Societat Catalana d'Obstetrícia i Ginecologia

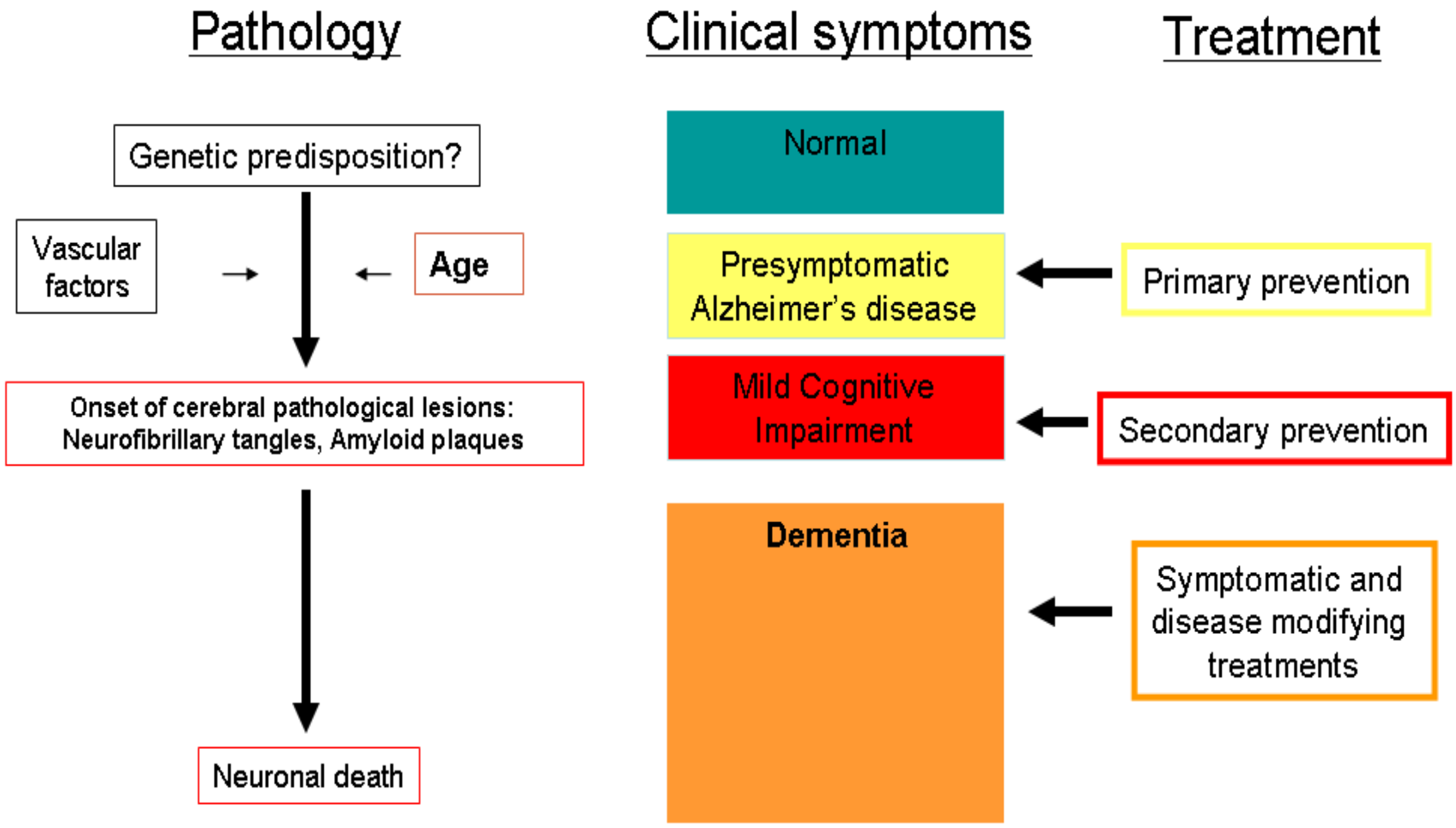
Menopausa, envelliment i Malaltia d'Alzheimer

Deteriorament cognitiu lleuger i biomarcadors

Merce Boada, neuróloga Directora Médica de Fundació ACE
Cap clínic. Àrea Malalties Neurodegeneratives .HVH-IR

L'Acadèmia
FUNDACIÓ ACADÈMIA DE CIÈNCIES MÈDIQUES I DE LA SALUT DE CATALUNYA I DE BALEARS

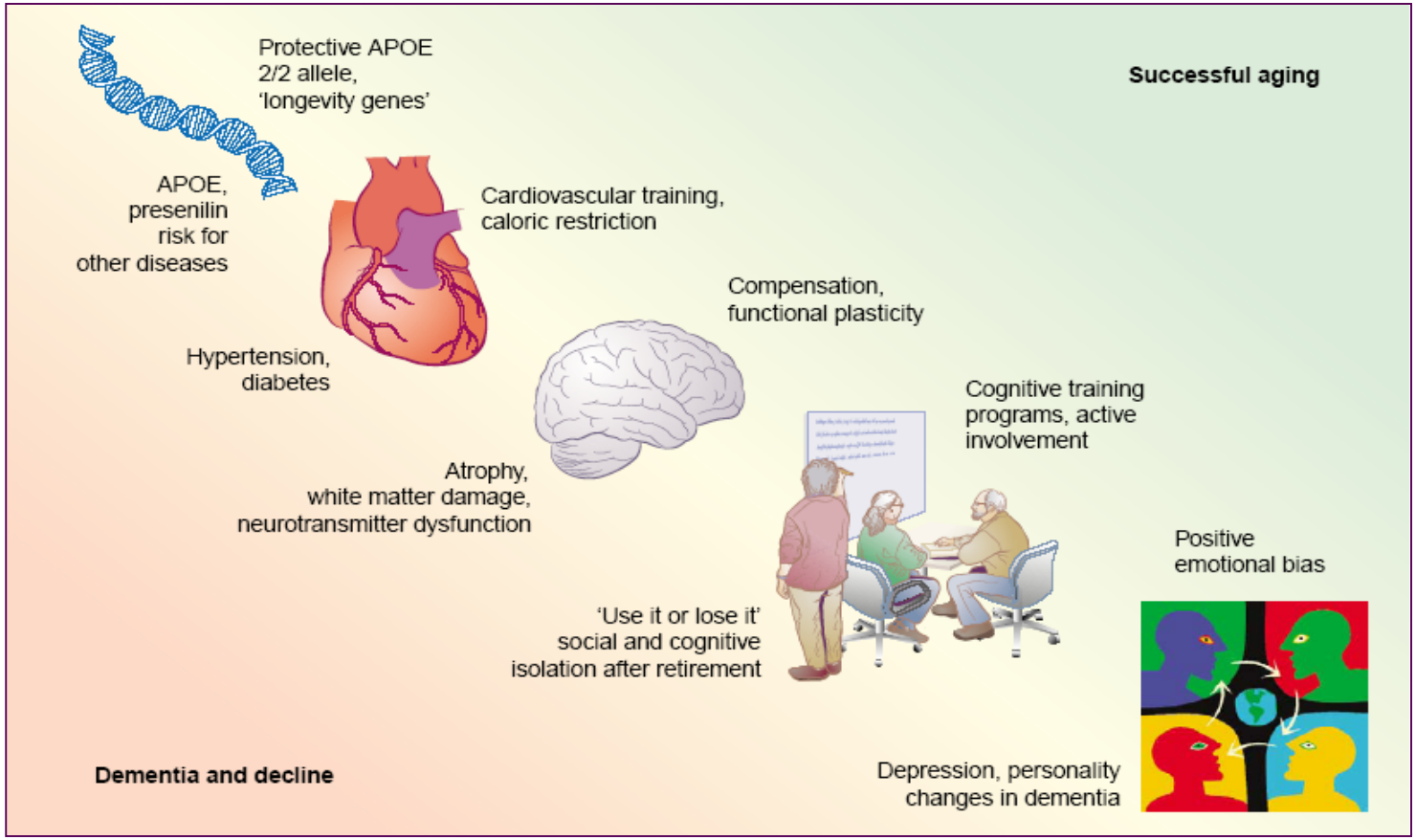
Relationship between primary and secondary prevention, clinical symptoms, and the pathological cascade



Variabilidad Interindividual

Predicting the rate of cognitive decline in aging and early Alzheimer disease

S. Adak, PhD; K. Illouz, MS; W. Gorman, MS; R. Tandon, MS; E.A. Zimmerman, MD; R. Guariglia, BSN; M.M. Moore, BS; and J.A. Kaye, MD



Vall d'Hebron
Hospital

Alzheimer: Prevention and early diagnosis

MCI

The NEW ENGLAND JOURNAL of MEDICINE

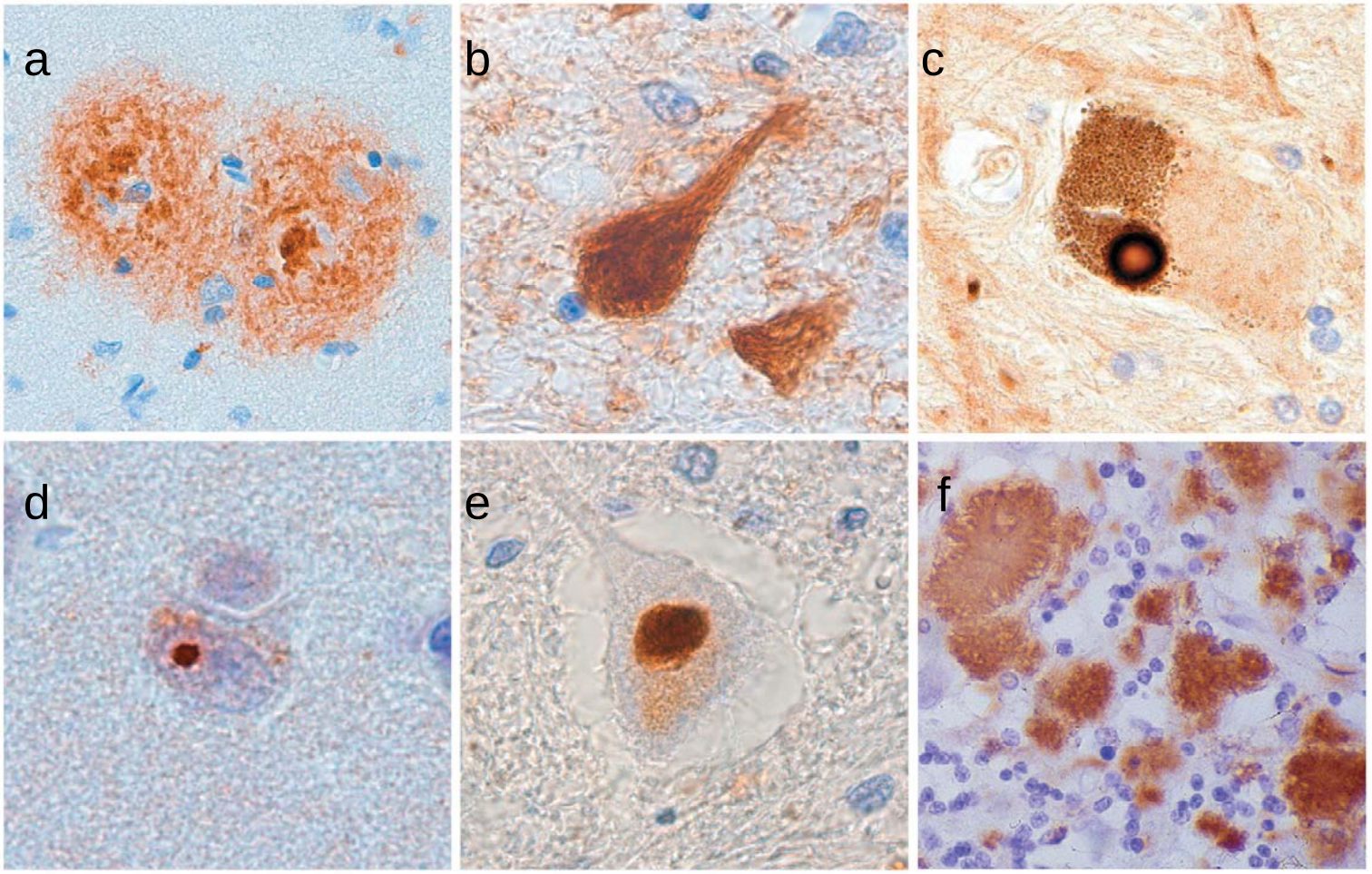
REVIEW ARTICLE

MECHANISMS OF DISEASE

Alzheimer's Disease

Henry W. Querfurth, M.D., Ph.D., and Frank M. LaFerla, Ph.D.

N Engl Med 2010;362:329-44



Protein aggregates in neurodegenerative disease. (**a**) Senile plaques in neocortex of Alzheimer disease. (**b**) NFTs in hippocampus of FTDP-17 (R406W mutation). (**c**) Lewy body in substantia nigra of Parkinson disease. (**d**) Intranuclear polyglutamine inclusion in neocortex of Huntington disease. (**e**) Ubiquitinylated inclusion in spinal cord motor neuron of ALS. (**f**) Protease-resistant PrP in cerebellum of CJD (panel **f** courtesy of Nigel Cairns).

Mark S Forman, John Q Trojanowski & Virginia M-Y Lee. ***Neurodegenerative diseases: a decade of discoveries paves the way for therapeutic breakthroughs.*** Nature Medicine. Vol. 10. Number 10. October 2004

Protein abnormalities in Alzheimer’s Disease

- B-amyloid
- Tau

The synapse in Alzheimer’s Disease

- Synaptic failure
- Depletion of neurotrophin and neurotransmitters

Mitochrondrial Dysfunction

- Oxidative stress
- Insulin-signaling pathway
- Vascular effects
- Inflamation
- Calcium
- Axonal transports deficits
- Aberrant cell-cycle reentry
- Cholesterol metabolism

Imaging and CSF biomarker categories in Alzheimer's disease

Brain Aβ-plaque deposition

- CSF $A\beta_{1-42}$
- PET Aβ imaging

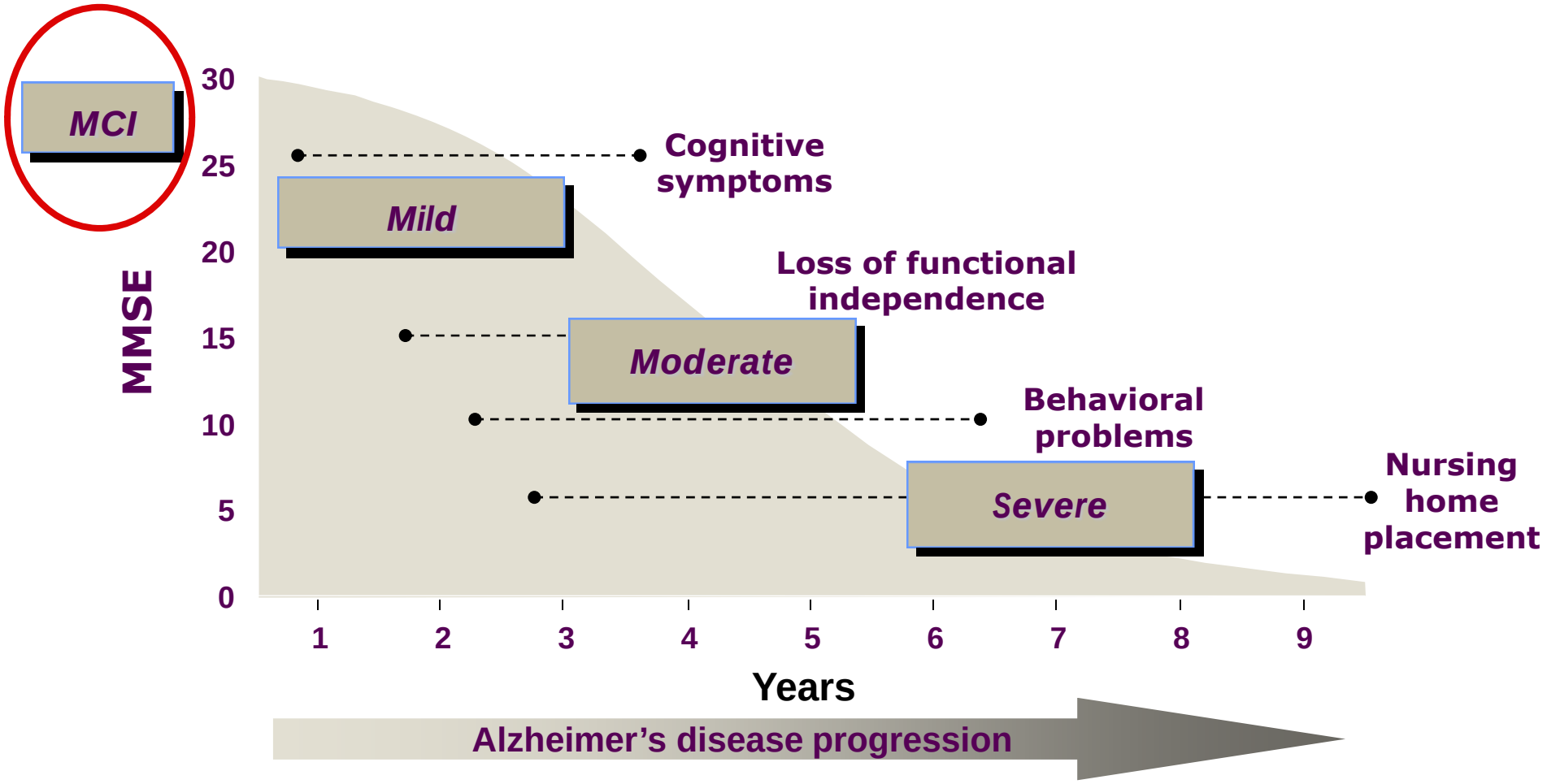
Neurodegeneration

- CSF tau
- Fluorodeoxyglucose-PET
- Structural MRI

Aβ=β-amyloid

Clifford R Jack jr, David S Knopman, Willian J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119-28

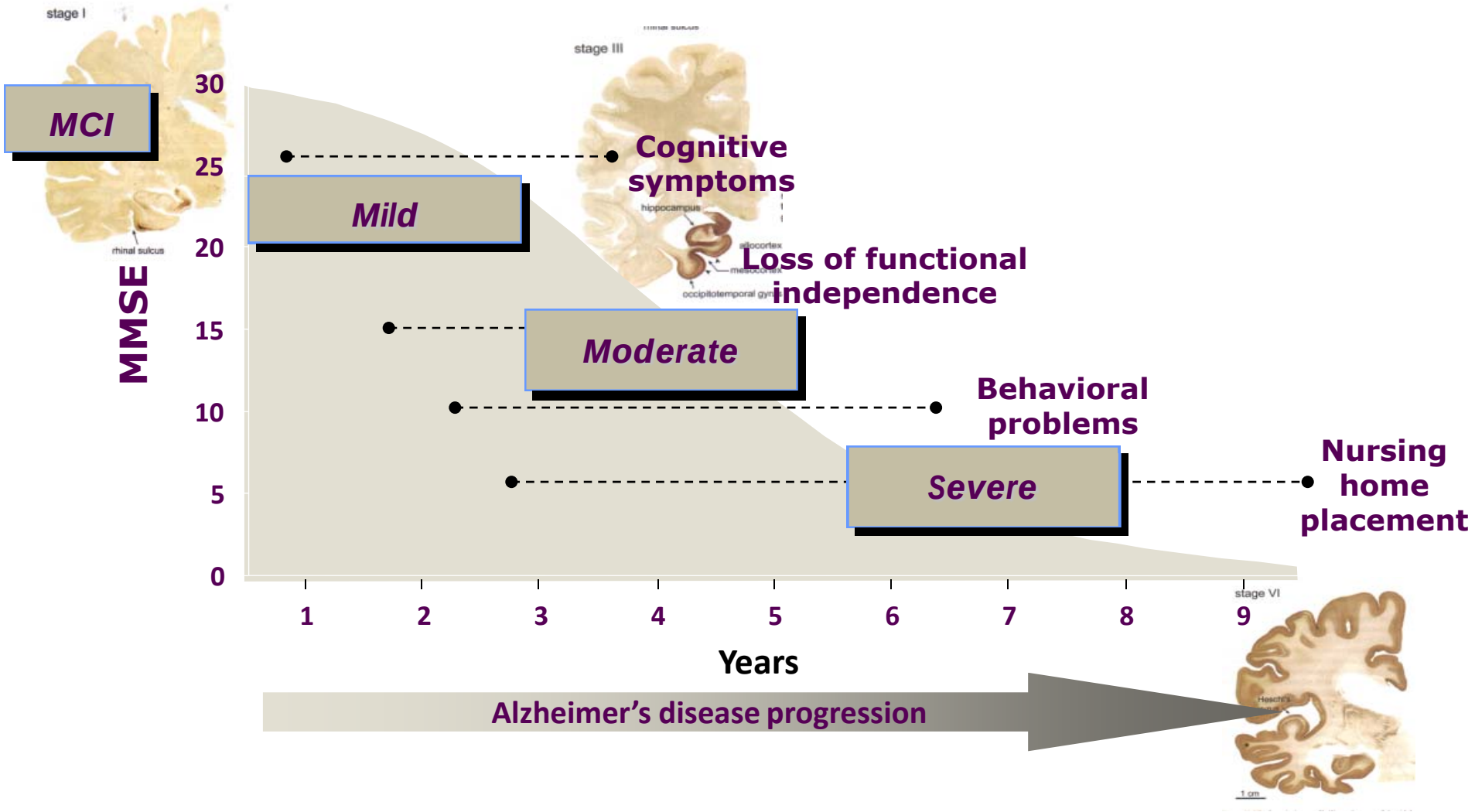
Symptomatic Course and Progression of AD



MMSE = Mini-Mental State Examination.

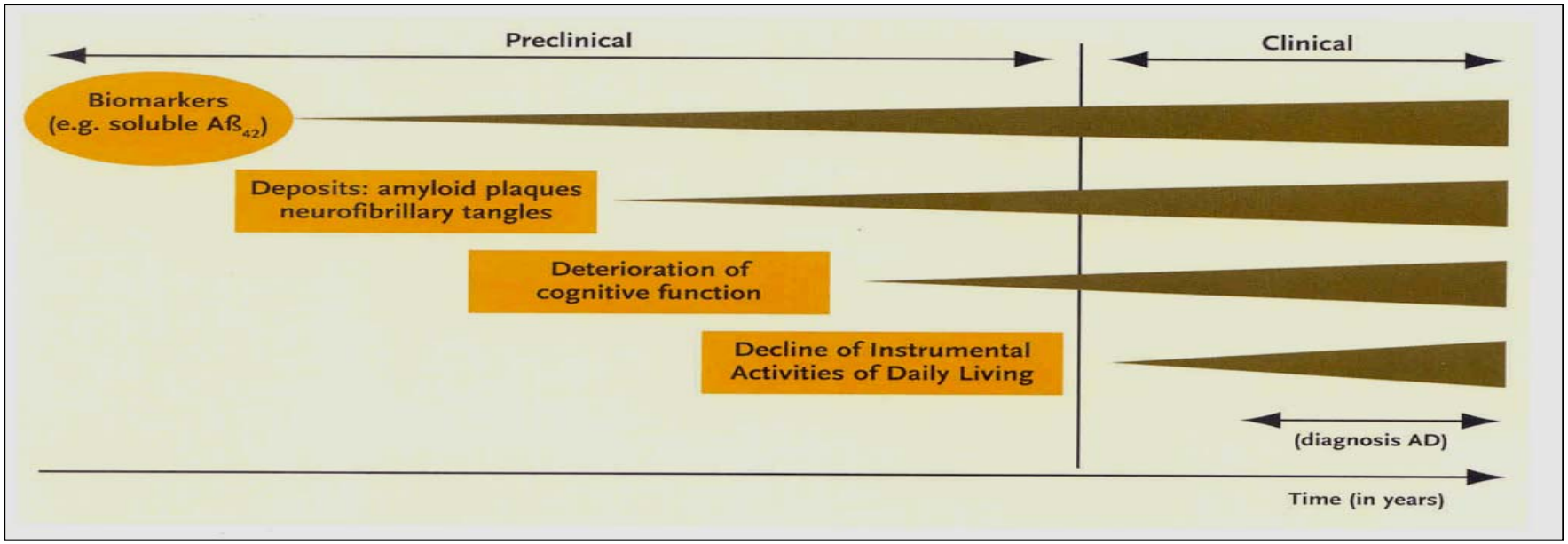
Feldman and Grundman. In: Gauthier, ed. Clinical Diagnosis and Management of Alzheimer's Disease. London: Martin Dunitz; 1999:249-268.

Symptomatic Course and Progression of AD



MMSE = Mini-Mental State Examination.

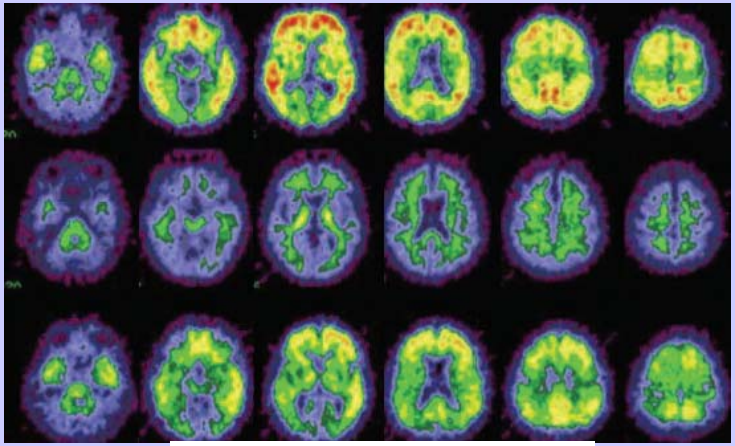
Feldman and Grundman. In: Gauthier, ed. Clinical Diagnosis and Management of Alzheimer's Disease. London: Martin Dunitz; 1999:249-268.



[11C]PIB in a nondemented population

Potential antecedent marker of Alzheimer disease

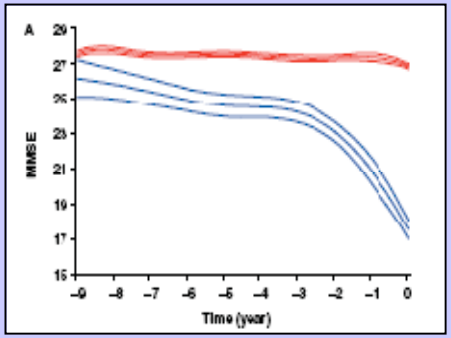
M.A. Mintun, MD; G.N. LaRossa; Y.I. Sheline, MD; C.S. Dence, MS; S.Y. Lee, PhD; R.H. Mach, PhD; W.E. Klunk, MD, PhD; C.A. Mathis, PhD; S.T. DeKosky, MD; and J.C. Morris, MD

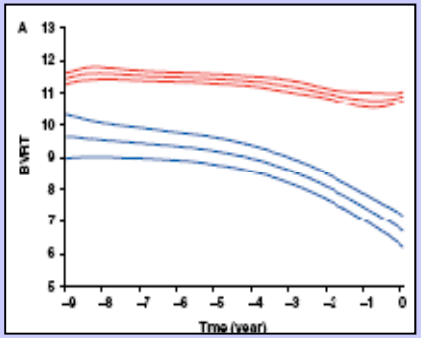


NEUROLOGY 2006;67:446–452

The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study

Hélène Amieva,[1] Hélène Jacqmin-Gadda,[2] Jean-Marc Orgogozo,[1,3] Nicolas Le Carret,[1] Catherine Helmer,[1] Luc Letenneur,[1] Pascale Barberger-Gateau,[1] Colette Fabrigoule[1] and Jean-François Dartigues[1,3]





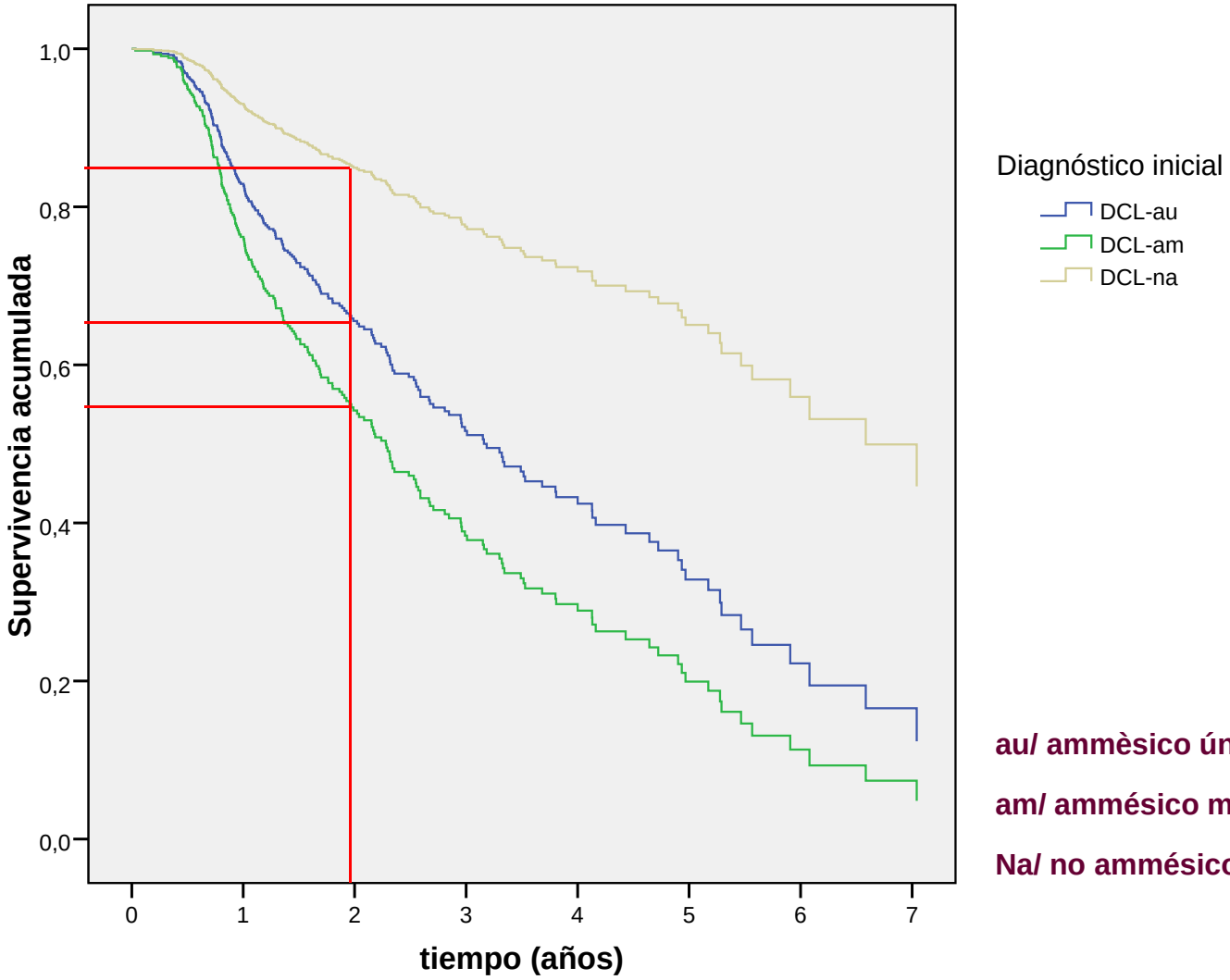
Brain (2005), **128**, 1093–1101

Fundacio ACE. Análisis retrospectivo 1996-2008

965 pacientes con MCI amnésico “probable”.

Seguimiento medio: **2,21 1,5 años**

220 (22,8%) sin seguimiento.



au/ ammèsico único dominio

am/ ammésico múltiple domini

Na/ no ammésico

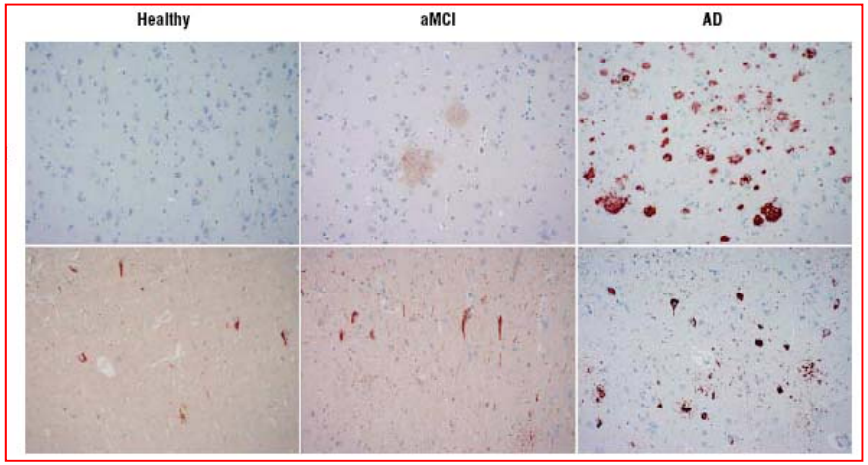
Proportion of Diagnoses of Cognitive Dysfunction in AD

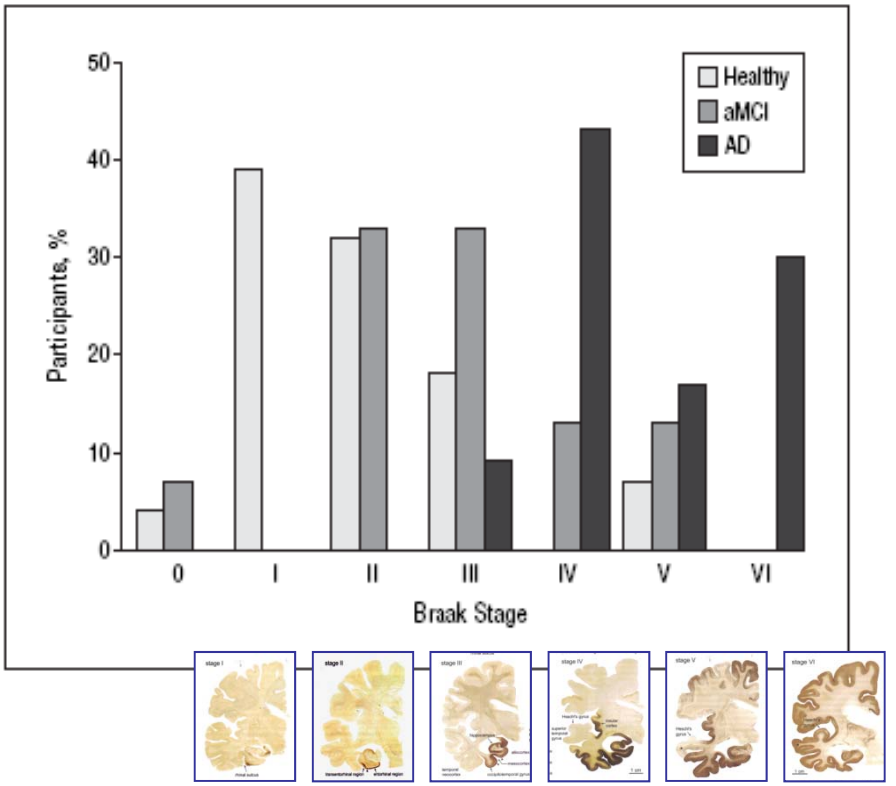
Diagnosed disorder	Level of impairment: None (*n* = 563)	Mild (*n* = 154)	Moderate (*n* = 279)	Severe (*n* = 308)
Agnosia	.000	.07	.30	.87
Apraxia	.003	.30	.52	.90
Aphasia	.011	.48	.51	.82
Judgement	.004	.52	.88	.996
Constructional defect	.007	.62	.77	.97
Abstract thinking	.011	.80	.97	1.00

Source: Helmes E., Østbye T. Beyond memory impairment. Cognitive changes in Alzheimer's disease. Arch Clin Neuropsychology 2002; 17: 179-193.

Neuropathologic Features of Amnestic Mild Cognitive Impairment

Conclusions: The neuropathologic features of aMCI matched the clinical features and seemed to be intermediate between the neurofibrillary changes of aging and the pathologic features of very early AD.





Ronald C. Petersen, PhD, MD; Joseph E. Parisi, MD; Dennis W. Dickson, MD; Kris A. Johnson, RN; David S. Knopman, MD; Bradley F. Boeve, MD; Gregory A. Jicha, MD, PhD; Robert J. Ivnik, PhD; Glenn E. Smith, PhD; Eric G. Tangalos, MD; Heiko Braak, MD; Emre Kokmen, MD†

Arch Neurol. 2006;63:665-672

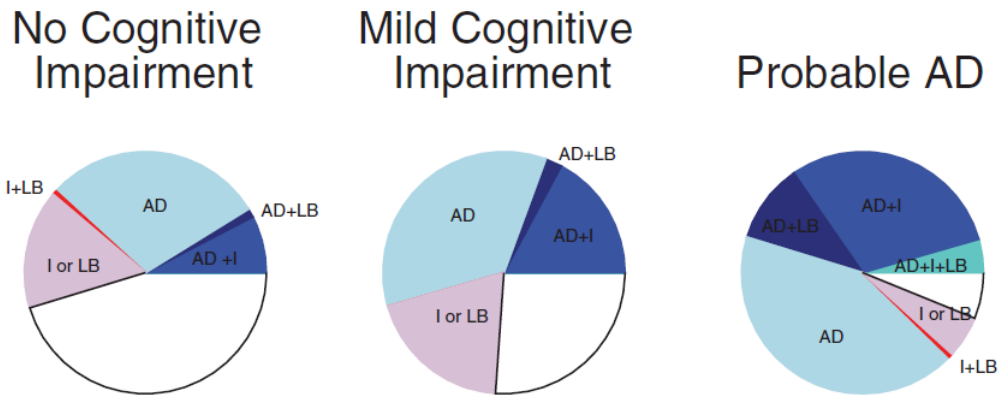
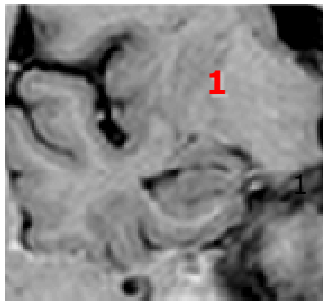


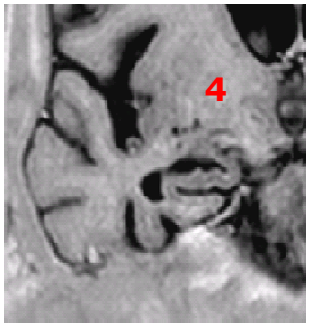
*Fig. Pathology by clinical status proximate to death. (*Blue shades*) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral infarcts (I); aqua = pathologic diagnosis of AD, I, and LB. (*Red shades*) I and/or LB (with no pathologic diagnosis of AD). Clockwise: pink = I or LB; red = I and LB. (*White*) No pathologic diagnosis of AD, no I, no LB.*

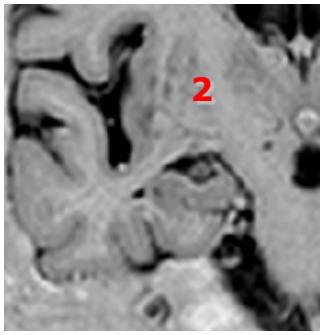
Julie A. Schneider, Zoe Arvanitakis,Sue E. Leurgans, and David A. Bennett ***The Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment. Ann Neurol 2009;66:200–208***

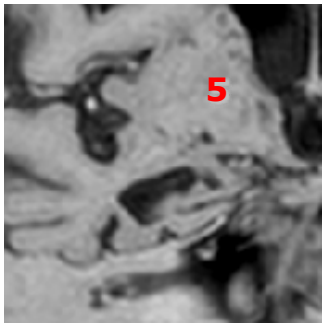
Medial Temporal Lobe (MTL)atrophy: Visual analysis scale

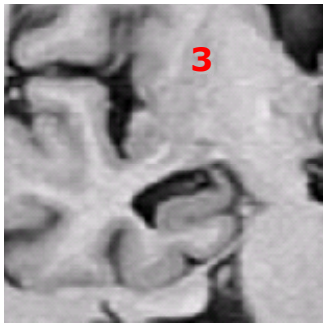
Korf E. et al. Medial temporal lobe atrophy on MRI predicts dementia with mild cognitive impairment. Neurology 2004;63:94-100 ***Scheltens et al. J Neurol Neurosurg Psychiatry 1992***

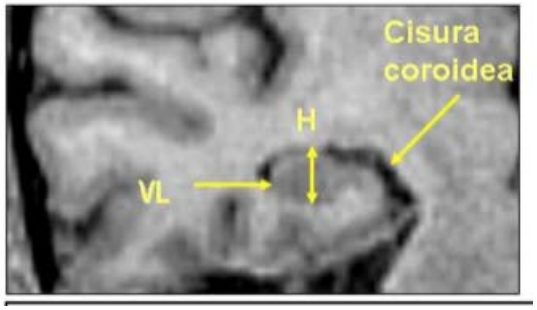


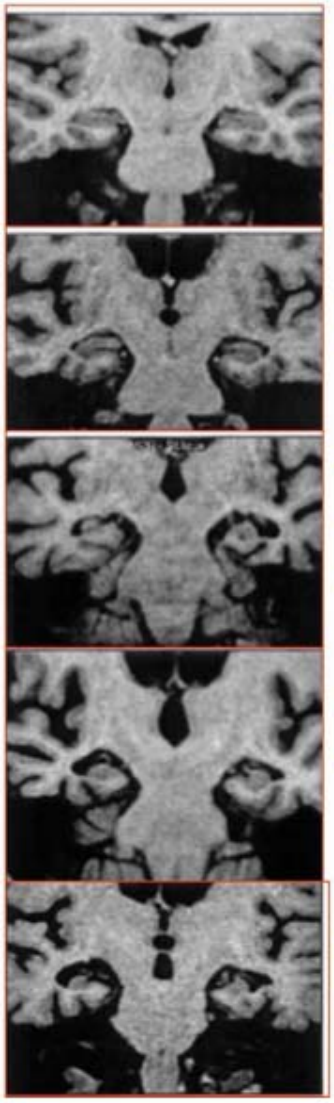












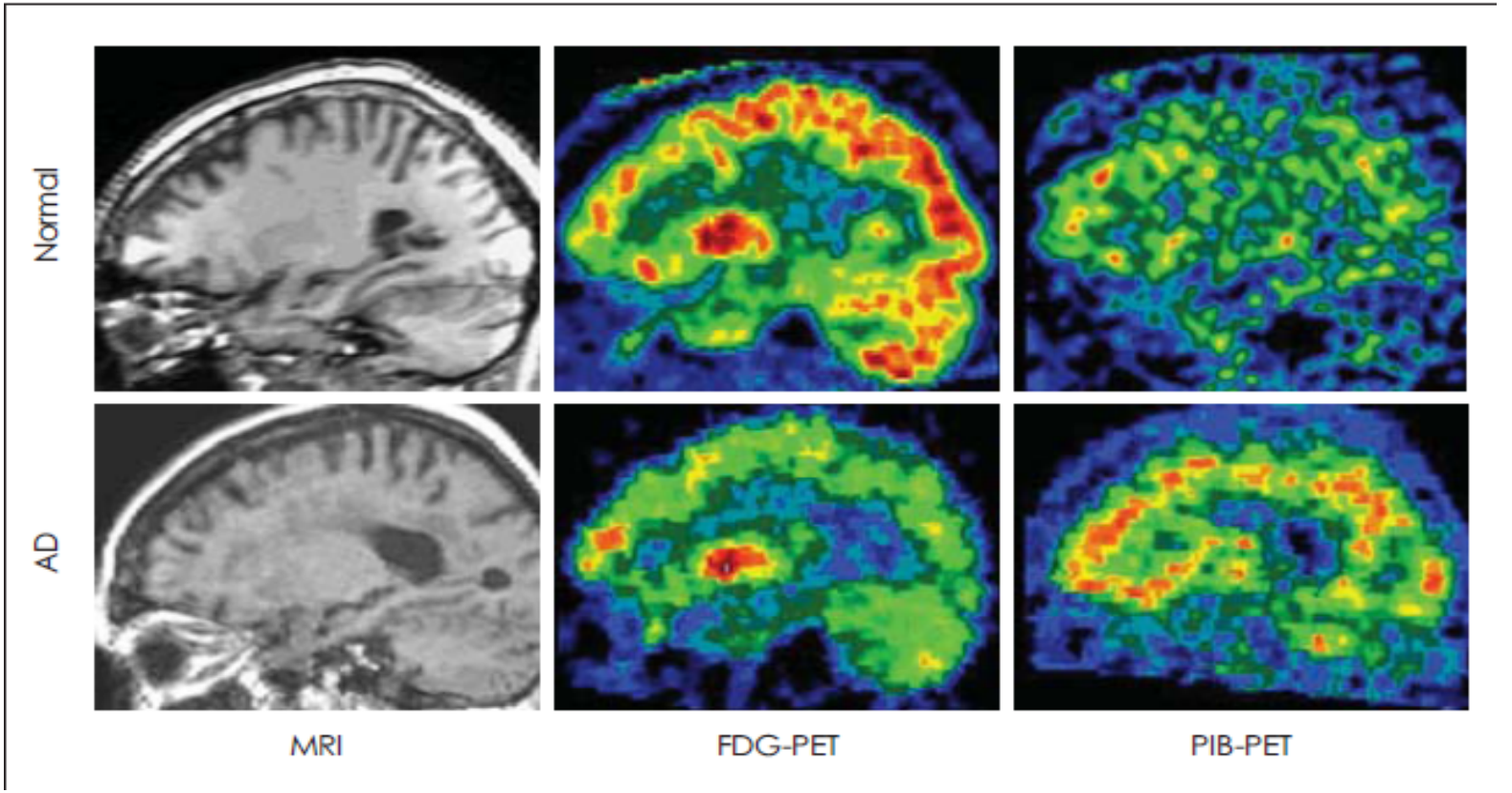
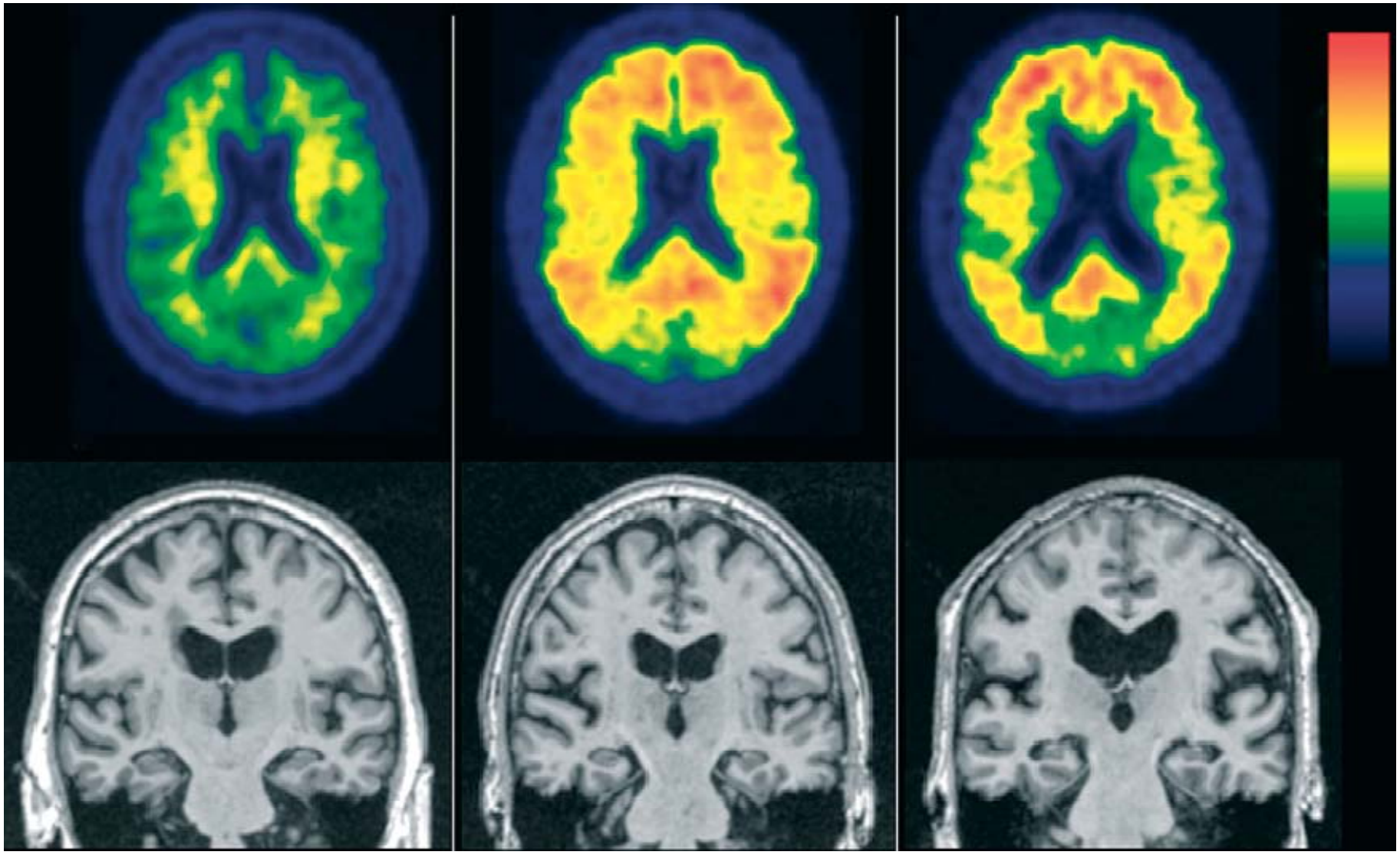


Fig. 1. Two representative cases: magnetic resonance image (MRI, left column), FDG-PET (middle column) and PIB-PET (right column) of a normal control (top row) and an AD patient (bottom row). FDG: 2-[^{18}F]fluoro-2-Deoxy-D-glucose, PIB: Pittsburgh Compound-B, AD: Alzheimer's disease.

Raquel Mistur, Lisa Mosconi, Susan De Santi, María Guzman, Yi Li, Wai Tsui, Mony J. De Leon.
Current Challenges for the Early Detection of AD: Brain Imaging and CSF Studies. J. Clin Neurol 2009;5:153-166



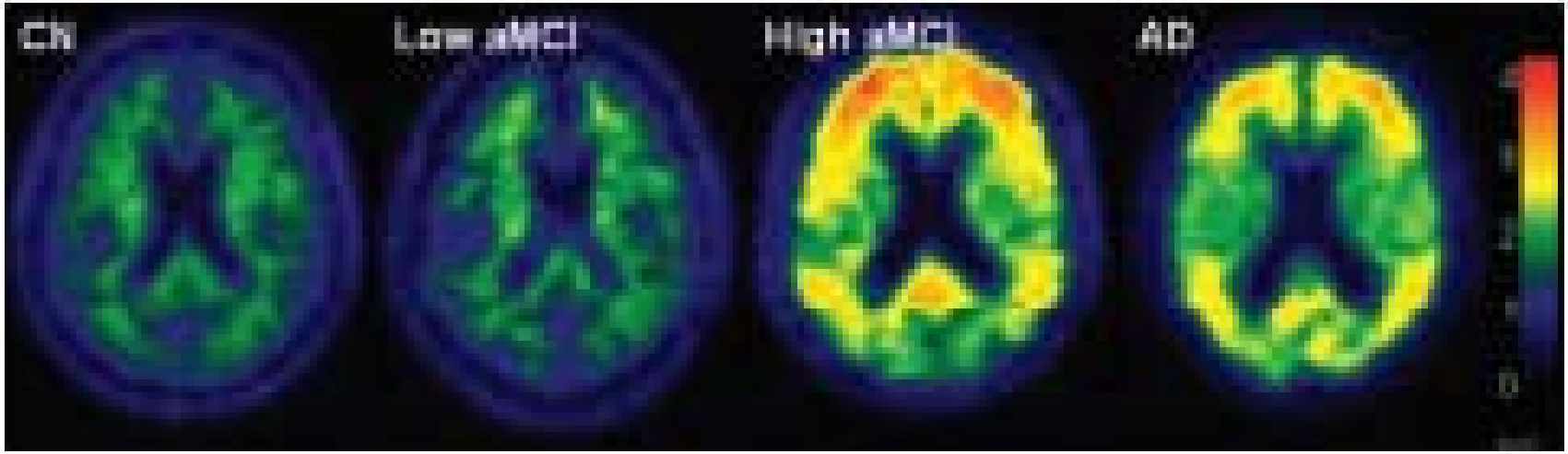
Ilustration of biomarkers staging of Alzheimer's disease.

Clifford R Jack jr, David S Knopman, Willian J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner et al. ***Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade***. Lancet Neurol. 2010;9:119-28

doi:10.1093/brain/awm336 *Brain* (2008), **131**, 665–680

^{11}C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment

Clifford R. Jack, Jr,[1] Val J. Lowe,[1] Matthew L. Senjem,[2] Stephen D. Weigand,[3] Bradley J. Kemp,[1] Maria M. Shiung,[1] David S. Knopman,[4] Bradley F. Boeve,[4] William E. Klunk,[5] Chester A. Mathis[5] and Ronald C. Petersen[4]

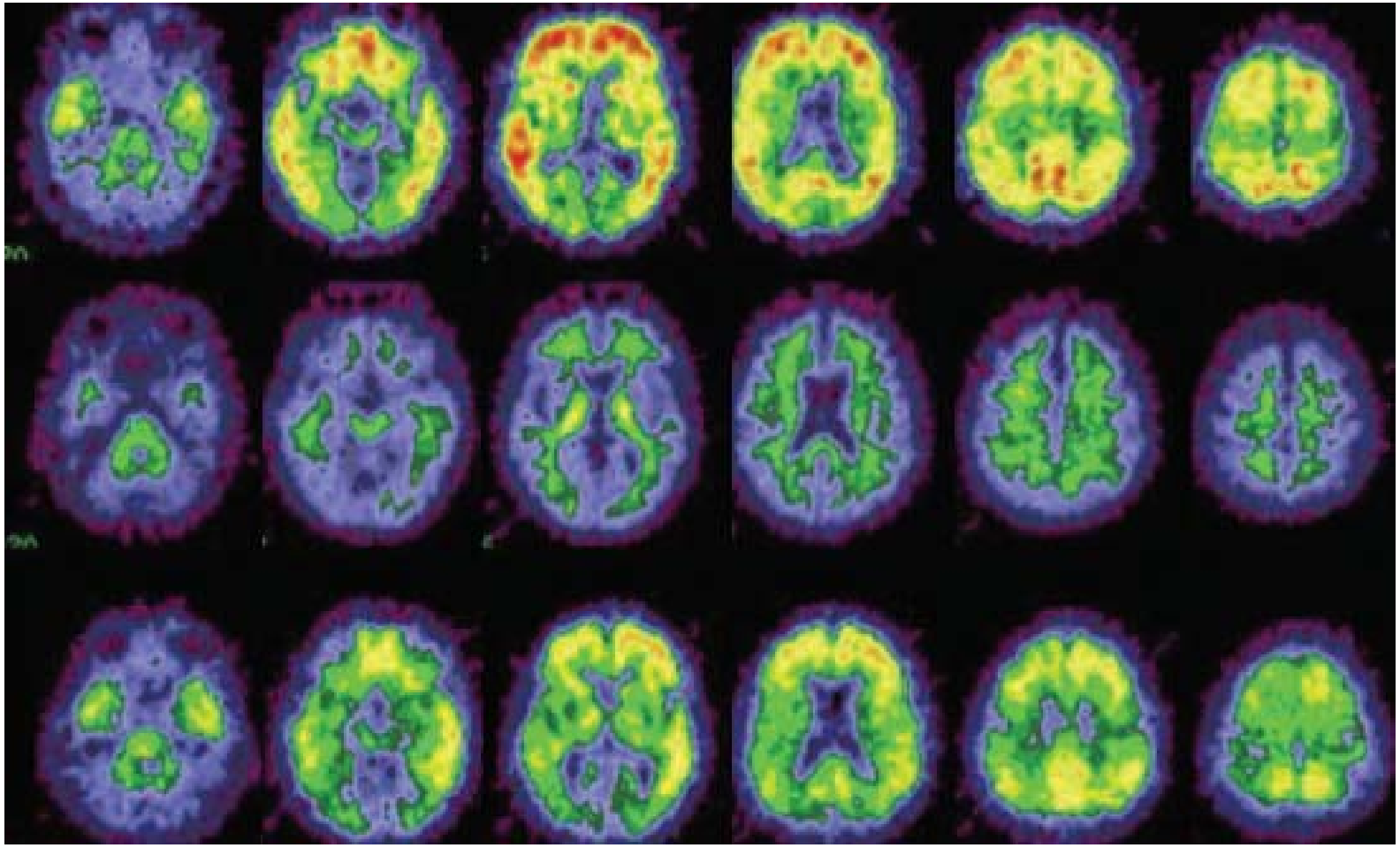


HIGH LIGHT

[^{11}C]PIB in a nondemented population

Potential antecedent marker of Alzheimer disease

M.A. Mintun, MD; G.N. LaRossa; Y.I. Sheline, MD; C.S. Dence, MS; S.Y. Lee, PhD; R.H. Mach, PhD; W.E. Klunk, MD, PhD; C.A. Mathis, PhD; S.T. DeKosky, MD; and J.C. Morris, MD



NEUROLOGY 2006;67:446–452

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

Clifford R Jack Jr, David S Knopman, William J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner, Ronald C Petersen, John Q Trojanowski

Currently available evidence strongly supports the position that the initiating event in Alzheimer's disease (AD) is related to abnormal processing of β-amyloid (Aβ) peptide, ultimately leading to formation of Aβ plaques in the brain. This process occurs while individuals are still cognitively normal. Biomarkers of brain β-amyloidosis are reductions in CSF $A\beta_{42}$ and increased amyloid PET tracer retention. After a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes. Biomarkers of neuronal injury and neurodegeneration are increased CSF tau and structural MRI measures of cerebral atrophy. Neurodegeneration is accompanied by synaptic dysfunction, which is indicated by decreased fluorodeoxyglucose uptake on PET. We propose a model that relates disease stage to AD biomarkers in which Aβ biomarkers become abnormal first, before neurodegenerative biomarkers and cognitive symptoms, and neurodegenerative biomarkers become abnormal later, and correlate with clinical symptom severity.

Lancet Neurol 2010; 9:119-28

Ronald C. Petersen. Alzheimer's disease: progress in prediction. The Lancet. Vol 9. January 2010

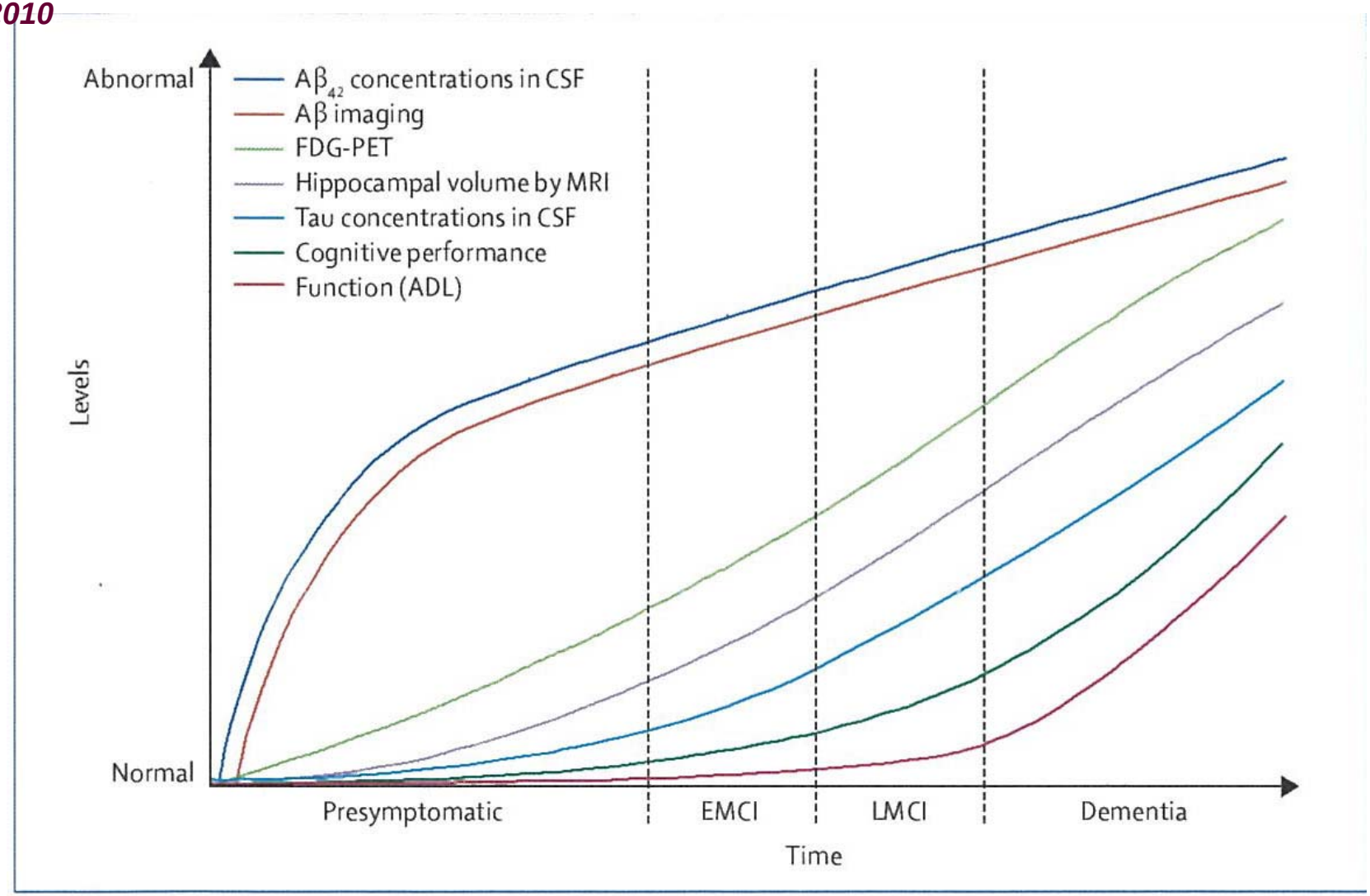
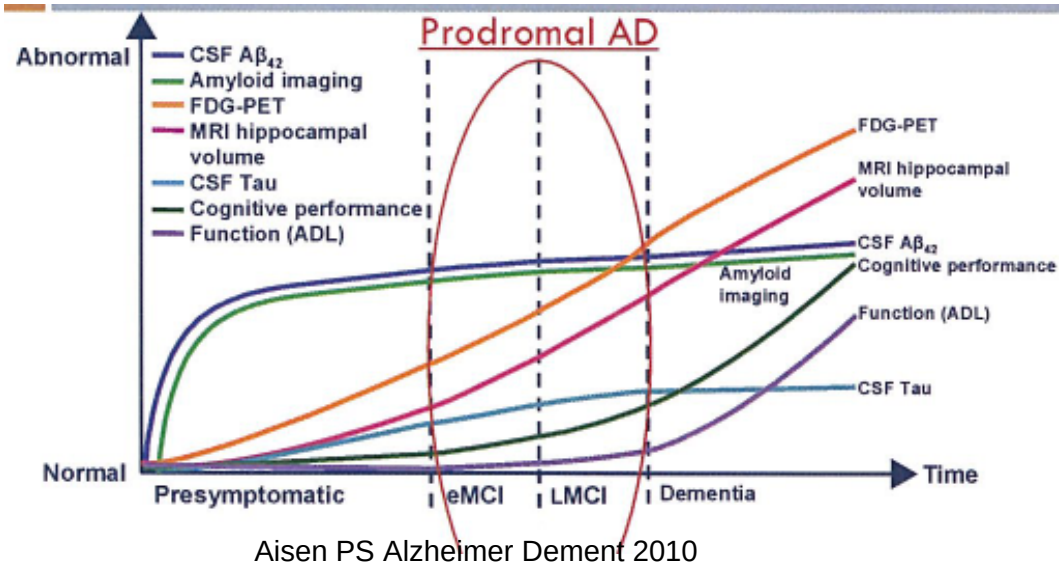


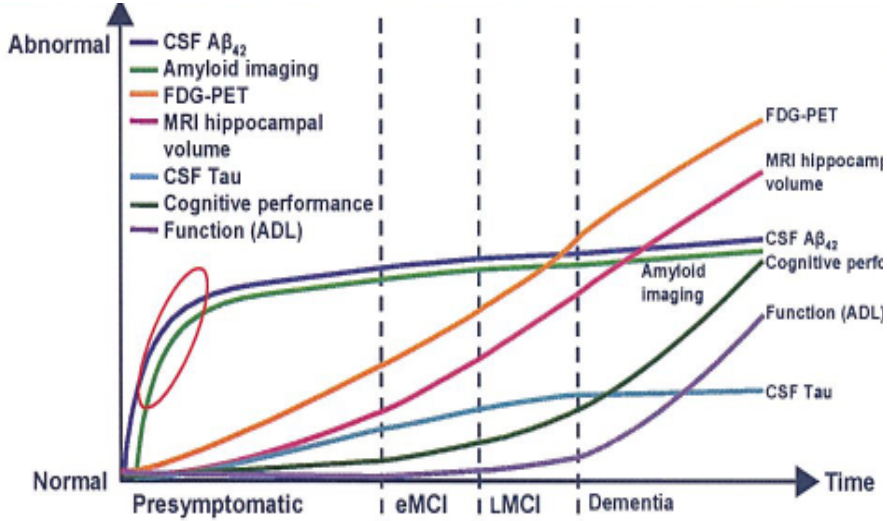
Figure: **Hypothetical progression of pathological and clinical events that lead to Alzheimer's disease, as detected by use of different imaging techniques, functional measures, or biomarkers**

Increases in the extent of pathological abnormality are shown for each imaging measure and biomarker. ADL=activities of daily living. EMCI=early MCI. FDG-PET=^{18}F-fluorodeoxyglucose PET. LMCI=late MCI.

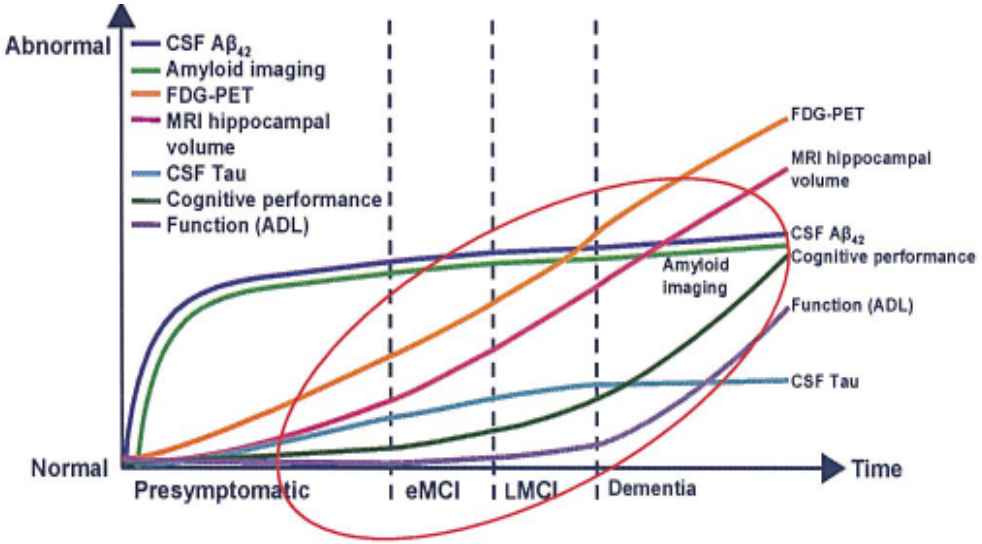
AD progresion



Aisen PS Alzheimer Dement 2010



Biomarkers to select Prodromal AD



Covariates (Indicators of Disease Stage)

Curr Opin Neurol Neurosurg. 1993 Feb;6(1):34-9.

Molecular genetics of neurodegenerative diseases.

Roses AD.

Department of Medicine, Duke University Medical Center, Durham, NC 27710.

Abstract

Recent progress in human neurogenetics has led to the discovery of new modes of inheritance and disease expression, including 1) stably inherited duplications in Charcot-Marie-Tooth disease type 1a, 2) dynamic mutations in fragile X syndrome and myotonic dystrophy, and 3) identical mutations with different phenotypes in fatal familial insomnia and Creutzfeldt-Jakob disease. The mechanisms by which known mutations of the amyloid precursor protein lead to early-onset Alzheimer's disease remain unexplained, despite hundreds of recent studies of beta-amyloid.

Proc Natl Acad Sci U S A. 1993 Mar 1;90(5):1977-81.

Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease.

Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD.

Department of Medicine (Neurology), Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University Medical Center, Durham, NC 27710.

Abstract

Apolipoprotein E is immunochemically localized to the senile plaques, vascular amyloid, and neurofibrillary tangles of Alzheimer disease. In vitro, apolipoprotein E in cerebrospinal fluid binds to synthetic beta A4 peptide (the primary constituent of the senile plaque) with high avidity. Amino acids 12-28 of the beta A4 peptide are required. The gene for apolipoprotein E is located on chromosome 19q13.2, within the region previously associated with linkage of late-onset familial Alzheimer disease. Analysis of apolipoprotein E alleles in Alzheimer disease and controls demonstrated that there was a highly significant association of apolipoprotein E type 4 allele (APOE-epsilon 4) and late-onset familial Alzheimer disease. The allele frequency of the APOE-epsilon 4 in 30 random affected patients, each from a different Alzheimer disease family, was 0.50 +/- 0.06; the allele frequency of APOE-epsilon 4 in 91 age-matched unrelated controls was 0.16 +/- 0.03 ($Z = 2.44$, $P = 0.014$). A functional role of the apolipoprotein E-E4 isoform in the pathogenesis of late-onset familial Alzheimer disease is suggested.

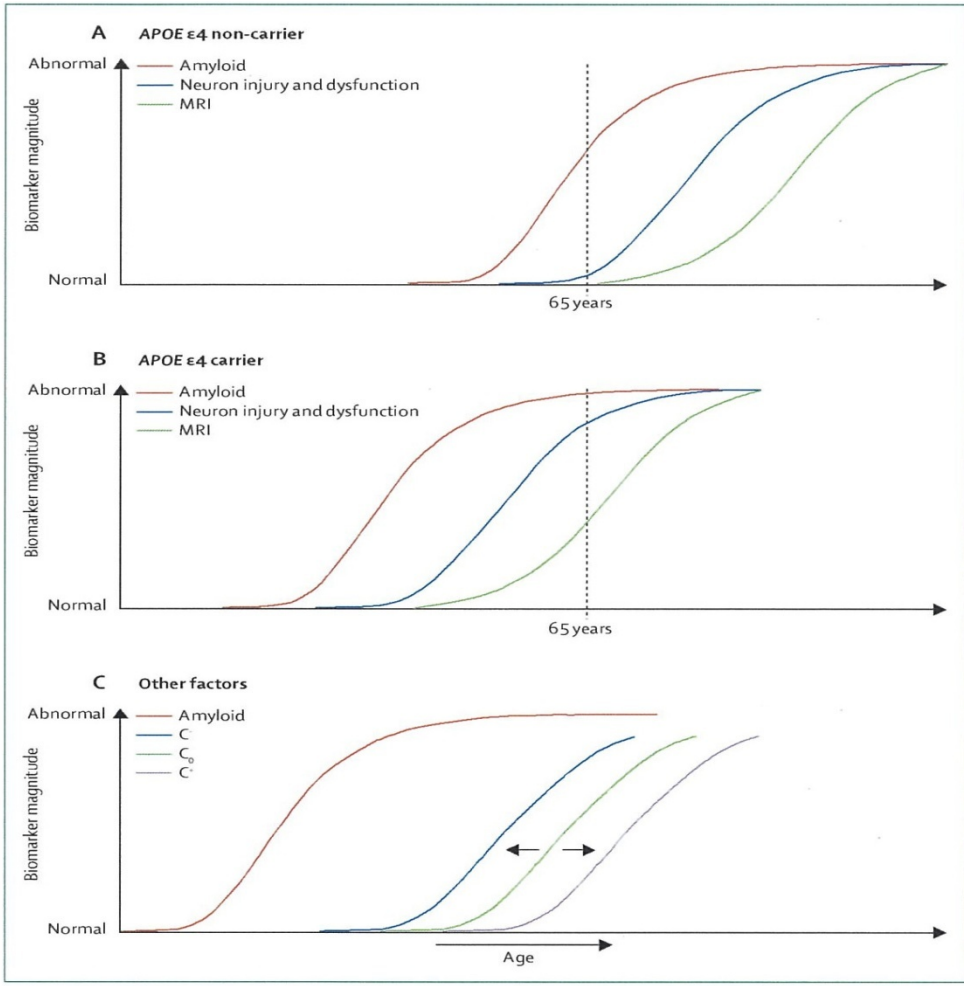


Figure 5: **Modulators of biomarker temporal relationships**
(A,B) Relative to a fixed age (here, 65 years), the hypothesised effect of *APOE* ε4 is to shift β-amyloid plaque deposition and the neurodegenerative cascade both to an earlier age compared with ε4 non-carriers. (C) The hypothesised effect of the presence of different diseases and genes on cognition: C^-=cognition in the presence of comorbidities (eg, Lewy bodies or vascular disease) or risk amplification genes; C^+=cognition in patients with enhanced cognitive reserve or protective genes; C_o=cognition in individuals without comorbidity or enhanced cognitive reserve.

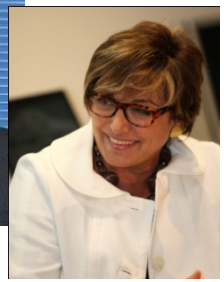
Clifford R Jack jr, David S Knopman, Willian J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner et al.

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119-28







Genome-wide Analysis of Genetic Loci Associated With Alzheimer Disease

Sudha Seshadri, MD; Annette L. Fitzpatrick, PhD; M. Arfan Ikram, MD, PhD; Anita L. DeStefano, PhD; Vilmundur Gudnason, MD, PhD; Merce Boada, MD, PhD; Joshua C. Bis, PhD; Albert V. Smith, PhD; Minerva M. Carassquillo, PhD; Jean Charles Lambert, PhD; Denise Harold, PhD; Elisabeth M. C. Schrijvers, MD; Reposo Ramirez-Lorca, PhD; Stephanie Debette, MD, PhD; W. T. Longstreth Jr, MD; A. Cecile J. W. Janssens, PhD; V. Shane Pankratz, PhD; Jean François Dartigues, PhD; Paul Hollingworth, PhD; Thor Aspelund, PhD; Isabel Hernandez, MD; Alexa Beiser, PhD; Lewis H. Kuller, MD; Peter J. Koudstaal, MD, PhD; Dennis W. Dickson, MD; Christophe Tzourio, MD; Richard Abraham, PhD; Carmen Antunez, MD; Yangchun Du, PhD; Jerome I. Rotter, MD; Yurii S. Aulchenko, PhD; Tamara B. Harris, MD; Ronald C. Petersen, MD; Claudine Berr, MD, PhD; Michael J. Owen, MB, ChB, PhD; Jesus Lopez-Arrieta, MD; Badri N. Varadarajan, MS; James T. Becker, PhD; Fernando Rivadeneira, MD, PhD; Michael A. Nalls, PhD; Neill R. Graff-Radford, MD; Dominique Campion, MD, PhD; Sanford Auerbach, MD; Kenneth Rice, PhD; Albert Hofman, MD, PhD; Palmi V. Jonsson, MD; Helena Schmidt, MD, PhD; Mark Lathrop, PhD; Thomas H. Mosley, PhD; Rhoda Au, PhD; Bruce M. Psaty, MD, PhD; Andre G. Uitterlinden, PhD; Lindsay A. Farrer, PhD; Thomas Lumley, PhD; Agustin Ruiz, MD, PhD; Julie Williams, PhD; Philippe Amouyel, MD, PhD; Steve G. Younkin, PhD; Philip A. Wolf, MD; Lenore J. Launer, PhD; Oscar L. Lopez, MD; Cornelia M. van Duijn, PhD; Monique M. B. Breteler, MD, PhD

for the CHARGE, GERAD1, and EADI1 Consortia

Context Genome-wide association studies (GWAS) have recently identified *CLU*, *PICALM*, and *CR1* as novel genes for late-onset Alzheimer disease (AD).

Objectives To identify and strengthen additional loci associated with AD and confirm these in an independent sample and to examine the contribution of recently identified genes to AD risk prediction in a 3-stage analysis of new and previously published GWAS on more than 35 000 persons (8371 AD cases).

Design, Setting, and Participants In stage 1, we identified strong genetic associations ($P<10^{-3}$) in a sample of 3006 AD cases and 14 642 controls by combining new data from the population-based Cohorts for Heart and Aging Research in Genomic Epidemiology consortium (1367 AD cases [973 incident]) with previously reported results from the Translational Genomics Research Institute and the Mayo AD GWAS. We identified 2708 single-nucleotide polymorphisms (SNPs) with $P<10^{-3}$. In stage 2, we pooled results for these SNPs with the European AD Initiative (2032 cases and 5328 controls) to identify 38 SNPs (10 loci) with $P<10^{-5}$. In stage 3, we combined data for these 10 loci with data from the Genetic and Environmental Risk in AD consortium (3333 cases and 6995 controls) to identify 4 SNPs with $P<1.7\times10^{-8}$. These 4 SNPs were replicated in an independent Spanish sample (1140 AD cases and 1209 controls). Genome-wide association analyses were completed in 2007-2008 and the meta-analyses and replication in 2009.

Main Outcome Measure Presence of Alzheimer disease.

Results Two loci were identified to have genome-wide significance for the first time: rs744373 near *BIN1* (odds ratio [OR],1.13; 95% confidence interval [CI],1.06-1.21 per copy of the minor allele; $P=1.59\times10^{-11}$) and rs597668 near *EXOC3L2/BLOC1S3/MARK4* (OR, 1.18; 95% CI, 1.07-1.29; $P=6.45\times10^{-9}$). Associations of these 2 loci plus the previously identified loci *CLU* and *PICALM* with AD were confirmed in the Spanish sample ($P<.05$). However, although *CLU* and *PICALM* were confirmed to be associated with AD in this independent sample, they did not improve the ability of a model that included age, sex, and *APOE* to predict incident AD (improvement in area under the receiver operating characteristic curve from 0.847 to 0.849 in the Rotterdam Study and 0.702 to 0.705 in the Cardiovascular Health Study).

Conclusions Two genetic loci for AD were found for the first time to reach genome-wide statistical significance. These findings were replicated in an independent population. Two recently reported associations were also confirmed. These loci did not improve AD risk prediction. While not clinically useful, they may implicate biological pathways useful for future research.

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PERSPECTIVE

Alzheimer's Prevention Initiative: a proposal to evaluate presymptomatic treatments as quickly as possible

We propose an Alzheimer's Prevention Initiative, which is now being reviewed and refined in partnership with leading academic and industry investigators. It is intended to evaluate the most promising presymptomatic AD treatments, help develop a regulatory pathway for their accelerated approval using reasonably likely surrogate end points and find demonstrably effective presymptomatic AD treatments as quickly as possible.

Eric M Reiman[1,2,3,4,5†], Jessica BS Langbaum[1,2,5] & Pierre N Tariot[1,2,5,6]

[†]Author for correspondence:
[1]The Banner Alzheimer's Institute, 901 E. Willetta St., Phoenix, AZ 85006, USA
Tel.: +1 602 839 6999
Fax: +1 602 839 6523
eric.reiman@bannerhealth.com
[2]Banner Health Research, Sun City, AZ, USA
[3]The University of Arizona, Tucson, AZ, USA
[4]The Translational Genomics Research Institute, Phoenix, AZ, USA
[5]The Arizona Alzheimer's Consortium, Phoenix, AZ, USA
[6]The Alzheimer's Disease Cooperative Study

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