Variation in the sequence of AD biomarkers according to brain regions and genetic factors

Gaël Chételat

Inserm-EPHE-Université de Caen/Basse-Normandie, Unité U1077, GIP Cyceron, CHU Côte de Nacre, Caen, France

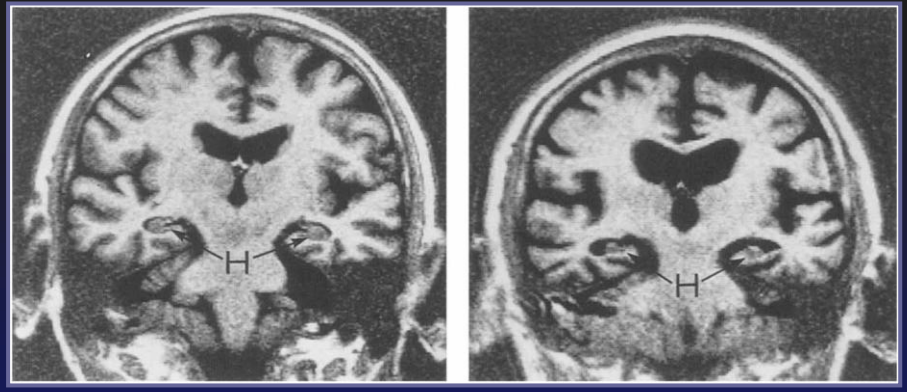
12th Annual Mild Cognitive Impairment (MCI) Symposium

Saturday, January 18th 2014

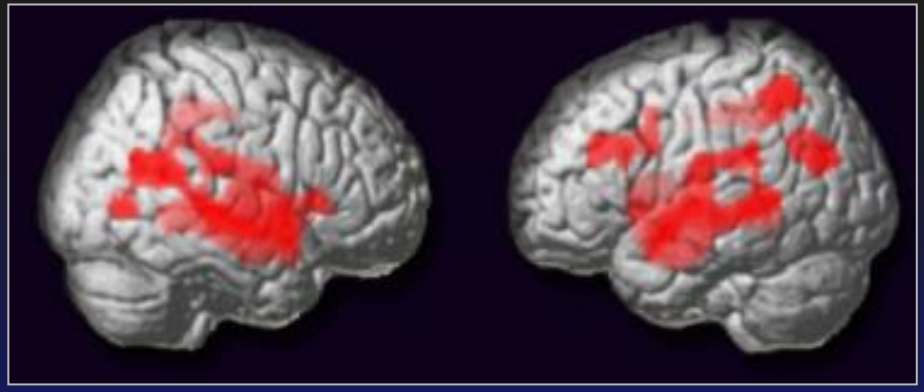
Inserm EPHE UNICAEN université de Caen Basse-Normandie Cyceron PLATEFORME D'IMAGERIE BIOMÉDICALE CHUCaen

Nothing to disclose

MRI

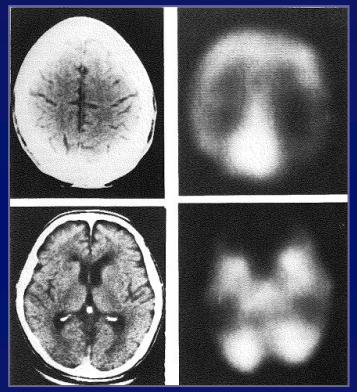


Seab et al., 1988 : **Hippocampal atrophy**

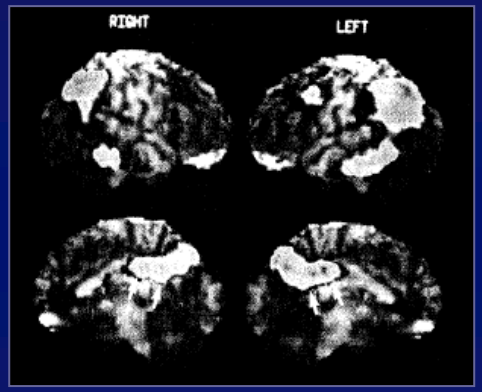


Baron et al., 2001 : throughout the whole brain

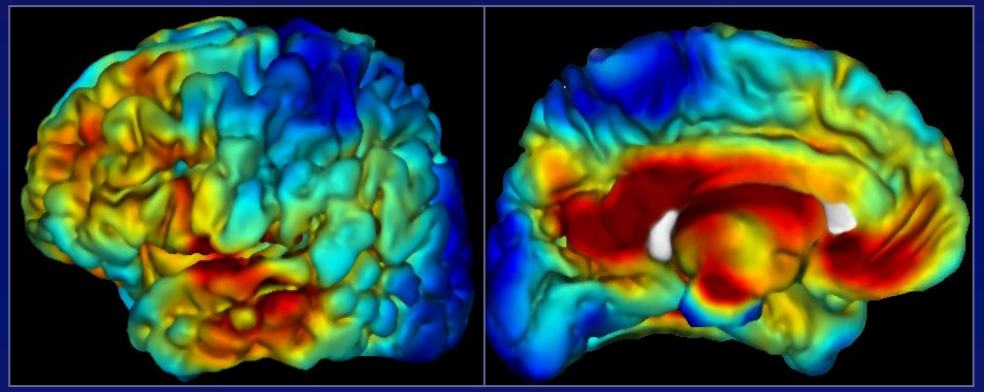
FDG-PET



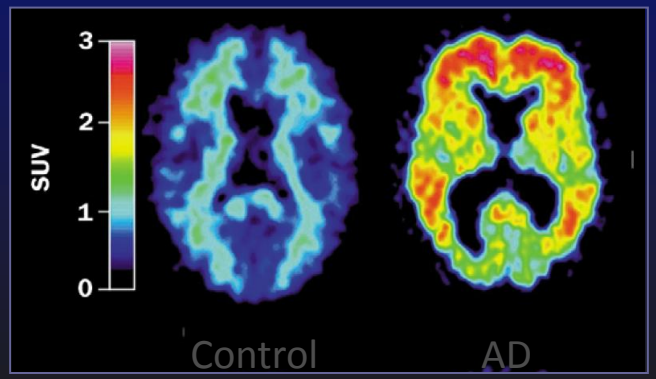
Ferris et al., 1980



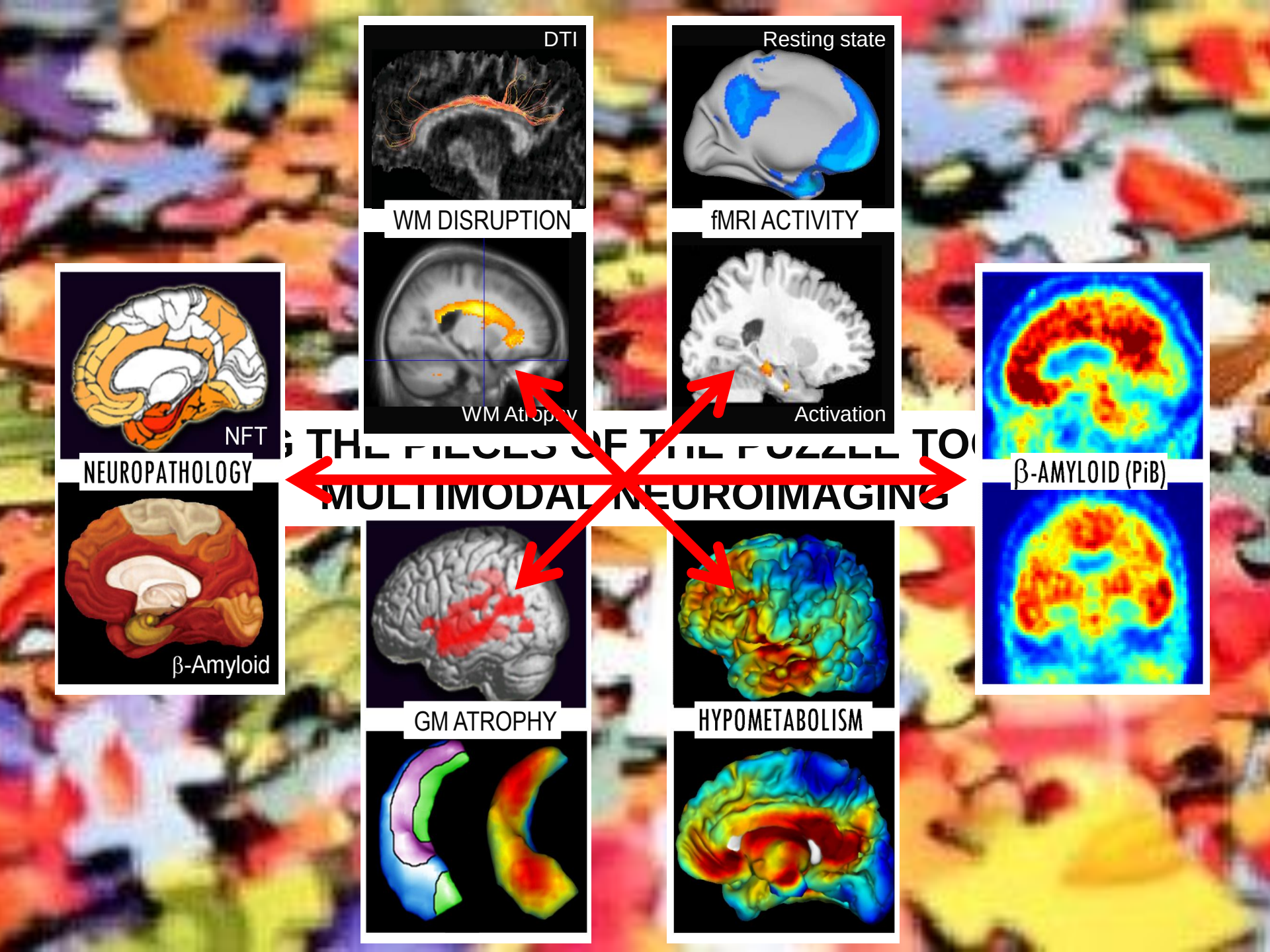
Minoshima et al., 1994



PiB-PET

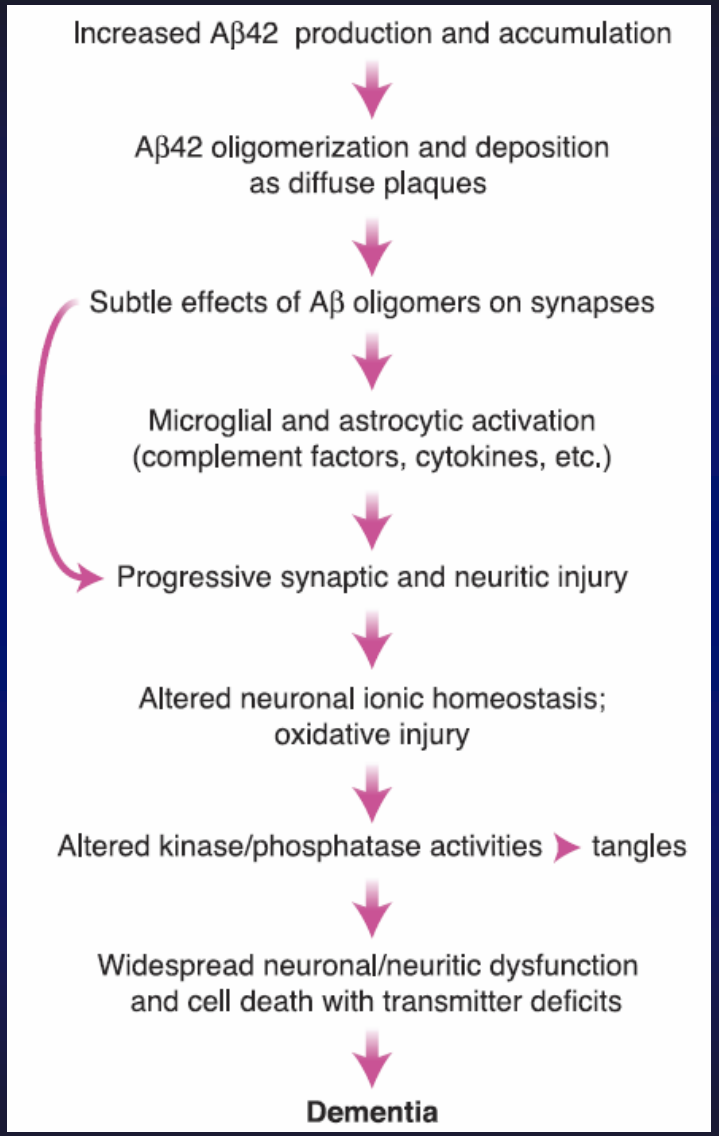


Klunk et al., 2004


DTI
WM DISRUPTION
Resting state
fMRI ACTIVITY
NFT
NEUROPATHOLOGY
β-Amyloid
β-AMYLOID (PiB)
GM ATROPHY
HYPOMETABOLISM
MULTIMODAL NEUROIMAGING

Sequence of events

THE AMYLOID HYPOTHESIS IS A LINEAR MODEL



Hardy et al., 1992; 2002

« Our hypothesis is that **deposition of amyloid β protein (Aβ)**, the main component of the plaques, is the **causative** agent of Alzheimer's pathology and that the **neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of this deposition**.»

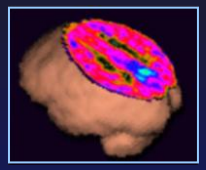
(Hardy & Higgins, 1992)

THE BIOMARKER MODEL FOLLOWS THE SAME ORDERING

Increased Aβ42 production and accumulation

↓

Aβ42 oligomerization and deposition as diffuse plaques → 1) Amyloid TEP imaging



↓

Subtle effects of Aβ oligomers on synapses

↓

Microglial and astrocytic activation (complement factors, cytokines, etc.)

↓

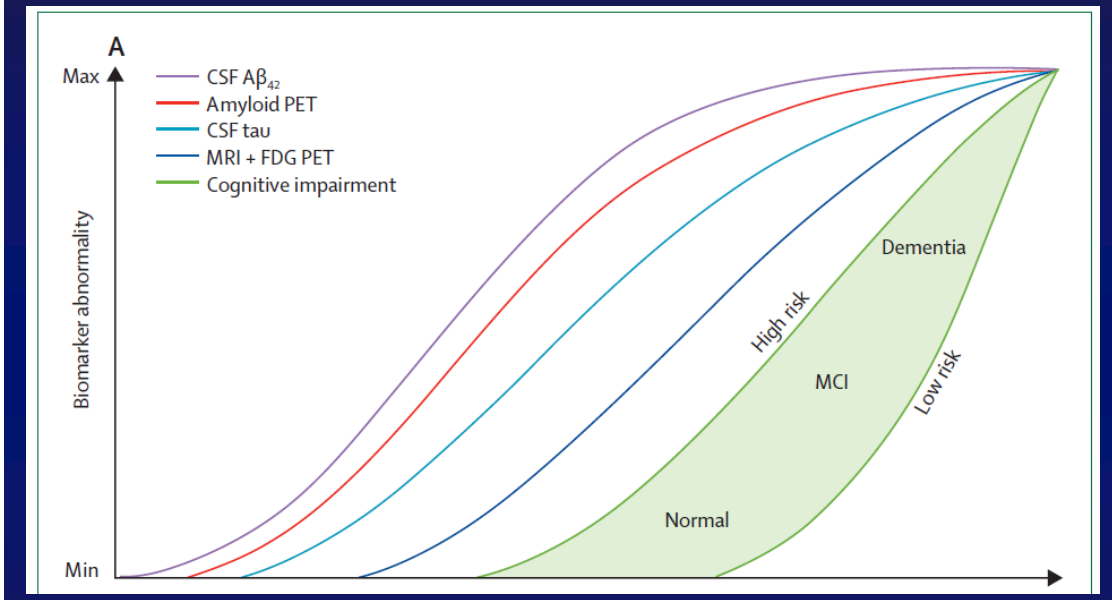
Progressive synaptic and neuritic injury

↓

Altered neuronal ionic homeostasis; oxidative injury

↓

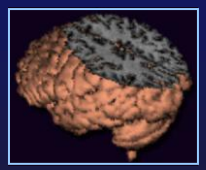
Altered kinase/phosphatase activities ➤ tangles

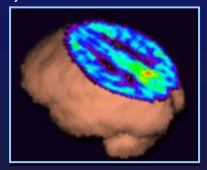


Jack et al., Lancet Neurol 2010; 2013

↓

Widespread neuronal/neuritic dysfunction and cell death with transmitter deficits → 2) Atrophy (MRI) and hypometabolism (FDG-PET)





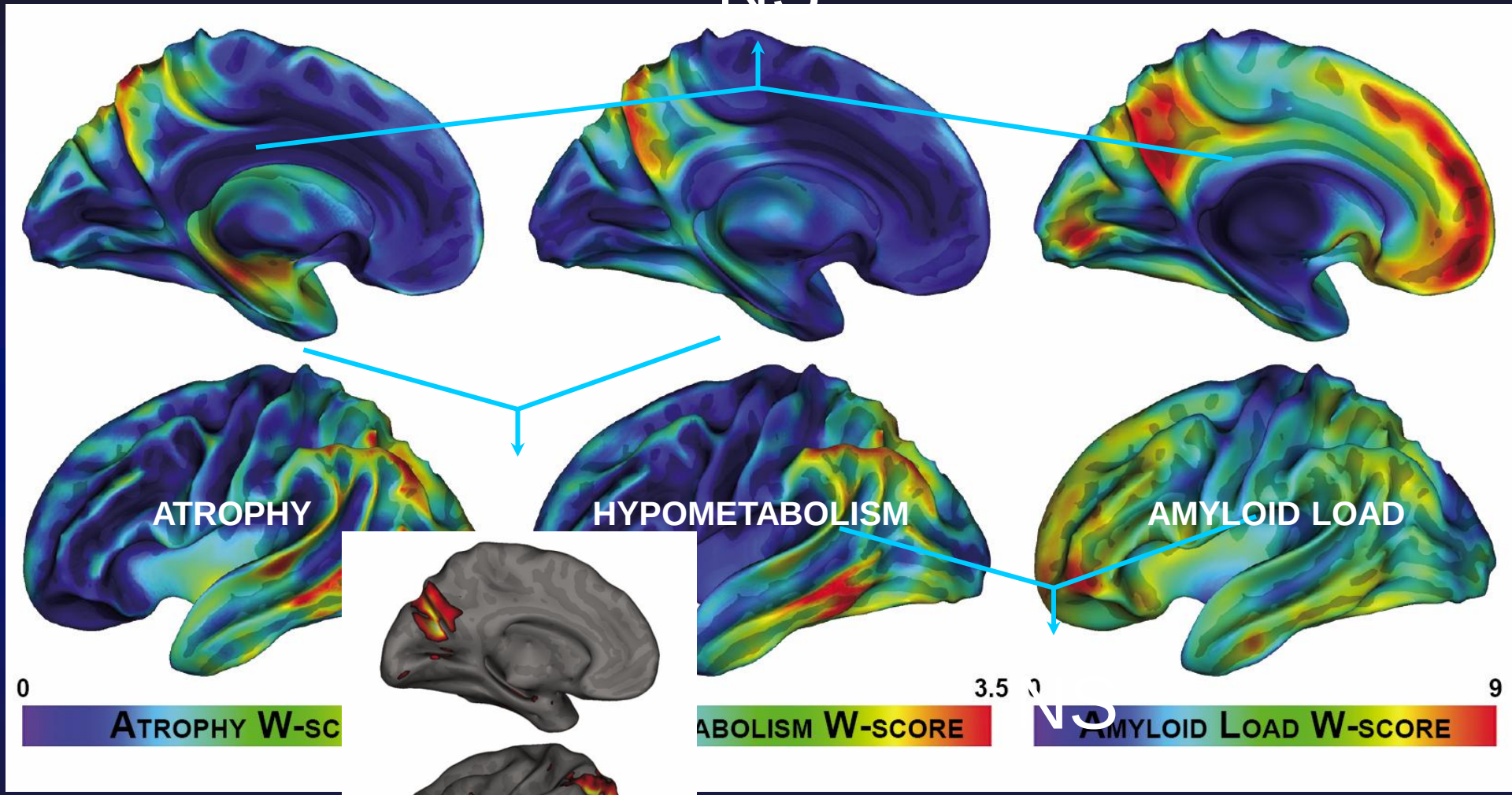
↓

Dementia → 3) Cognitive deficits

Hardy et al., 1992; 2002

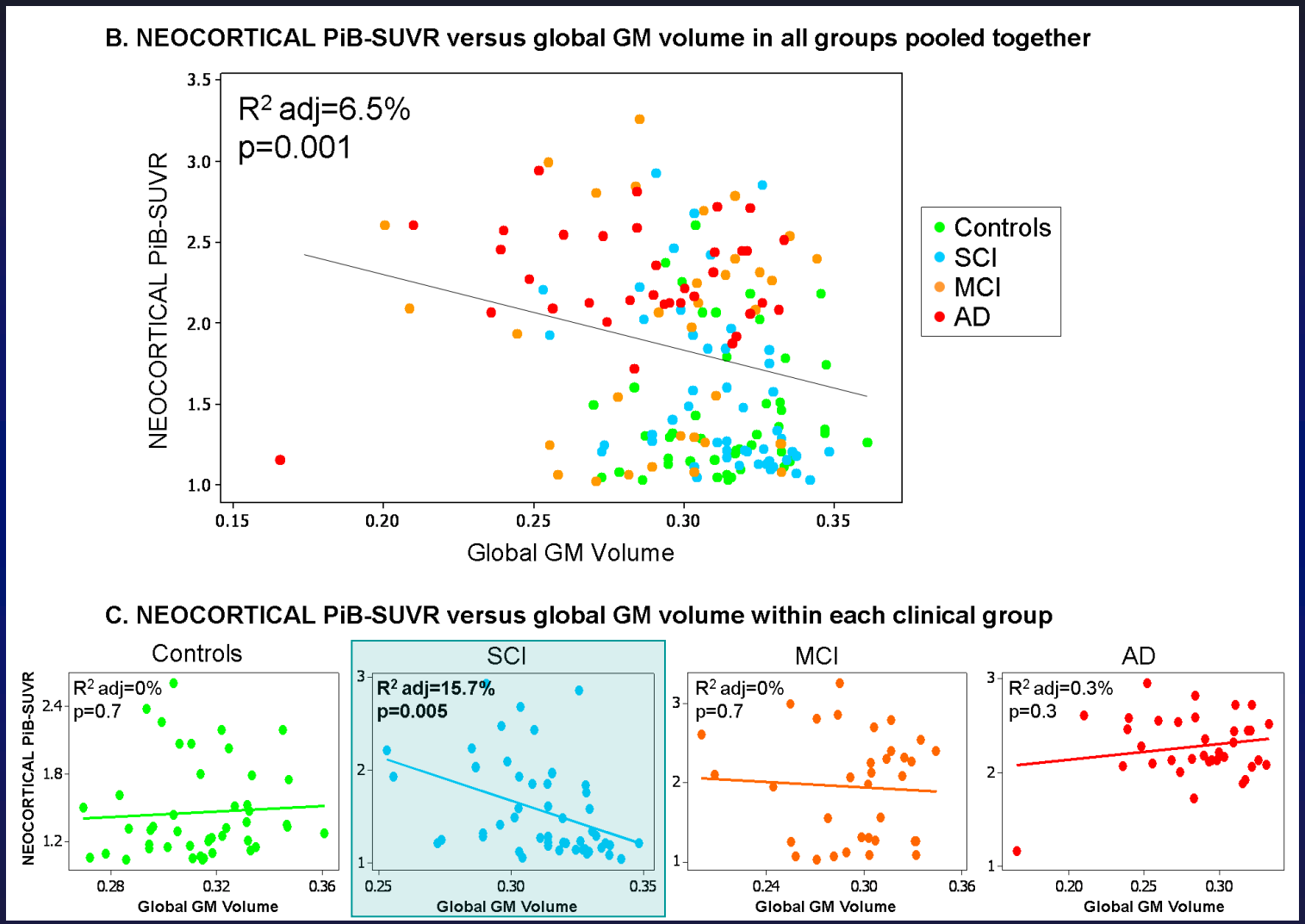
1) Regional discrepancy

RELATIONSHIPS BETWEEN BIOMARKERS: VOXELWISE CORRELATIONS



La Joie et al., J Neurosci, 2012

Correlations between baseline PiB and baseline atrophy



Controls: healthy elderly without memory complaints

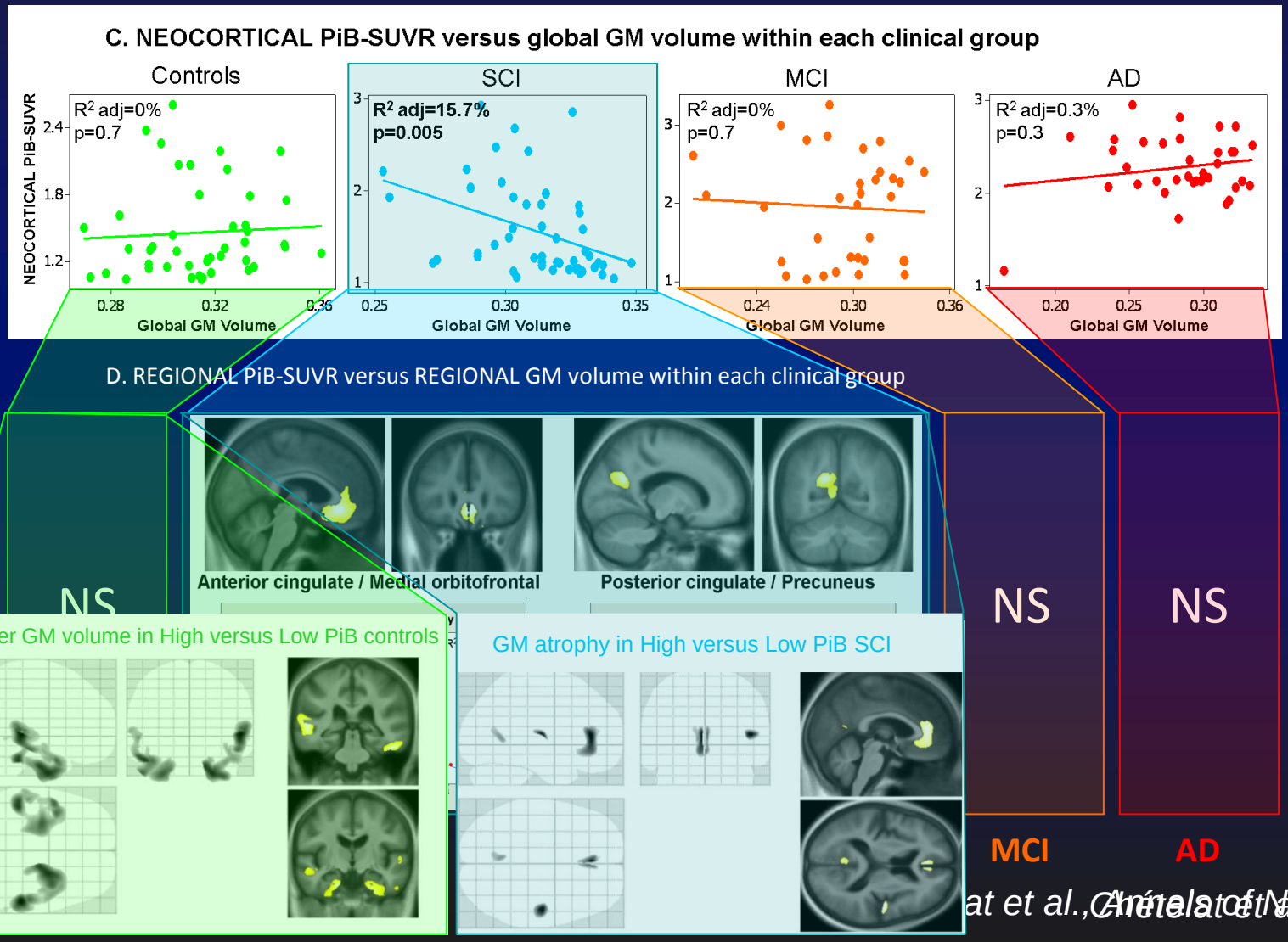
SCI: elderly with subjective cognitive impairment (memory complaints)

MCI: patients with mild cognitive impairment (Petersen et al., 2005)

AD: patients with Alzheimer's disease (NINCDS-ADRDA)

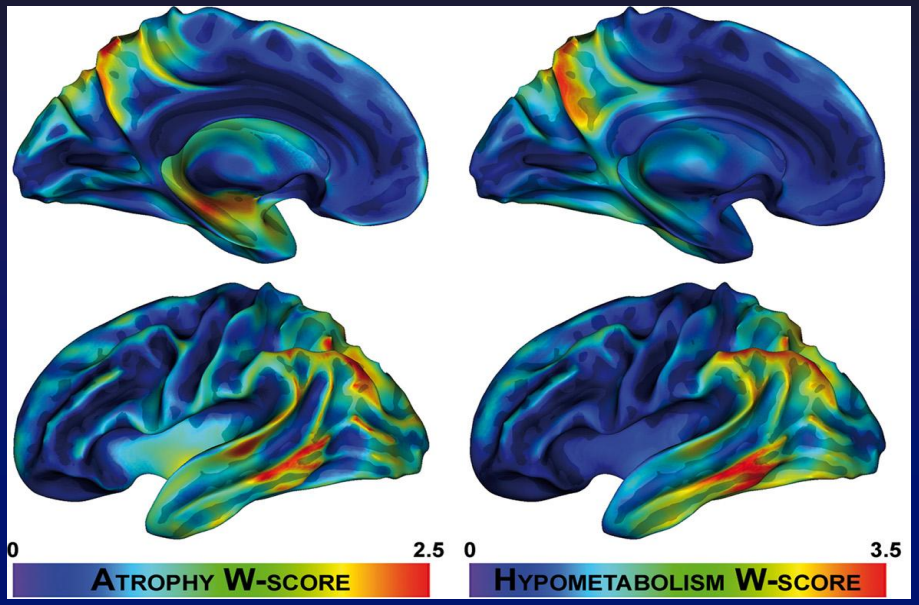
Chételat et al., Annals of Neurology, 2010

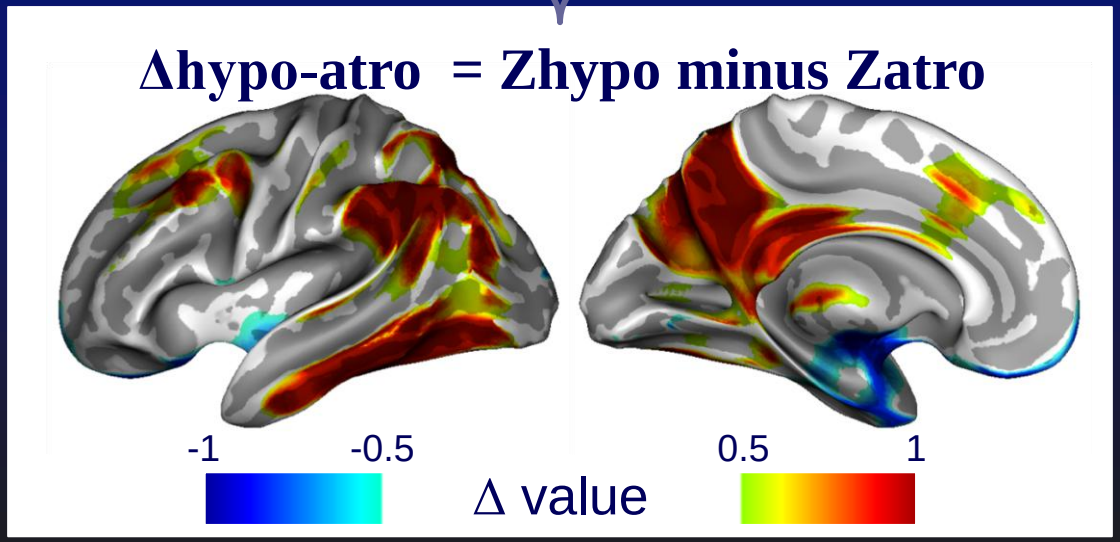
Correlations between baseline PiB and baseline atrophy



Chételat et al., Annals of Neurology, 2010

VOXELWISE COMPARISON BETWEEN HYPOMETABOLISM AND ATROPHY IN AD

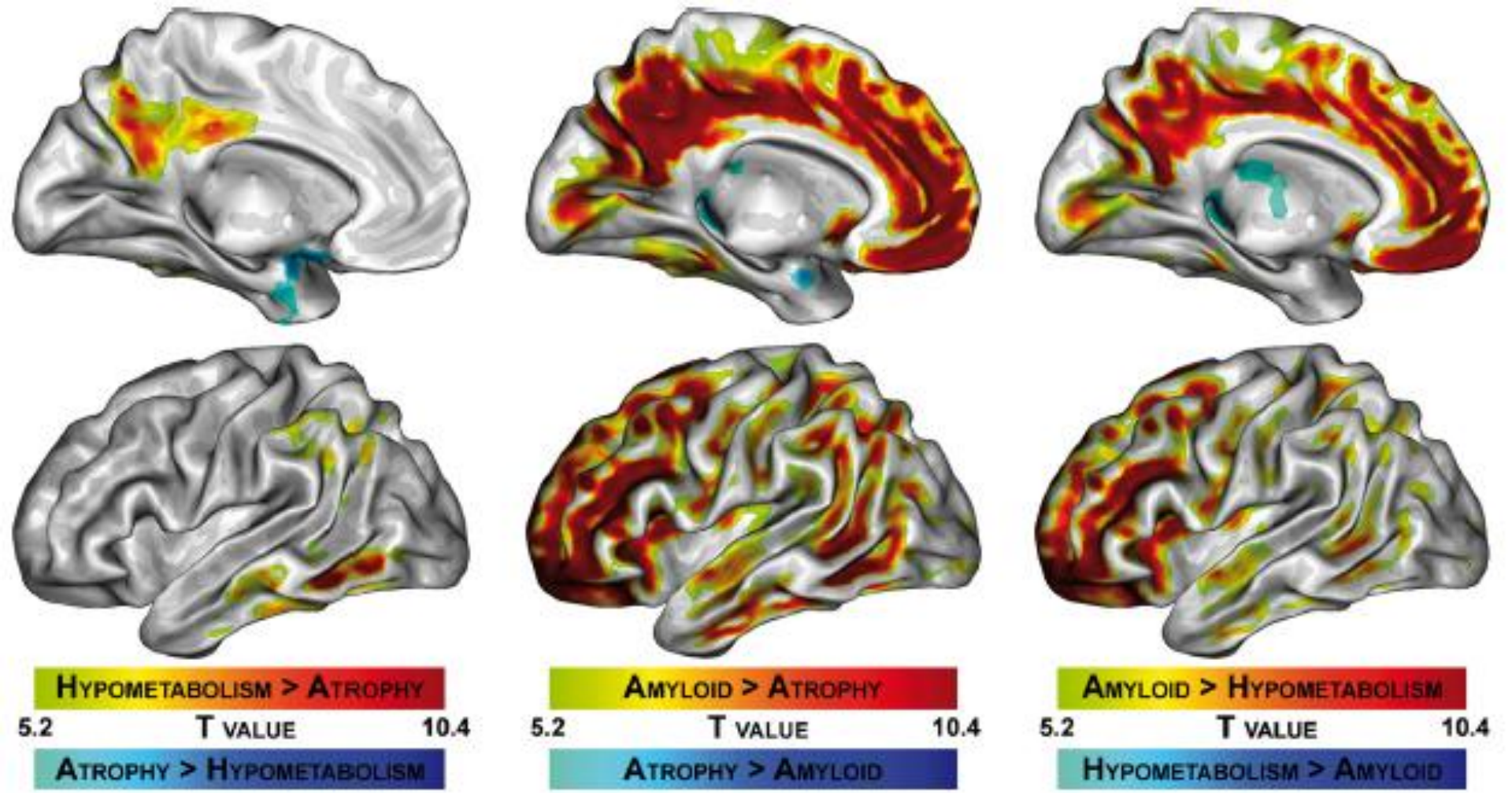




Chételat et al., Brain, 2008

La Joie et al., J Neurosci, 2012

DIRECT VOXEL-BASED COMPARISON BETWEEN GREY MATTER HYPOMETABOLISM, ATROPHY, AND AMYLOID DEPOSITION IN ALZHEIMER'S DISEASE



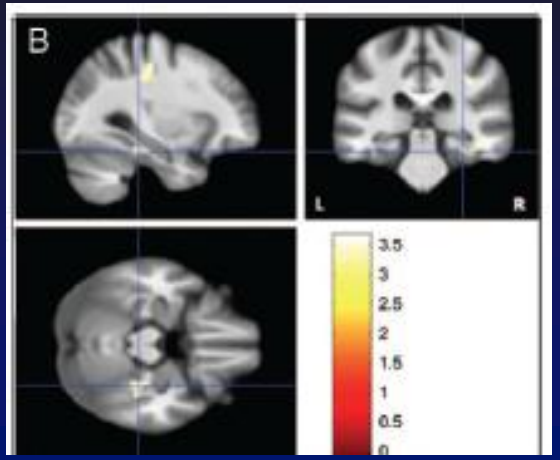
La Joie et al., J Neurosci, 2012

HIPPOCAMPAL UPREGULATION?

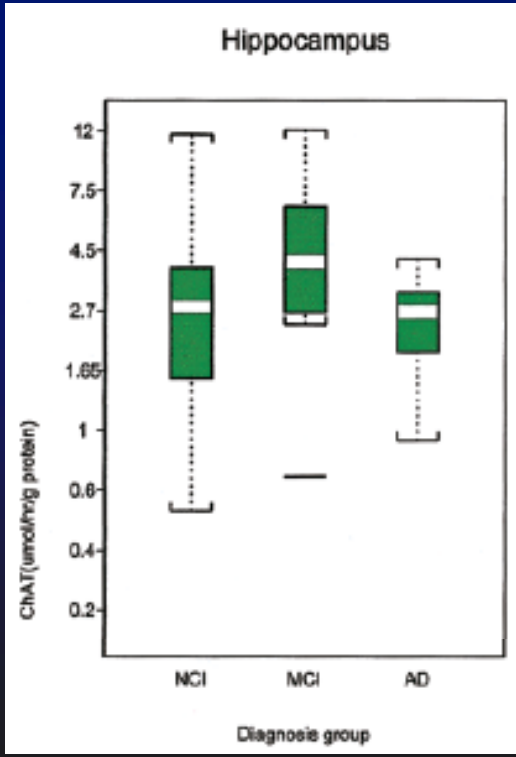
Ann Neurol 2002;51:145–155
DOI 10.1002/ana.10069

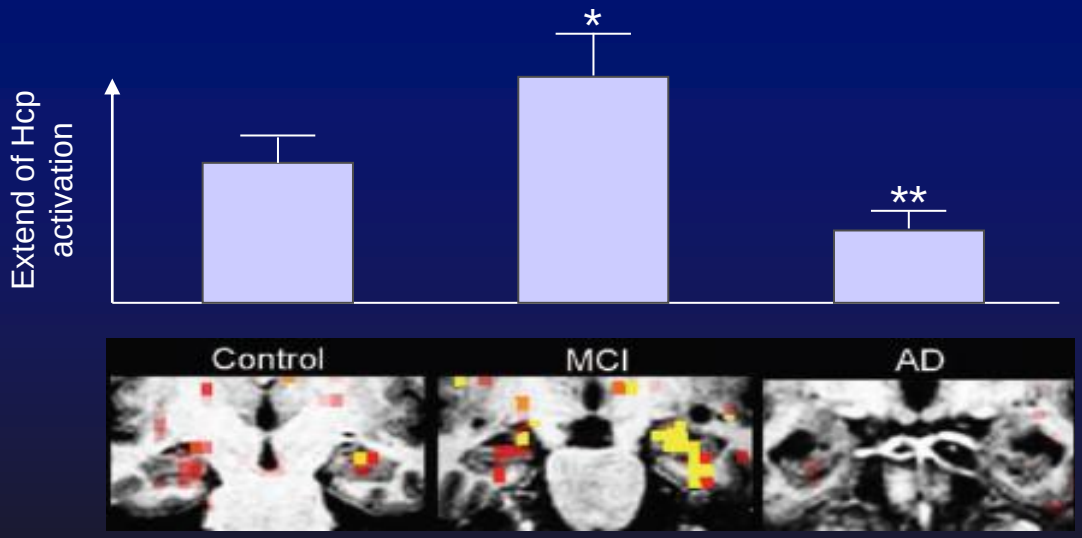
Upregulation of Choline Acetyltransferase Activity in Hippocampus and Frontal Cortex of Elderly Subjects with Mild Cognitive Impairment

Steven T. DeKosky, MD,[1,2] Milos D. Ikonomovic, MD,[2] Scot D. Styren, PhD,[2] Laurel Beckett, PhD,[4] Stephen Wisniewski, PhD,[3] David A. Bennett, MD,[4] Elizabeth J. Cochran, MD,[4] Jeffrey H. Kordower, PhD,[4] and Elliott J. Mufson, PhD[4]



Scheef et al., Neurology 2012





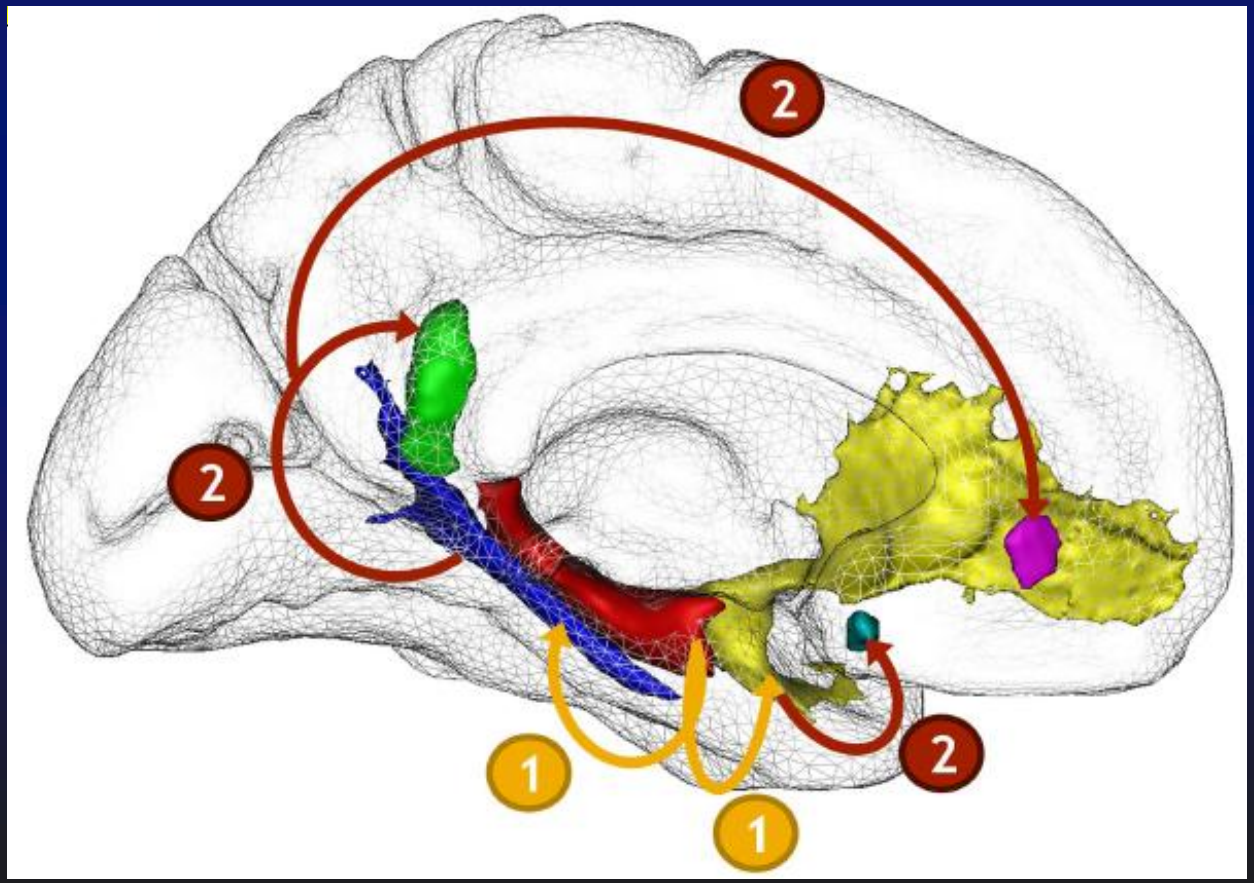
Dickerson et al., Neurology 2005

DISCONNECTION / DIASCHISIS HYPOTHESIS

Hippocampal atrophy → Cingulum bundle disruption → Posterior cingulate hypometabolism

Cingulum bundle disruption → Anterior cingulate cortex(BA32)

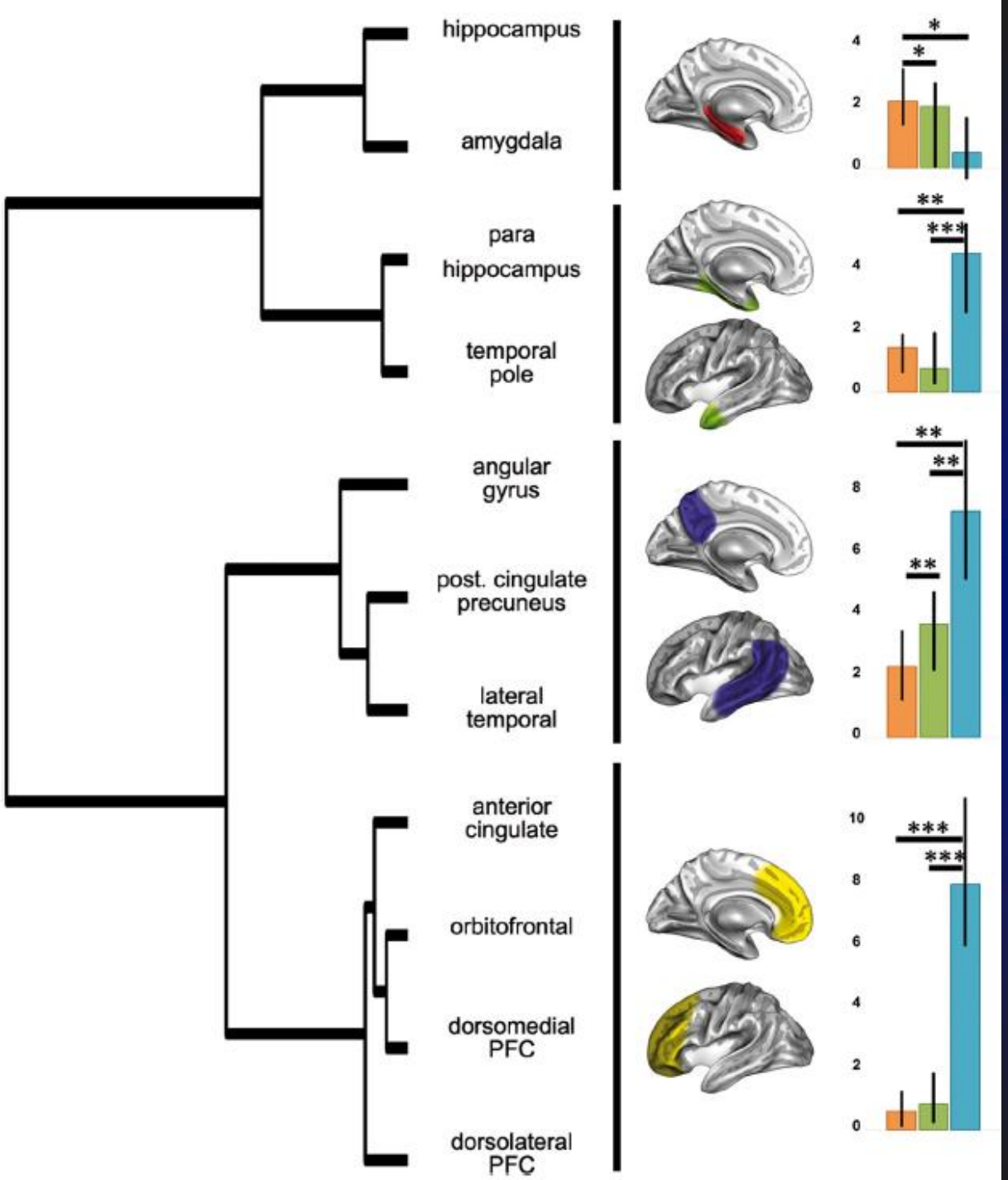
Hippocampal atrophy → Uncinate fasciculus → Subgenual cortex (BA25)

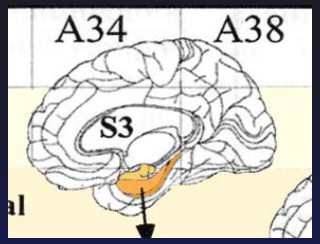


Villain et al., Brain, 2010

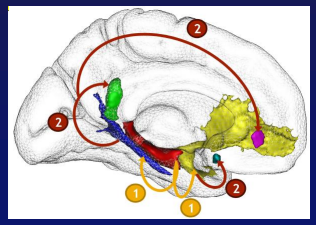
Fouquet et al., Brain, 2009

Villain et al., J Neurosci, 2008

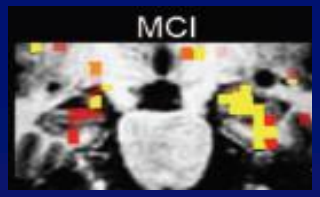




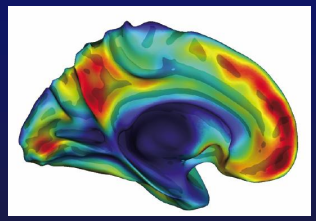
Delacourte et al., Duyckaerts et al; Braak and Braak



Disconnexion processes



Up-regulation



Weak relationships between Aβ deposition and atro/hypo

La Joie et al., J Neurosci, 2012

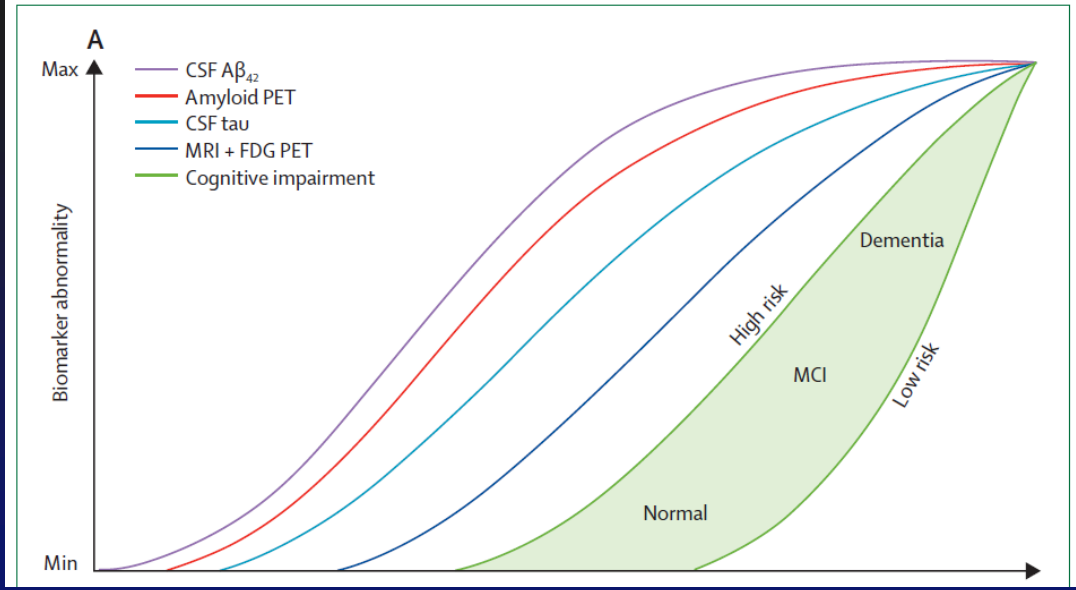
ALZHEIMER RESEARCH FORUM

NETWORKING FOR A CURE

Integrated Brain Imaging Emphasizes Regional Differences in What Changes When on the Long Descent Into Alzheimer's

Live discussion / Webinar of the Alzheimer research forum: www.alzforum.com

2) Variation of the sequence



Toward defining the preclinical stages of Alzheimer's disease:

	Aβ (PET or CSF)	**Markers of neuronal injury** (tau, FDG, sMRI)	**Evidence of subtle cognitive change**
Stage 0	-	-	-
Stage 1	+	-	-
Stage 2	+	+	-
Stage 3	+	+	+

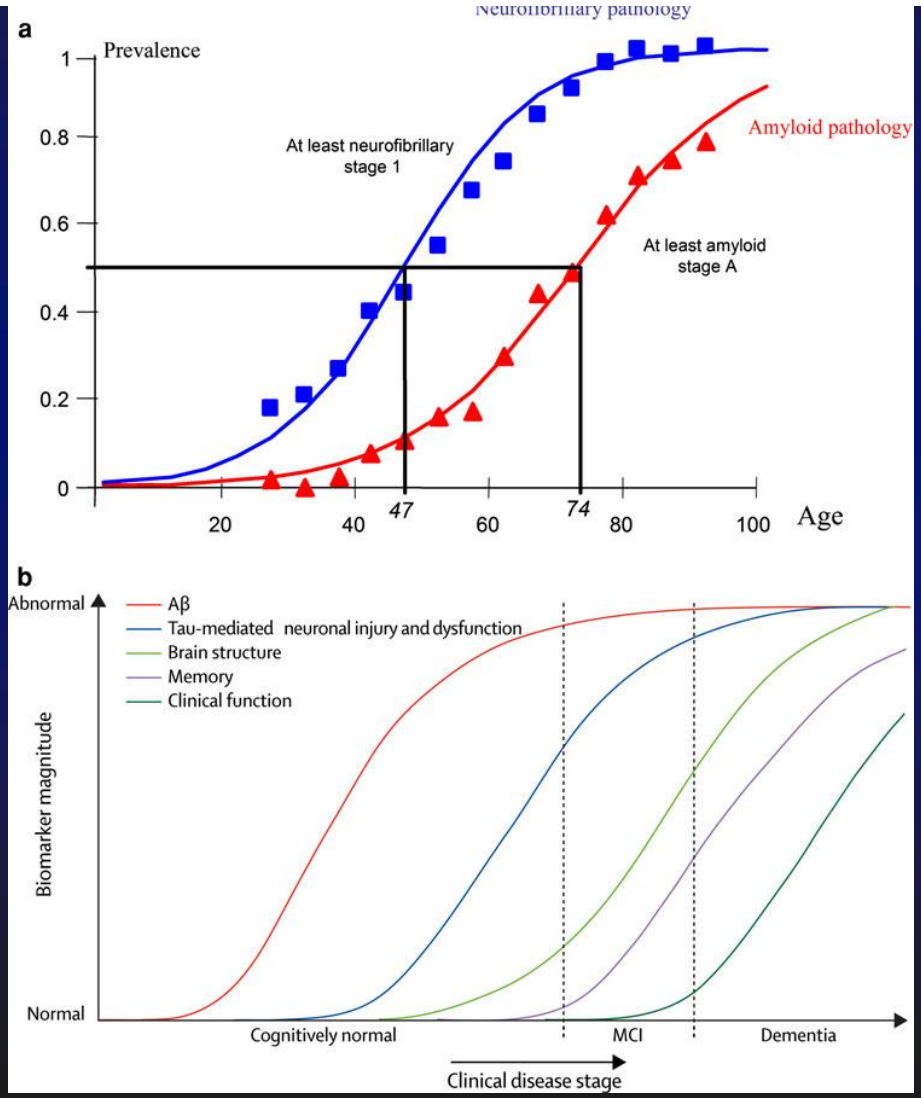
Sperling al., Alzheimer's & Dementia, 2011

Acta Neuropathol (2011) 121:145–147
DOI 10.1007/s00401-010-0794-7

EDITORIAL

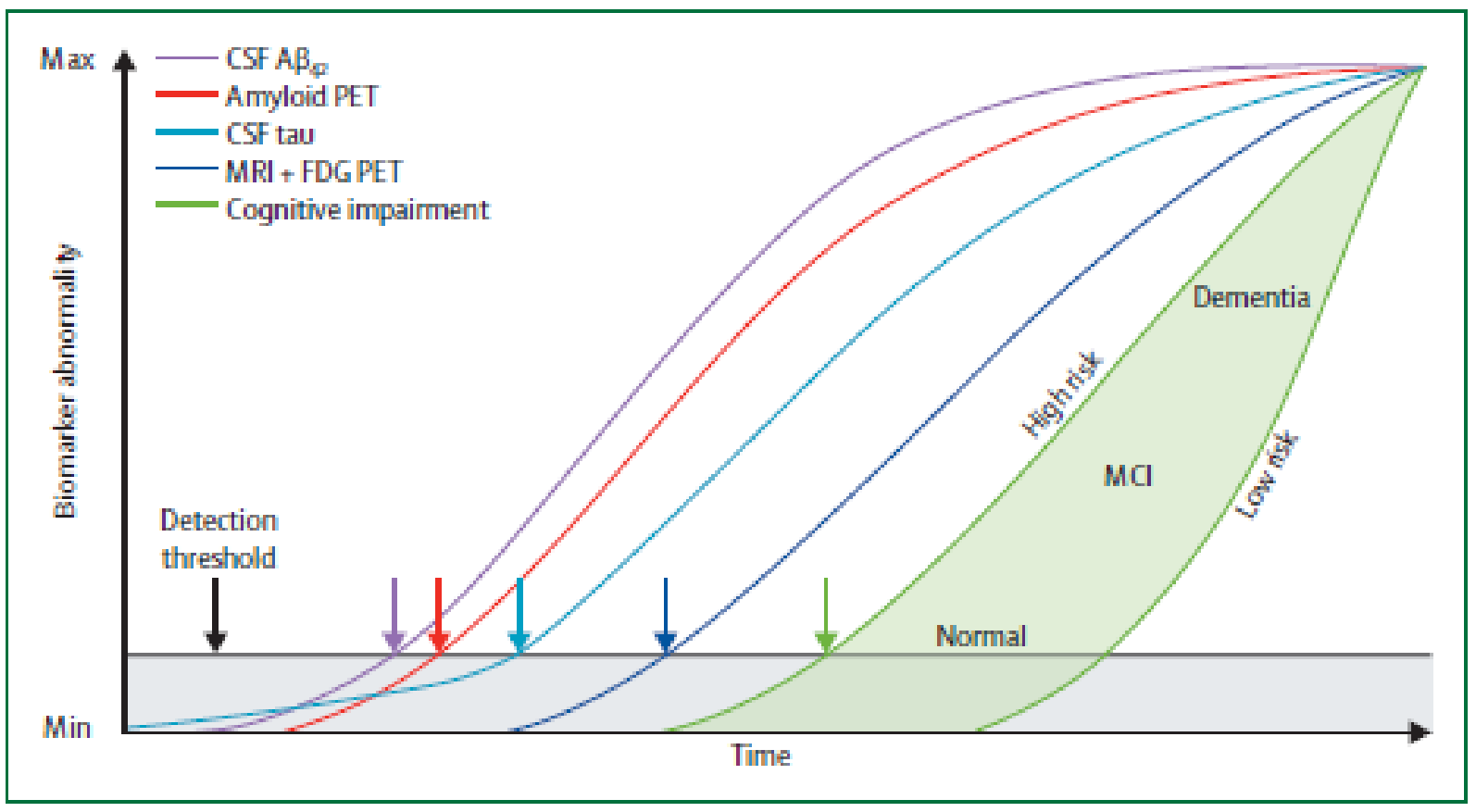
Tau pathology in children and young adults: can you still be unconditionally baptist?

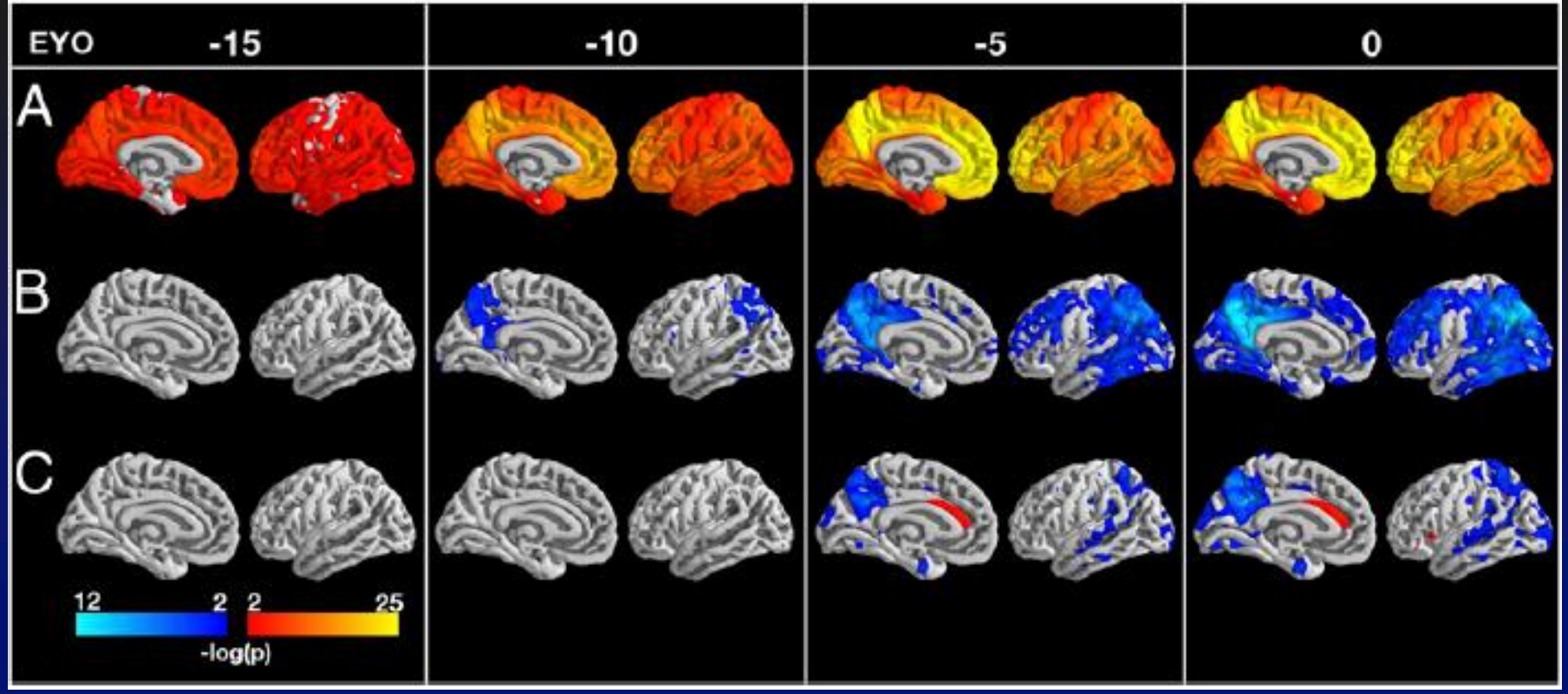
Charles Duyckaerts

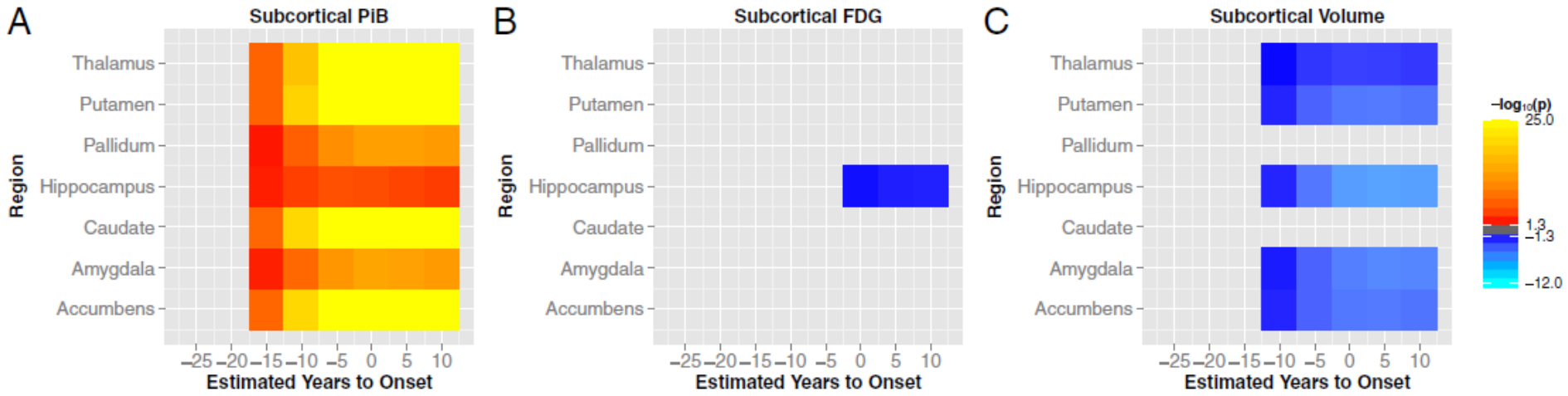


Duyckaerts, Acta Neuropathologica, 2011

This has been integrated in a new version of the model for the pathological processes; the biomarker sequence remains unchanged







Benzinger et al., PNAS, 2013

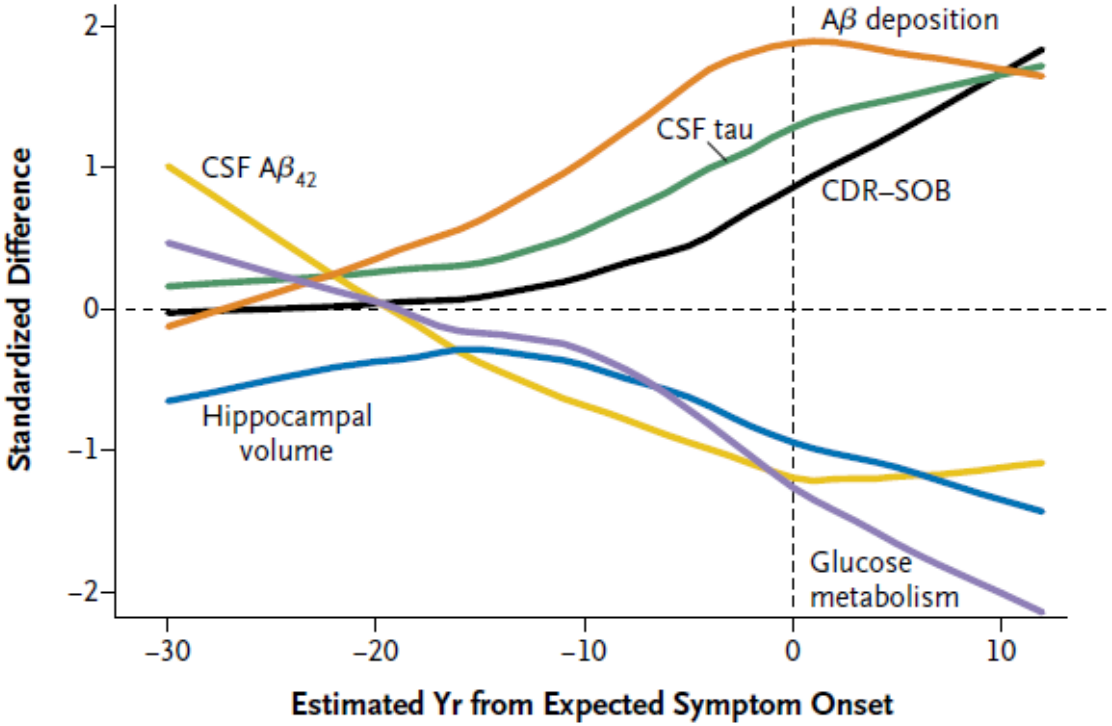
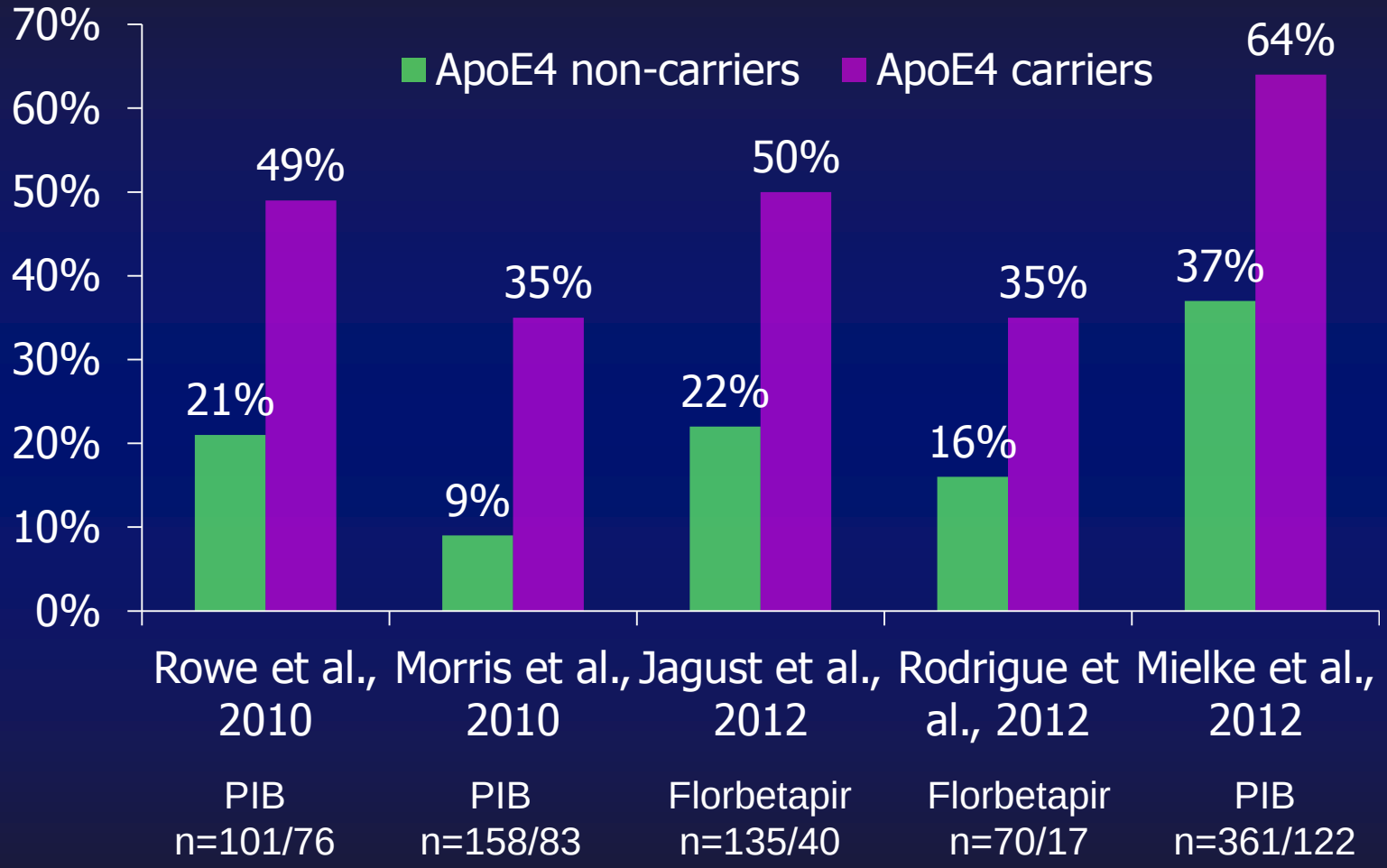


Figure 2. Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset.

The normalized differences between mutation carriers and noncarriers are shown versus estimated years from expected symptom onset and plotted with a fitted curve. The order of differences suggests decreasing $A\beta_{42}$ in the CSF (CSF $A\beta_{42}$), followed by fibrillar $A\beta$ deposition, then increased tau in the CSF (CSF tau), followed by hippocampal atrophy and hypometabolism, with cognitive and clinical changes (as measured by the Clinical Dementia Rating–Sum of Boxes [CDR-SOB]) occurring later. Mild dementia (CDR 1) occurred an average of 3.3 years before expected symptom onset. 95% confidence interval bands are shown in Figure S2 in the Supplementary Appendix.

Bateman et al., N Engl J Med, 2012

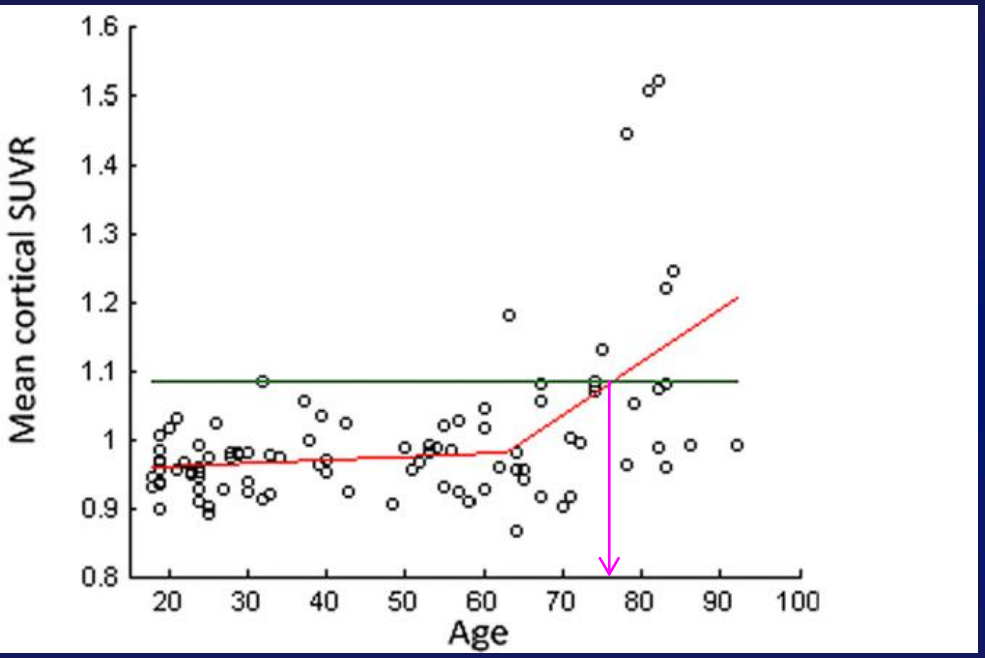
APOE4 is associated with a significant increase in Aβ deposition, a greater proportion of amyloid-positive individuals in normal elderly



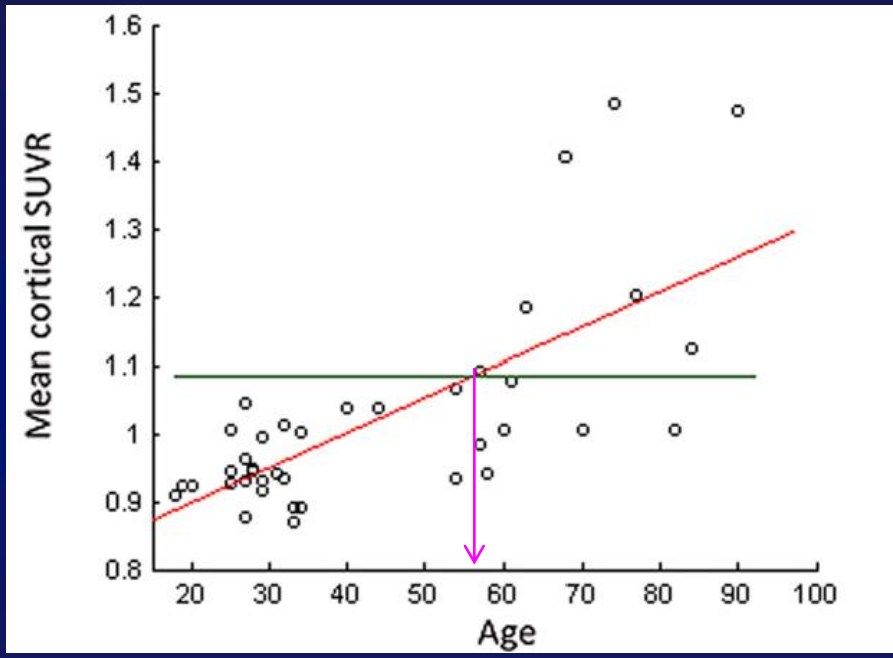
Courtesy of Renaud La Joie, PhD

For review, cf Chételat et al., Neuroimage: clinical, 2013

… and a decrease in the age of predicted amyloid-positivity



APOE4 non-carriers → **76 yrs**

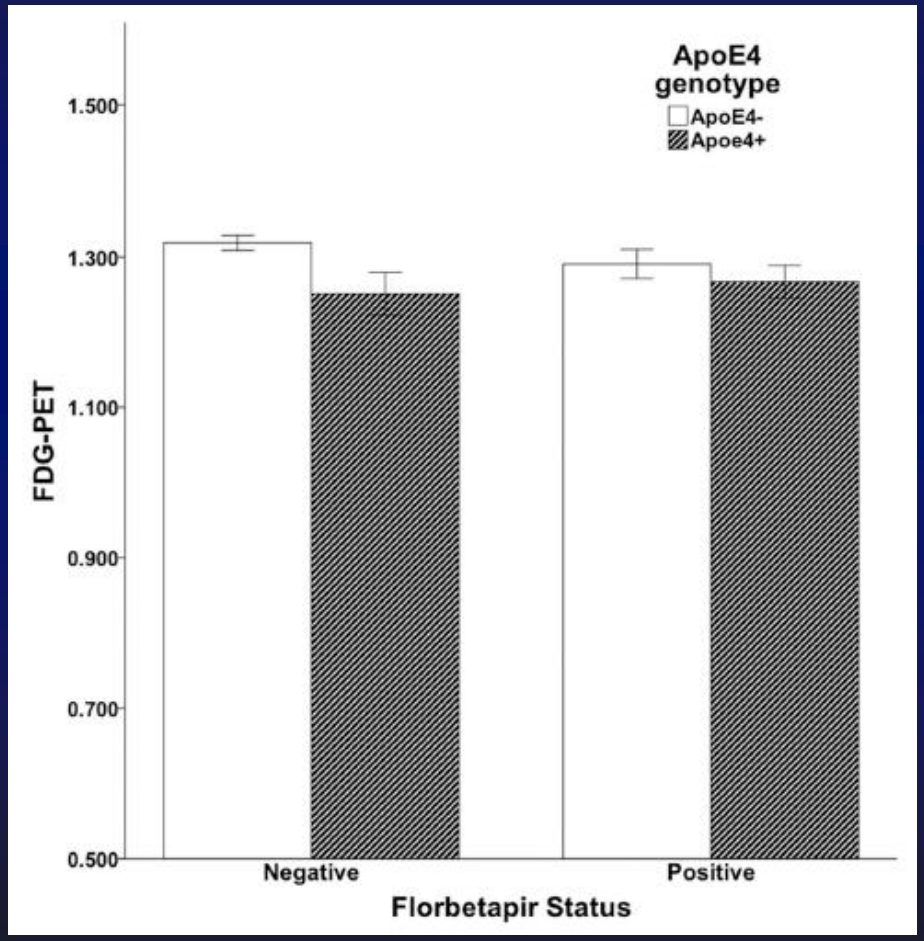


APOE4 carriers → **56 yrs**

(Fleisher et al., 2013)

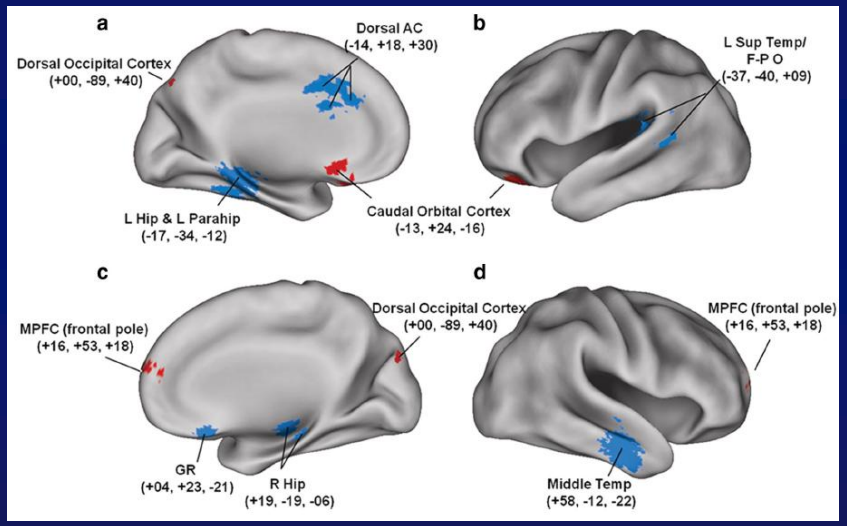
Neuroimaging studies show evidence for AD-like neurodegenerative changes without Aβ deposition

Apolipoprotein E, not Fibrillar β-amyloid, Reduces Cerebral Glucose Metabolism in Normal Aging



Jagust et al., J Neurosci, 2012

Disruption of functional connectivity in **PIB-negative** asymptomatic ApoE4 carriers



Sheline et al., J Neurosci, 2010

1) APOE4 exerts a graded effect:

Amyloid deposition > metabolism > brain structure

2) There are both Aβ-dependent and Aβ-independent effects of APOE4

Huang, 2010; Huang et Mucke 2012; Liu et al., 2013; Desikan et al., 2013; Sheline et al., 2010; Jagust et al., 2012

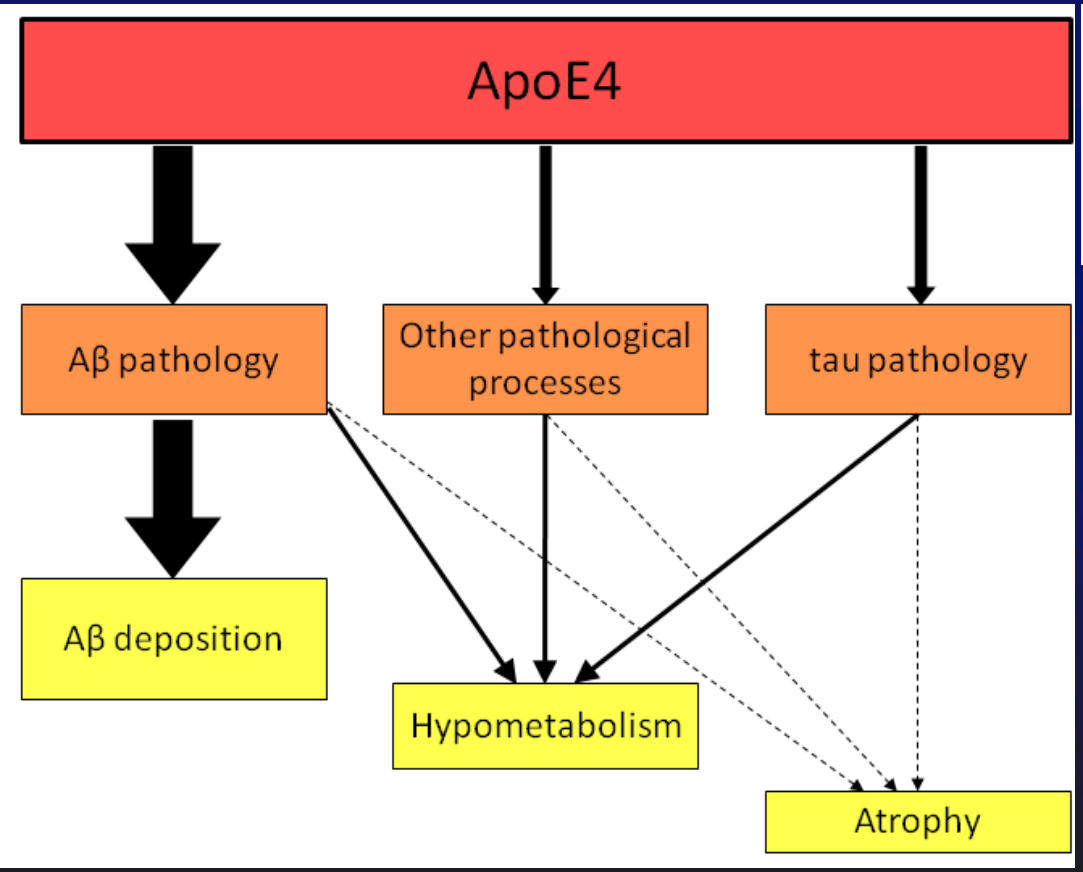


Fig. 1 – Schematic representation illustrating the graded effect of APOE4 on amyloid deposition, metabolism and brain structure, showing a clear predominance of its effect on Aβ pathology (thick arrows). This figure also illustrates that ApoE4 operates through both Aβ-dependent and Aβ-independent processes.

Chételat & Fouquet, Rev Neurol, 2013

Annals of Neurology
Volume 71, Issue 6, Article first published online: 9 APR 2012
Abstract | Full Article (HTML) | References | Cited By

ORIGINAL ARTICLE

Application of the criteria questions the model

An Operational Approach to National Institute on Aging–Alzheimer's Association Criteria for Preclinical Alzheimer Disease

Clifford R. Jack, Jr, MD,[1] David S. Knopman, MD,[2,3] Stephen D. Weigand, MS,[4] Heather J. Wiste, BA,[4] Prashanthi Vemuri, PhD,[1] Val Lowe, MD,[1] Kejal Kantarci, MD,[1] Jeffrey L. Gunter, PhD,[1] Matthew L. Senjem, MS,[1] Robert J. Ivnik, PhD, LP,[5] Rosebud O. Roberts, MBBCh,[3,6] Walter A. Rocca, MD, MPH,[2,6] Bradley F. Boeve, MD,[2,7] and Ronald C. Petersen, MD, PhD[2,3,6]

Objective: A workgroup commissioned by the Alzheimer's Association (AA) and the National Institute on Aging (NIA) recently published research criteria for preclinical Alzheimer disease (AD). We performed a preliminary assessment of these guidelines.

Methods: We employed Pittsburgh compound B positron emission tomography (PET) imaging as our biomarker of cerebral amyloidosis, and ^{18}fluorodeoxyglucose PET imaging and hippocampal volume as biomarkers of neurodegeneration. A group of 42 clinically diagnosed AD subjects was used to create imaging biomarker cutpoints. A group of 450 cognitively normal (CN) subjects from a population-based sample was used to develop cognitive cutpoints and to assess population frequencies of the different preclinical AD stages using different cutpoint criteria.

Results: The new criteria subdivide the preclinical phase of AD into stages 1 to 3. To classify our CN subjects, 2 additional categories were needed. *Stage 0* denotes subjects with normal AD biomarkers and no evidence of subtle cognitive impairment. *Suspected non-AD pathophysiology* (SNAP) denotes subjects with normal amyloid PET imaging, but abnormal neurodegeneration biomarker studies. At fixed cutpoints corresponding to 90% sensitivity for diagnosing AD and the 10th percentile of CN cognitive scores, 43% of our sample was classified as stage 0, 16% stage 1, 12 % stage 2, 3% stage 3, and 23% SNAP.

Interpretation: This cross-sectional evaluation of the NIA-AA criteria for preclinical AD indicates that the 1–3 staging criteria coupled with stage 0 and SNAP categories classify 97% of CN subjects from a population-based sample, leaving only 3% unclassified. Future longitudinal validation of the criteria will be important

ANN NEUROL 2012;71:765–775

	Aβ (PET or CSF)	**Markers of neuronal injury** (tau, FDG, sMRI)	**Evidence of subtle cognitive change**	**Proportion of individuals in each stage :** **N = 450**
Stage 0	-	-	-	43%
Stage 1	+	-	-	16%
Stage 2	+	+	-	12%
Stage 3	+	+	+	3%
SNAP*	-	+	+/-	23%

* Suspected Non-AD Pathophysiology

Jack et al., Ann Neurol, 2012

Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease

Neurology. 2012 May 15;78(20):1576-82. doi: 10.1212/WNL.0b013e3182563bbe. Epub 2012 May 2.

D.S. Knopman, MD*
C.R. Jack, Jr., MD*
H.J. Wiste, BA
S.D. Weigand, MS
P. Vemuri, PhD
V. Lowe, MD
K. Kantarci, MD
J.L. Gunter, PhD
M.L. Senjem, MS
R.J. Ivnik, PhD, LP
R.O. Roberts, MBBCh
B.F. Boeve, MD
R.C. Petersen, MD, PhD

Correspondence & reprint requests to Dr. Knopman: knopman@mayo.edu

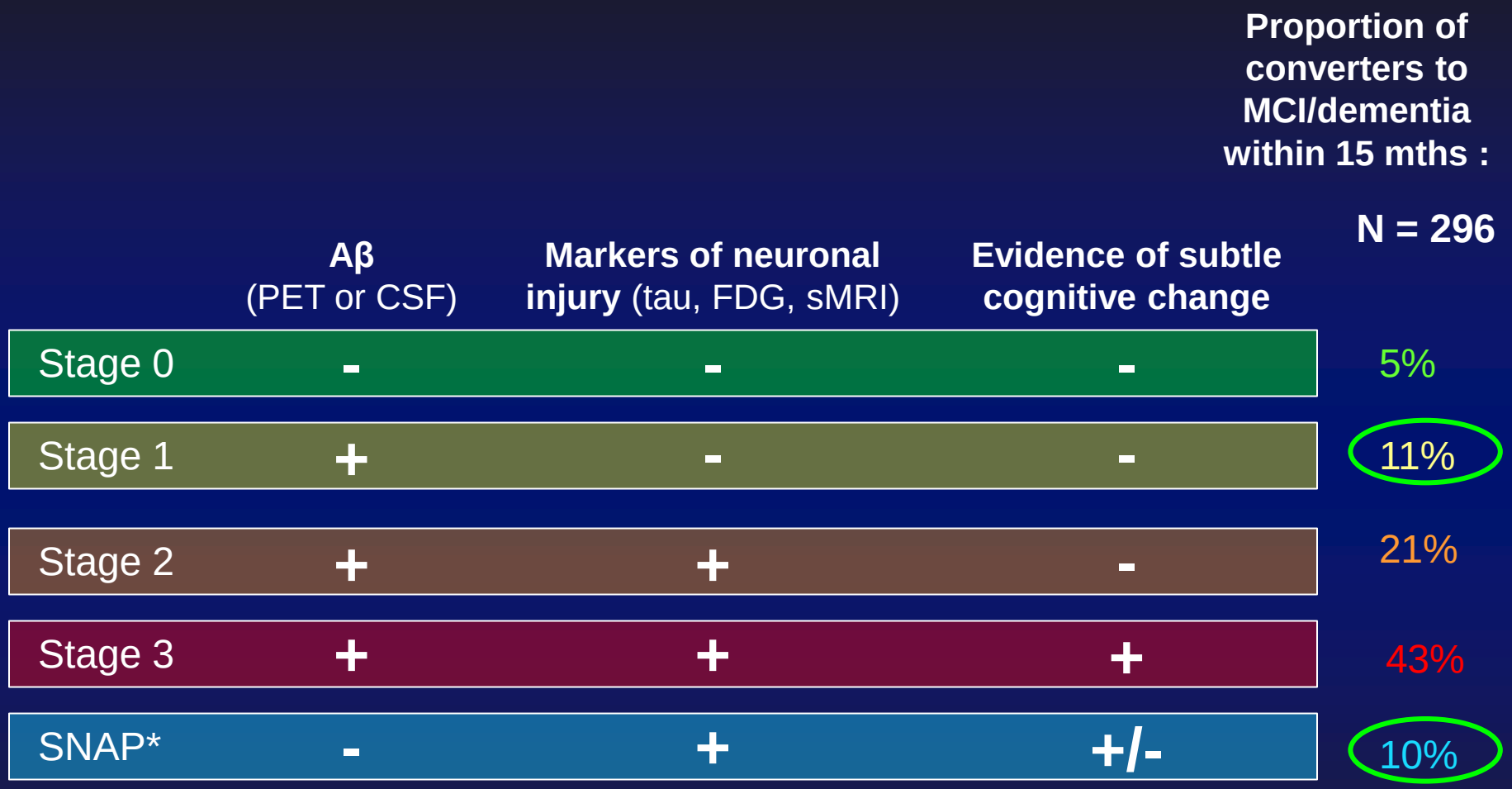
ABSTRACT

Objective: Recommendations for the diagnosis of preclinical Alzheimer disease (AD) have been formulated by a workgroup of the National Institute on Aging and Alzheimer's Association. Three stages of preclinical AD were described. Stage 1 is characterized by abnormal levels of β-amyloid. Stage 2 represents abnormal levels of β-amyloid and evidence of brain neurodegeneration. Stage 3 includes the features of stage 2 plus subtle cognitive changes. Stage 0, not explicitly defined in the criteria, represents subjects with normal biomarkers and normal cognition. The ability of the recommended criteria to predict progression to cognitive impairment is the crux of their validity.

Methods: Using previously developed operational definitions of the 3 stages of preclinical AD, we examined the outcomes of subjects from the Mayo Clinic Study of Aging diagnosed as cognitively normal who underwent brain MRI or [^{18}F]fluorodeoxyglucose and Pittsburgh compound B PET, had global cognitive test scores, and were followed for at least 1 year.

Results: Of the 296 initially normal subjects, 31 (10%) progressed to a diagnosis of mild cognitive impairment (MCI) or dementia (27 amnestic MCI, 2 nonamnestic MCI, and 2 non-AD dementias) within 1 year. The proportion of subjects who progressed to MCI or dementia increased with advancing stage (stage 0, 5%; stage 1, 11%; stage 2, 21%; stage 3, 43%; test for trend, $p < 0.001$).

Conclusions: Despite the short follow-up period, our operationalization of the new preclinical AD recommendations confirmed that advancing preclinical stage led to higher proportions of subjects who progressed to MCI or dementia. **Neurology® 2012;78:1576-1582**



Knopman et al., Neurology, 2012

Annals of Neurology
Early View, Article first published online: 19 FEB 2013

ORIGINAL ARTICLE

Brain Injury Biomarkers Are Not Dependent on β-Amyloid in Normal Elderly

David S. Knopman, MD,[1,2] Clifford R. Jack,Jr, MD,[2,3] Heather J. Wiste, BA,[4] Stephen D. Weigand, MS,[4] Prashanthi Vemuri, PhD,[1] Val J. Lowe, MD,[3] Kejal Kantarci, MD,[3] Jeffrey L. Gunter, PhD,[3] Matthew L. Senjem, MS,[3] Michelle M. Mielke, PhD,[5] Rosebud O. Roberts, MBBCh,[5] Bradley F. Boeve, MD,[1,2] and Ronald C. Petersen, MD, PhD[1,2,5]

Objective: The new criteria for preclinical Alzheimer disease (AD) proposed 3 stages: abnormal levels of β-amyloid (stage 1), stage 1 plus evidence of brain injury (stage 2), and stage 2 plus subtle cognitive changes (stage 3). However, a large group of subjects with normal β-amyloid biomarkers have evidence of brain injury; we labeled them as the "suspected non-Alzheimer pathophysiology" (sNAP) group. The characteristics of the sNAP group are poorly understood.

Methods: Using the preclinical AD classification, 430 cognitively normal subjects from the Mayo Clinic Study of Aging who underwent brain magnetic resonance (MR), ^{18}fluorodeoxyglucose (FDG), and Pittsburgh compound B positron emission tomography (PET) were evaluated for FDG PET regional volumetrics, MR regional brain volumetrics, white matter hyperintensity volume, and number of infarcts. We examined cross-sectional associations across AD preclinical stages, those with all biomarkers normal, and the sNAP group.

Results: The sNAP group had a lower proportion (14%) with apolipoprotein E ε4 genotype than the preclinical AD stages 2 + 3. The sNAP group did not show any group differences compared to stages 2 + 3 of the preclinical AD group on measures of FDG PET regional hypometabolism, MR regional brain volume loss, cerebrovascular imaging lesions, vascular risk factors, imaging changes associated with α-synucleinopathy, or physical findings of parkinsonism.

Interpretation: Cognitively normal persons with brain injury biomarker abnormalities, with or without abnormal levels of β-amyloid, were indistinguishable on a variety of imaging markers, clinical features, and risk factors. The initial appearance of brain injury biomarkers that occurs in cognitively normal persons with preclinical AD may not depend on β-amyloidosis.

ANN NEUROL 2012;00:000–000

The investigators compared the SNAP group to those with preclinical AD stages 2+3 on various measures. As the most frequent non-AD pathophysiological processes are cerebrovascular disease and α-synucleinopathy, the SNAP group was expected to differ from the preclinical AD group on these parameters.

TABLE 3: Cerebrovascular Features of Participants according to Stage or Group

Characteristic	Stage 0, n = 191	Stage 1, n = 68	Stage 2, n = 56	Stage 3, n = 13	sNAP, n = 102
WMH fractional volume, median (IQR)	0.017 (0.012, 0.026)[a,b]	0.019 (0.011, 0.028)[a,b]	0.030 (0.014, 0.047)	0.029 (0.017, 0.043)	0.022 (0.016, 0.035)
Cortical infarctions					
Present, No. [%]	6 [3]	3 [4]	4 [7]	1 [8]	10 [10]
1	3 [2]	2 [3]	4 [7]	1 [8]	6 [6]
2	2 [1]	0 [0]	0 [0]	0 [0]	2 [2]
3+	1 [1]	1 [1]	0 [0]	0 [0]	2 [2]
Supratentorial subcortical infarctions					
Present, No. [%]	32 [17]	9 [13]	11 [20]	3 [23]	18 [18]
1	25 [13]	7 [10]	6 [11]	1 [8]	8 [8]
2	5 [3]	1 [1]	4 [7]	1 [8]	6 [6]
3+	2 [1]	1 [1]	1 [2]	1 [8]	4 [4]

[a]Differs from sNAP group, $p < 0.01$; [b]differs from preclinical Alzheimer disease stages 2 + 3 combined, $p < 0.01$. IQR = interquartile range; sNAP = suspected non-Alzheimer pathophysiology; WMH = white matter hyperintensities.

TABLE 4: Cardiovascular Risk Factors of Participants according to Stage or Group

Self-Reported Cardiovascular Risk Factors[a]	Stage 0, n = 191	Stage 1, n = 68	Stage 2, n = 56	Stage 3, n = 13	sNAP, n = 102
Diabetes	24 (13)[a,b]	13 (19)	14 (25)	4 (31)	33 (32)
Hypertension	109 (57)[a]	46 (68)	38 (68)	10 (77)	77 (75)
Smoking	91 (48)	26 (38)	24 (43)	6 (46)	52 (51)
Stroke	10 (5)	4 (6)	7 (12)	1 (8)	10 (10)
Myocardial infarction	19 (10)	10 (15)	8 (14)	2 (15)	16 (16)
Coronary bypass surgery	6 (3)[a]	9 (13)	3 (5)	3 (23)	11 (11)
Angioplasty	23 (12)	12 (18)	7 (12)	2 (17)	13 (13)
Congestive heart failure	4 (2)	2 (3)	1 (2)	0 (0)	5 (5)
Atrial fibrillation	15 (8)[a]	9 (13)	10 (18)	2 (15)	21 (21)
Angina	26 (14)	10 (15)	6 (11)	1 (8)	22 (22)
Coronary artery disease	38 (20)	21 (31)	14 (25)	6 (46)	30 (29)

[a]Differs from sNAP group, $p < 0.01$; [b]differs from preclinical Alzheimer disease stages 2 + 3 combined, $p < 0.01$. sNAP = suspected non-Alzheimer pathophysiology.

TABLE 5: Features Associated with α-Synucleinopathy of Participants according to Stage or Group

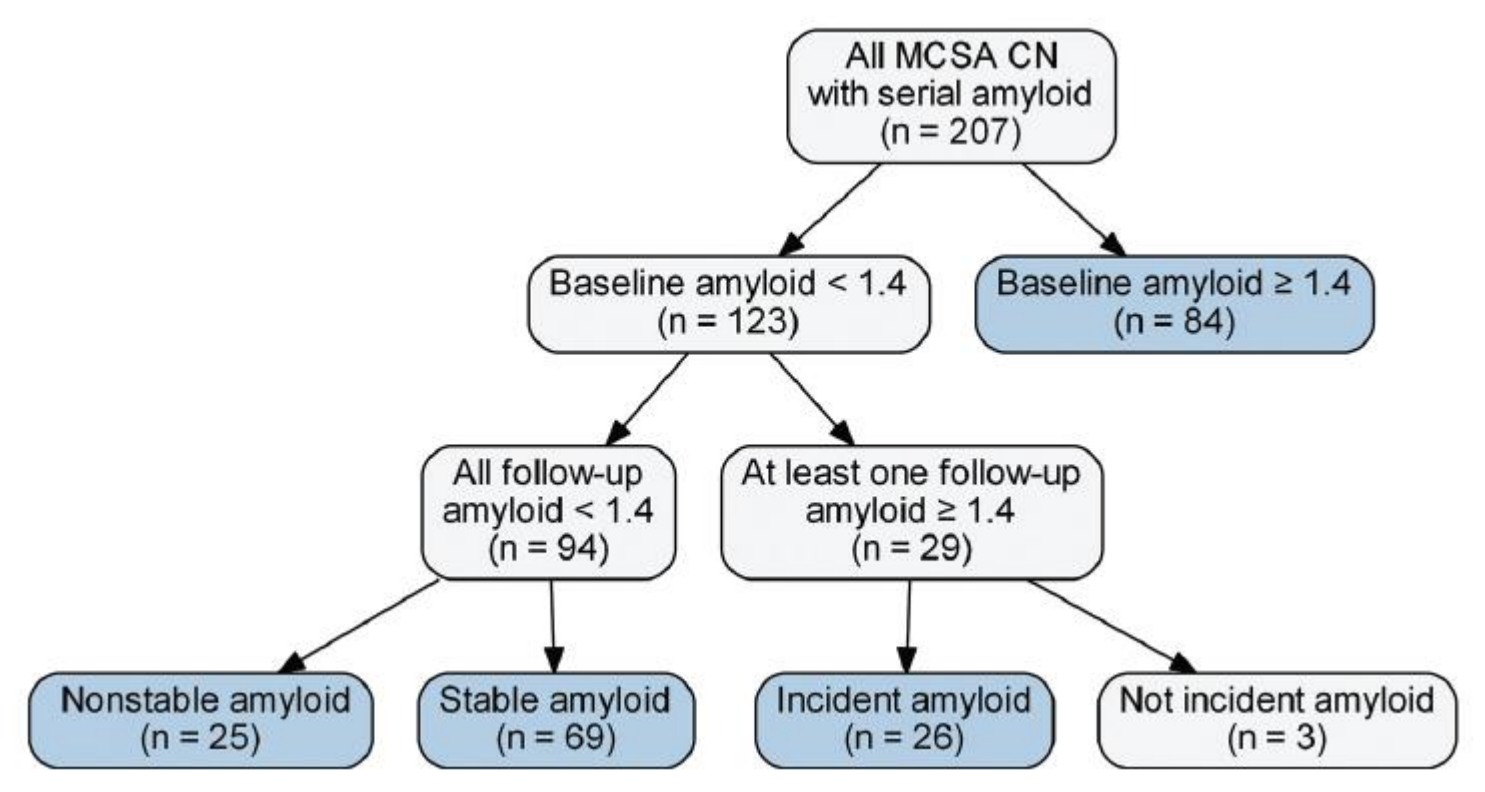
Characteristic	Stage 0, n = 191	Stage 1, n = 68	Stage 2, n = 56	Stage 3, n = 13	sNAP, n = 102
UPDRS parkinsonism total, median (IQR)	0.0 (0.0, 0.0)[a]	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.0 (0.0, 2.5)	0.0 (0.0, 2.0)
UPDRS parkinsonism ≥1, No. [%]	34 [18][a]	16 [24]	13 [24]	6 [55]	36 [37]
Gait speed, seconds to walk 25 feet, median (IQR)	7 (6, 8)	7 (6, 8)	7 (6, 8)	8 (7, 9)	7 (6, 8)
Midbrain GM volume, % of TIV, median (IQR)	0.0043 (0.0033, 0.0056)	0.0042 (0.0034, 0.0051)	0.0044 (0.0032, 0.0056)	0.0055 (0.0037, 0.0079)	0.0047 (0.0037, 0.0059)
Occipital FDG PET ratio, median (IQR)	1.58 (1.51, 1.65)[a,b]	1.57 (1.47, 1.63)[a,b]	1.46 (1.39, 1.55)	1.51 (1.44, 1.54)	1.47 (1.40, 1.56)
Posterior cingulate/(precuneus + occipital) FDG PET ratio, median (IQR)	1.09 (1.03, 1.13)	1.07 (1.02, 1.13)	1.09 (1.02, 1.13)	1.07 (1.01, 1.10)	1.07 (1.03, 1.13)

[a]Differs from sNAP group, $p < 0.01$; [b]differs from preclinical Alzheimer disease stages 2 + 3 combined, $p < 0.01$.FDG = ^{18}fluorodeoxyglucose; GM = gray matter; IQR = interquartile range; PET = positron emission tomography; sNAP = suspected non-Alzheimer pathophysiology; TIV = total intracranial volume; UPDRS = Unified Parkinson's Disease Rating Scale.

Interpretation: Cognitively normal persons with brain injury biomarker abnormalities, with or without abnormal levels of β-amyloid, were indistinguishable on a variety of imaging markers, clinical features, and risk factors. The initial appearance of brain injury biomarkers that occurs in cognitively normal persons with preclinical AD may not depend on β-amyloidosis.

ANN NEUROL 2012;00:000–000

Jack et al., Neurology, 2013



11 of our 26 incident amyloid PET-positive subjects had abnormal hippocampal volume (n = 4), FDG (n = 2), or both (n = 5) at baseline. These 11 therefore had abnormal neurodegenerative biomarkers (FDGPET or hippocampal volume) with normal amyloid PET at baseline, but later become amyloid-positive.

However, our data do show that both amyloid- first and neurodegeneration-first biomarker profiles characterize incident amyloid positivity. Amyloid positivity defines preclinical AD; therefore, both amyloid-first and neurodegeneration-first biomarker profile pathways to preclinical AD exist.

Aβ-independent processes—rethinking preclinical AD

Gaël Chételat

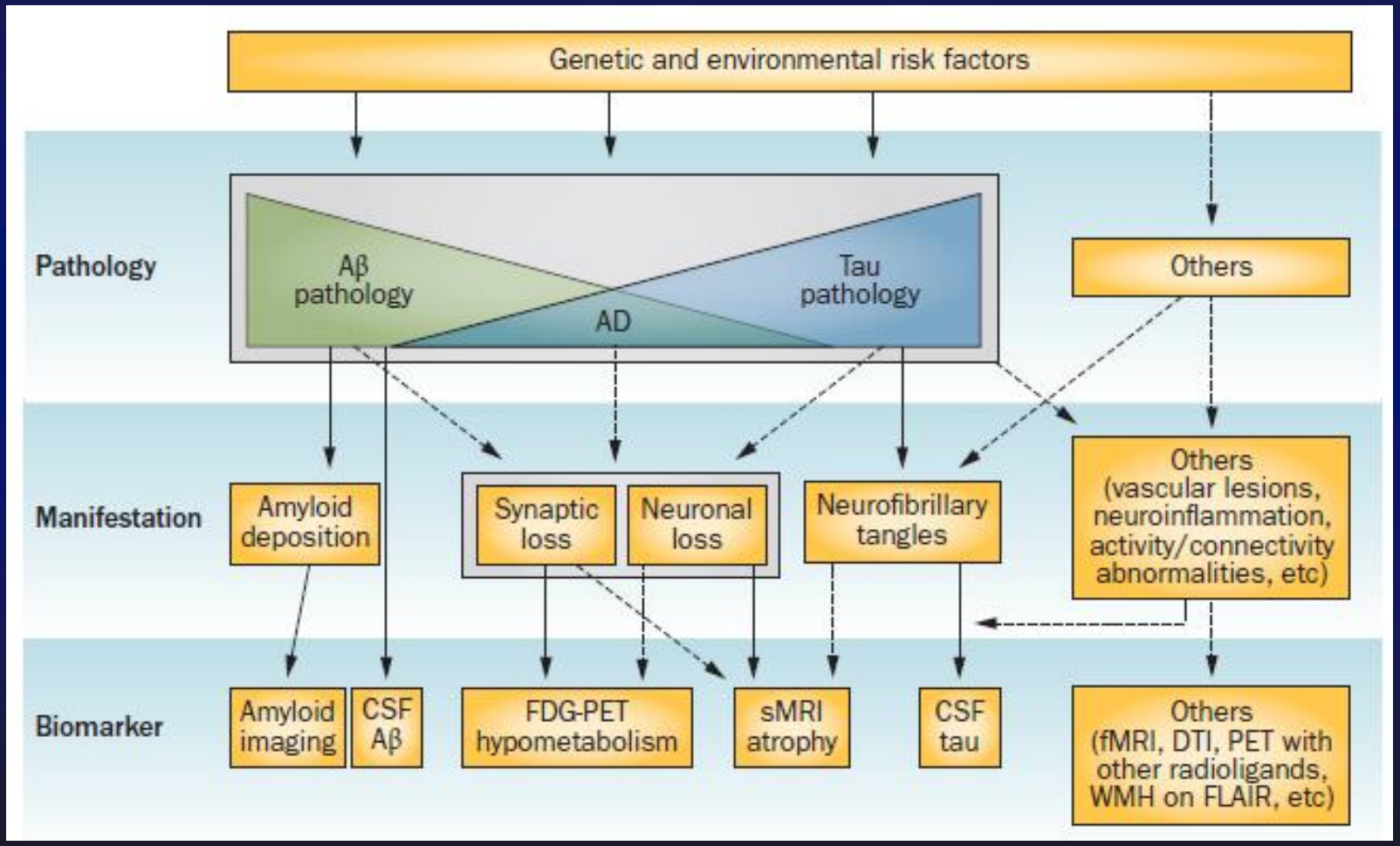
The amyloid cascade hypothesis, which posits that amyloid-β accumulation is the key event in Alzheimer disease neurodegeneration, has dominated the field for 20 years. Recent findings, however, show that neuronal-injury biomarkers are independent of amyloid-β, calling for reconsideration of the pathological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

Neuronal injury could be caused by different factors (with various possible sequences): Aβ and tau patholgies 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

CORRESPONDENCE

Nature Reviews Neurology published online 14 May 2013; doi:10.1038/nrneurol.2013.21-c1

CORRESPONDEN

Nature Reviews Neurology published online 14 May 2013; doi:10.1038/nrneurol.2013.21-c2

Ca

Venu

REPI

Th

Gaë

DEMENTIA IN 2012

Further insights into Alzheimer disease pathogenesis

Michael W. Weiner

In 2C
AD, a
supp
evide
amyl

Weiner,
doi:10.

www.

12)70256-9

Comment

Mol Neurobiol
DOI 10.1007/s12035-011-8228-7

Neuroimaging Results Impose New Views on Alzheimer's Disease—the Role of Amyloid Revised

Anders M. Fjell · Kristine B. Walhovd

Journal of Nuclear Medicine, published on July 15, 2013 as doi:10.2967/jnumed.112.117341

Novel ^{18}F-Labeled Arylquinoline Derivatives for Noninvasive Imaging of Tau Pathology in Alzheimer Disease

Nobuyuki Okamura[1], Shozo Furumoto[1,2], Ryuichi Harada[1], Tetsuro Tago[2], Takeo Yoshikawa[1], Michelle Fodero-Tavoletti[3], Rachel S. Mulligan[4], Victor L. Villemagne[4], Hiroyasu Akatsu[5], Takayuki Yamamoto[5], Hiroyuki Arai[6], Ren Iwata[2], Kazuhiko Yanai[1], and Yukitsuka Kudo[7]

Journal of Alzheimer's Disease 34 (2013) 457–468
DOI 10.3233/JAD-122059
IOS Press

Early Clinical PET Imaging Results with the Novel PHF-Tau Radioligand [F-18]-T807

doi:10.1093/brain/awr038 Brain 2011: 134; 1089–1100 | 1089

BRAIN
A JOURNAL OF NEUROLOGY

^{18}F-THK523: a novel *in vivo* tau imaging ligand for Alzheimer's disease

Michelle T. Fodero-Tavoletti,[1,2] Nobuyuki Okamura,[3] Shozo Furumoto,[3] Rachel S. Mulligan,[4] Andrea R. Connor,[1,2] Catriona A. McLean,[5] Diana Cao,[6] Angela Rigopoulos,[6] Glenn A. Cartwright,[6] Graeme O'Keefe,[4] Sylvia Gong,[4] Paul A. Adlard,[1,7] Kevin J. Barnham,[1,2,7] Christopher C. Rowe,[4] Colin L. Masters,[7] Yukitsuka Kudo,[8] Roberto Cappai,[1,2] Kazuhiko Yanai[3] and Victor L. Villemagne[4,7]

Thanks

Inserm-EPHE-Université de Caen/Basse-Normandie, ***Unité U1077****,*
GIP Cyceron, CHU Côte de Nacre, ***Caen****, France*