Disclaimer

Any mention or discussion of specific approaches, methods, commercial products, trade names, organizations, their sources, or their use in connection with material reported in this workshop is not to be construed as either an actual or implied endorsement of such products, methods, or approaches by FDA, the Department of Health and Human Services, or United States Government.

Current State of Amyloid PET Imaging

Mechanistic/observational/descriptive research (academic)

- Often part of multimodal assessment
- Natural history studies include staging, longitudinal, early detection, prognosis
- Usually quantitative
- Some standardization – ADNI approach of image smoothing to common resolution, centiloids

Clinical applications

- Limited to date based on payment
- Visual interpretation
- Limited motivation for early detection, staging or longitudinal observation

What Do We Need From Quantitation?

Reliability and validity

Thresholds – categorize as positive/negative

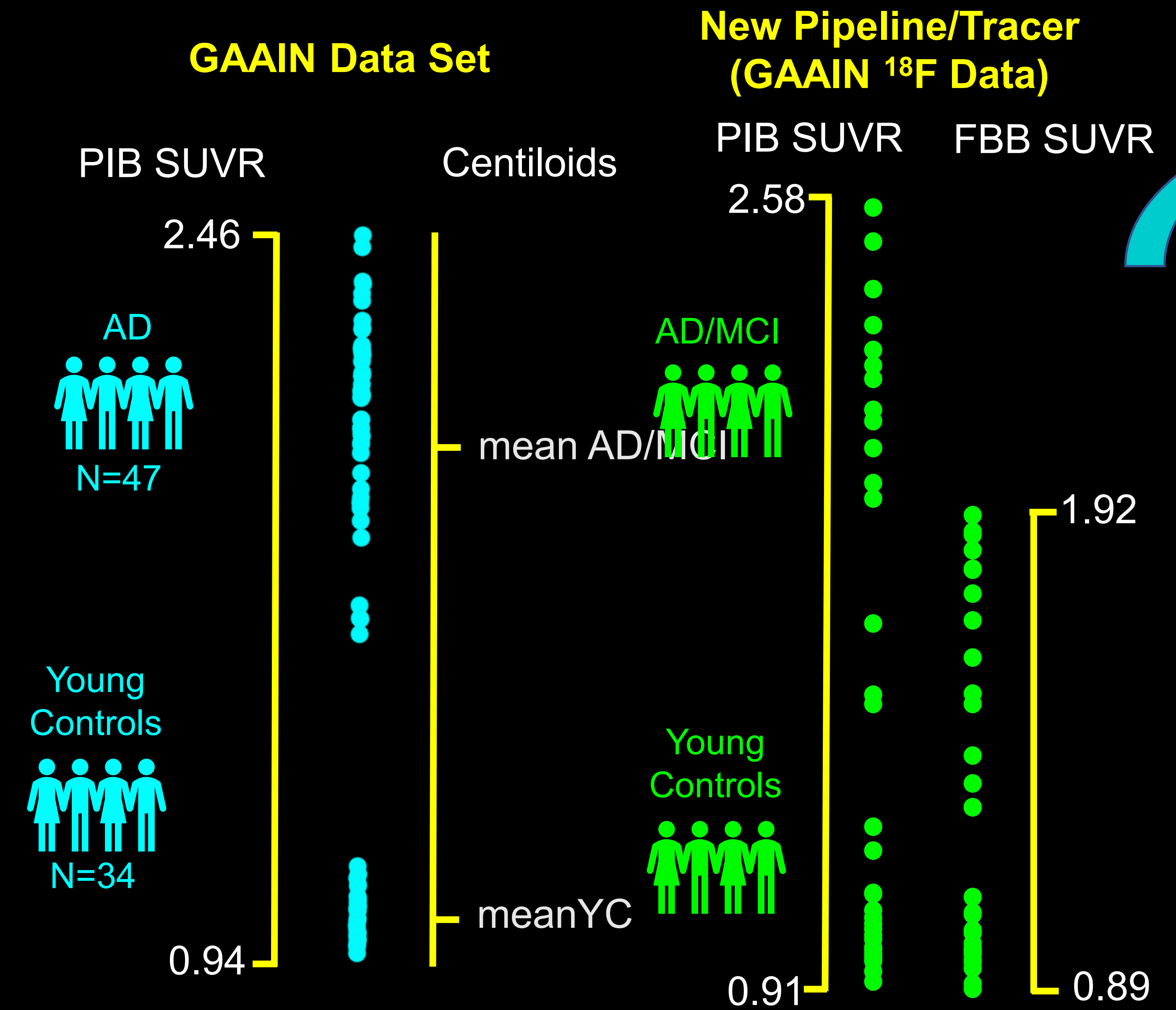
- Sensitive or specific?

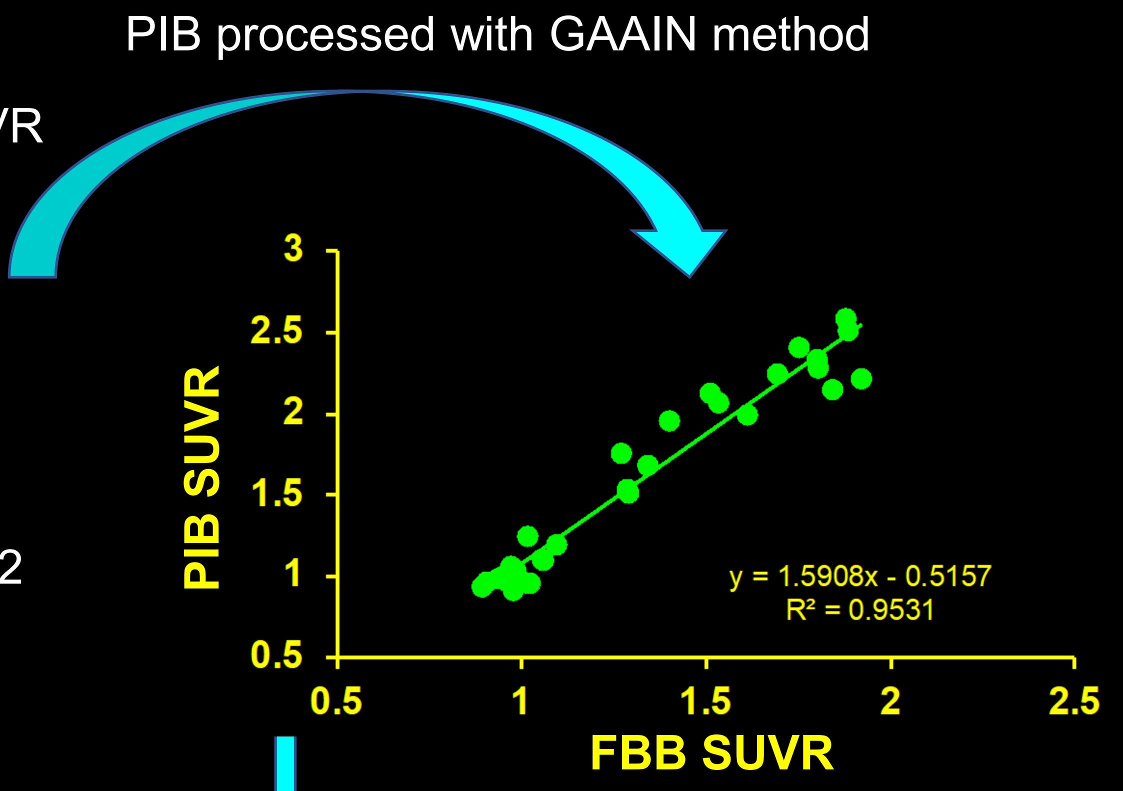
Longitudinal change

- How precise vs how costly?
- Complexity is greater than assigning positive/negative

Interoperability/standardization

- Across tracers, scanners, analysis methods





Conversion of a new tracer to centiloids:

1. Requires the GAAIN data to scale 0-100 anchors
2. Creates a new conversion equation for every tracer and processing pipeline

$$CL_i = \frac{SUVR_i - SUV_{meanYC}}{SUVR_{meanAD/MCI} - SUV_{meanYC}} \times 100$$

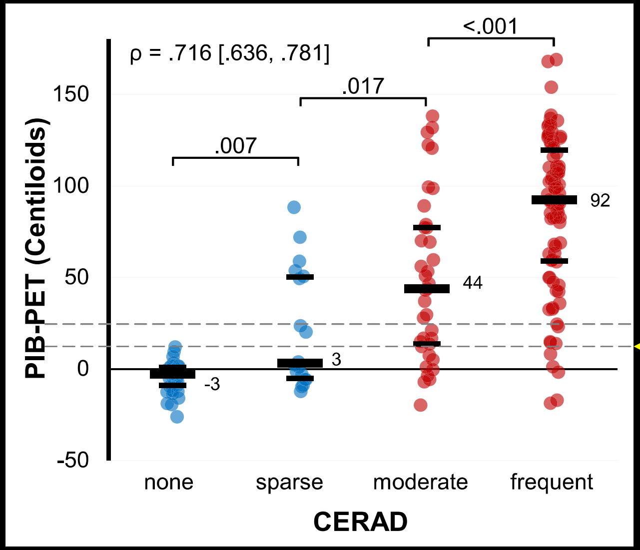
What is a "Positive" Amyloid Scan?

Comparison of quantitation with pathology:
ROC for none/sparse vs moderate/frequent CERAD plaque score

Many tracers have been correlated with pathology and thresholds established

In general, similar sensitivity/specificity for detection of amyloid plaques

PIB



12.2 CL for CERAD Plaques

Sensitivity 89
Specificity 86

La Joie *Alz & Dementia* 2019

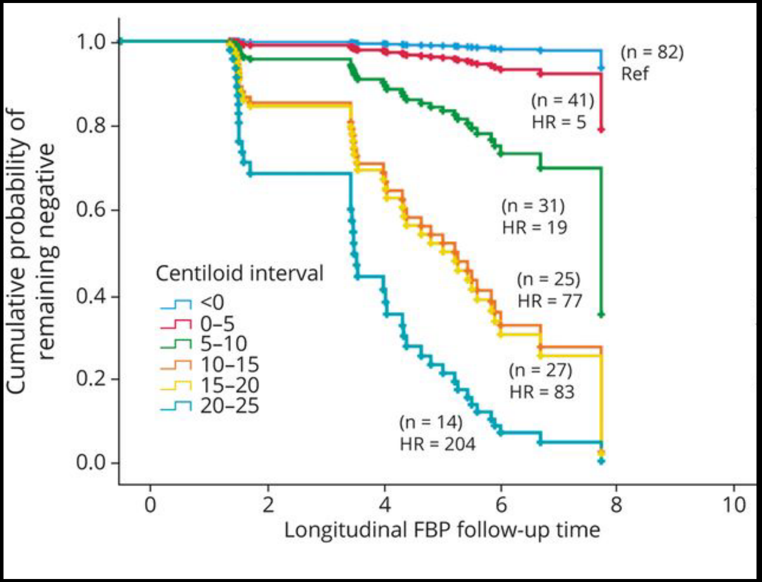
<u>Other approaches:</u>
2-3 SD above young controls or clearly negative normal
Gaussian mixture modeling to differentiate positive/negative
K-means or other clustering methods
Comparison with CSF or visual read
Prediction of disease progression

Thresholds Don't Tell the Whole Story

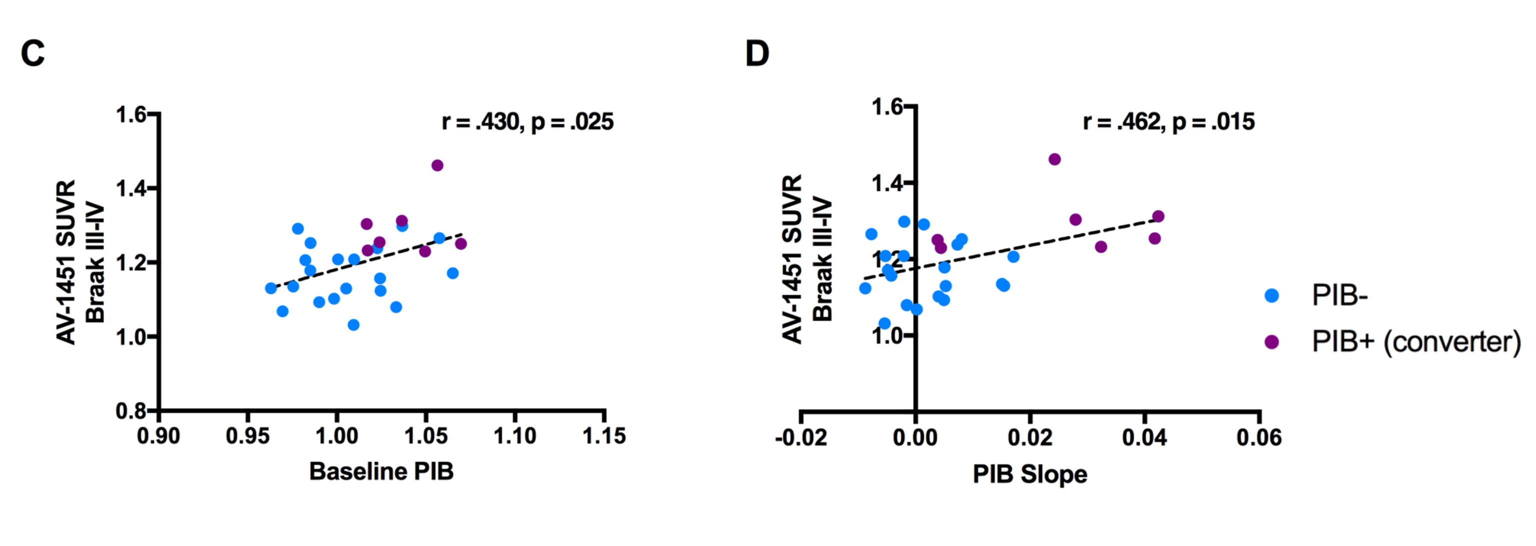
Many individuals below threshold are accumulating β-amyloid

Increasing brain amyloid, even in amyloid negative individuals, are associated with cognitive decline

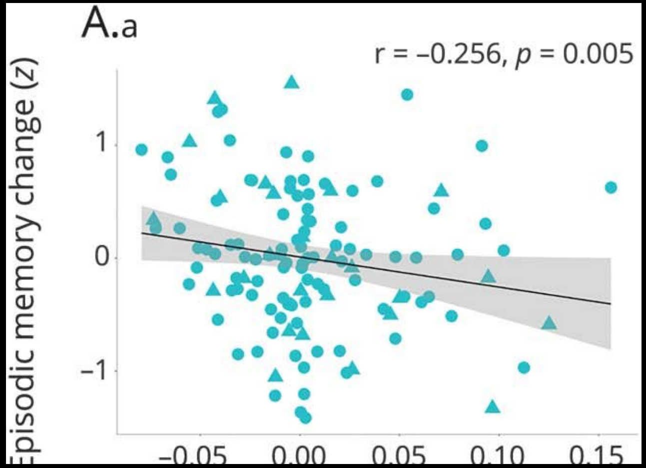
Individuals below threshold with higher Aβ PET levels deposit more tau over time



Jagust & Landau, *Neurology* 2021



Leal et al *J Neuroscience* 2018



Farrell et al *Neurology* 2018

Many Remaining Questions

Do centiloids solve the standardization problem?

- Instrument differences unaddressed
- Pipeline dependent

How much precision is necessary?

- Different applications have different requirements
- Defining positivity vs longitudinal tracking

Can quantitation be applied and standardized at scale?

Center for Alzheimer Research & Treatment

HARVARD AGING BRAIN

Massachusetts General Hospital ~ Harvard Medical School ~ Brigham and Women's Hospital

The case for quantitation in amyloid PET: Preclinical Alzheimer's disease

Reisa Sperling, MD

Brigham and Women's Hospital

Massachusetts General Hospital

Harvard Medical School

BWH VE RI TAS MGH 1811

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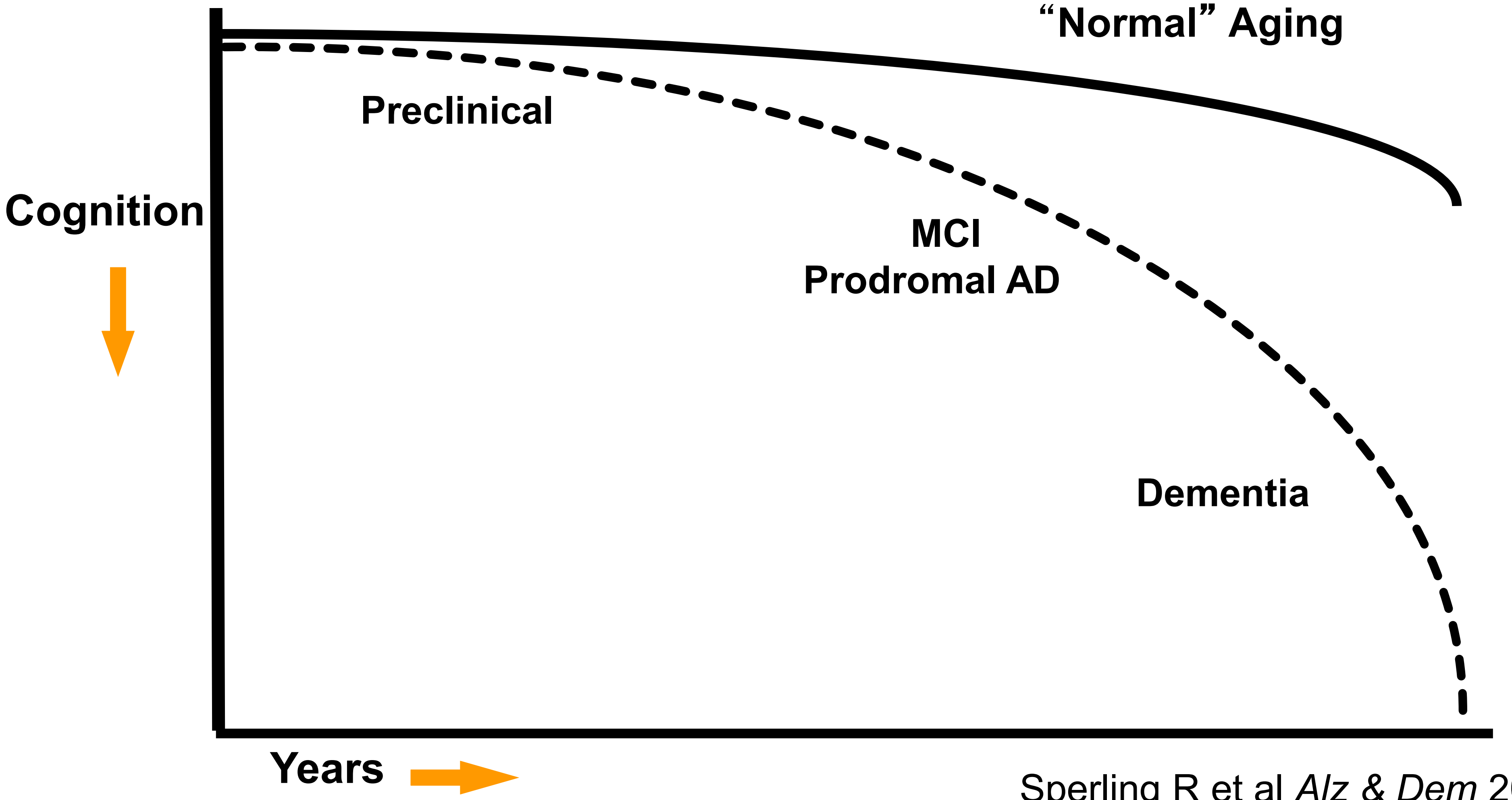
Alzheimer's Association

Fidelity Biosciences, GHR Foundation, Gates Ventures

Eli Lilly, Eisai

Accelerating Medicines Partnership FNIH

The continuum of Alzheimer's disease

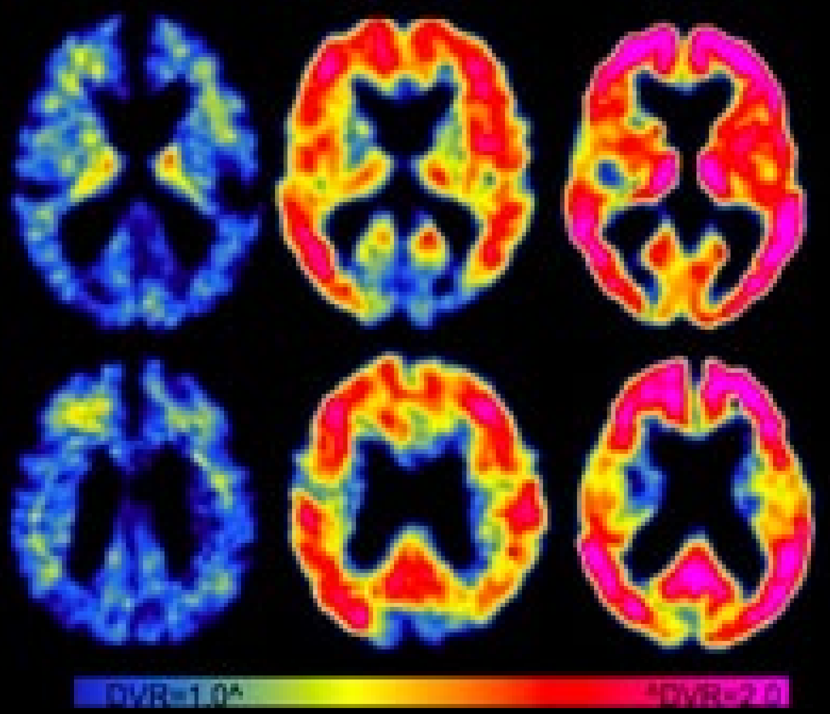


Sperling R et al *Alz & Dem* 2011
NIA-AA Preclinical Workgroup
Jack C et al *Alz & Dem* 2018

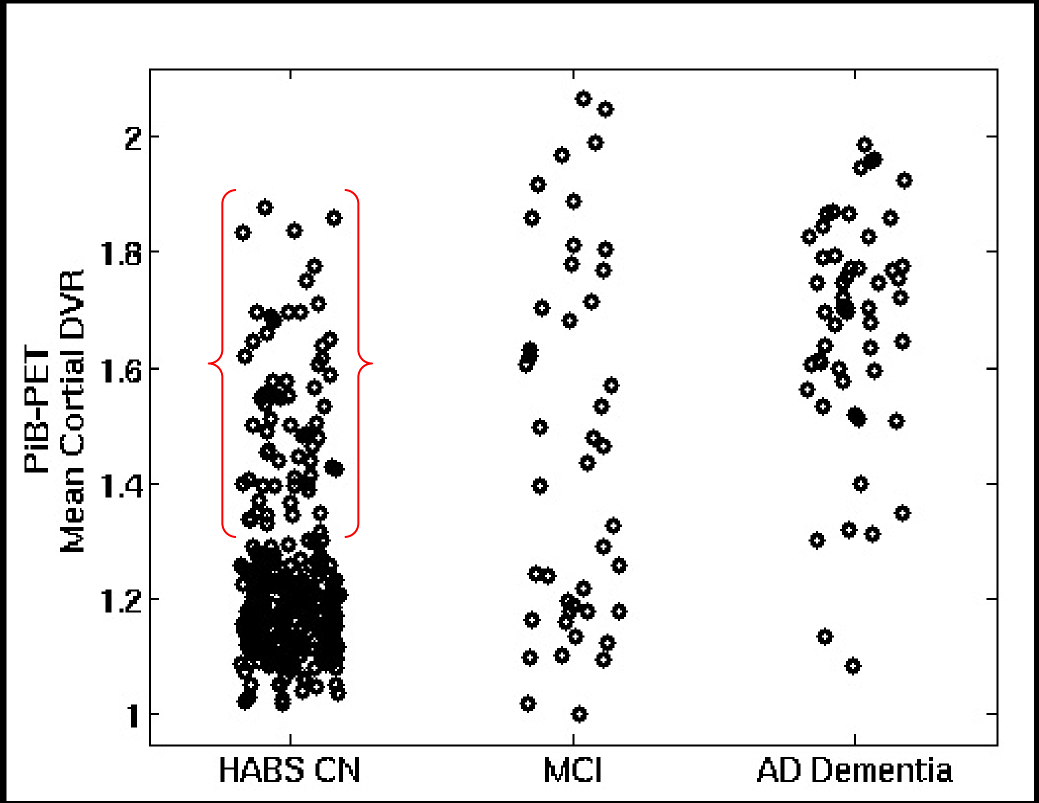
Quantitative Amyloid PET

- Likely most important in detection and monitoring of early amyloid-β accumulation
- Clinically impaired patients typically already entering plateau phase of amyloid-β accumulation – visual read may be adequate for most (but perhaps not all) cases
- Preclinical AD typically in rapid accumulation phase of amyloid-β begins well prior to "positivity" on visual read
  - Tau accumulation and early cognitive decline in parallel
- Quantitative approach critical for selection for trials and monitoring outcomes in preclinical AD
  - Potential for tailored dosing strategies

PET Amyloid Imaging
Across the Clinical Spectrum of AD



CN Aβ−   CN Aβ+   AD Aβ+

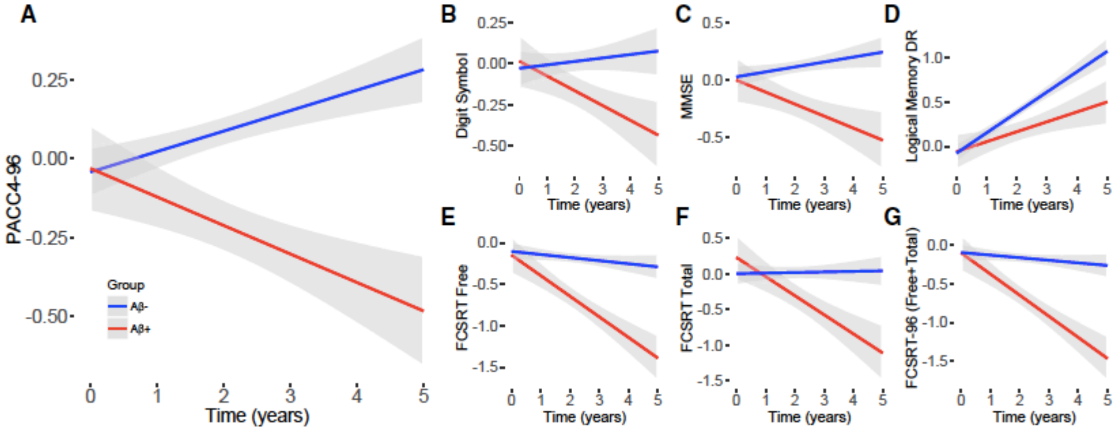


Harvard Aging Brain Sudy

Sperling, Mormino, Johnson *Neuron* 2014

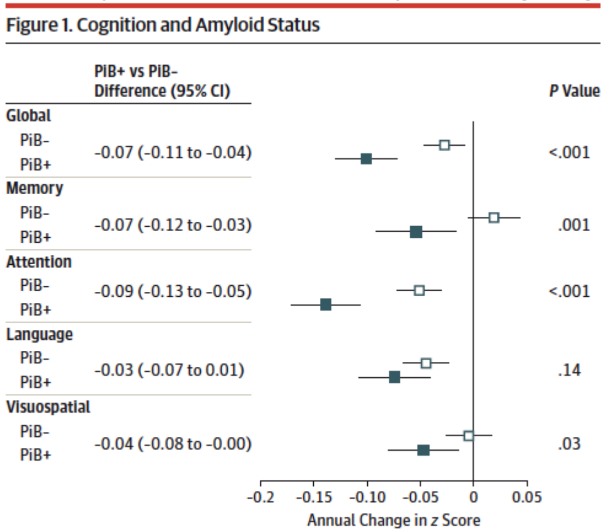
High Risk of Cognitive Decline in “Amyloid Positive” Normals

Harvard Aging Brain Study



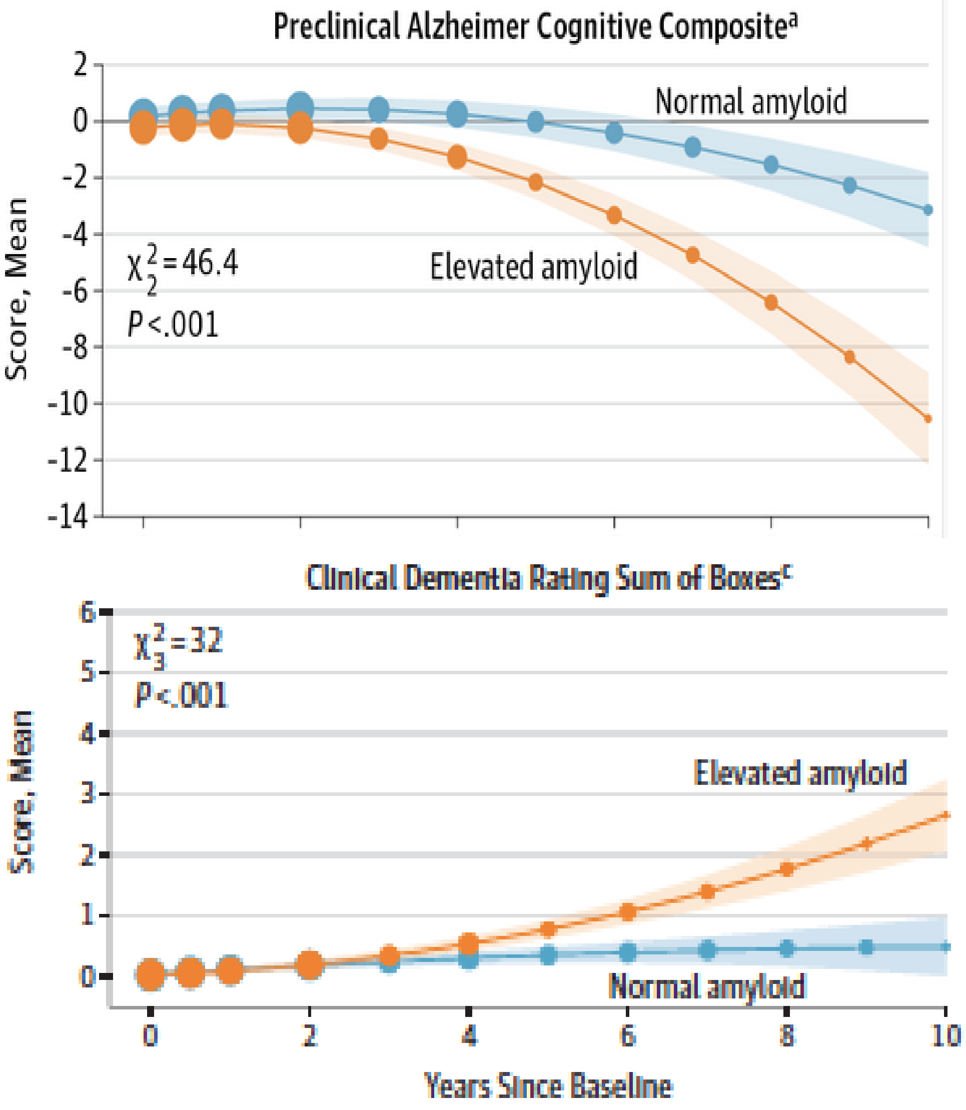
Mormino E et al. *Alz & Dementia* 2017

Mayo Clinic Study of Aging



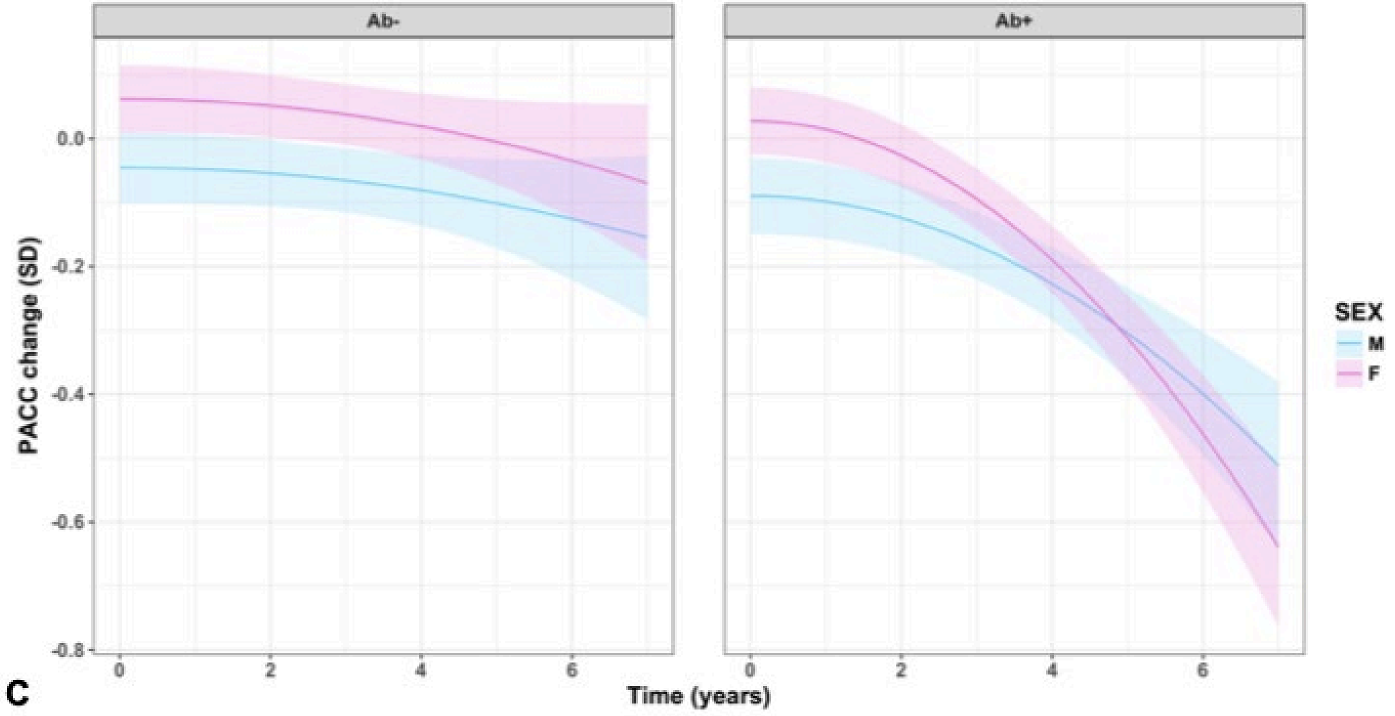
Petersen R et al. *JAMA Neurology* 2015

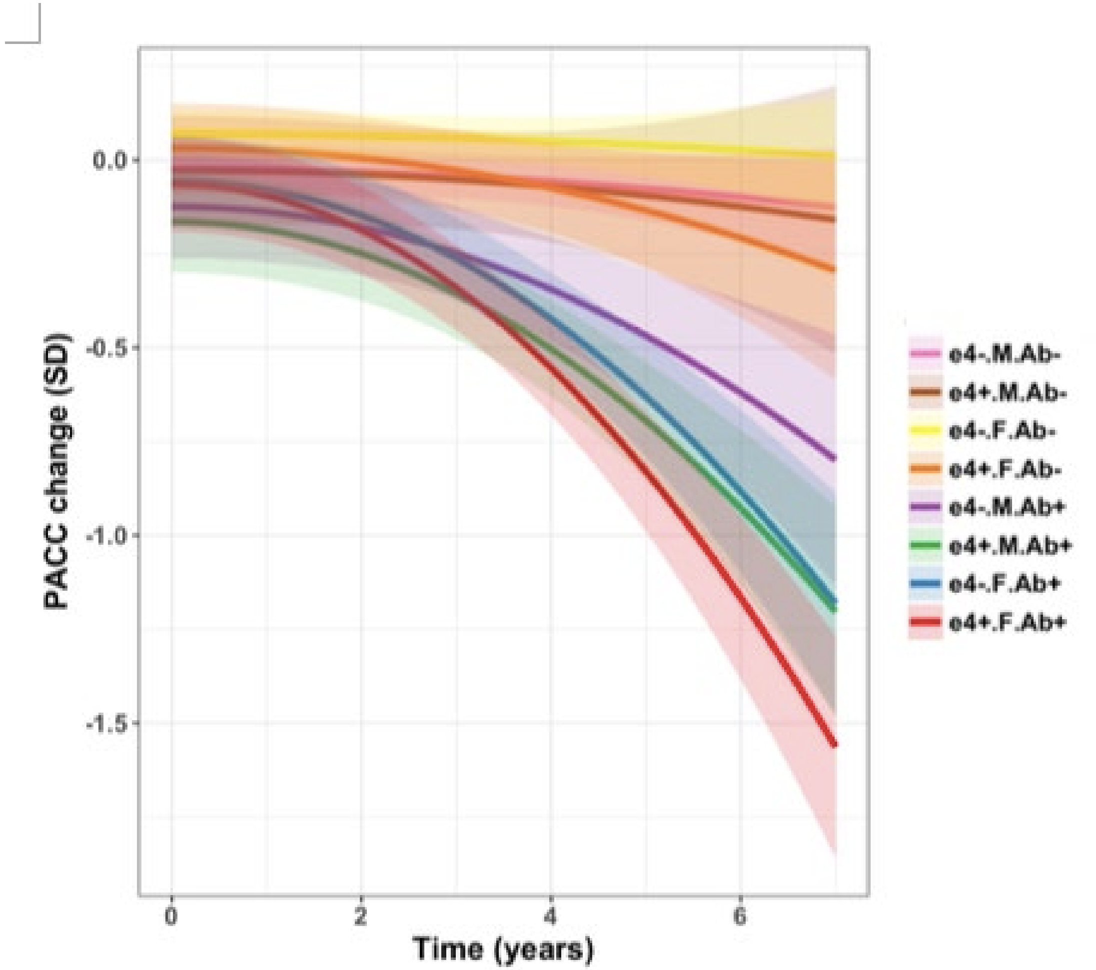
ADNI



Donohue M, Sperling R et al. *JAMA* 2017

Amyloid x APOE x Sex Effects on Cognitive Decline

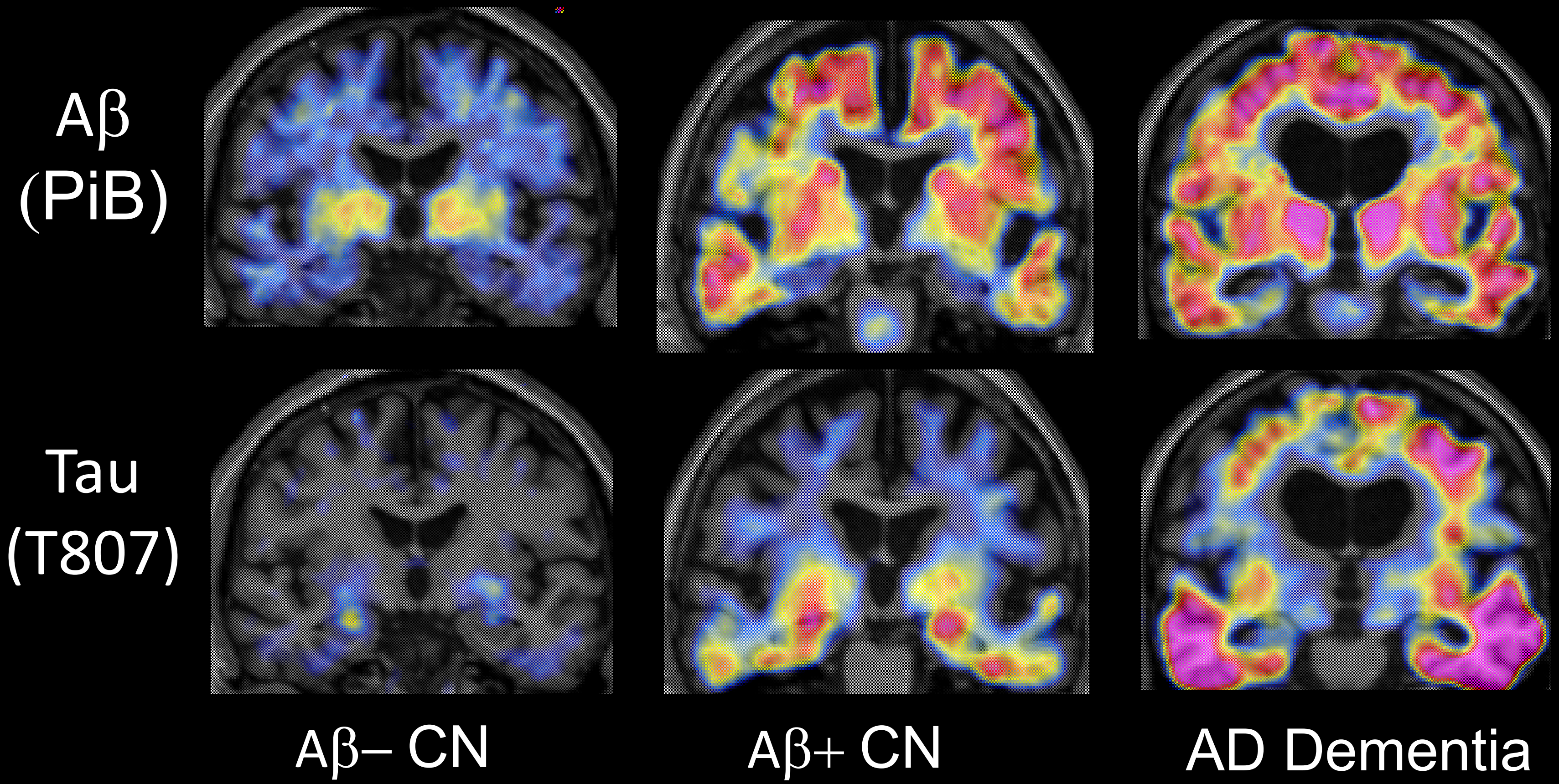




Harvard Aging Brain Study Study (HABS)
Australian Imaging Biomarker Lifestyle (AIBL)
Alzheimer's Disease Neuroimaging Initiative (ADNI)

Buckley R et al *Alz & Dementia* 2018

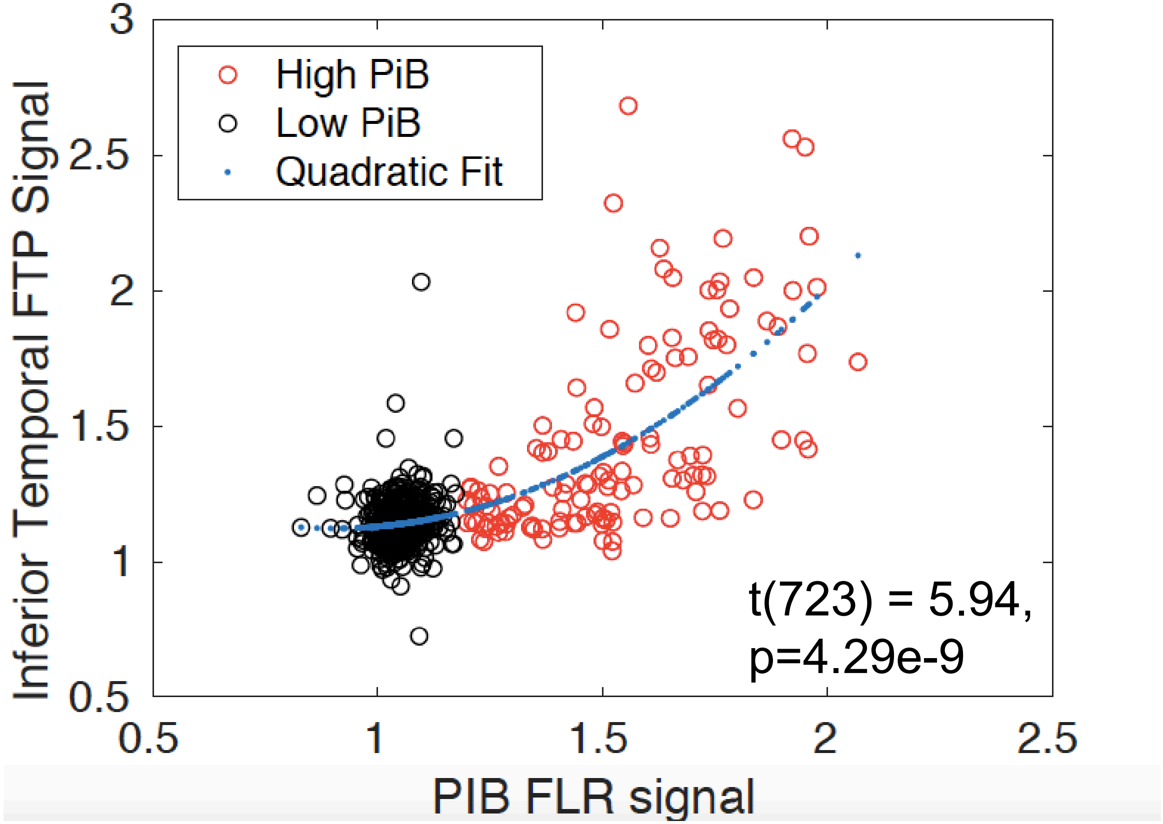
Amyloid and Tau PET Imaging



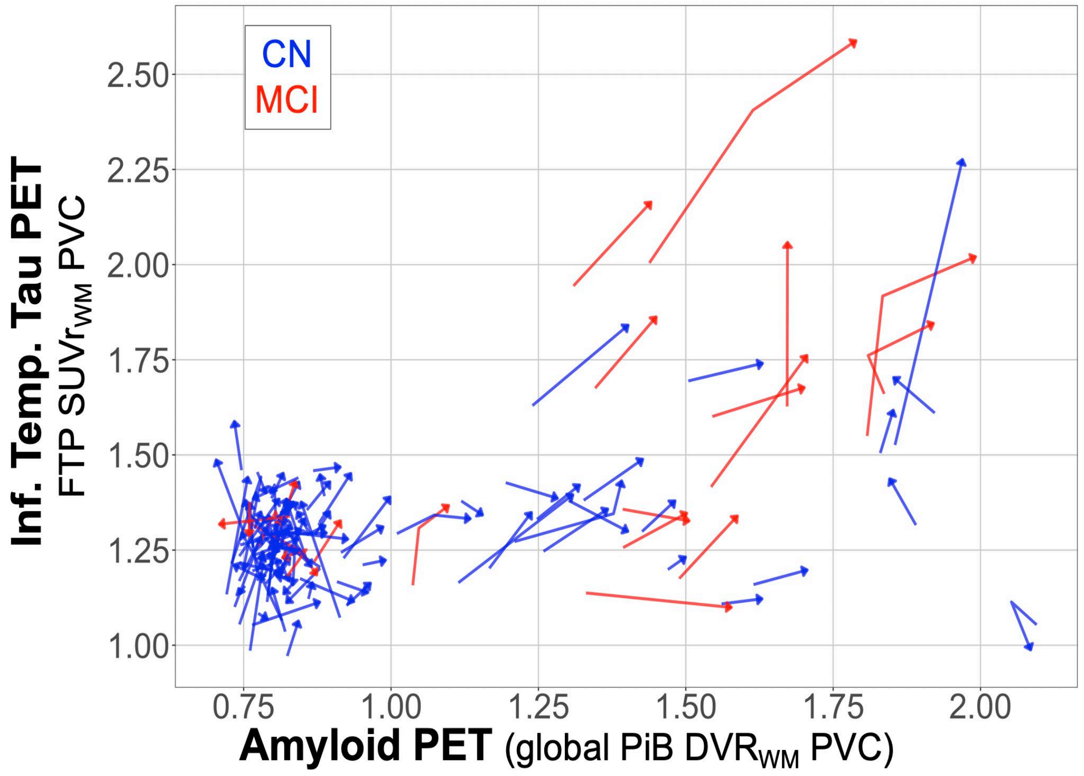
Sperling, Mormino, Johnson *Neuron* 2014

Is there a critical level of Amyloidosis associated with rapid Tau accumulation (“ca-tau-strophe”)?

Cross-Sectional HABS data

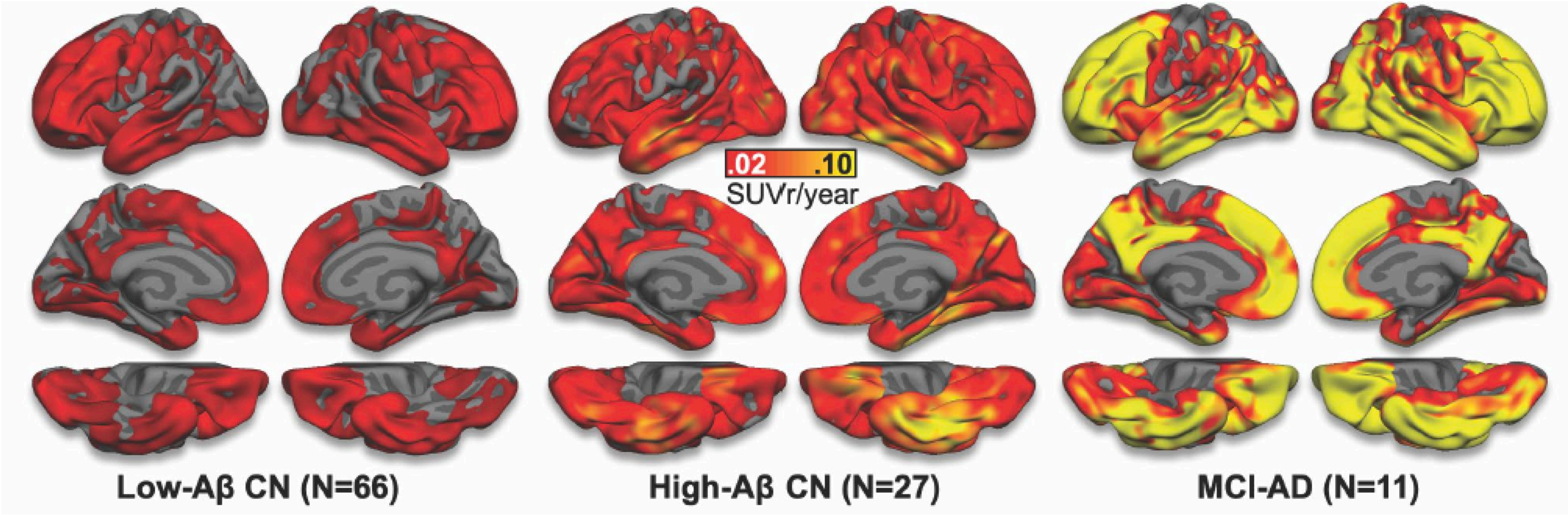


Longitudinal HABS data



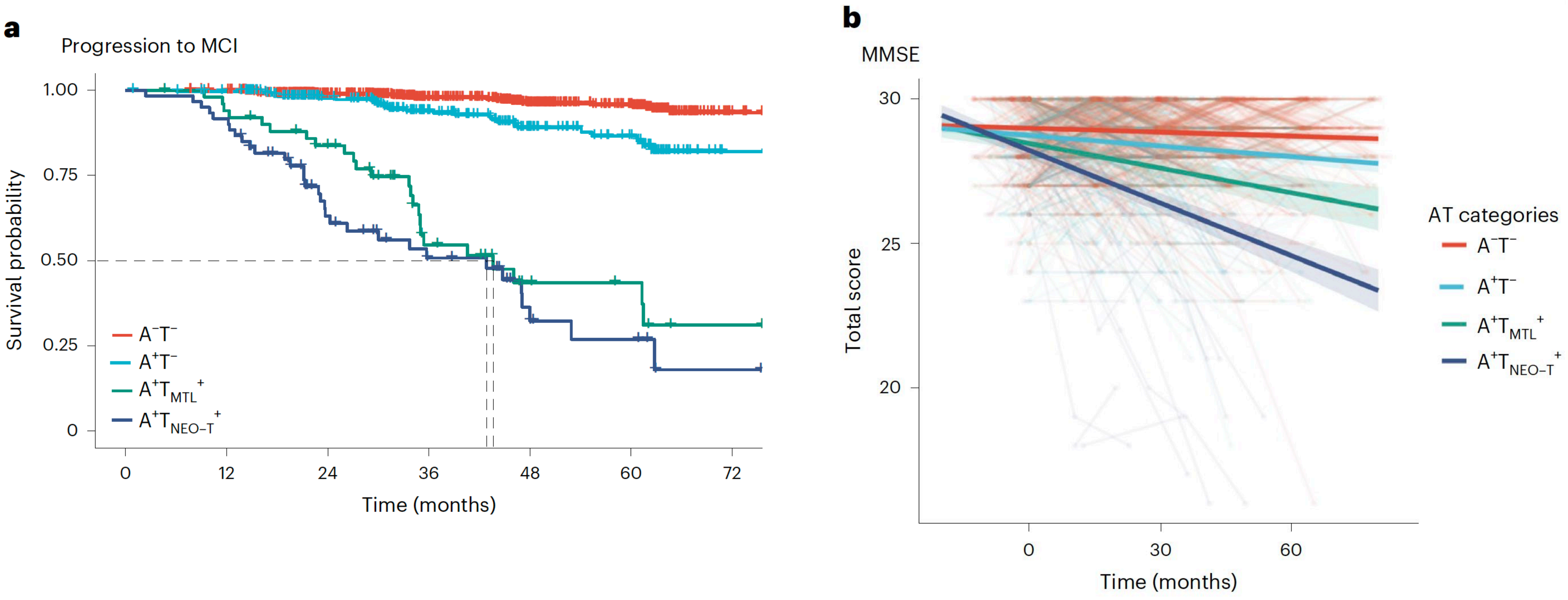
Keith Johnson - Harvard Aging Brain Study

Tau Accumulation *In Vivo* - Annual change in Tau PET



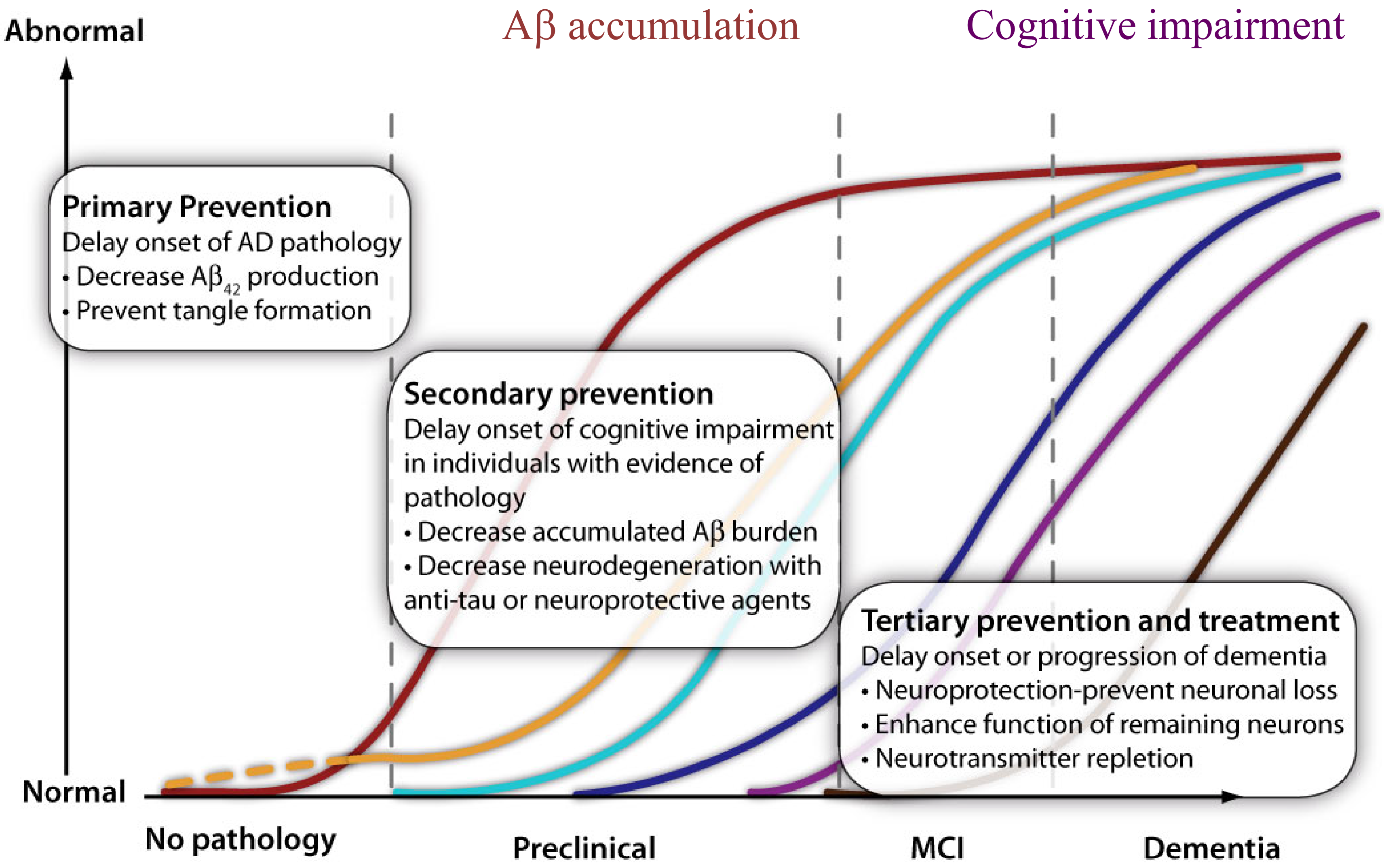
Sanchez J…Johnson K *Science Trans Med* 2021

High Risk of Cognitive Decline in “Amyloid Positive” Normals Primarily Driven by A+ Tau+



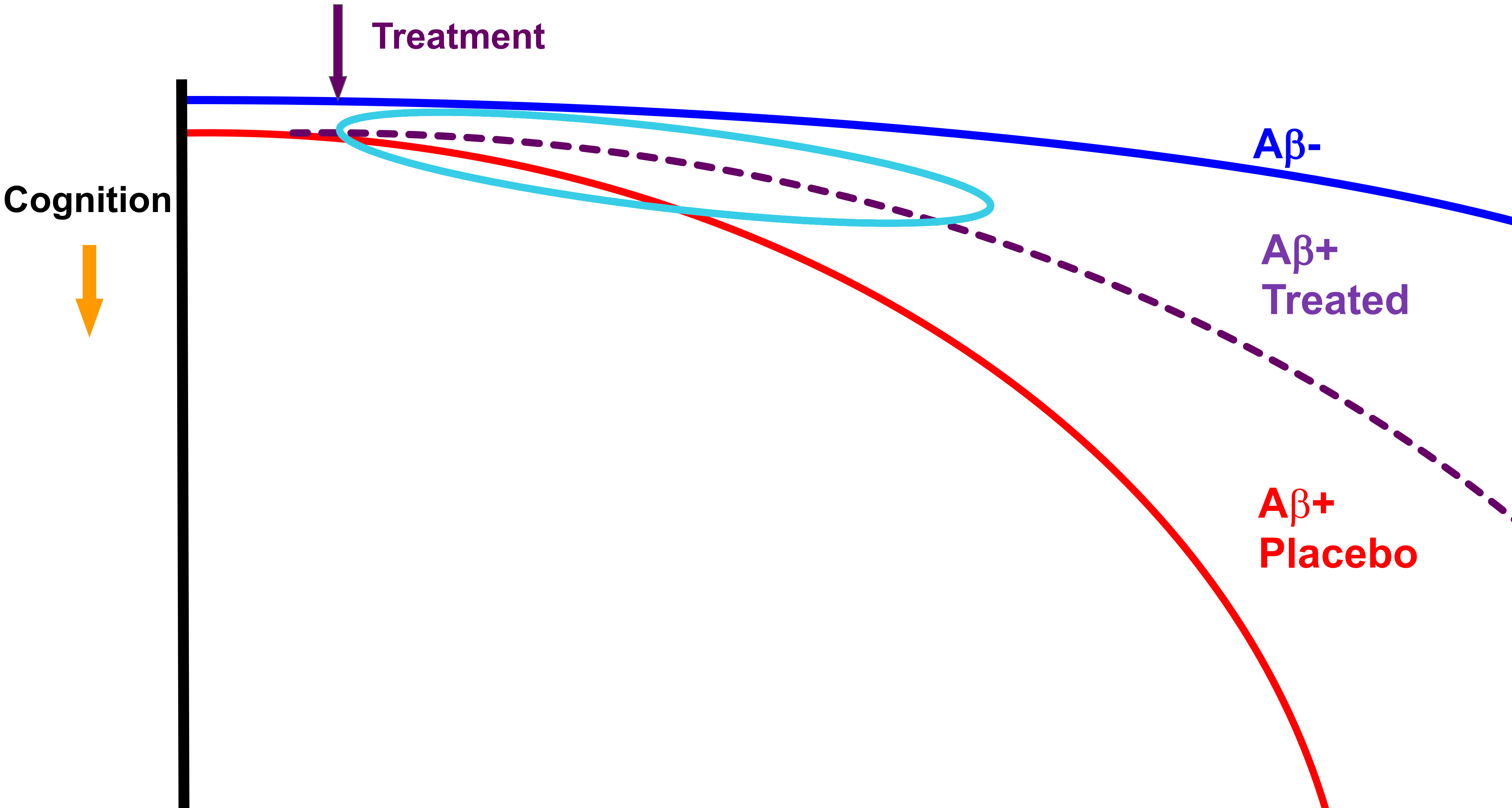
Ossenkoeppele R et al *Nature Medicine* 2022

Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease

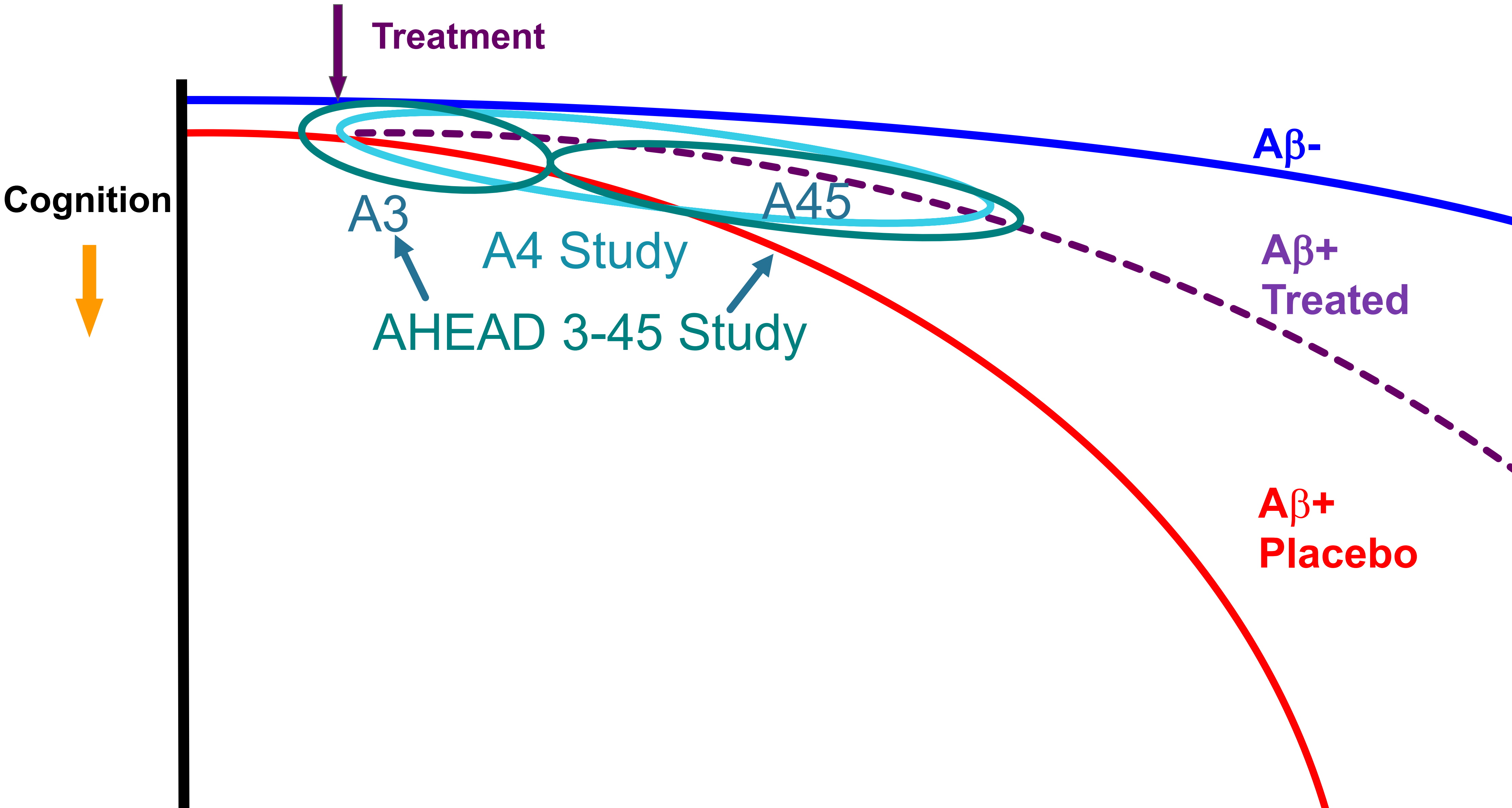


Sperling, Jack, Aisen *Science Trans Med* 2011

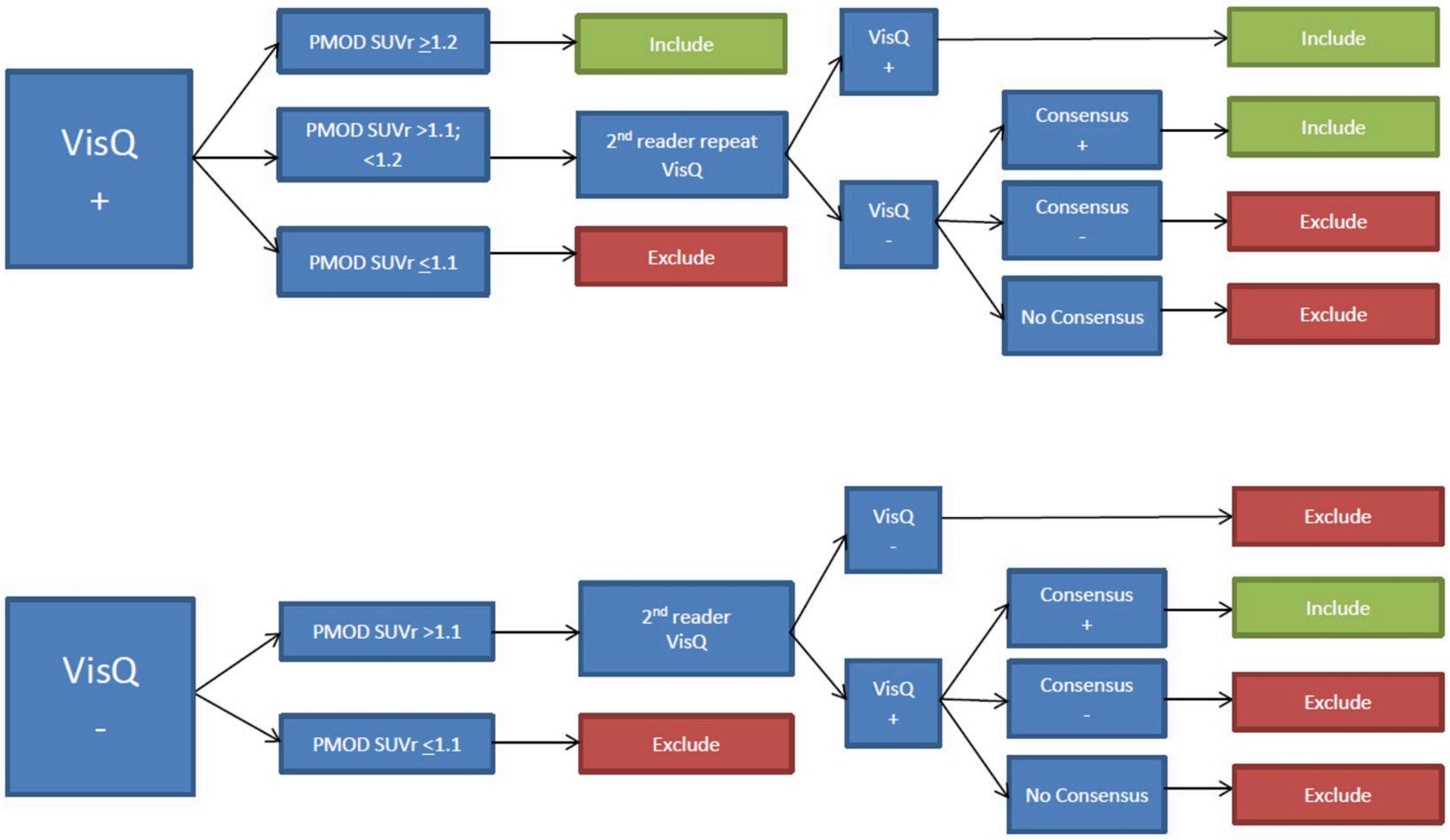
How early do we need to intervene along the continuum of Alzheimer's disease to actually prevent dementia?



How early do we need to intervene along the continuum of Alzheimer's disease to actually prevent dementia?



Initial A4 Study Amyloid PET algorithm



A4 Study VisQ + Quant Eligibility Algorithm (Study Start to 18-Dec-2014).

Sperling R et al. *JAMA Neurology* 2020

Revised A4 Study Amyloid PET algorithm

A4 Study: VisQ + Quant Eligibility Algorithm (18-Dec-2014 to Current)

Sperling R et al. *JAMA Neurology* 2020

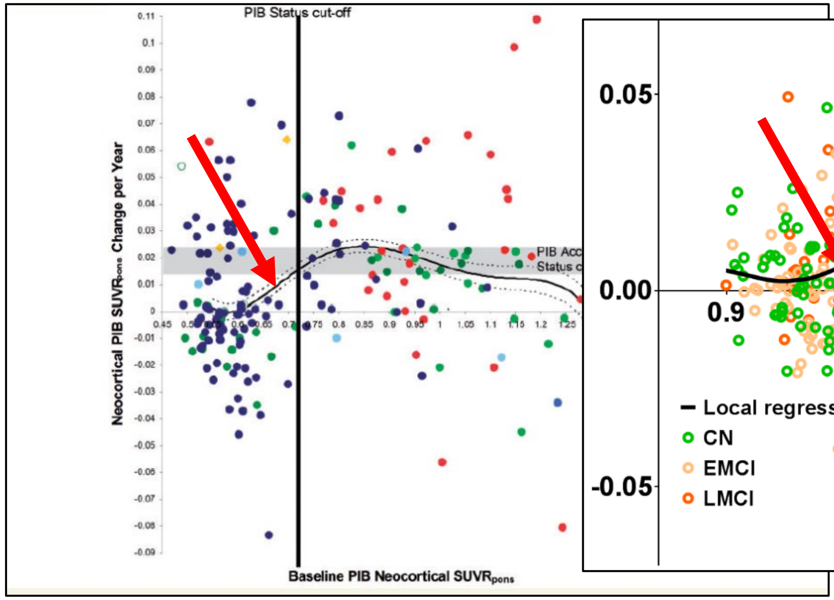
A4 Study Amyloid Eligibility Determination

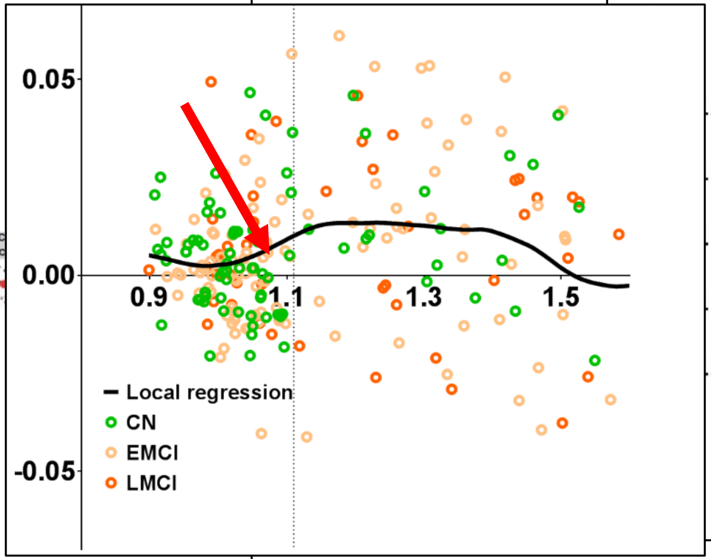
- Based on screening algorithm 1323/4486 (29.5%) were characterized as Aβ positive (eligible to continue screening)
  - Mean SUVr of Aβ+ = 1.33
- Of those overall Aβ+ 663/1323 (50.1%) were visual read positive
- Of those overall Aβ+ 12/1323 (0.1%) were visual read positive but SUVr < 1.15
- In the tau PET substudy (all Aβ+ N=392), 56% already have substantial neocortical tau deposition

The A4 Study
NOW IS THE TIME

Optimal Time to Intervene to Prevent Aβ Accumulation

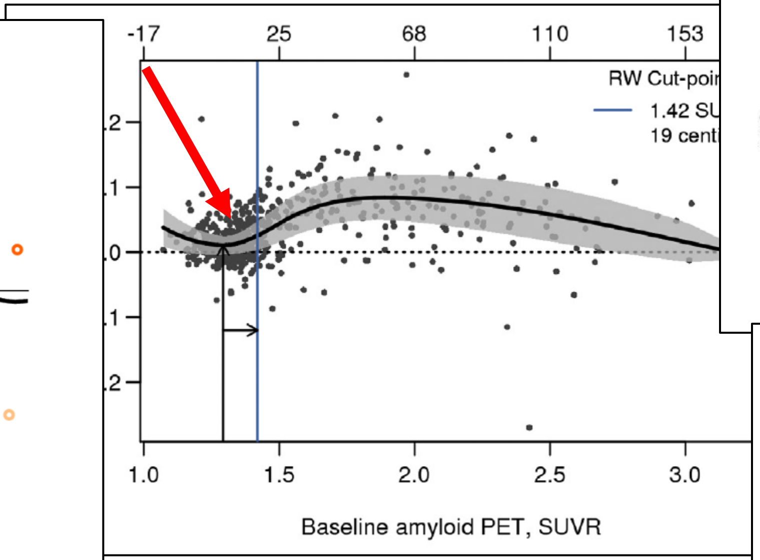
Targeting Interval of Rapid Acceleration (Rationale for A3 Trial)



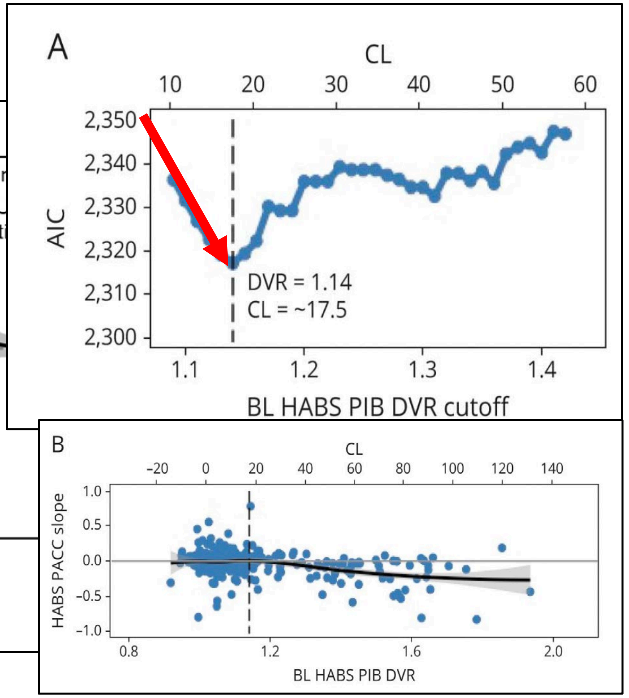


AIBL data
Villain et al *Brain* 2012

ADNI data
Courtesy of John Sims

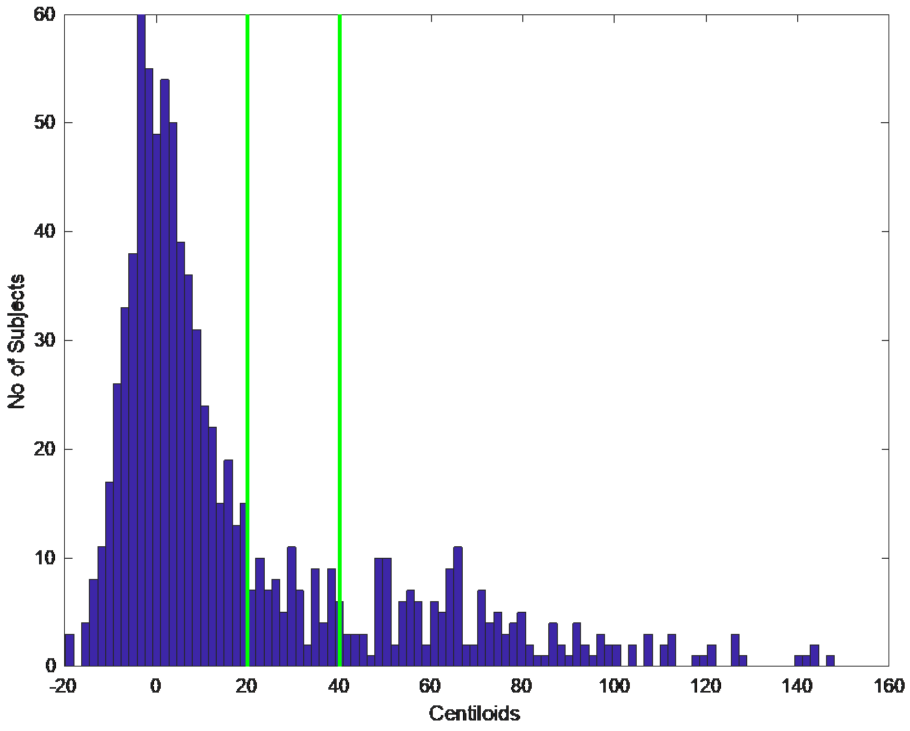


Mayo Clinic data
Jack C et al *Alz & Dem* 2016

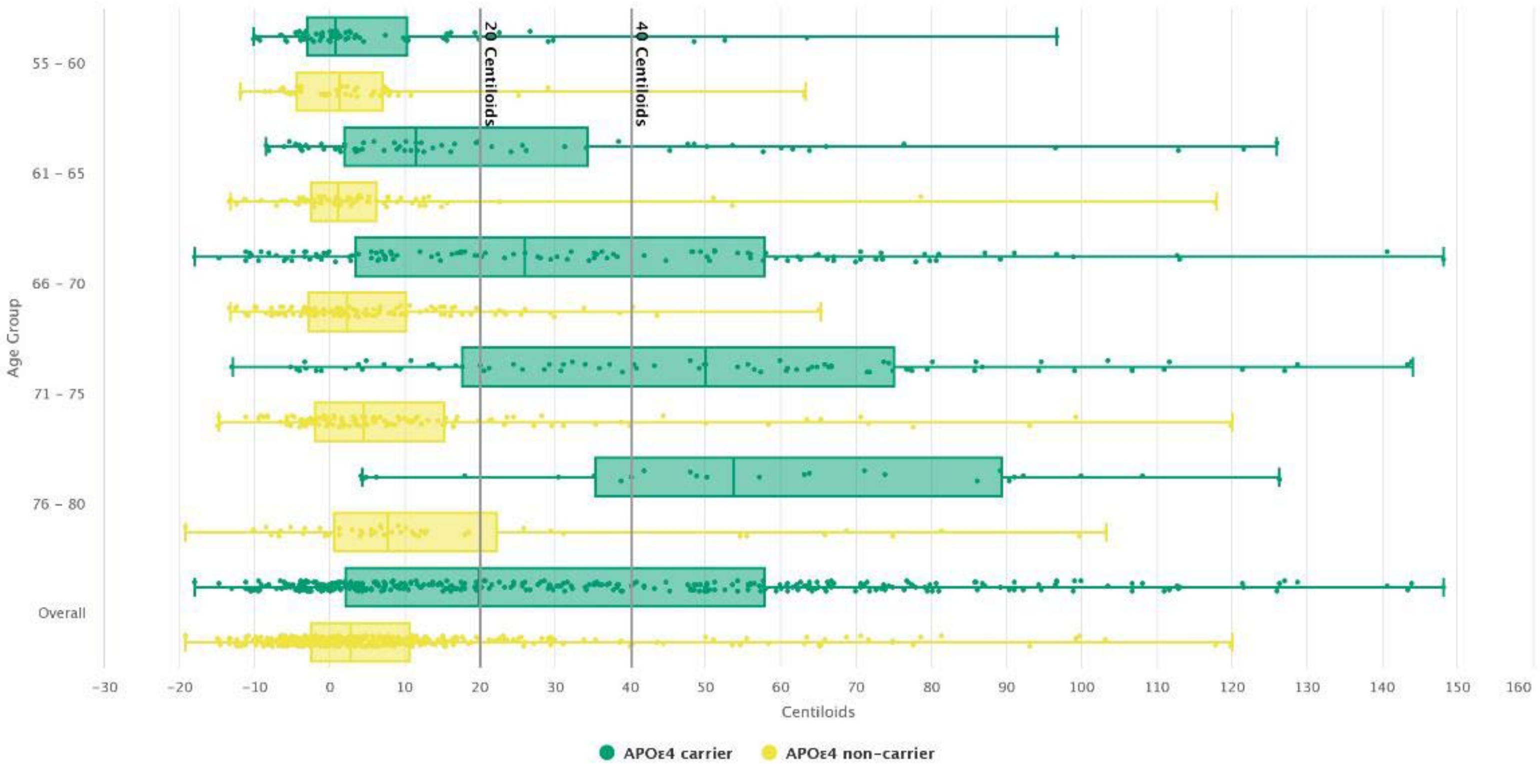


Harvard Aging Brain Study
Farrell M et al *Neurology* 2021

Screening ^{18}F NAV4694 Amyloid PET data (n=880 as of Oct 6, 2021)



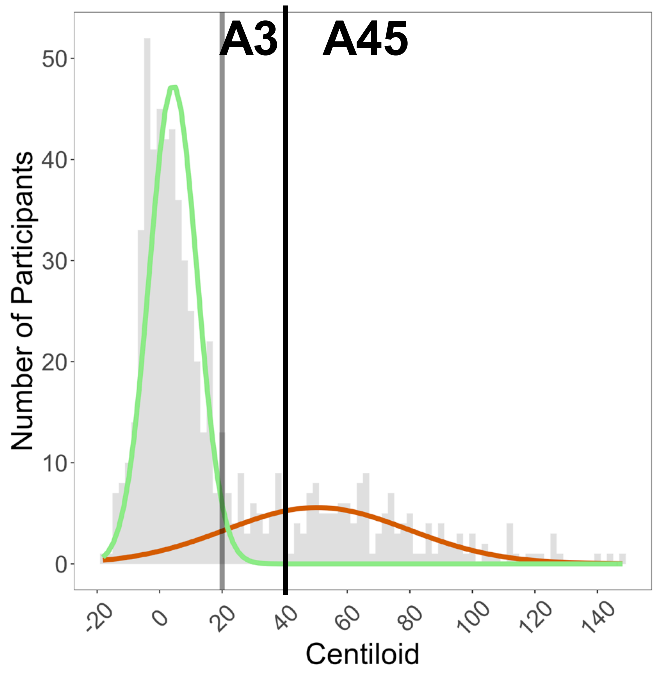
Courtesy of InVicro

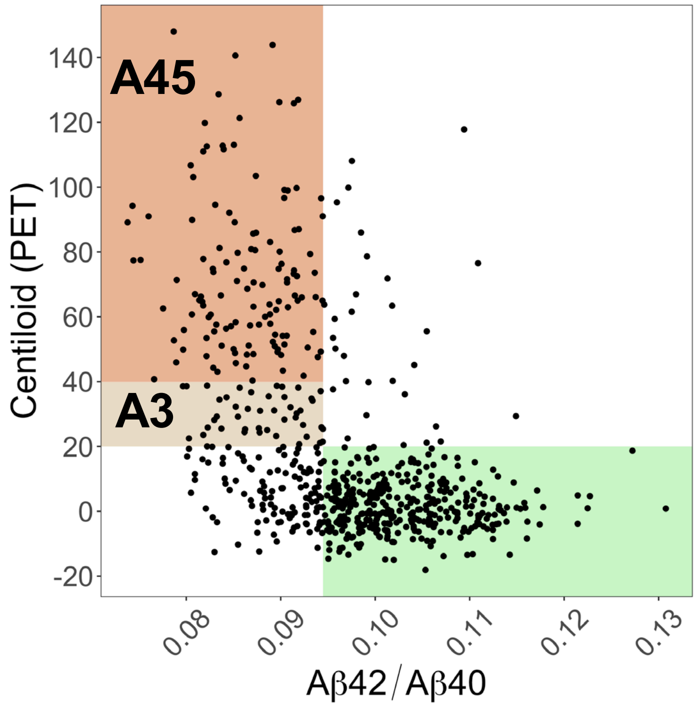


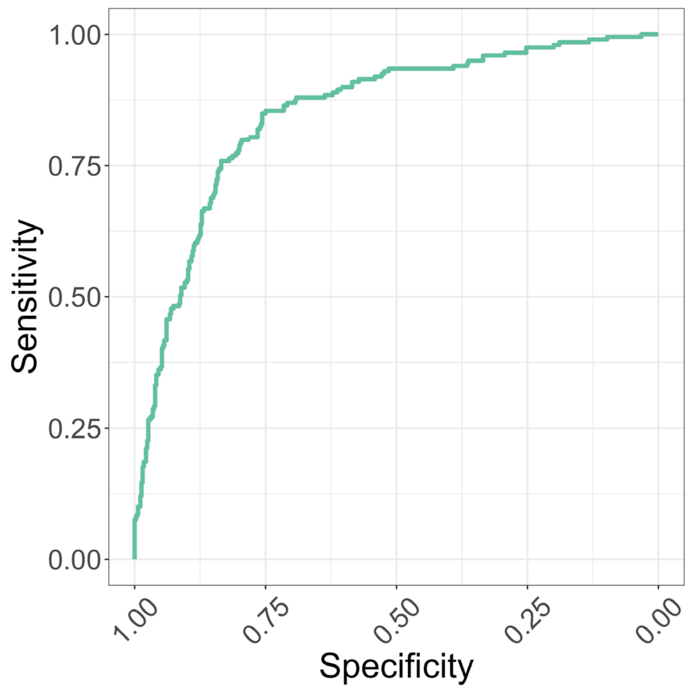
Courtesy of ATRI Biostats

AHEADSTUDY.ORG

Plasma Aβ42/40 Ratio by Amyloid PET (N=659)



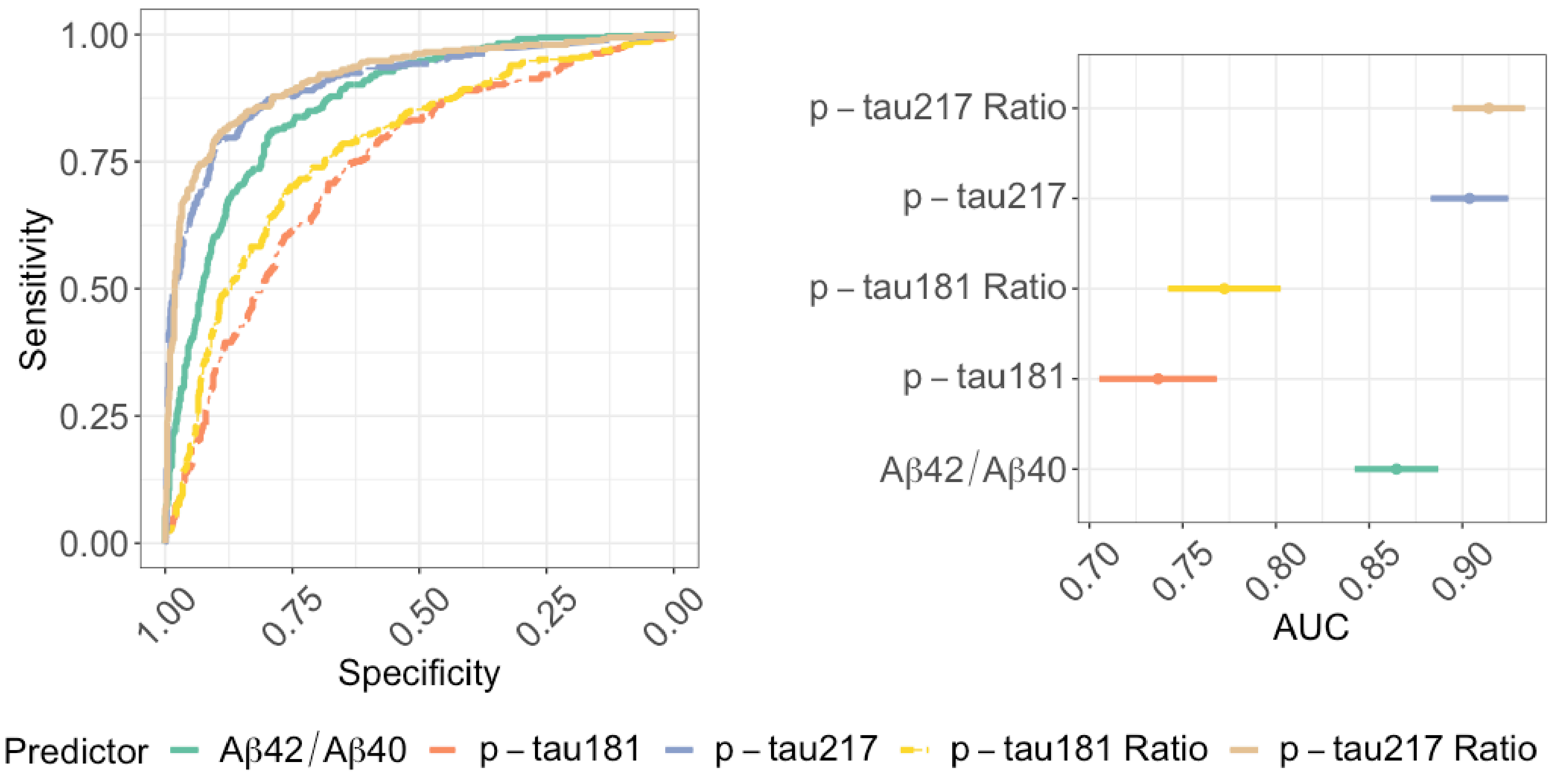




Biomarker	AUC	Cut Point	Accuracy	Youden	Sensitivity	Specificity	PPV	NPV
Plasma Aβ42/Aβ40	**0.851** (0.818, 0.883)	0.094	0.78	0.61	0.85	0.76	0.60	0.92

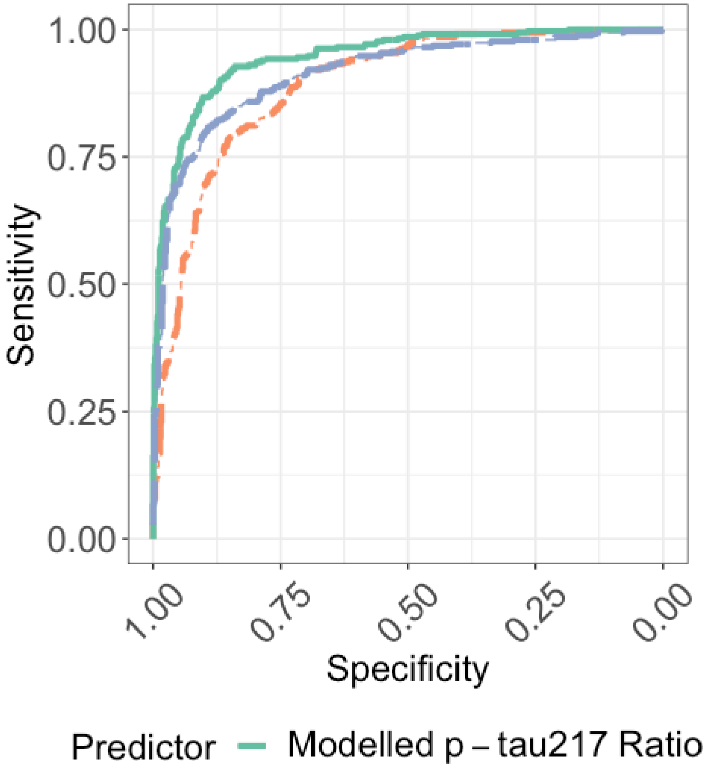
Sperling R et al *CTAD* 2021

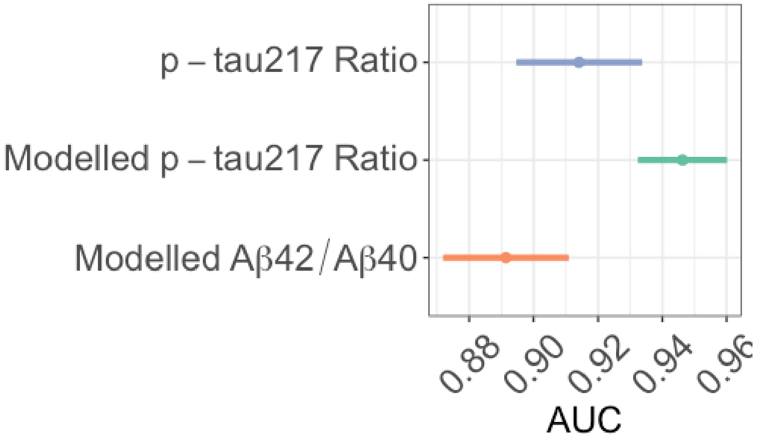
ROC Analyses for Identifying Amyloid PET >20CL (N=1085)



Predictor	N	AUC	Cut Point	Accuracy	Youden	Sensitivity	Specificity	PPV	NPV
Aβ42/Aβ40	1085	0.865 (0.842, 0.887)	0.095	0.796	0.601	0.812	0.789	0.642	0.900
p-tau181	1085	0.737 (0.705, 0.768)	9.395	0.688	0.387	0.707	0.680	0.507	0.833
p-tau217	1085	0.904 (0.883, 0.925)	1.214	0.860	0.685	0.794	0.891	0.772	0.903
p-tau181 Ratio	1085	0.772 (0.742, 0.803)	16.462	0.743	0.456	0.687	0.769	0.581	0.840
p-tau217 Ratio	1085	0.914 (0.895, 0.934)	1.554	0.865	0.701	0.809	0.892	0.777	0.909

Modeled plasma ratios to predict Amyloid PET >20CL (N=1085)





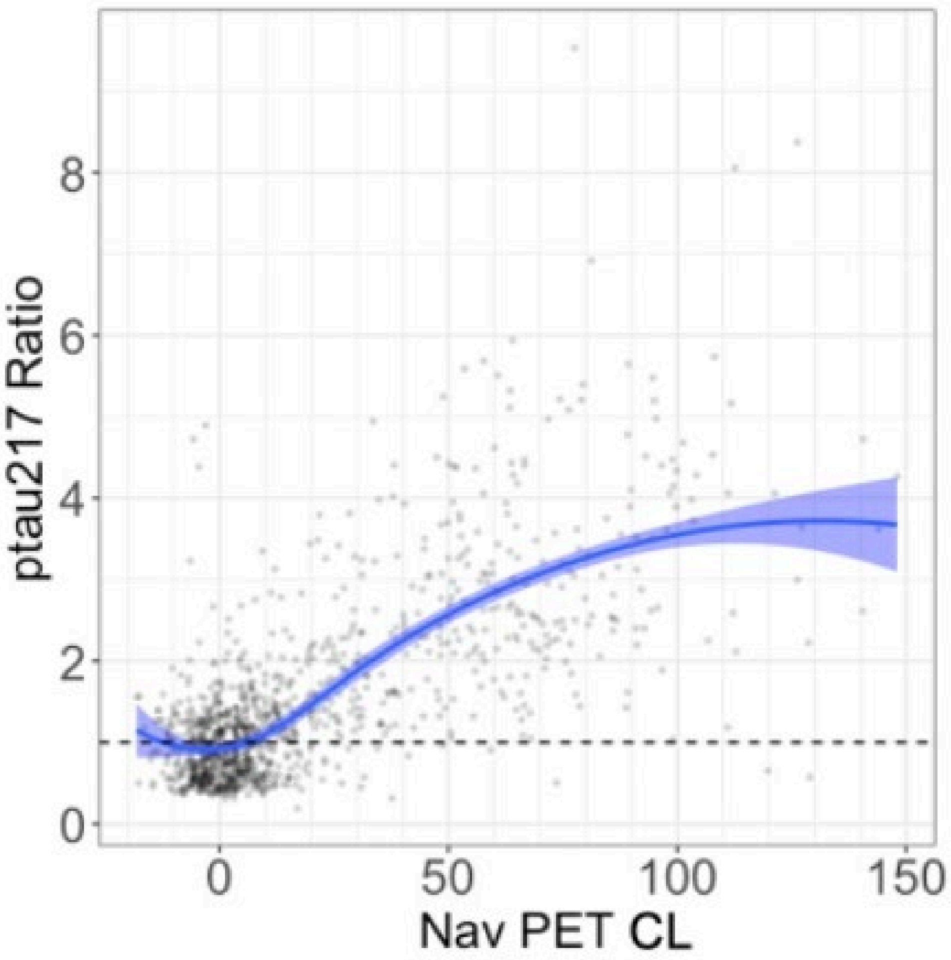
Model for p-tau217 ratio includes Age, APOE, Aβ42/40

Model for Aβ42/40 includes Age, APOE

Predictor	N	AUC	Cut Point	Accuracy	Youden	Sensitivity	Specificity	PPV	NPV
Modelled p-tau217 Ratio	1085	0.946 (0.932, 0.960)	14.690	0.879	0.770	0.901	0.869	0.762	0.950
Modelled Aβ42/Aβ40	1085	0.891 (0.872, 0.911)	24.332	0.830	0.638	0.788	0.850	0.710	0.896
p-tau217 Ratio	1085	0.914 (0.895, 0.934)	1.554	0.865	0.701	0.809	0.892	0.777	0.909

Rissman R et al (to be presented) *CTAD* 2022

How early does p-tau217 begin to change in sporadic AD?



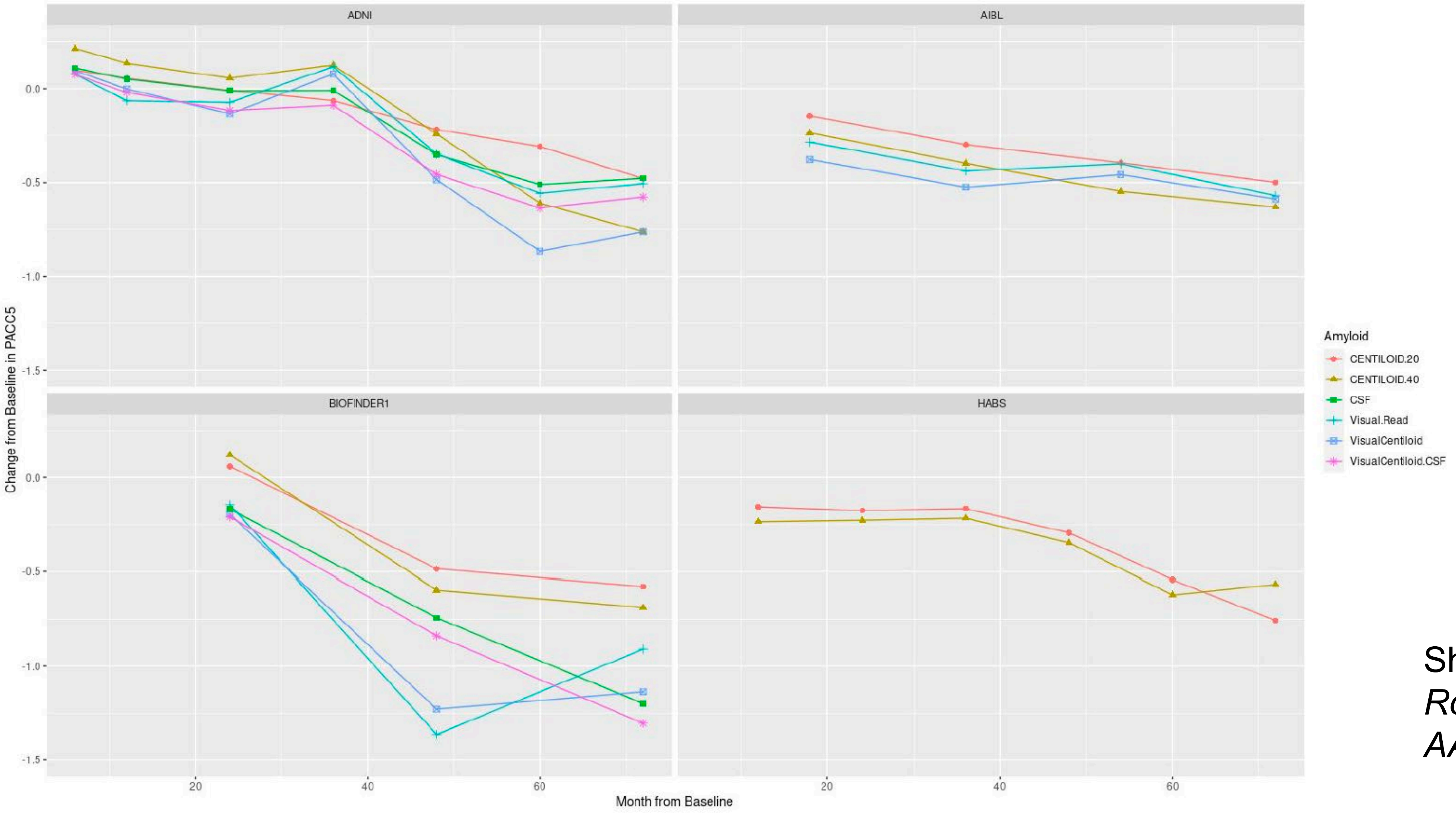
AHEAD Study (N=1085) Courtesy of ATRI Biostats

Relationship of CL to Visual Reads in Preclinical AD across Cohorts

Shiffman C et al
Roche
AAIC 2022

	Study	Centiloid Threshold 10	20	30	40	50
Amyloid positive prevalence (%)	ADNI (n=248)	55	35	26	20	16
	BioFINDER-1 (n=172)	60	24	18	15	13
	AIBL (n=630)	39	26	21	17	15
	HABS (n=238)	53	32	23	19	17
PPV for VR+ (assuming 15% VR+) (%)	ADNI (n=248)	27	41	52	66	77
	BioFINDER-1 (n=172)	24	53	68	74	80
	AIBL (n=630)	35	53	66	72	76
NPV for VR+ (assuming 15% VR+) (%)	ADNI (n=248)	99	98	96	96	96
	BioFINDER-1 (n=172)	100	100	100	99	98
	AIBL (n=630)	100	100	100	98	98
Sensitivity of VRs (%)	ADNI (n=248)	96	89	80	80	76
	BioFINDER-1 (n=172)	100	100	100	94	89
	AIBL (n=630)	100	100	99	87	90
Specificity of VRs (%)	ADNI (n=248)	55	77	87	93	96
	BioFINDER-1 (n=172)	45	84	92	94	96
	AIBL (n=630)	67	84	91	94	95

Risk of Cognitive Decline in “A+” Normals – Various Definitions

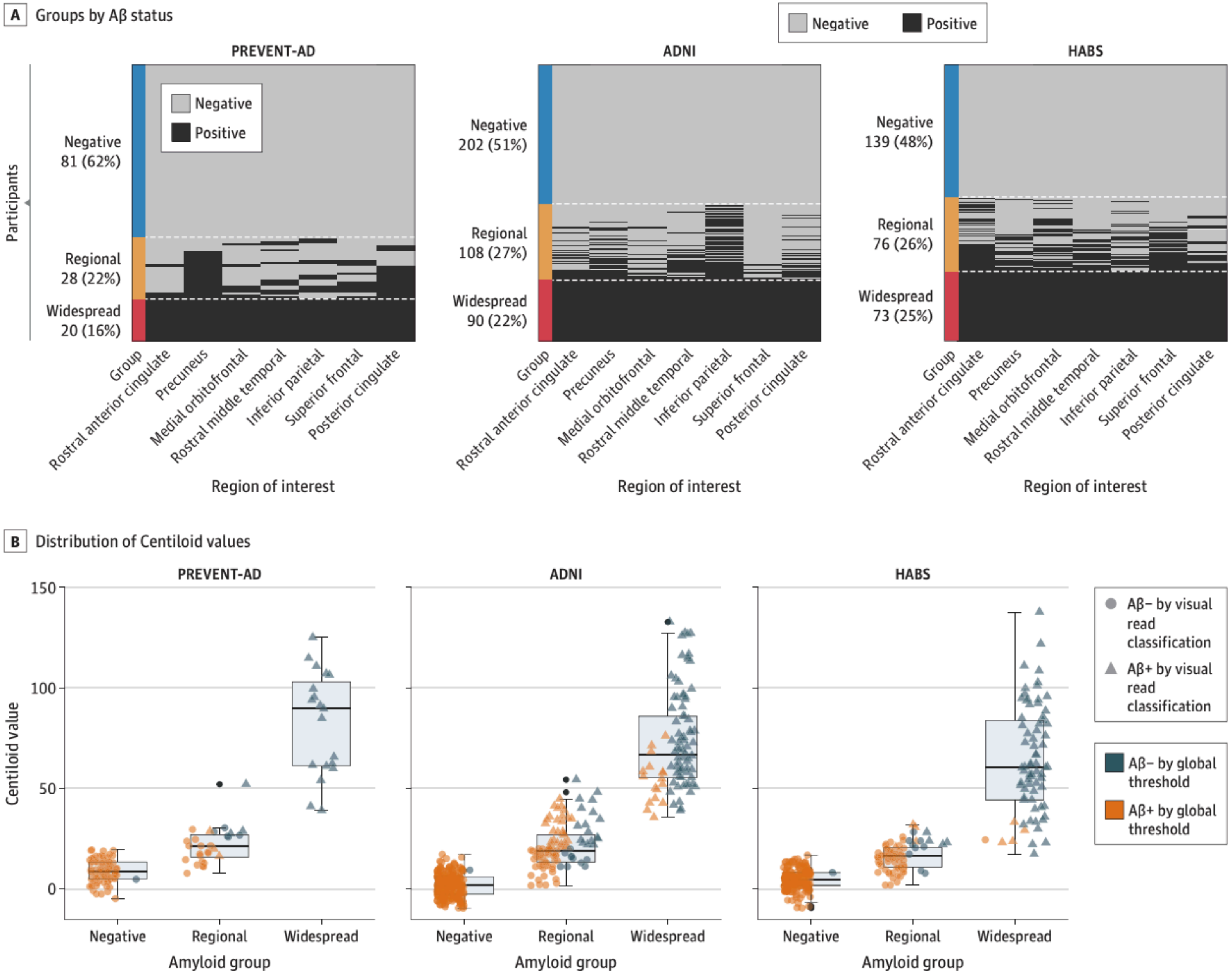


Shiffman C et al
Roche
AAIC 2022

Quantitative Amyloid PET
Additional Considerations

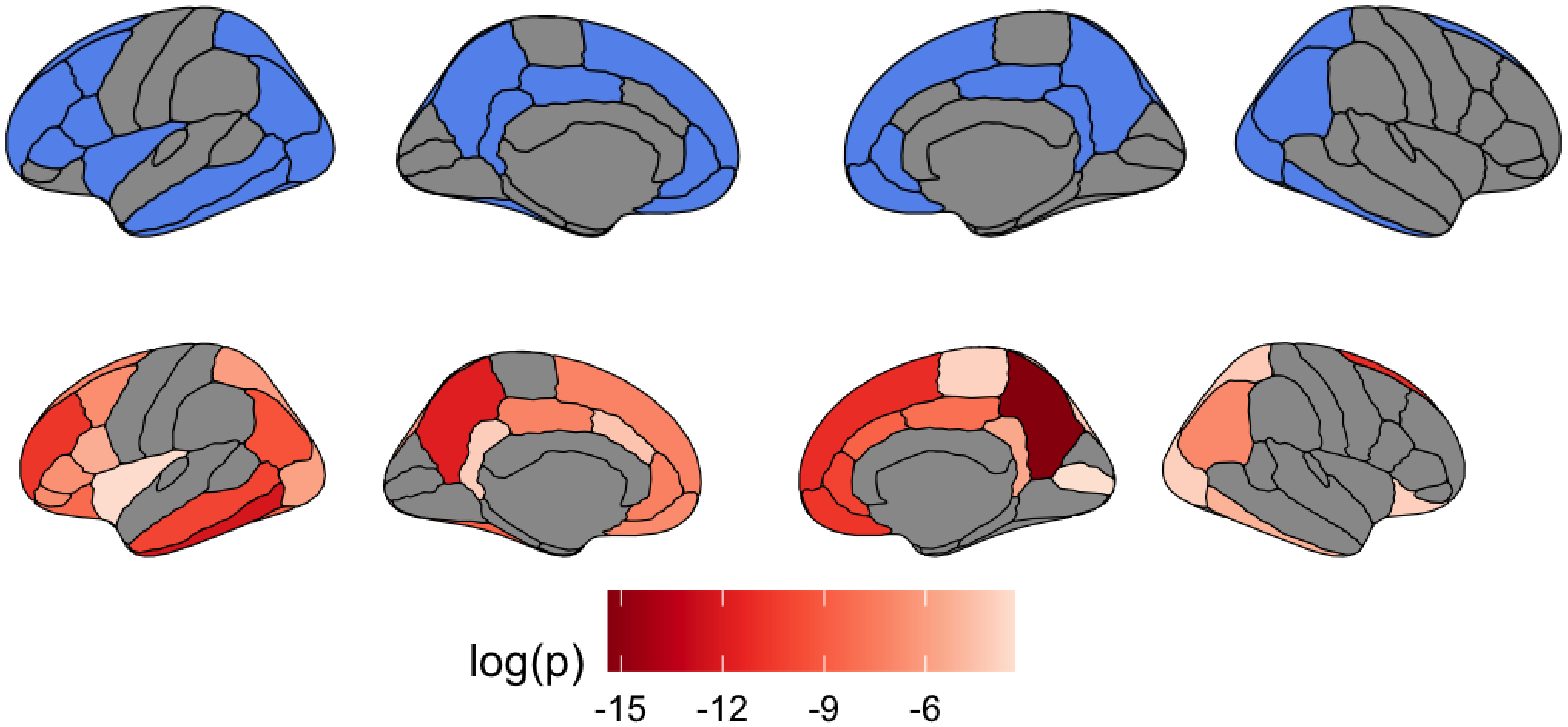
- Data from clinical trials – careful QC of all data, centralized quantitative analyses
- Much of the observational data uses 11C-PiB, most 18F tracers have more noise at low levels “zone of ambiguity”
  - 18F-NAV4694 much stronger correlation with PiB than other 18F tracers
- Relatively large cortical composite of regions of interest in standardized template
  - By stage of “positivity” high correlation among cortical regions
  - Early regions – posterior cingulate, precuneus, prefrontal, temporal
  - Extent vs. magnitude assessments

Spatial Extent Assessment of Amyloid PET



Ozlen H et al
JAMA Neurology 2022

Spatial Extent Assessment of Amyloid PET – Regional



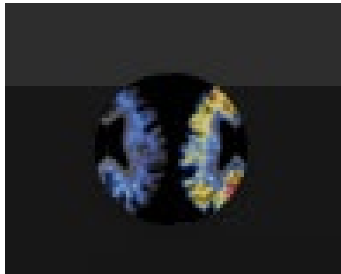
Farrell M et al (to be presented) *CTAD* 2022

Summary

- Quantitative PET is particularly important for preclinical AD
  - Prediction of future cognitive decline
  - Selection of participants for trials and eventually treatment
  - Targeted dosing?
- Plasma measures may function as proxy for amyloid PET
- Longitudinal patient monitoring likely to require quantitative amyloid PET
  - Tau PET may be more closely related to cognitive change
- Need to consider standardization for quantitative analyses
  - Centiloids helpful but cannot completely overcome tracer issues at lower levels of amyloid

Acknowledgments

- Keith Johnson and Harvard Aging Brain Study
- Paul Aisen and A4 and AHEAD 3-45 Teams at ATRI/ACTC
- A4 Teams at Eli Lilly and Avid; AHEAD Teams at Eisai
- Mayo Clinic, InVicro, Cogstate, Cerveau
- A4/LEARN, AHEAD3-45 Study Site Teans
- Funding from National Institute on Aging, Alzheimer's Association, Fidelity, GHR Foundation, Gates Ventures, Accelerating Medicines Partnership
- Most of the all - the research participants and their study partners!



Characteristics of brain Aβ tracers: Impact on quantification

Victor L Villemagne, MD

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Departmental and Personal Disclosures

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♦ **Consulting Relationships**:
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- Life Molecular Imaging
- Eli Lilly
- Hospicom

♦ **Stock Equity:**
- None. (*Not a gambler)*

♦ **Speaker's Honoraria:**
- Avid Radiopharmaceuticals
- Life Molecular Imaging
- Eli Lilly
- ACE Barcelona
- International Atomic Energy Agency

♦ **Editorial Boards**:
- Alzheimer's Research & Therapy
- J Neurochemistry
- Eur J Nucl Med Mol Imaging

♦ **Fees > $10,000**
- N/A. Not that lucky (*but open to offers)*

  (Please see me at the end of the presentation, or email me an offer I can't refuse to victor.villemagne@gmail.com)

Travel and lodging expenses for this talk covered by the Food and Drug Administration

Outline

Many tracers, same target

Tracer idiosyncrasies:

- *Binding characteristics*
- *Tracer kinetics*
- *Adequacy and stability of "reference" region*
- *Discriminatory power to resolve the "ambiguous" zone*
- *Degree of non-specific binding*

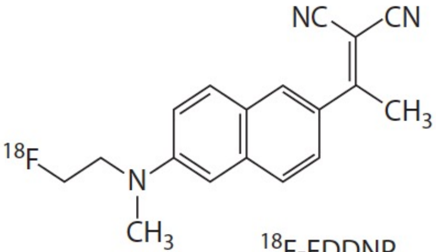
From many tracers and scales to one scale for all tracers

- Centiloid transformation

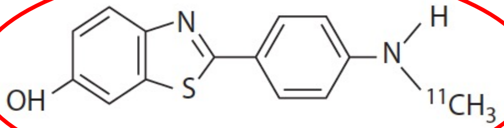
Value of semiquantification

- Research
  - *Natural history (role of APOE, PVC, change of tracer and/or PET scanner, etc.)*
- Clinical
  - *Improve diagnosis*
  - *Prediction of cognitive decline (cortical tau)*
- Trials
  - *Proof of target engagement*
  - *Establish optimal time-window for intervention*
  - *Participant selection/staging/theragnosis*
  - *Outcome measure*

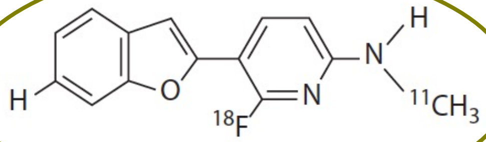
Aβ imaging



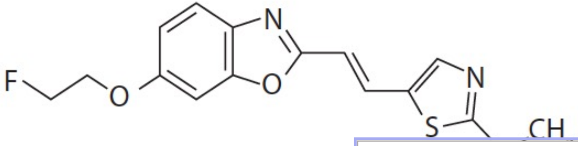
^{18}F-FDDNP



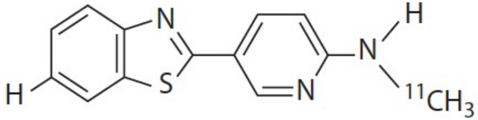
^{11}C-PiB



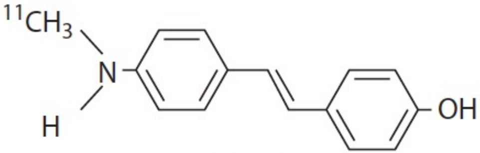
^{18}F-NAV4694



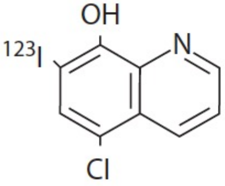
^{11}C-BF227



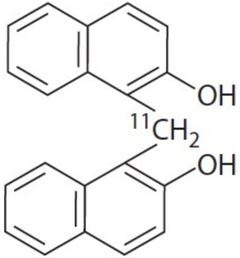
^{11}C-AZD2184



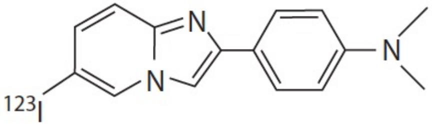
^{11}C-SB13



^{123}I-CQ

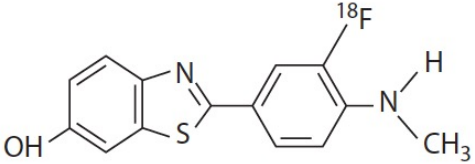


^{11}C-ST1859

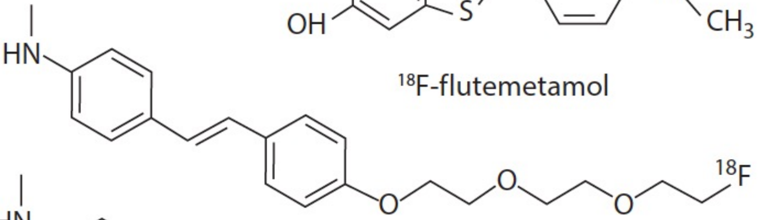


^{123}I-IMPY

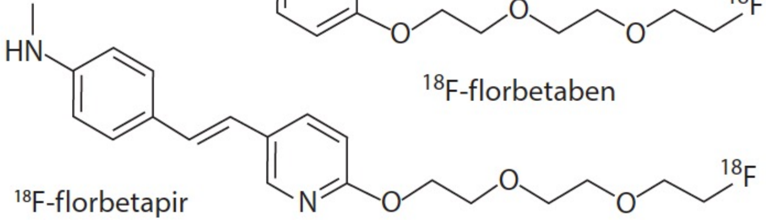
FDA/EMA approved



^{18}F-flutemetamol

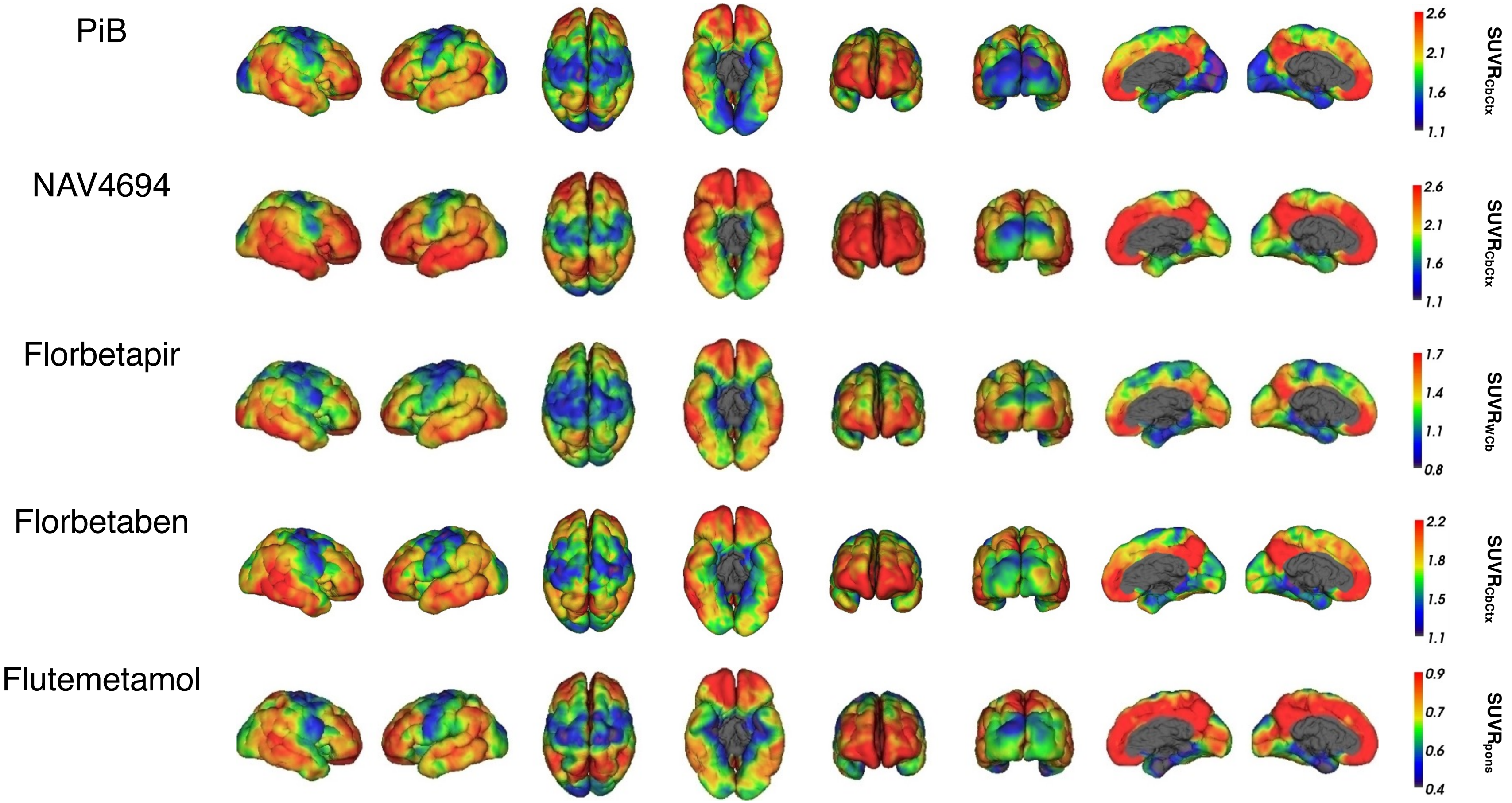


^{18}F-florbetaben



^{18}F-florbetapir

Aβ imaging in Alzheimer's disease



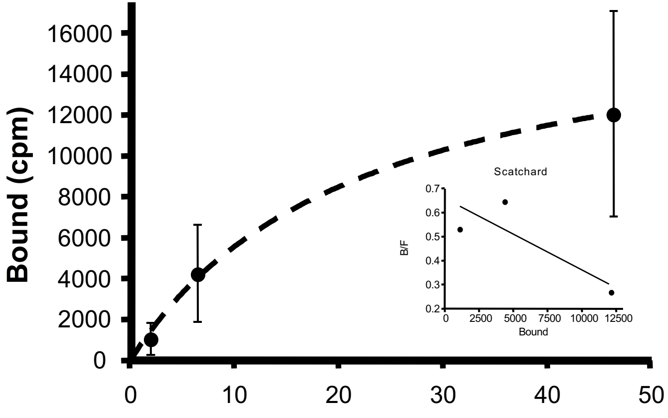
Images generated with CapAIBL® (capaibl-milxcloud.csiro.au)
CSIRO Biomedical Imaging Group

Aβ tracers are markers of fibrillar Aβ

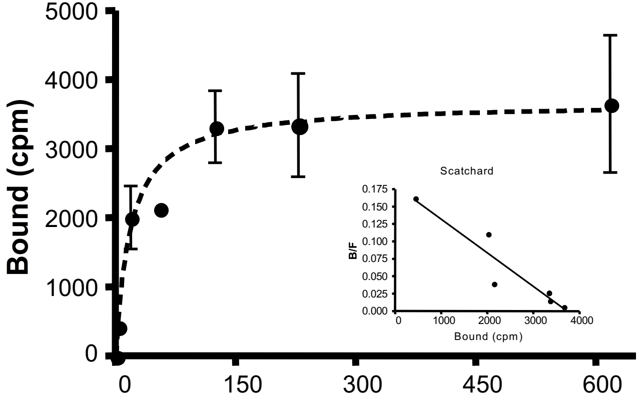
IHC/Fluorescence studies

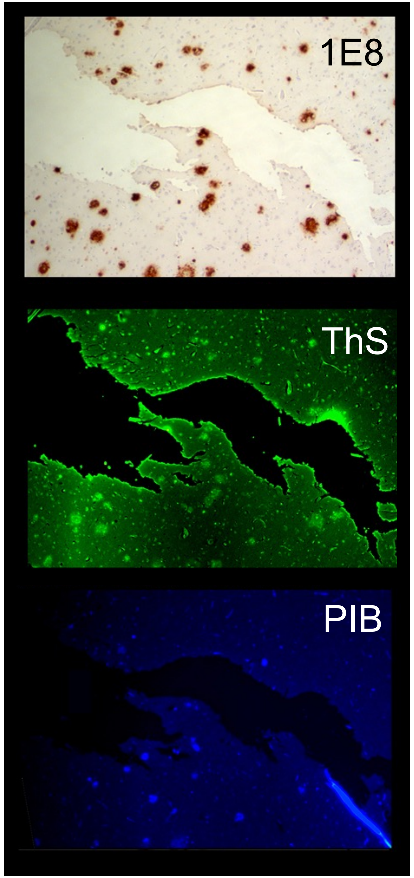
^{3}H-PIB in vitro binding saturation studies

Aβ42 fibrils



AD Brain Homogenates

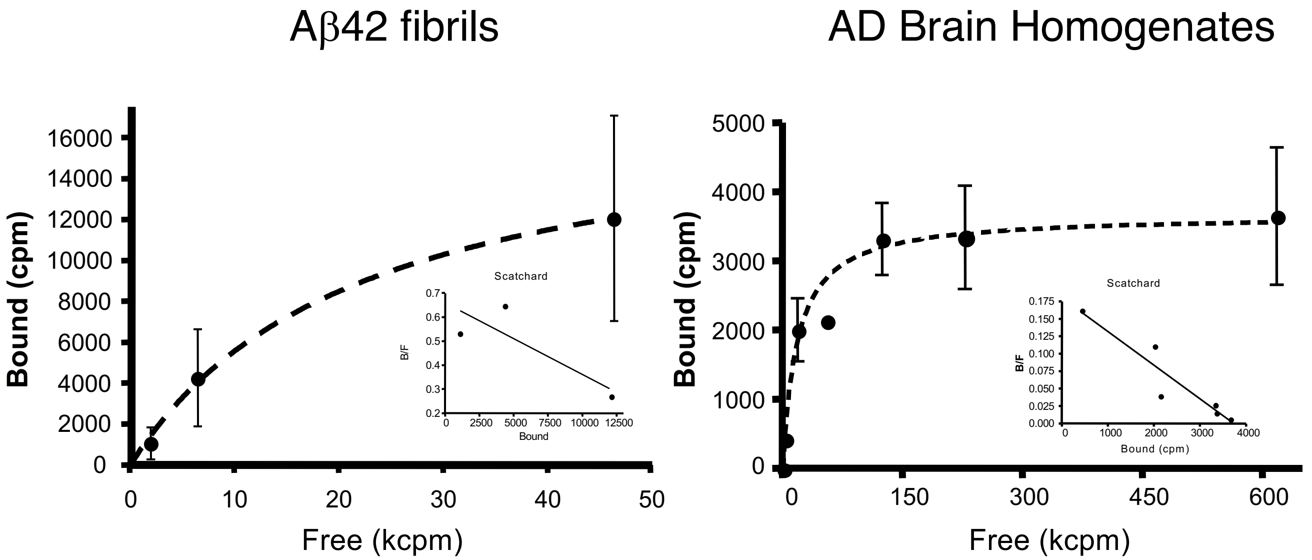


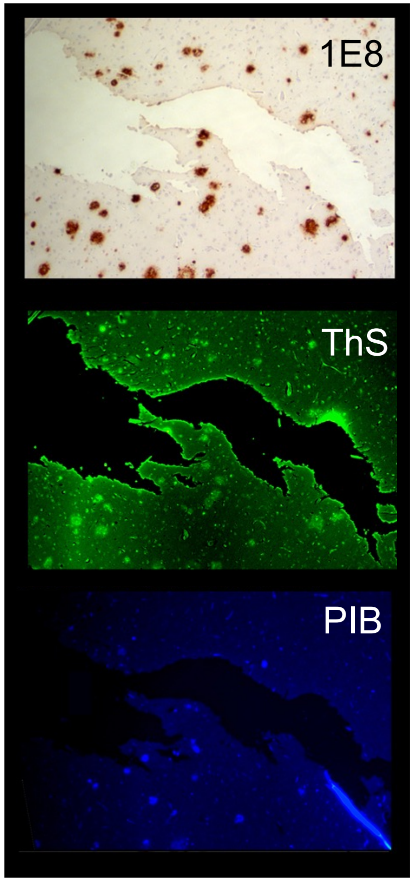


Aβ tracers are markers of fibrillar Aβ

IHC/Fluorescence studies

^{3}H-PIB in vitro binding saturation studies





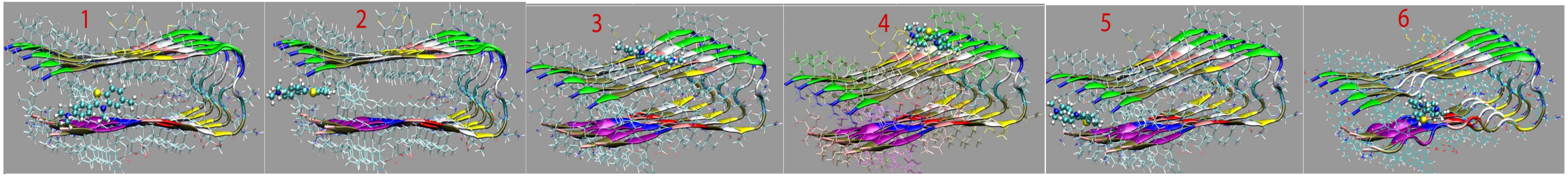
Aβ tracers bind Aβ oligomers with much lower affinity (3-4x lower)
Aβ oligomers represent ~1% of all in the brain
Aβ oligomers last in soluble form ~2-3 hours before forming fibrils

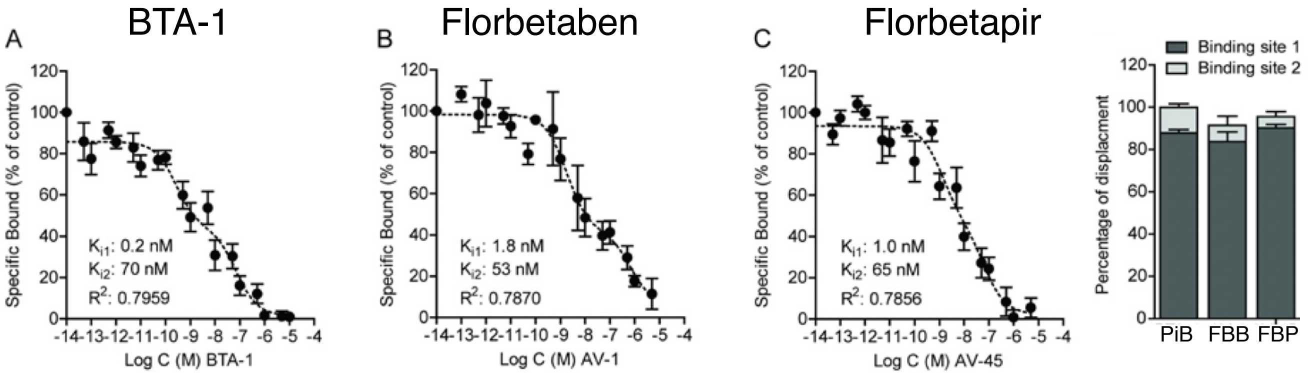
Aβ tracers are markers of fibrillar Aβ

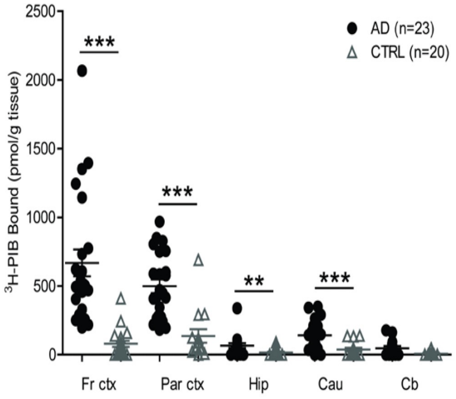
Amyloid Fibril-Induced Structural and Spectral Modifications in the Thioflavin-T Optical Probe

N. Arul Murugan,*,† Jógvan Magnus Haugaard Olsen,‡ Jacob Kongsted,‡ Zilvinas Rinkevicius,† Kestutis Aidas,§ and Hans Ågren†

J. Phys. Chem. Lett. 2013, 4, 70–77



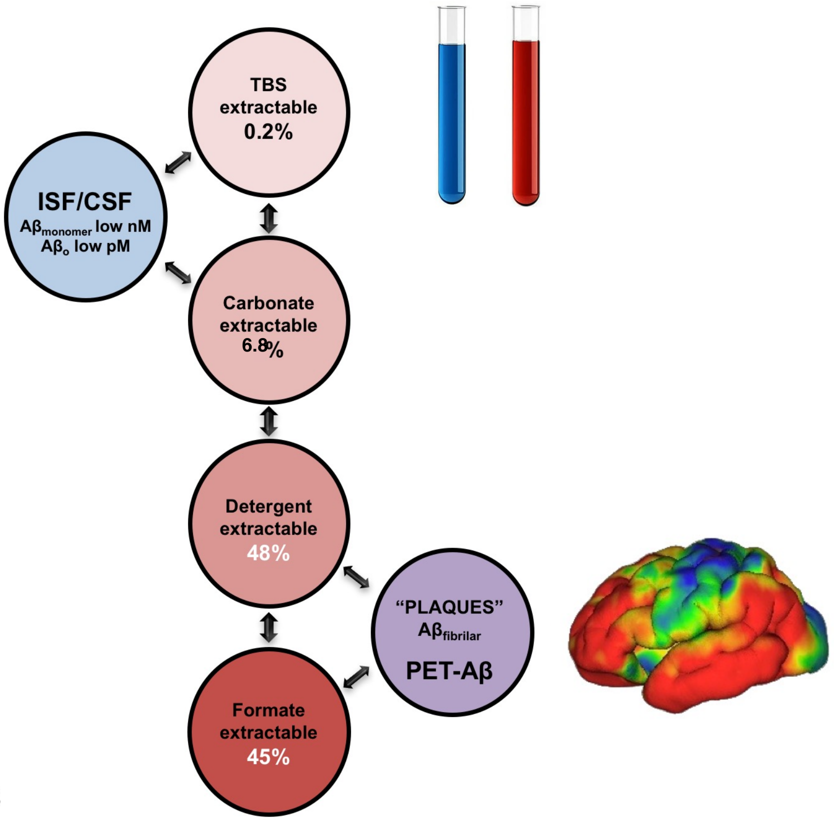




The relative proportion of high-affinity to low-affinity sites is 6:1 in the frontal cortex and 3:1 in the hippocampus.

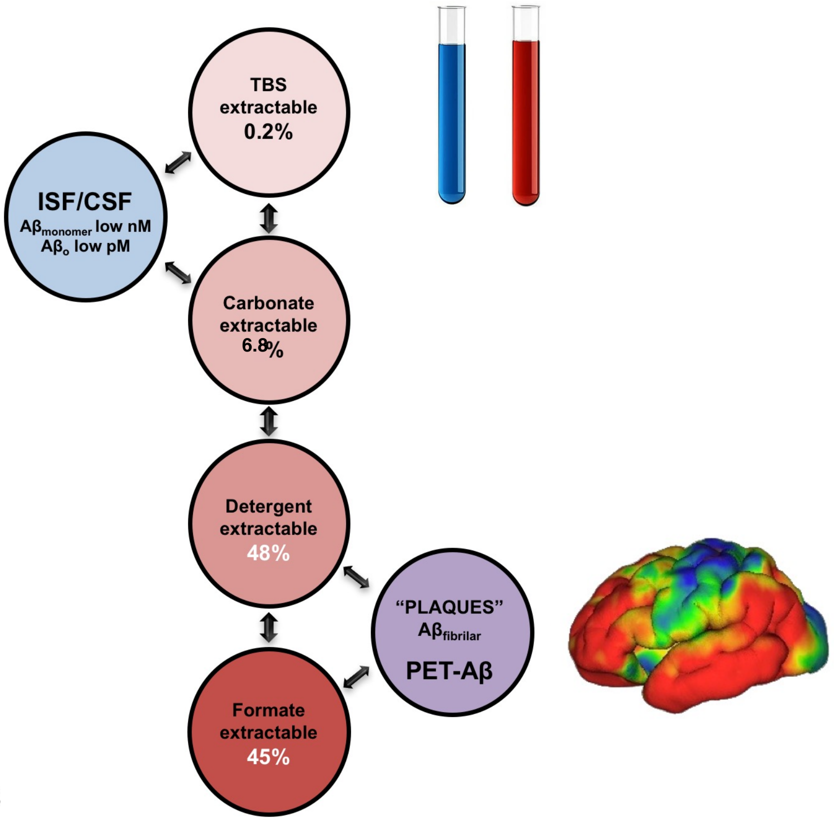
adapted from Ni et al., Brain, 2013.

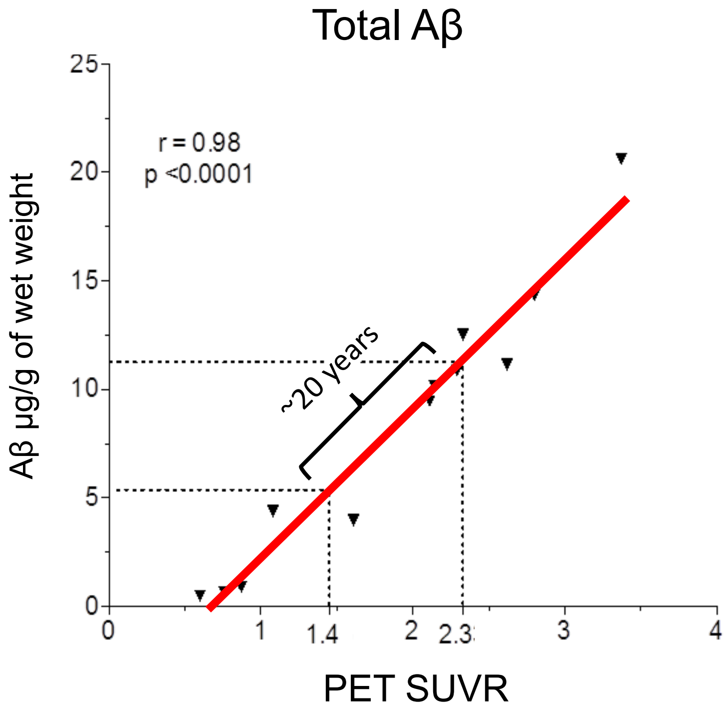
Relationship between PET SUVR and brain Aβ



adapted from Roberts et al, Brain, 2017

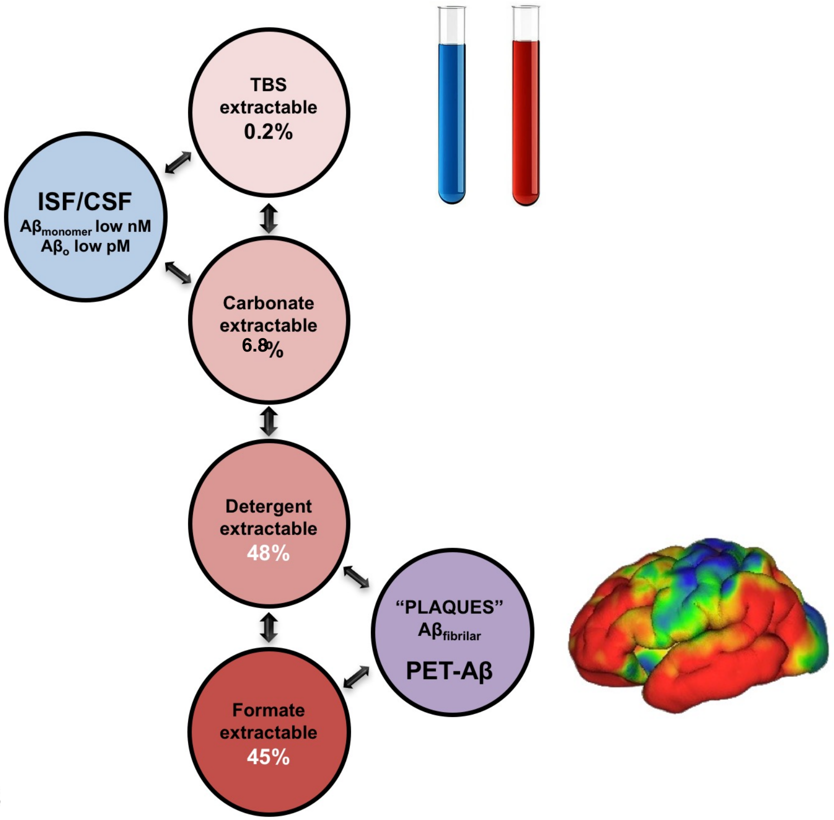
Relationship between PET SUVR and brain Aβ



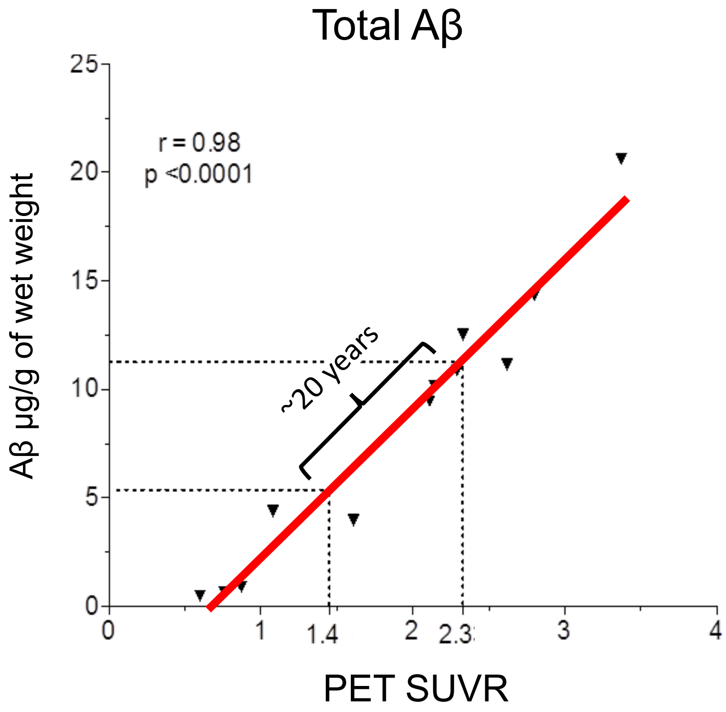


adapted from Roberts et al, Brain, 2017

Relationship between PET SUVR and brain Aβ



adapted from Roberts et al, Brain, 2017



PET SUVR in Aβ mass units

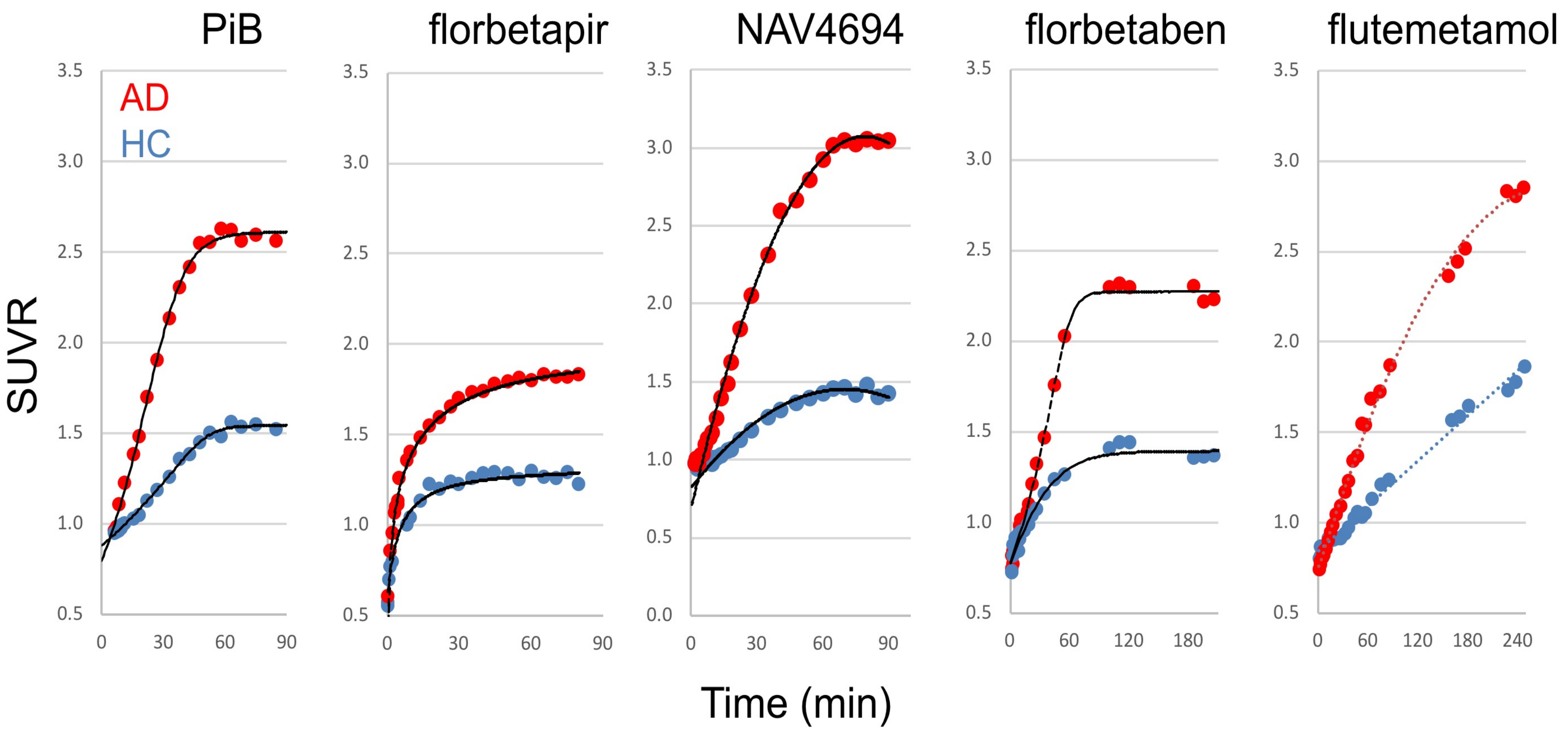
1.4 SUVR = 5.0 µg Aβ/g of grey matter

2.3 SUVR = 11.2 µg Aβ/g of grey matter

estimated rate of Aβ accumulation = **28 ng/hr**

(~2-5% decrease in clearance rates)

Aβ imaging: tracer kinetics

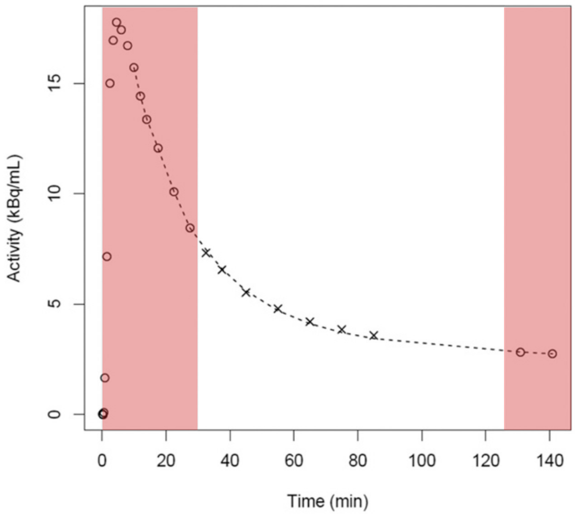


Alternatives to full dynamic acquisitions

Optimized dual-time-window protocols for quantitative [^{18}F]flutemetamol and [^{18}F]florbetaben PET studies

Heeman *et al. EJNMMI Research* (2019) 9:32
https://doi.org/10.1186/s13550-019-0499-4

Fiona Heeman[1*], Maqsood Yaqub[1], Isadora Lopes Alves[1], Kerstin Heurling[2], Johannes Berkhof[3], Juan Domingo Gispert[4,5,6], Santiago Bullich[7], Christopher Foley[8], and Adriaan A. Lammertsma[1] on behalf of the AMYPAD Consortium



Exploiting the Full Potential of β-Amyloid and Tau PET Imaging for Drug Efficacy Testing

The Journal of Nuclear Medicine • Vol. 61 • No. 8 • 2020

Henryk Barthel[1], John Seibyl[2], Adriaan A. Lammertsma[3], Victor L. Villemagne[4,5], and Osama Sabri[1]

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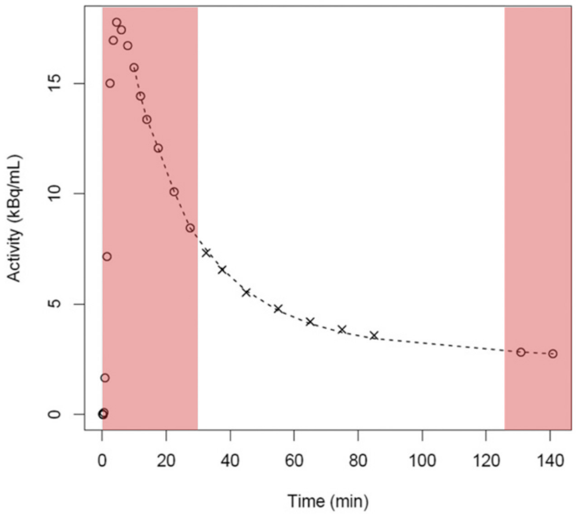
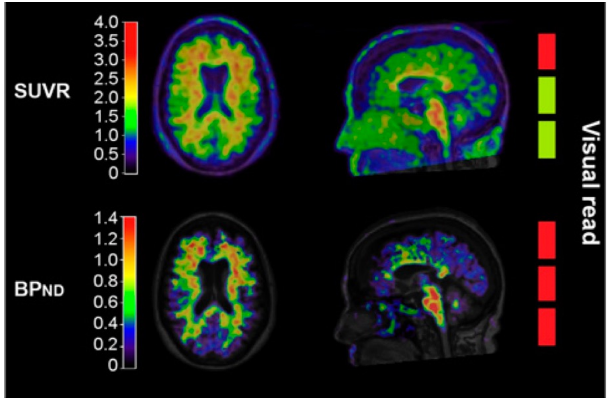
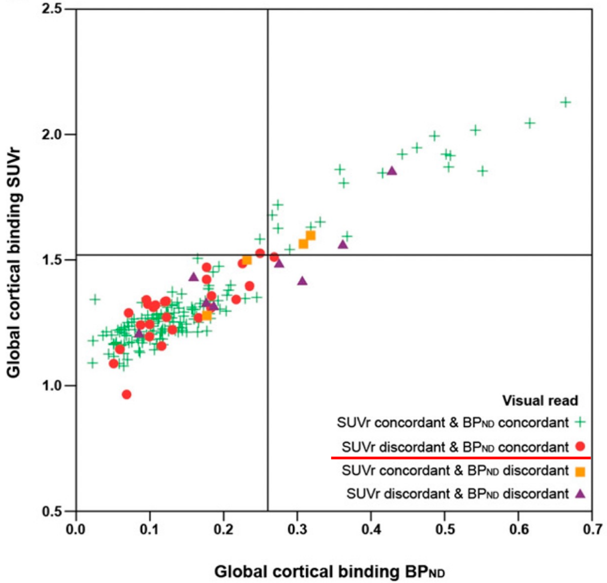


Assessing Amyloid Pathology in Cognitively Normal Subjects Using ^{18}F-Flutemetamol PET: Comparing Visual Reads and Quantitative Methods

J Nucl Med 2019; 60:541–547

Lyduine E. Collij*[1], Elles Konijnenberg*[2], Juhan Reimand[1,3,4], Mara ten Kate[2], Anouk den Braber[2,5], Isadora Lopes Alves[1], Marissa Zwan[2], Maqsood Yaqub[1], Daniëlle M.E. van Assema[6], Alle Meije Wink[1], Adriaan A. Lammertsma[1], Philip Scheltens[2], Pieter Jelle Visser[2], Frederik Barkhof[1,7], and Bart N.M. van Berckel[1]





Exploiting the Full Potential of β-Amyloid and Tau PET Imaging for Drug Efficacy Testing

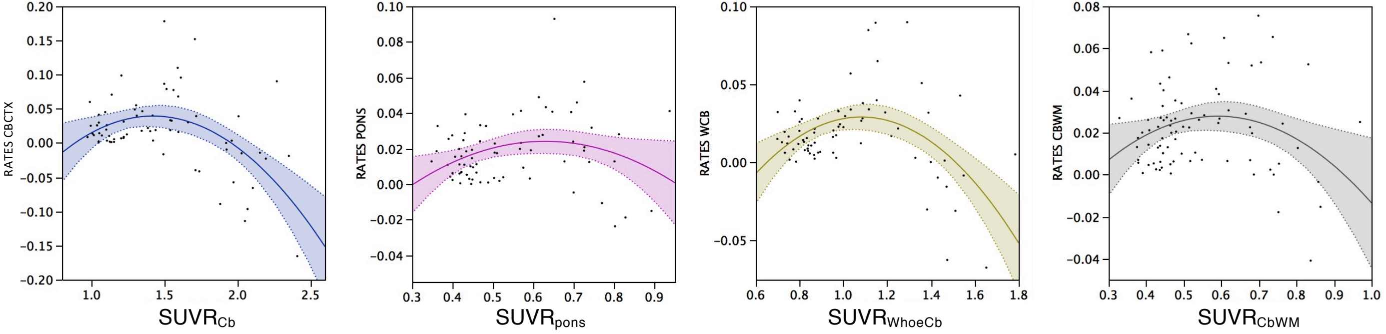
The Journal of Nuclear Medicine • Vol. 61 • No. 8 • 2020

Henryk Barthel[1], John Seibyl[2], Adriaan A. Lammertsma[3], Victor L. Villemagne[4,5], and Osama Sabri[1]

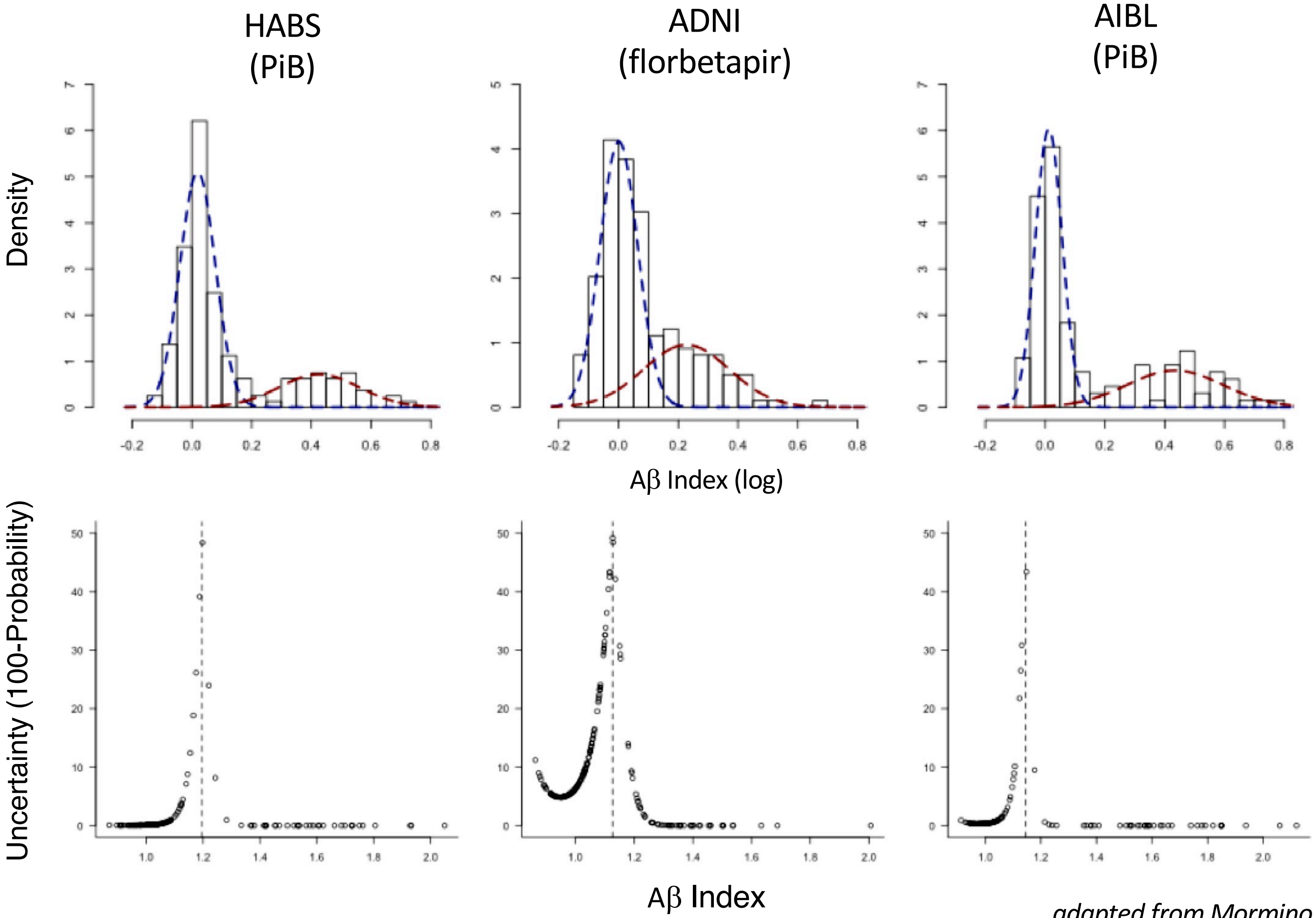
Aβ imaging: effect of “reference region”

	n (HC/MCI/AD)	CB CTX	WHOLE CB	PONS	CB WM	SWM	SWMKCER	SWMKCER"	WHOLE CB + PONS	SWM + PONS	SWMKCER + PONS	SWMKCER" + PONS	SWM + WHOLE CB + PONS	SWMKCER + PONS + WHOLE CB	SWMKCER" + PONS + WHOLE CB
ACROSS Dx															
PiB	206/68/53	optimal	n.s.	n.s.	n.s.	p=0.047	n.s.	n.s.	n.s.	p=0.047	n.s.	n.s.	p=0.01	n.s.	n.s.
FLUTE	180/61/15	n.s.	n.s.	n.s.	n.s.	P=0.05	n.s.	n.s.	optimal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
FBP	166/15/8	n.s.	n.s.	n.s.	n.s.	n.s.	optimal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
FBB	132/49/31	optimal	p=0.026	p<0.001	p=0.0015	p=0.001	p=0.005	p=0.0044	p=0.013	p=0.0019	p=0.0025	p=0.0022	p=0.0033	p=0.0063	p=0.0055
NAV	57/17/8	optimal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ACROSS TIME															
PiB	121/27/11	optimal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
FLUTE	122/28/9	n.s.	n.s.	n.s.	n.s.	n.s.	optimal	n.s.	p=0.025	p=0.095	n.s.	n.s.	n.s.	n.s.	n.s.
FBP	102/5/2	p<0.001	p=0.017	p=0.042	n.s.	n.s.	optimal	n.s.	p=0.074	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
FBB	25/39/5	n.s.	n.s.	optimal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
NAV	57/17/8	optimal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ACROSS Aβ status															
PiB	206/68/53	n.s.	n.s.	n.s.	optimal	p<0.001	p<0.001	p=<0.001	n.s.	p<0.001	p=0.01	p=0.0055	p<0.001	p=0.0022	p=0.001
FLUTE	180/61/15	p=0.098	n.s.	p=0.056	n.s.	p=0.0013	n.s.	n.s.	n.s.	n.s.	optimal	n.s.	p=0.046	n.s.	n.s.
FBP	166/15/8	optimal	n.s.	n.s.	n.s.	p=0.0047	n.s.	n.s.	n.s.	p=0.047	n.s.	n.s.	p=0.028	n.s.	n.s.
FBB	132/49/31	n.s.	n.s.	n.s.	n.s.	p=0.043	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	optimal
NAV	57/17/8	optimal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

FLUTEMETAMOL

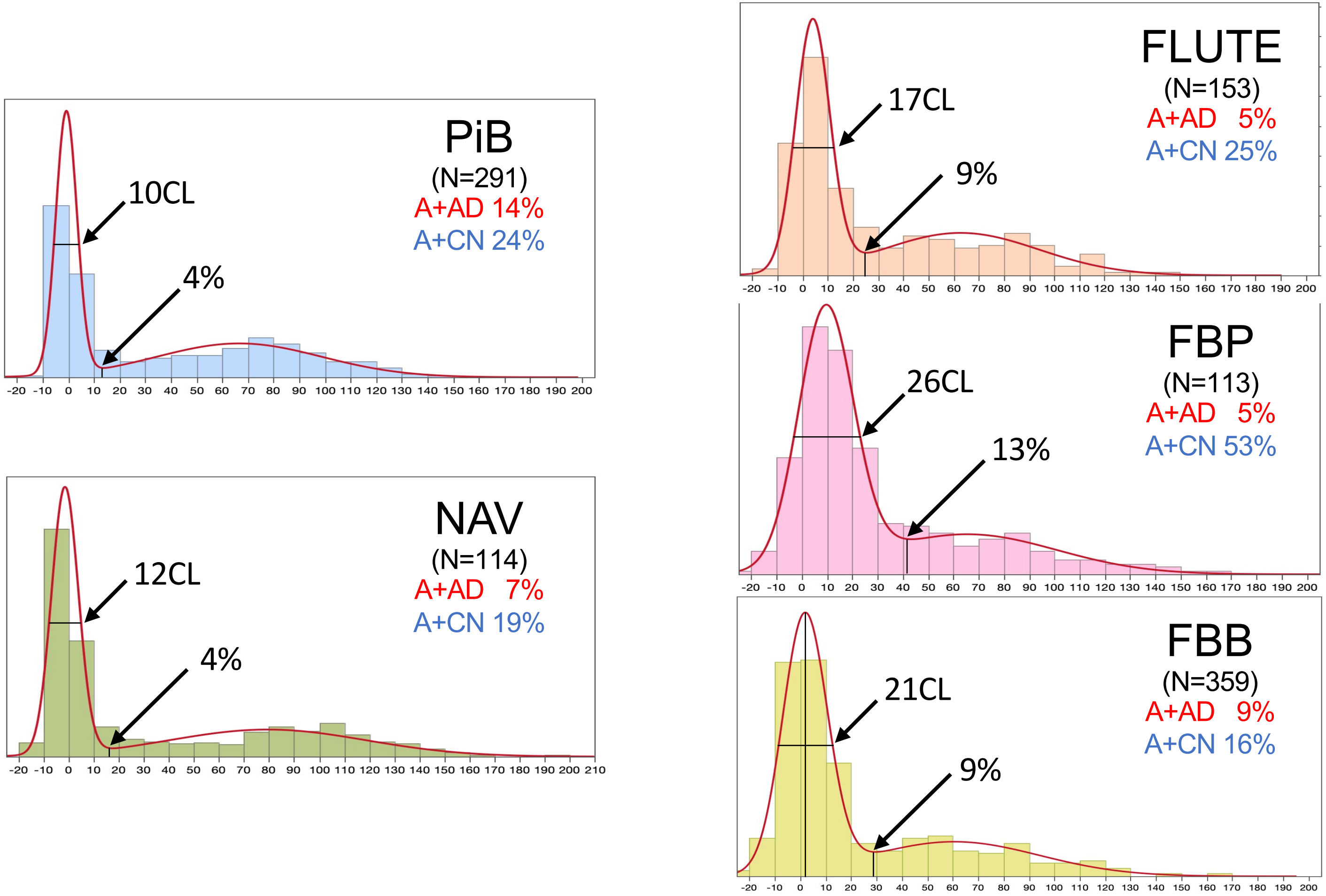


Discriminatory power of PiB and FBP

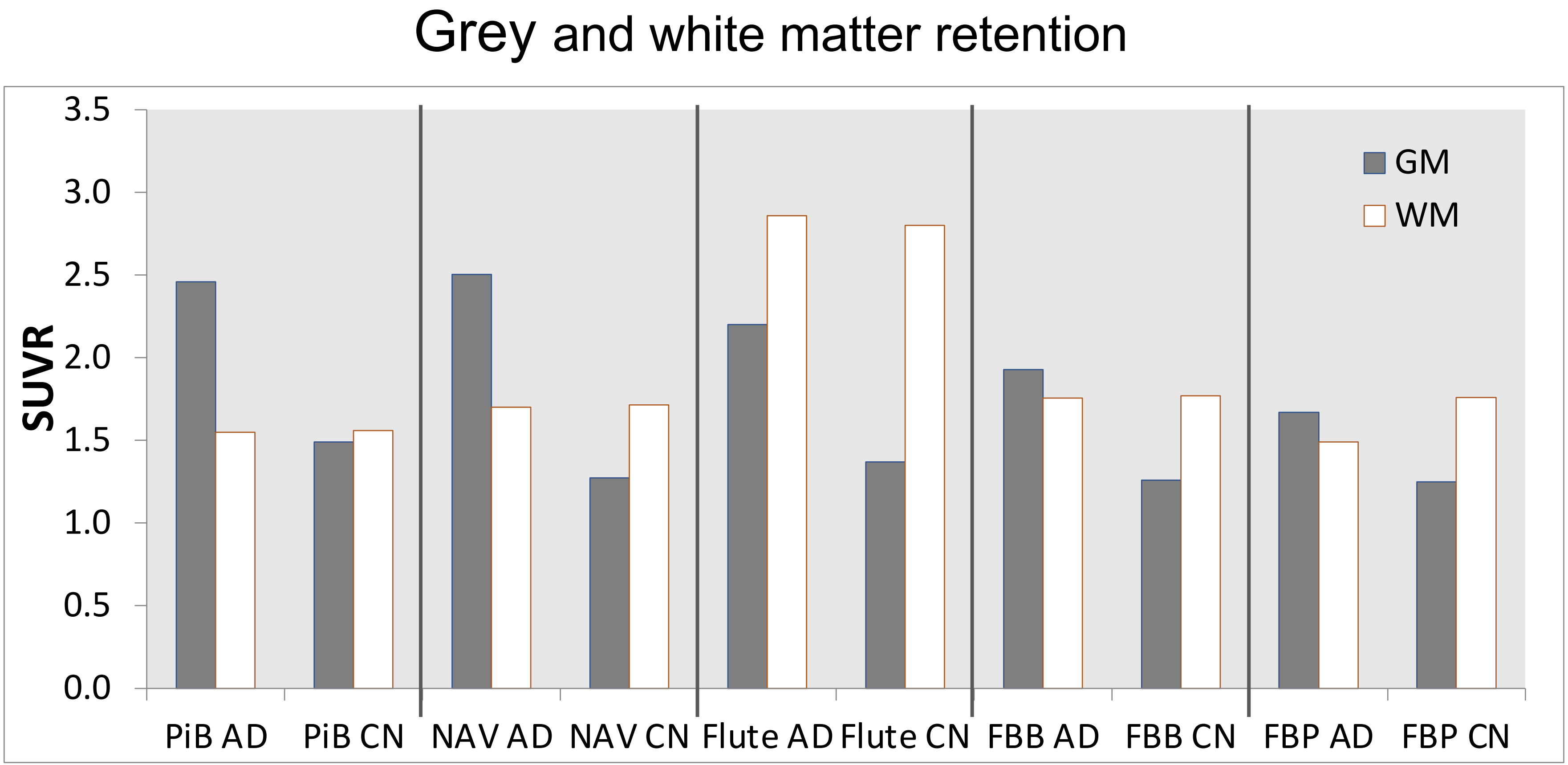


adapted from Mormino et al., Neurology, 2014

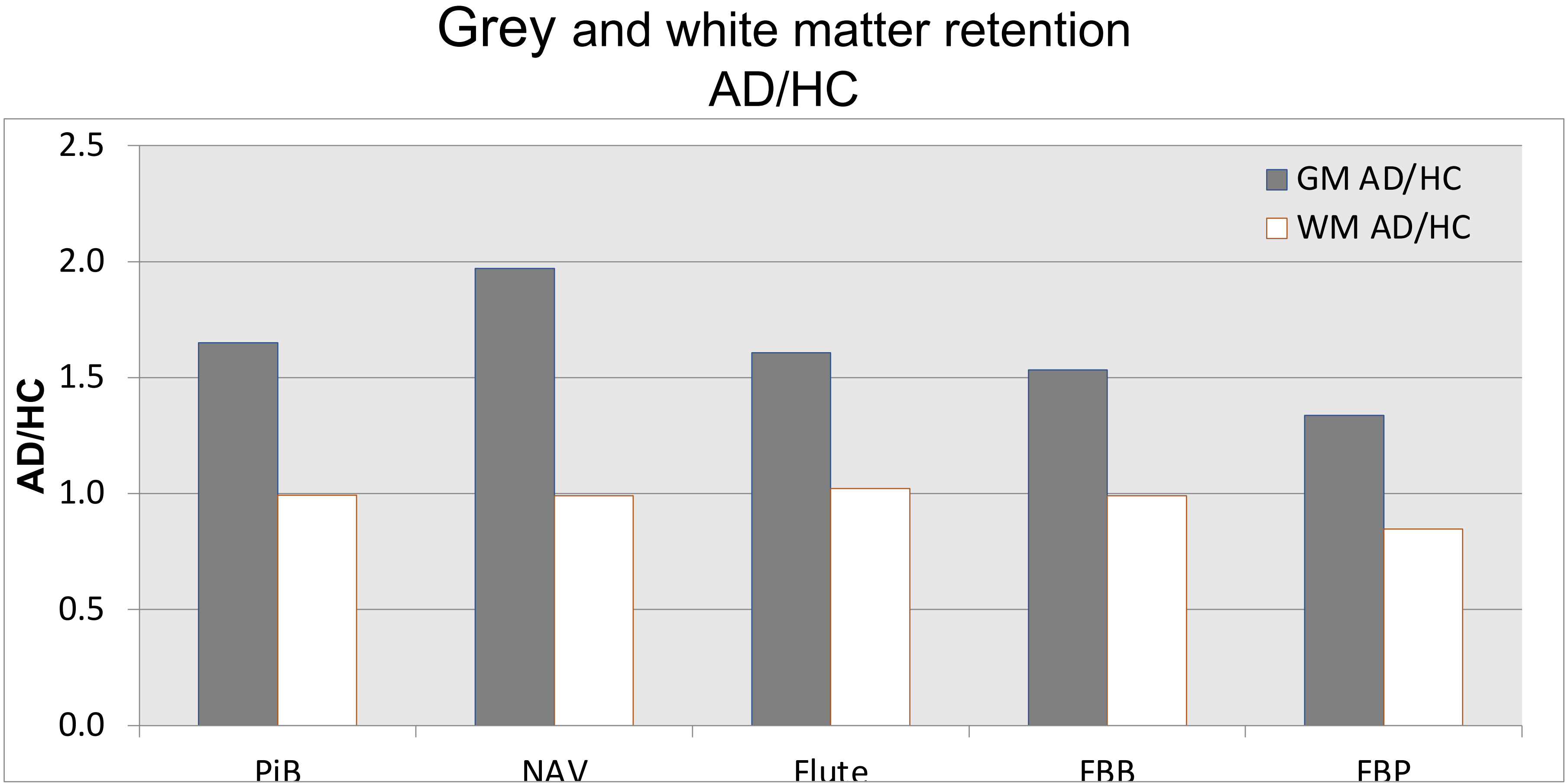
Discriminatory power of Aβ tracers



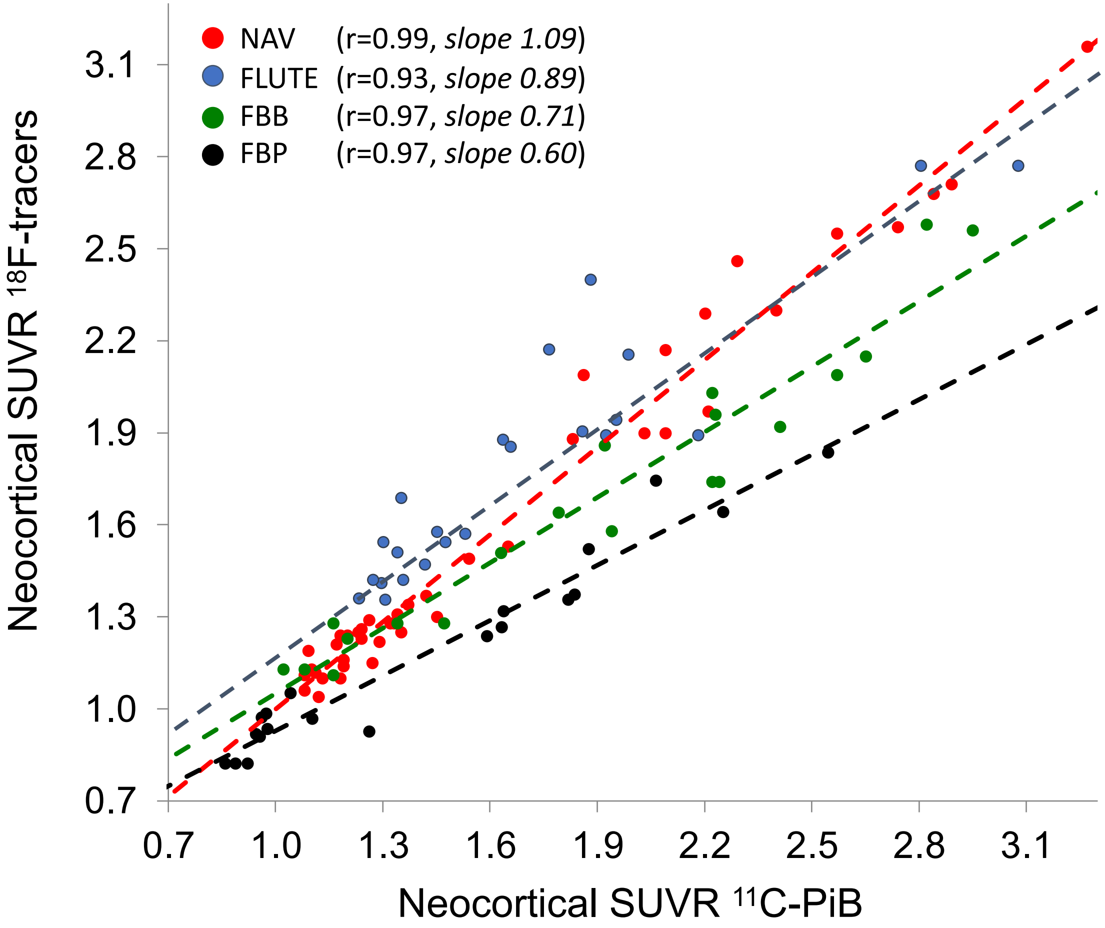
Aβ imaging in Alzheimer's disease



Aβ imaging in Alzheimer's disease



Comparison of ^{18}F-amyloid ligands vs ^{11}C-PiB

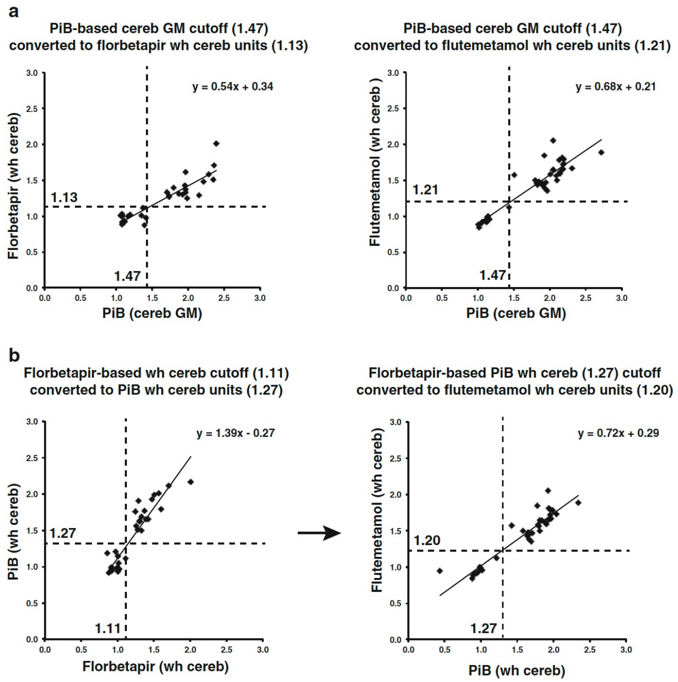


Precursors of Centiloid

Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers

Eur J Nucl Med Mol Imaging (2014) 41:1398–1407

S. M. Landau · B. A. Thomas · L. Thurfjell · M. Schmidt · R. Margolin · M. Mintun · M. Pontecorvo · S. L. Baker · W. J. Jagust · the Alzheimer's Disease Neuroimaging Initiative



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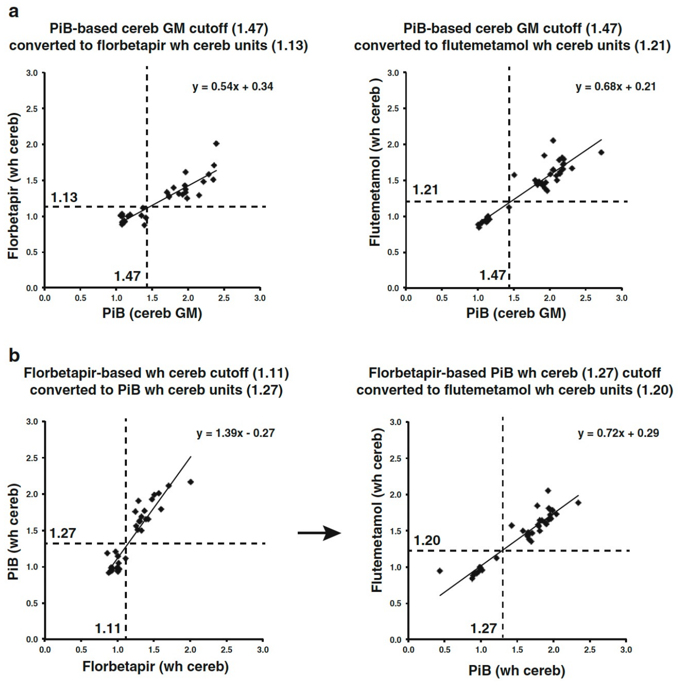
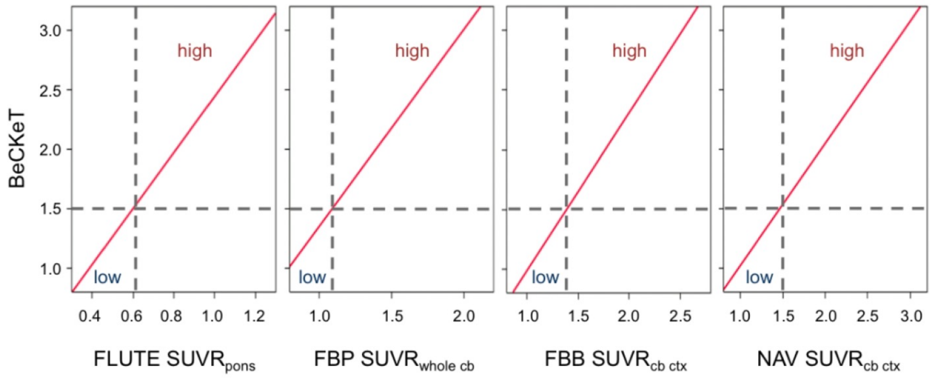


En Attendant Centiloid

Victor L. Villemagne[1,2,3*], Vincent Doré[4], Paul Yates[1], Belinda Brown[5], Rachel Mulligan[1], Pierrick Bourgeat[4], Robyn Veljanoski[1], Stephanie R. Rainey-Smith[5,6], Kevin Ong[1], Alan Rembach[2], Robert Williams[1], Samantha C. Burnham[7], Simon M. Laws[5,6], Olivier Salvado[4], Kevin Taddei[4], S. Lance Macaulay[7], Ralph N. Martins[5,6,8], David Ames[9,10], Colin L. Masters[2] and Christopher C. Rowe[1]

Advances in Research
2(12): 723-729, 2014, Article no. AIR.2014.12.003



(BeCKeT: Before the Centiloid Kernel Transformation)

Centiloid transformation

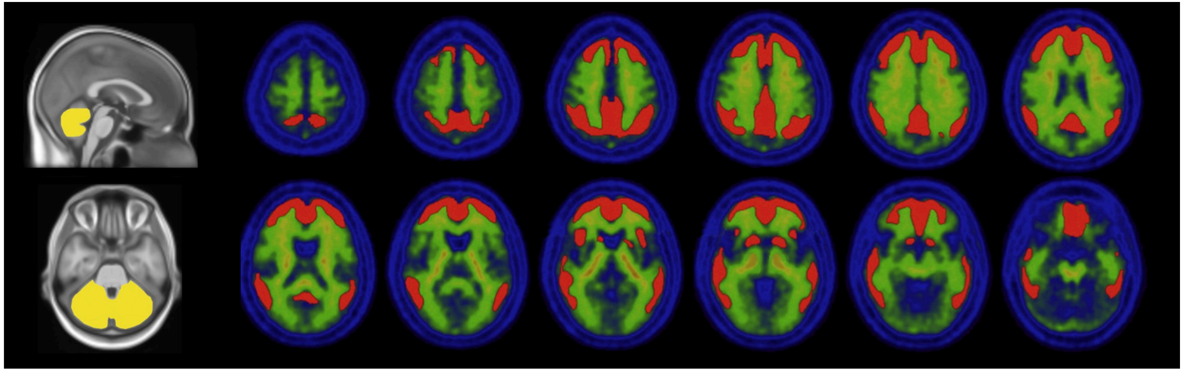
The centiloid project: Standardizing quantitative amyloid plaque estimation by PET

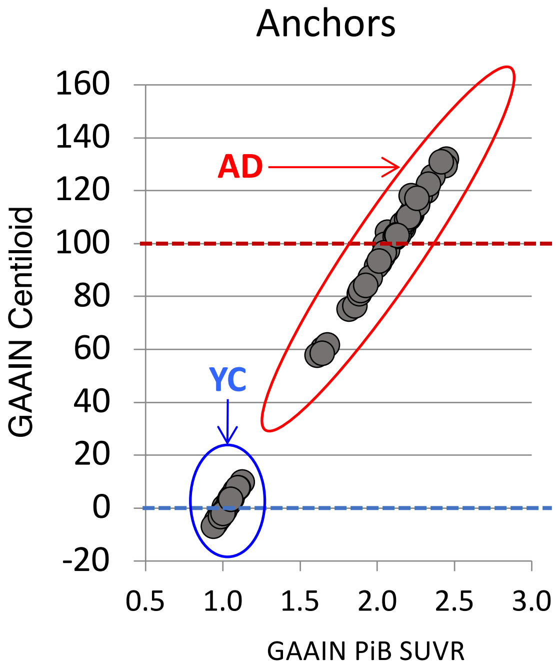
William E. Klunk[a,b,*], Robert A. Koeppe[c], Julie C. Price[d], Tammie L. Benzinger[e,f], Michael D. Devous, Sr.,[g,h], William J. Jagust[i], Keith A. Johnson[e,j], Chester A. Mathis[k], Davneet Minhas[d], Michael J. Pontecorvo[l], Christopher C. Rowe[m], Daniel M. Skovronsky[l], Mark A. Mintun[l]

ELSEVIER
Alzheimer's & Dementia

Defines the *0* (young controls) and *100* (mild AD+) anchor points
Spatial normalization w/ SPM8 of MRI and co-registered PET into MNI-158

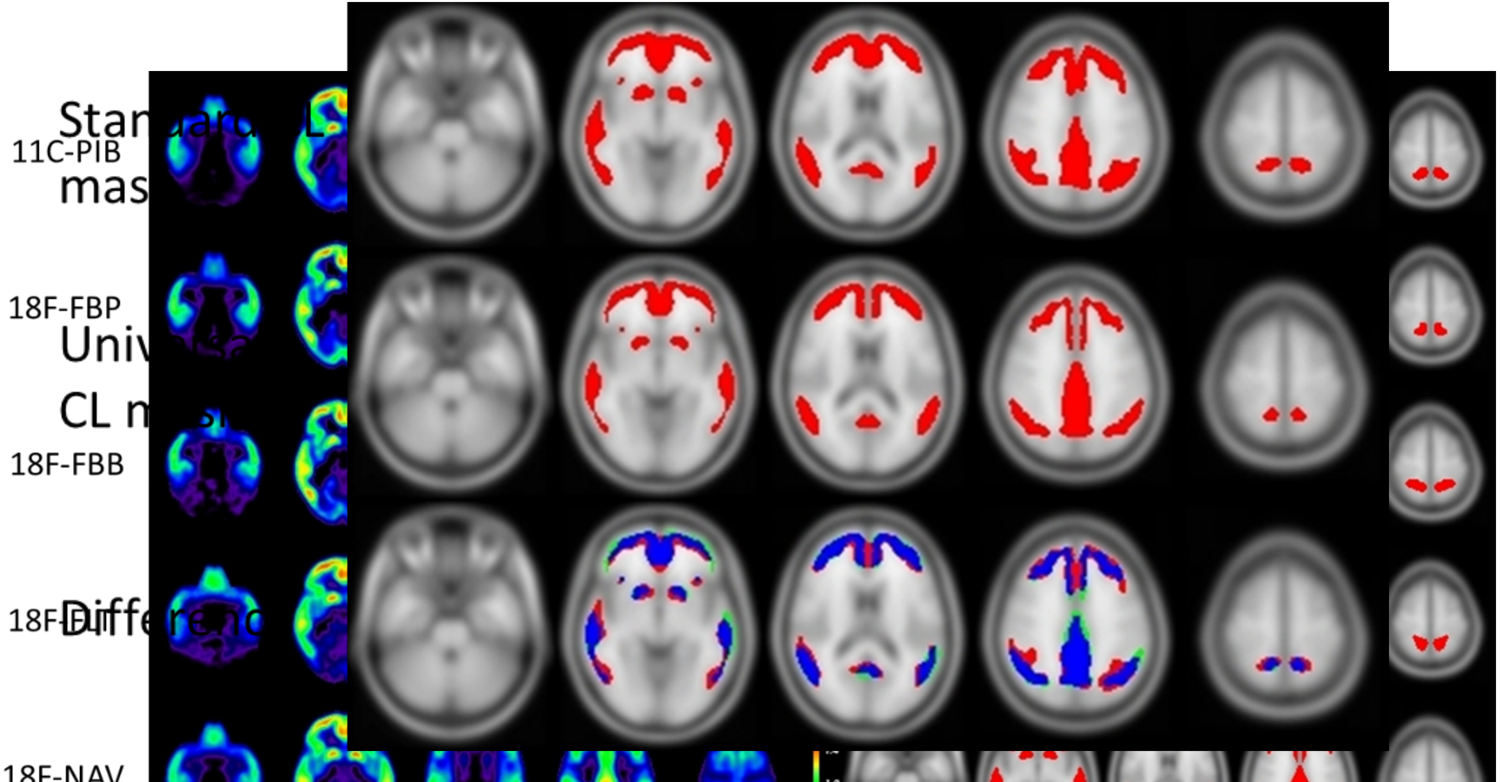
- Standard VOIs
  - One Cortical VOI (Aβ+ areas after subtracting EC from AD)
  - Four reference regions: **WCB** -





Images & VOI available at the Global Alzheimer's Association Information Network (GAAIN; http://www.gaain.org)

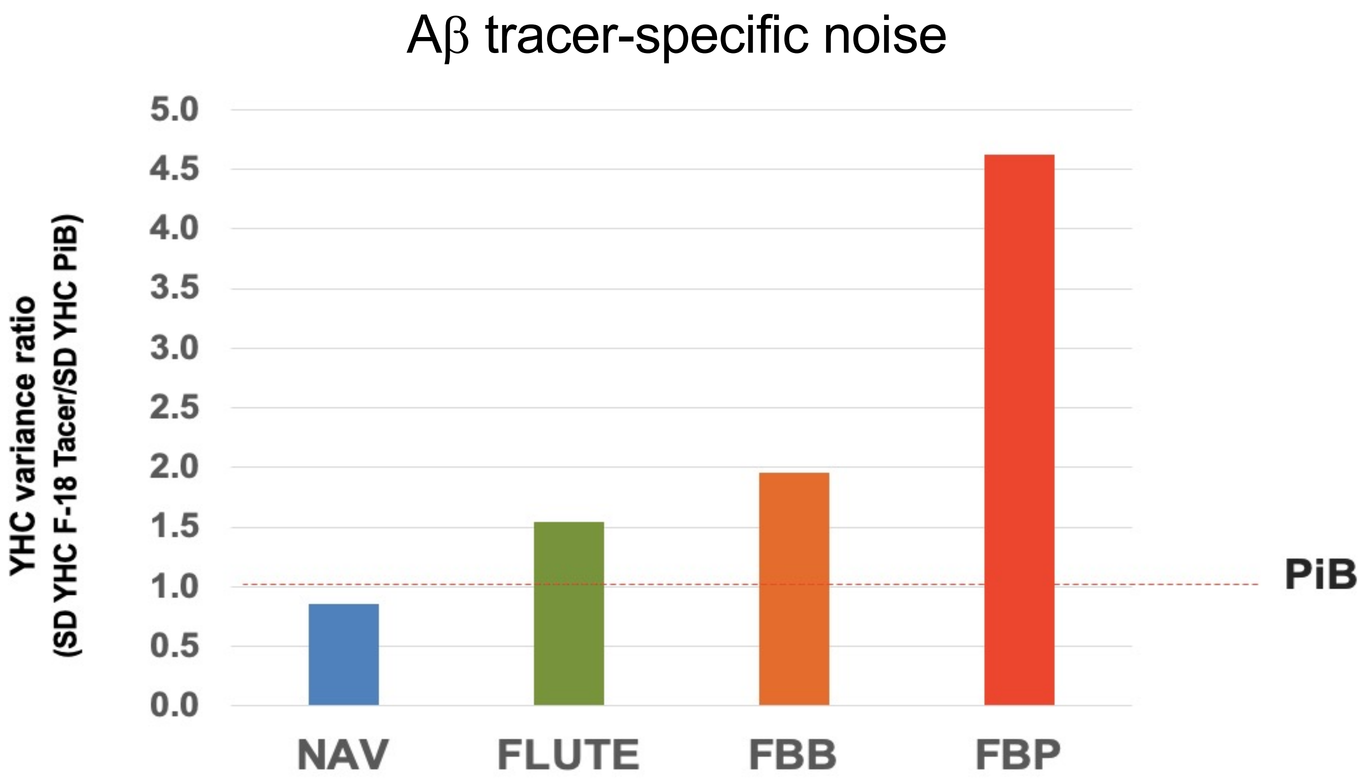
Centiloid cortical mask



While the universal mask was 26% smaller than the standard [illegible], the overlap was high (Dice=0.74), it only led to a small reduction in the vari[illegible] between each of the ^{11}C-PiB/^{18}F-tracer pairs (+0.25%), and a slightly higher effect-size between HC/AD (1.895 vs 1.956) and HC/MCI (0.599 vs 0.601). Those increases were however relatively small indicating that the existing standard CL mask is suitable for the quantification of all Aβ tracers.

Bourgeat et al. HAI, 2023.

Aβ imaging in Alzheimer's disease



PiB: Klunk et al., Alzheimer Dement, 2015.
NAV: Rowe et al., J Nucl Med, 2016.
FBB: Rowe et al., EJNMMI, 2017.
FBP: Navitsky et al., Alzheimer Dement, 2018.
FLT: Battle et al., EJNMMI Research, 2018.

Centiloid Thresholds

Neuropathology

PiB (*La Joie et al., Alzheimers Dement. 2019*) 12-24 CL

Florbetaben (*Doré et al., Alzheimers Dement.. 2019, Bullich et al., AR&T, 2021*) 13-21-36 CL

Florbetapir (*Navitsky et al., Alzheimers Dement. 2018*) 24 CL

Flutemetamol (*Battle et al., EJNMMI Res. 2018*) (25-30 CL)*

Specificity threshold (95%ile YC)

PiB (*Su et al., Neuroimage: Clinical. 2018*) 6-12 CL

Reliable worsening method

PiB (*Jack et al., Alzheimers Dement. 2017*) 19 CL

PiB (*Su et al., Neuroimage: Clinical. 2018*) 11 CL

CSF

Flutemetamol (*Salvadó et al, Alzheimers Res Ther. 2019*) 12-30 CL

Tipping point

PiB (*Schindler et al, Neurology, 2021*) 7 CL

Risk of cognitive decline/clinical progression

PiB (*extended from Rowe Ann Neurol, 2013*) 20 CL

PiB-FBP (*Farell et al., Neurology, 2021*) 15-18.5 CL

Centiloid Thresholds

Neuropathology

PiB (*La Joie et al., Alzheimers Dement. 2019*)
Florbetaben (*Doré et al., Alzheimers Dement.. 2019, Bullich et al., AR&T, 2021*)
Florbetapir (*Navitsky et al., Alzheimers Dement. 2018*)
Flutemetamol (*Battle et al., EJNMMI Res. 2018*)

Specificity threshold (95%ile YC)

PiB (*Su et al., Neuroimage: Clinical. 2018*)

18-20 CL

Reliable worsening method

PiB (*Jack et al., Alzheimers Dement. 2017*)
PiB (*Su et al., Neuroimage: Clinical. 2018*)

CSF

Flutemetamol (*Salvadó et al, Alzheimers Res Ther. 2019*)

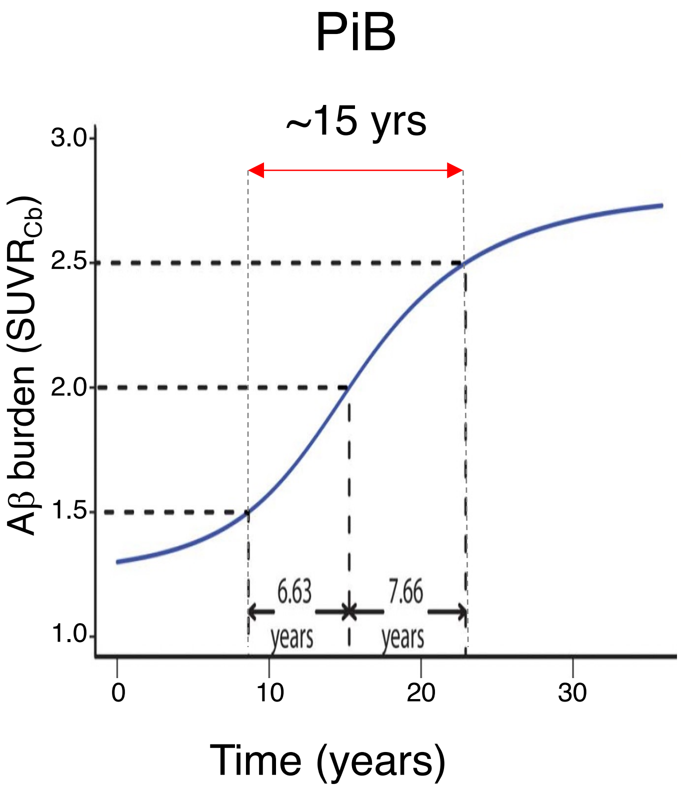
Tipping point

PiB (*Schindler et al, Neurology, 2021*)

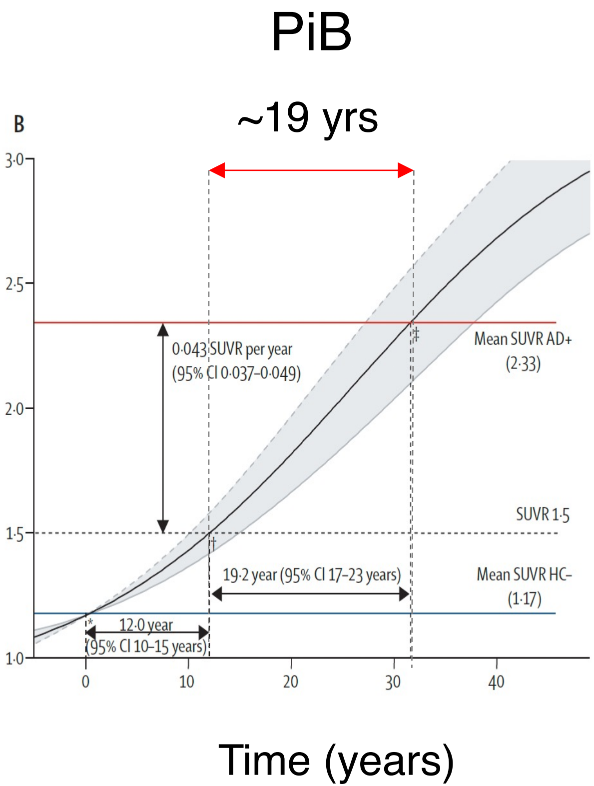
Risk of cognitive decline/clinical progression

PiB (*extended from Rowe Ann Neurol, 2013*)
PiB-FBP (*Farell et al., Neurology, 2021*)

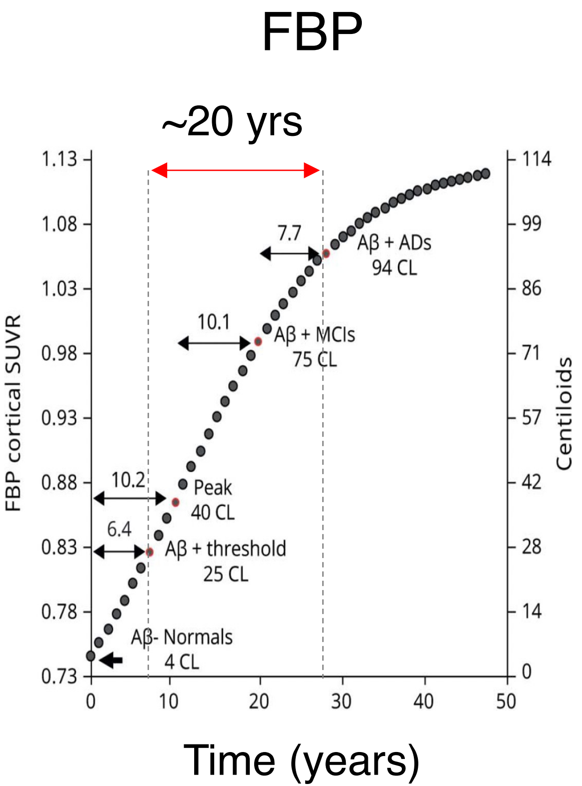
Aβ deposition over time



adapted from Jack et al., Neurology, 2013



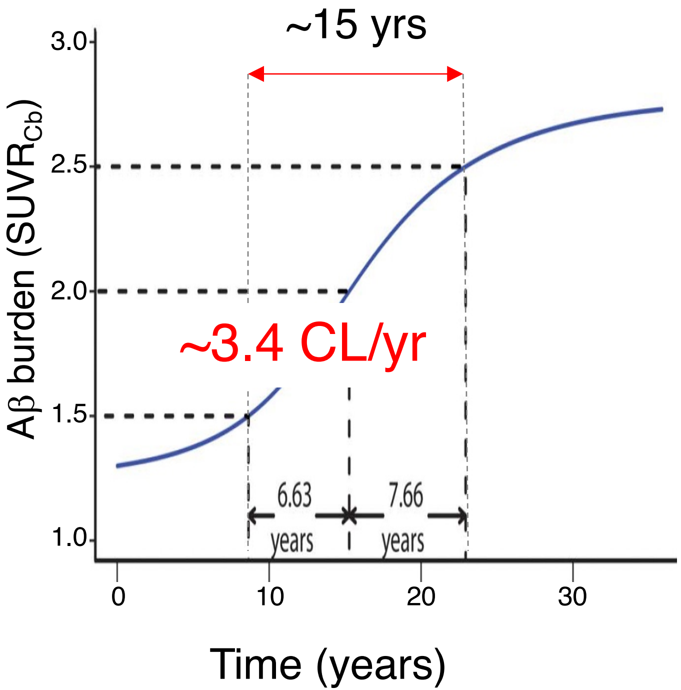
adapted from Villemagne et al., Lancet Neurol, 2013



adapted from Landau et al., Neurology, 2021

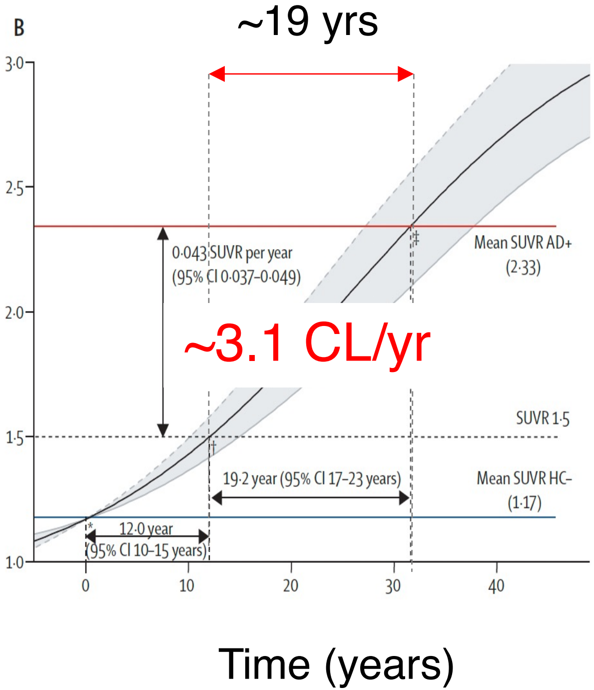
Aβ deposition over time

PiB



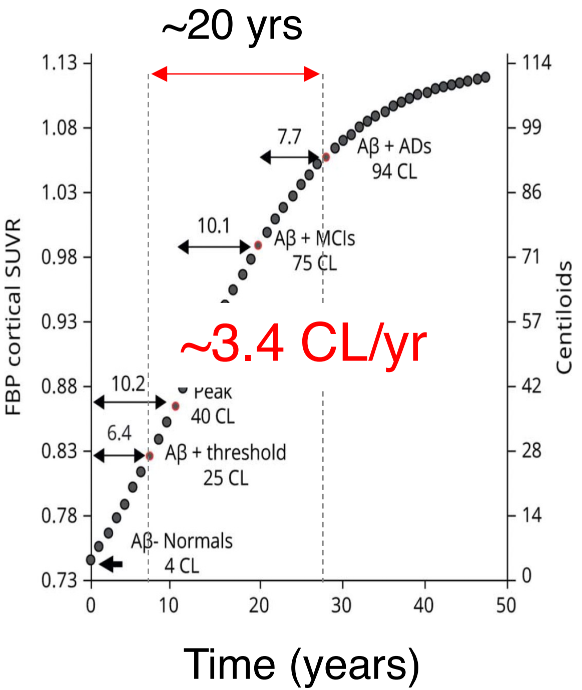
adapted from Jack et al., Neurology, 2013

PiB



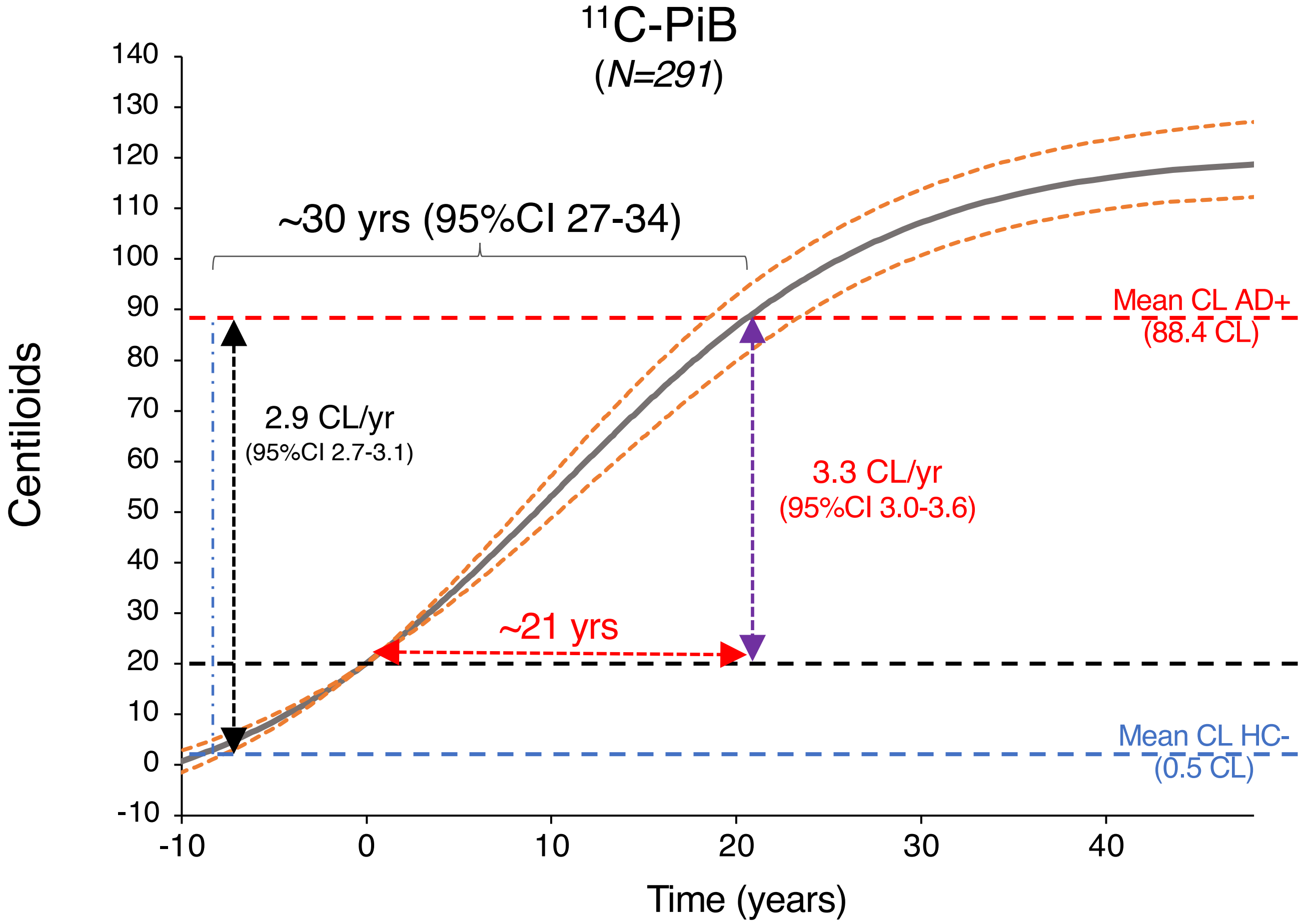
adapted from Villemagne et al., Lancet Neurol, 2013

FBP

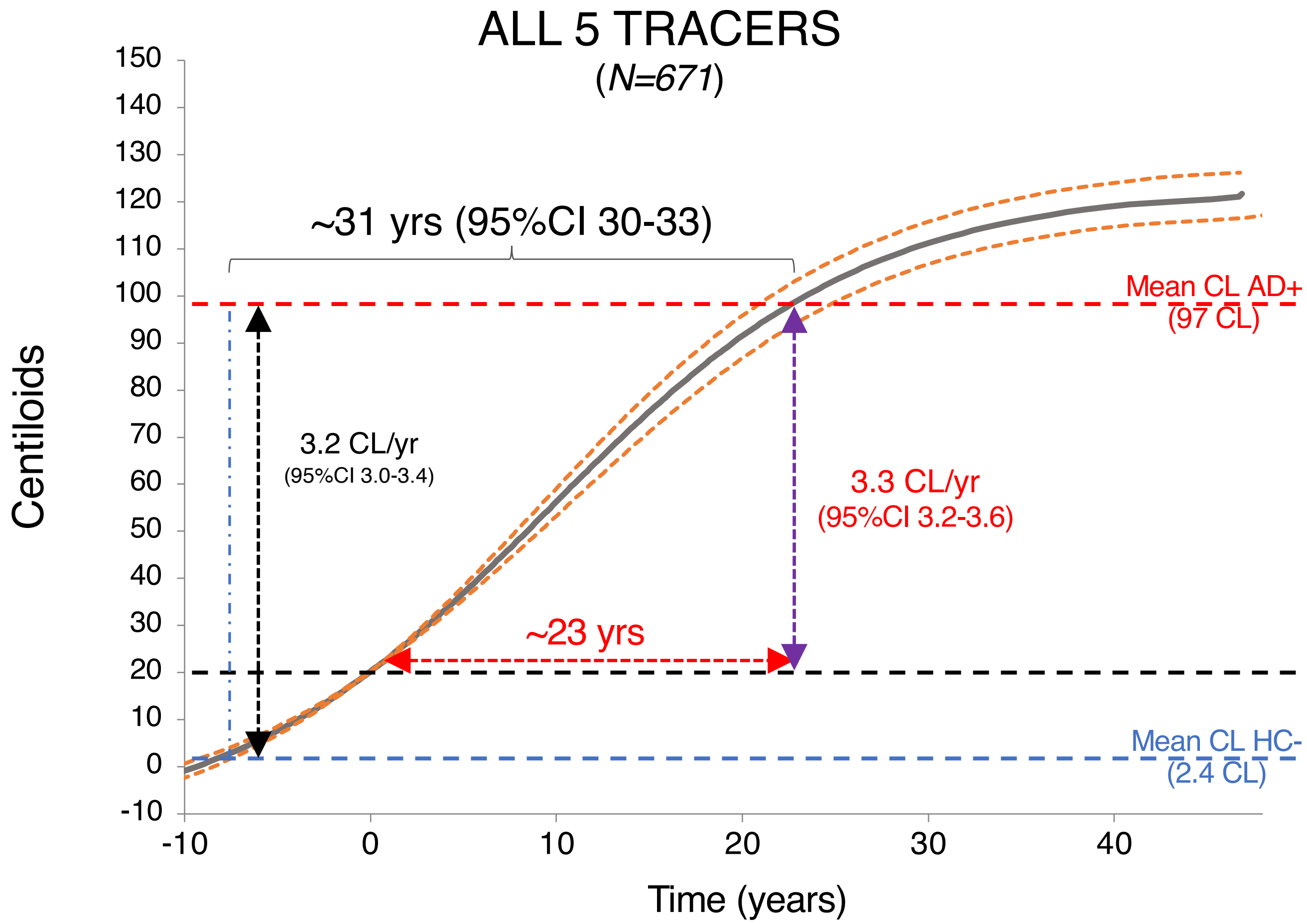


adapted from Landau et al., Neurology, 2021

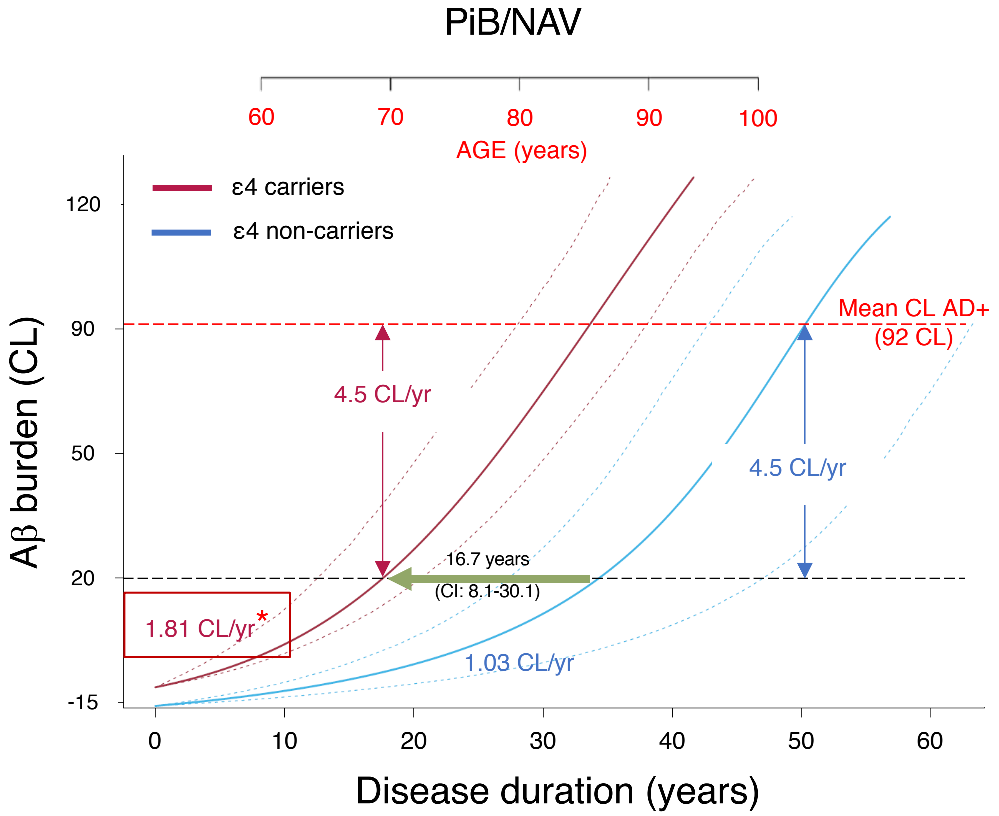
Aβ deposition over time



Aβ deposition over time



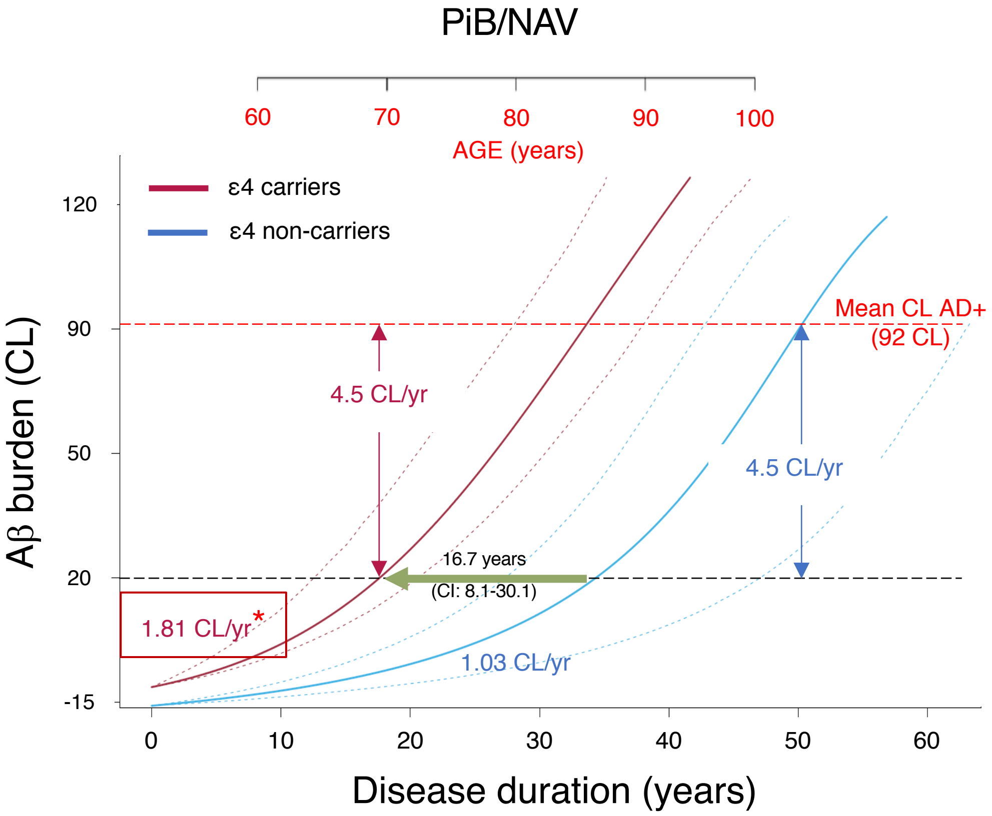
Aβ accumulation: effect of APOE



adapted from Burnham et al., Neurobiol Aging, 2020

**significantly different from APOE4 non-carriers (p=0.027)*

Aβ accumulation: effect of APOE



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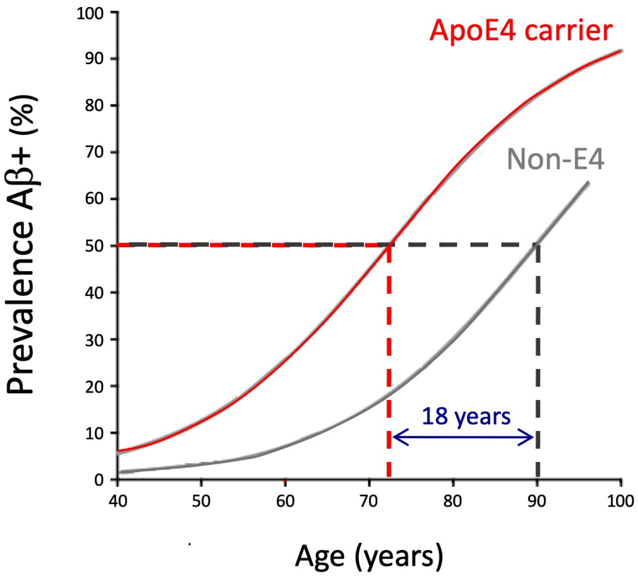
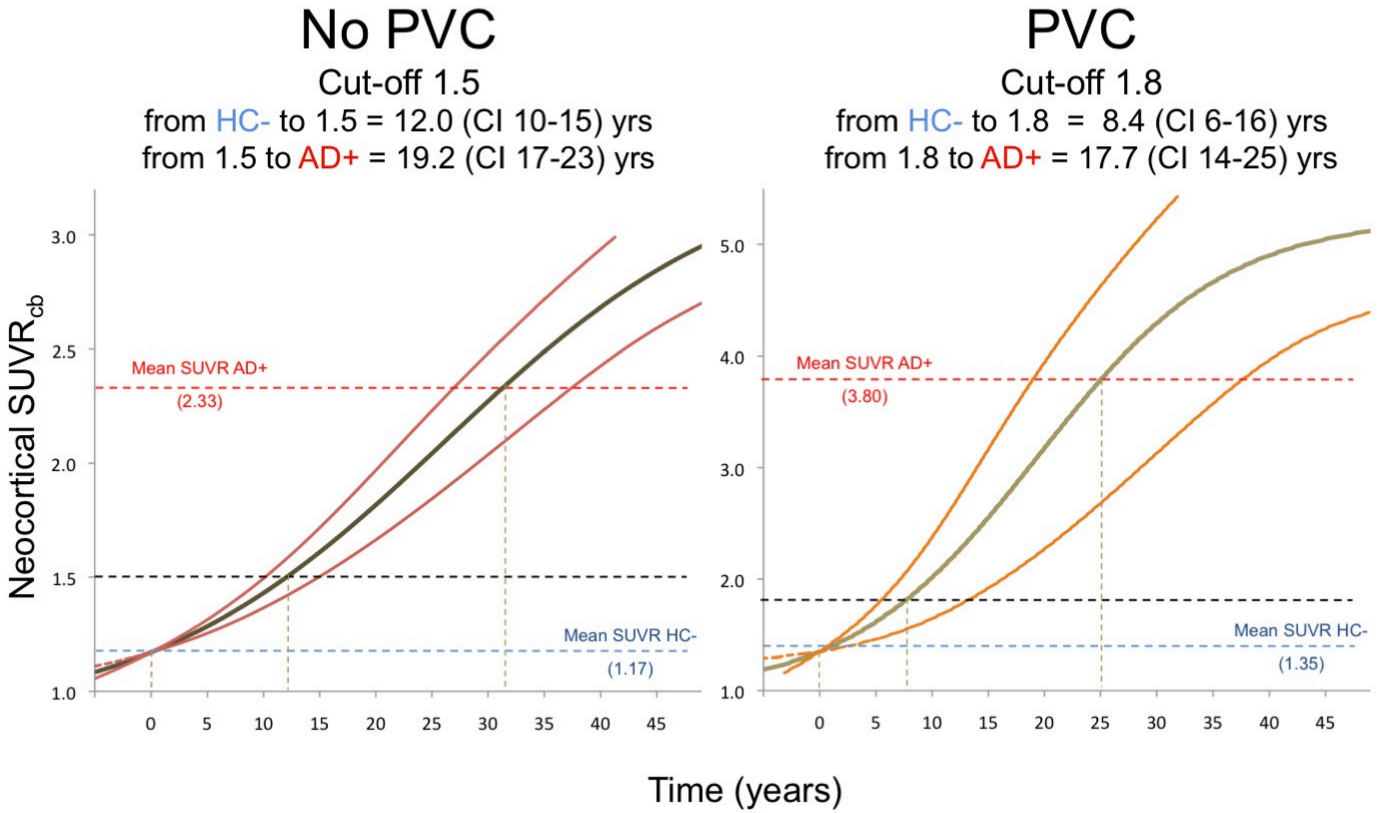


adapted from Jansen et al., JAMA, 2015.

**significantly different from APOE4 non-carriers (p=0.027)*

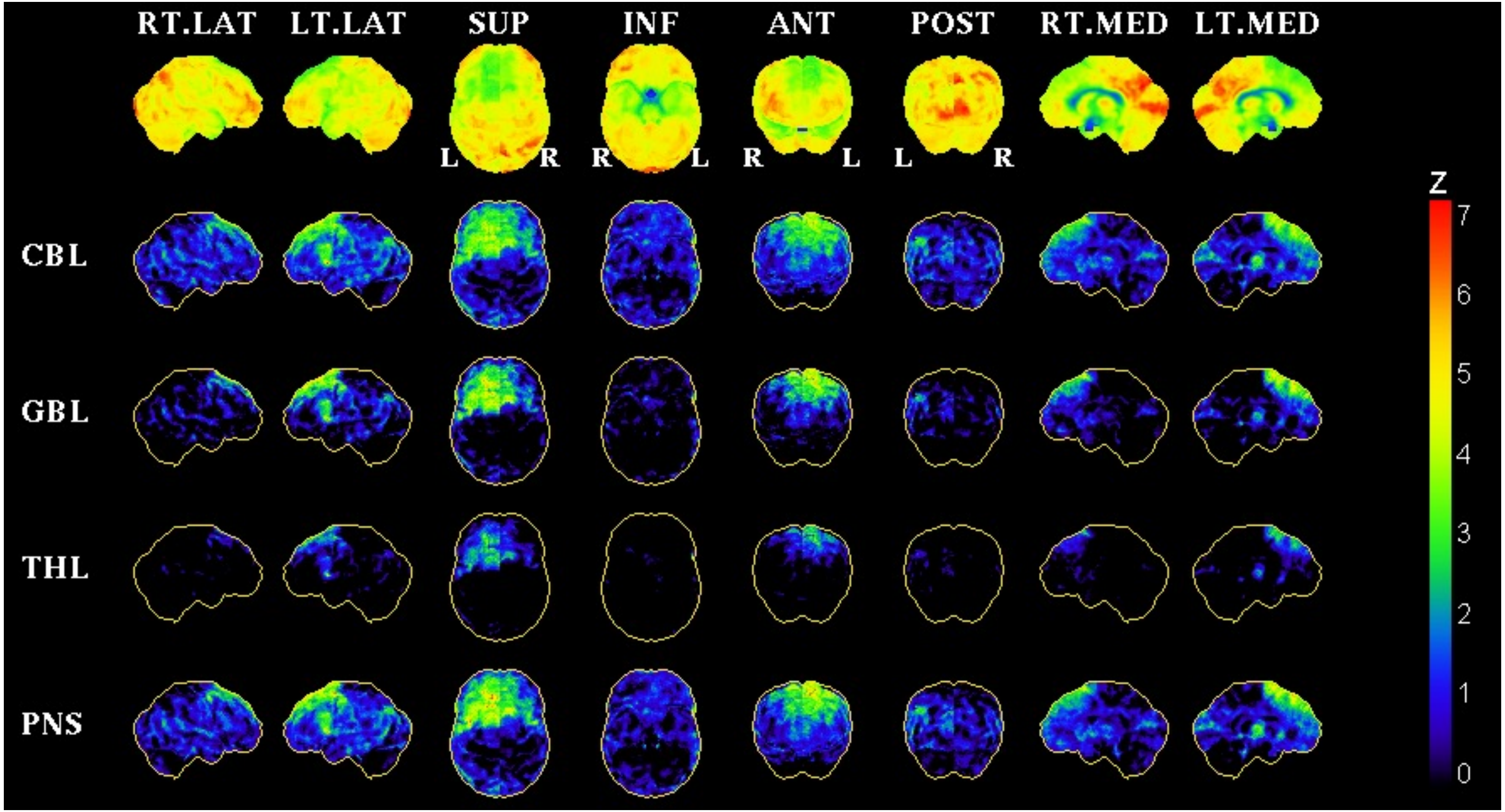
Aβ imaging: effect of partial volume correction



Villemagne et al., Lancet Neurol, 2013

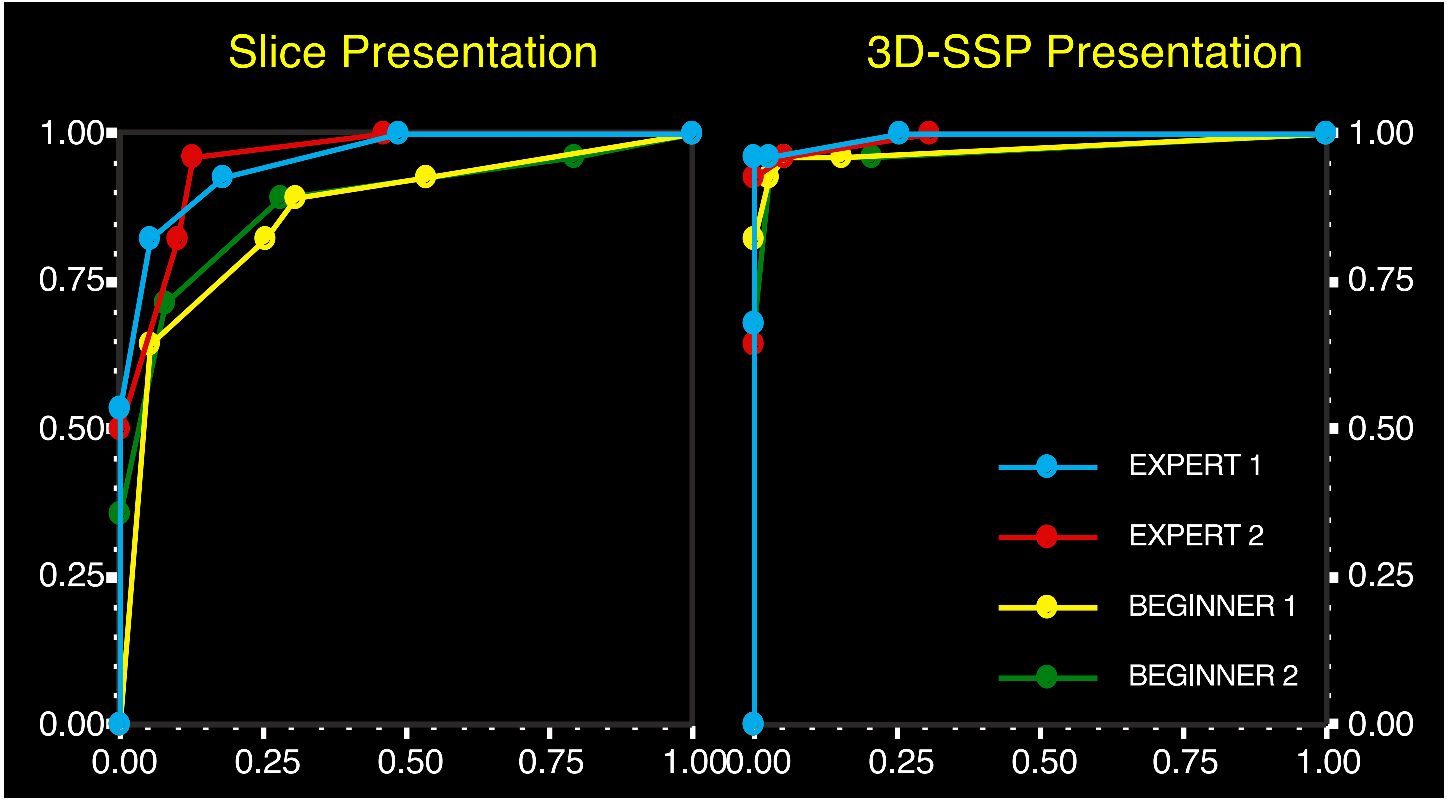
Improvement in visual reads by adding quantification

NeuroStat 3D-SSP: 3D surface projection



Improvement in visual reads by adding quantification

FDG-Neurostat 3D-SSP improves accuracy and reader consistency for Mild AD vs Non-AD



Burdette, et al. Radiology 1996

Towards a universal visual readout for Aβ imaging studies

Toward a Universal Readout for ^{18}F-Labeled Amyloid Tracers: The CAPTAINs Study

Gérard N. Bischof[1], Peter Bartenstein[2], Henryk Barthel[3], Bart van Berckel[4], Vincent Doré[5,6], Thilo van Eimeren[1,7,8], Norman Foster[9], Jochen Hammes[1], Adriaan A. Lammertsma[4], Satoshi Minoshima[9], Chris Rowe[5,6], Osama Sabri[3], John Seibyl[10], Koen Van Laere[11], Rik Vandenberghe[12], Victor Villemagne[5,6], Igor Yakushev[13], and Alexander Drzezga[1,8,14]

J Nucl Med 2021; 62:999–1005
DOI: 10.2967/jnumed.120.250290

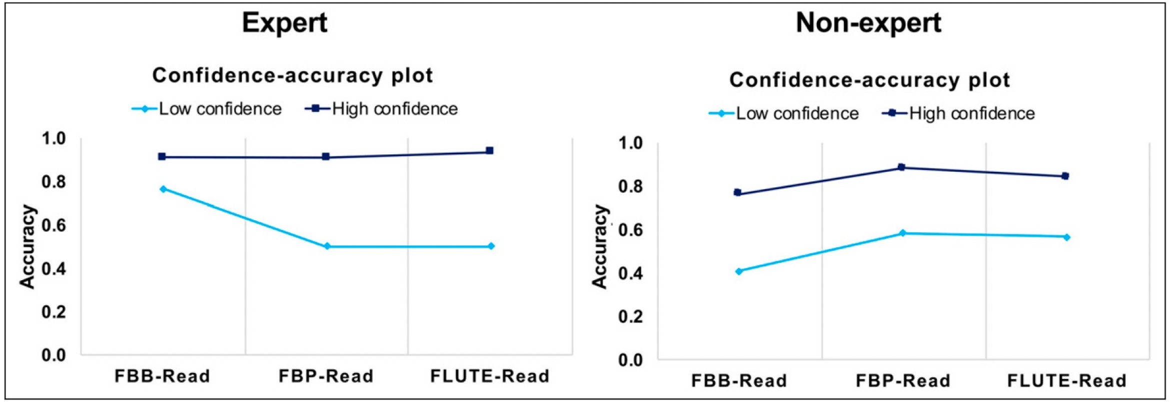
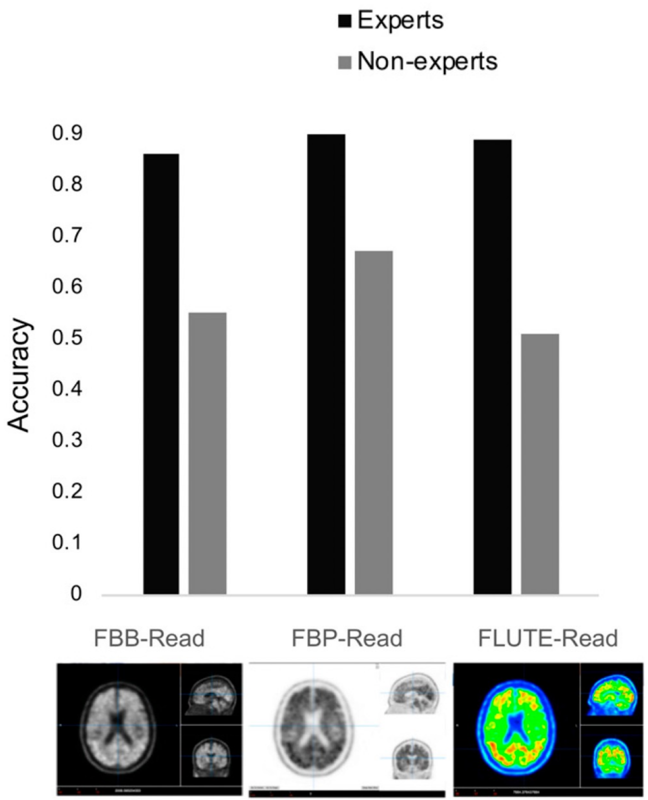


FIGURE 2. CAC separately by experts (left) and nonexperts (right). Light blue represents low confidence judgments by accuracy values, and dark blue represents high-confidence judgments by accuracy. CAC are shown by visual rating method. FBB = ^{18}F-florbetaben; FBP = ^{18}F-florbetapir; FLUTE = ^{18}F-flutemetamol.



Aβ quantification increases confidence/consistency for visual reads

Quantification of amyloid PET for future clinical use: a state-of-the-art review

Hugh G. Pemberton[1,2,3] · Lyduine E. Collij[4] · Fiona Heeman[4] · Ariane Bollack[2] · Mahnaz Shekari[5,6,7] · Gemma Salvadó[5,8] · Isadora Lopes Alves[4,9] · David Vallez Garcia[4] · Mark Battle[1,8] · Christopher Buckley[1] · Andrew W. Stephens[10] · Santiago Bullich[10] · Valentina Garibotto[11,12] · Frederik Barkhof[2,3,4] · Juan Domingo Gispert[5,6,7,13] · Gill Farrar[1] · on behalf of the AMYPAD consortium

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:3508–3528
https://doi.org/10.1007/s00259-022-05784-y

Quantitative Evaluation of ^{18}F-Flutemetamol PET in Patients With Cognitive Impairment and Suspected Alzheimer's Disease: A Multicenter Study

frontiers in Neurology

Hiroshi Matsuda[1,2,3*], Kengo Ito[4], Kazunari Ishii[5,6], Eku Shimosegawa[7], Hidehiko Okazawa[8], Masahiro Mishina[9], Sunao Mizumura[10], Kenji Ishii[11], Kyoji Okita[1], Yoko Shigemoto[2,3], Takashi Kato[12], Akinori Takenaka[12], Hayato Kaida[5,6], Kohei Hanaoka[13], Keiko Matsunaga[7], Jun Hatazawa[13], Masamichi Ikawa[14], Tetsuya Tsujikawa[8], Miyako Morooka[10], Kenji Ishibashi[11], Masashi Kameyama[15], Tensho Yamao[1,3,16], Kenta Miwa[1,16], Masayo Ogawa[1] and Noriko Sato[2]

Quantitation of PET signal as an adjunct to visual interpretation of florbetapir imaging

Michael J. Pontecorvo[1] · Anupa K. Arora[1] · Marybeth Devine[1] · Ming Lu[1] · Nick Galante[1] · Andrew Siderowf[1] · Catherine Devadanam[1] · Abhinay D. Joshi[1] · Stephen L. Heun[1] · Brian F. Teske[1] · Stephen P. Truocchio[1] · Michael Krautkramer[1] · Michael D. Devous Sr.[1] · Mark A. Mintun[1]

Eur J Nucl Med Mol Imaging (2017) 44:825–837
DOI 10.1007/s00259-016-3601-4

Augmenting Amyloid PET Interpretations With Quantitative Information Improves Consistency of Early Amyloid Detectior

Nicholas R. Harn, MD, PhD, Suzanne L. Hunt, MS,† Jacqueline Hill, PhD,* Eric Vidoni, PhD,‡ Mark Perry, MD,* and Jeffrey M. Burns, MD‡*

(*Clin Nucl Med* 2017;42: 577–581)

ORIGINAL RESEARCH Open Access

Voxel-based statistical analysis and quantification of amyloid PET in the Japanese Alzheimer's disease neuroimaging initiative (J-ADNI) multi-center study

Go Akamatsu[1,2,3*], Yasuhiko Ikari[1,2], Akihito Ohnishi[1,2,4], Keiichi Matsumoto[1,2,5], Hiroyuki Nishida[1,2], Yasuji Yamamoto[1,2,6,7], Michio Senda[1,2] and Japanese Alzheimer's Disease Neuroimaging Initiative

EJNMMI Research (2019) 9:91

Aβ quantification increases confidence/consistency for visual reads

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European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:3508–3528
https://doi.org/10.1007/s00259-022-05784-y

Quantification supplements visual inspection

1. *less experienced readers*
2. *equivocal ("grey zone") cases*
3. *assessing isolated regional uptake*
4. *In clinical trials (selection/staging/outcomes)*

Quantitative Evaluation of ^{18}F-Flutemetamol PET in Patients With Cognitive Impairment and Suspected Alzheimer's Disease: A Multicenter Study

frontiers in Neurology

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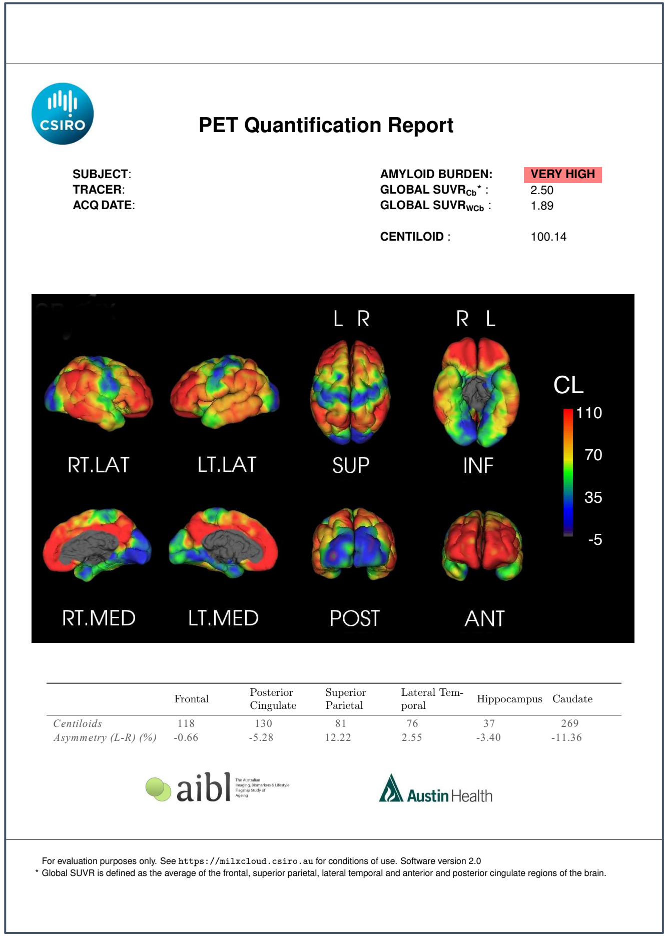
(*Clin Nucl Med* 2017;42: 577–581)

Streamlining quantification: CapAIBL



PET Quantification Report

SUBJECT:
TRACER:
ACQ DATE:

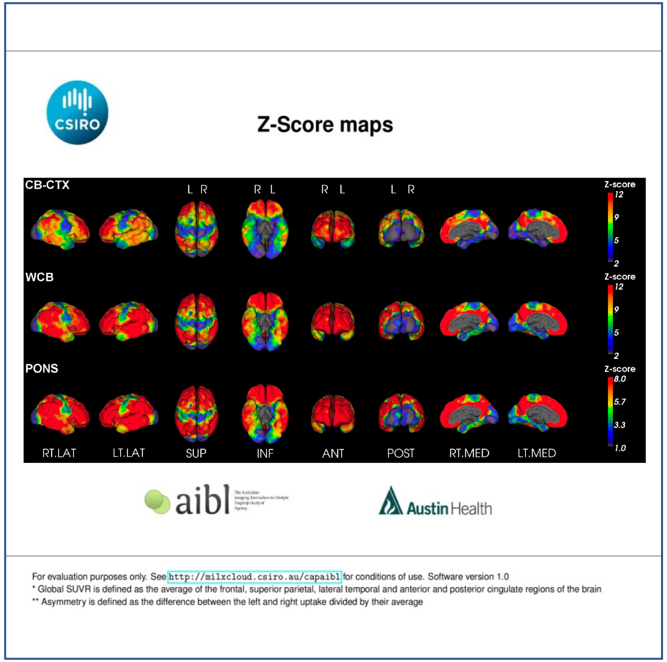
AMYLOID BURDEN: VERY HIGH
GLOBAL $SUVR_{Cb}$* : 2.50
GLOBAL $SUVR_{WCb}$: 1.89

CENTILOID : 100.14

	Frontal	Posterior Cingulate	Superior Parietal	Lateral Temporal	Hippocampus	Caudate
Centiloids	118	130	81	76	37	269
Asymmetry (L-R) (%)	-0.66	-5.28	12.22	2.55	-3.40	-11.36

aibl Austin Health

For evaluation purposes only. See https://milxcloud.csiro.au for conditions of use. Software version 2.0
* Global SUVR is defined as the average of the frontal, superior parietal, lateral temporal and anterior and posterior cingulate regions of the brain.



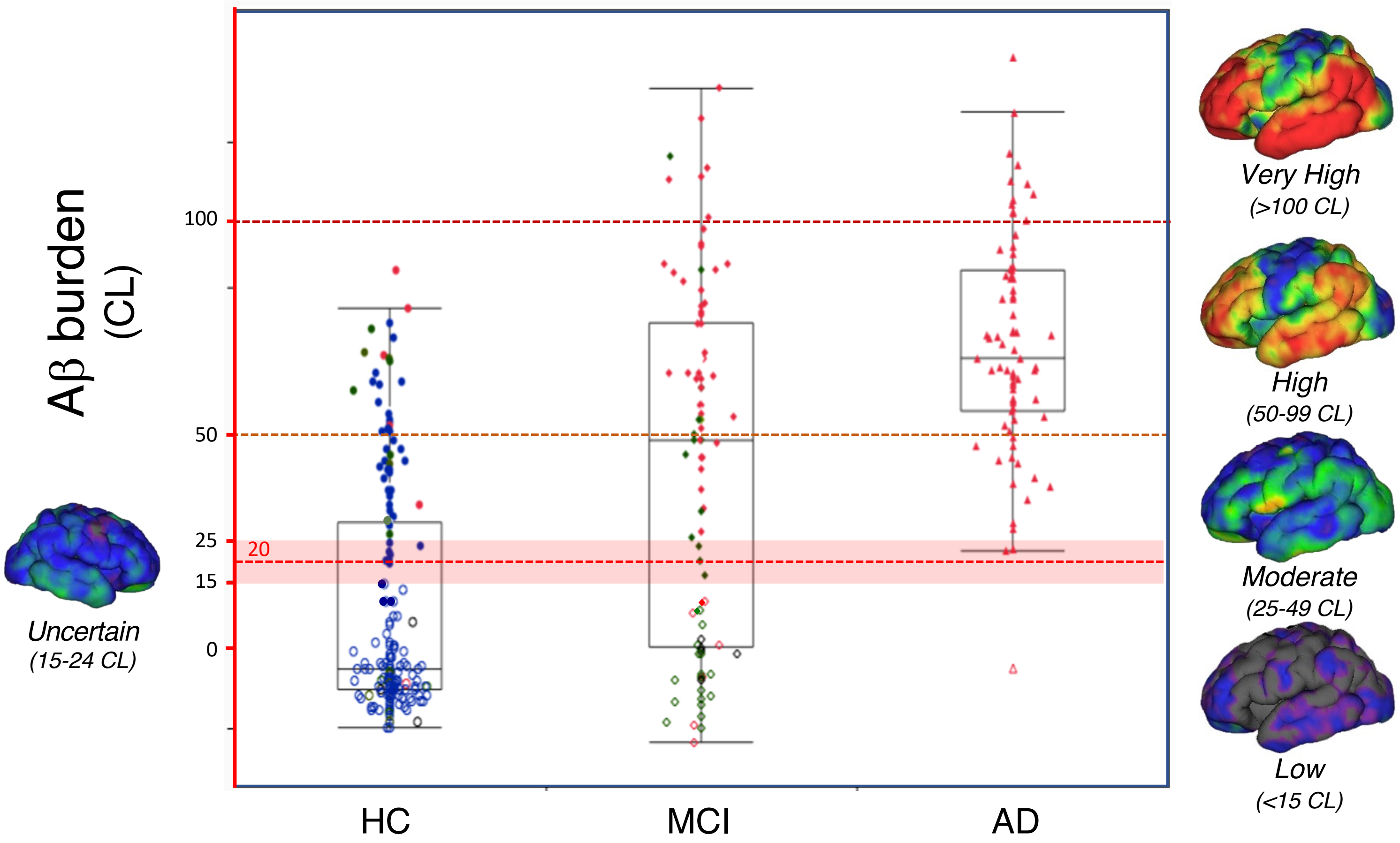
Z-Score maps

aibl Austin Health

For evaluation purposes only. See http://milxcloud.csiro.au/capaibl for conditions of use. Software version 1.0
* Global SUVR is defined as the average of the frontal, superior parietal, lateral temporal and anterior and posterior cingulate regions of the brain
** Asymmetry is defined as the difference between the left and right uptake divided by their average

- **Cloud-based**
- **CSV spreadsheet** with regional values based on different templates
- **QC** of the input data and spatial normalization
- **PET images** in MNI space

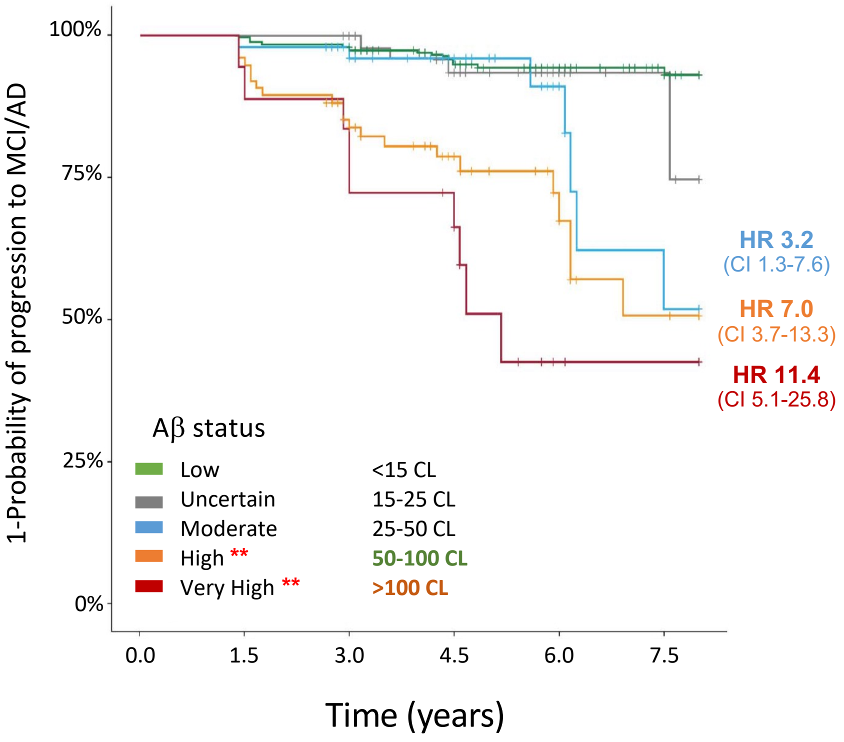
Aβ burden as predictor of disease progression



adapted from Rowe et al., *Ann Neurol*, 2013

Aβ burden as predictor of disease progression

Healthy controls, 8-year follow-up



adapted from van der Kall et al, Neurology, 2021

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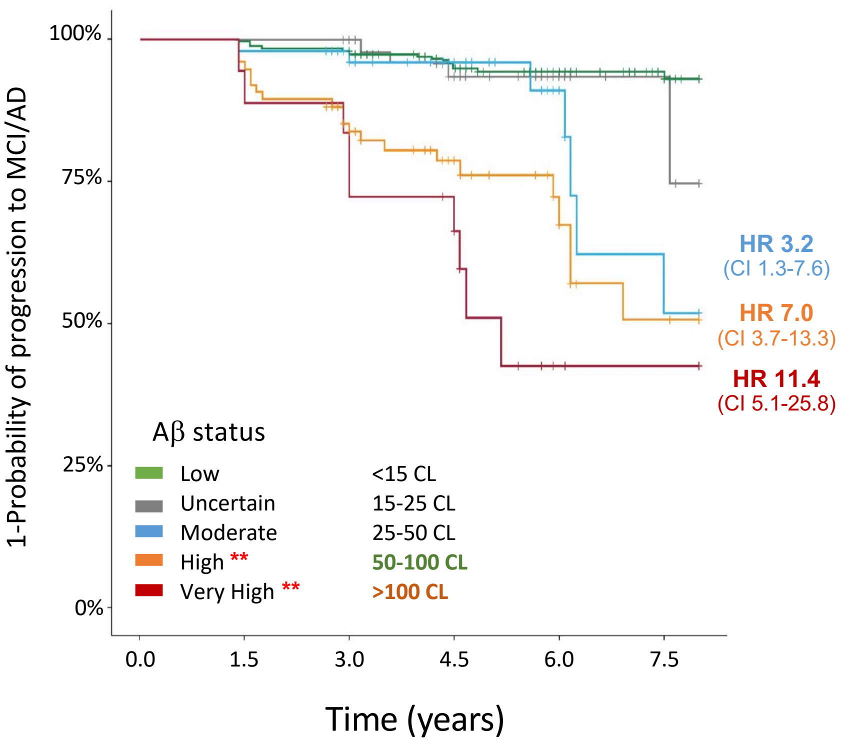
Healthy controls, 8-year follow-up



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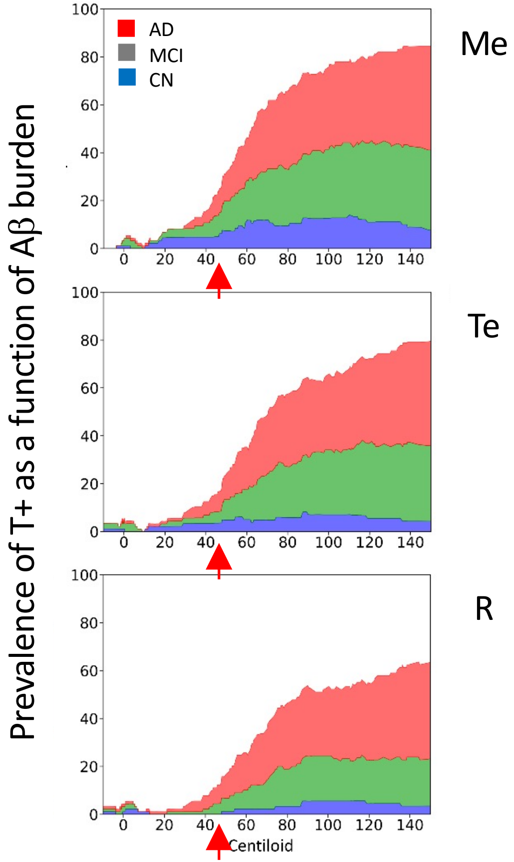
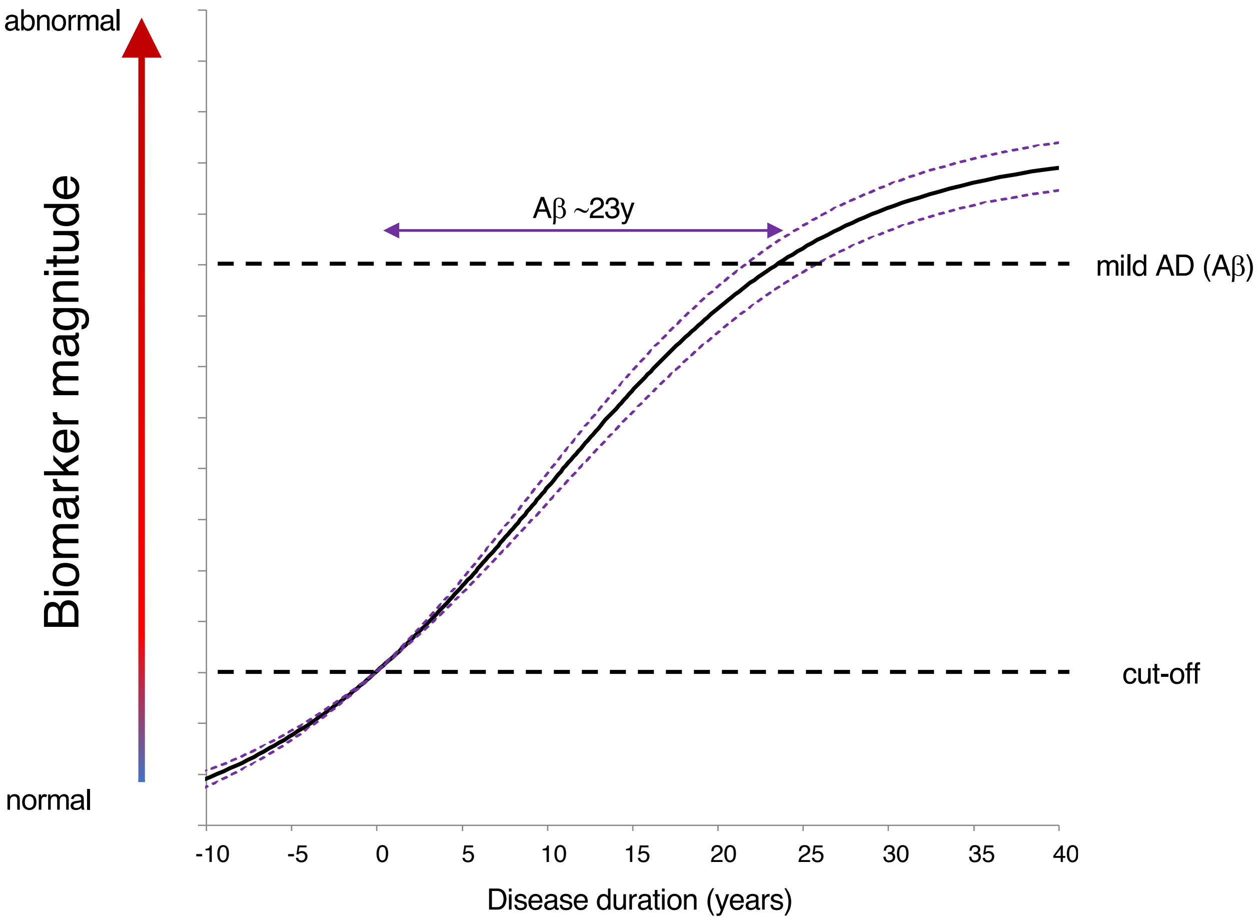


adapted from Doré et al, EJNMMI, 2021

The natural history of Aβ (& tau) deposition



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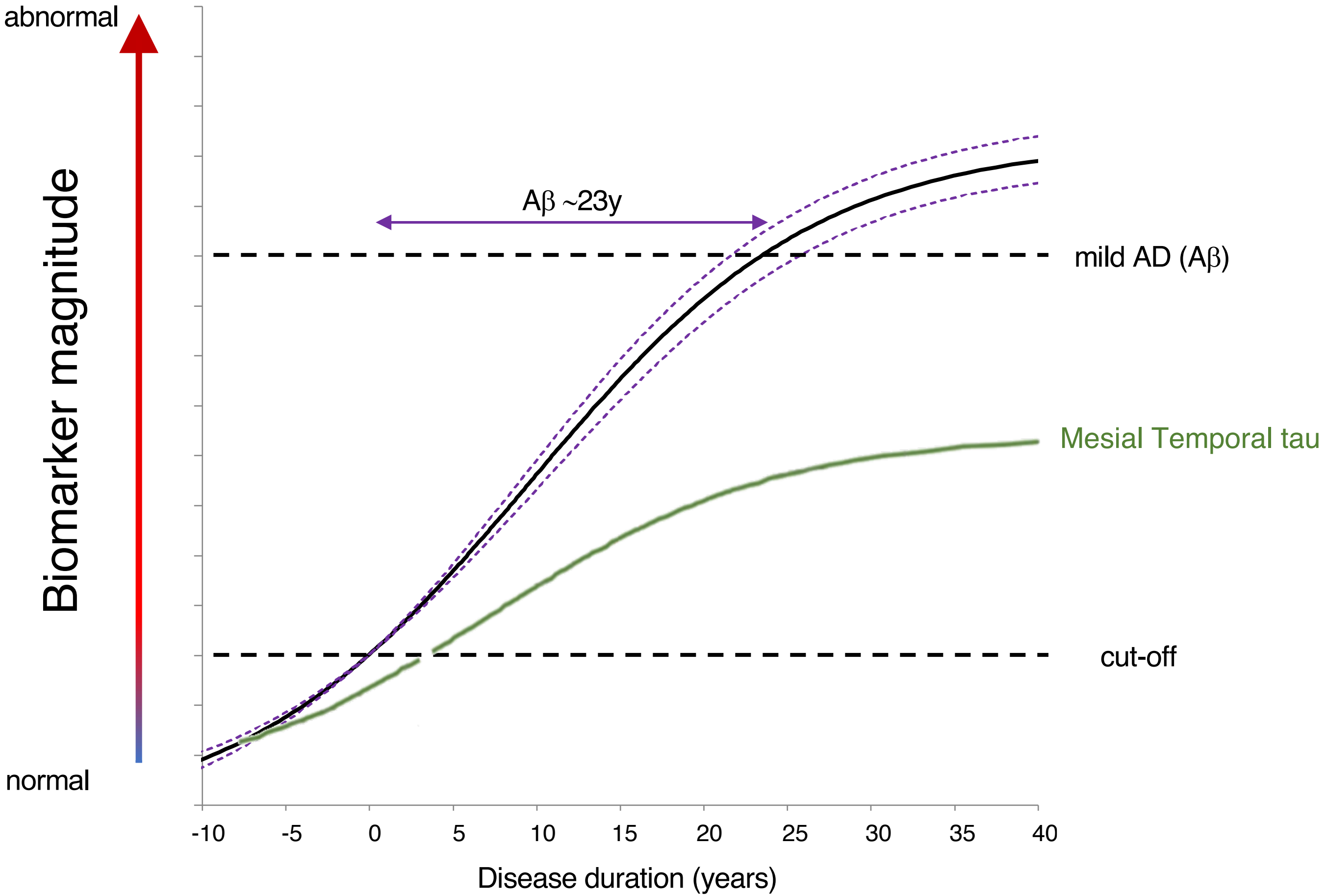

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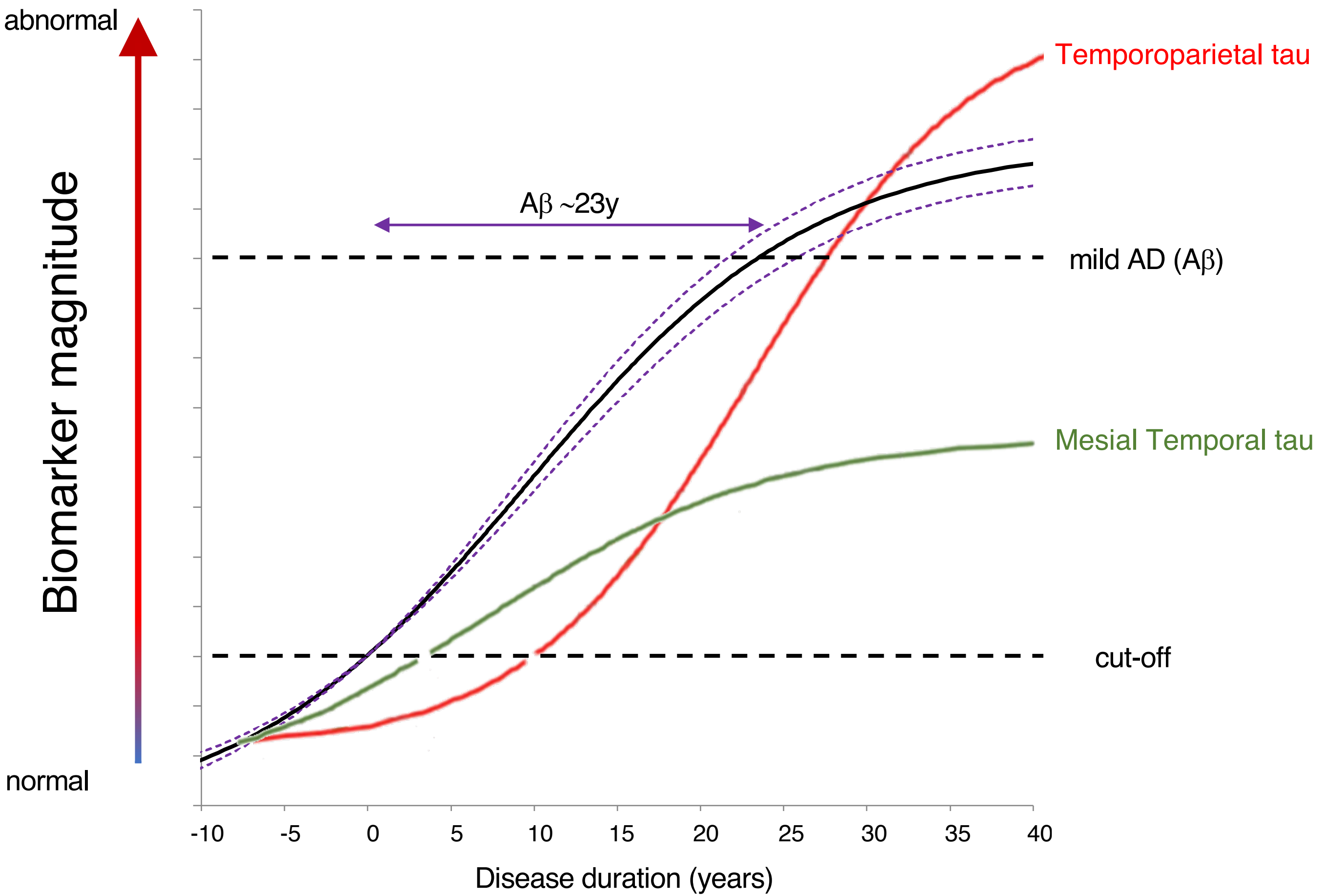

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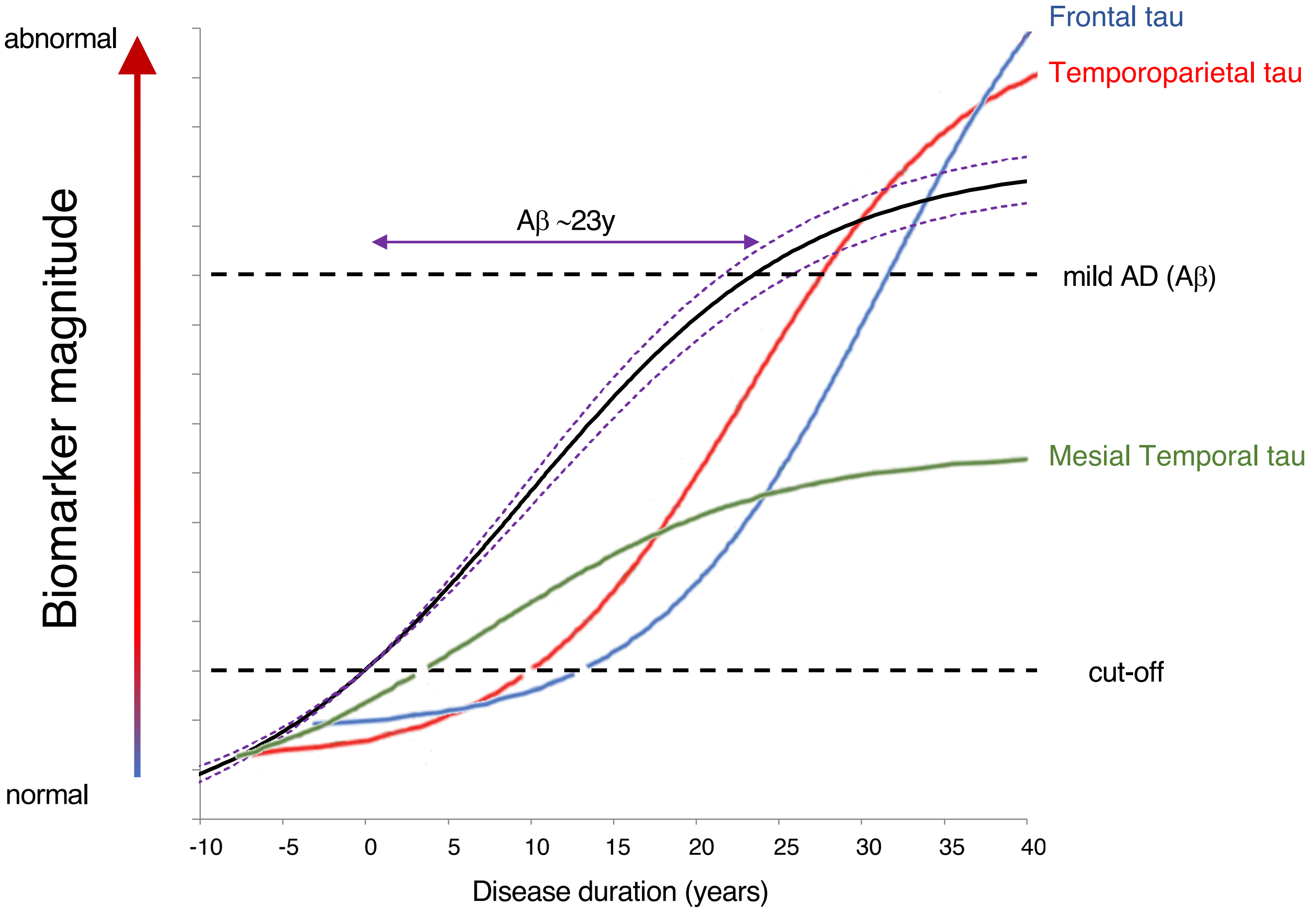

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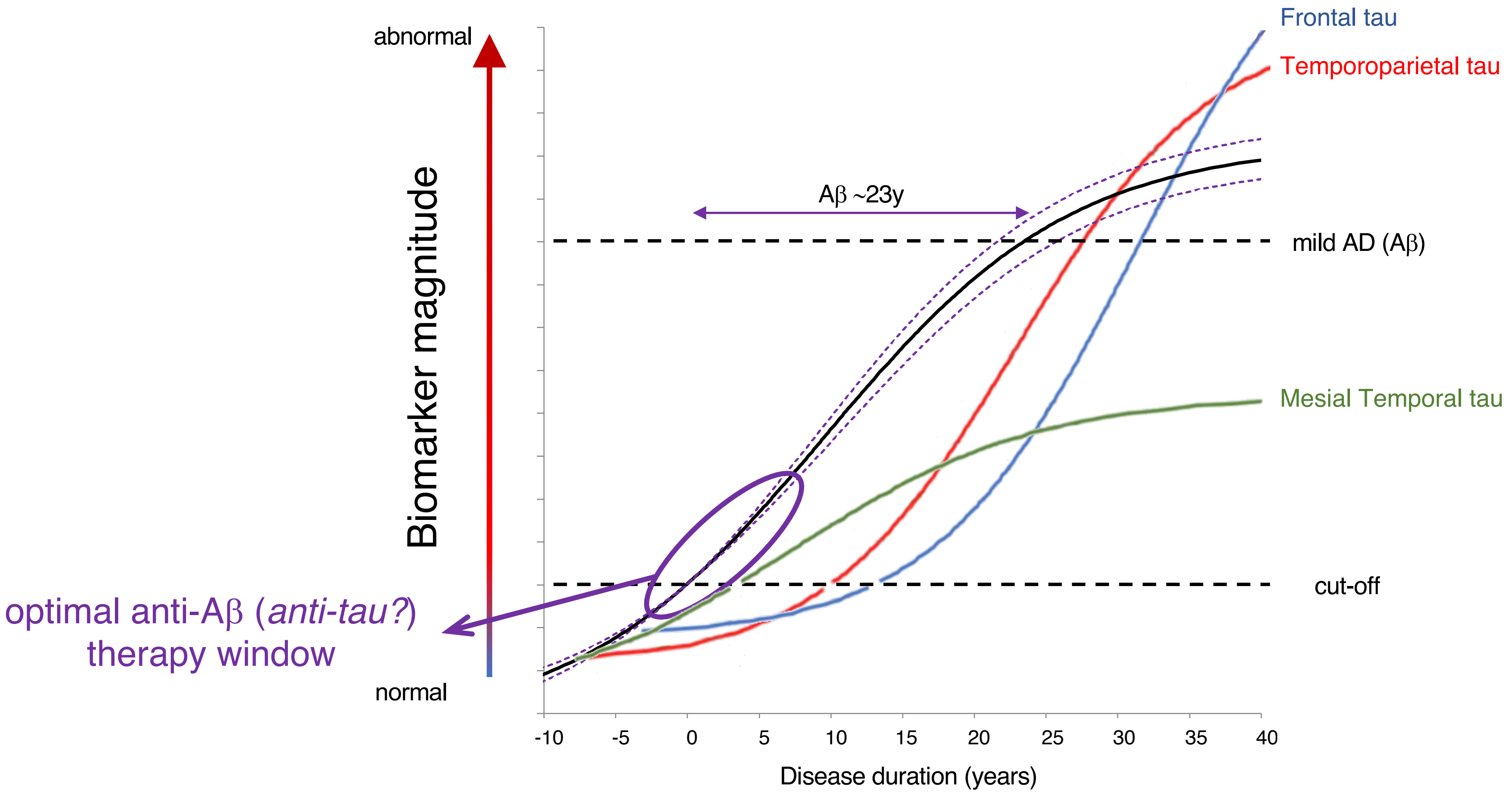

Summary

- There are five Aβ tracers commonly used, three of them (^{18}F-florbetapir, ^{18}F-flutemetamol and ^{18}F-florbetaben) are already FDA approved for visual binary reads (high/low).
- While showing almost identical regional distribution in the brain, these tracers have different degrees of non-specific binding, different kinetics and yield a different dynamic range of values in their semiquantification.
- Despite these differences they can be expressed together under the same semiquantitative scale (Centiloids and others)
- Despite criticisms (equations derived from a small sample size, suboptimal mask) longitudinal data from different tracers expressed in Centiloids can be pooled together, with rates of Aβ accumulation not differing from the ones obtained with each tracer separately (3-4 CL/yr).

Conclusions: Aβ imaging semiquantification

- has allowed to elucidate the natural history of brain Aβ accumulation as well as how this is affected by different factors (age, sex, APOE, etc), while also allowing to establish the optimal time window for therapeutic interventions.

- provides proof of target engagement, and can be used for disease staging, theragnosis, monitoring, and, most importantly, as outcome measure.

- supplements visual reads, by increasing confidence in the reads and clarifying borderline cases. It also allows for stratification of Aβ levels, relevant for predicting clinical progression. *Therefore, Aβ imaging semiquantification should be incorporated to clinical practice as a supplementary tool to visual reads.*

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Austin Health
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Svetlana Pejoska
Fiona Lamb
Kung Huang,
Graeme O'Keefe
Christopher C Rowe

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Jo Robertson
Kevin Barnham
Colin Masters

Avid Radiopharmaceuticals
Mike Pontecorvo

Lifetime Molecular Imaging
Andrew Stephens

GE Healthcare
Gill Farrar

University of Pittsburgh

THE UNIVERSITY OF MELBOURNE

Austin HEALTH

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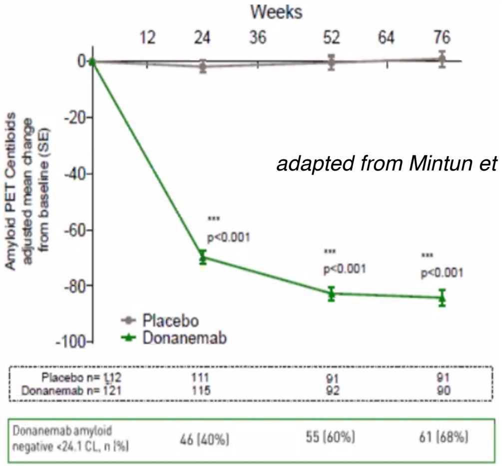
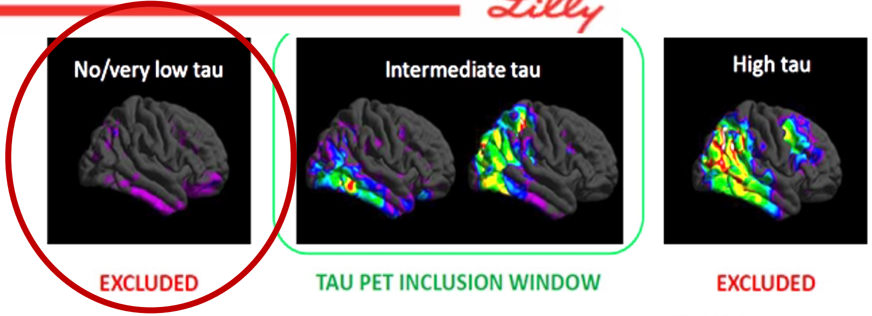
TRAILBLAZER-ALZ iADRS

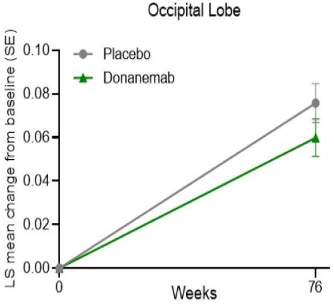
DONANEMAB IS THE FIRST PLAQUE CLEARING AGENT TO ACHIEVE A DISEASE MODIFICATION PRIMARY ENDPOINT

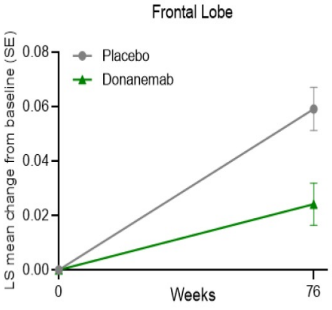
AVERAGE AMYLOID PLAQUE REDUCTION OF 85 CENTILOIDS AT 76 WEEKS

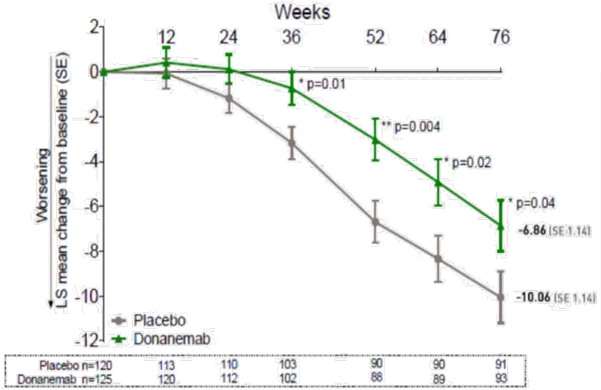


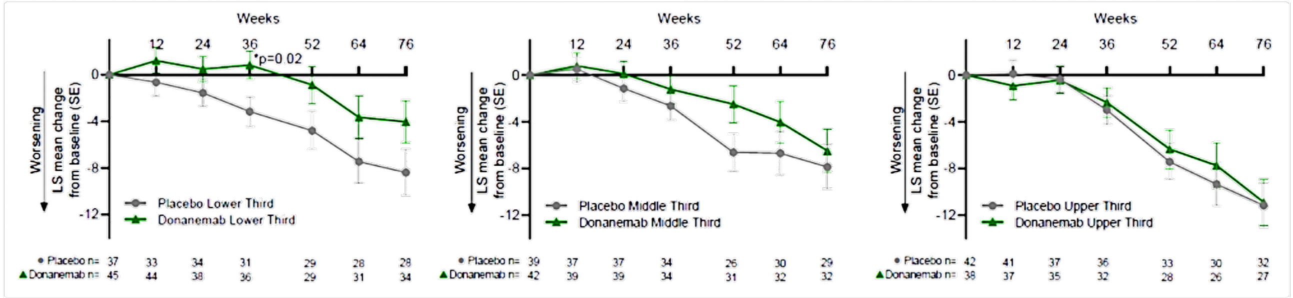
adapted from Mintun et al, *N Engl J Med 2021*











from https://www.alzforum.org/news/conference-coverage/donanemab-confirms-clearing-plaques-slows-decline

iDEAS

Imaging Dementia—Evidence For Amyloid Scanning

Co-Chairs:
Rabinovici, Carrillo, Gatsonis, Hillner, Siegel, Whitmer

IDEAS-Study@acr.org
IDEAS-Study.org

Single arm, multi-site, longitudinal study evaluating the clinical utility of amyloid PET in Medicare beneficiaries with MCI or dementia meeting Appropriate Use Criteria (Johnson 2013)

~18,200 patients enrolled between Feb 2016-Jan 2018, followed for 12 months

Recruited from ~600 memory clinics; Scanned at ~350 PET facilities

PET performed with FDA-approved Aβ PET ligand

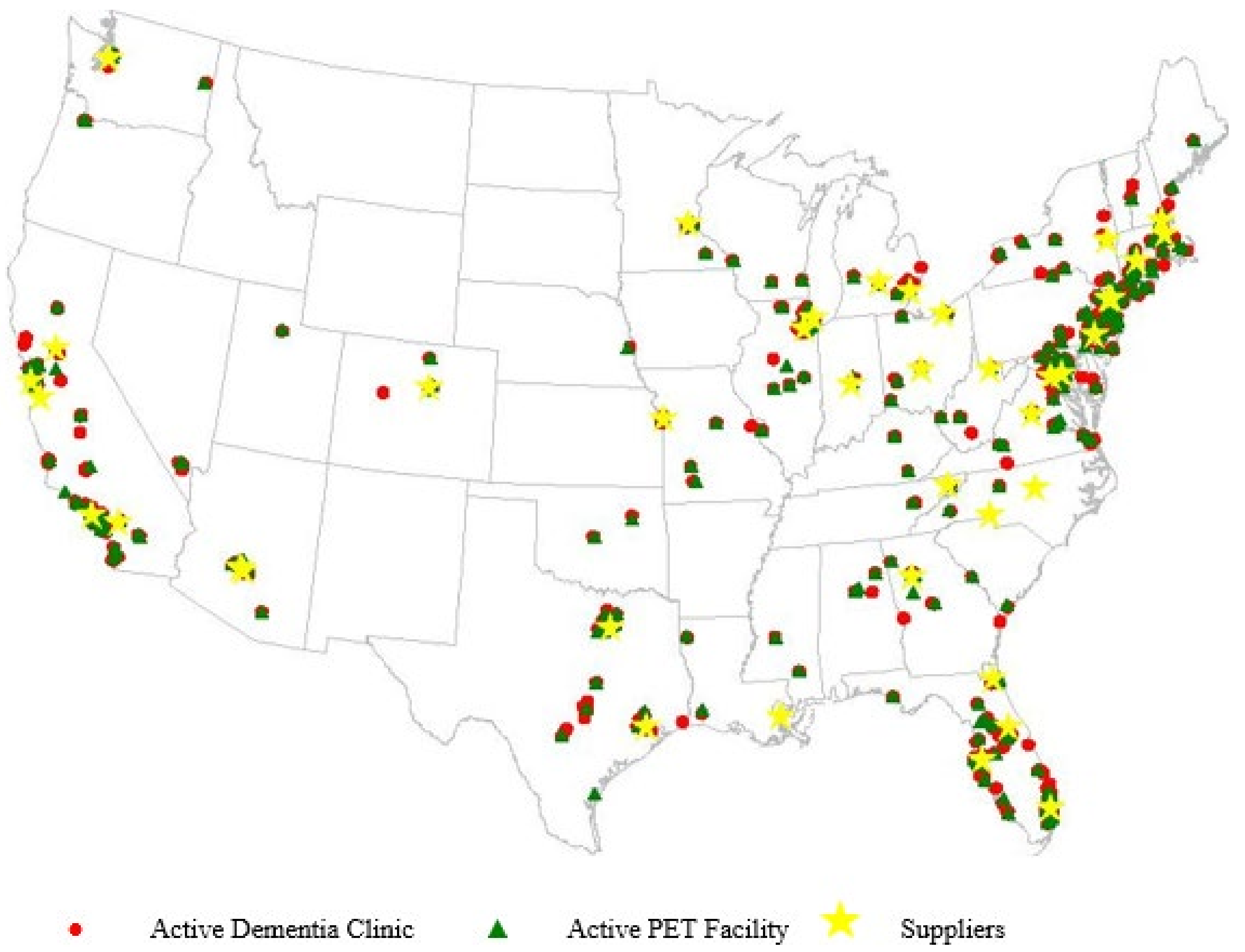
^{18}F-florbetaben, ^{18}F-florbetapir, ^{18}F-flutametamol

Scans read by local radiologists who completed vendor-specific training

Aim 1: Impact of scan on patient management plan at 3 months

Aim 2: Impact on major medical outcomes at 12 months

The primary hypothesis is that, in diagnostically uncertain cases, amyloid PET will lead to significant changes in patient management, and these will translate into improved outcomes



Rabinovici et al. JAMA 2019

Quantification of Amyloid PET Scans in IDEAS

	All (n=8,895)
Age (mean ± SD)	76 ± 6
MMSE* (mean ± SD)	24.5 ± 4.9
MoCA# (mean ± SD)	21.0 ± 5.2
Female	51.1%
Dementia / MCI	36.4% / 63.6%
^{18}f-florbetaben	29.1%
^{18}f-florbetapir	64.8%
^{18}f-flutemetamol	6.1%
Visually Positive&	62.1%
Quantitatively Positive (Centiloids > 24.4)	60.2%

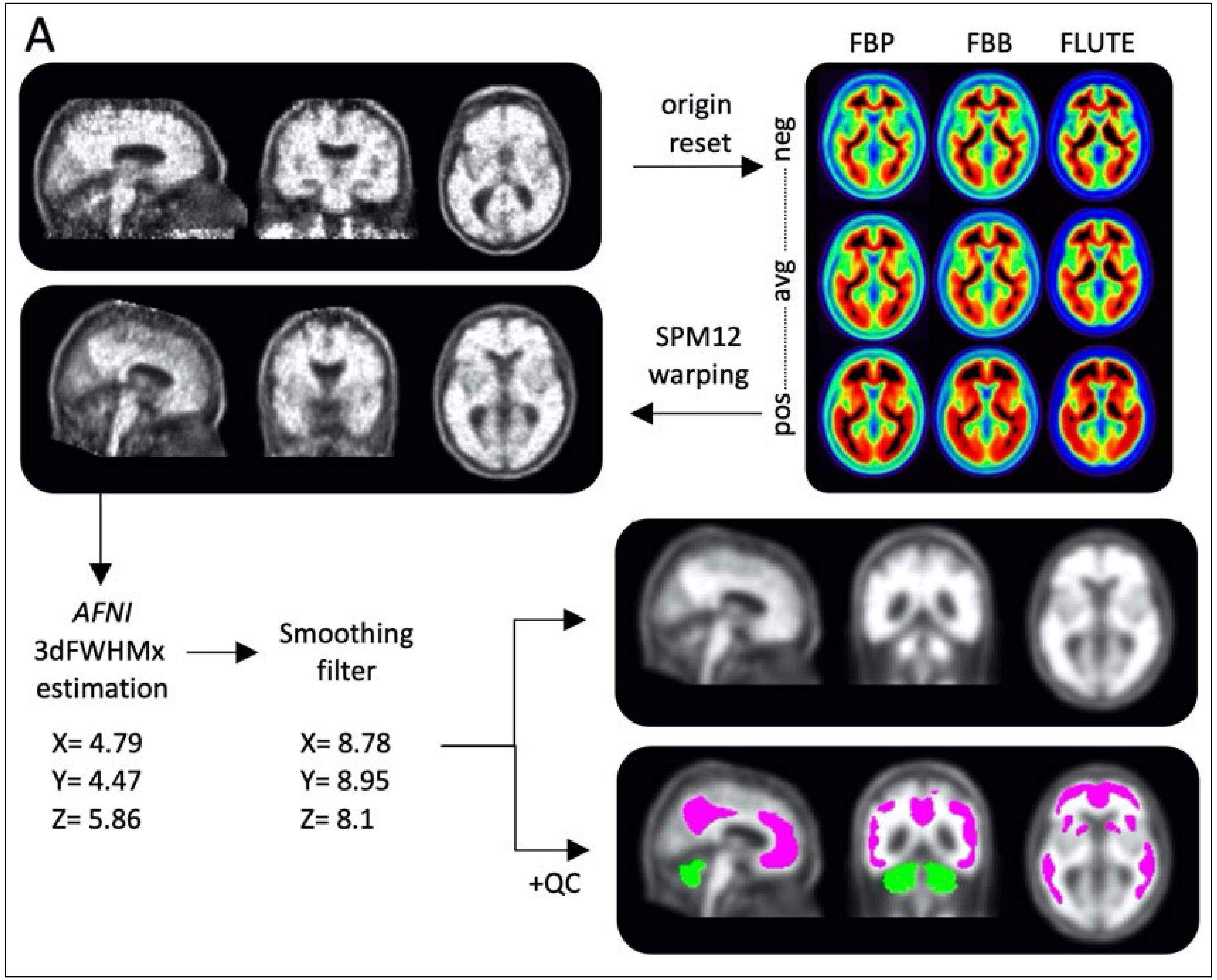
Table 1: Patient and Scan characteristics.

Zeltzer, Mundada, Iaccarino…La Joie, Rabinovici, unpublished

Quantification of IDEAS PET Archive

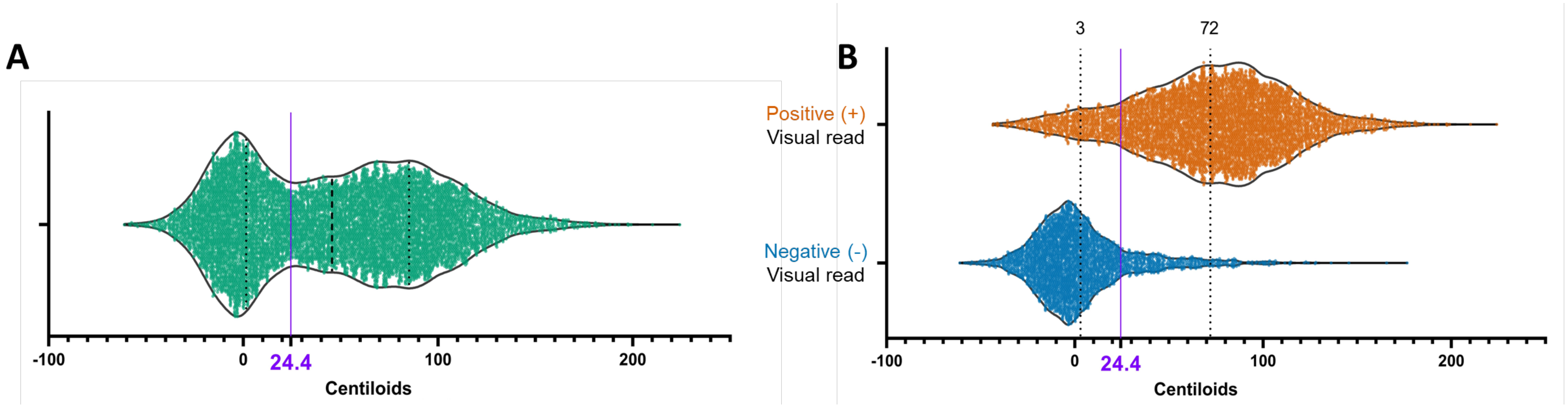
Robust PET-Only Processing (rPOP)

- Warp to template space (SPM12)
- Smooth to 10mm (AFNI)
- Quantification (GAAIN CL ROIs)
- Centiloid conversion
- Source code: https://github.com/leoiacca/rPOP



Iaccarino et al. Neuroimage 2022

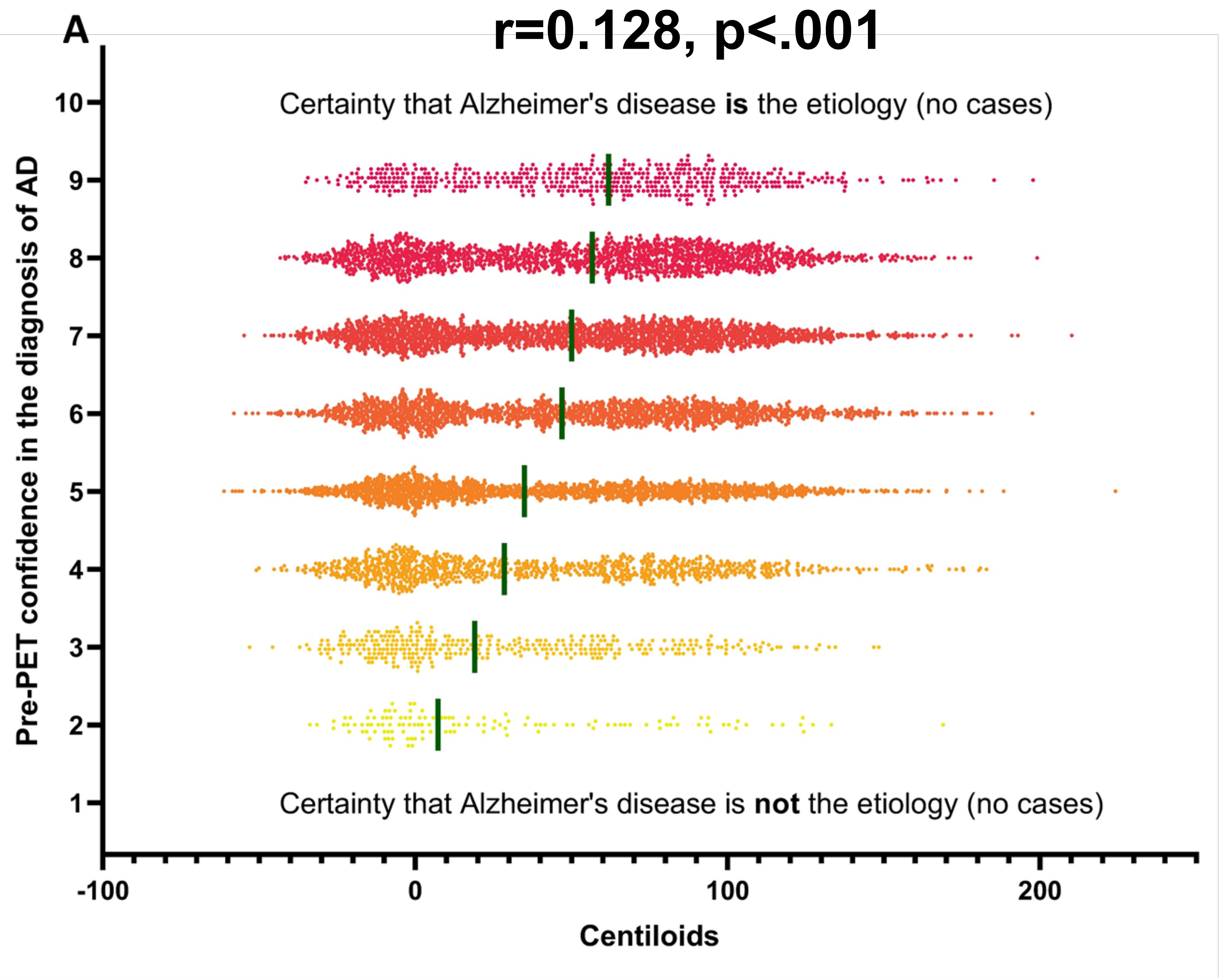
Quantification of Amyloid PET Scans in IDEAS

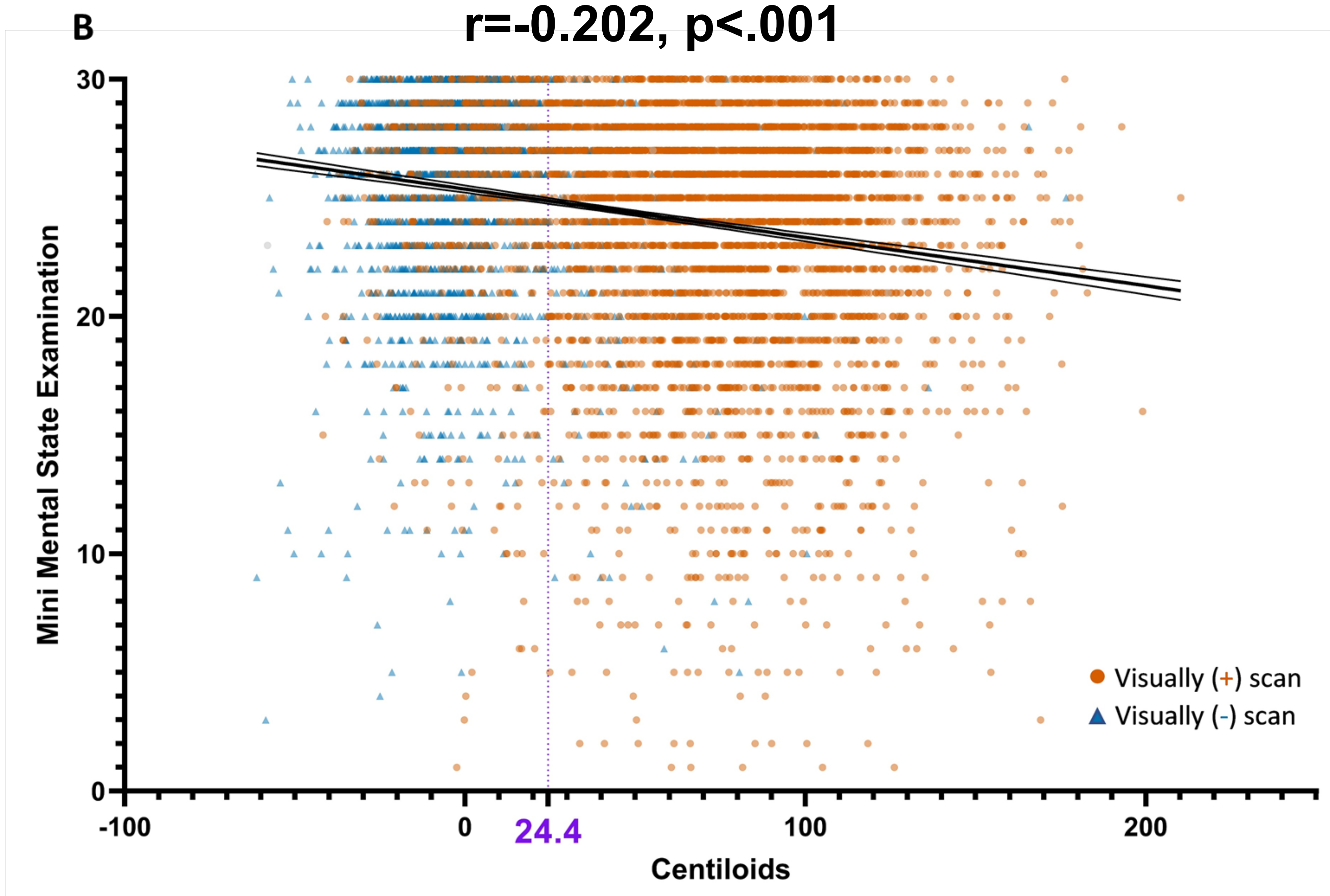


K = 0.72 (0.70-0.74)

Zeltzer, Mundada, Iaccarino…La Joie, Rabinovici, unpublished

Correlation with Clinical Measures





Zeltzer, Mundada, Iaccarino…La Joie, Rabinovici, unpublished