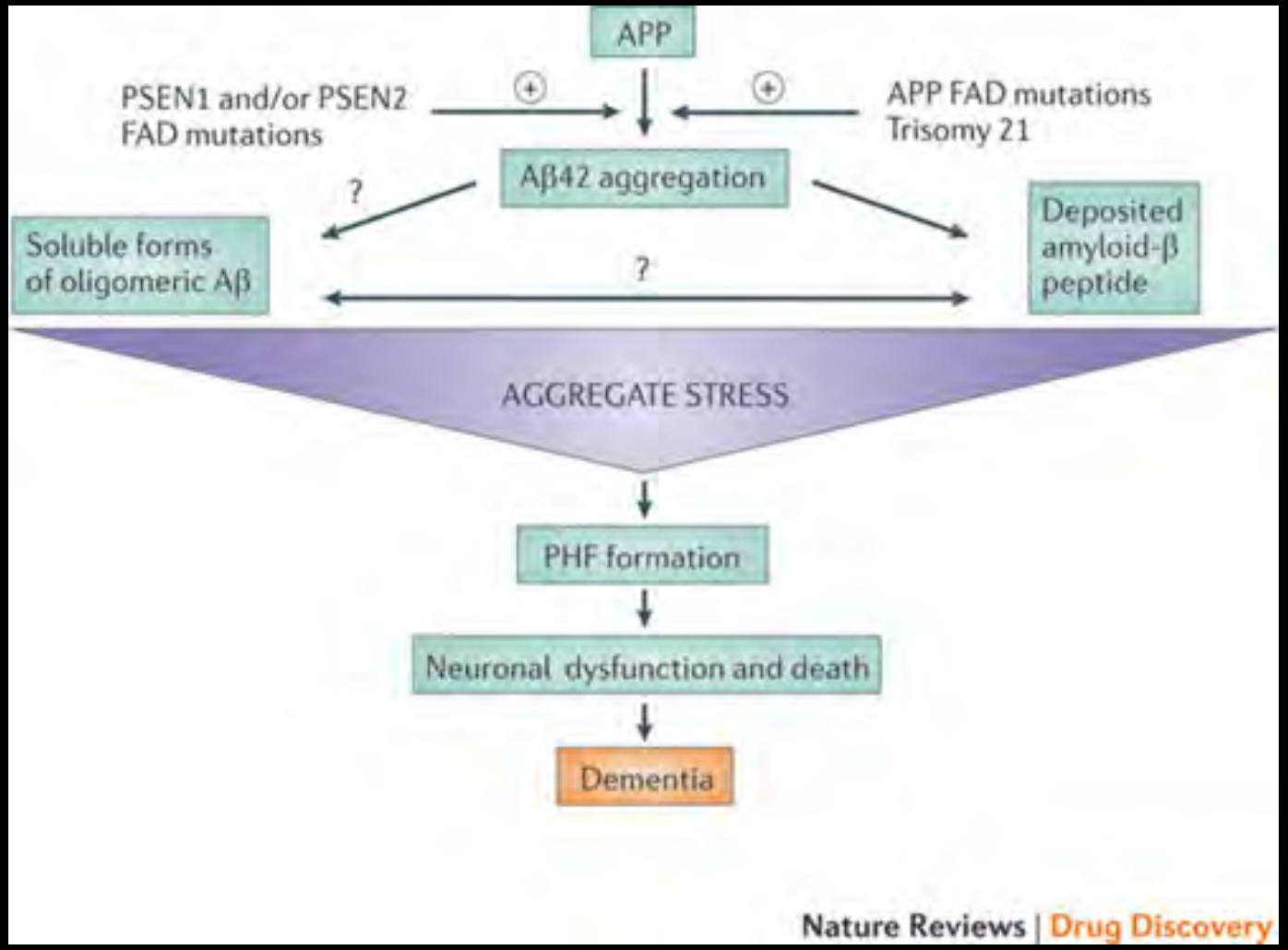


DeKosky et al. JAMA 2008: 300: 2253-2262

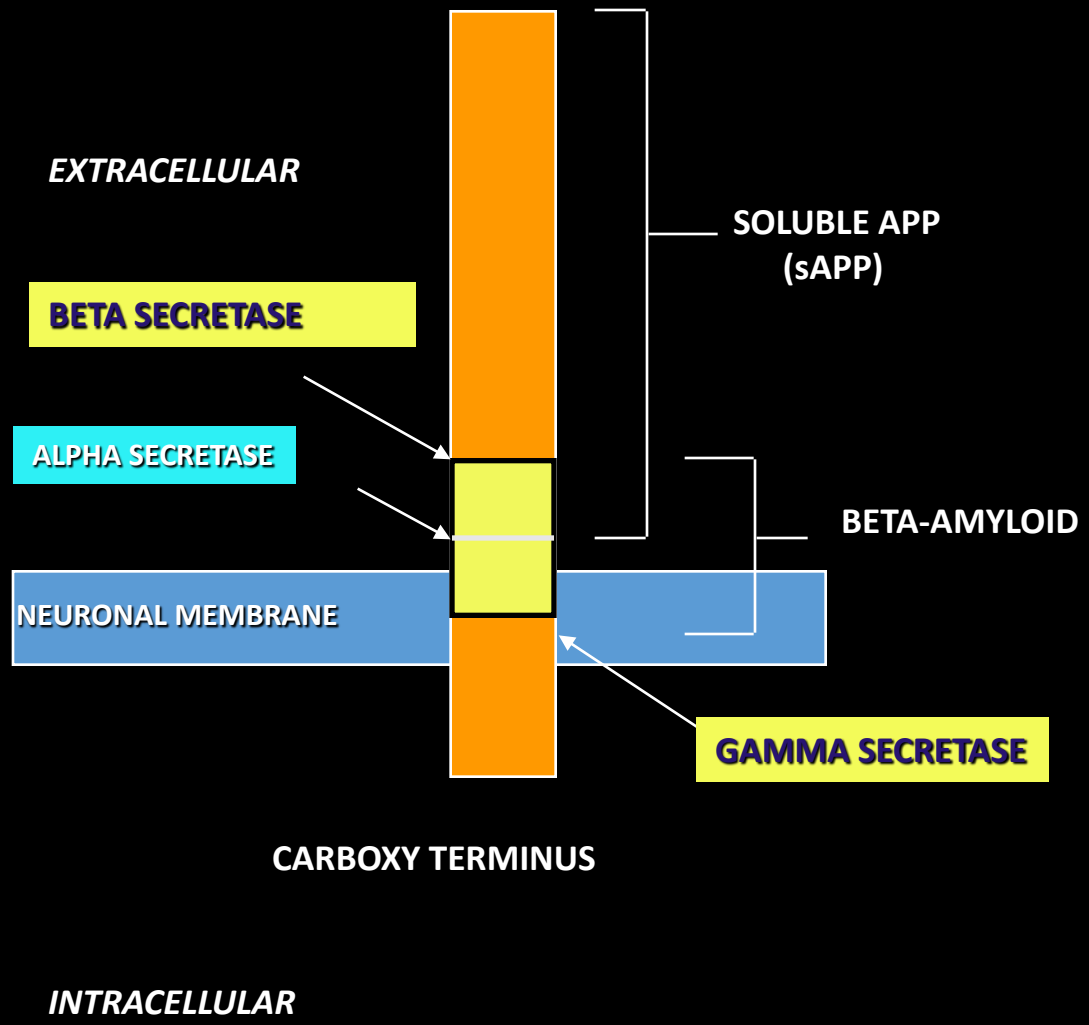
Amyloid

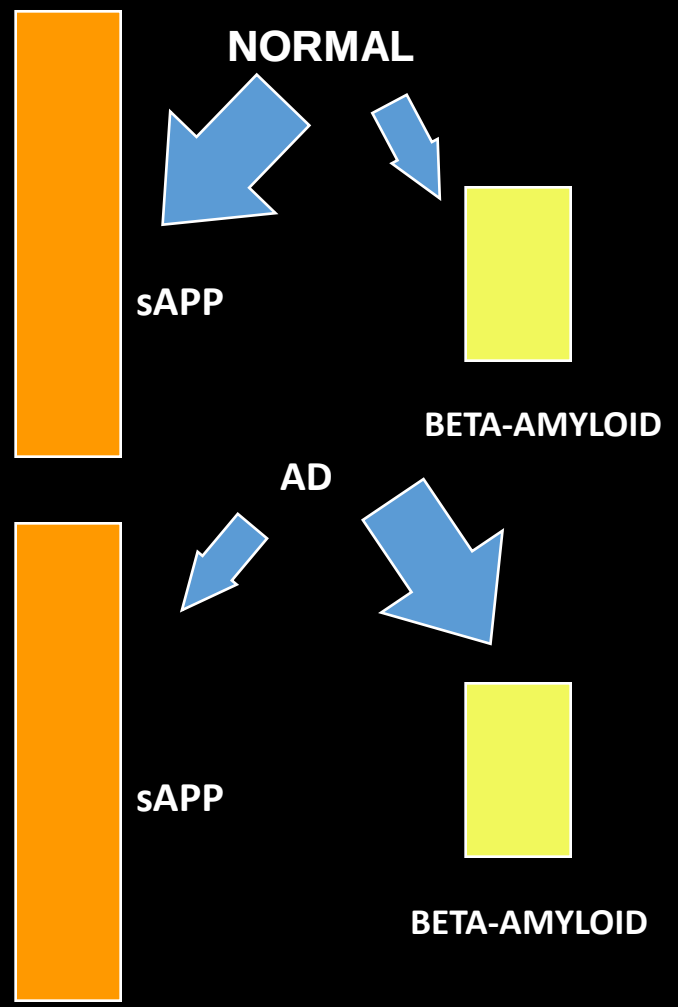
Therapies targeting amyloid-β peptide currently represent approximately 50% of drugs now being developed for Alzheimer's disease

The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics



Amyloid Precursor Protein [APP] Metabolism





Experimental Therapies for Alzheimer's Disease

Symptomatic treatments

- Cholinergic agonists (Nicotinic and Muscarinic M1 agonist)
- Histamine H3 receptor (H3R) antagonists
- Anti-hypertensives (ACE inhibitors)
- Psychotropics (Lithium, Valproic Acid, SSRIs)
- Anti-inflammatories (ibuprofen, celecoxib)
- Ketogenic diet (Axona)
- Neuroprotection (Resveratrol)
- Neurosteroids (Allopregnanolone)
- Nootropic agents (Piracetam)
- Nutraceuticals (huperazine)

Disease Modifying Treatments

- Passive and active immunizations (IV-Ig, bapineuzumab)
- Beta and Gamma Secretase inhibitors or modulators (Semagestat)
- Aβ RAGE Inhibitors (TTP488)
- Amyloid plaque proliferation or aggregation blockers (Scyllo-Inositol, Chelators [Clioquinol])
- Anti-NFT, or hyper-phosphorilation of tau protein inhibitors (GSK-3 inhibitors)
- Diabetes compounds with effects on amyloid metabolism (Rosiglitazone, Liraglutide, insulin)
- Reduction of β-amyloid protein deposits by inhibiting retinoid X receptors (Bexarotene)

Cell Therapies

- Stem cell therapy
- Gene therapy


10
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Acknowledgment

Oscar Lopez

Bruno Dubois

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