Alzheimer's Imaging and Biomarkers

- **Amyloid (PiB) Imaging**
- **Tau Imaging**
- **FDG** (hypoperfusion w/ 18F-fluorodeoxyglucose)
- **Atrophy and Cortical Thinning**
- **Functional Connectivity**
- **CSF Markers** (lumbar puncture)
- **Blood Plasma Markers**

<u>Other Elements of NBOA Diagnostics:</u>

- Cut Points
- MMSE & Neuropsych Testing

Montreal Cognitive Assessment vs. Mini Mental Status Exam

Update from the Clinics

MOCA vs. MMSE Essay:

Both are rapid assessments of cognitive functioning, and used for all manner of cognitive concerns (not just aging). While MMSE has been used more extensively and is highly prevalent in aging-research articles, both are good for quick assessments. MOCA is newer, a bit stronger on assessing executive function and more widely used internationally. Both have 30 point scales, which show marked fall-off with severe dementia, but *they are not* interchangeable scales.

While both scales correlate with degree of dementia, neither is definitively diagnostic because other kinds of damage or ongoing pathology can produce low MOCA/MMSE scores.

Neurologist and Primary Care MDs are supposed to complete certification training before using these measures but even in world-class clinical units, there can be uneven scoring of patient responses! **Neuropsychologists**, b/c they have intensive training on a great catalog of cognitive assessments can easily administer MOCA or MMSE tests but in general they do NOT use these basic measures. This is because they typically perform a significant number of quite detailed assessments and the different "bits of assessment" found e.g. in the MMSE can easily cause interference effects. But, records of such assessments by other clinicians can be very useful both as a chronological record and additional data on patient performance.

DQ: Why are these tests relevant to Biomarkers / Chapter 18?

Classes / Key Biomarkers for Alzheimer's

To date, there are at least 7 complementary biomarkers for AlzD in two major categories: *complex decisions, competing objectives*

Imaging Measures of brain amyloid, tau deposition, more

- especially amyloid and tau PET imaging + hypoperfusion [regional hypometabolism of fluorodeoxyglucose (FDG) PET] and perhaps functional connectivity / DMN measures
- atrophy on structural MRI

↑↑**skim Chap. 17 for more**↑↑

Other Correlates of neurodegenerative processes

- increases in CSF total tau and phosphorylated tau; decreased A-beta-42 [CSF AB42/AB40 ratio]
  plasma measures of A-beta, other biomarkers ← new item

Clinical Measures: not "biomarkers" per se, but is one THE BEST?

- neurological exam, MMSE, **neuropsychological tests**
- functional assessments, ADLs (activities of daily living)

Aging Generally + Dementia: Independence is Key vs. when they take my Car Keys = ☹

Steven Greenberg Slide

CHAT NOW:

Which of these pathologies is the best *Biomarker*?

Boyle, Schneider Religious Orders/ Rush Memory and Aging
Ann Neurol 2018;83:74

Neuropathology seen at autopsy

	Path present (n=1079)	Proportion cog decline when present
AD	704	57.9%
Gross infarcts	388	28.8%
Cerebral amyloid angiopathy	386	20.6%
TDP-43	377	30.5%
Atherosclerosis	358	27.4%
Arteriolosclerosis	338	27.5%
Cortical Lewy bodies	143	45.1%
Hippocampal sclerosis	112	28.1%

FQ: how does this slide comprise my *AlzD diagnosis* argument?

ANSWER: none of them!

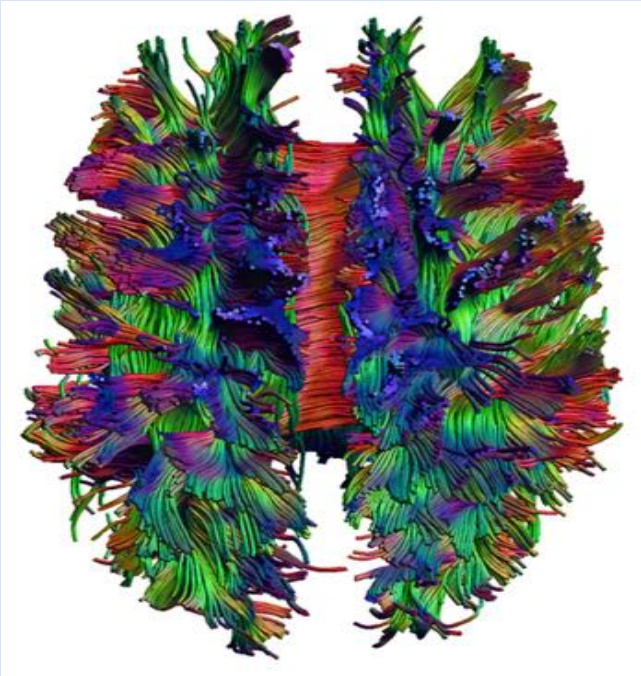
or “None of the Above”

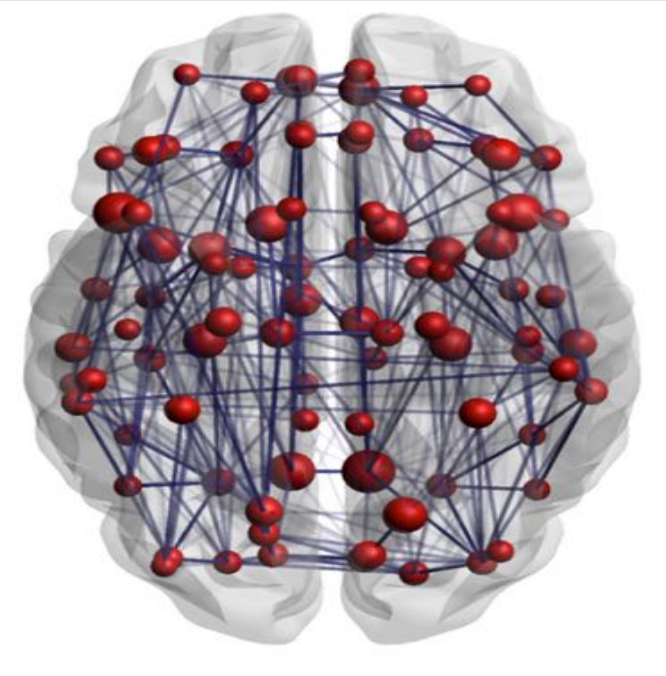
CAA = Cerebral Amyloid Angiopathy: chap 19

Steven Greenberg Slide

excerpts of SG slides with annotations: TBP

CAA-related brain lesions
Altered connectivity





FA = measure of directionality of diffusion [***fractional anisotropy, DTI***]

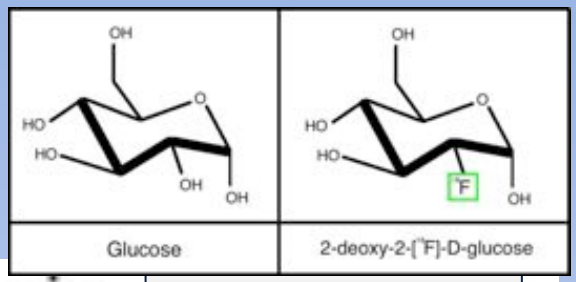
Global efficiency = inverse of shortest FA-weighted path length between every pair of nodes

more WM – vascular connections

Reijmer *Brain* 2015;138:179

Before Tackling the 900 lb. Gorilla…EOAD!

EOAD patients as *Living Biomarkers?*



Lancet, 2018

2 F's, 1 fluorine!

Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study

Brian A Gordon*, Tyler M Blazey*, Yi Su, Anzhe Hari-Raj, Aylin Dincer, Shaney Flores, Jon Christensen, Eric McDade, Guoqiao Wang, Chengjie Xiong,

Autosomal Dominant means Early Onset AlzD – symptoms begin btw ages 30 and 50
mutations in: APP (amyloid precursor protein) and Presenilins 1/2 (gamma secretase)

Michael M Weiner, David M Holtzman, Marcus E Raichle, John C Morris, Randall J Bateman, Tammie L S Benzinger

Biomarkers Studied: PET amyloid (PiB), PET-FDG, GM atrophy (volume change, thinning)

Summary

Background Models of Alzheimer's disease propose a sequence of amyloid β (Aβ) accumulation, hypometabolism, and structural decline that precedes the onset of clinical dementia. These pathological features evolve both temporally and spatially in the brain. In this study, we aimed to characterise where in the brain and when in the course of the disease neuroimaging biomarkers become abnormal.

Focus of the DIAN study

Methods Between Jan 1, 2009, and Dec 31, 2015, we analysed data from mutation non-carriers, asymptomatic carriers, and symptomatic carriers from families carrying gene mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*) enrolled in the Dominantly Inherited Alzheimer's Network. We analysed ^{11}C-Pittsburgh Compound B (^{11}C-PiB) PET, ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET, and structural MRI data using regions of interest to assess change throughout the brain. We estimated rates of biomarker change as a function of estimated years to symptom onset at baseline using linear mixed-effects models and determined the earliest point at

Lancet Neurol 2018; 17: 241–50
Published Online January 31, 2018
http://dx.doi.org/10.1016/S1474-4422(18)30028-0
See Comment page 208
*Contributed equally
Mallinckrodt Institute of Radiology (B A Gordon PhD, T M Blazey BS, Y Su PhD, A Hari-Raj BA, A Dincer BA, S Flores BS, J Christensen BS,

DIAN-TU not to be confused with **Dantooine**, an outer-rim world and Rebel Alliance base

FDG in SNCD: p.134, 154, 182

Mandalorian?

DIAN = Dominantly Inherited AlzD Network *in US, Germany, Japan, Argentina and Korea!*

OUR RESEARCH
For Investigators
Our Collaborators
Registry
Clinical Trial
Study Sites
Research Updates
FAQs
Leadership
Observational Study
Funding and Study Team

Director: Randall Bateman
Wash. Univ., St. Louis

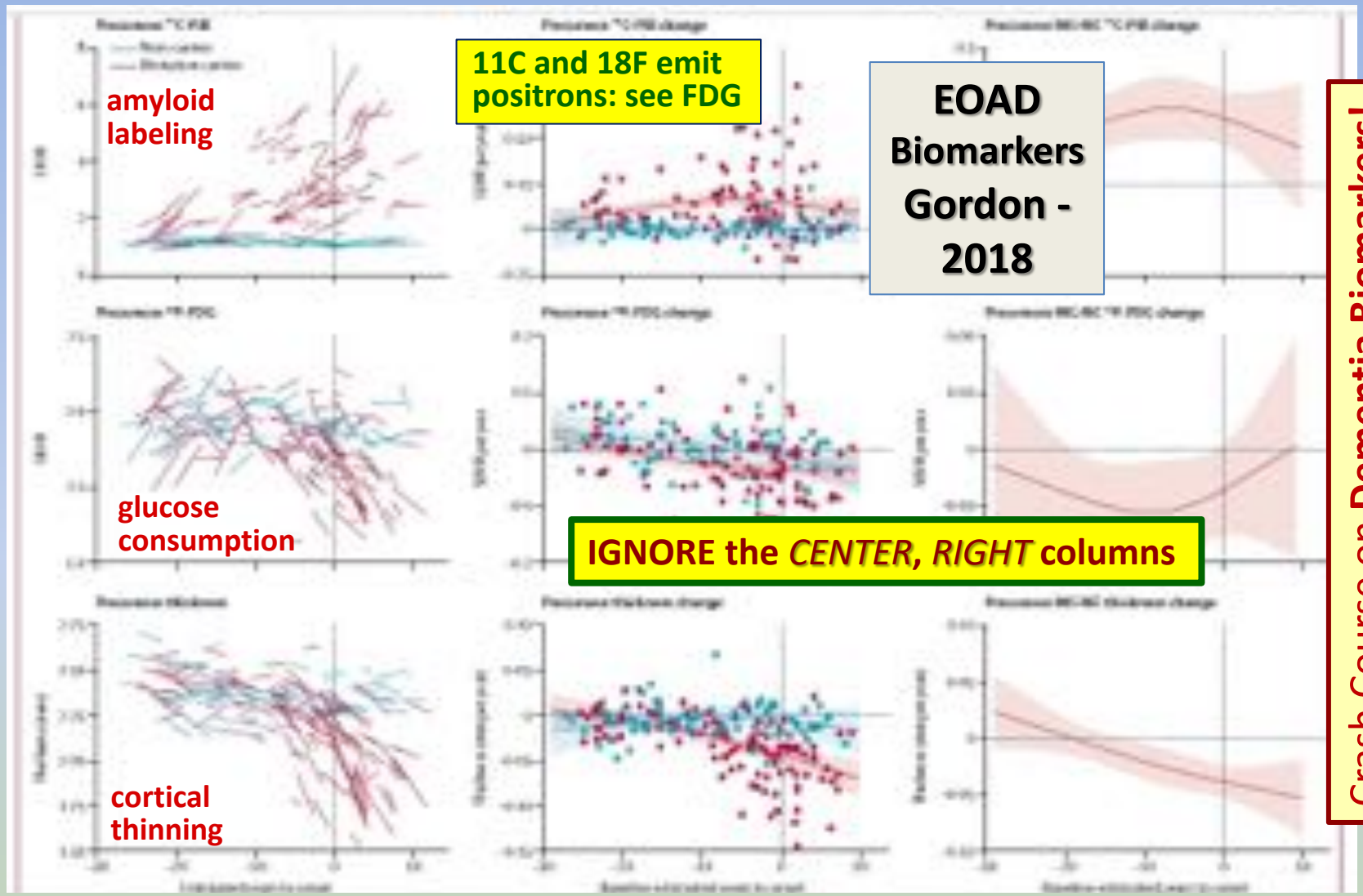
Clinical Trial

Why show an Ad? This DIAN study is a nice exemplar of clinical research.

REMOVES AMYLOID!

Meet a man affected by Dominantly Inherited Alzheimer's Disease and learn why he participates in the DIAN clinical trial.

Trial name: DIAN-TU-001: A Phase II/III Randomized, Double-Blind, Placebo-Controlled Multi-Center Study of 2 Potential Disease Modifying Therapies in Individuals at Risk for and with Dominantly Inherited Alzheimer's Disease.



Focus on our old friend Precuneus! Orientation System, DMN, ABM (w/ cingulate)
Subjects: **mutation carriers** and **non-carriers of:** EOAD genes (APP, presenilins 1/2

Biomarkers: PET amyloid (PiB), PET-FDG, Grey Matter atrophy (volume change, cortical thinning)
RED = Carriers: increasing PiB, decreasing FDG, decreasing thickness. "**Years to Onset**" known for EOAD

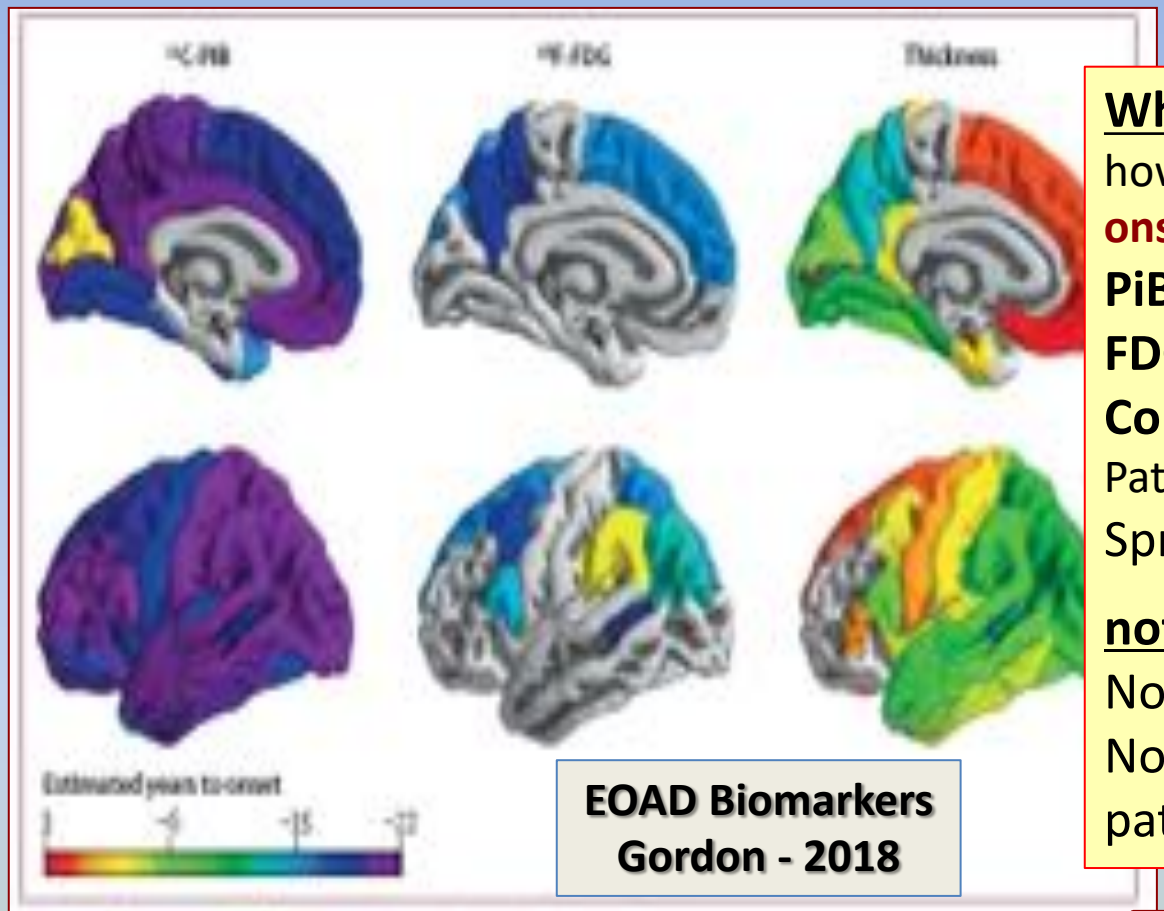


Figure 2: Emergence of differences in neuroimaging biomarkers

The colour scale represents the first point in the disease relative to estimated years to onset at which rates of biomarker change in that cortical region are significantly different between mutation carriers and non-carriers (akin to the first point where credible interval are different from zero in figure 1 right panels). There is a temporal evolution where increased Aβ deposition precedes hypometabolism that in turn is followed by cortical thinning. Information for all methods and regions is presented in numerical form in the appendix. ^{11}C-PiB=^{11}C-Pittsburgh Compound B; ^{18}F-FDG=^{18}F-Fluorodeoxyglucose

What Figure 2 Reveals: *it shows*

how many years **before symptom-onset** one sees changes in biomarkers:

PiB – 22 years

FDG – 14 years

Cortex Thinning – 6 years

Pathology evident FIRST in **Precuneus**

Spreads to other cortical regions

notes: [more notes below]

Not every brain region is identical

Not every patient is identical

pattern in sporadic AlzD differs?

why not ERC? maybe it's an EOAD vs. sporadic AlzD thing?

Two Problems:

i. these are population measures, but not so robust at predicting individual onset times

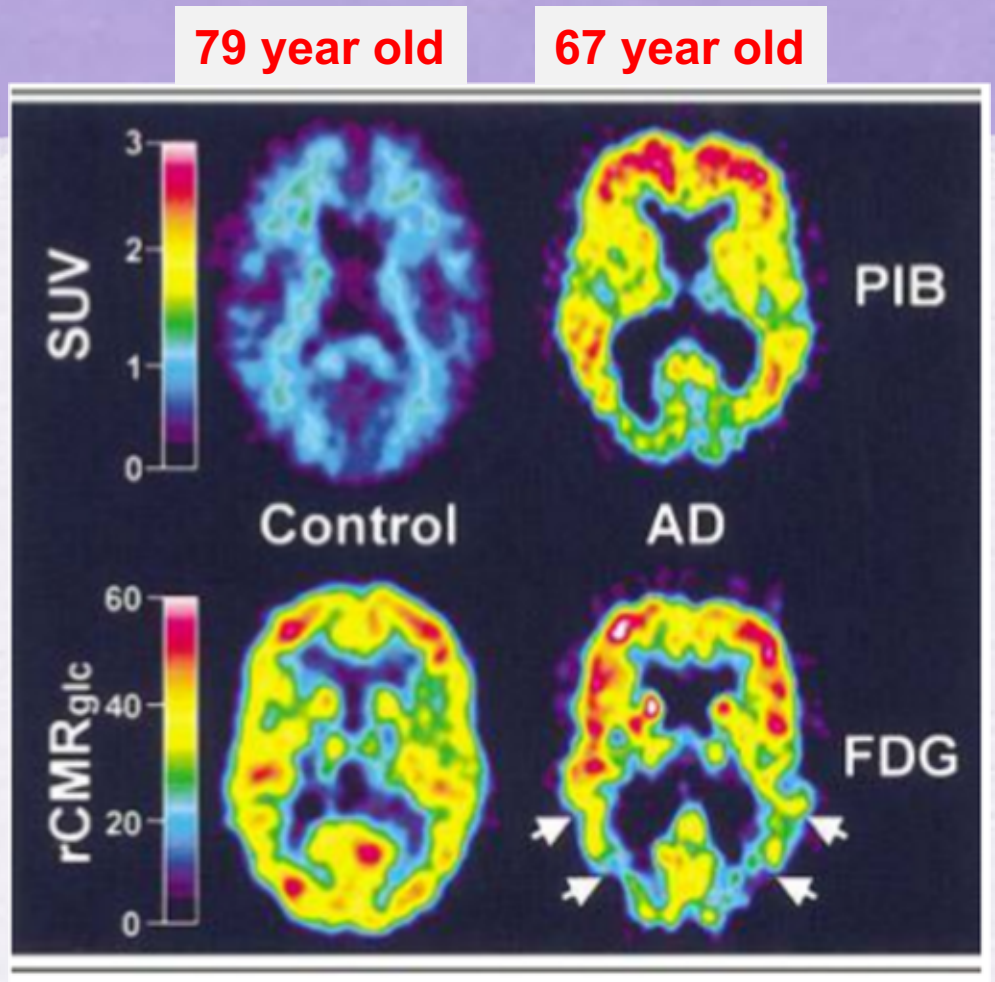
ii. this sequence does not map perfectly onto progression of regular (sporadic) AlzD

more on this in Chapter 19!

Two Biomarkers: PiB and Hypoperfusion

switch: **EOAD to "sporadic" AlzD**

- **Pittsburgh Compound B (PiB) is a PET** imaging compound / analog of Thioflavin-T, which has been used to stain amyloid deposits in neocortex: it appears to label both plaques and vascular amyloid deposits (i.e. CAA):
- **Klunk, 2004, Ann. Neurol.** [67 yr old AlzD vs. 79 yr. old ctrl]



Thioflavin T is a histological stain for misfolded protein aggregates such as amyloid
SUV in PET imaging = Standardized Uptake Value = measure of the PET-PiB signal
rCMR = regional cerebral metabolic rate via fluorodeoxyglucose (FDG) uptake

Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B

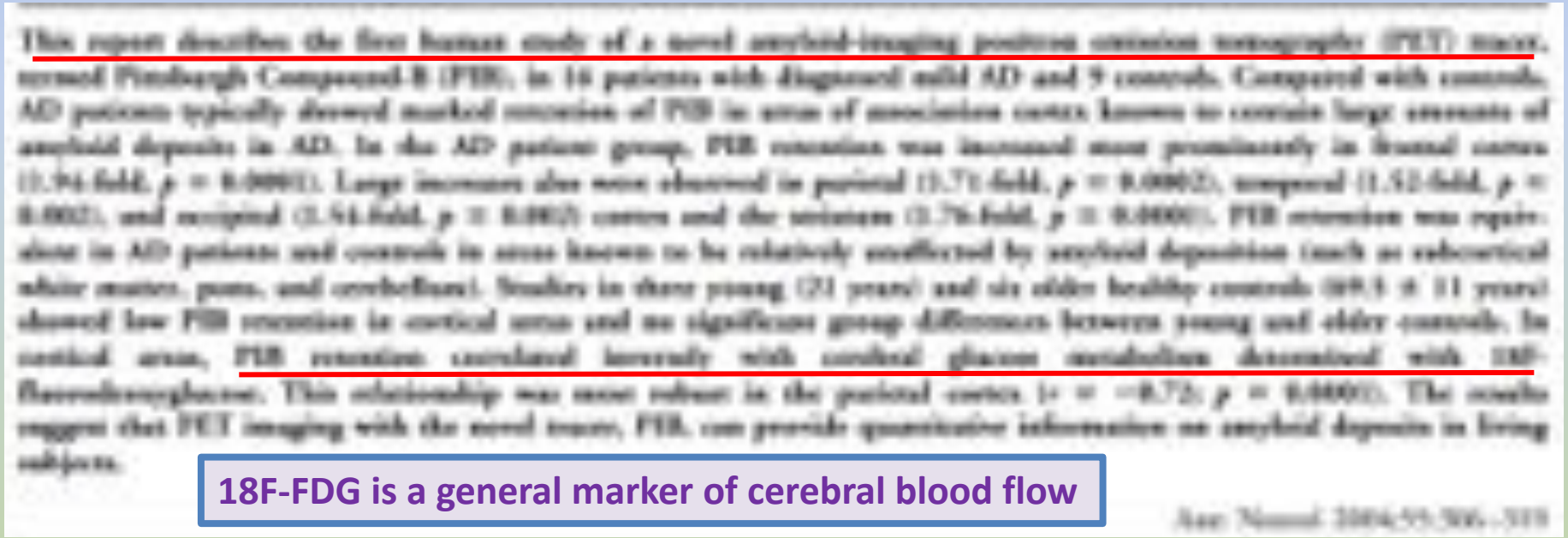
William E. Klunk, MD, PhD; Henry Engler, MD;[2] Agneta Nordberg, MD, PhD;[3,4] Yanming Wang, PhD;[5]

2004!

PiB derived from Thioflavin T w/ positron-emitter incorporated [carbon-11]
tested on controls and patients with mild AlzD; does not stain NFTs

PiB retained in frontal, association cortices (pathology must be there by "mild" stage)
young folks AND old controls showed no such labeling

Parietal hypoperfusion correlated with PiB staining [DQ: can't we see this w/ fMRI?] see notes



This report describes the first human study of a novel amyloid-imaging positron emission tomography (PET) tracer, termed Pittsburgh Compound-B (PIB), in 16 patients with diagnosed mild AD and 9 controls. Compared with controls, AD patients typically showed marked retention of PIB in areas of association cortex known to contain large amounts of amyloid deposits in AD. In the AD patient group, PIB retention was increased most prominently in frontal cortex (1.94-fold, $p = 0.0001$). Large increases also were observed in parietal (1.71-fold, $p = 0.0002$), temporal (1.52-fold, $p = 0.002$), and occipital (1.44-fold, $p = 0.002$) cortex and the striatum (1.76-fold, $p = 0.0001$). PIB retention was equivalent in AD patients and controls in areas known to be relatively unaffected by amyloid deposition (such as subcortical white matter, pons, and cerebellum). Studies in three young (21 years) and six older healthy controls (69.3 ± 11 years) showed low PIB retention in cortical areas and no significant group differences between young and older controls. In cortical areas, PIB retention correlated inversely with cerebral glucose metabolism determined with 18F-fluorodeoxyglucose. This relationship was most robust in the parietal cortex ($r = -0.72$; $p = 0.0001$). The results suggest that PET imaging with the novel tracer, PIB, can provide quantitative information on amyloid deposits in living subjects.

18F-FDG is a general marker of cerebral blood flow

Ann Neurol 2004;55:306–319

This was no Klunker! 3957 cites and counting! 4375 in '21

...setting aside my normal antipathy towards: "we have shown for the first time..."

Inverse Relation between In Vivo Amyloid Imaging Load and Cerebrospinal Fluid $A\beta_{42}$ in Humans

Anne M. Fagan, PhD,[1–3] Mark A. Mintun, MD,[2,4] Robert H. Mach, PhD,[2,4] Sang-Yoon Lee, PhD,[4]

2006!

In AlzD, AB42 should be HIGHER but it's NOT!

Ann. Neurol. 2006:59:512

CSF AB42 is low in AlzD

Objective: Amyloid β_{42} ($A\beta_{42}$) appears central to Alzheimer's disease (AD) pathogenesis and is a major component of amyloid plaques. Mean cerebrospinal fluid (CSF) $A\beta_{42}$ is decreased in dementia of the Alzheimer's type. This decrease may reflect plaques acting as an $A\beta_{42}$ "sink," hindering transport of soluble $A\beta_{42}$ between brain and CSF. We investigated this hypothesis. *Methods:* We compared the in vivo brain amyloid load (via positron emission tomography imaging of the amyloid-binding agent, Pittsburgh Compound-B [PIB]) with CSF $A\beta_{42}$ and other measures (via enzyme-linked immunosorbent assay) in clinically characterized research subjects. *Results:* Subjects fell into two nonoverlapping groups: those with positive PIB binding had the lowest CSF $A\beta_{42}$ level, and those with negative PIB binding had the highest CSF $A\beta_{42}$ level. No relation was observed between PIB binding and CSF $A\beta_{40}$, tau, phospho-tau_{181}, plasma $A\beta_{40}$, or plasma $A\beta_{42}$. Importantly, PIB binding and CSF $A\beta_{42}$ did not consistently correspond with clinical diagnosis; three cognitively normal subjects were PIB-positive with low CSF $A\beta_{42}$, suggesting the presence of amyloid in the absence of cognitive impairment (ie, preclinical AD). *Interpretation:* These observations suggest that brain amyloid deposition results in low CSF $A\beta_{42}$, and that amyloid imaging and CSF $A\beta_{42}$ may potentially serve as antecedent biomarkers of (preclinical) AD.

3

There is an **INVERSE** relationship between **CSF A-beta 42** and **PiB positive** individuals.
Plasma AB-42 was "not correlated" w/ PiB -- but stay tuned!!!
ALSO, no association w/ **CSF** tau, P-tau or AB40. **THM: CSF AB42/AB40 ratio is biomarker.**

A-beta 42 is the longer AB-peptide associated with ABOs, AlzD. A-beta 40 as described by Dr. Greenberg is the form assoc. with CAA. **Low AB42 in CSF is assoc. with high AlzD risk**.

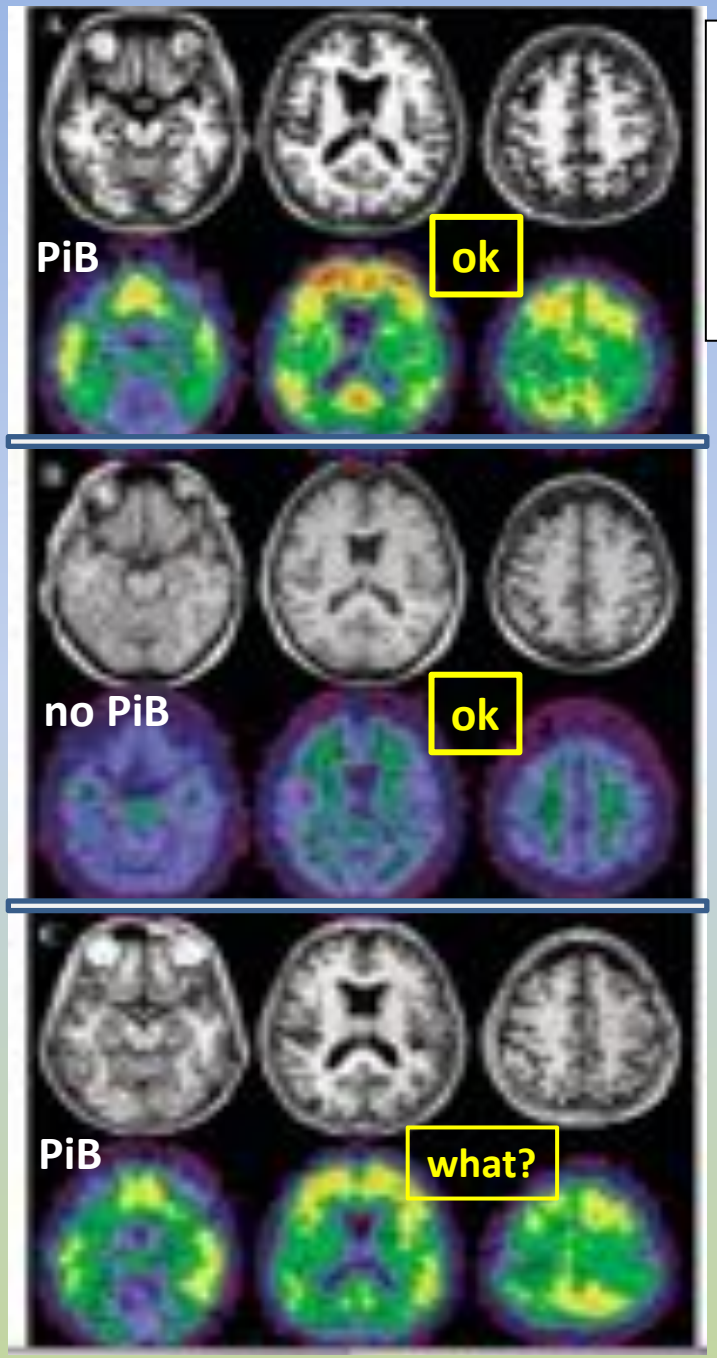


Fig 1. Distribution of Pittsburgh Compound-B (PIB) in three subjects as viewed by positron emission tomography (PET). For each subject, the three magnetic resonance (MR) images (black and white) are at three different levels above the anterior commissure–posterior commissure line. The PET images (in color) are taken from the same levels as the MR images and reflect the PET activity summed from 30 to 60 minutes after injection of PIB. PET data were scaled to normalize for activity in the cerebellar cortex. (A, C) Increased binding of PIB in many brain regions in these two subjects, particularly the prefrontal cortex, the medial and lateral parietal cortex, and the lateral temporal cortex (PIB-positive), is shown. (B) Only low levels of nonspecific PIB binding in white matter structures in this subject and no evidence of binding in cortices (PIB-negative) are shown.

Subjects (A), (C) = PiB positive; 30 to 60 min

B&W = structural MRI of same patients

Subject (A) is PiB positive WITH Cog. impairment

Subject (B) is PIB negative and Cog-Normal.

Subject (C) is PiB positive and Cog-Normal.

PiB-positive cases show amyloid in PFC and temporal cortex, precuneus, other regions. None in cerebellum or brainstem.

Not the Final Word, BUT:

reveals challenges to clinicians

reveals disparity of AlzD measurements

raises issues re: DIAGNOSIS of AlzD

7 of 24 subjects were PiB POSITIVE

Subject No.	CDR	Dx	Age	ApoE	MMSE[a]	Logical Memory[b]	CSF (pg/ml)				Plasma (pg/ml)		PiB Mean Cx (mean cortical, Cx) as Binding Potential (unitless ratio)
							Tau	$P\text{-tau}_{181}$	$A\beta_{42}$	$A\beta_{42}$	$A\beta_{40}$	$A\beta_{42}$	
14	0	nldem	65	2,3	28	9.0	267	43	9,583	750	168	64	−0.092
15	0	nldem	77	3,3	29	7.5	231	37	9,006	593	199	69	−0.063
10	0	nldem	85	2,3	29	12.5	588	107	19,483	1,071	357	951	−0.055
7	0	nldem	49	3,3	30	4.0	175						
13	0	nldem	85	3,3	30	15.0	157						
9	0	nldem	48	3,4	30	12.0	326						
18	0	nldem	59	3,4	29	10.0	246						
16	0	nldem	64	3,4	30	15.0	319						
12	0	nldem	75	3,4	30	18.0	437						
23	0	nldem	58	2,2	30	10.5	190						
20	0	nldem	61	3,3	30	8.0	164						
17	0	nldem	60	3,3	29	13.5	229						
22	0	nldem	61	3,4	30	8.0	413						
21	0	nldem	65	3,4	30	8.5	157						
24	0	nldem	58	3,3	27	13.0	265	48	12,530	790	144	67	0.050
1	0.5	nDAT	77	3,4	25	5.0	265	59	5,583	588	163	117	−0.047
3	0.5	nDAT	77	3,3	28	7.5	380	69	9,670	572	207	165	0.010
19	***0***	***nldem***	***61***	***3,3***	***28***	***8.0***	***461***	***84***	***14,013***	***443***	***365***	***110***	***0.299***
4	***0***	***nldem***	***72***	***3,4***	***30***	***7.0***	***1,068***	***181***	***15,080***	***526***	***365***	***143***	***0.587***
8	***0***	***nldem***	***74***	***3,4***	***25***	***9.0***	***467***	***64***	***16,903***	***359***	***131***	***101***	***0.777***
11	***1***	***DAT***	***73***	***3,3***	***24***	***4.0***	***315***	***54***	***8,194***	***266***	***196***	***129***	***0.418***
2	***2***	***DAT***	***73***	***3,4***	***13***	***0.0***	***963***	***121***	***13,937***	***426***	***157***	***71***	***0.570***
6	***1***	***DAT***	***79***	***3,3***	***21***	***3.5***	***1,358***	***241***	***16,159***	***240***	***144***	***113***	***0.776***
5	***0.5***	***DAT***	***81***	***3,4***	***26***	***6.5***	***319***	***51***	***9,075***	***273***	***157***	***151***	***1.085***

Bold italics indicates subjects who were Pittsburgh Compound-B (PiB)–positive on visual inspection of positron emission tomography images.

[a]Range 0 to 30, higher value indicates better performance.

[b]Logical Memory component of the Wechsler Memory Scale (range, 0-25, higher value indicates better performance).

CSF = cerebrospinal fluid; CDR = Clinical Dementia Rating; Dx = clinical diagnosis; ApoE = apolipoprotein E genotype (alleles, alleles); MMSE = Mini-Mental State Examination; ptau = phospho-tau; Cx = cortex; nldem = not demented; n.d. = not done; nDAT = non-DAT;

Are we using Biomarkers to VALIDATE Biomarkers?

YES! WHY?

chat your answer!

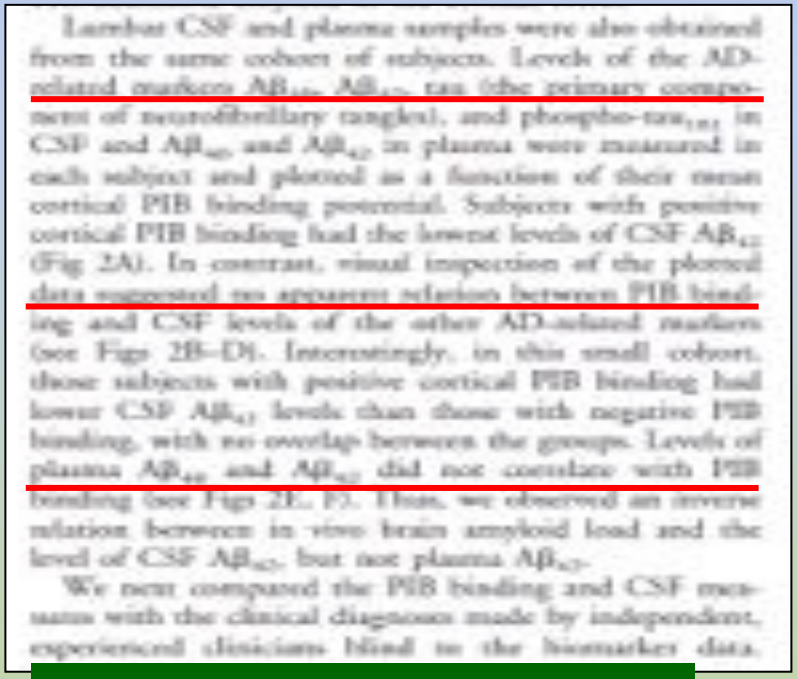
SEE Summary on Next Slide. **Table is mainly if yo interested.**

Fagan, 2006

Positive PiB subjects (7/24) had the LOWEST $A\beta_{42}$ in CSF. 3 of 7 had mild or moderate AlzD (DAT). but the remaining 4 had lower memory scores than PiB-negative normals (15 people). **NO OTHER MEASURE** (CSF or plasma) correlated with PiB positive scan.

One PiB negative was diagnosed with FTD.

You can get a Lumbar Puncture ANYWHERE!



Lumbar CSF and plasma samples were also obtained from the same cohort of subjects. Levels of the AD-related markers $A\beta_{1-40}$, $A\beta_{1-42}$, tau (the primary component of neurofibrillary tangles), and phospho-tau_{181} in CSF and $A\beta_{1-40}$ and $A\beta_{1-42}$ in plasma were measured in each subject and plotted as a function of their mean cortical PIB binding potential. Subjects with positive cortical PIB binding had the lowest levels of CSF $A\beta_{1-42}$ (Fig. 2A). In contrast, visual inspection of the plotted data suggested no apparent relation between PIB binding and CSF levels of the other AD-related markers (see Figs. 2B–D). Interestingly, in this small cohort, those subjects with positive cortical PIB binding had lower CSF $A\beta_{1-42}$ levels than those with negative PIB binding, with no overlap between the groups. Levels of plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ did not correlate with PIB binding (see Figs. 2E, F). Thus, we observed an inverse relation between in vivo brain amyloid load and the level of CSF $A\beta_{1-42}$, but not plasma $A\beta_{1-42}$.

We next compared the PIB binding and CSF measures with the clinical diagnoses made by independent, experienced clinicians blind to the biomarker data.

This is 2006 Plasma technology. Why is this relevant?

Some important discrepancies were observed. Of the seven subjects exhibiting positive PIB binding and low CSF $A\beta_{1-42}$ values, three were diagnosed as having mild or moderate DAT (CDR 1 or 2; see filled squares in Fig. 2 and also Fig. 2A) and one was diagnosed with very mild DAT (CDR 0.5; see open triangles in Fig. 2). Importantly, however, the remaining three PIB-positive subjects with low CSF $A\beta_{1-42}$ values were diagnosed as being cognitively normal (CDR 0; see open circles in Fig. 2), suggesting the presence of cortical amyloid and low CSF $A\beta_{1-42}$ in these subjects in the absence of cognitive impairment. The PET images of one of these subjects are shown in Figure 3C. These subjects all scored within the lower reference range on the Logical Memory component of the Wechsler Memory Scale, with the mean value intermediate to those of normal, normal PIB-negative subjects and demented PIB-positive subjects with DAT (Fig. 3). Also notable is that two additional subjects in our cohort had very mild dementia (CDR 0.5; see solid triangles in Fig. 2), but with impairments considered not to be caused by AD. One subject was diagnosed with frontotemporal lobar degeneration, a group of disorders characterized, in part, by the absence of cerebral amyloid deposition.[20] The other subject had received a CDR score of 0.5, but clinical reassessment indicated a questionable impairment that was perhaps attributable to hypnotic drug therapy initiated for a chronic sleep disorder. These two non-DAT subjects with a CDR score of 0.5 exhibited negative PIB binding and a high CSF $A\beta_{1-42}$ value, a pattern different from the subjects whose cognitive impairments were believed to be due to AD. Our finding of an absence of PIB binding and high CSF $A\beta_{1-42}$ values in these two non-DAT subjects with a CDR score of 0.5 suggests that these biological measures may be useful for excluding brain $A\beta$ amyloidosis as an underlying contributor to cognitive impairment.

text boxes help w/ my summary boxes **Fagan, 2006**

Fagan, 2006

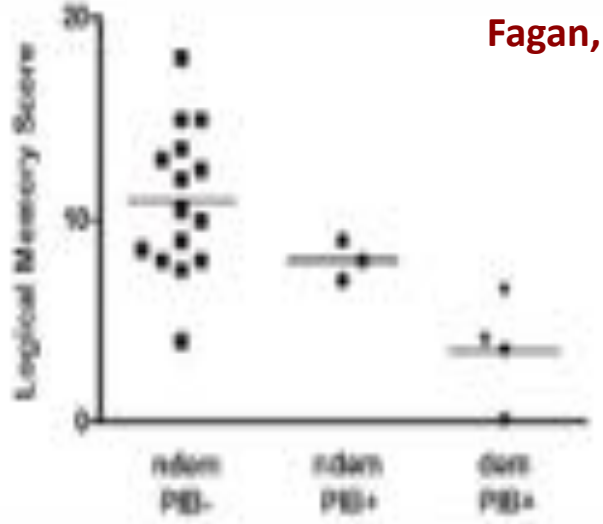


Fig 3. Scatterplot of scores on the Logical Memory component of the Wechsler Memory Scale from subjects who were nondemented and Pittsburgh Compound-B (PIB)–negative, nondemented and PIB-positive, or demented (dementia of the Alzheimer's type [DAT]) and PIB-positive. Scores for the nondemented subjects who were PIB-positive are within the lower range of performance of the nondemented, PIB-negative group, but superior to the scores for demented (DAT), PIB-positive subjects. Squares indicate nondemented (Clinical Dementia Rating [CDR] 0), PIB-negative (n = 15); circles indicate nondemented (CDR 0), PIB-positive (n = 3); triangles indicate demented (DAT), PIB-positive (n = 4); horizontal lines indicate the mean values for each group. One-

If PiB can *identify* folks who HAVE bona fide AlzD, this is huge.

If PiB can *predict* cog-normals who will GET AlzD, that is hugeiest!

Today PiB is an expensive and selectively available, yet increasingly common PET test. AND of considerable practical import.

But this article was about CSF AB-42

DQ: why the emphasis on PiB?

see notes

Is PiB the BEST?

more PET probes for amyloid have been developed: coming SOON!

maybe yes…

Tau Positron Emission Tomographic Imaging in Aging and Early Alzheimer Disease

2016

Keith A. Johnson, MD,[1,2,3,4,5] Aaron Schultz, PhD,[1,4,6]
Rebecca A. Betensky, PhD,[7,8] J. Alex Becker, PhD,[1,3] Jorge Sepulcre, MD,[1,2,3,5,6]
Dorene Rentz, PsyD,[2,4,5] Elizabeth Mormino, PhD,[2,8] Jasmeer Chhatwal, MD,[2,4,5]
Rebecca Amariglio, PhD,[2,4,5] Kate Papp, PhD,[2,4,5] Gad Marshall, MD,[2,4,5]
Mark Albers, MD,[2,5] Samantha Mauro, BS,[1,3] Lesley Pepin, BS,[1,3]
Jonathan Alverio, BS,[1,3] Kelly Judge, BS,[1,3] Marie Philiossaint, BS,[1,3]
Timothy Shoup, PhD,[1,3] Daniel Yokell, PharmD,[1,3,5] Bradford Dickerson, MD,[1,2,5,6]
Teresa Gomez-Isla, MD,[2,5] Bradley Hyman, MD,[2,5]
Reisa Sperling, MD[2,4,5,6]

PhD is NOT required!

This is World Class Cooperation!

Objective: Detection of focal brain tau deposition during life could greatly facilitate accurate diagnosis of Alzheimer disease (AD), staging and monitoring of disease progression, and development of disease-modifying therapies.
Methods: We acquired tau positron emission tomography (PET) using ^{18}F T807 (AV1451), and amyloid-β PET using ^{11}C Pittsburgh compound B (PiB) in older clinically normal individuals, and symptomatic patients with mild cognitive impairment or mild AD dementia.
Results: We found abnormally high cortical ^{18}F T807 binding in patients with mild cognitive impairment and AD dementia compared to clinically normal controls. Consistent with the neuropathology literature, the presence of elevated neocortical ^{18}F T807 binding particularly in the inferior temporal gyrus was associated with clinical impairment. The association of cognitive impairment was stronger with inferior temporal ^{18}F T807 than with mean cortical ^{11}C PiB. Regional ^{18}F T807 was correlated with mean cortical ^{11}C PiB among both impaired and control subjects.
Interpretation: These findings suggest that ^{18}F T807 PET could have value as a biomarker that reflects both the progression of AD topography and the emergence of clinical impairment.

ANN NEUROL 2016;79:110–119

To assign credit for a paper, divide the total credit by the number of authors: .03 papers/author.

research does not occur in a vacuum

PhDs do the work & MDs get the credit?

Subjects and Methods

Participants

Participants were recruited from the Harvard Aging Brain Study, a longitudinal study on aging and AD, from Memory Disorders Clinics at the Massachusetts General and Brigham and Women's Hospitals, and from the Massachusetts Alzheimer's Disease Research Center. All participants provided informed consent and were studied under protocols approved by the Partners Human Research Committee. All subjects underwent at least 1 comprehensive medical and neurological evaluation, and none had medical or neurological disorders that might contribute to cognitive dysfunction; a history of alcoholism, drug abuse, or head trauma; or a family history of autosomal dominant AD. None was clinically depressed at the time of study (Geriatric Depression Scale < 11) or had other psychiatric illnesses.[11] Each participant underwent a cognitive evaluation that included the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating (CDR) Scale, and the Logical Memory delayed recall (LM).[9–11]

Participants were either clinically normal (CN) or cognitively impaired (Table 1). CN subjects ($n = 56$) had a CDR global score of 0, MMSE > 25, and performance within 1.5 standard deviations (SD) of age- and education-adjusted norms on cognitive testing at the time of recruitment into the Harvard Aging Brain Study.[12–14] Cognitively impaired participants fulfilled National Institute on Aging research criteria for either MCI ($n = 13$; global CDR = 0.5) or AD dementia ($n = 6$; global CDR = 1).[15,16] Patients with atypical clinical syndromes,

TABLE 1. Demographics

Characteristic	All	CN
No. (% F)	75 (45)	56 (48)
Age, yr	73 ± 8 [49–90]	75 ± 6 [65–89]
Education, yr	16 ± 3 [12–20]	16 ± 3 [12–20]
MMSE	28 ± 4 [11–30]	29 ± 1 [26–30]
CDR-SB	1 ± 2 [0–11]	0 ± 0 [0–1.5]
^{11}C PiB DVR	1.32 ± 0.3 [1.05–2]	1.24 ± 0.2 [1.05–1.81]

What is Normal?

CN = Cognitively Normal

MCI = Mild Cognitively Impaired

AD = AlzD = significant impairment

NEXT SLIDE:

	TAU	PiB level
A.	low	low
B.	ITC	high 1.2
C.	ITC	high 1.8

D-G: show increasing tau

- sparing only primary cortex
- "PET Braak" is *in vivo* staging

Elevated T807

elevated in widespread cortical regions across parietal lobe plus cingulate/precune illustrated in "contrast maps" in Figure 2

Tau T807

Tau T807-views

amyloid:

tau-staging

SEE IMAGE ON NEXT SLIDE

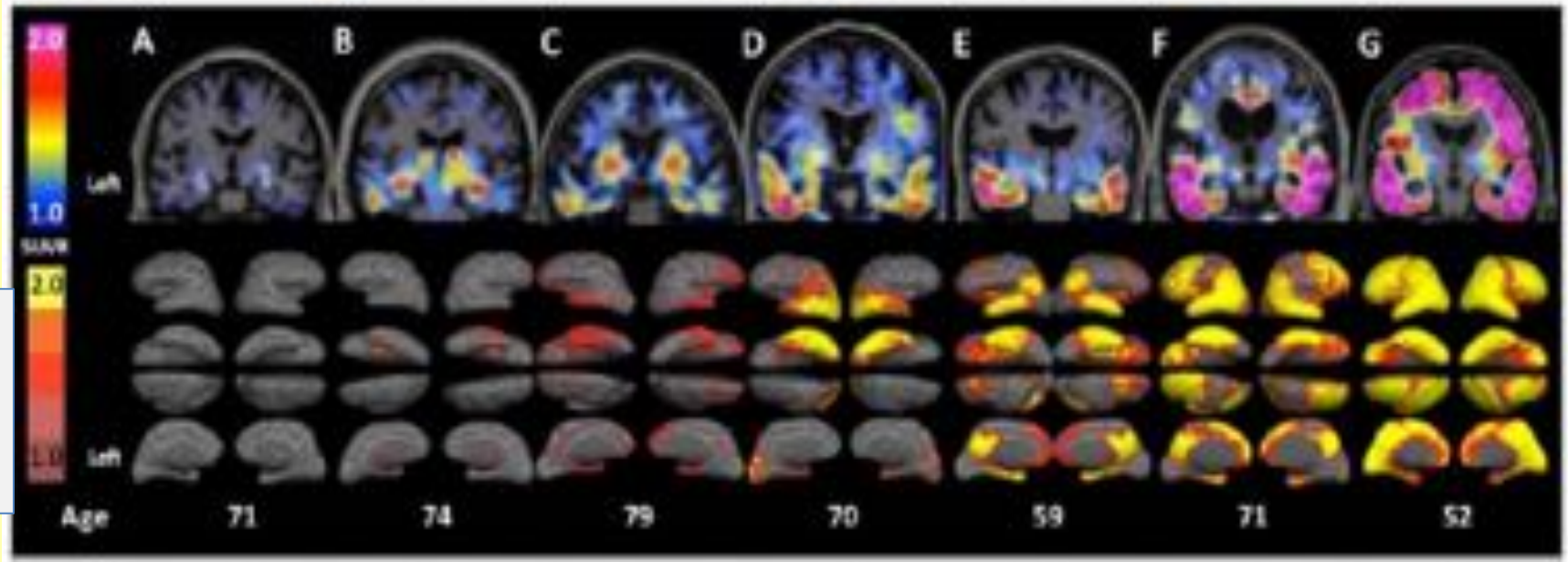
MMSE	30	30	29	27	26	23	11
PiB (DVR)	Low (1.0)	High (1.2)	High (1.8)	High (1.5)	High (1.7)	High (1.3)	High (1.5)
Dx	CN	CN	CN	MCI	MCI	AD	AD
PET Braak	II, I-II	III-IV	III-IV	III-IV	III-IV	V-VI	V-VI

FIGURE 1: Cortical patterns of ^{18}F T807 binding. Coronal ^{18}F T807 positron emission tomographic (PET) images (top row) and whole-brain surface renderings of standardized uptake value ratio (SUVR; cerebellar reference; second row) from 3 clinically normal (CN) and 4 impaired (2 mild cognitive impairment [MCI] and 2 mild Alzheimer dementia [AD] dementia) participants. Top: (A) A 71-year-old CN subject with low amyloid β (Aβ) by Pittsburgh compound B (PiB) PET (mean cortical distribution volume ratio [DVR] = 1.0) had low, nonspecific ^{18}F T807 binding in cortex, consistent with a Braak stage less than II/IV. (B) A 74-year-old CN subject with high Aβ (DVR = 1.3) with ^{18}F T807 binding in inferior temporal cortex, left>right, consistent with Braak stage III/IV. (C) A 79-year-old CN subject with high Aβ (DVR = 1.8) had binding in inferior temporal neocortex, consistent with Braak stage of III/IV. B and C show focally intense subcortical uptake that is likely due to off-target binding (see Discussion). (D–G) Cognitively impaired participants all with high Aβ and with successively greater levels of cortical ^{18}F T807 binding successively involving temporal, parietal, frontal, and occipital cortices. Bottom: ^{18}F T807 SUVR calculated at vertices (see Subjects and Methods) indicating the extent of cortical binding, with left hemisphere views (lateral, inferior, superior, medial) at left. The 62-year-old AD dementia patient (G) showed confluent ^{18}F T807 binding that is nearly pancortical, sparing only portions of primary cortex and consistent with Braak stage V/VI. Dx = classification; MMSE = Mini-Mental State Examination; PET Braak = estimate of Braak stages based on the anatomic pattern of T807 binding assessed visually and quantitatively in regions

An assortment of patients and pathology: note the ages and MMSE!

Tau T807 suvr

Tau T807-contrast views



MMSE	30	30	29	27	26	23	11
amyloid: PiB (DVR)	Low (1.0)	High (1.2)	High (1.8)	High (1.5)	High (1.7)	High (1.5)	High (1.5)
Dx	CN	CN	CN	MCI	MCI	AD	AD
tau-staging PET Braak	0, I-II	III-IV	III-IV	III-IV	III-IV	V-VI	V-VI

a good figure needs no legend!

MOLECULAR BASIS OF T807, OTHER TAU PROBES: see Chapter 18

MMSE: Mini-Mental Status Exam. **PiB**: Pitts. Compound B. **Dx**: Differential Diagnosis

"SPM contrast" is the visualization of PET signal onto an MRI map, in this case showing the intensity of the T807 in mci/AlzD patients relative to controls. The T807 signal was elevated in the MCI/AD group in widespread neocortical regions, most prominently in inferior and lateral temporoparietal, parieto-occipital, and posterior cingulate/precuneus...

... with increasing tau burden.

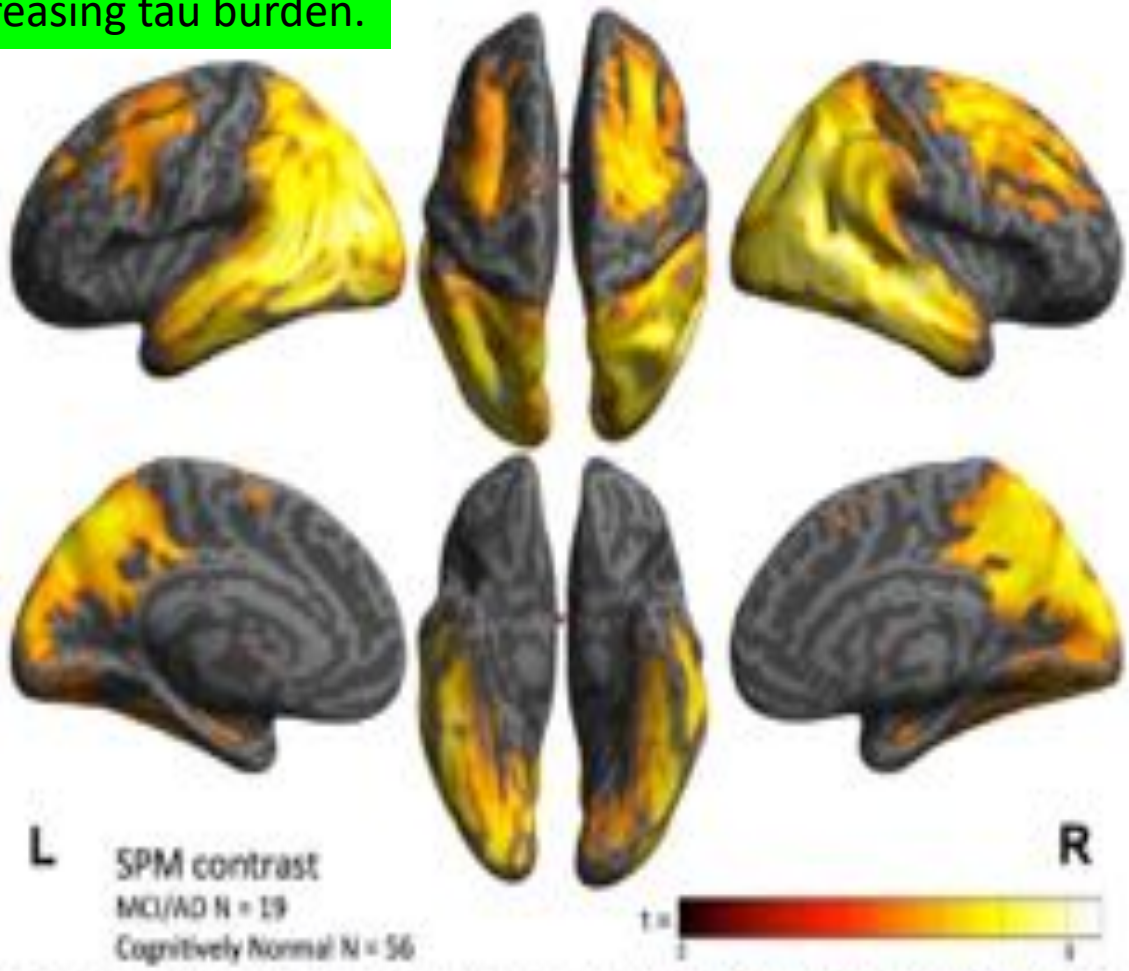


FIGURE 2: Cortical distribution of T807 binding: contrast between the combined mild cognitive impairment (MCI)/Alzheimer disease (AD) group (n = 19) and the cognitively normal group (n = 56; threshold $p < 10^{-3}$).

contrast: yellow means greatest difference btw AlzD and normal brains

← nice lut

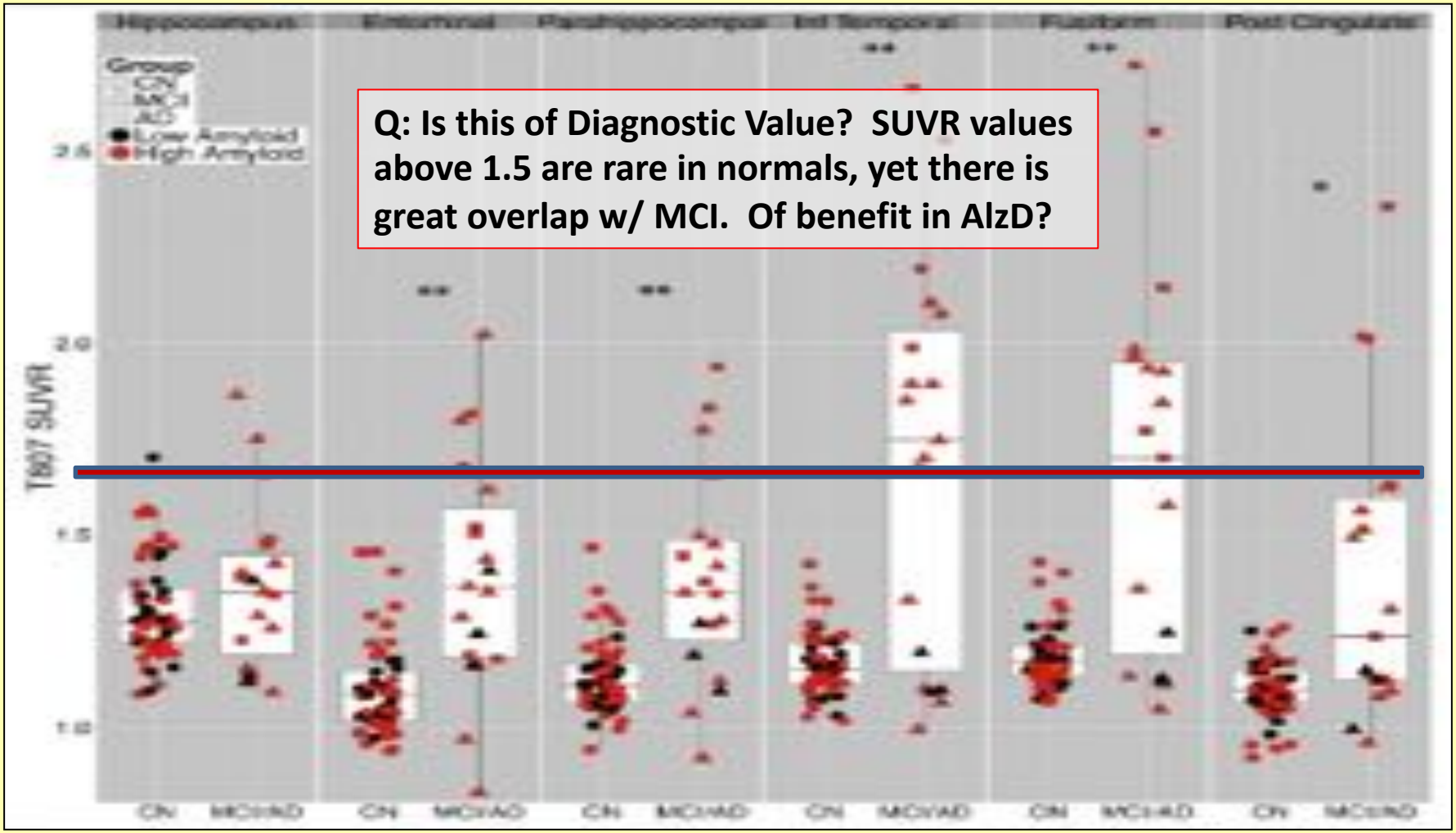
lut = lookup table

Regional analysis of both TAU and PiB for CNs vs. mci/alzD

THM of paper: we can now see Tau inside living brains AND this correlates with **progression** of AlzD, including MCI.

CHAT DEBATE: Is Tau-PET **BETTER** than PiB-PET?

← new edit



Q: Is this of Diagnostic Value? SUVR values above 1.5 are rare in normals, yet there is great overlap w/ MCI. Of benefit in AlzD?

Another THM from paper:

spread of T807 helps confirm the tau-spread hypothesis, i.e. our bedrock view that pathology spreads from ERC outward

OTHERWISE: **SKIP THIS SLIDE**: unless you want to explain Cohen d to me!

TABLE 2. T807 Binding in ROIs, Comparing MCI, AD, and Combined MCI/AD Groups with CN Subjects

ROI	CN, n = 56	MCI, n = 13	MCI, *d*	AD, n = 6	AD, *d*	MCI/AD	MCI/AD, *d*
PiB DVR	1.24 (0.18)	1.48 (0.30)	1.12[a]	1.76 (0.21)	2.72[b]	1.57 (0.30)	1.50[b]
Inferior temporal	1.17 (0.08)	1.47 (0.40)	1.60	2.19 (0.36)	7.63[b]	1.69 (0.51)	1.97[c]
Fusiform	1.18 (0.08)	1.49 (0.39)	1.70	2.09 (0.46)	5.87[b]	1.68 (0.49)	1.94[b]
Posterior cingulate	1.10 (0.07)	1.24 (0.23)	1.22[a]	1.73 (0.48)	3.98[b]	1.40 (0.39)	1.43[b]
Parahippocampal	1.13 (0.09)	1.31 (0.25)	1.37[a]	1.54 (0.28)	3.32[b]	1.38 (0.27)	1.61[b]
Entorhinal	1.10 (0.12)	1.36 (0.32)	1.47[c]	1.48 (0.26)	2.76[b]	1.40 (0.26)	1.62[b]
Hippocampus	1.31 (0.13)	1.36 (0.23)	0.32	1.39 (0.19)	0.58	1.37 (0.22)	0.38

d = Cohen *d*, effect size of group versus CN.

[a] $p < 0.05$.

[b] $p < 10^{-3}$.

[c] $p < 0.01$, as defined by Mann–Whitney *U* probability value of group versus CN. The Bonferroni-adjusted probability value threshold for 6 brain regions is 0.008. We did not correct for analyses of different subgroups of subjects within regions due to the high correlation among these subgroups and overconservatism of Bonferroni in that setting.

AD = Alzheimer disease dementia; CN = cognitively normal; DVR = distribution volume ratio; MCI = mild cognitive impairment; PiB = Pittsburgh compound B; ROI = region of interest.

see Notes Below re: Cohen d parameter

Good Grief: authors did not bother to explain this Figure (one line in Results), so I won't bother trying to figure out what exactly they are trying to displayed here.

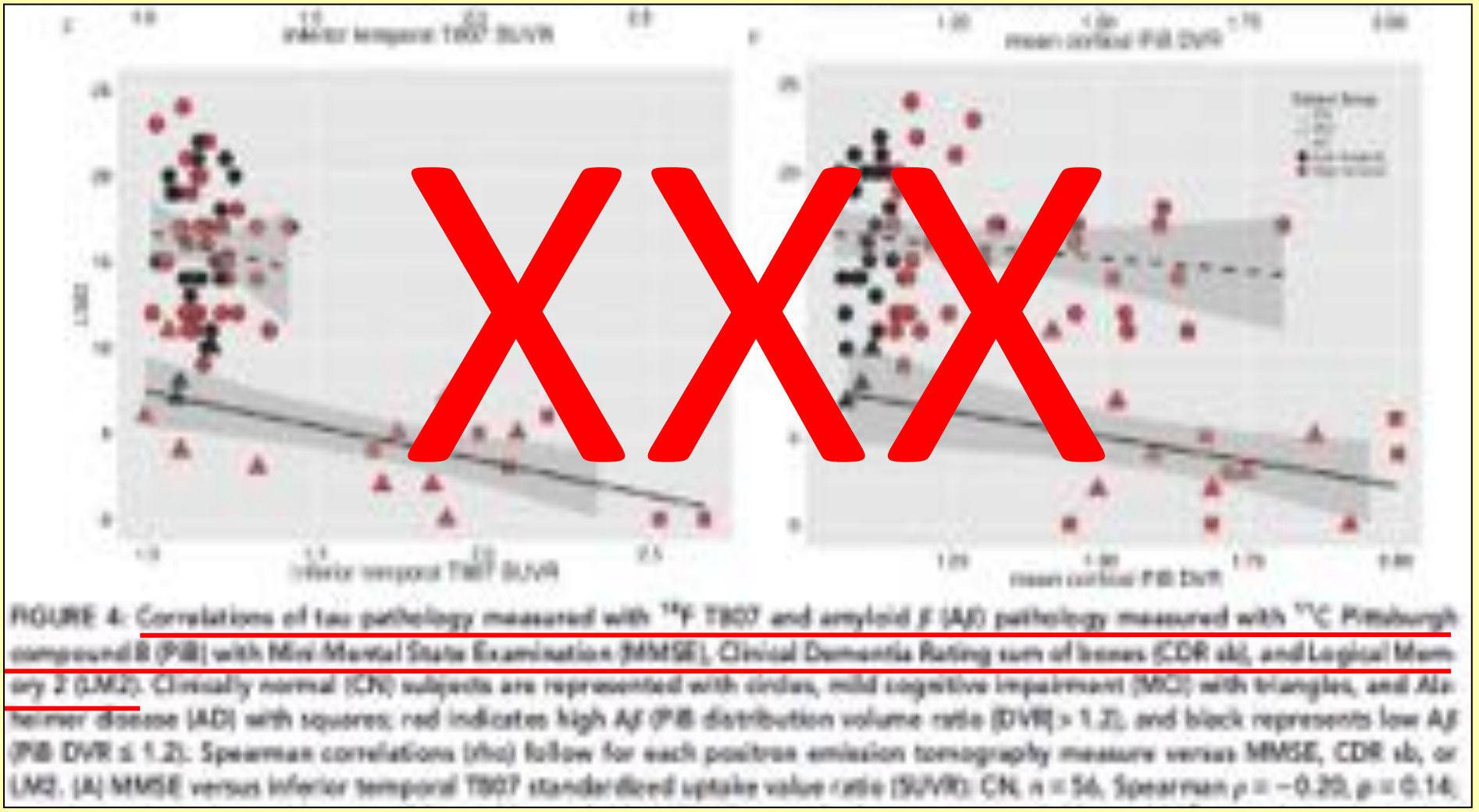


FIGURE 4: Correlations of tau pathology measured with ^{18}F T807 and amyloid β (Aβ) pathology measured with ^{11}C Pittsburgh compound B (PiB) with Mini Mental State Examination (MMSE), Clinical Dementia Rating sum of boxes (CDR sb), and Logical Memory 2 (LM2). Clinically normal (CN) subjects are represented with circles, mild cognitive impairment (MCI) with triangles, and Alzheimer disease (AD) with squares; red indicates high Aβ (PiB distribution volume ratio [DVR] > 1.2), and black represents low Aβ (PiB DVR ≤ 1.2). Spearman correlations (rho) follow for each positron emission tomography measure versus MMSE, CDR sb, or LM2. (A) MMSE versus inferior temporal T807 standardized uptake value ratio (SUVR): CN, $n = 56$, Spearman $\rho = -0.20$, $p = 0.14$;

ignore: (E) is Logical Memory 2 score vs. IT-T807 while (F) plots LM2 vs. PiB

Logical Memory entails recall of details from reading passages (incl. gist and verbatim recall)

Association of cortical PiB with Inferior Temporal Cortex T807 suggests (methinks) a strong involvement of both pathologies in the cognitive damage done in temporal cortex.

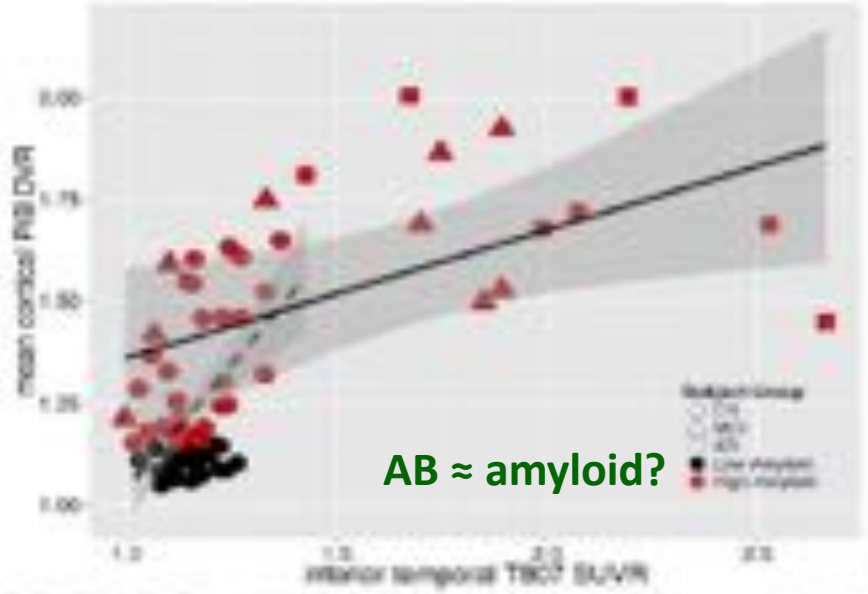


FIGURE 5: Correlations of tau pathology measured with inferior temporal ^{18}F T807 and amyloid β (Aβ) pathology measured with mean cortical ^{11}C Pittsburgh compound B (PiB). Clinically normal (CN) subjects are represented with circles, mild cognitive impairment (MCI) with triangles, and Alzheimer disease (AD) with squares; red indicates high Aβ (PiB distribution volume ratio [DVR] > 1.2), and black indicates low Aβ (PiB DVR ≤ 1.2). Separate linear fit lines

staging predictions, we did not see a consistent pattern of successively greater ^{18}F T807 in the hippocampus with more advanced disease. We postulate that this observation may be due in part to off-target binding adjacent to hippocampus; however, PET detection of 18F T807 binding in hippocampus is particularly susceptible to artifact when atrophy is a factor, due to small volume and surrounding cerebrospinal fluid.

Second, ^{18}F T807 binding to an area near the substantia nigra is more likely to be off-target because limited neurofibrillary pathology occurs in this structure. The potential for off-target binding of ^{18}F T807 or other ligands may be a limitation for their use in staging tau pathology. Ex vivo autoradiography may clarify this issue by identifying off-target ^{18}F T807 binding, including sources of a suspected confound of signal spill-in from structures adjacent to the hippocampus (see Fig 1).[33] Postmortem correlative studies are clearly necessary, as they continue to be for Aβ PET, to identify biological substrates. However, preliminary experience with ^{18}F T807 suggests that a PET-based staging of AD pathology could be established on the basis of cortical ^{18}F T807

All high-Tau are red (high AB)
All low-AB are low Tau
some low Tau are CogN & high AB

↑↑ Off-Target Binding

PET RESULTS: AB predicts progression, Tau predicts severity. How might this be useful?

Tau Positron Emission Tomographic Imaging in Aging and Early Alzheimer Disease

What have we Learned?

- **there are 2 distinct ways now to image AlzD-specific pathology in living humans**
  [this in addition to generic WM-damage, atrophy and Δ's in functional connectivity]
- **some cog-normals have T807 (and PiB)**
- **52 year old is markedly impaired (MMSE=11) w/ massive T807 signal = EOAD?**
- **off-target binding seen in vicinity of hippocampus. UNCLEAR implications**
- **correlational variability of PET vs. dementia ≈ post-mortem vs. dementia**

.

- **authors show the utmost in political correctness, but**
- is congruent with tau hypothesis (vs. amyloid school of dementia) ← ****old view****

What have we Learned? a few more things to consider…

medicare, plasma AB42, Lady Christchurch, . . .

anyone here cognitively normal?

The Washington Post

PET scans show many Alzheimer's patients may not actually have the disease

2017 - 2019

By Tara Bahrampour
July 19, 2017

A significant portion of people with mild cognitive impairment or dementia who are taking medication for Alzheimer's may not actually have the disease, according to interim results of a major study underway to see how PET scans could change the nature of Alzheimer's diagnosis and treatment.

The findings, presented Wednesday at the Alzheimer's Association International Conference in London, come from a four-year study launched in 2016 that is testing over 18,000 Medicare beneficiaries with mild cognitive impairment (MCI) or dementia to see if their brains contain the amyloid plaques that are one of the two hallmarks of the disease.

4,000 Medicare patients (of 18,000 planned): Percentage of those diagnosed with MCI / AlzD that are actually PET-amyloid positive: MCI=54% AlzD=70%

"If someone had a putative diagnosis of Alzheimer's disease, they might be on an Alzheimer's drug like Aricept or Namenda," **said James Hendrix, the** Alzheimer Association's director of global science initiatives who co-presented the findings.

← **i.e. NOT AlzD!**

AMERICAN ACADEMY OF NEUROLOGY.

any Stones fans?

April 09, 2019; 92 (15 Supplement) MAY 6, 2019

Amyloid PET Leads to Frequent Changes in Management of Cognitively Impaired Patients: the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study (Plen01.001)

Gil Rabinovici, Constantine Gatsonis, Charles Apgar, Kiran Chau, Rachel Whitmer, Maria Carrillo

First published April 16, 2019.

but if you have MCI *and* are PIB+, you getting AlzD!

https://n.neurology.org/content/92/15_Supplement/Plen01.001.abstract

Differences in gray and white matter ^{18}F-THK5351 uptake between behavioral-variant frontotemporal dementia and other dementias

2019

Hye Joo Son[1] · Jungsu S. Oh[1] · Jae Hoon Roh[2] · Sang Won [illegible] · Jae Seung Kim[1]

Any FTD PET? "we're trying"

Received: 21 March 2018 / Accepted: 1 August 2018 / Published online: 14 August 2018

European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:357–366

Abstract

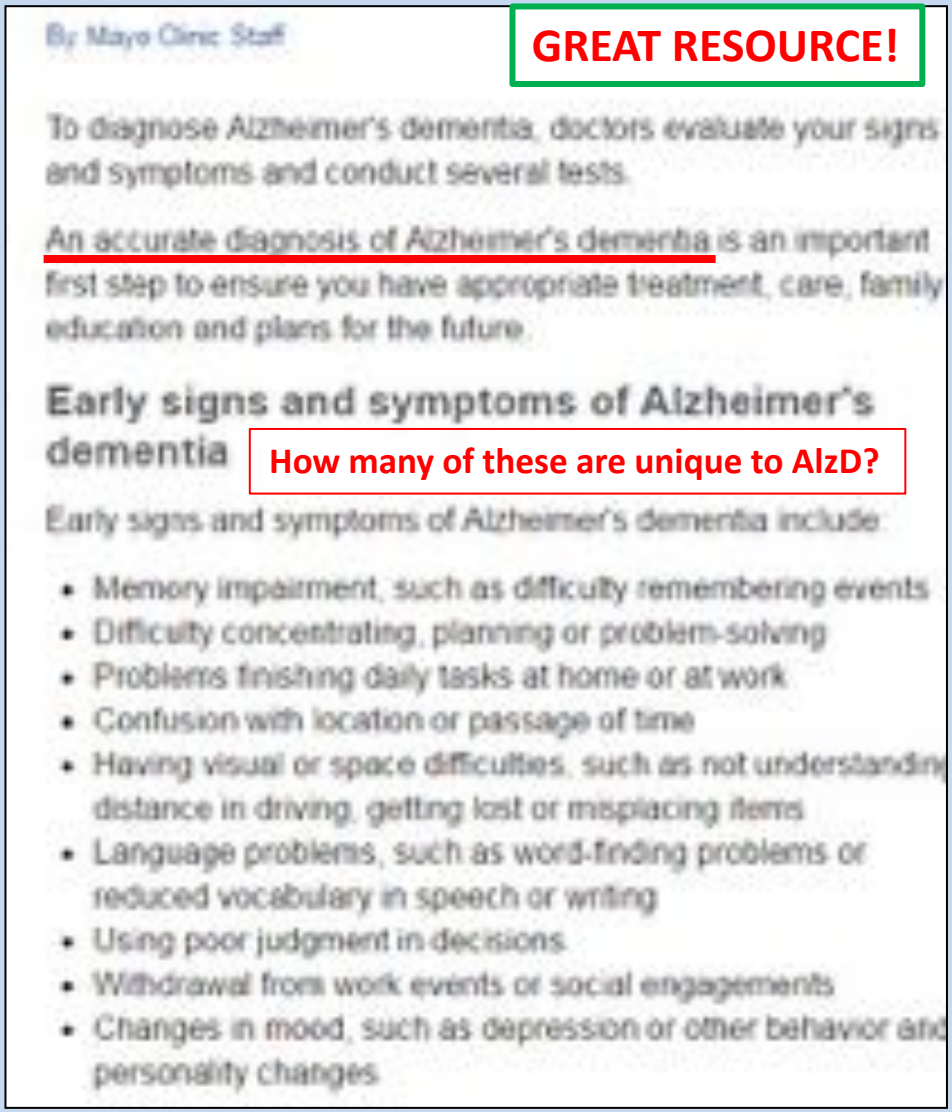
Purpose We investigated the regional distribution of ^{18}F-THK5351 uptake in gray (GM) and white matter (WM) in patients with behavioral-variant frontotemporal dementia (bvFTD) and compared it with that in patients with Alzheimer's disease (AD) or semantic dementia (SD).

Methods ^{18}F-THK-5351 positron emission tomography (PET), ^{18}F-florbetaben PET, magnetic resonance imaging, and neuropsychological testing were performed in 103 subjects including 30, 24, 9, and 8 patients with mild cognitive impairment, AD, bvFTD, and SD, respectively, and 32 normal subjects. Standardized uptake value ratios (SUVRs) of ^{18}F-THK-5351 PET images were measured from six GM and WM regions using cerebellar GM as reference. GM and WM SUVRs and WM/GM ratios, the relationship between GM SUVR and WM/GM ratio, and correlation between SUVR and cognitive function were compared.

Results In AD, both parietal GM ($p < 0.001$) and WM ($p < 0.001$) SUVRs were higher than in bvFTD. In AD and SD, the WM/GM ratio decreased as the GM SUVR increased, regardless of lobar region. In AD, memory function correlated with parietal GM ($\rho = -0.74$, $p < 0.001$) and WM ($\rho = -0.53$, $p < 0.001$) SUVR. In SD, language function correlated with temporal GM SUVR ($\rho = -0.69$, $p = 0.006$). The frontal WM SUVR was higher in bvFTD than in AD ($p = 0.003$) or SD ($p = 0.017$). The frontal WM/GM ratio was higher in bvFTD than in AD ($p < 0.001$). In bvFTD, the WM/GM ratio increased more prominently than the GM SUVR only in the frontal lobe ($R^2 = 0.026$). In bvFTD, executive function correlated with frontal WM SUVR ($\rho = -0.64$, $p = 0.014$).

Conclusions Frontal WM ^{18}F-THK5351 uptake was higher in bvFTD than in other dementias. The increase in frontal WM uptake was greater than the increase in GM uptake and correlated with executive function. This suggests that frontal lobe WM ^{18}F-THK5351 uptake reflects neuropathological differences between bvFTD and other dementias.

NEXT: Will post-mortem *diagnosis* of AlzD die out?



By Mayo Clinic Staff

GREAT RESOURCE!

To diagnose Alzheimer's dementia, doctors evaluate your signs and symptoms and conduct several tests.

An accurate diagnosis of Alzheimer's dementia is an important first step to ensure you have appropriate treatment, care, family education and plans for the future.

Early signs and symptoms of Alzheimer's dementia

How many of these are unique to AlzD?

Early signs and symptoms of Alzheimer's dementia include:

- Memory impairment, such as difficulty remembering events
- Difficulty concentrating, planning or problem-solving
- Problems finishing daily tasks at home or at work
- Confusion with location or passage of time
- Having visual or space difficulties, such as not understanding distance in driving, getting lost or misplacing items
- Language problems, such as word-finding problems or reduced vocabulary in speech or writing
- Using poor judgment in decisions
- Withdrawal from work events or social engagements
- Changes in mood, such as depression or other behavior and personality changes

But is this AlzD diagnosis definitive?
What are patients told? Do they get PET scans? Lumbar punctures? What benefits ensue from invasive procedures? **see notes**

My "CLAIM": Alzheimer's Disease can be diagnosed only at autopsy because one might find at Autopsy definitive evidence for a different disease, with few plaques or tangles, thus proving that the person did not have AlzD. *#Scenario1*

← **This working, clinical definition** of the *Mayo Clinic*, might not match the accepted scientific or research or MD definitions.

My Claim vs. Mayo's Story:
It is true that living biomarkers might come to predict a set of core AlzD symptoms better than post-mortem pathology, but as long as AlzD is defined by plaques and tangles, there remains the possibility that one might encounter living cases of "severe AlzD" patients, but later find no post-mortem plaques or tangles.

PREDICTION: *this view will fade with time...*

Prodromal = Incipient Symptoms;
quasi predictive of oncoming disease

Personal View
of Clifford Jack

amnestic MCI = **prodromal AlzD**
pre-MCI but PIB+ = **preclinical AlzD**

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

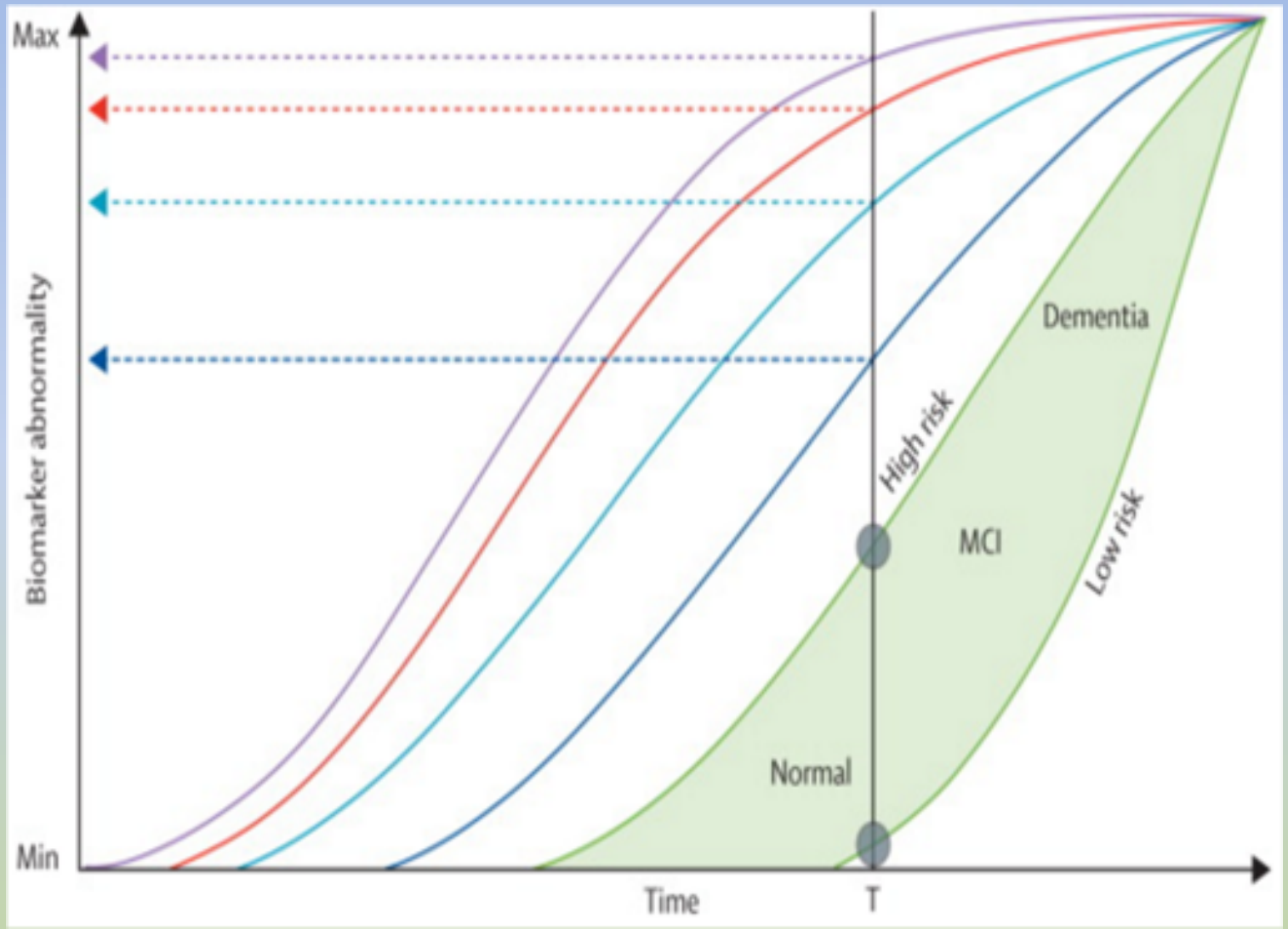
In 2010, we put forward a hypothetical model of the major biomarkers of Alzheimer's disease (AD). The model was received with interest because we described the temporal evolution of AD biomarkers in relation to each other and to the onset and progression of clinical symptoms. Since then, evidence has accumulated that supports the major assumptions of this model. Evidence has also appeared that challenges some of our assumptions, which has allowed us to modify our original model. Refinements to our model include indexing of individuals by time rather than clinical symptom severity; incorporation of interindividual variability in cognitive impairment associated with progression of AD pathophysiology; modifications of the specific temporal ordering of some biomarkers; and recognition that the two major proteinopathies underlying AD biomarker changes, amyloid β (Aβ) and tau, might be initiated independently in sporadic AD, in which we hypothesise that an incident Aβ pathophysiology can accelerate antecedent limbic and brainstem tauopathy.

Department of Radiology
Department of Neurology
Department of Biomedical Statistics and Informatics

What are the BEST Biomarkers for AlzD?
it depends upon your assumptions, theory of disease

MYSTERY GRAPHS

stay tuned….



student notes below: *not* edited

Temporal Ordering of Biomarker Abnormalities

Study followed 137 patients an average of 9.2 years w/ baseline CSF

- all patients diagnosed with MCI at baseline
- 54% of patients progressed to AD
- **CSF Aβ fully abnormal 5-10 years or more befo diagnosis**
- **both CSF t-tau and p-tau became progressively more abnormal** as the time to dementia diagnosis decreased
- study concluded that **amyloid deposition is an early event** that precedes hippocampal atrophy

SKIP FOR NOW:
reconciling w/ Chapter 19

2nd study followed up on individuals w/ mild AD using longitudinal FDG PET and amyloid PET concluded that amyloid deposition was static (little change in extent over time) whereas expansion of FDG hypometabolism was continuing with time

Overall:

amyloid biomarkers become abnormal first, followed by biomarkers of neurodegeneration and then clinical symptoms

p-tau = hyperphosphorylated tau. t-tau = total tau.

Tau Pathology & Amyloid Hypothesis: *student notes*

Tau Pathology

- begins in the locus coeruleus and then spreads to other brainstem nuclei, ERC, perhaps by cell to cell transmission. **Old Don Note:** sketchy basis for this claim. **DQ: WHY is (was) this improbable?**

Controversies

- based on its pathology, it has been proposed that **subcortical tau deposition is the starting point of the AD pathophysiological cascade**, beginning as early as the first decade of life
- alternative point of view suggests that **since subcortical and medial temporal limbic tauopathy occurs in such a high proportion of clinically asymptomatic individuals, subcortical tau deposition does not represent the beginning** of the AD pathophysiological cascade *but instead is a variant of ageing that alone might lead to subtle cognitive impairm*

Amyloid Hypothesis

- assumes serial casual events, with abnormal
  causes tau hyperphosphorylation and AB accumulation might be independent processes that share a common upstream cause
  - specifically protracted exposure to upregulation of cellular activity related to neural plasticity
  - also suggested that they are independent processes but with pathogenic synergy

SKIP FOR NOW:
reconciling w/ Chapter 19

Integration of Conflicting Theories

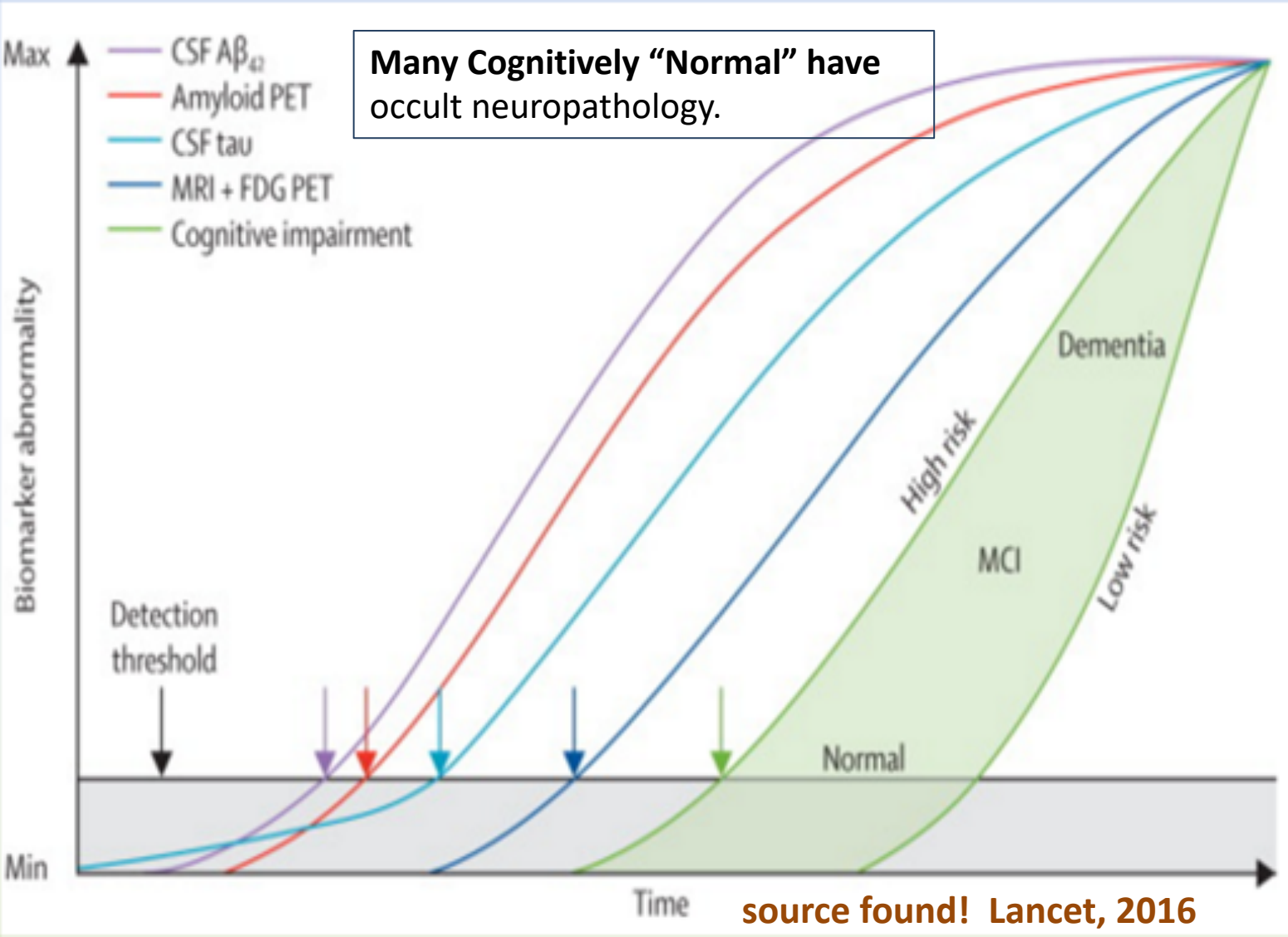
Continues the theme that AB pathophysiology and tauopathy arise independently

SKIP FOR NOW:
reconciling w/ Chapter 19

- recognizes that the earliest evidence of AD pathophysiological changes lies beneath detection threshold of in-vivo AD biomarkers
- proposes that subcortical tauopathy is the first AD pathophysiological process to arise in many individuals and is only detectable by immunostaining methods however, it does not itself lead to AD
- AB pathophysiology arises later and independently from pre-existing tauopathy
- As AB pathophysiological changes qualitatively transform (mechanism remains unknown), it accelerates the antecedent subcortical tauopathy leading to neocortical spread of NFT
- **acceleration of initial slowly developing tauopathy occurs only after AB biomarkers become abnormal**
  - FDG-PET and MRI biomarker changes then occur followed by subsequent onset of overt clinical symptoms

Integration Model iaw Students

X-MYSTERY GRAPH



An Operational Approach to NIA-AA Criteria for Preclinical Alzheimer's Disease

Ann Neurol. 2012 June ; 71(6): 765–775.

2012

Objective—A workgroup commissioned by the Alzheimer's Association (AA) and the National Institute on Aging (NIA) recently published research criteria for preclinical Alzheimer's 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 cut-points. A group of 450 cognitively normal (CN) subjects from a population based sample was used to develop cognitive cut-points and to assess population frequencies of the different preclinical AD stages using different cut-point criteria.

Results—The new criteria subdivide the preclinical phase of AD into stages 1–3. To classify our CN subjects, two 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 cut-points 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

orresponding author: Clifford R. Jack, Jr., Department of Radiology, Mayo Clinic and Foundation, 200 First Street SW, Rochester, N 55905. Phone: 507-284-9778, Fax: 507-284-2511, jack.clifford@mayo.edu

- **PIB-PET imaging**
- **18-FDG PET** as biomarker of neurodegeneration
- **C.I. = Cognitive Impairment**

Staging of Pre-Clinical AlzD

0 = no biomarker or C.I.

SNAP = non-AlzD

Stage 1 to 3: nx slide

3 = subtle C.I.

QED: affirmed 3 NIA categories

and added 2 more

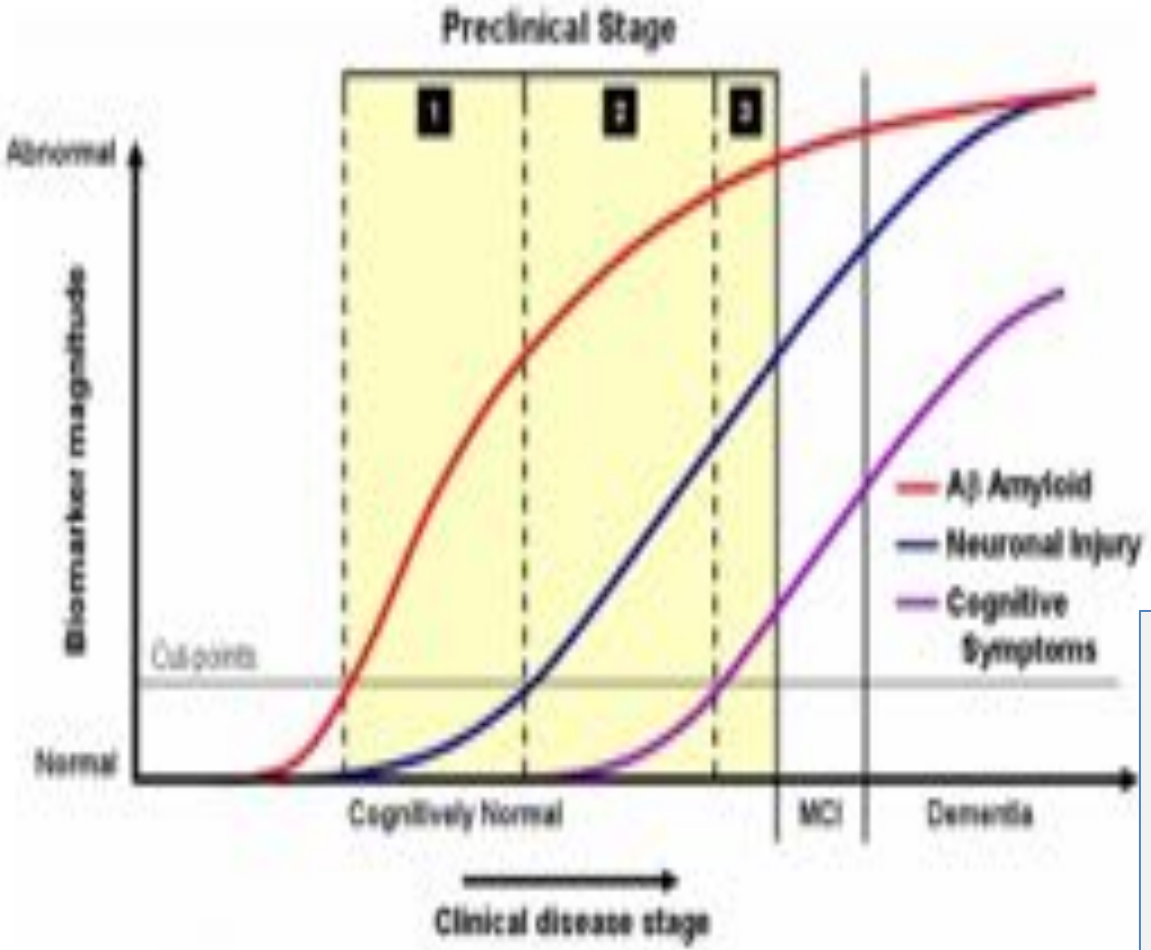


Figure 1.
Preclinical stages 1–3 of AD (indicated by the yellow highlighted sections) in relation to our model of biomarkers of the AD pathological cascade. The horizontal axis indicates clinical stages of AD: cognitively normal, mildly impaired (MCI), and dementia. The vertical axis indicates the changing values of each biomarker – scaled from maximally normal (bottom) to maximally abnormal (top). Aβ amyloid biomarker is PET amyloid imaging (red line). Biomarkers of neuronal injury are FDG-PET or atrophy on MRI (blue line). Onset of worsening of cognitive symptoms is determined from cognitive testing scores (purple line). The horizontal "cut-points" line represents the cut-points used to operationalize preclinical staging.

Cut Points

- Biomarkers are Continuous Tests
- NIA criteria require that every biomarker is scored <u>normal or not</u>
- also applies to cognitive tests
- cannot use autopsy results
  …too many "not dead yet"
- see paper for details on how their cut points were determined
  [optional, paper not assigned]

COGNITIVE TESTING

The neuropsychological battery was constructed as previously described [7, 8]. Domain specific measures are formulated from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Memory Scale-Revised (WMS-R), Auditory Verbal Learning Test (AVLT), Trail Making Test (TMT), category fluency test, and Boston Naming Test (BNT). Four cognitive domains are assessed: Executive (TMT: Part B, WAIS-R Digit Symbol); Language (BNT, category fluency); Memory (WMS-R Logical Memory-II (delayed recall), WMS-R Visual Reproduction-II (delayed recall), AVLT delayed recall); and Visuospatial (WAIS-R Picture Completion, WAIS-R Block Design). Individual test scores were first converted to z-scores using the mean and standard deviation from the MCSA 2004 enrollment visit for subjects that were CN (n=1624). The individual z-scores were averaged to create 4 domain scores which were then also converted to z-scores. A *global cognitive* summary score was formed from the average of the 4 domain z-scores and then converted to a z-score by subtracting the mean and dividing by the standard deviation. This global summary score was used to assess cognitive impairment in our subjects.

Life as a Neuropsychologist

- lots of testing
- lots of analysis
- lots of report writing
- work w/ neurologists, and Social Work!**

****SW is the one way we can actually help families**

Imaging Methods

MRI was performed at 3T with a 3D-MPRAGE sequence [9] Images were corrected for distortion due to gradient non-linearity and for bias field [10, 11]. Our primary MRI measure was hippocampal volume measured with FreeSurfer software (version 4.5.0) [12]. Each subject's raw hippocampal volume was adjusted by his/her total intracranial volume [13] to form an adjusted hippocampal volume (HVa). We calculated HVa as the residual from a linear regression of hippocampal volume (y) versus total intracranial volume (x).

DISCUSSION

Based on our operational approach to the NIA-AA criteria, at 90% biomarker and 10% cognitive cut-points, 31% of our CN subjects met the NIA-AA criteria for preclinical AD (stages 1–3), 43% were in stage 0 and 23% fell into the SNAP category. Only 3% of subjects could not be classified by our approach. The concept of preclinical AD originated with a literature documenting the presence of AD pathology in approximately a third of elderly CN subjects who came to autopsy [24–28]. Many studies have documented the presence of AD pathophysiological processes in living cognitively normal elderly subjects using PIB-PET imaging [17, 23, 29–39], ^{18}FDG-PET imaging [33, 34, 40, 41], CSF assays [20, 42–48], and structural MR [49–56]. We hypothesize that stage 1–3 subjects have entered the AD pathway and, if they live long enough, will progress to incident MCI and then AD dementia. Subjects in stage 0, as defined, neither have subtle cognitive impairment nor abnormal AD biomarkers now. It is possible that some stage 0 subjects could move to stage 1 or beyond in the future.

Approximately a quarter of our CN subjects, 23%, were designated as SNAP. We believe that SNAP does not represent a stage of pre clinical AD, but rather a distinct biologically-based category where amyloid biomarkers are normal but neuronal injury biomarkers are abnormal. We suspect, but can not prove at this time, that such subjects represent the pre clinical stage of non-AD pathophysiological processes. While most cases of dementia in elderly subjects are found at autopsy to have multiple pathologies that include AD, up to one-third are primarily attributable to pathologies other than AD, primarily cerebrovascular disease and synucleinopathy [57–62]. It is therefore expected that preclinical forms of the non-AD pathologies must exist in elderly CN subjects recruited from a population-based sample. Subjects with predominantly cerebrovascular disease or synuclein pathologies but little or no AD pathology should present with a biomarker profile of normal amyloid PET and abnormalities on MRI and FDG [63, 64]. The low proportion of SNAP APOE e4

DQ: Why worry about Pre-AlzD?

QQ: What has this do to w/ C.R.?
[cognitive reserve]

← we need to know HOW LONG*
***every elderly man dies w/ prostate cancer**

SNAP = Suspected Non-AlzD Pathophysiology

SNAP cases: few ApoE4
Stages 1-3: ApoE4 common

deadly syn's = ParkDis, Lewy-body disease

3 reasons. good τ to test, τ to treat, disease mech. insights

2018 version of NIA Framework on AlzD

ELSEVIER

Alzheimer's & Dementia

Alzheimer's & Dementia 14 (2018) 535-562

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

This is NOT a CLINICAL DIRECTIVE: it is a Research Framework

Clifford R. Jack, Jr.[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

NIA honchos

[a]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*

"Disease modifying interventions must engage biologically defined targets, and the dementia syndrome does not denote a specific biological target(s). Furthermore, in order to discover interventions that prevent or delay the initial onset of symptoms a biologically based definition of the disease that includes the preclinical phase is needed"

Supplemental PDF on Factors Associated w/ AlzD. Mainly FYI.
Includes: olfaction, sleep references.

Potential Prodromes for Alzheimer's Disease: A Review

Abstract

Alzheimer's Disease affects millions of people in the United States alone. As the disease progresses it can affect the ability of patients to carry out activities of daily living and therefore their ability to live independently. Because of its severe effects on lifestyle and cognitive functioning, it is important to identify the disease early, providing more opportunities for treatment and prevention plans. The following text discusses some potential early indicators or risk factors for Alzheimer's disease, including depression, loss of olfaction ability, and non-apnea sleep disorders. With more research into the mechanisms of these markers and how Alzheimer's disease can be treated or prevented at signs of onset, there could eventually be a decrease in the number and severity of disease cases in the elderly population.

Mild Cognitive Impairment and Depression

In the study by Makizako et al., researchers investigated the idea that patients with mild cognitive impairment (MCI) and depression together would be more likely to develop dementia than patients with one of those conditions alone [4]. In order to study this, the researchers conducted a longitudinal study amongst a group of approximately 4000 elderly people. Baseline depression and cognitive impairment were assessed at the beginning of the study. After two years, the group was reassessed to see how many people had developed dementia. The study found that initial presence of MCI and depression were significantly correlated with development of dementia later on [4].

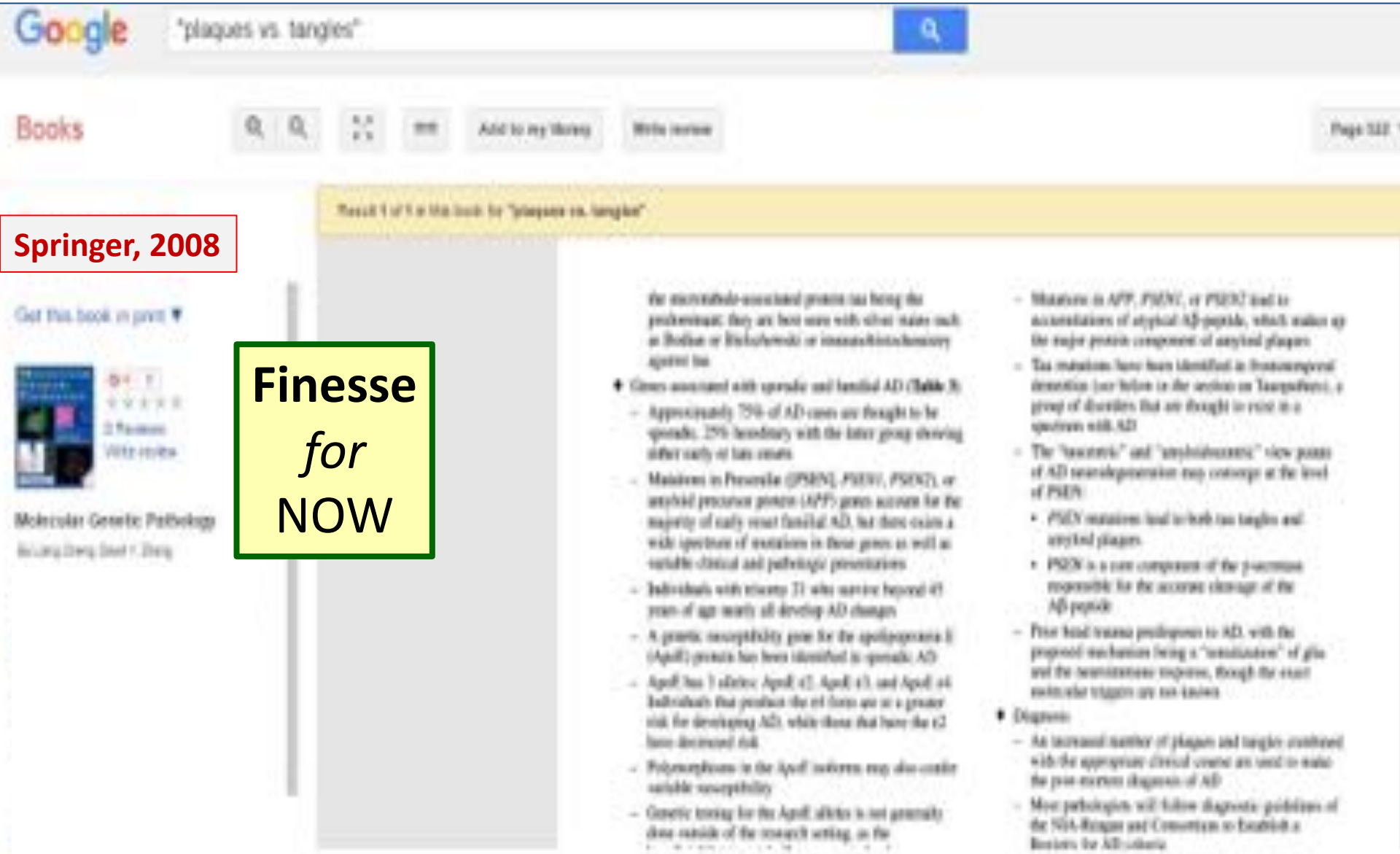
Kida et al. further examined the relationship between MCI subtypes and later onset of

Finesse *for* NOW

Plaques vs. Tangles

or

How I learned to quit worrying about beta-amyloid and love hyperphosphorylated tau



Google "plaques vs. tangles"

2008

Finesse *for* NOW

ratio results only in AD pathology. These findings suggest that the underlying pathologies are specific to the mutations.

There was a long-standing debate about the primacy of plaques vs. tangles as two pathological hallmarks of AD, in the disease pathogenesis. This was resolved by the discovery of mutations in the Microtubule Associated Protein Tau (*MAPT*) gene, which can also cause dementia (Hutton et al., 1998, Poorkaj et al., 1998). It has been shown that missense and splicing mutations in *MAPT* are associated with inherited forms of frontotemporal dementia with parkinsonism, progressive supranuclear palsy and Pick's disease, but not AD. These data showed that tangles could be directly initiated by *MAPT* mutations, resulting a disease with tangles but no plaques. Studies in double transgenic mice which carried mutations in *MAPT* and *APP* showed that elevated Aβ increased the formation of tau deposits in neurons, but not the opposite (Lewis et al., 2001).

um, exactly how resolved is this?

Late-Onset Alzheimer's Disease

While we have some knowledge about the causes of the early onset familial form of AD, age is the single most important risk factor for LOAD (Ritchie and Kildea 1995) and, to date, apolipoprotein E (*APOE*) is the only known genetic risk factor for LOAD. The *APOE* gene is located on chromosome 19. ApoE carries and clears lipids in the bloodstream. The gene has

risk factors: age and ApoE (e4)

LOAD = Late Onset AlzD = sporadic AlzD = AlzD!

While we have some knowledge about the causes of the early onset familial form of AD, age is the single most important risk factor for LOAD (Ritchie and Kildea 1995) and, to date, apolipoprotein E (*APOE*) is the only known genetic risk factor for LOAD. The *APOE* gene is located on chromosome 19. ApoE carries and clears lipids in the bloodstream. The gene has three alleles — *ε2, ε3* and *ε4* — and inheritance of the *ε4* allele is regarded as a risk factor for developing LOAD. Further, it is hypothesized that the *ε2* allele acts as a [illegible] for AD and *ε3* plays a neutral role in disease development. The *APOE* polymorphism has been genotyped in many populations, and consistently show evidence for association with LOAD (Bertram et al., 2007; Finckh et al., 2003). Most individuals homozygous for the *APOE4* allele have been shown to develop LOAD by 80 years of age (Corder et al., 1993). Additionally, in certain populations, like European-Americans, a dose dependent effect is observed. Individuals, heterozygous for the *APOE4* allele, exhibit a threefold increase in risk, while homozygotes show nearly an eightfold increase in risk. Further, it has been shown that the allelic architecture at the *APOE* locus may also explain some of the variance seen in age-of-onset in kindreds with known FAD mutations: mutation carriers who have an *APOE4* allele have an earlier age-of-onset than relatives with a disease causing mutation but no *APOE4* allele (Pastor et al., 2003). A number of hypotheses regarding interactions between APOE and Aβ underlying the pathogenesis of LOAD have been proposed. Patients carrying at least one *APOE4* allele have a greater number of plaques than patients without an *APOE4* allele (Schmechel et al., 1993). *In vitro*, APOE4 binds to Aβ with higher affinity than APOE3

Finesse *for* NOW

Remember Craig's Mice: McDonald's Kills

DQ: are book contents ever *better* than peer-reviewed *articles*? worse?

the *APOE* gene is expressed (Bales et al., 1997). A study by Holtzman *et al.* suggests that APOE4 may influence fibril formation and clearance of Aβ, causing increased Aβ deposition (Holtzman et al., 2000). The same group also showed that mice with *APOE4* alleles developed earlier and more severe pathological phenotypes (Fryer et al., 2003). *In vitro* experiments show that APOE3 binds to tau with a higher affinity than APOE4, suggesting that APOE may also have some effect on neurofibrillary tangles (Strittmatter et al., 1994). Some studies also suggest that promoter variants in *APOE* are associated with LOAD risk (Wang et al., 2000). *APOE2*, which is the rarest allele in most populations, seems to be protective [illegible] in higher age-of-onset of disease. Mouse studies also suggest that Aβ cannot [illegible] deposits in the presence of APOE2 (Fryer et al., 2003). Mayeux et al. showed [illegible] gical effects of head injury may increase risk for AD through a synergistic [illegible] th the *APOE4* allele (Mayeux et al., 1995). The *APOE* genotype has also b[illegible] as a risk factor in a number of other diseases including coronary artery disease (Corder et al., 1996; Contois et al., 1996). *APOE4* is certainly a major risk factor for LOAD, however, there are likely to be other factors, because *APOE4* shows only a modest effect on risk in Amish and Hispanic patients (Pericak-Vance et al., 1996; Tang et al., 1998) and approximately 50% of Caucasian AD patients do not carry an *APOE4* allele.

Finesse *for* NOW

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Gray matter networks and clinical progression in subjects with predementia Alzheimer's disease 2018

Betty M. Tijms[a,*], Mara ten Kate[a], Alida A. Gouw[a,b], Andreas Berta[c], Sander Verfaillie[a], Charlotte E. Teunissen[d], Philip Scheltens[a], Frederik Barkhof[e,f], Wiesje M. van der Flier[a,g]

This SOUNDS normal, but…you say what?

ABSTRACT

1. Which is the *earliest* biomarker sign of AlzD?

a. Tau PET positivity
b. PiB PET positivity
c. plasma Aβ42 levels
d. cortical thinning
e. expanding grey matter networks

2. A common PET-FDG finding when evaluating AlzD patients' blood flow is:

a. hypo-perfusion of posterior neocortical regions
b. hyper-perfusion of posterior neocortical regions
c. hypo-perfusion of prefrontal cortex (PFC)
d. oscillating levels of perfusion in many small pockets in the temporal lobe
e. oscillating levels of perfusion in many small pockets in the occipital lobe

3. 50% of people with this rare mutation show Alzheimer's Disease symptoms by the age of 40:

a. APOE4 allele b. APOE3 allele
c. FDG-18F d. E280A e. AAN56

4. Which of the following ApoE genotypes is associated with the highest risk for developing Alzheimer's disease?

a. E2/E3 b. E3/E3 c. E3/E4 d. E4/E4 e. E5/E5

5. What is Anomia?

a. an inability to recall the names of things, e.g. everyday objects
b. an inability to recognize faces
c. an inability to process the sense of smell
d. an inability to read or write
e. an absence of glucoses

RLA questions:

sending now via email

These are various F-Conn metrics applied to "gray matter" regions.
Ostensibly shows that declining parameters track progression of dementia
BUT these *are not* fMRI-type F-Conn measures and *are not* DTI connectivity measures.
WHAT ARE THEY?

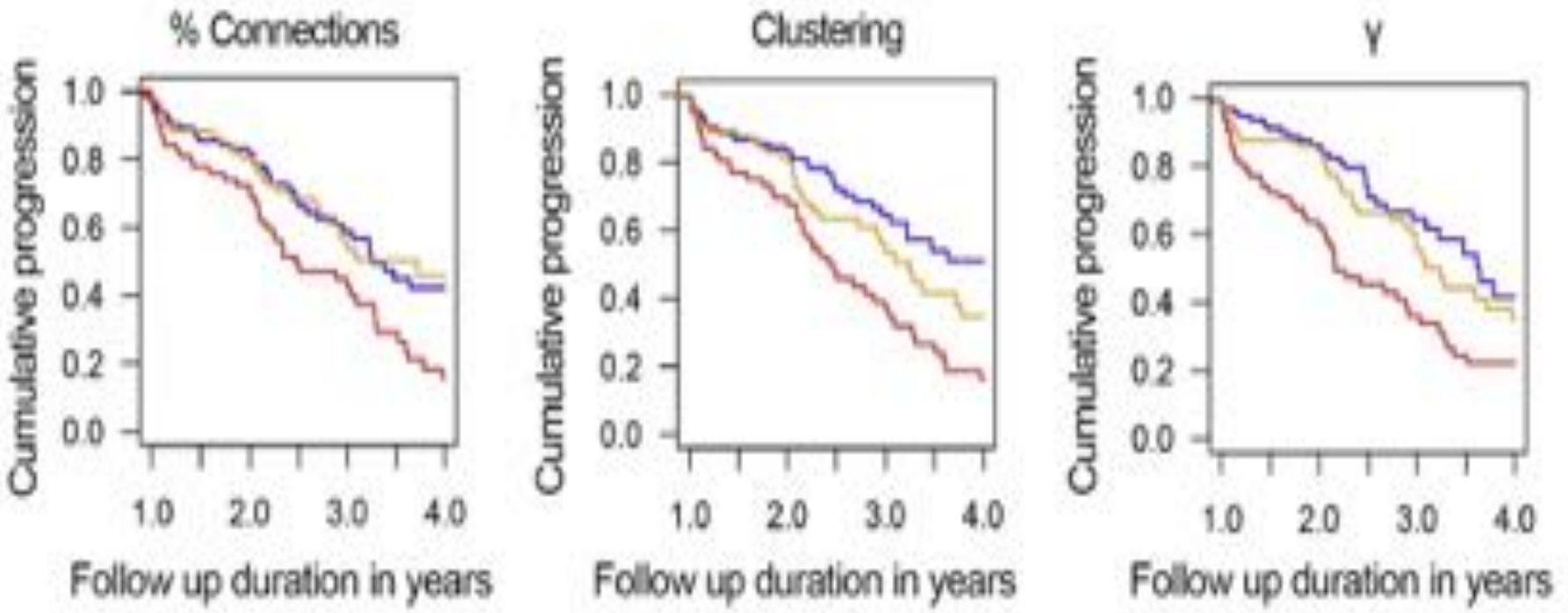


Fig. 1. Clinical progression curves for the time to dementia onset in subjects with subjective cognitive decline or mild cognitive impairment for connectivity density, clustering, and normalized clustering according to tertiles, adjusted for age, gender, total brain volume, baseline cognitive status, and MRI scanner. Clustering and γ were additionally adjusted for connectivity density. Blue lines represent subjects with network property values in the highest tertile, orange with intermediate values, and red line with the lowest values. Abbreviation: MRI, magnetic resonance imaging. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

GM NETWORKS: parameters associated w/ clinical progression in AlzD
Networks were extracted from gray matter structural magnetic resonance imaging (MRI), and 9 parameters were calculated. Cox proportional hazards models were used to test associations between each connectivity predictor and rate of progression to MCI or dementia. After a median time of 2.2 years, 122 (55%) subjects showed clinical progression. Lower network parameter values were associated with increased risk for progression. Our results suggest that at pre-dementia stages, gray matter network parameters may have use to identify subjects who will show fast clinical progression.

ignore plots

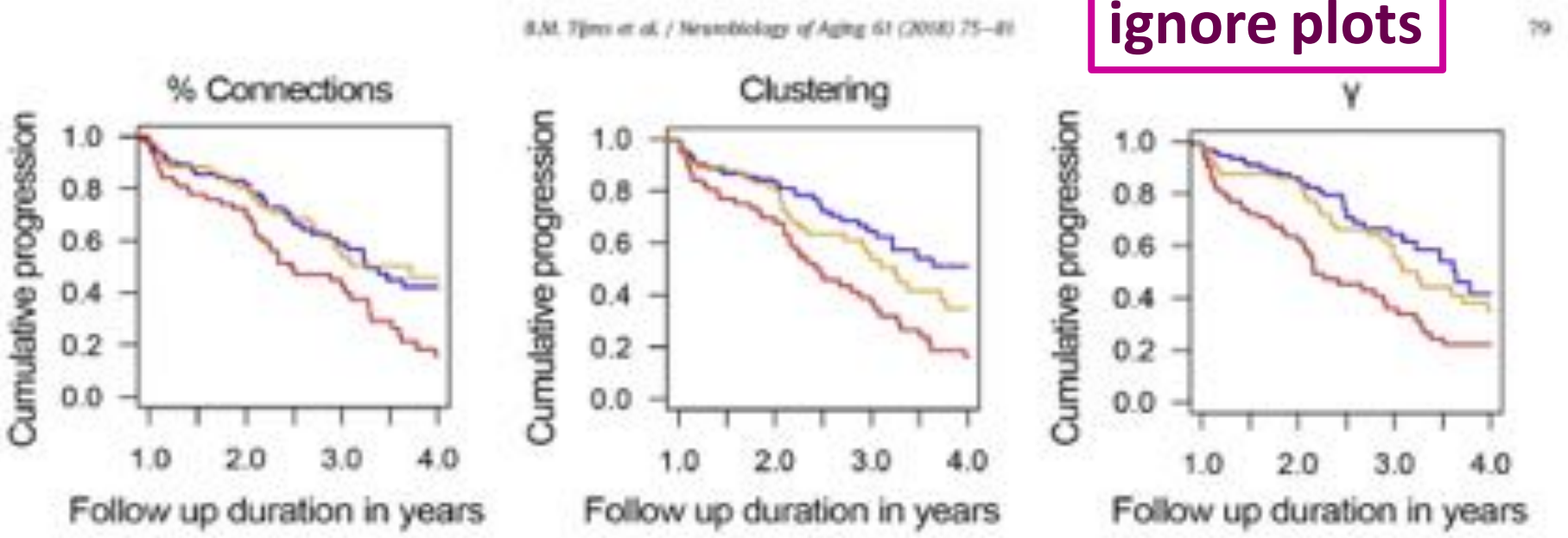


Fig. 1. Clinical progression curves for the time to dementia onset in subjects with subjective cognitive decline or mild cognitive impairment for connectivity density, clustering, and normalized clustering according to tertiles, adjusted for age, gender, total brain volume, baseline cognitive status, and MRI scanner. Clustering and γ were additionally adjusted for connectivity density. Blue lines represent subjects with network property values in the highest tertile, orange with intermediate values, and red line with the lowest values. Abbreviation: MRI, magnetic resonance imaging. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

[preclinical subjects w/ CSF amyloid markers; 62 with subjective cognitive decline]
[160 with MCI; age = 68 ± 8 years; MMSE) = 28 ± 2.4)]

Getting WEIRD in 2012

Similarity-Based Extraction of Individual Networks from Gray Matter MRI Scans

Betty M. Tijms[1,2], Peggy Seriès[1], David J. Willshaw[2] and Stephen M. Lawrie[3]

Saw similarities in retina, LGN, V1
- also saw similarities in DMN components!
- but seriously: is *THIS* ANYTHING?

The characterization of gray matter morphology of individual brains is an important issue in neuroscience. Graph theory has been used to describe cortical morphology, with networks based on co-variation of gray matter volume or thickness between cortical areas across people. Here, we extend this research by proposing a new method that describes the gray matter morphology of an individual cortex as a network. In these large-scale morphological networks, nodes represent small cortical regions, and edges connect regions that have a statistically similar structure. The method was applied to a healthy sample (n = 14, scanned at 2 different time points). For all networks, we described the spatial degree distribution, average minimum path length, average clustering coefficient, small-world property, and betweenness centrality (BC). Finally, we studied the reproducibility of all these properties. The networks showed more clustering than random networks and a similar minimum path length, indicating that they were "small world." The spatial degree and BC distribution corresponded closely to those from group-derived networks. All network property values were reproducible over the 2 time points examined. Our results demonstrate that intracortical similarities can be used to provide a robust statistical description of individual gray matter morphology.

connected when they covary in thickness or volume across individuals (He, Chen, et al. 2007; Bassett et al. 2008; Chen et al. 2008; He et al. 2008). Such an approach requires mapping of individual brains into a standard space and requires prior models to extract anatomical regions. These requirements might obscure subtle structural differences that are of particular interest in clinical populations. Therefore, it is important to study gray matter networks derived from individual cortices. In order to do this, we propose to represent the cortical morphology of individual subjects as networks, using information about the similarity of gray matter structure within the cortex.

Covariation of cortical morphology might be related to anatomical connectivity, induced by mutually trophic influences (Pezawas et al. 2004) or caused by experience-driven plasticity (e.g., Andrews et al. 1997; Draganski et al. 2004; Mechelli et al. 2004). Lerch et al. (2006) were the first to show that cortical thickness correlations qualitatively match a diffusion tensor imaging (DTI) tract track, implying that anatomical connectivity could be measured indirectly using information from the cortical surface. In animal tracer

and THIS derives from work by…**Ed Bullmore**! Investigation underway, **subpoenas issued**…

Imaging structural co-variance between human brain regions

Aaron Alexander-Bloch[1,2,3], Jay N. Giedd[1] and Ed Bullmore[3,4,5]

Abstract | Brain structure varies between people in a markedly organized fashion. Communities of brain regions co-vary in their morphological properties. For example, cortical thickness in one region influences the thickness of structurally and functionally connected regions. Such networks of structural co-variance partially recapitulate the functional networks of healthy individuals and the foci of grey matter loss in neurodegenerative disease. This architecture is genetically heritable, is associated with behavioural and cognitive abilities and is changed systematically across the lifespan. The biological meaning of this structural co-variance remains controversial, but it appears to reflect developmental coordination or synchronized maturation between areas of the brain. This Review discusses the state of current research into brain structural co-variance, its underlying mechanisms and its potential value in the understanding of various neurological and psychiatric conditions.

Nature Reviews Neurosci. - 2013

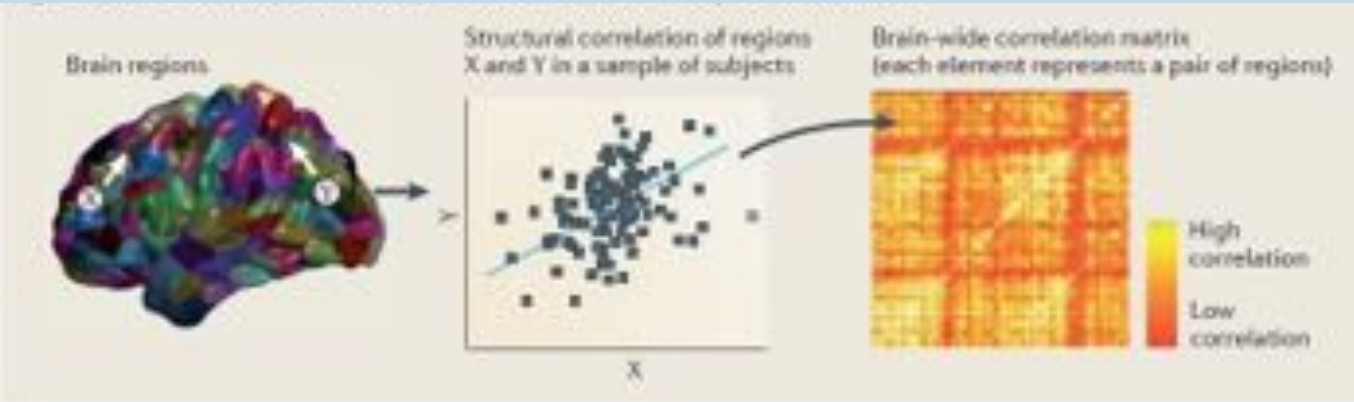
Gray Matter Networks

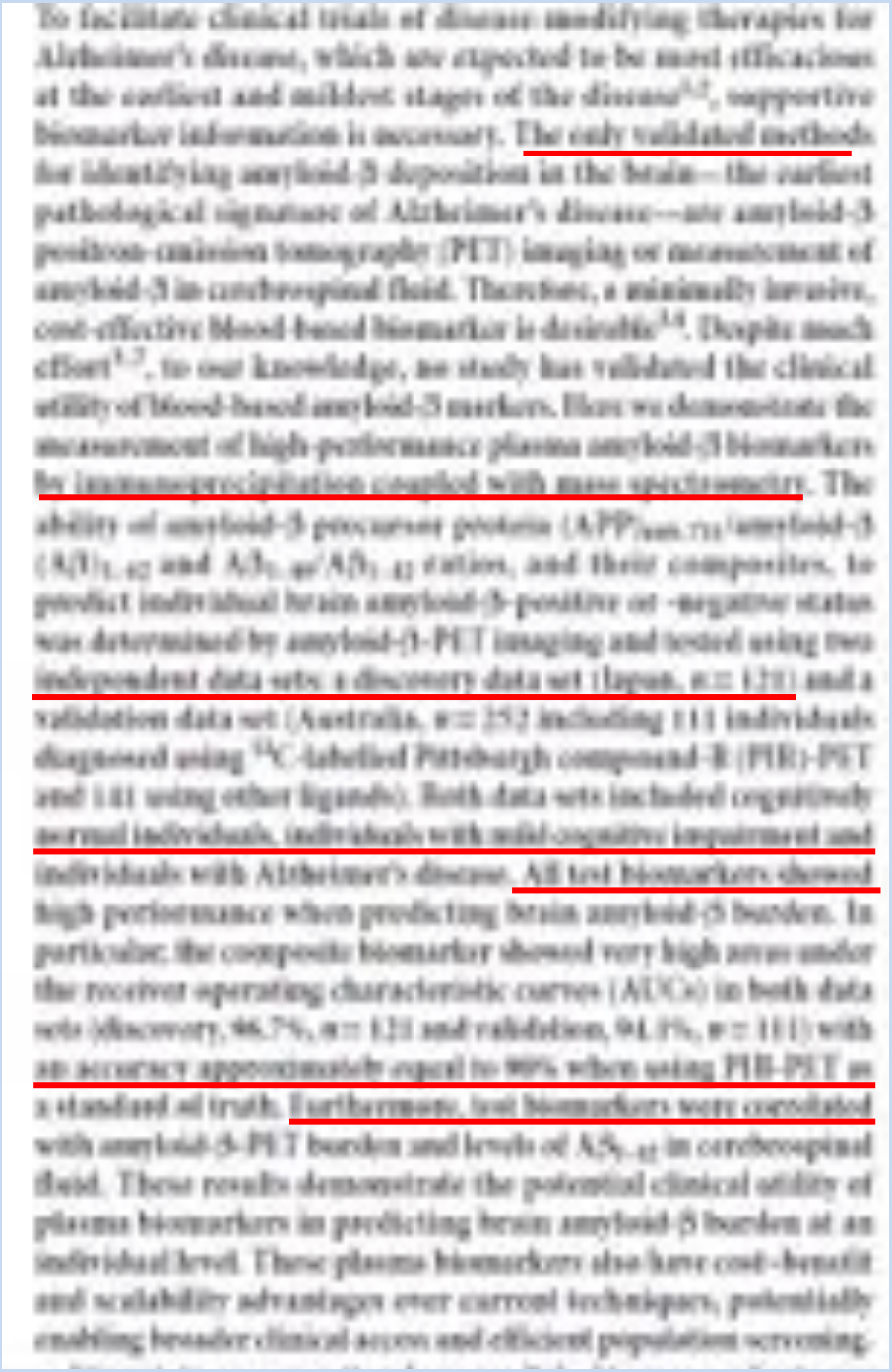
- **not obviously "distinguished"**
- **all regions in neocortex are richly interconnected**
- **no way, no how!**

Topology
The pattern of connections or relations between nodes within a network.

Segregation
The existence, in the brain, of relatively distinct anatomical, physiological or functional units

Modularity





An AlzD BLOOD TEST!

LETTER

Nature, 2018

doi:10.1038/nature25456

High performance plasma amyloid-β biomarkers for Alzheimer's disease

Akinori Nakamura[1], Naoki Kaneko[2], Victor L. Villemagne[3,4], Takashi Kato[2,3], James Doecke[5], Vincent Doré[3,4], Chris Fowler[5],

Reports detection of plasma AB!

only "validated AB tests" were PET, CSF

they used immuno-precipitation w/ MALDI/TOV

were able to quantify blood AB!

2 studies with normals, MCI, AlzD

looked at ratios (e.g. AB40/AB42)

achieved 90% accuracy = PiB

ratio correlated w/ PiB burden, CSF AB42

Q: how available is mass spectrometry?

Q: anyone down with **ROC** curves/analysis?

receiver-operating curves, AUCs

everybody wants to do the biology, nobody wants to do the stats

LETTER

Nature, 2018

High performance plasma amyloid-β biomarkers for Alzheimer's disease

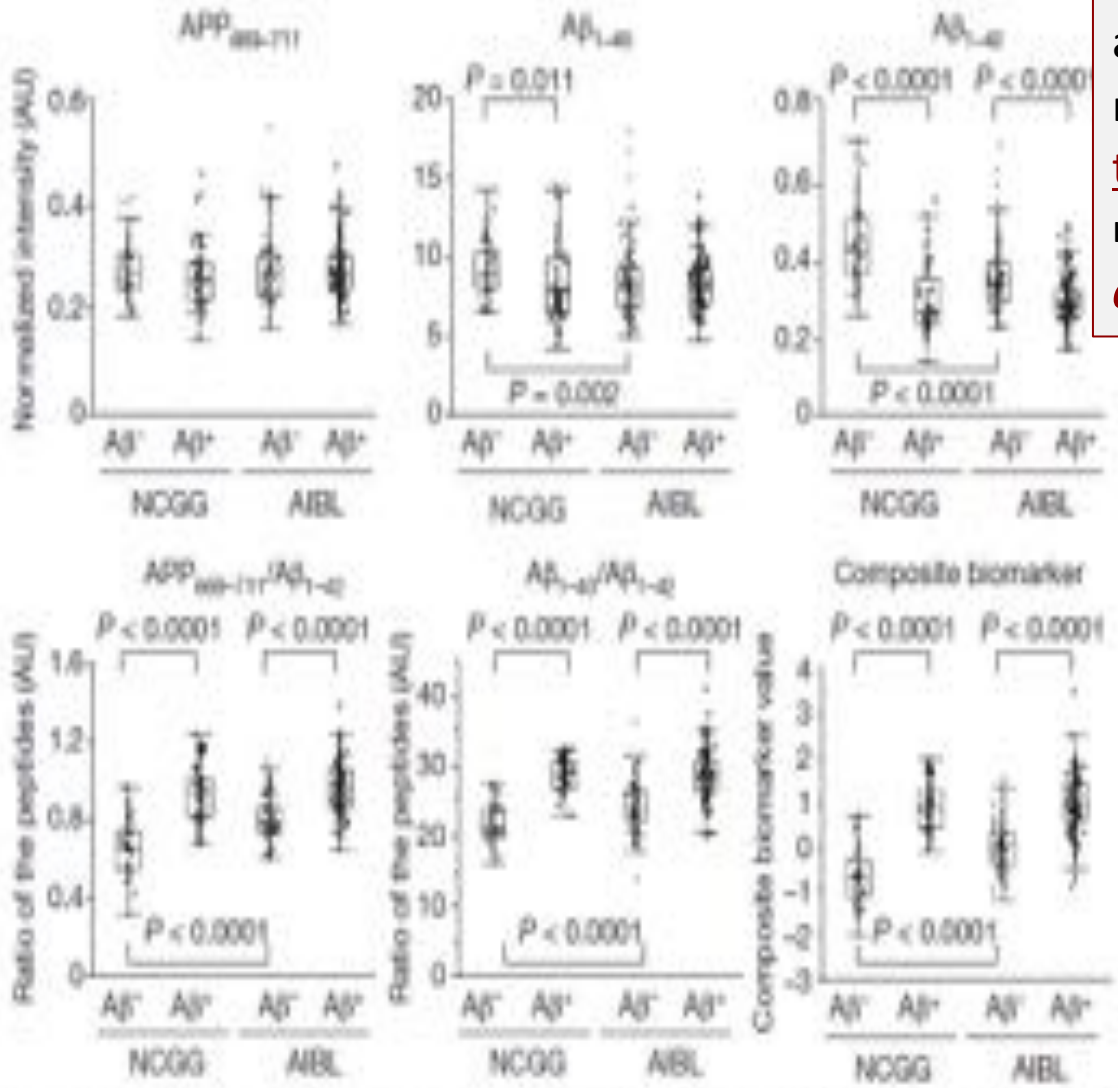


Figure 1 | The peptide and biomarker values in each study site. Box plots

MAIN FINDINGS w/ plasma AB

immuno-precipitation w/ mass spec

measured peptide levels – **Top Row**

also looked at ratios (e.g. AB40/AB42)

reminder: why are Ratios better?

two sites: Japan, Australia

ratios correlated w/ PiB burden, CSF AB42

composite biomarker is best

TIME to VOTE for:

Best New Biomarker

1. Plasma Measures
2. Grey Matter Networks

High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis

Neurology, 2019

Suzanne E. Schindler, MD, PhD, James G. Bollinger, PhD, Vitaliy Ovod, MS, Kwasi G. Mawuenyega, PhD, Yan Li, PhD, Brian A. Gordon, PhD, David M. Holtzman, MD, John C. Morris, MD, Tammie L.S. Benzinger, MD, PhD, Chengjie Xiong, PhD, Anne M. Fagan, PhD, and Randall J. Bateman, MD

Correspondence
Dr. Bateman
batemanr@wustl.edu

Neurology® 2019;TBD:1-13. doi:10.1212/WNL.0000000000006081

recognize any names?

Objective

We examined whether plasma β-amyloid (Aβ)42/Aβ40, as measured by a high-precision assay, accurately diagnosed brain amyloidosis using amyloid PET or CSF p-tau181/Aβ42 as reference standards.

Methods

Using an immunoprecipitation and liquid chromatography-mass spectrometry assay, we measured Aβ42/Aβ40 in plasma and CSF samples from 158 mostly cognitively normal individuals that were collected within 18 months of an amyloid PET scan.

Results

Plasma Aβ42/Aβ40 had a high correspondence with amyloid PET status (receiver operating characteristic area under the curve [AUC] 0.88, 95% confidence interval [CI] 0.82–0.93) and CSF p-tau181/Aβ42 (AUC 0.85, 95% CI 0.79–0.92). The combination of plasma Aβ42/Aβ40, age, and *APOE* ε4 status had a very high correspondence with amyloid PET (AUC 0.94, 95% CI 0.90–0.97). Individuals with a negative amyloid PET scan at baseline and a positive plasma Aβ42/Aβ40 (<0.1218) had a 15-fold greater risk of conversion to amyloid PET-positive compared to individuals with a negative plasma Aβ42/Aβ40 ($p = 0.01$).

Conclusions

Plasma Aβ42/Aβ40, especially when combined with age and *APOE* ε4 status, accurately diagnoses brain amyloidosis and can be used to screen cognitively normal individuals for brain amyloidosis. Individuals with a negative amyloid PET scan and positive plasma Aβ42/Aβ40 are at increased risk for converting to amyloid PET-positive. Plasma Aβ42/Aβ40 could be used in prevention trials to screen for individuals likely to be amyloid PET-positive and at risk for Alzheimer disease dementia.

would THIS change your vote?

These folks argue (in sporadic AlzD) that Plasma AB42 *predicts* conversion to PiB (amyloid) positive scan!

note: in diagnostics context, when referring to AB42, this often refers to the ratio of the AB42/AB40 peptides: this eliminates noise from variable protein recovery!

Lewczuk et al. Alzheimer's Research & Therapy (2018) 10:71
https://doi.org/10.1186/s13195-018-0404-9

Alzheimer's
Research & Therapy

RESEARCH Open Access

Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease

Piotr Lewczuk[1,2*], Natalia Ermann[1], Ulf Andreasson[5,6], Christian Schultheis[5], Jana Podhorna[6], Philipp Spitzer[1], Juan Manuel Maler[1], Johannes Kornhuber[1], Kaj Blennow[3,4] and Henrik Zetterberg[3,4,7,8]

Abstract

Background: A growing body of evidence suggests that the plasma concentration of the neurofilament light chain (NFL) might be considered a plasma biomarker for the screening of neurodegeneration in Alzheimer's disease (AD).

Methods: With a single molecule array method (Simoa, Quanterix), plasma NfL concentrations were measured in

Neurofilaments are tangled up with Tau in NFTs

what would this look like w/out the errant data point?

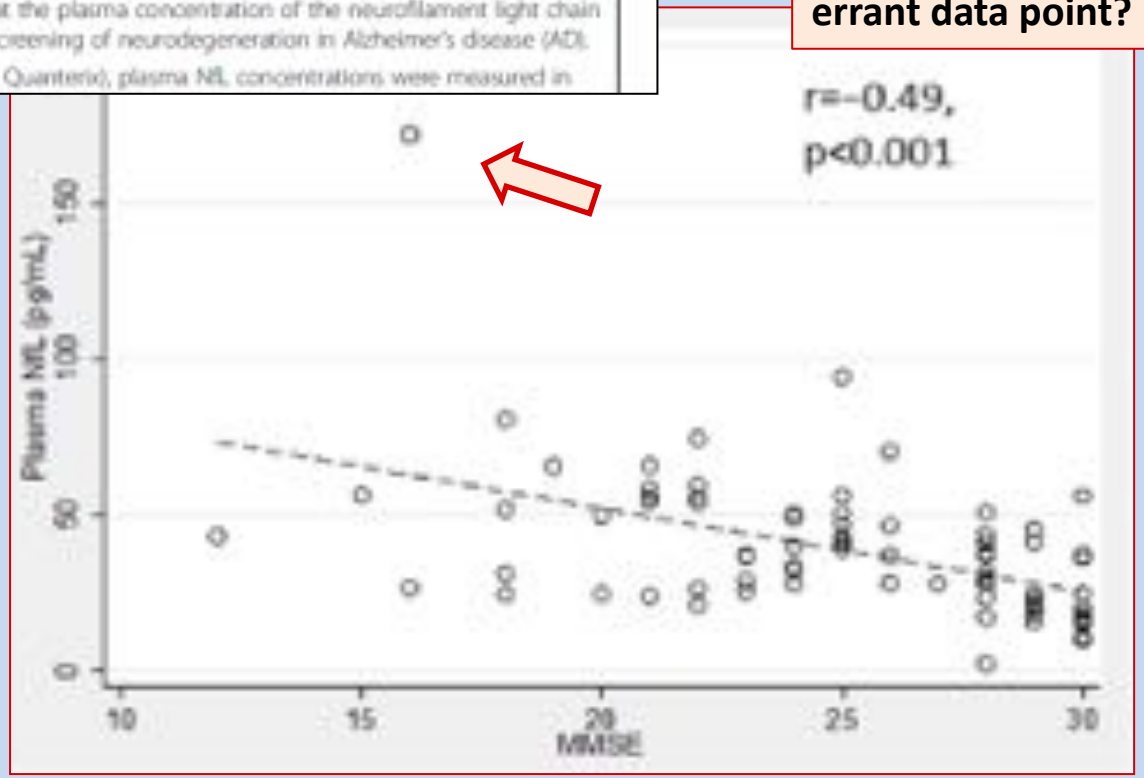


Figure 5. Good correlation of plasma NfL but useless as a biomarker?

nature medicine

Serum is blood plasma minus the clotting proteins

why are DOIs lame?

LETTERS

2019

Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease

Preische et al.

Ultrasensitive immunoassay showed CSF NfL levels correlate with serum (n = 405) CSF. Rate of NfL changes discriminate mutation carriers from non-carriers a decade earlier than cross-sectional NfL levels: 16.2 versus 6.8 years before symptom onset.

Tarenie L. S. Benzinger, John C. Morris, Randall J. Bateman, Guoqiao Wang, Anne M. Fagan, Eric M. McDade, Brian A. Gordon, Mathias Jucker and Dominantly Inherited Alzheimer Network

Aren't these people on ENOUGH papers already? ***Sheesh***!

This is for EARLY ONSET AlzD. "Longitudinal Advantage" noted above is STRIKING!

Neurodegeneration

2018 JNNP

SHORT REPORT

Evidence that iron accelerates Alzheimer's pathology: a CSF biomarker study

Scott Ayton,[1] Ibrahima Diouf,[1,2] Ashley Ian Bus

ABSTRACT

Objective To investigate whether cerebrospinal fluid (CSF) ferritin (reporting brain iron) is associated with longitudinal changes in CSF β-amyloid (Aβ) and tau.

Methods Mixed-effects models of CSF $Aβ_{1-42}$ and tau were constructed using data from 296 participants who had baseline measurement of CSF ferritin and annual measurement of CSF tau and $Aβ_{1-42}$ for up to 5 years.

Results In subjects with biomarker-confirmed Alzheimer's pathology, high CSF ferritin (>6.2 ng/mL) was associated with accelerated depreciation of CSF $Aβ_{1-42}$ (reporting increased plaque formation; p=0.0001). CSF ferritin was neither associated with changes in CSF tau in the same subjects, nor longitudinal changes in CSF tau or $Aβ_{1-42}$ in subjects with low baseline pathology. In simulation modelling of the natural history of Aβ deposition, which we estimated to occur over 31.4 years, we predicted that it would take 12.6 years to reach the pathology threshold value of CSF Aβ from healthy normal levels, and this interval is not affected by CSF ferritin. CSF ferritin influences the fall in CSF Aβ over the next phase, where high CSF ferritin accelerated the transition from threshold preclinical Aβ levels to the average level of Alzheimer's subjects from 18.8 to 10.8 years.

Conclusions Iron might facilitate Aβ deposition in Alzheimer's and accelerate the disease process.

Iron: not really a Biomarker

effect on CSF AB seen late in the game…

BUT the natural history of AlzD espoused

- intrigues: 31.4 year progress
- 12.6 year to pathology threshold
- does THIS mean to Tau Ignition?

ALSO a note of concern re: Introduction:

- is *ANYONE* even reading these days?

INTRODUCTION

In the natural history of Alzheimer's disease (AD), β-amyloid (Aβ) accumulation, detected either by Aβ-positron emission tomography (PET) imaging or measuring falling cerebrospinal fluid (CSF) $Aβ_{1-42}$ levels, progresses in a prodromal period lasting decades decade-long prodromal period.[1–4] Risk factors that underlie the considerable variability of amyloid accumulation rate are uncertain. Major genetic factors, such as familial AD mutations, or the ε4 isoform of APOE, cause amyloid to commence accumulation earlier, but they have little impact on Aβ accumulation rate.[5 6]

anyone publishing gibberish should be banned from publishing

Biochimie 2018

journal homepage: www.elsevier.com/locate/biochi

Review

Biosensors for Alzheimer's disease biomarker detection: A review

Bingqing Shui [a, 1], Dan Tao [a, 1], Anca Florea [b], Jing Cheng [a], Qin Zhao [a], Yingying Gu [a], Wen Li [c], Nicole Jaffrezic-Renault [d, ***], Yong Mei [a, **], Zhenzhong Guo [a, *]

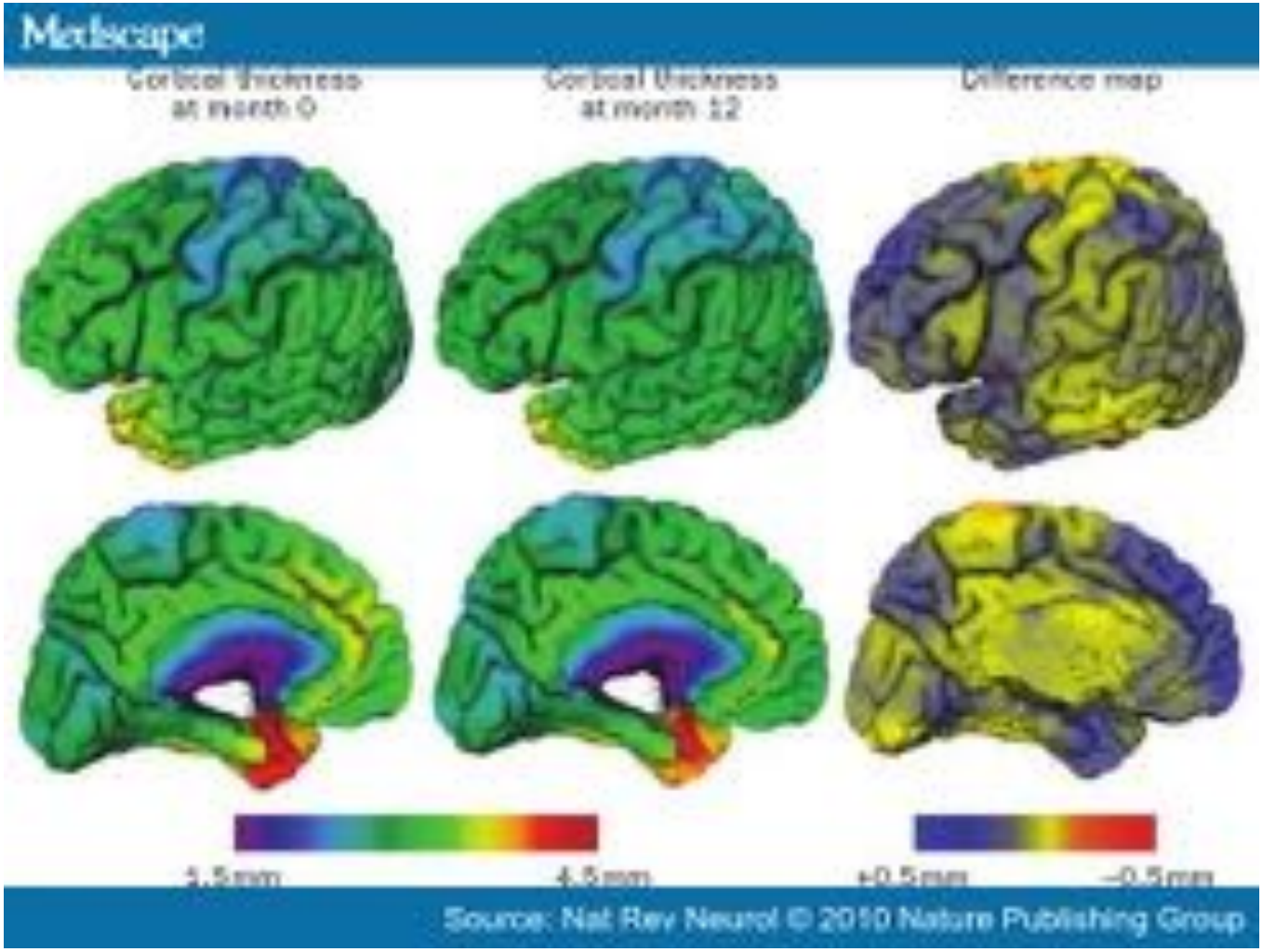
a Biomarker *Burn*!

Table 1
Techniques for AD diagnosis and their limitations.

Technique	Limitations
MS	Expensive Strict low-pressure requirements Depend strongly on energy, collision gas, pressure, and other factors
MRI	Expensive Low scanning velocity Motion artifacts Insensitive to calcifications
ELISA	Time consuming and inefficient Insensitive to low level markers False positives
Western-blot	Low stability An imbalance in any step of the procedure may skew the entire process
IHC	Variable antibody reactivity Interpretation is often subjective
sMAP	Expensive The results are low to medium resolution A small number of heterozygous ambiguities
PET	Expensive Poor spatial resolution Artifacts of movements

They propose using *Biosensors* to better monitor *Biomarkers*. Too EARLY to make a call on this one!

Cortical Thinning: a topic for another day…



https://curealz.org/about-us/

Drug Development Strategy: Three Points of Attack

Is this a good strategy?
Is this a good organization?

POSTED JAN 28, 2014

In view of an emerging consensus on how Alzheimer's disease develops and progresses, the Cure Alzheimer's Fund Research Consortium aggressively is focusing on three opportunities for possible intervention—at the early stage of the disease, the middle stage and the late stage. This comprehensive strategy addresses the whole picture of how Alzheimer's disease develops and progresses, and attacks all three points simultaneously.

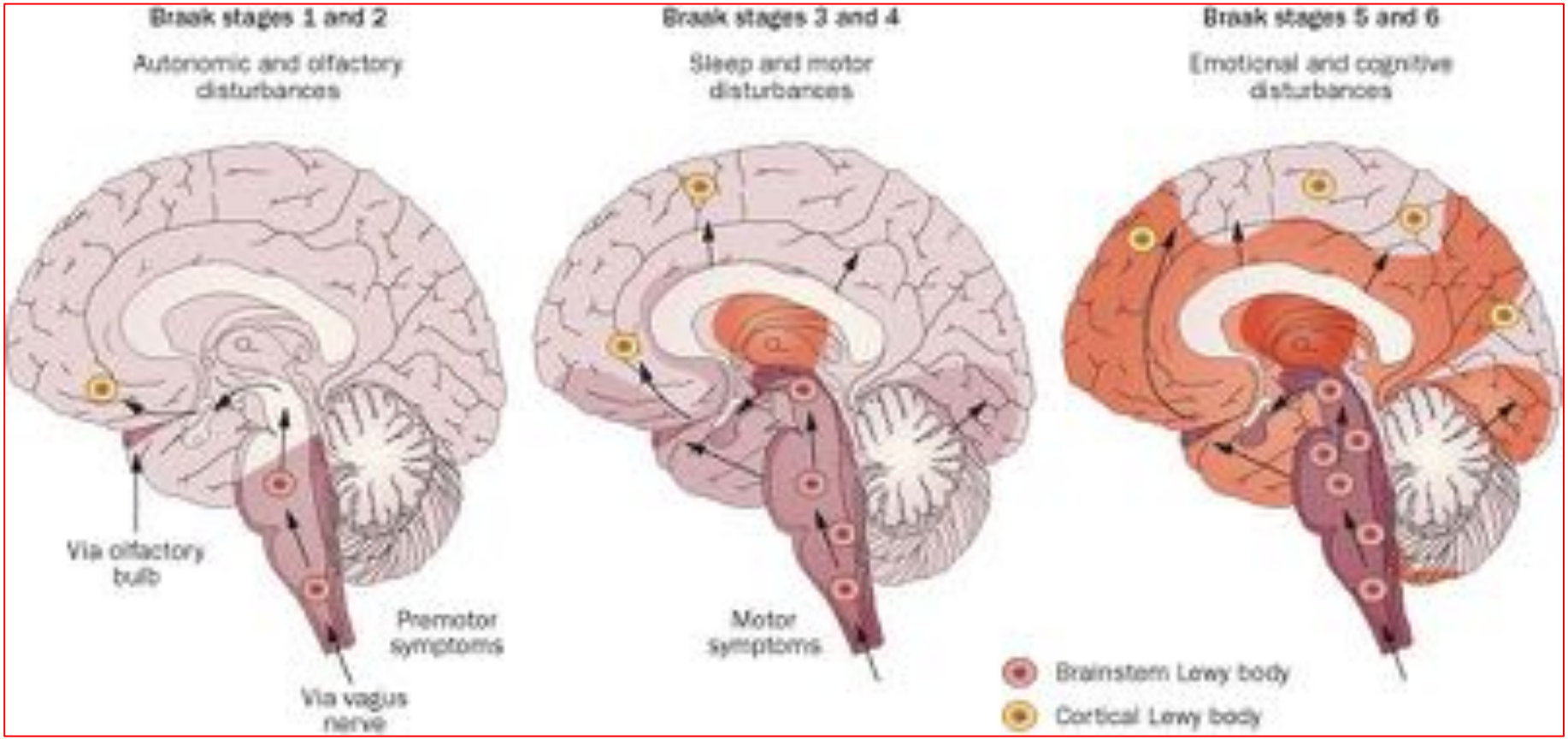
What we know

For too long, Alzheimer's research has been distracted by arguments over "plaques" vs. "tangles." Some thought the key to treatment was clearing plaques, while others argued that eliminating tangles would cure the disease. Most researchers now agree it is necessary to attack both plaques and tangles, as well as other elements of the pathology, to stop the disease's progression. **(they didn't ask me …)**

The Research Consortium now shares the understanding that Alzheimer's is a vicious cycle of destruction that begins with the production of excessive beta-amyloid peptides (Abeta) that aggregate into clusters called "oligomers," then proceeds to the creation of tangles from the protein tau that originate inside cells but that recently have been shown to spread to other cells. Both of these create inflammation in the brain, which stimulates more creation of Abeta, thus continuing a cycle that is deadly for brain cells. This destructive cycle can be envisioned as follows:

(but seems well informed)

Braak Stages in PD?



Addendum to Chapter 12: for future students