The Relationship between Abeta Deposition, Neurodegeneration and Cognitive Function in Normal and Impaired Individuals

MCI Symposium 2014

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No relevant disclosures

Or

How does AD relate to other age-associated pathological and non pathological processes that lead to cognitive decline – address the theme of Abeta independent vs dependent AD

Background

Alzheimer's disease – defined pathologically (plaques, tangles, etc), presence of clinical syndrome not required

Abeta and amyloid used interchangeably

Discussions of biomarkers are interwoven with biology of the disease which the biomarkers measure

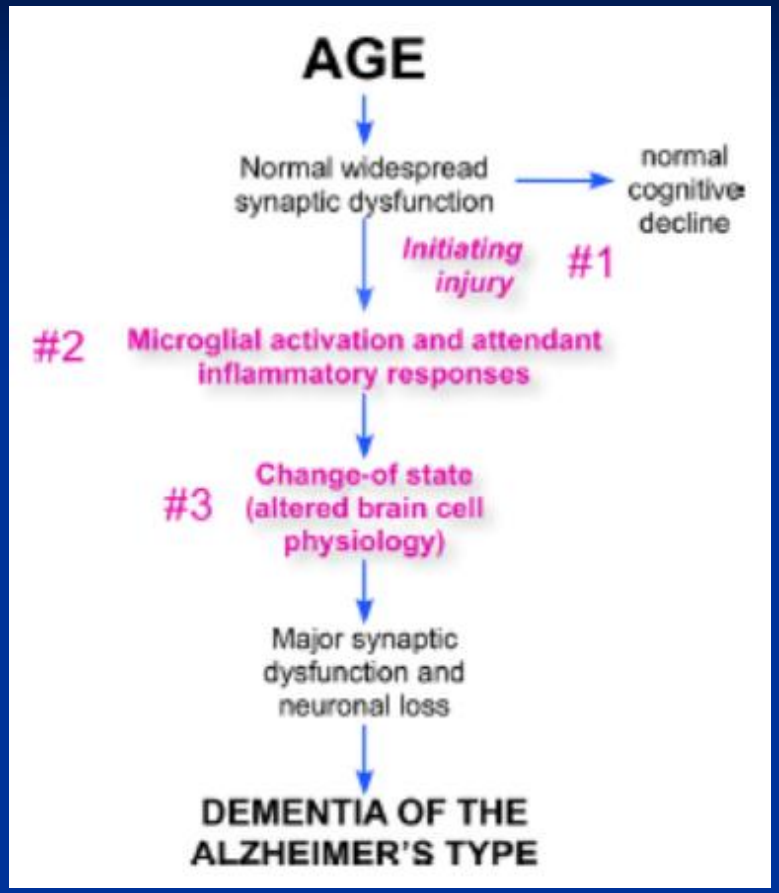
Outline

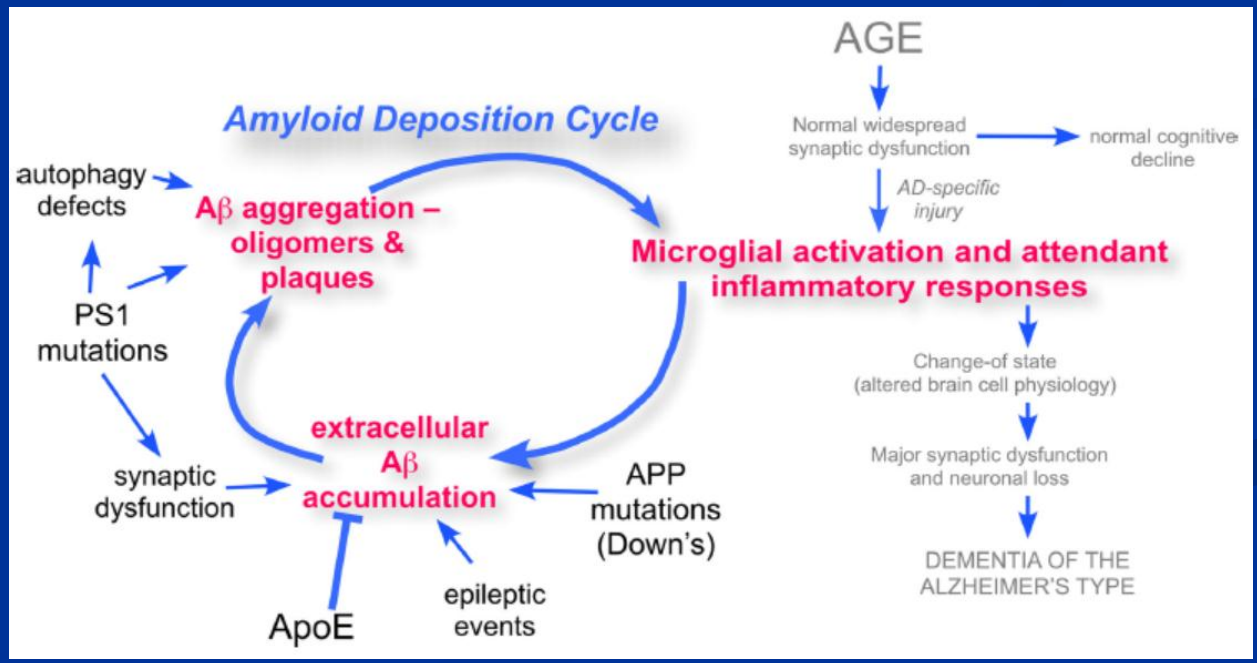
- Statement of argument: Abeta independent vs dependent AD
- Specificity of biomarkers
- Arguments for/against Abeta independent vs dependent AD
- Biomarker models for early vs late onset AD

models of AD pathophysiology and biomarkers of pathophysiology

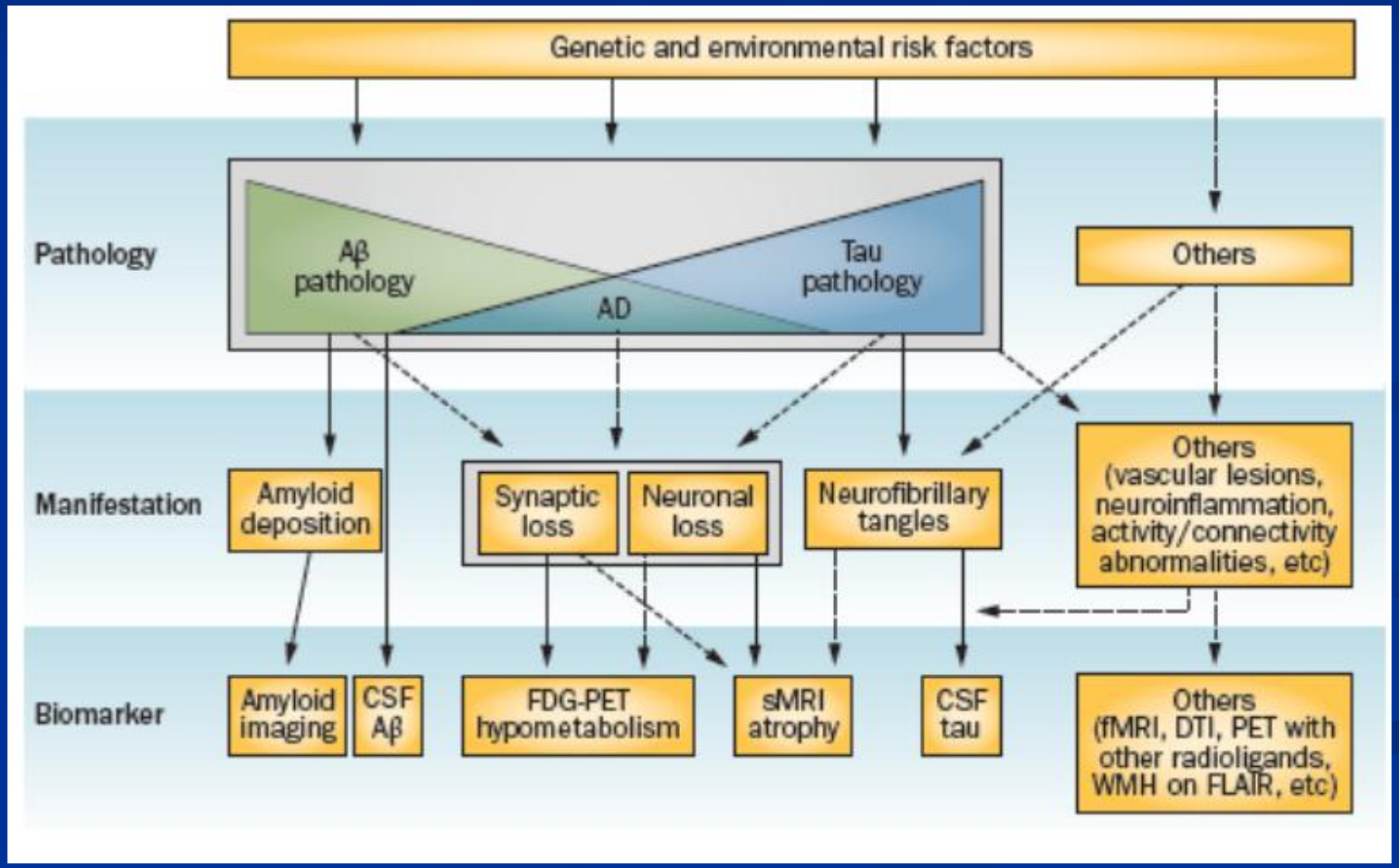
- **Ab dependent AD** – if Ab is the initiator or driver of the disease, then biomarkers of Ab should appear first/early
- **Ab independent AD** – if non-Ab processes can initiate AD, then biomarkers of non-Ab processes should appear first

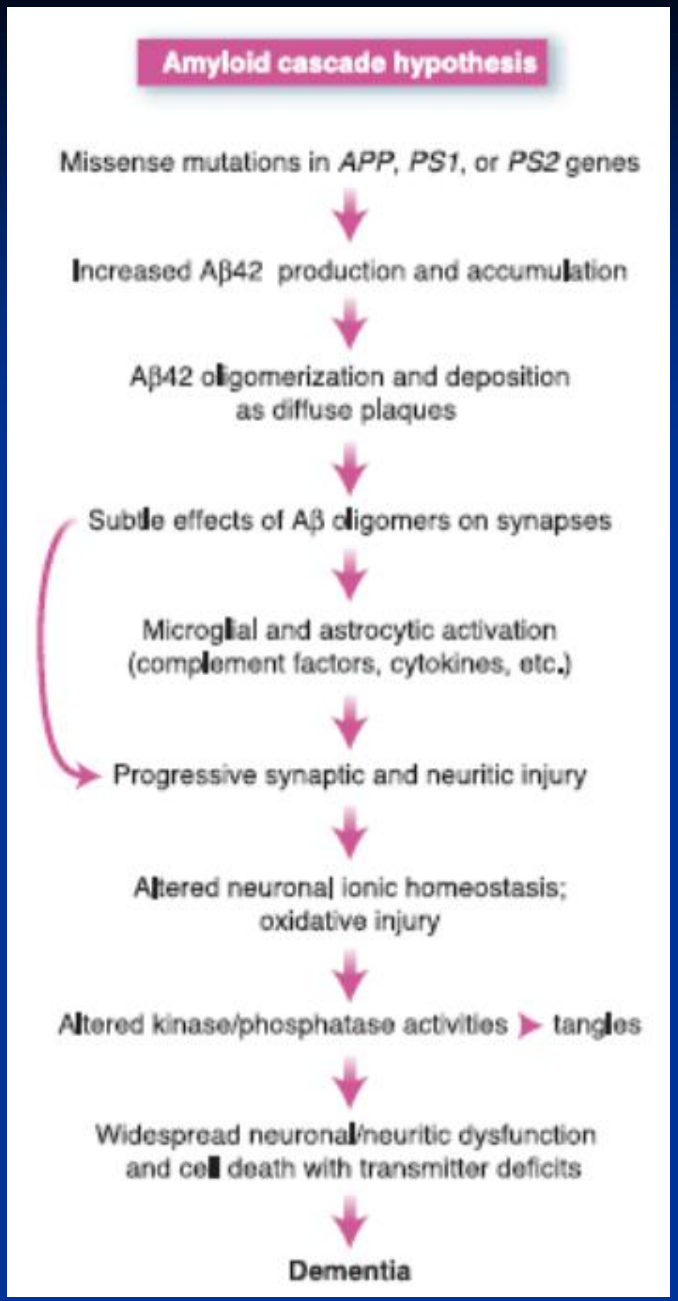
Abeta independent AD - Herrup (2010)





Aβ-independent processes - rethinking preclinical AD, Chetelat Nat Rev Neurol 2013





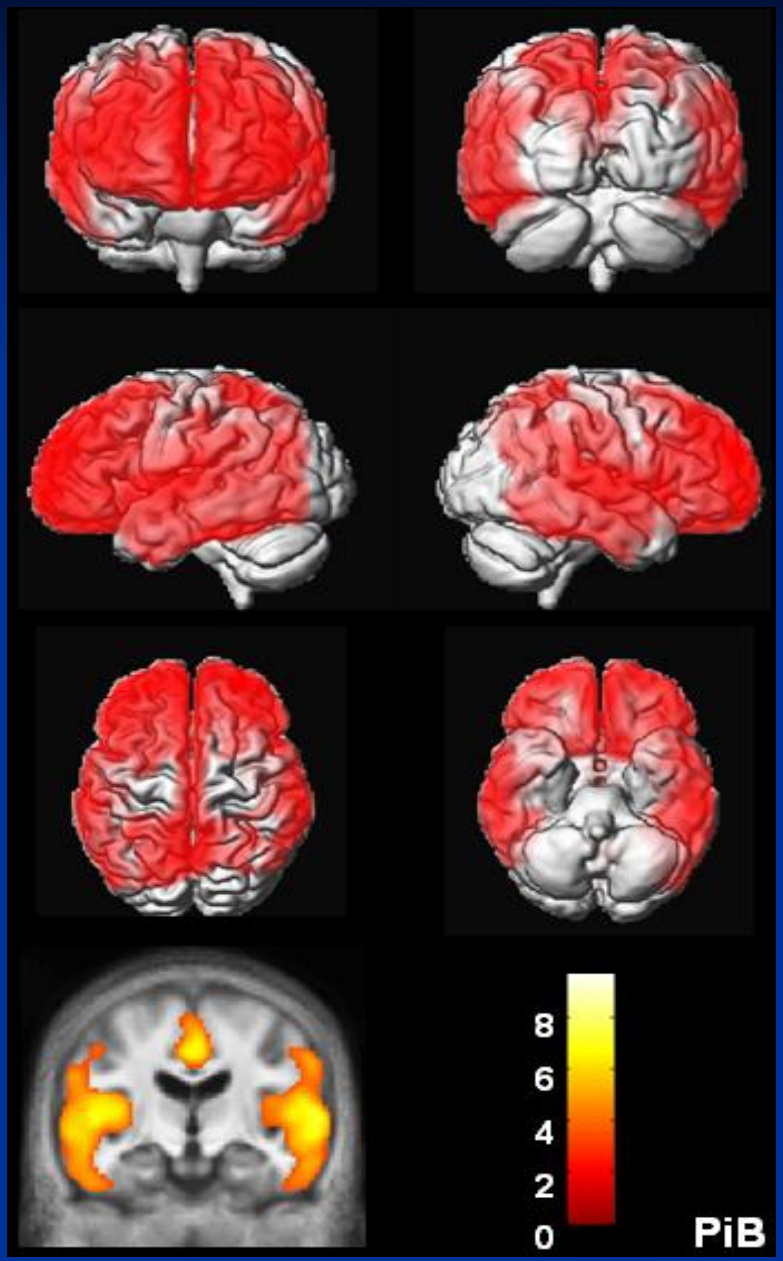
Sporadic AD: Failure of AB42 clearance

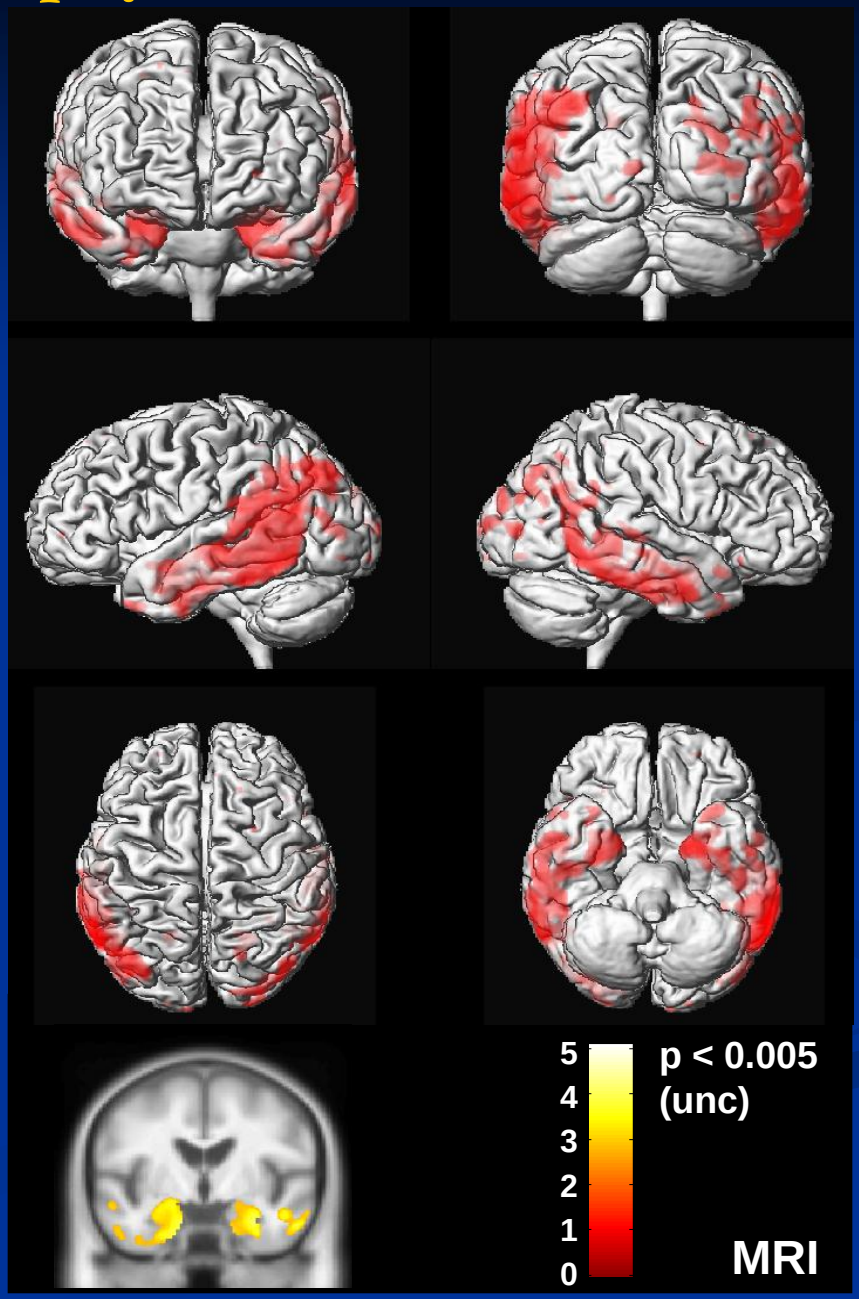
The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics

Hardy and Selkoe, Science 2002

AD vs. Control: Topography

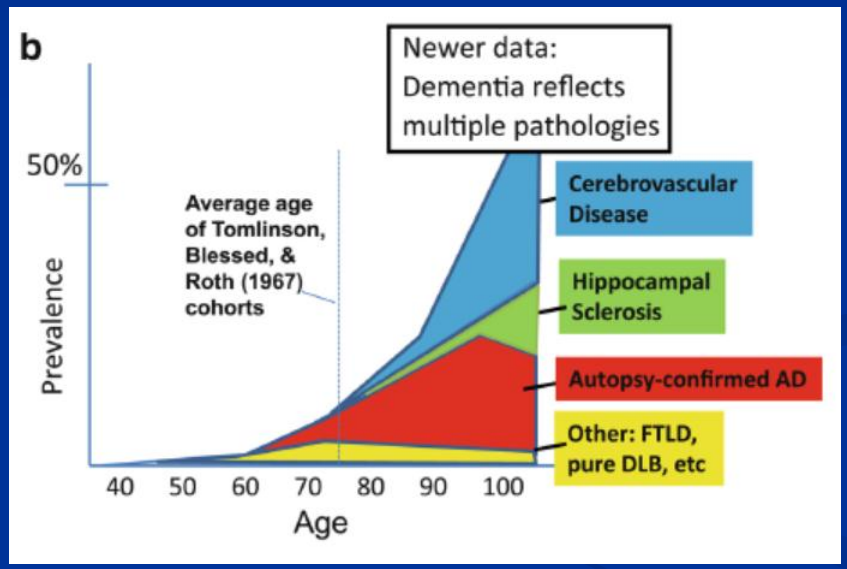
Jack et al, Brain 2008





Pathological heterogeneity in old age

- Most demented (& many cog normal, Sonnen Archives 2011) have multiple pathologies: AD (NP and neocortical NFT), brainstem/MTL NFT with no amyloid, LB, CVD, HS, grain disease, TDP43, yet unknown pathologies
- Nelson, Acta Neuropath 2011



- Pure AD is an abstraction in elderly (Markesbery 2006, Schneider 2009, Sonnen 2011) ➔ yet this is what we assume when modeling AD biomarker empirically (without autopsies in all subjects)

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AD Biomarkers are Proxies for AD pathophysiology

5 major biomarkers – 2 categories

Measures of brain Aβ deposition – amyloid plaques

- **Amyloid PET**
- **CSF *Aβ* 42**

Measures of Neurodegeneration (defined as progressive loss of neurons or their processes (axons and dendrites) with a corresponding progressive impairment in neuronal function)

- **CSF tau (t-tau and p-tau)**
- **FDG PET**
- **Structural MRI**

What is known about sensitivity & specificity?

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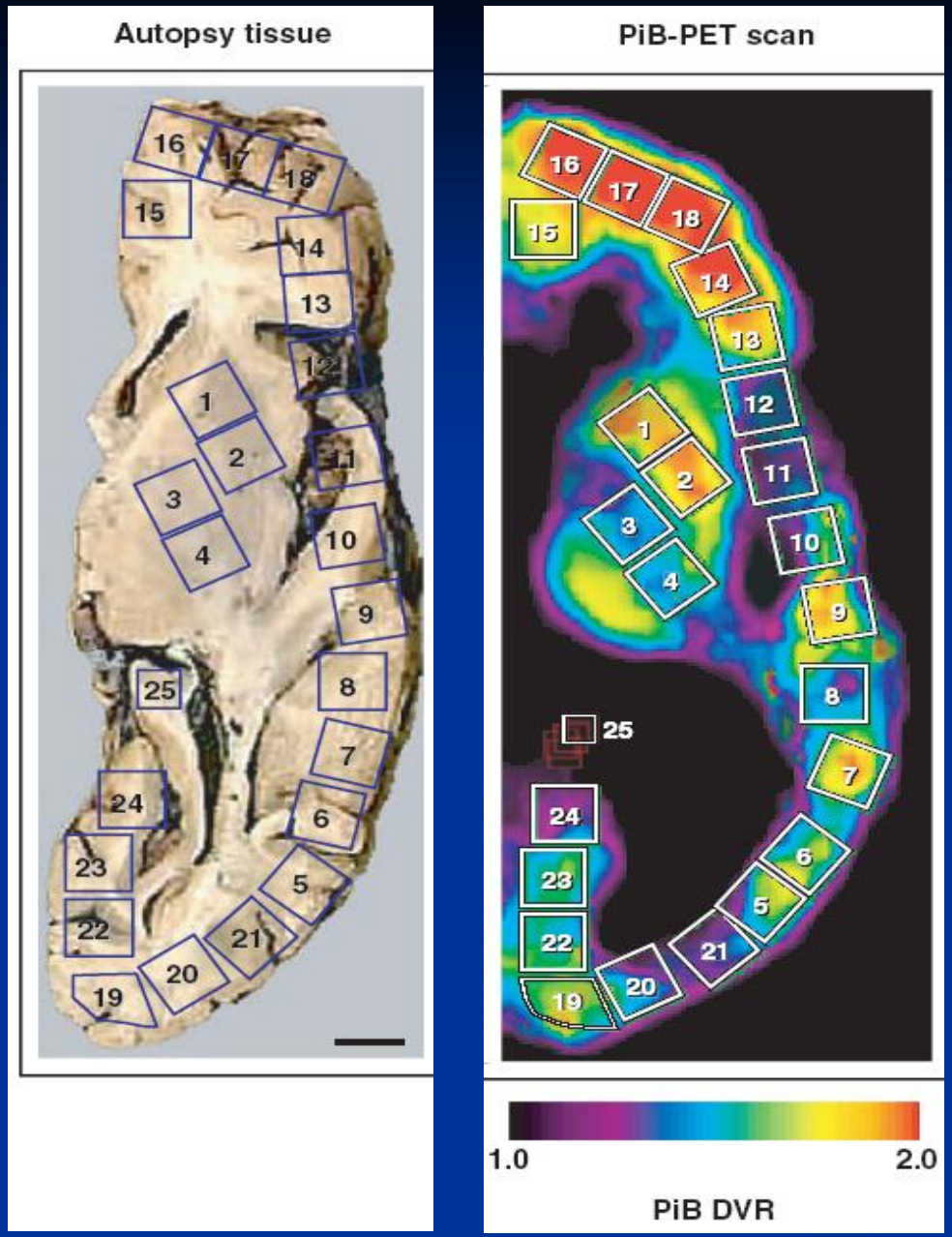
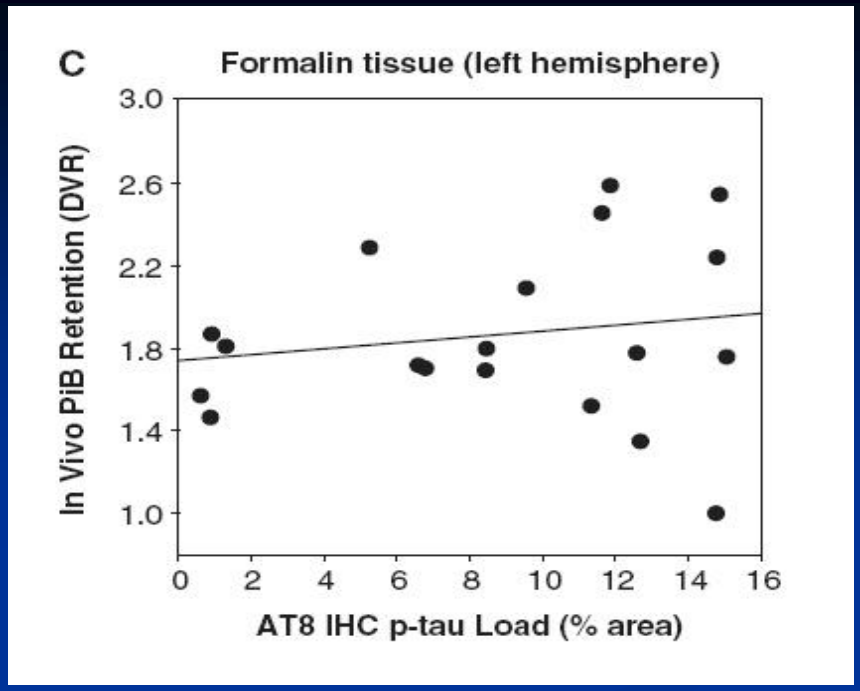
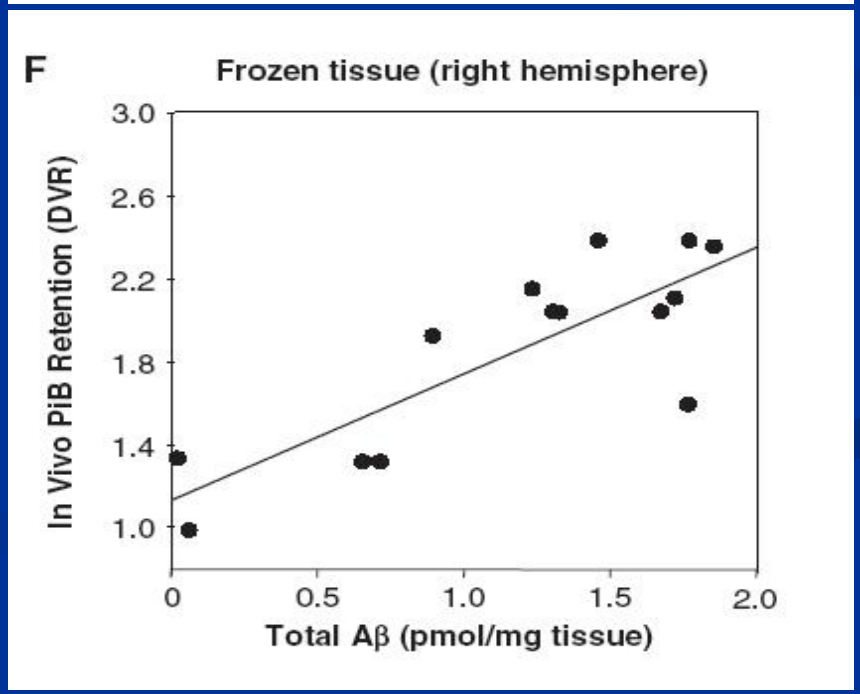
Sensitivity/specificity of biomarkers for AD neuropathology – autopsy validation

- Abeta amyloid biomarkers: are specific – autopsy biomarker correlations (Strozyk, 2003; Tapiola, 2009; Ikonomovic, 2008; Fleisher, 2011; Sojkova, 2011; Clark 2011, Driscoll 2012) Jagust & Rabinovici groups HAI 2014
- Neurodegenerative biomarkers are sensitive to NFT mediated neurodegeneration in AD – autopsy biomarker correlations (DeCarli, 1992; Jack, 2002; Tapiola, 2009; Buerger, 2006; Tapiola, 2009; Bobinski, 2000; Zarow, 2005; Vemuri, 2008; Whitwell, 2008 & 2012; Josephs, 2008)
- Neurodegenerative biomarkers not specific for AD (esp. atrophy and FDG PET): elevated t-tau, decreased FDG, atrophy occur in non-AD conditions that cause cognitive impairment/dementia in elderly persons – eg. CVD, LBD, TBI, FTLD, CJD, hippocampal sclerosis, MTL NFT with no amyloid ? (Jack, 2002; Jagust 2009; Dawe 2011; Erten-Lyons 2013)
- NFT not specific for AD – FTLD, FCD, prion dz, CTE, viral encephalitis, etc







Ikonomovic, Brain (2008), 131, 1630-1645

MRI autopsy validation; sensitive to neurodegeneration but not specific for AD

- Hippocampal volume correlates with neuron counts (Bobinski 2000, Zarow 2005)
- Hippocampal volume correlates with Braak stage in AD –Jack, 2002
- grey matter density correlates with Braak stage and tau density by immunostain in AD (Whitwell, 2008 & 2012)
- grey matter density does not correlate with Abeta immunostain density in AD (Josephs 2008)
- Hippocampal volume and grey matter density not specific for AD eg. CVD, FTLD, hippocampal sclerosis, (Jack 2002; Jagust 2009)

Hippocampal Volume vs CA1 neuron counts

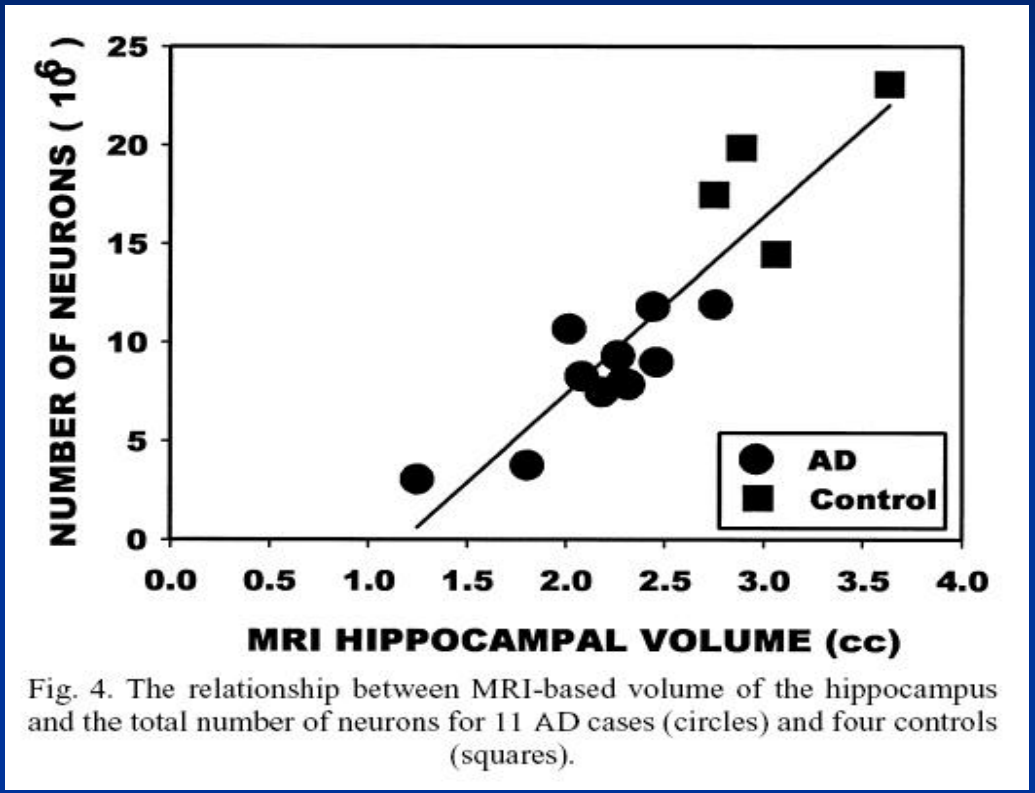


Fig. 4. The relationship between MRI-based volume of the hippocampus and the total number of neurons for 11 AD cases (circles) and four controls (squares).

Bobinski, Neuroscience 95, 2000

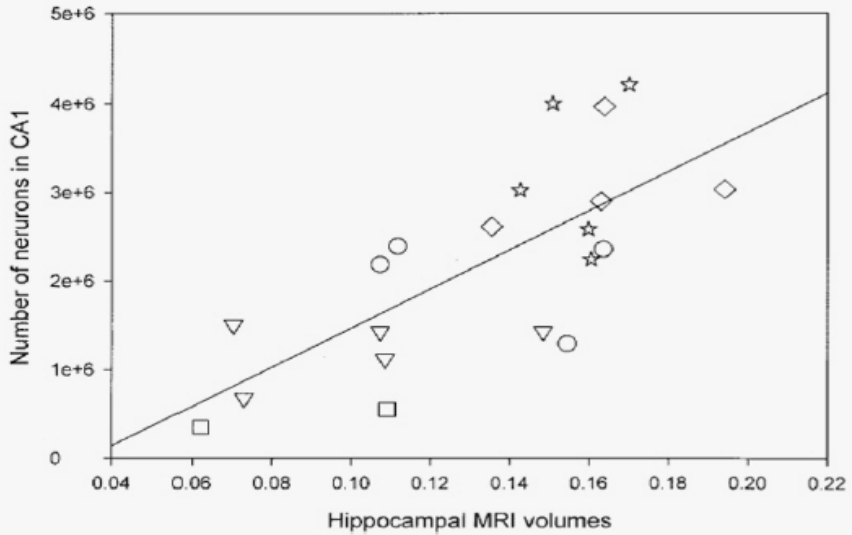


Fig 2.
Estimated number of neurons in cornu ammonis 1 region of the hippocampus (CA1) is strongly correlated with the volume of the hippocampus determined from magnetic resonance imaging. *Stars* indicate healthy control subjects; *circles* indicate cognitively impaired not meeting criteria for Alzheimer's disease (AD); *triangles* indicate AD; *squares* indicate AD with hippocampal sclerosis; and *diamonds* indicate ischemic vascular dementia. MRI = magnetic resonance imaging.

Zarow, Ann Neurol, 2005

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Hippocampal W score by diagnosis in those with a single path Dx

Diagnosis	Braak and Braak stage, median (range)	W score, median (range)
Typical aging (n = 25)	2.5 (0.0 to 4.0)	−0.5 (−2.1 to 1.5)
AD (n = 23)	5.0 (2.0 to 6.0)	−2.1 (−2.9 to 0.5)
HS (n = 3)	1.5 (0.0 to 2.0)	−2.5 (−2.7 to −1.9)
DLBD (n = 3)	2.0 (2.0 to 3.0)	0.5 (−1.3 to 0.7)
FTD (n = 2)	0.0 (0.0 to 0.0)	−2.3 (−2.4 to −2.2)
NFT (n = 1)	3.5	−2.5

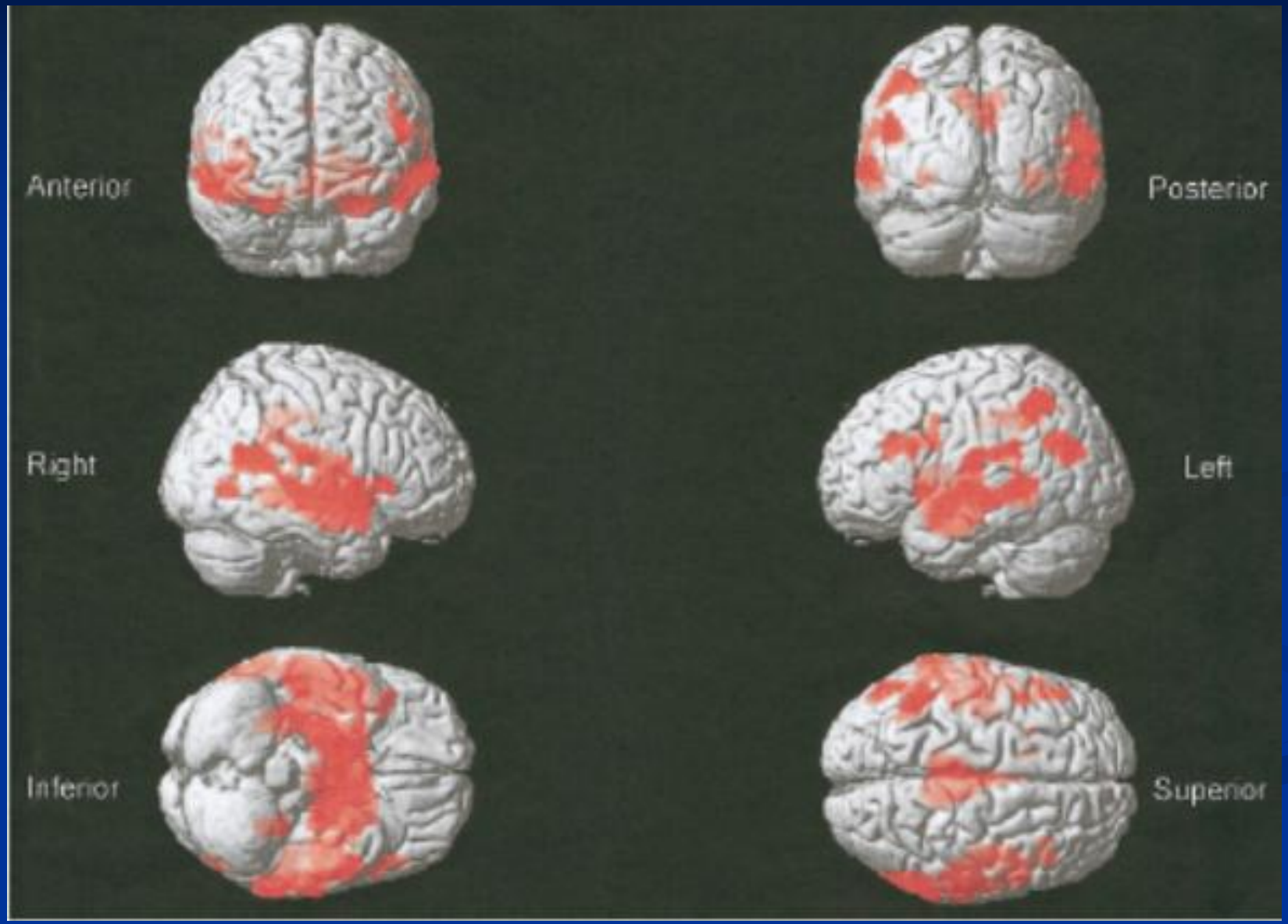
HS = hippocampal sclerosis; DLBD = diffuse Lewy body disease;
FTD = frontotemporal degeneration; NFT = Neurofibrillary tangle-only dementia

Jack *Neurology 2002*

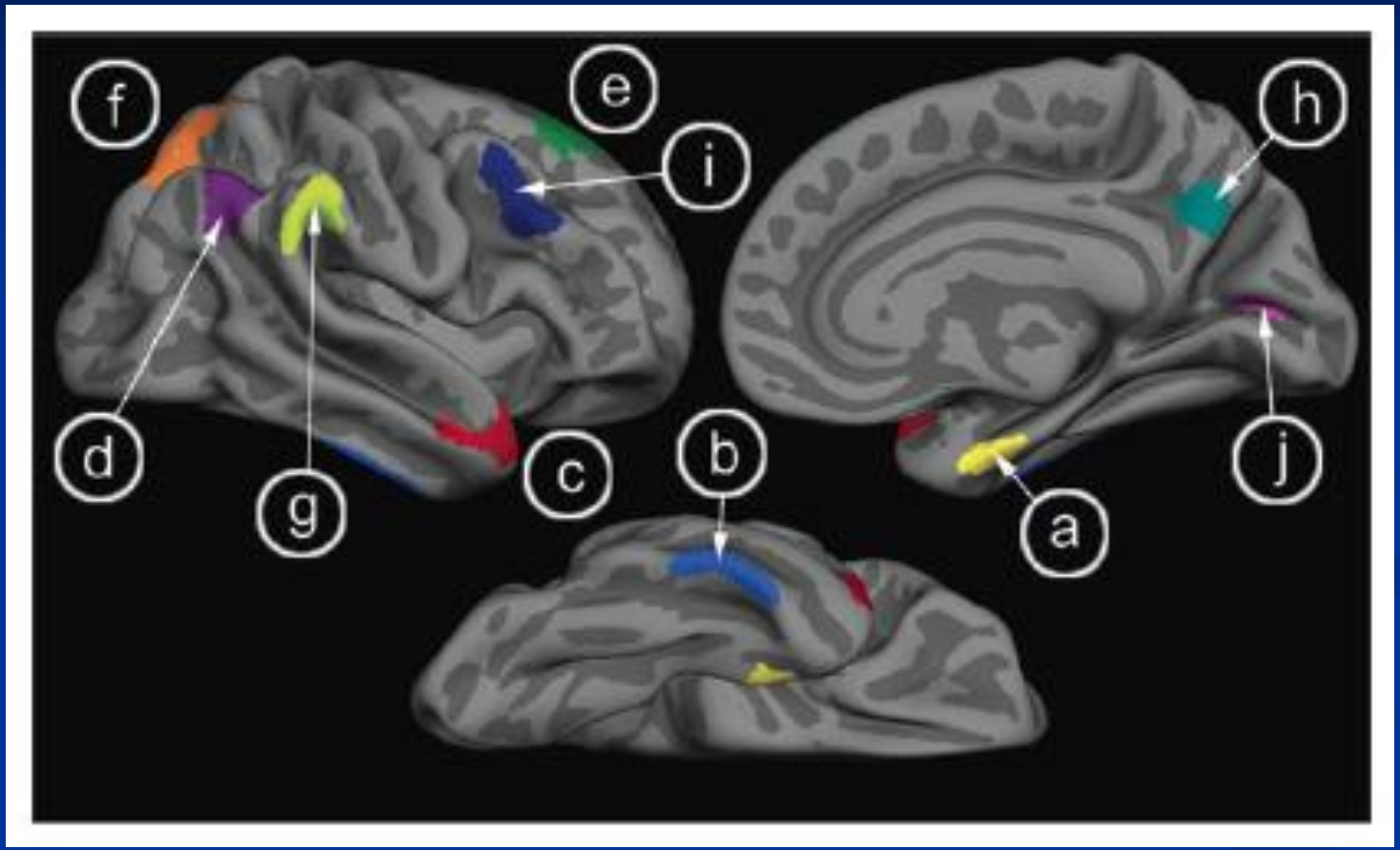
Are AD-signature FDG/MRI ROIs – specific for AD?

- History - FDG PET and MRI: AD signature meta ROIs originated from VBM/SPM
- Obtain ROIs from AD vs CN (or amyloid + vs -) mapping comparisons
  - Hua and Thompson, Neuroimage, 2008
  - Dickerson, Cerebral Cortex 2009
- machine learning/classifier algorithms: AD vs CN
  - Davazikos 2008
  - Vemuri 2008
  - Kloppel 2008

VBM grey matter loss in AD Baron 2001



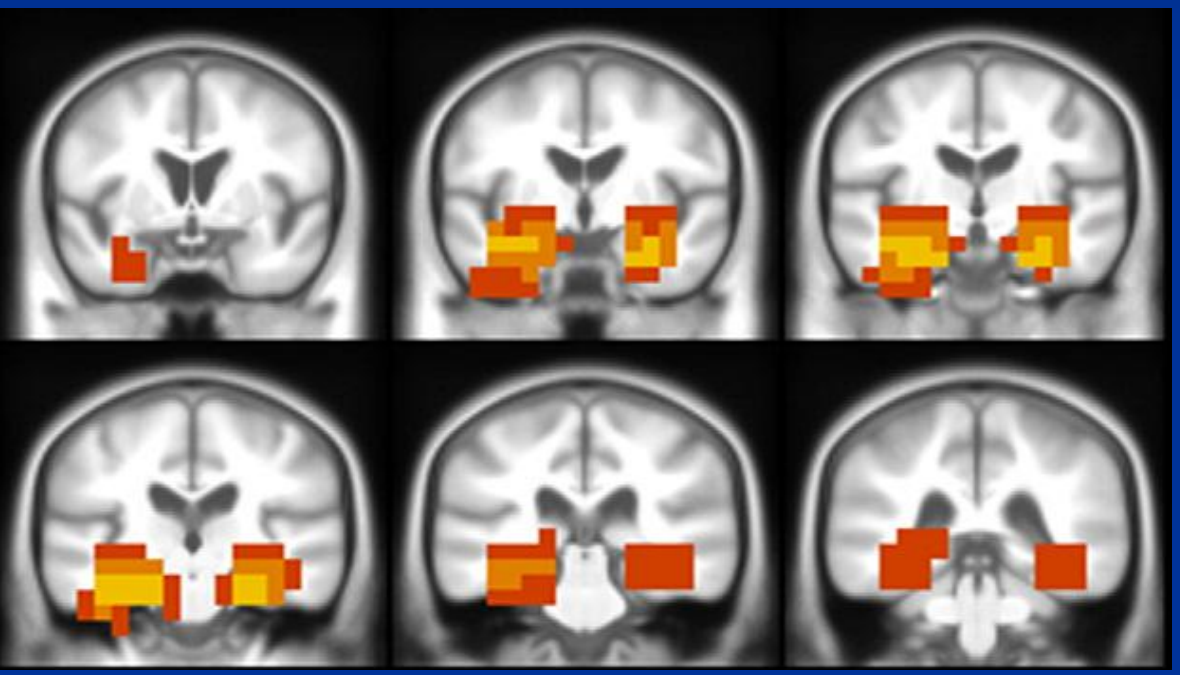
Dickerson et al. Cereb Cortex 2009; Neurology 2011

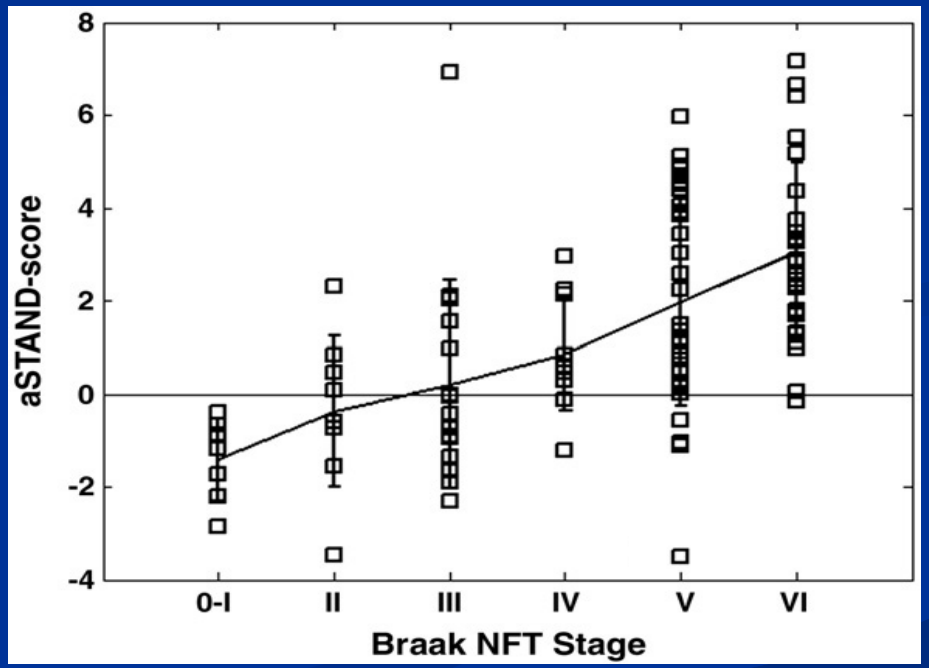


(A) Medial temporal cortex, (B) Inferior temporal gyrus, (C) Temporal pole, (D) Angular Gyrus, (E) Superior frontal gyrus, (F) Superior parietal lobule, (G) Supramarginal gyrus, (H) Precunes, (I) Inferior frontal sulcus, (J) visual reference

STAND algorithm for Individual Subject Diagnosis

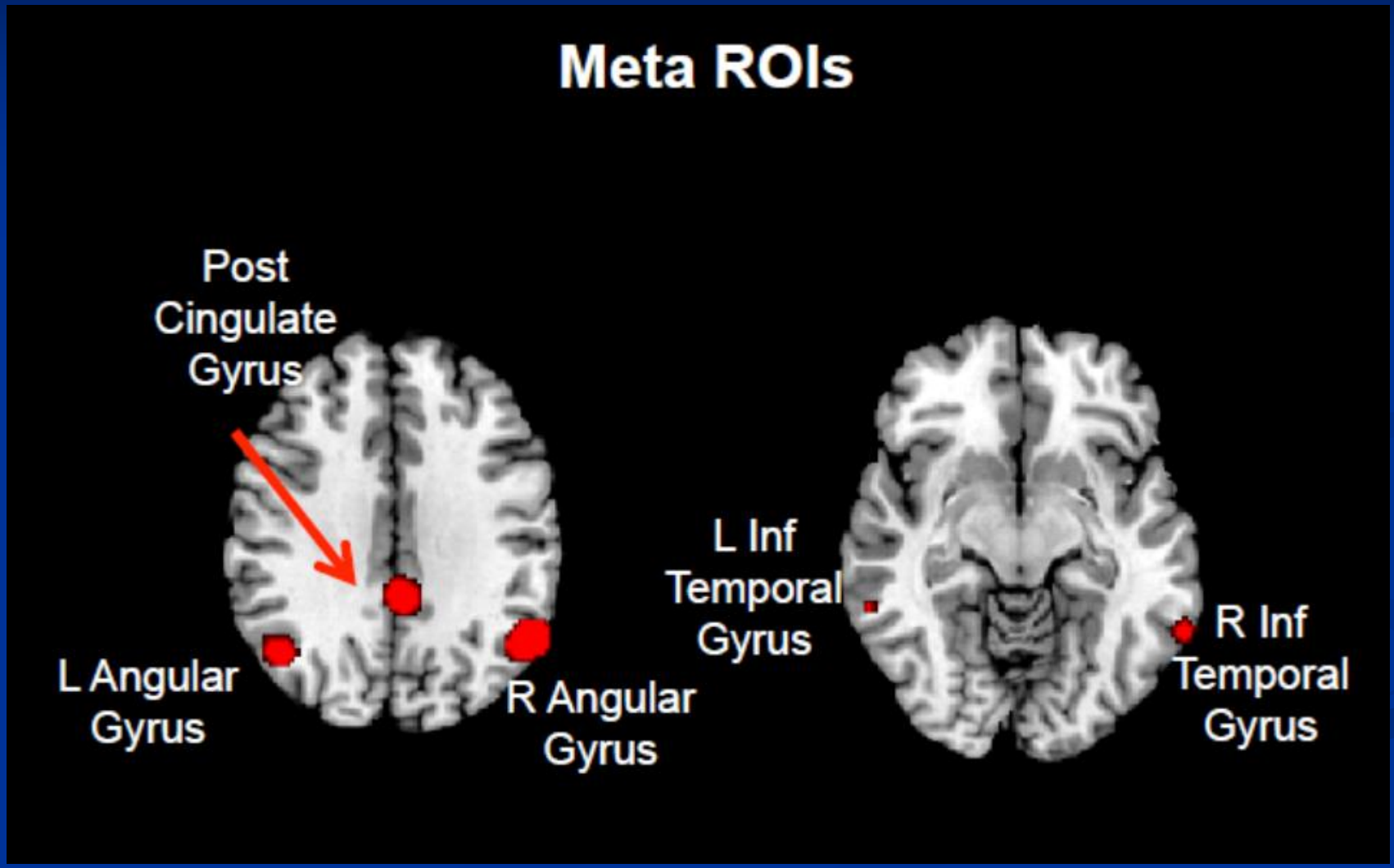
Vemuri, Neuroimage 2008; 39(3):1186-97 and Neuroimage 2008; 42(2):559-67





FDG PET AD Meta ROI

Landau Neurobiol Aging 2009

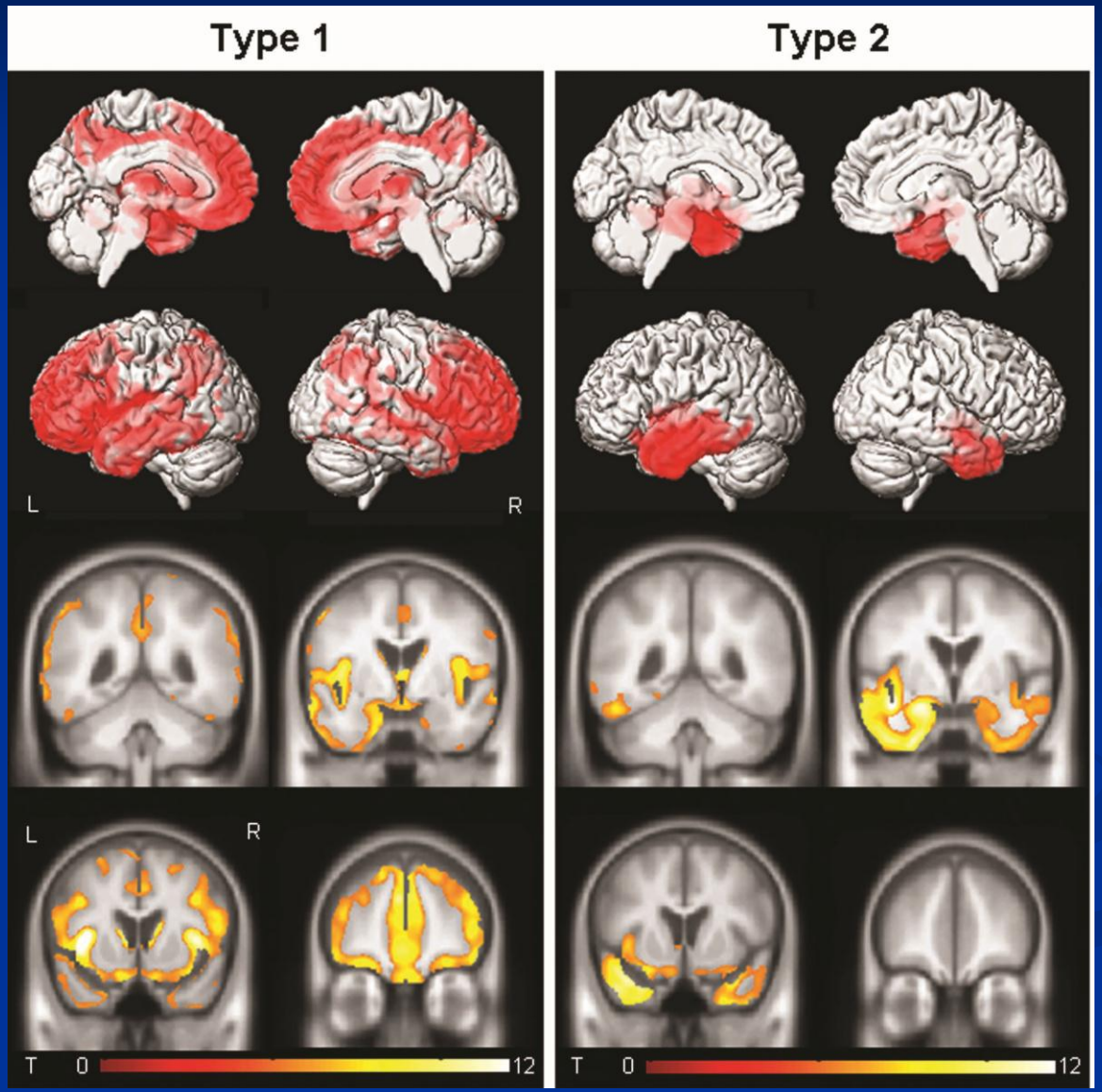


specificity of AD signature FDG or MRI ROIs? Autopsy verification?

- AD signature MRI and FDG abnormalities associated with vascular Dz – Wirth, JAMA Neurol 2012

Autopsy proven TDP 43

Whitwell Neurology 2010



Outline

- Statement of argument: Abeta independent vs dependent AD
- Specificity of biomarkers
- Arguments for/against Abeta independent vs dependent AD
  - General trends and specific papers that have been or could be interpreted to support Abeta independent vs dependent AD
  - Point / counterpoint
- Biomarker models for early vs late onset AD

Cognitive correlations with autopsy & imaging

- Cognitive impairment correlates with tau and neurodegeneration better than amyloid at autopsy (Gomez-Isla 1997)
- Cognitive impairment correlates with FDG and MRI better than amyloid PET
- Rates of amyloid plateau vs MRI FDG parallel cog decline

- #1 – amyloid not causative
- #2 – amyloid is causative, but is upstream from cognitive decline.

Genetics of familial AD

- Along with Down syndrome, all known autosomal-dominant mutations leading to AD influence processing of APP in a manner resulting in increased production of Ab42 or all Ab species
- primary tauopathies lead to FTLD, CBD, PSP but never to pathological AD
- Excess AB42 alone is sufficient to cause AD. Not true for tau.

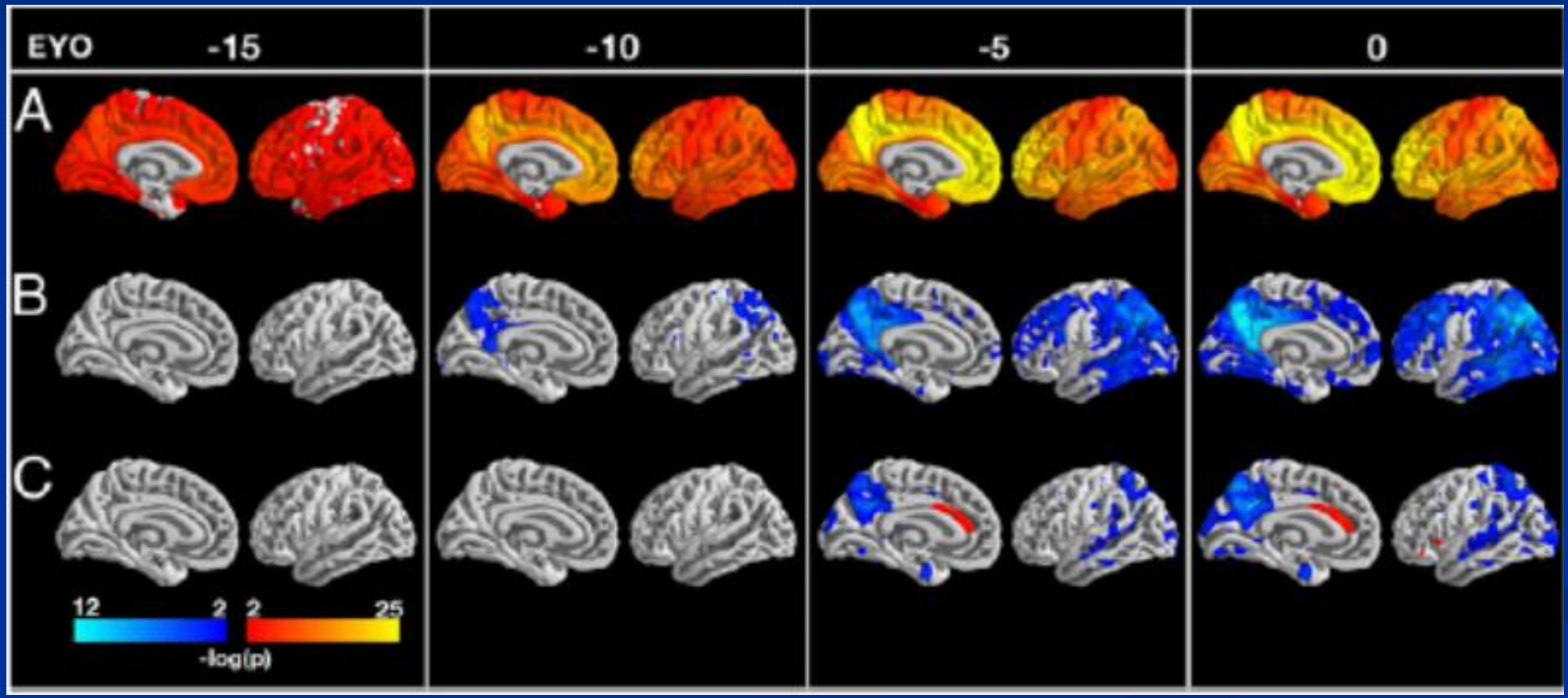
- #1 – early onset and late onset AD are different diseases & late onset has Abeta dependent and independent forms
- #2 –EOAD and LOAD are same dz – occur on different backgrounds.

<u>Biomarker order</u>: Familial AD is Abeta driven, but if non-Ab biomarkers precede amyloid PET, casts doubt on LOAD studies where early amyloid used as evidence for initiating role

- Reiman 2012 – (20) 18-26yo carrier vs non 20yrs <EAO: high CSF & plasma AB42; greater hipp activation, less PC deactivation; VBM GM loss; no diff CSF tau
- Fleischer 2012 -AV45 begins at 28yo: conclude sMRI and fMRI precede plaque formation (but only 8 in both)
- Bateman 2012: CSF AB42 decline begins 25 yrs < MCI; Fig 1 - separation between carrier and non trend lines → PIB 18 yrs, CSF tau 12, FDG & HV 7
- Benzinger 2012 – (n ~120) mapping and ROIs: PIB more than 15 yrs before EAO; FDG 10 yrs; MRI 5-10 yrs

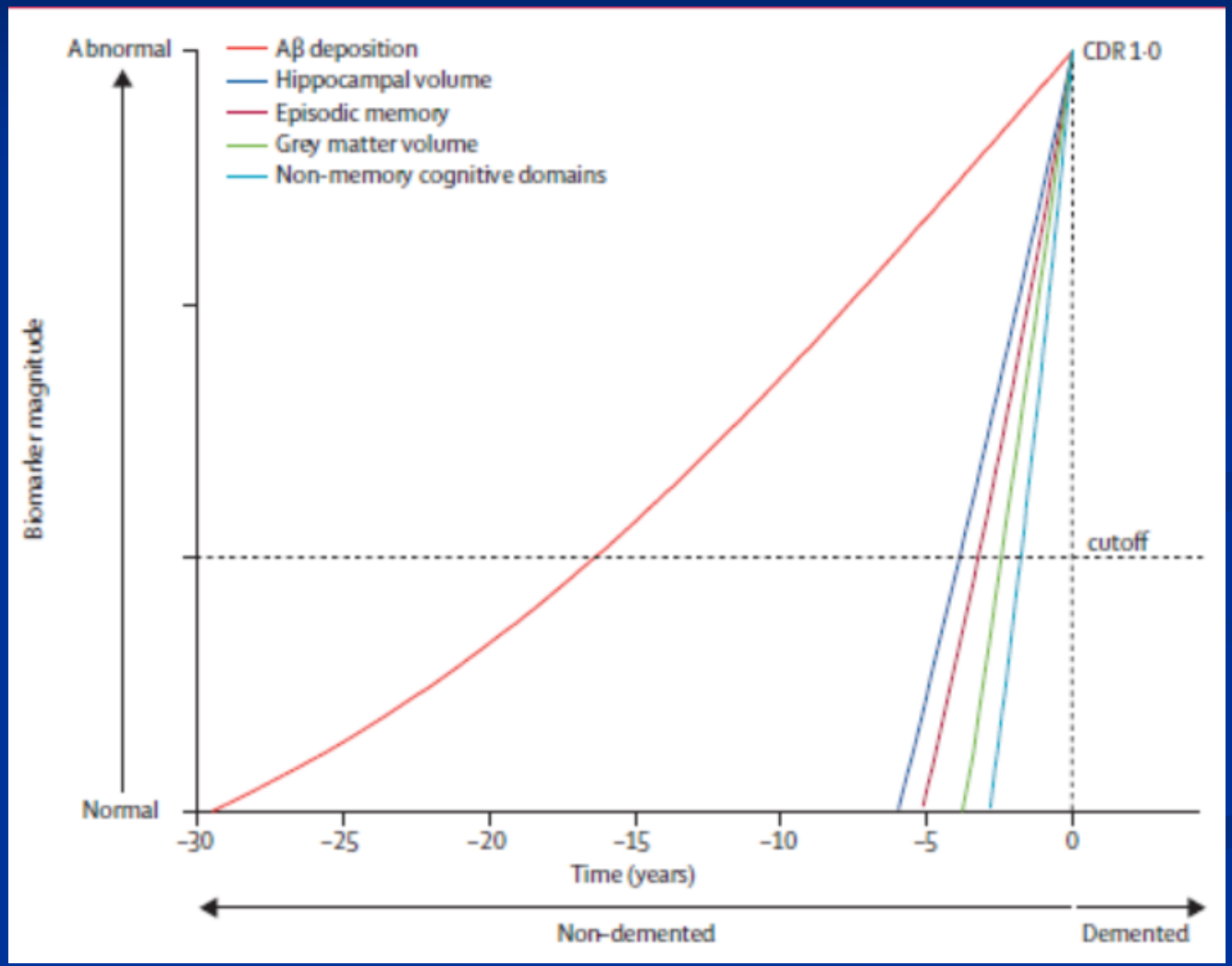
Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease Benzinger 2012

(Mutation carries, PIB n = 121; FDG n= 116; MRI n= 137)



Subcortical MRI ROI analyses – hippocampus, amygdala, N accumbens all - 10 yrs in carriers

Amyloid first in pre clinical late onset AD (PIB accumulators) Villemange 2013

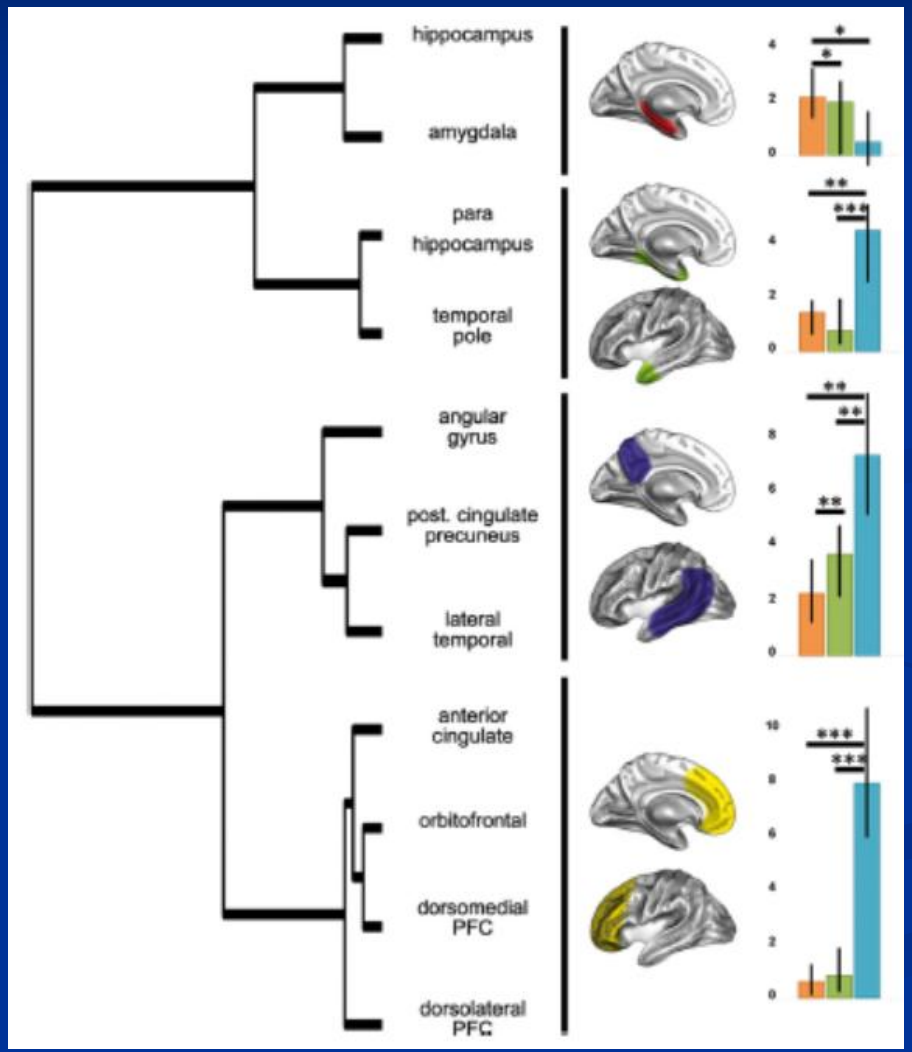


Regional comparisons of amyloid, atrophy, FDG

- regional heterogeneity in the load of atrophy, hypo metabolism and amyloid (Edison 2007; Chetelat 2008; Jack 2008; La Joie 2012; Borgeat 2010)
- "may reflect (1) a lack of deleterious effect of local Abeta deposits, (2) a (locally varying) difference in the timing of the different biomarkers, or (3) the presence of (locally varying) compensation processes" – La Joie 2012

- #1 – Ab independent mechanisms - option 2 from La Joie
- #2 – Ab dependent – **A** and T→N→C have different topography; Ab exerts local and distant effects – brain functions through spatially distributed networks – not isolated compartments, which have to express path identically

Region-Specific Hierarchy between Atrophy, Hypometabolism, and Amyloid Load in Alzheimer's Disease Dementia La Joie 2012



FGD, sMRI & fMRI in APOE4 wo amyloid

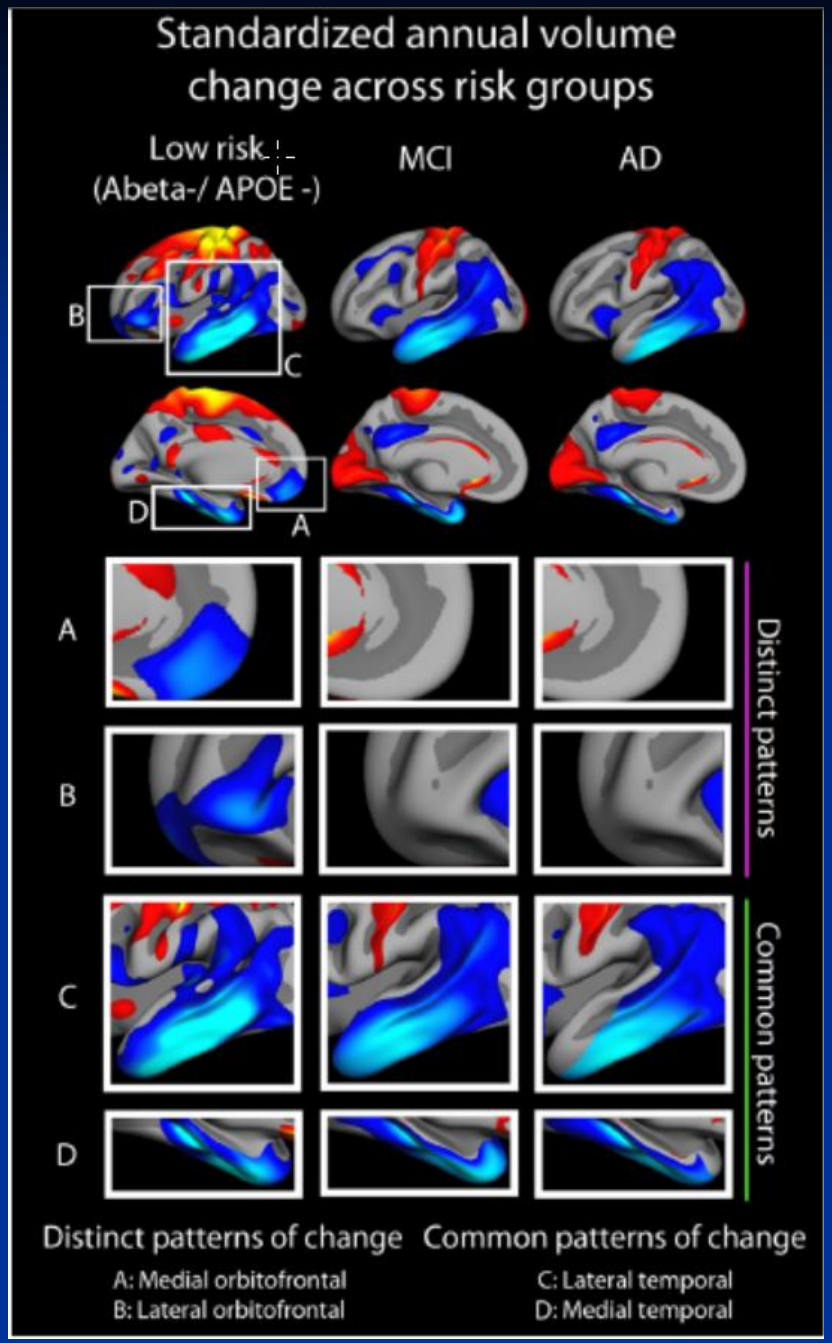
- Too young: fMRI Filippini 2009; FDG Reiman 2004; sMRI Shaw 2007 –ERC (e2>e3>e4) – fixed non-progressive effect; sMRI Alexopoulos 2011 hippocampus (e2>e4) but no memory diff
- Proven amyloid negative: Jagust and Landau, 2012; Sheline, 2010

- #1 - APOE4 carriers much more likely to develop AD in the future therefore represent pre amyloid AD findings
- #2 – this is a non progressive developmental effect that might weaken resistance to AD, but is NOT a measure of an active disease process (Sx wont manifest for 60-70 yrs)
  - APOE4 has many effects (Bu) and these could be non-AD effects of APOE4 on vulnerable networks

AD signature abnormalities are not associated with amyloid (not APOE effect per se)

- **MRI** -- Dickerson and Wolk 2012: 60% of ADSig low had abnormal CSF AB, but 40% ADSig low were amyloid neg
- **MRI and FDG**– Wirth JAMA Neurol 2013 and J Neurosci 2013 - neurodegeneration occurs within AD regions irrespective of amyloid deposition – and decreased cognition is associated with AD sig neurodegenerative independent from amyloid

- #1 – evidence of Abeta independent pathways to AD
- #2 – evidence of non-AD etiologies damaging networks that are vulnerable to insults from AD and non-AD etiologies – ie etiological non-specificity of AD sig MRI and FDG



MRI rates in APOE4- and CSF AB negative CN, vs MCI and AD

Fjell J Neuro Sci 2013

atrophy is scaled within group and changes are relative to group means. Across groups, see common patterns of standardized change in the lateral and medial temporal lobe, and a distinct pattern characterizing low risk healthy elderly in the prefrontal cortex, especially the orbitofrontal part

Conclude: volume loss that includes AD sig regions not amyloid, not APOE4, and therefore not AD but rather "general feature of normal aging"

An operational approach to the NIA-AA criteria for preclinical Alzheimer's disease

Jack, Ann Neurol 2012

- 450 MCSA CN: 43% stage 0; 31% stages 1-3; 23% SNAP. SNAP is not an APOE4 effect.
- #1 –SNAP indicates non-amyloid paths to AD
- #2 – all neurodegeneration in elderly is not AD, other processes exist. SNAP = non-AD pathology or ageing related neurodegeneration in networks that are vulnerable to AD and non-AD etiologies

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

Knopman Neurology 2012

- Examined short term outcomes in 296 of those staged in Ann Neurol paper
- conversion to MCI within 1 year- preclinical AD stage 0 (5%), stage 1 (12%); stage 2 (21%); stage 3 (43%); SNAP 10%

- #1 – no difference between the SNAP and stages 1–3 (10% vs 18%, p 0.18) – therefore SNAP may be pre clinical AD
- #2 – pre clinical staging valid, lack of statistical difference between SNAP and pre clinical AD 1-3 is small N

Brain Injury Biomarkers Are Not Dependent on b-Amyloid in Normal Elderly, Knopman Annals 2013

- compared the SNAP group to those with preclinical AD stages 1–3 (and stage 0) on various measures
- SNAP & pre clin1-3 were indistinguishable on any measures of cerebrovascular risk factors or α-synucleinopathy, only APOE4
- But prevalence of CVD/LBD less in stage 0

- #1 - SNAP indicates non-amyloid paths to AD
- #2 - SNAP and stages 1-3 are same age and 4-6 yrs older than stage 0. LBD & CVD are age related, so no reason indicators should be different in elderly with Ab (stages 1-3) as without Ab (SNAP) if they were same age.

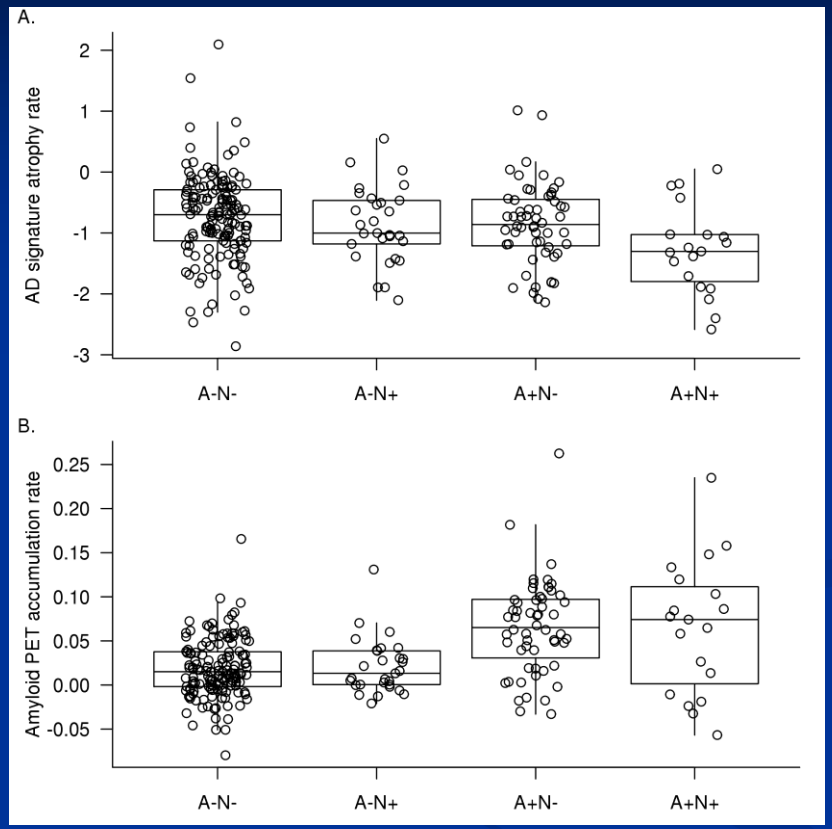
Amyloid-First and Neurodegeneration-First Profiles Characterize Incident Amyloid PET Positivity, Jack Neurology 2013

- 15/26 (58%), incident amyloid positivity occurred prior to abnormalities in FDG PET and hippocampal volume
- However, 11/26 (42%) of incident amyloid positive subjects had biomarker evidence of neurodegeneration prior to incident amyloid positivity

- #1- proves amyloid independent pre-clinical AD exists
- #2 - If non-AD path and aging neurodegenerative changes are age related (and they are) then this is expected. Neurodegeneration-first incident amyloid positives had combinations of pre-existing non-AD and aging neurodegeneration and then newly entered the amyloid pathway.

Rates of β-Amyloid Accumulation are Independent of Hippocampal Neurodegeneration, Jack Neurology 2014

- 252 CN with serial MRI and amyloid PET



- #1- AB independent?
- #2 – amyloid is upstream driver of neurodegeneration, not the reverse. (Villain 2010)

The rate of amyloid accumulation is not influenced by neurodegeneration and thus may be a biologically independent process. Amyloid pathophysiology increases or catalyzes neurodegeneration

Outline

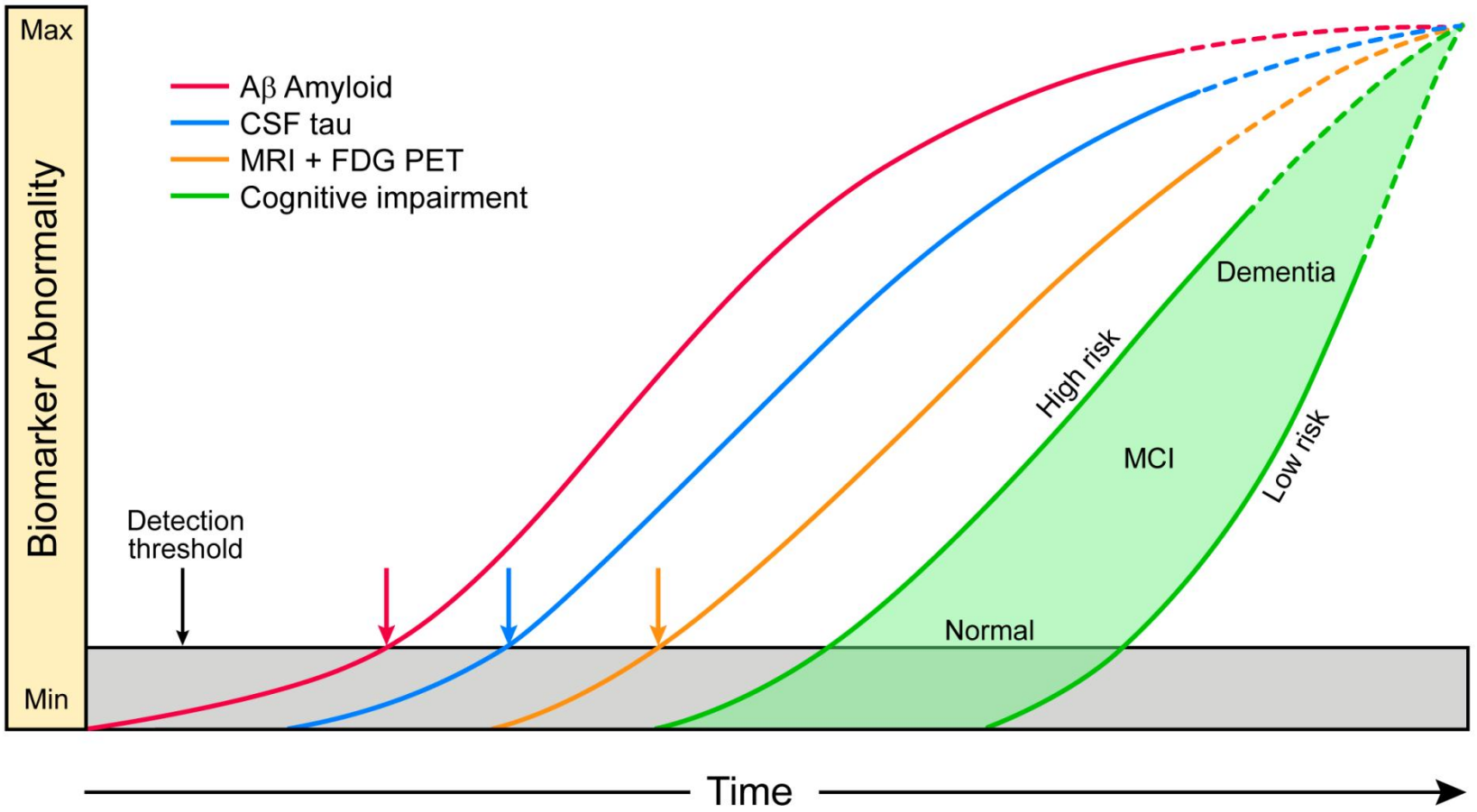
- Statement of argument: Abeta independent vs dependent AD
- Specificity of biomarkers
- Arguments for/against Abeta independent vs dependent AD
- Biomarker models for early vs late onset AD
  - need a conceptual framework for late onset AD that recognizes
    - etiological heterogeneity of neurodegeneration in elderly, AD is embedded in neurodegeneration due to : (1) non-AD pathologies, (2) aging changes
    - etiologically non-specific nature of measures of neurodegeneration - esp. FDG and MRI

Context and AD biomarker modeling: 2 scenarios

- Pure AD – (familial AD, APOE4/4)
- Mixed AD with co- occurring pathologies / aging – (late onset AD)
  - Biomarker sequence : amyloid first or neurodegeneration first
  - Biomarker sequence depends on timing of onset of AD cascade (i.e. incident amyloidosis) in relation to non-AD and aging changes. Unique to each individual
- The disease is not different; the environment in which it develops is

Context and AD biomarker modeling

pure AD: no confounding path or aging

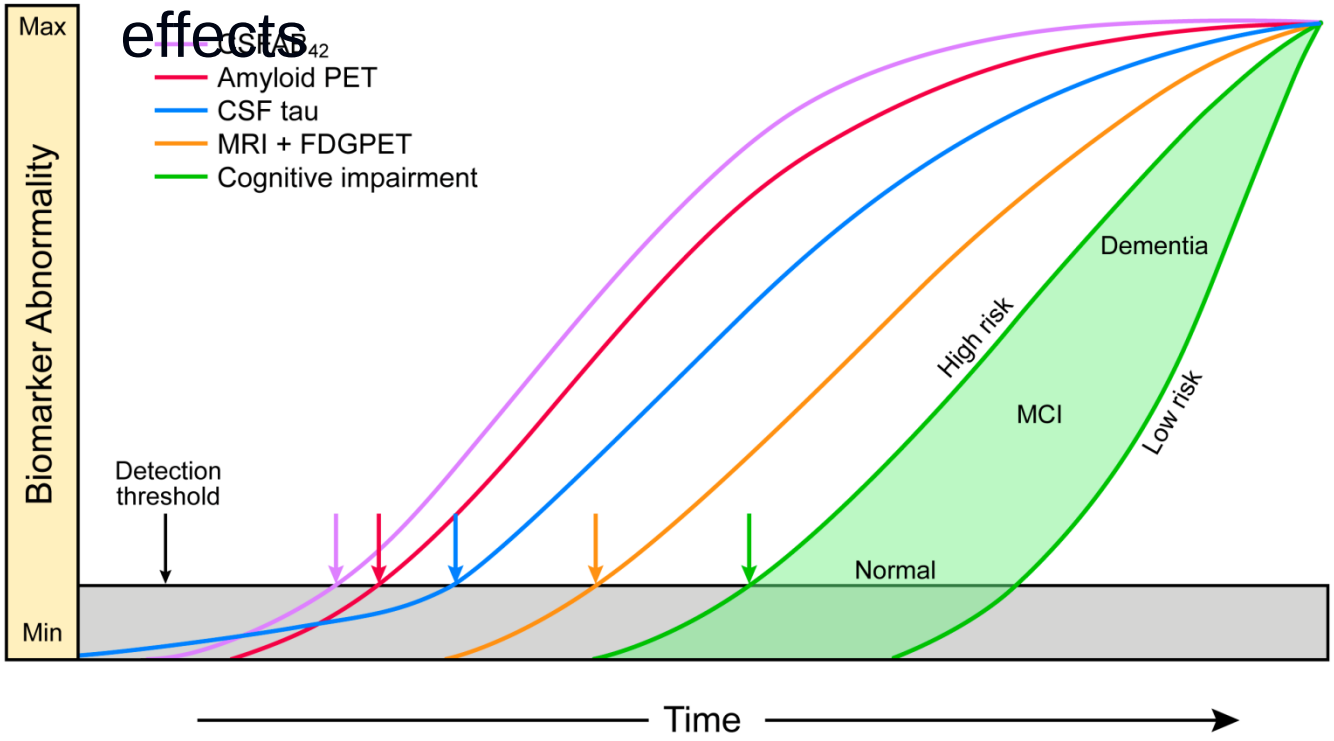


Jack and Holtzman, Neuron 2013

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

Late onset AD – only AD pathology effects



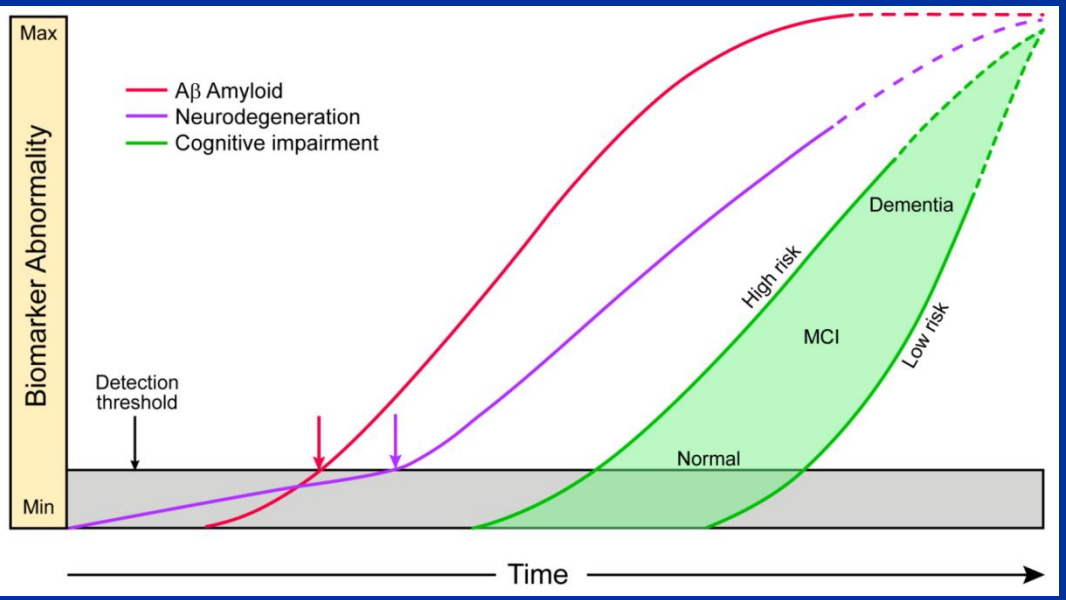
Lancet Neurology, Feb, 2013

3209427-3B

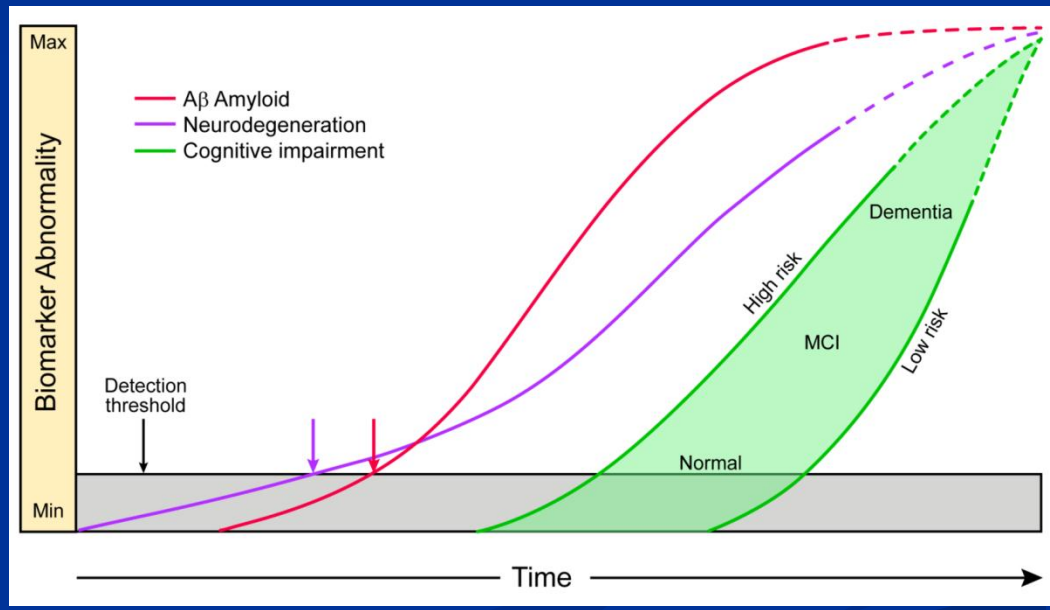
Context and AD biomarker modeling

Mixed AD: exact composition of neurodegeneration unknown

Amyloid-first biomarkers



Neurodegeneration-first biomarkers



Jack and Holtzman, Neuron 2013