Mass General Brigham

Quantitative Brain Amyloid PET Imaging in Patients with Alzheimer's Disease

Semi-Quantitative and Quantitative Metrics

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Basic Requirements for Tracer Kinetic Study

Trace quantities of radiotracer introduced into system (non-perturbing)

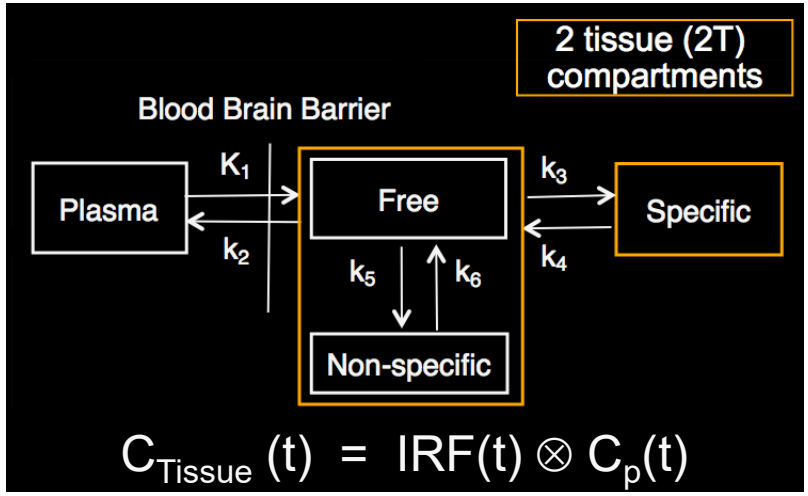
Studies conducted at high specific activity (SA), where SA is a measure *of the amount of radioactivity per mass (radioactive+non-radioactive) of sample and, for radiotracer studies, is commonly expressed in proportional units (e.g., Ci/mmole)*

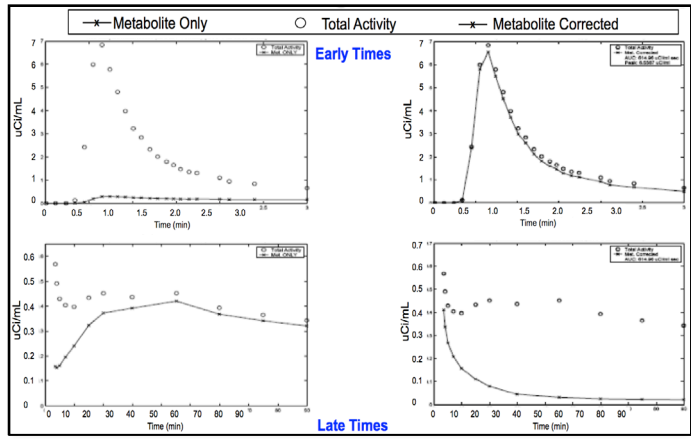
Steady-state. The rate of transport or reaction of the system is not changing with time, amount of substance in any part of the system is constant during the measurement period and this is maintained after tracer introduction and despite the tracer kinetics

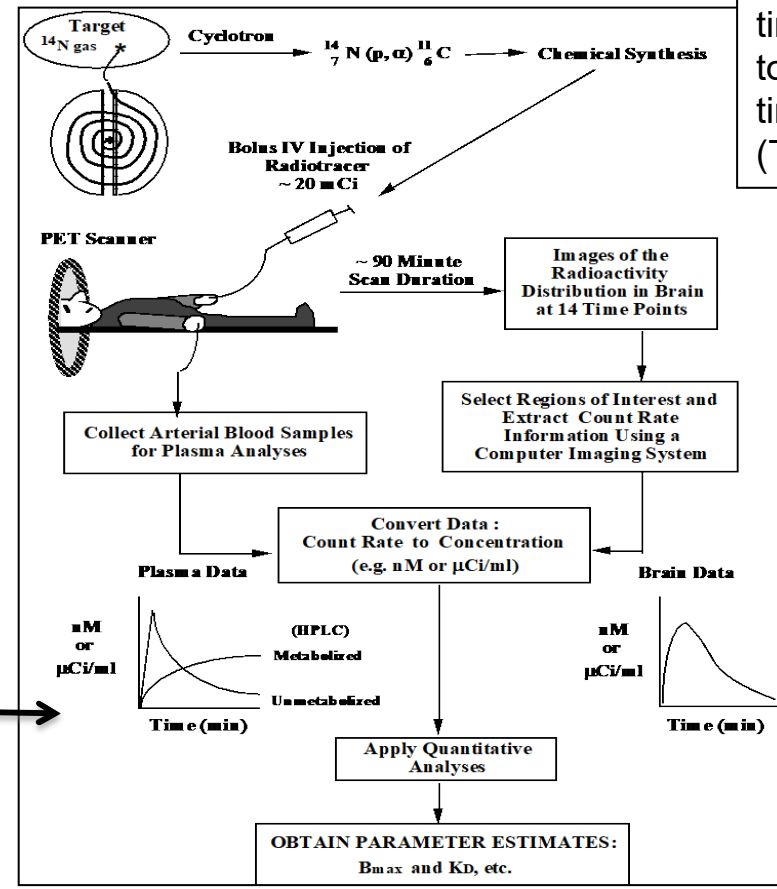
Tracer Linearity. The kinetics of the radiotracer can be completely represented by a response function (kinetic measurements are convolution of input function and system response function) due to valid application of tracer principle

Lassen and Perl 1979; Huang and Phelps 1986

PET Pharmacokinetic Modeling







Dynamic PET imaging begins at time of radiotracer injection over typical time of 60 – 90 min to measure full PET time-activity curve (TAC)

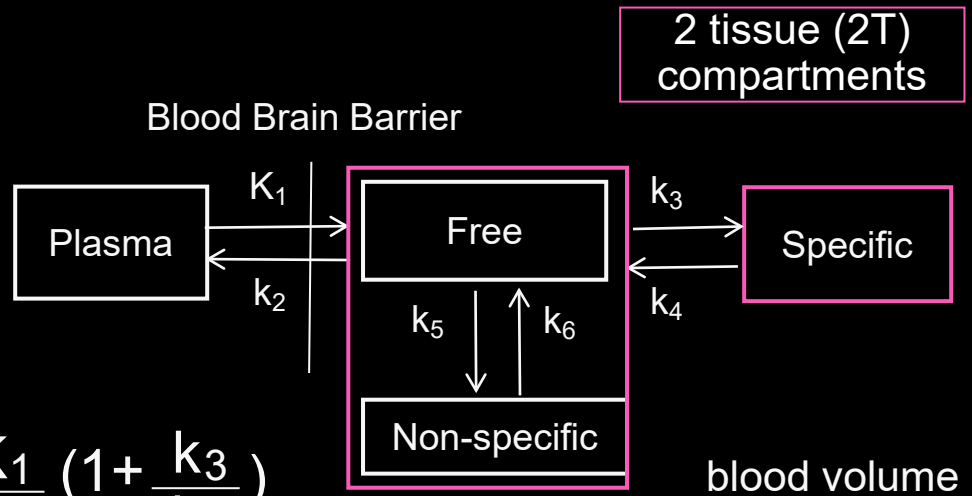
Spectral Analysis: Non-linear

$$IRF(t) = \sum_{i=1}^{n} A_i e^{-\beta_i t} \qquad C_{Tissue}(t) = IRF(t) \otimes C_p(t)$$

Compartmental Model: Non-linear

$$IRF(t) = A_1 e^{-\beta_1 t} + A_2 e^{-\beta_2 t}$$

$$= \frac{K_1}{(\beta_2 - \beta_1)} \left[(k_3 + k_4 - \beta_1) e^{-\beta_1 t} + (\beta_2 - k_3 - k_4) e^{-\beta_2 t} \right]$$



$$\mathbf{2T\ V_T} = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right)$$

blood volume accounted for

Logan Graphical Method: Linear

$$\frac{\int_0^T C_{ROI}(t)dt}{C_{ROI}(T)} = \text{Slope} \frac{\int_0^T C_p(t)\,dt}{C_{ROI}(T)} + \text{y-intercept}$$

Slope = V_T (includes blood volume)

Common Analysis Methods OUTCOMES

* Generally fully dynamic acquisition of 90 min or 60 min

Compartmental Modeling* V_T, DVR, BP

- Arterial Input (2T-4k)

Needed for characterization but not feasible

90 min not likely, maybe 60 min – moderately feasible

(Simplified) Reference Tissue Model* Relative delivery, BP

- (SRTM) Cerebellar Data as Input

Regression Methods (Linear Logan, Bilinear Ichise)* V_T, DVR, BP

- Arterial Input (ART90)
- Cerebellar Data as Input (CER90)
- Arterial Input Image-derived, population metabolites (CAR90)

Late-scan Uptake Ratio (generally static, e.g., 20 or 30 min) SUVR

- Standardized Uptake Value, scaled by inj. dose & mass (SUV)
- SUVR is Tissue:Cerebellum Ratio

Some methodological assumptions & related questions

The outcome measure

- should not be dependent of blood flow
- should not be time dependent
- should have good test-retest reproducibility over all follow-up periods

(Simplified) Reference Tissue Model

Q. Are reference tissue kinetics well-described by 1-tissue compartment model
Q. Is radioligand delivery comparable for specific ROIs and reference?

Regression Method (Linear Logan; Bilinear Ichise)

Q. Are data consistent with regression assumptions ?
Q. To what extent can any noise-induced bias be minimized?
Q. Is steady-state parameter t* providing stable measures across subjects/ROIs

Late-scan Uptake Ratio

Q. To what extent might steady-state assumptions be violated?
Q. To what extent can any blood flow dependence be minimized?

Q. How to a compromise between accuracy, precision and study feasibility?

Compartmental Modeling

Explicit description of tracer compartments (Model Equations)

- Transport of tracer into and out of compartments
  Rate constants
  Tracer leaving compartment proportional to total amount in compartment

- All tracer injected will exist in one of multiple compartments

- Uniform radiotracer concentration within compartment
  No concentration gradients

- Model Equations
  Mathematical equations describe the time rate of change of the compartmental concentrations (differential equations)

Example Assumptions

- Bi-directional Blood-Brain Barrier (BBB) Transport
  - Diffusion
  - Facilitated Transport

PET

- Includes vascular radioactivity concentration (V_{vasc})
- Constant free fraction in blood or plasma (f_P)
- Homogeneous free fraction in brain (f_{ND})
- No (radioactive) metabolites in brain

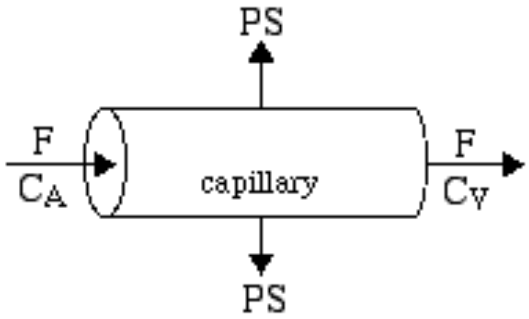
Plasma

- Free radiotracer only crosses BBB (protein binding)

Kinetics

- Transient, Steady-state, Equilibrium ...

Capillary Exchange



$$F * E = F(1-e^{-PS/F})$$

- Renkin-Crone model describes the extraction of tracer across the blood-brain barrier (BBB) based upon a rigid cylinder model

  Tracer, with arterial concentration C_A, is delivered to a site by the blood flow (F: mL/g/min) and extracted from the vasculature across the capillary walls into brain. Tracer remaining in the vasculature is cleared away with venous concentration C_V.

- Tracer extraction depends on tracer permeability for the capillary wall (P: cm/min) and the capillary surface area (S: cm^2/g) as expressed in terms of the single pass extraction fraction (E) and PS product ($cm^3/g/min$)

Renkin et al 1959; Crone et al 1964

Volume of Distribution (V_T)

The V_T is the volume of tissue that the tracer would distribute itself in, if it had the same concentration in brain as it does in blood.

This parameter is equivalent to the equilibrium (Eq) ratio of the brain and blood tracer concentrations

The V_T is mathematically equivalent to the partition coefficient

$$V_T = \left.\frac{C_T}{C_P}\right|_{Eq} = \frac{\text{(mL of radiotracer in tissue water space/cm}^3\text{ brain tissue)}}{\text{(mL of radiotracer in plasma water space/mL blood or plasma)}} \text{ (mL/cm}^3\text{)}$$

Lassen and Perl, l979; Huang et al., 1986; Gjedde et al., 1990

Example:

If the concentration of a radiopharmaceutical at equilibrium is 100 kBq/cm^3 in striatum (C_T) and 5 kBq/mL in plasma (C_P), then its volume of distribution (V_T) is 20 mL/cm^3 *(Innis et al. JCBFM 2007)*

Free Fractions and Volumes of Distribution

- Free fraction of drug or radioligand in plasma is fraction of ligand not bound to plasma proteins at equilibrium, i.e., that which is freely diffusible in plasma water. The plasma free fraction is referred to as $\mathbf{f_P}$ and the concentration of free drug in plasma C_{FP} can be calculated as $\mathbf{C_{FP} = f_P C_P}$
- Fraction of drug that is freely dissolved in tissue water, $\mathbf{f_{ND}}$ is expressed relative to the *nondisplaceable* compartment, $\mathbf{C_{FT} = f_{ND} C_{ND}}$ and is, thereby, usually assumed to be equal in receptor-rich and receptor-free regions, assuming nonspecific binding is the same in both areas

$$V_T = C_T/C_P = V_{FT} + V_{NS} + V_S = V_{ND} + V_S$$

$$\text{where } V_{ND} = C_{ND}/C_P \text{ and } V_S = C_S/C_P$$

Reversible Ligand Binding

Innis et al. 2007

Components of tissue uptake (reversible binding)

Athinoula A. Martinos Center For Biomedical Imaging

Tissue may contain radioligand that is **specifically bound** to receptors (**S**), **Nonspecifically bound** (**NS**) or **free** in tissue water (**F**). Thus, total concentration of radioligand in the tissue (C_T) can be expressed as :

$$C_T = C_S + C_{NS} + C_{FT}$$

Furthermore, **nondisplaceable (ND) uptake** is the sum of the nonspecific (NS) and free ligand in tissue.

$$C_{ND} = C_{FT} + C_{NS}$$

The volume of distribution of these **3** components equals the ratio ***at equilibrium*** of each concentration to that of the parent radioligand (C_p) in plasma separated from radiometabolites.

$$V_T = C_T / C_P = V_{FT} + V_{NS} + V_S = V_{ND} + V_S$$

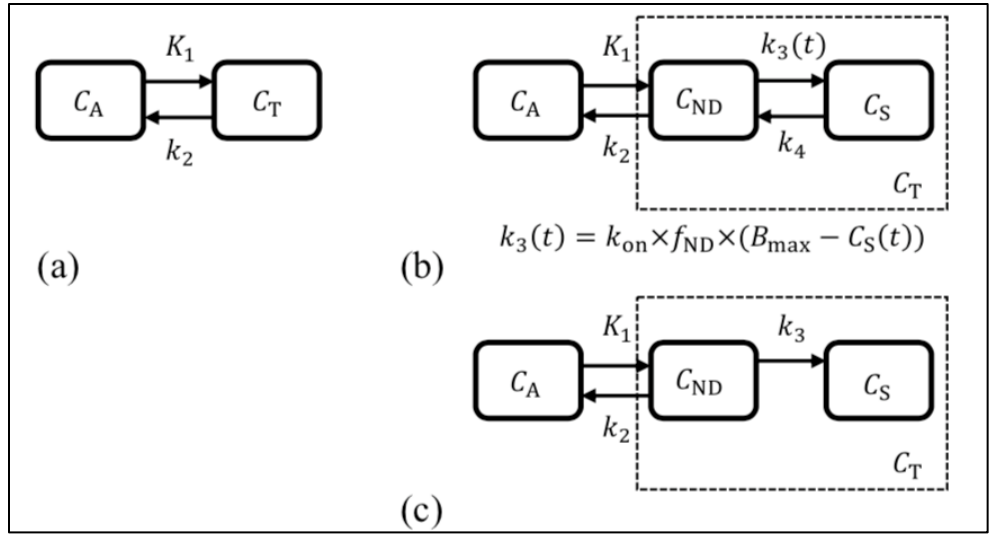
$$V_{NS} = C_{NS} / C_P$$

$$V_{ND} = C_{ND} / C_P$$

$$V_S = C_S / C_P$$

Innis et al., Journal of Cerebral Blood Flow & Metabolism (2007) 27, 1533–1539

Pharmacokinetics : Compartmental Models

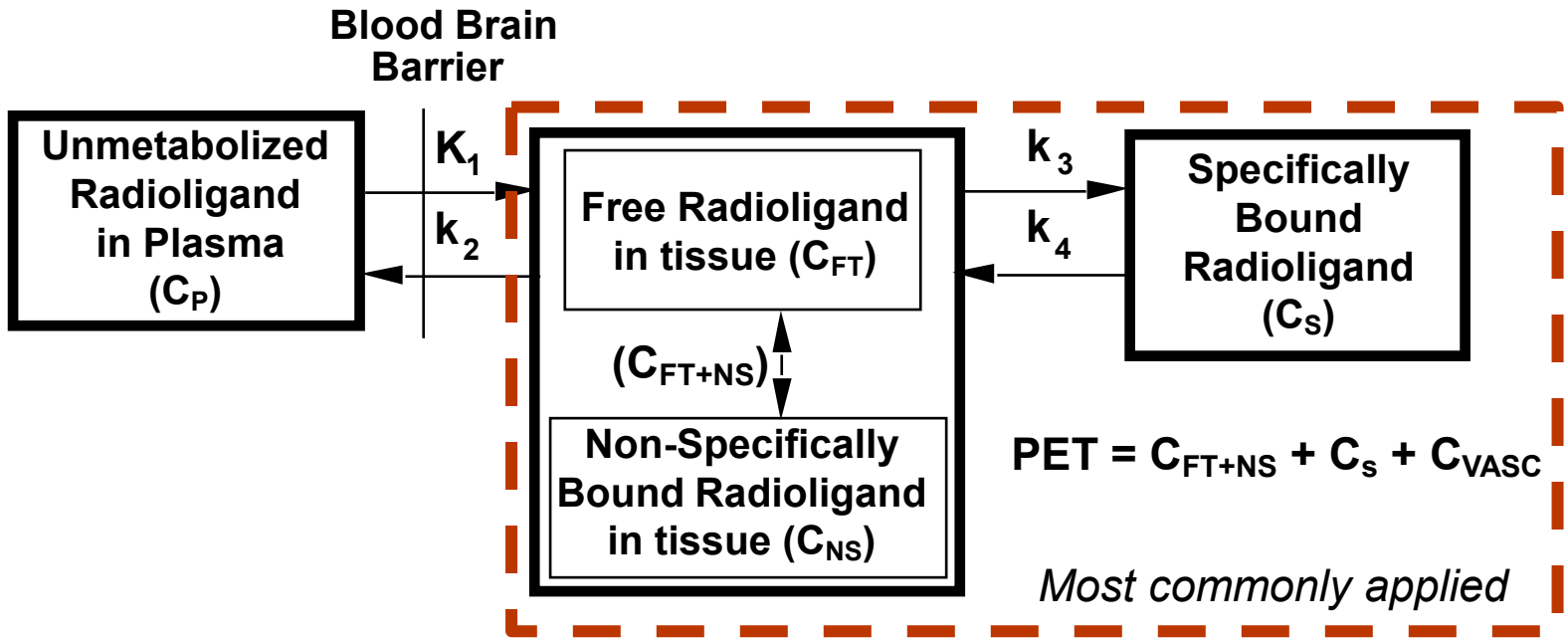


A range of PET compartmental models commonly used to quantify PET radiotracers. These include models for tracers that exhibit reversible and irreversible kinetics and models that use either plasma or reference region time activity data as input

Gallezot et al., IEEE Transactions on Radiation and Plasma Medical Sciences, 2020

Gunn et al., Physics in Medicine and Biology, 2015

Ligand-Protein binding 2-Tissue Compartment (2T-4k, Reversble)



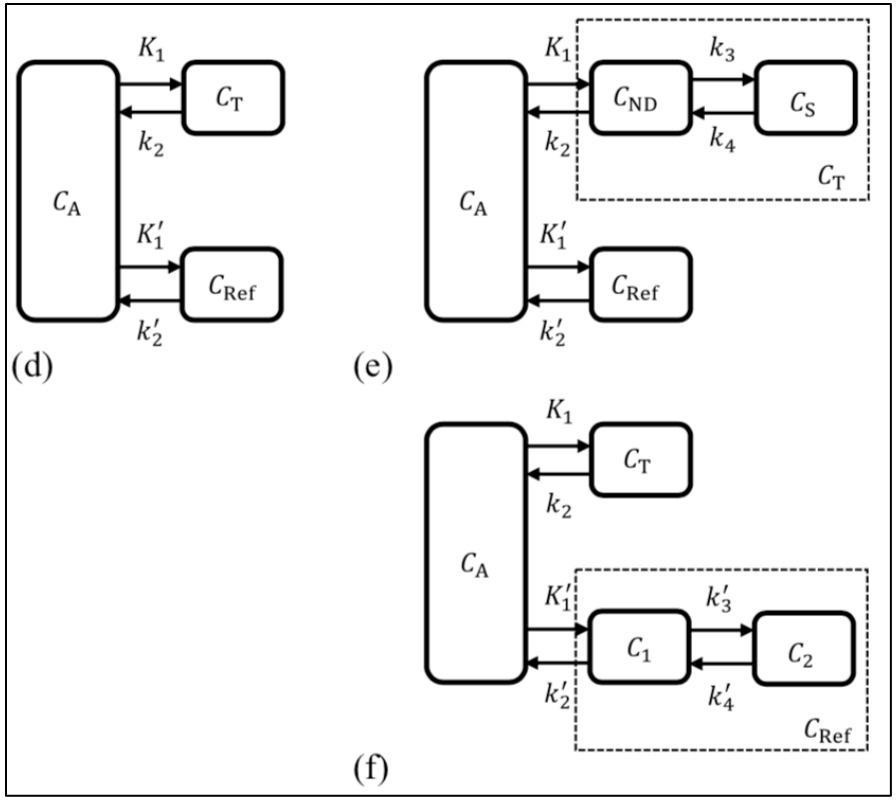
K_1 = Flow * E, (mL/cm^3/min)

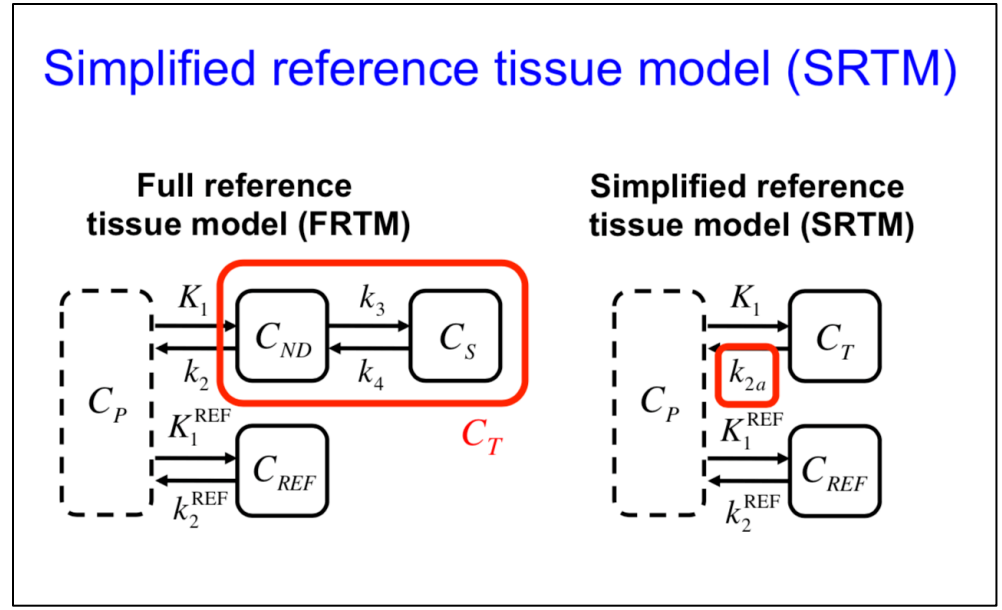
k_2 = Rate of drug removal from tissue back to blood, (min^{-1})

k_3 = Pseudo-first order specific binding association rate constant ($k_{on}f_{ND}B_{avail}$), (min^{-1})

k_4 = First order dissociation rate constant (k_{off}), (min^{-1})

Pharmacokinetics : Reference Tissue Models





Gallezot et al., IEEE Transactions on Radiation and Plasma Medical Sciences, 2020

Gunn et al., Physics in Medicine and Biology, 2015

Volume of Distribution (V_T) and Binding Potential (BP)

Reversible Ligand Binding

$$V_T = C_T/C_P = V_{FT} + V_{NS} + V_S = V_{ND} + V_S$$

where $V_{ND} = C_{ND}/C_P$ and $V_S = C_S/C_P$

3-Tissue Compartment

$$V_T = K_1/k_2\,(1 + k_3/k_4 + k_5/k_6)$$

$$k_3 = k_{on}\,B_{avail}$$

$$BP = k_3/k_4 = B_{avail}/K_D$$

2-Tissue Compartment

$$V_T = K_1/k_2\,(1 + k_3/k_4)$$

$$k_3 = k_{on}\,f_{ND}\,B_{avail}$$

$$BP_{ND} = k_3/k_4 = f_{ND}\,B_{avail}/K_D$$

1-Tissue Compartment

$$V_T = K_1/k_2$$

k_2 includes BP_{ND}

Binding Potentials (2T-4k)

Binding potential quantifies the equilibrium concentration of specific binding as a ratio to some other reference concentration.

Table 1 Definitions of three *in vivo* binding potential values

Binding potential	*In vitro analog*	*Volume of distribution*	*Rate constants*	*Specific compared to:*	*Units*	*Plasma sample?*	f_P*?*
BP_F =	B_{avail}/K_D =	$(V_T - V_{ND})/f_P$ =	$\frac{K_1 k_3}{f_P k_2 k_4}$	Free plasma concentration	$mL \cdot cm^{-3}$	Yes	Yes
BP_P =	$f_P B_{avail}/K_D$ =	$V_T - V_{ND}$ =	$\frac{K_1 k_3}{k_2 k_4}$	Total plasma concentration	$mL \cdot cm^{-3}$	Yes	No
BP_{ND} =	$f_{ND} B_{avail}/K_D$ =	$(V_T - V_{ND})/V_{ND}$ =	$\frac{k_3}{k_4}$	Nondisplaceable uptake	Unitless	No	No

Rate constants are for the two-tissue compartment model. The two rightmost columns show whether each of the three binding potential values requires measurement of the concentration of radioligand in plasma (often arterial plasma) or the measurement of its plasma free fraction f_P. See Table 2 for definitions.

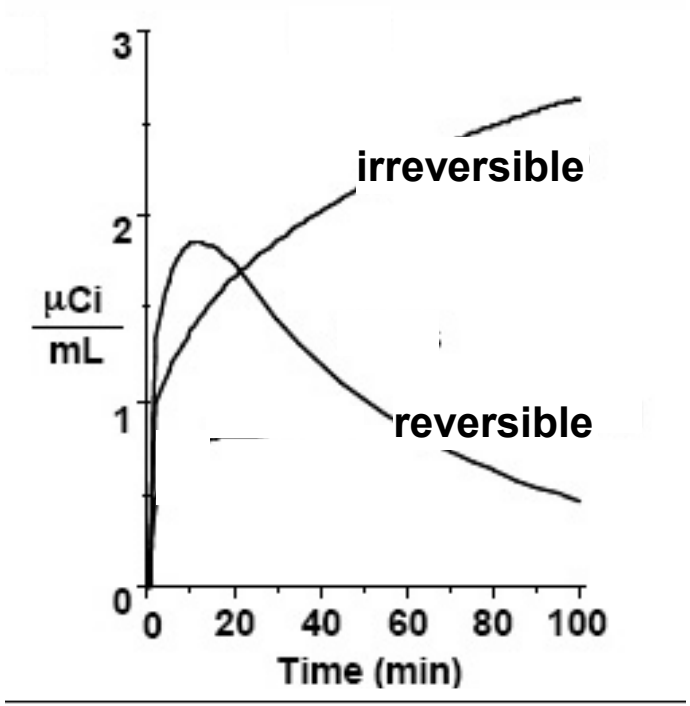
Innis et al 2007

Linearizations

Simplifies data analysis process

- Reformulate nonlinear problem to linear problem, $y = mx + b$
- Enables simple and routine data analysis
  e.g., linear regression rather than iterative curve fitting
  but performance can be degraded by data noise and correlation
- Results obtainable even if underlying model configuration unknown
- Linear outcomes can be more reproducible than those derived from nonlinear curve fitting
- Linear methods are amenable to parametric image generation

Linearizations: Graphical "Plots"



Patlak method (also known as Gjedde-Patlak plot) was derived for irreversible tissue uptake and widely applied to FDG

Logan method derived for reversible tissue kinetics and has been widely applied to studies of ligand-binding interactions (e.g., neuroreceptor binding studies)

Linearizations: Logan Plot

Generally applied to reversible kinetics ($k_4 > 0$)

Rapid dissociation rates and rates of efflux from tissue

After steady state time (t*), a linear relationship exists:

$$\frac{\int_0^t C_{ROI}(t)\,dt}{C_{ROI}(T)} = \text{Slope}\,\frac{\int_0^t C_p(t)\,dt}{C_{ROI}(T)} + \text{y-intercept}$$

with model configuration assumed:
K_1 = -slope/intercept (ideally)

C_p : arterial plasma concentration of radiotracer

Not dependent on specific model configuration

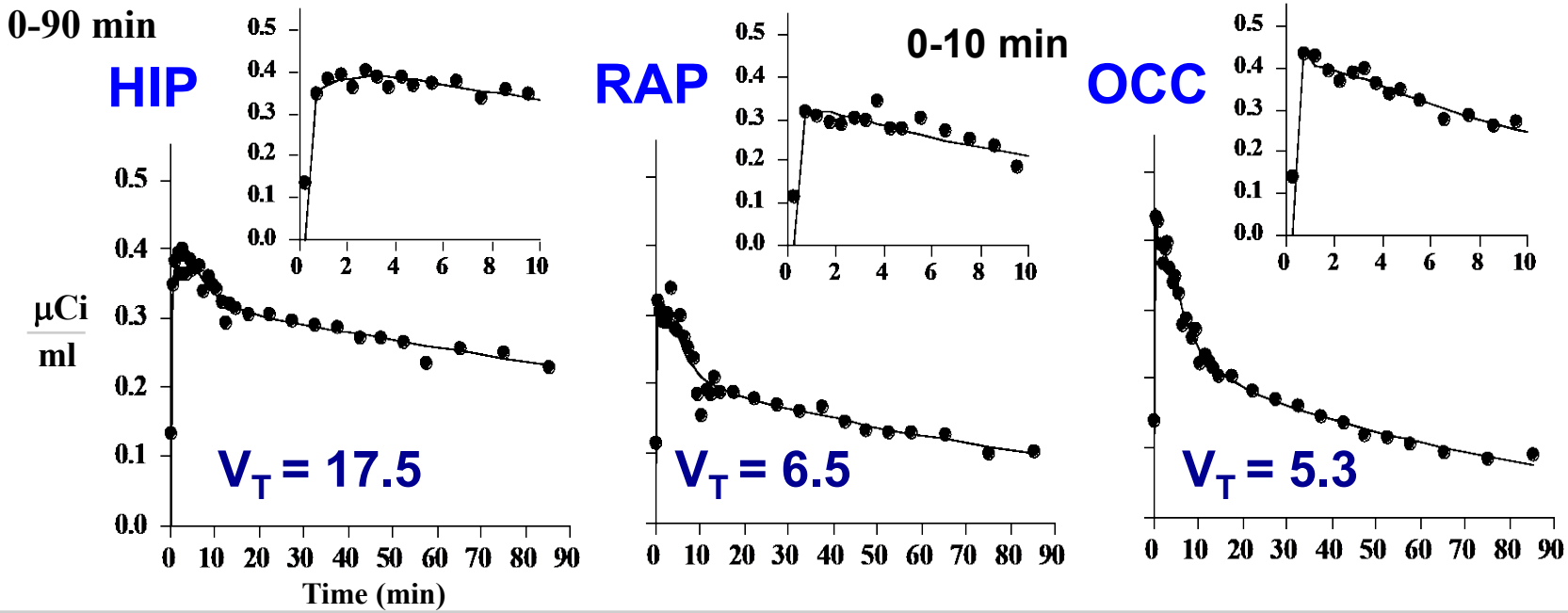
Slope: measure of total radiotracer distribution volume, V_T (mL/cm^3)

For ligand-binding interactions: $DVR = V_T/V_{ND}$, where $BP_{ND} = DVR - 1$ and ND is nondisplaceable tissue uptake (determined in reference region)

1) Logan, J et al. JOBFM, 1990
2) Logan et al. Nuclear Medicine & Biology, Vol. 27, pp. 661–670, 2000
3) Kimura et al. Annals Nuclear Medicine Vol. 21, No. 1, 1–8, 2007

2-Tissue Comp

[^{11}C]WAY 100635

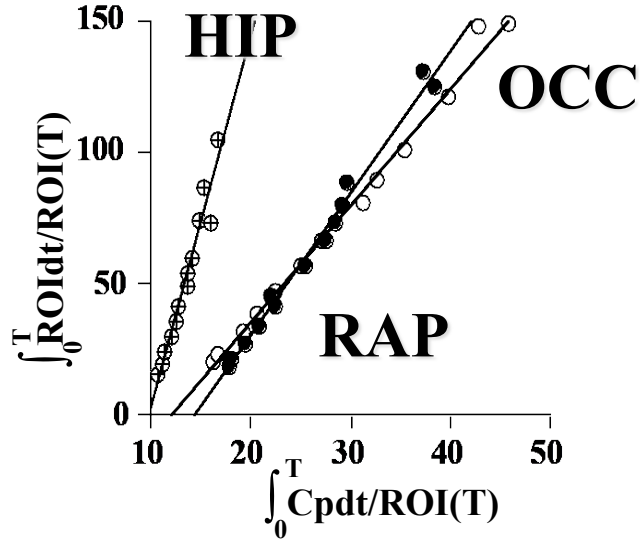


Logan V_T

HIP: 16.2

RAP: 6.9

OCC: 5.6



# points	t*	HIP V_T
n=12	17.52	15.7
n=10	27.52	16.2
n=8	37.52	16.2
n=6	47.52	15.9
n=4	57.52	12.9

Linearizations: Parametric Imaging

Extension of linear methods to voxel basis

- Image voxel corresponds to outcome measure
  (e.g., K_1, K_i, DVR, BP_{ND})
- No specific model configuration (generally) required
  Generally can obtain result, despite noisy voxel data
  but bias in outcome measure can be substantial
  Noise-reduction by smoothing/processing methods
- Can enable direct reconstruction of parametric image
  Review: Rahmim and Tang (2009), Am Assoc Phys Med

Linearizations: When it is not so easy

Choice of the t* steady state time for integral evaluation

- Can vary between regions with different kinetics
- If t* is late, regression may include only a few data points
  - accuracy/precision trade-off
- Possible for results to vary substantially for different t* values

Potential for measurement bias

- Adherence to assumptions of linear method, e.g. linear regression
  - Sufficient linearity between dependent and independent variables?
  - Error: uncorrelated, constant variance, normality ?
  - Additional data processing (e.g., smoothing, averaging) may help

Linearizations: When it is not so easy

Is it worth the cost(s)?

Need to evaluate outcome bias for given application

For radiotracer, across regions and for subject group

Is bias minor or acceptable for what is gained by feasibility?

Use of alternate formulations – less prone to such bias

Strategies to improve neuroreceptor parameter estimation by multilinear regression analysis:

Ichise M et al. (2002). J Cereb Blood Flow Metab

$$C(T) = -\frac{V}{b}\int_0^T C_p(t)dt + \frac{1}{b}\int_0^T C(t)dt$$

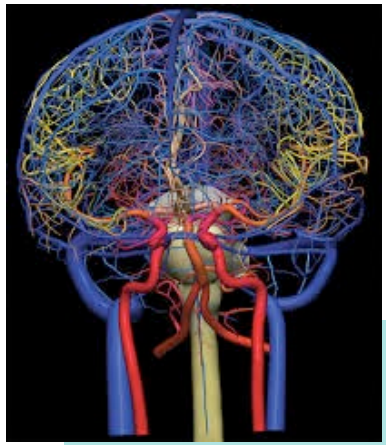
Basis function approach for spectral analysis (V_T)

Reference graphical methods

Logan

MRTM

Coffee break protocol (Lammertsma)



SUVR (late scan tissue ratio)

- Standardized uptake value tissue ratio (SUVR) is a simple and feasible in vivo PET measure that improves study feasibility for patient populations and repeated follow-up imaging.
- Relative to quantitative outcomes, SUVR often favored because of low measurement variability (image-based ratio) increasing statistical power for detection of group differences and longitudinal change.

Image: http://n.neurology.org/content/79/2/e10x

SUVR

- SUVR is surrogate measure of radiotracer volume of distribution (V_T) that is the tissue:blood concentration ratio, at equilibrium.
- Accuracy of SUVR, depends on whether equilibrium is established, when target:background tissue uptake ratio is constant, when dC(t)/dt = 0 in blood and brain. Violation of equilibrium leads to errors in SUVR, particularly notable after bolus injection of brain PET radiotracers with reversible kinetics *(Carson 2000; Slifstein 2008)*.

Basic assumptions

- steady-state between radiotracer concentration in specific-binding region and reference region exists
- radiotracer delivery is the same to both areas

Assumptions not strictly met for leading Aβ and tau imaging agents because of radiotracer clearance in both the ROI and reference tissues, although tissue ratios may be fairly constant. Plasma also clearing.

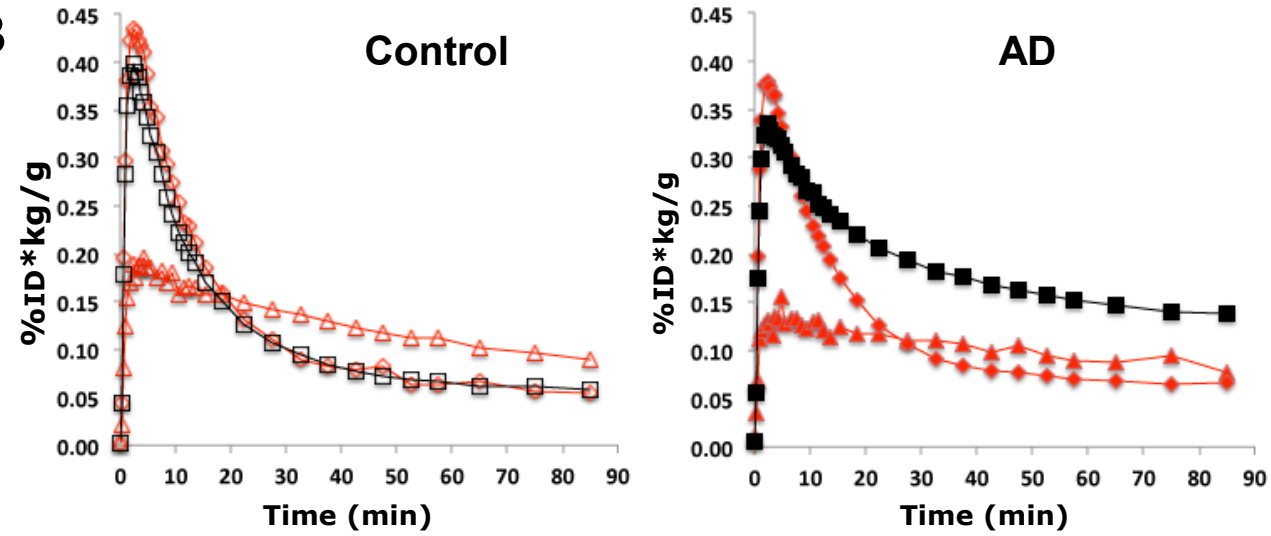
Relevant for longitudinal changes in target protein deposition

- patients with accelerated cerebral atrophy that gives rise to blood flow differences across repeated follow-ups (e.g., treatment evaluation) or between specific cortical area and reference region

Carson RE (2000) PET physiological measurements using constant infusion. Nucl Med Biol 27:657-60

Slifstein M (2008) Revisiting an old issue: the discrepancy between tissue ratio-derived binding parameters and kinetic modeling-derived parameters after a bolus of the serotonin transporter radioligand 123I-ADAM. J Nucl Med 49:176-8

[^{11}C]PiB

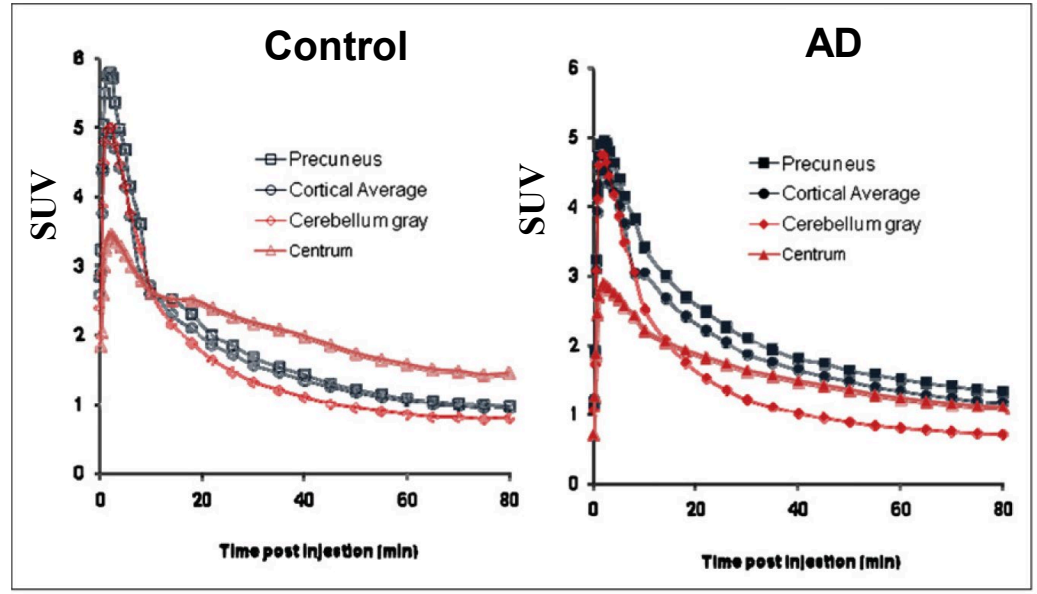


Rather than higher white matter uptake, Florbetapir has relatively **lower cortical** signal and **lower noise** (important for visual reads)

Koeppe et al, Human Amyloid Imaging 2012

Florbetapir

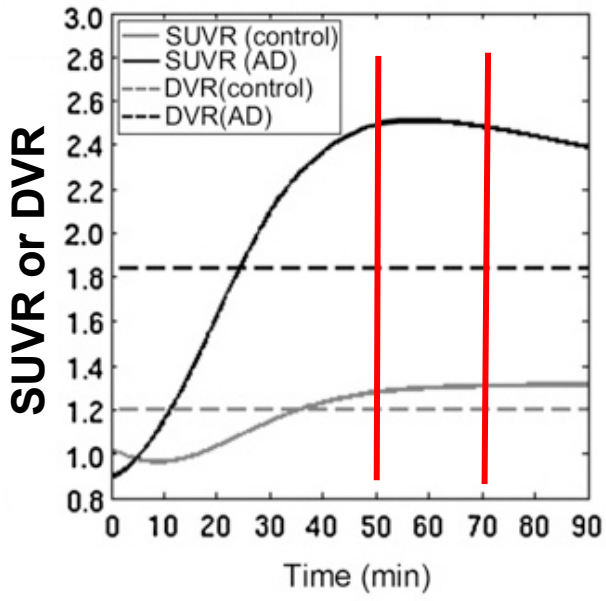
Wong et al. JNM 2010



IS06: Advances in Tau imaging, SNMMI 2022, Price

[^{11}C]PiB SUVR Tissue Ratio Time Window

McNamee et al. J Nucl Med 50:348-55 (2009)



[^{11}C]PiB Computer Simulations

Rate constants	Control		AD	
	Cerebellum	PCM	Cerebellum	PCM
K1	0.2860	0.2907	0.2916	0.2626
K2	0.1517	0.1675	0.1429	0.1234
K3	0.0098	0.0170	0.0098	0.0471
K4	0.0130	0.0131	0.0077	0.0157

SUV and DVR curves generated using average rate constants (above) and arterial blood for AD (n=11) and control (n=16) groups. Curves were generated for mid-posterior cingulate (PCM) and cerebellum

- 50-70-min time window provided good compromise between physiologic validity, stability, sensitivity, and clinical feasibility across control, MCI, and AD subjects
- 40-60-min window had many advantages and desirable for dose-limited studies

ORIGINAL RESEARCH Open Access

Impact of cerebral blood flow and amyloid load on SUVR bias

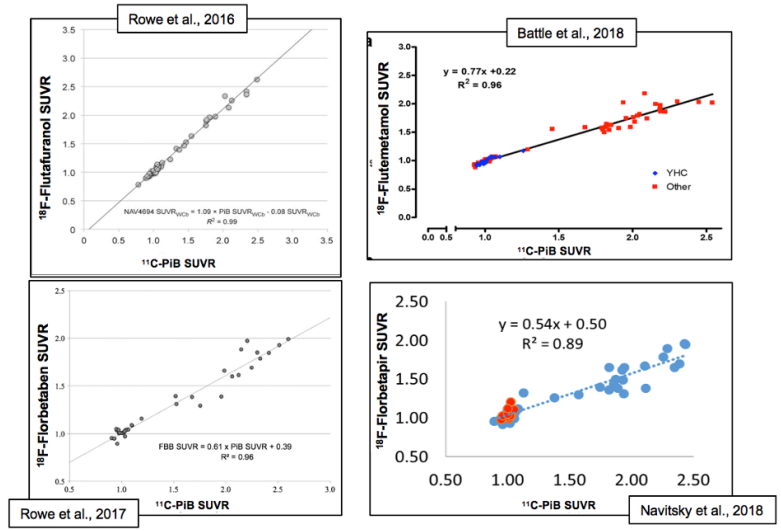
Fiona Heeman[1*], Maqsood Yaqub[1], Janine Hendriks[1], Bart N. M. van Berckel[1], Lyduine E. Collij[1], Katherine R. Gray[2], Richard Manber[2], Robin Wolz[2], Valentina Garibotto[3,4], Catriona Wimberley[5], Craig Ritchie[5], Frederik Barkhof[1,6], Juan Domingo Gispert[7,8,9,10], David Vállez García[1], Isadora Lopes Alves[1], Adriaan A. Lammertsma[1] on behalf of the AMYPAD Consortium

Heeman *et al. EJNMMI Research (2022) 12:29*

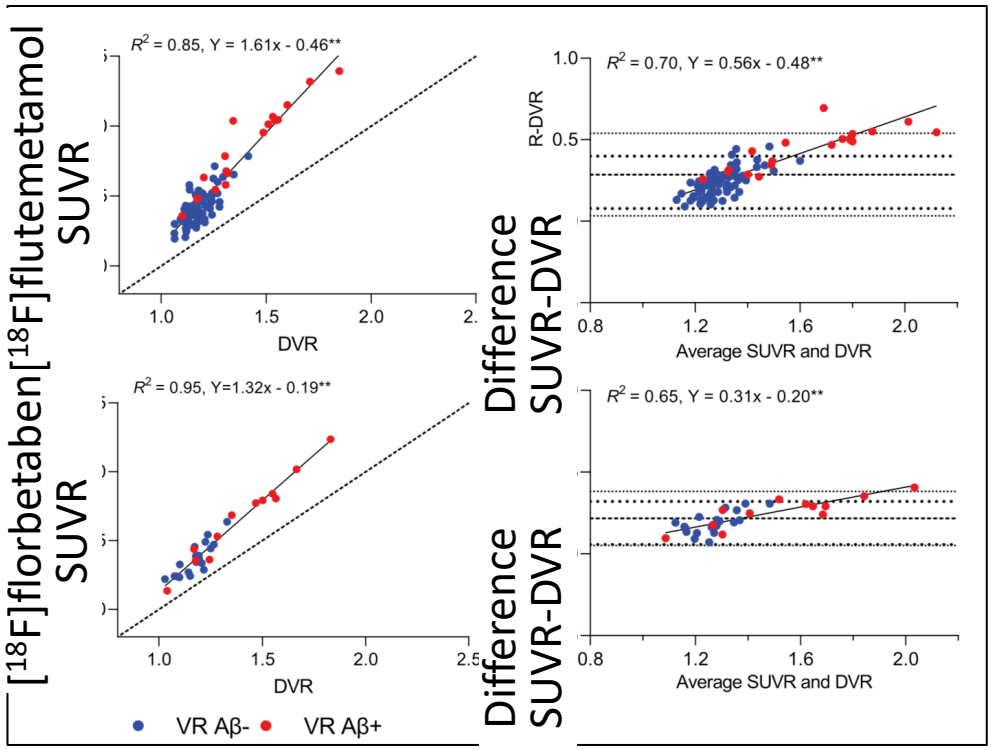
[^{18}F]flutemetamol (*N* = 90) or [^{18}F] florbetaben (*N* = 31

- The present study investigated whether bias in SUVR relative to DVR could be explained by factors such as underlying Aβ burden and relative CBF (as measured by *R*1). For both tracers, strong correlations were observed

- Scan Protocol : Early dynamic scan 0 to 30 min post-injection (p.i.) followed by a 60 min break and late dynamic scan from 90 to 110 min p.i.



Heeman et al. EJNMMI Research (2022) 12:29



Results: Despite high correlations (GCA: *R*2 ≥ 0.85), large overestimation and proportional bias of SUVR relative to DVR was observed. Negative associations were observed between both SUVR or SUVRbias and *R*1, albeit non-significant.

Conclusion: The present findings demonstrate that bias in SUVR relative to DVR is strongly related to underlying Aβ burden. Furthermore, in a cohort consisting mainly of cognitively unimpaired individuals, the effect of relative CBF on bias in SUVR appears limited.

Amyloid IQ

Whittington, J Nucl Med 2018; 59:822–827

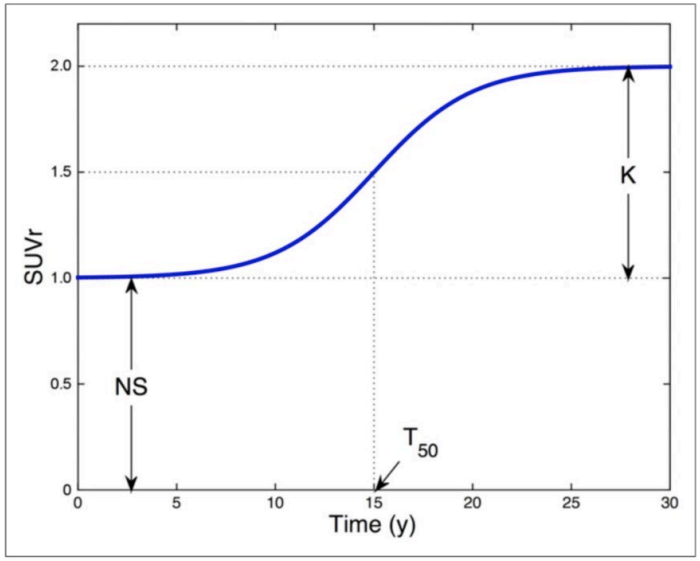


FIGURE 1. Logistic growth model describing Aβ PET imaging signal over time as function of PET NS, *K*, T_{50}, and *r*.

$$\begin{aligned} \mathrm{SUVr}(t) &= \mathrm{NS} + \mathrm{A\beta}(t) \\ &= \mathrm{NS} + \frac{K}{1 + e^{-r(t-T_{50})}}, \end{aligned} \qquad \text{Eq. 1}$$

Longitudinal Model of Aβ Accumulation

We introduce a logistic growth model to describe the accumulation of Aβ in the human brain. The model assumes that the rate of change of Aβ concentration is proportional to the product of the current concentration of Aβ and a term limiting growth due to the *K* of the local environment. The model is defined by the following differential equation:

$$\frac{d\mathrm{A\beta}(t)}{dt} = r\mathrm{A\beta}(t)\left(1 - \frac{\mathrm{A\beta}(t)}{K}\right). \qquad \text{Eq. 2}$$

Solving the differential equation yields a function for the concentration of Aβ over time:

$$\mathrm{A\beta}(t) = \frac{K}{1 + e^{-r(t-T_{50})}}. \qquad \text{Eq. 3}$$

In vivo PET amyloid tracers are quantified in terms of the SUVr between a target region containing amyloid and a reference region containing only background NS, and therefore:

$$\mathrm{SUVr}(t) = \mathrm{NS} + \mathrm{A\beta}(t). \qquad \text{Eq. 4}$$

Substituting Equation 3 for Aβ(*t*) into equation 4 yields the bottom line of Equation 1, which describes the temporal evolution of the in vivo PET Aβ signal over time (with the 4 parameters NS, *r*, T_{50}, and *K*).

Definition of $A\beta_L$

Whittington, J Nucl Med 2018; 59:822–827

Introduce the logistic growth model to provide a mathematical description of a sigmoidal increase in Ab concentration over time, where

- t is the time through the accumulation process (a t of 0 corresponds to a time point at which Ab levels are minimal) SUVr(t) is th
- Ab(t) is the concentration of Ab at time t,
- NS is the tracer nonspecific binding,
- r is the exponential uninhibited growth rate,
- T_{50} is the time of half-maximal Ab concentrat

$$\begin{aligned} \mathrm{SUVr}(t) &= \mathrm{NS} + \mathrm{A}\beta(t) \\ &= \mathrm{NS} + \frac{K}{1 + e^{-r(t-T_{50})}}, \end{aligned} \qquad \text{Eq. 1}$$

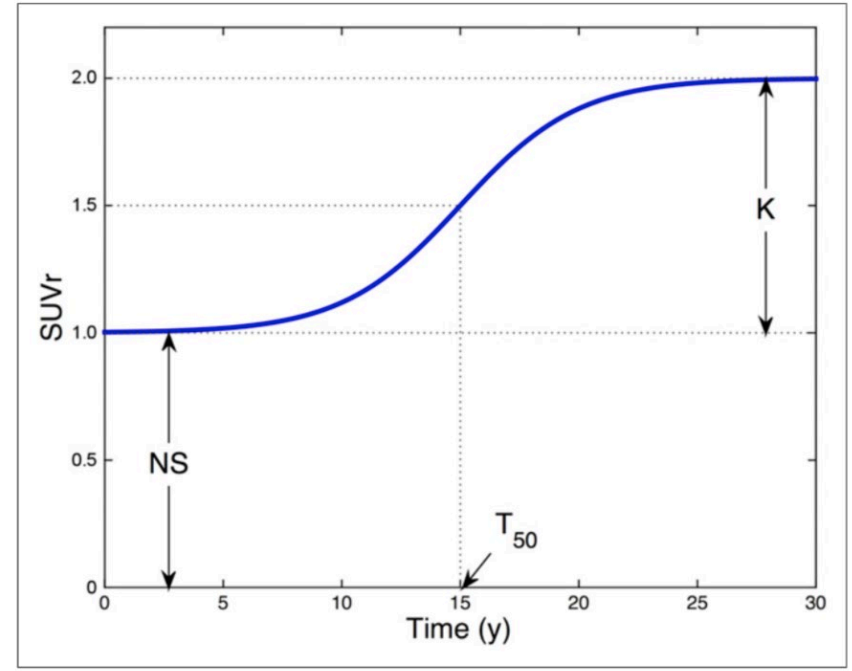


FIGURE 1. Logistic growth model describing Aβ PET imaging signal over time as function of PET NS, *K*, T_{50}, and *r*.

Summary across approaches (Strengths/weaknesses)

- Atrophy
- Variability and noise
- Influence of off-target uptake (e.g., voxel erosion/partial volume correction)
- Multiple Radioligands (e.g., multi-site -- harmonization)
    - different distribution in gray and white matter ?
    - differing kinetics in controls and/or control vs. patients
- Underlying Analysis Assumptions
    - What is being lost and what is gained by simplification

Quantifying the Variability of Amyloid-β PET in Centiloid Units

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AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

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Disclosures

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This communication reflects the views of the authors and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein.

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Quantification of Amyloid-β PET: SUVR

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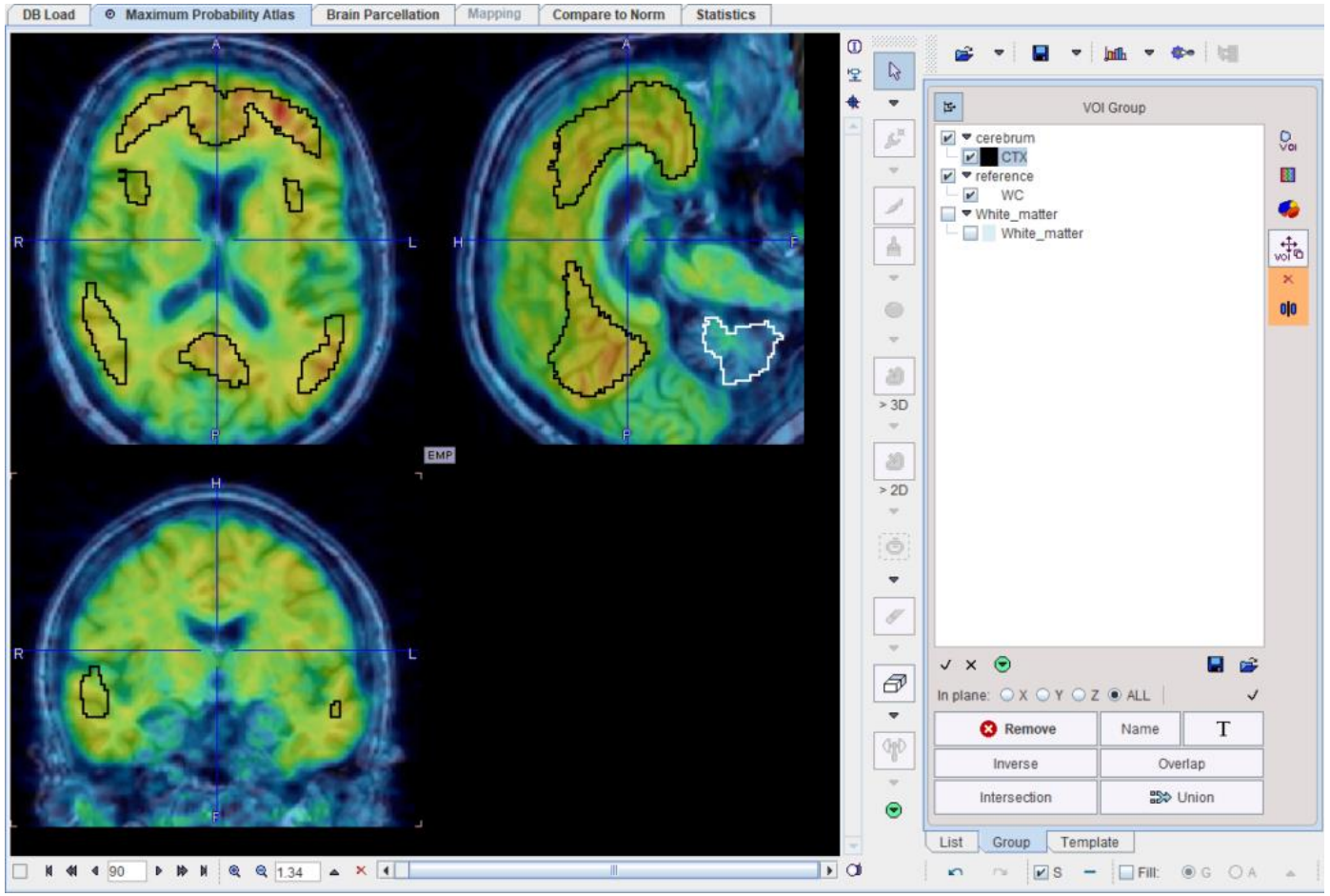
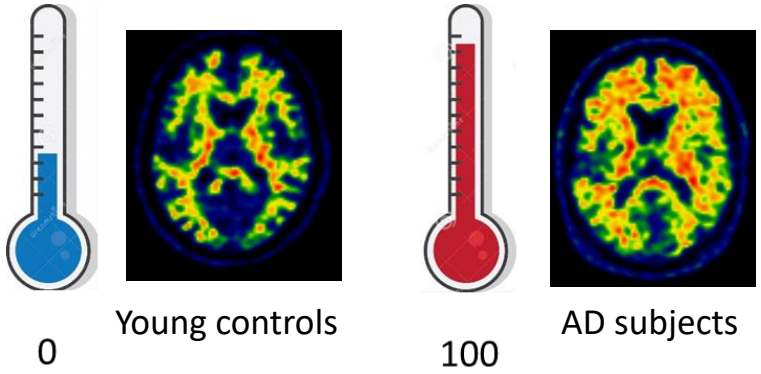
- SUVR (Standard Uptake Value Ratio)
  - The most widely used metric to quantify Aβ load from PET scans
- Convenient:
  - ‘Static acquisition’ (like in clinical practice)
  - Ratio between target and reference ROIs (insensitive to calibration errors)
- Provides a single value summarizing Aβ load in the whole brain
  - Can be used to generate parametric SUVR images

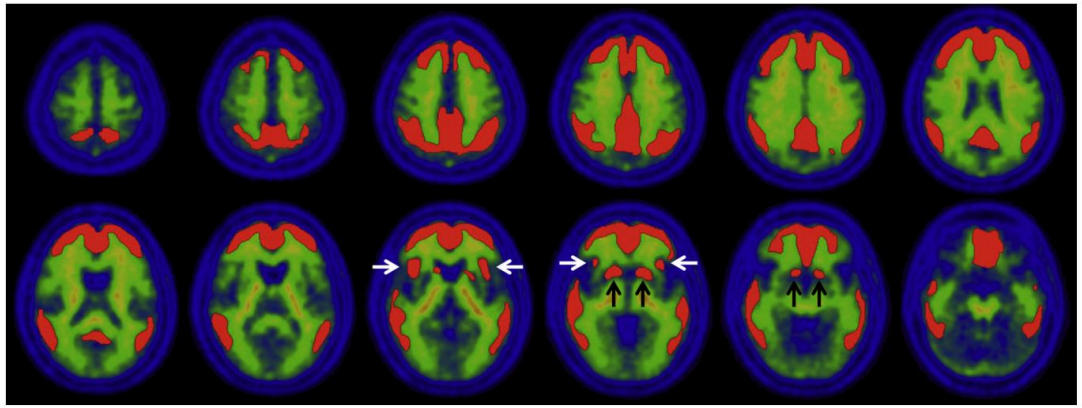


The Centiloid (CL) Method

- Designed to render universal metrics of amyloid load



- Irrespective of
  - Tracer
  - Reference Region
  - Quantification Pipeline



Calibration Method

Tracer	Equation
PIB	**$CL = 79.72 \times SUVR_{PIB} - 93.04$**
NAV4694	**$CL = 85.18 \times SUVR_{NAV} - 87.56$**
Florbetaben	**$CL = 153.4 \times SUVR_{FBB} - 154.9$**
Flutemetamol	**$CL = 121.42 \times SUVR_{FTM} - 121.16$**
Florbetapir	**$CL = 175.56 \times SUVR_{FBP} - 182.64$**

Klunk *et al.* Alz & Dement 2015; http://gaain.org/centiloid-project

Centiloid provides a universal metric to quantify Aβ burden

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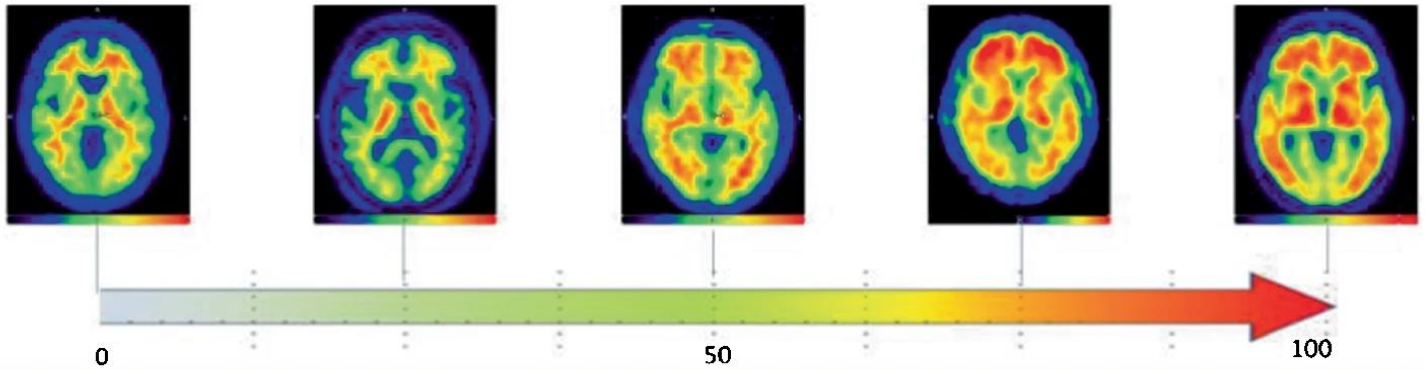


Neuropathology [141]	**<10** = neuritic plaques absent, rule out AD **>20** = at least moderate plaque density **~50** = strongest correlation with AD diagnosis	
"Grey-zone" Visual Read	**12**----------**30** = equivocal, from earliest detectable (12)[96,140] to established Aβ (30)[96,139] **17** = optimal visual cut-off for highly experienced readers [25] **26** = high correlation with positive visual read[141]	
Disease Progression	**19** = "reliable worsening" of CL rate of change[142] **26** = optimal prediction of progression to dementia 6 years after PET[149]	
Clinical trial inclusion criteria (AHEAD 3-45)	**20**----------**40** "intermediate Aβ" Early preclinical AD	**>40** = "elevated Aβ"

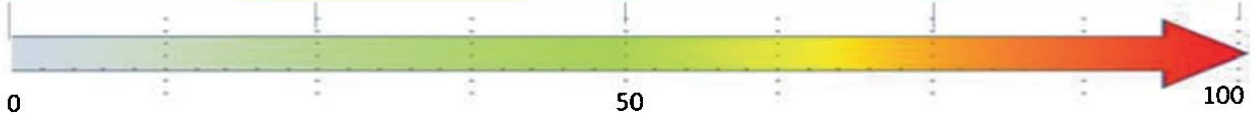


Table 2 Centiloid Values Corresponding to Alzheimer's Disease Neuropathologic Changes (ADNC)

Centiloid unit (CL)	Neuropathology
<15	No Aβ plaques
15-24	Sparse Aβ plaques
>25	Moderate or frequent Aβ neuritic plaques "positive scan"
>40	Tau PET abnormal
>50	Likely to meet ADNC criteria
100	Typical mild or moderate AD

Krishnadas *et al.* Semin Nucl Med. 2021

Pemberton *et al.* EJNMMI 2022

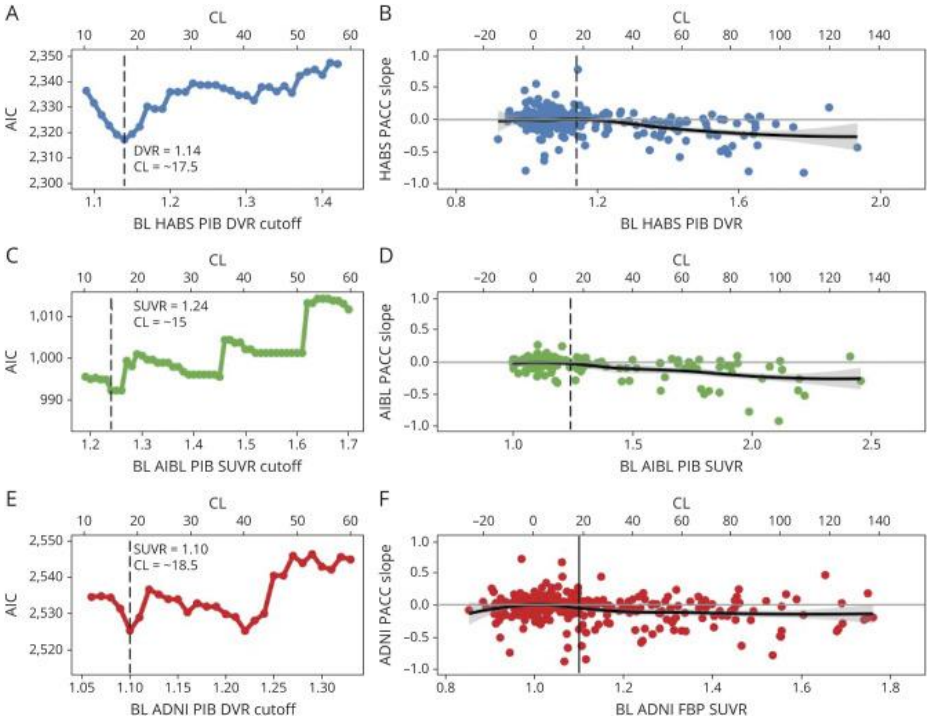
Prognostic Value of Centiloid Levels

- CL = 15-18.5 predicts cognitive decline in the PACC in clinically normal individuals
  - Median follow-up: HABS: 4.21 (SD = 2.34); AIBL: 7.48 (1.97); ADNI: 2.05 (1.60) years

Table 1 Sample Descriptives for HABS, AIBL, and ADNI

	HABS			AIBL			ADNI			Sample Difference
	All	Aβ−	Aβ+	All	Aβ−	Aβ+	All	Aβ−	Aβ+	*F* or χ^2 (*p*)
No.	342	265	77	157	106	51	356	252	104	6.74 (0.03)
Age, y	71.7 (8.00)	70.8 (8.05)	74.8 (6.48)	72.5 (6.72)	70.8 (6.34)	75.8 (6.28)	74.6 (6.50)	73.9 (6.60)	76.5 (5.88)	14.6 (<0.001)
Education, y	15.78 (3.01)	15.8 (2.97)	16.1 (2.94)	14.54 (3.1)	14.2 (3.2)	14.7 (3.0)	16.54 (2.59)	16.7 (2.56)	16.2 (2.61)	NA
Sex, n female (%)	206 (60)	160 (60)	46 (60)	86 (55)	59 (56)	27 (53)	189 (56)	125 (50)	64 (62)	3.79 (0.15)
APOE ε4, n (%)	89/324 (27)	44/251 (18)	45/73 (62)	54 (34)	27 (25)	27 (53)	94 (26)	50 (20)	44 (42)	3.61 (0.16)
Baseline PET	1.14 DVR (0.18)	1.06 DVR (0.05)	1.43 DVR (0.17)	1.32 SUVR (0.35)	1.12 SUVR (0.06)	1.75 SUVR (0.30)	1.12 SUVR (0.18)	1.02 SUVR (0.06)	1.36 SUVR (0.161)	NA
Baseline CL	18.15 (25.90)	6.10 (6.94)	59.6 (24.4)	23.19 (33.51)	3.35 (5.81)	64.4 (29.4)	21.65 (33.28)	3.64 (10.3)	65.3 (29.1)	1.85 (0.16)
Baseline PACC5 score	0.06 (0.68)	0.07 (0.68)	0.01 (0.68)	0.08 (0.62)	0.12 (0.63)	0.01 (0.60)	−0.05 (0.69)	−0.00 (0.71)	−0.15 (0.62)	3.14 (0.04)
Median PACC5 score follow-up, y	4.21 (2.34)	4.15 (2.40)	4.43 (2.07)	7.48 (1.97)	7.49 (1.65)	6.33 (2.38)	2.97 (2.33)	2.85 (2.35)	4.02 1.98	215 (<0.001)
Median PiB follow-up, y	2.81 (2.14)	2.80 (2.16)	2.89 (2.09)	3.06 (1.83)	3.16 (1.75)	1.79 (1.94)	2.05 (1.60)	2.07 (1.60)	2.02 (1.59)	21.8 (<0.001)
Progression to MCI/dementia, n (%)	21 (6)	6 (2)	15 (21)	22 (14)	12 (11)	10 (20)	59 (18)	29 (12.4)	30 (30.6)	18.9 (<0.001)

Abbreviations: Aβ = β-amyloid; ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging, Biomarker and Lifestyle; CL = Centiloid; DVR = distribution volume ratio; HABS = Harvard Aging Brain Study; MCI = mild cognitive impairment; NA = not applicable; PACC5 = Preclinical Alzheimer Cognitive Composite 5 version; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio.
Descriptives are shown for both each full sample and dichotomized into Aβ+/− groups using gaussian mixture model (figure 1). Means (SDs) are displayed for continuous variables and numbers (percents) for categorical variables. To demonstrate which variables varied across sample, 1-way analysis of variance *F* statistics are reported in the final column for continuous variables and χ statistics for categorical variables, as well as *p* values. Some participants in HABS did not have *APOE* data available, so total with genetic data are also displayed. Education was measured differently in AIBL and is not directly comparable to education in HABS or ADNI. Baseline PET measures are provided for within-sample description and baseline CL for between-sample comparison.



Farrell *et al.* Neurology 2021

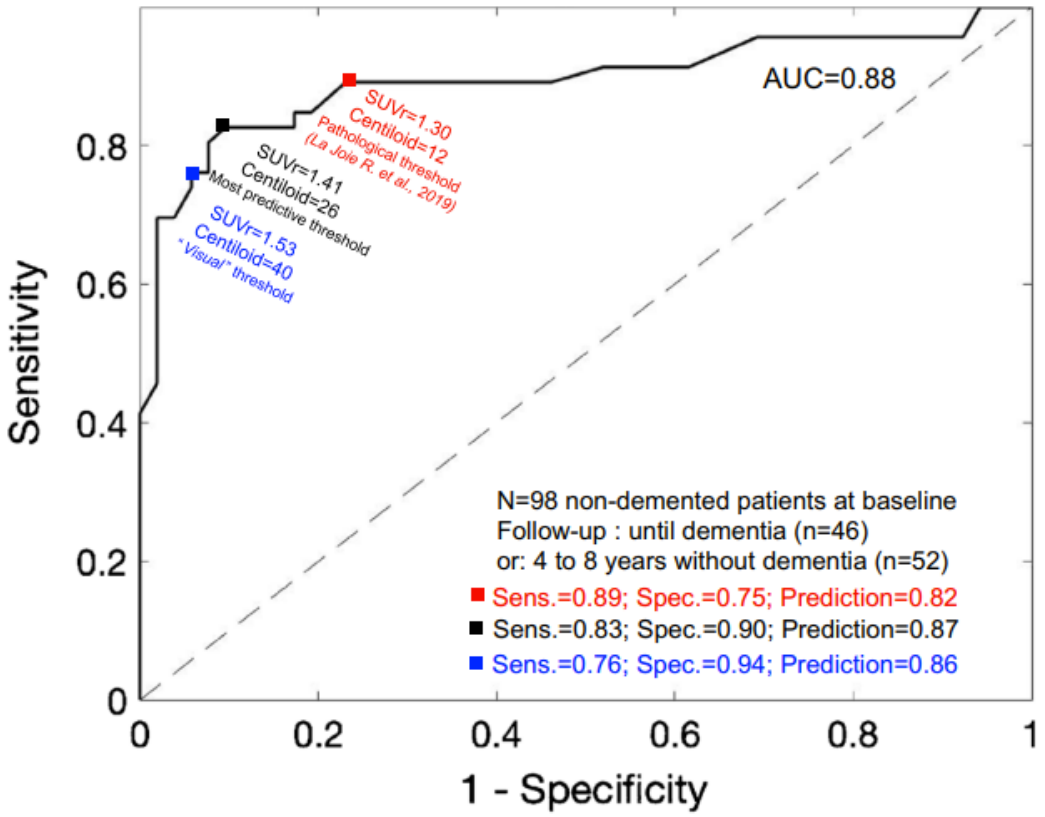
Prognostic Value of Centiloid Levels

- CL = 26 optimally predicts progression to dementia 6 years after PET in a mixed sample (CN/SCD/MCI) with cognitive complaints

Table 1 Characteristics of the participants

	All	Visually negative	Visually borderline	Visually positive
Number included	160	91	7	62
Age (years)	71.4 ± 7.5 (54–86)	70.6 ± 7.2 (54–86)	71.0 ± 8.8 (59–82)	72.4 ± 7.9 (54–83)
ε4 carriers: number (%)	66 ε4 (46%) 16 missing	19 ε4 (23%) 8 missing	4 ε4* (67%) 1 missing	43 ε4** (78%) 7 missing
Education (years)	14.4 ± 4.6 (6–20)	14.0 ± 4.7 (6–20)	16.3 ± 2.9 (12–18)	14.7 ± 4.5 (6–18)
Female: number (%)	81 ♀ (51%)	46 ♀ (51%)	4 ♀ (57%)	31 ♀ (50%)
Baseline MMSE score (/30)	27.3 ± 1.8 (24–30)	27.9 ± 1.7 (24–30)	27.7 ± 1.4 (26–30)	26.4 ± 1.6** (24–30)
Clinical diagnoses (CN/SCD/MCI)	31/35/94	26/25/40	3/2/2	2/8/52**
Neocortical flutemetamol SUVr	1.50 ± 0.33 (0.91–2.44)	1.25 ± 0.09 (0.91–1.47)	1.48 ± 0.11** (1.28–1.62)	1.87 ± 0.21** (1.43–2.44)
Centiloids	36.2 ± 41.2 (−33–140)	3.9 ± 11.7 (−33–44)	39.9 ± 8.5** (29–53)	82.4 ± 41.2** (45–140)
Number with long clinical follow-up[$]	98	58	2	38
Clinical diagnoses (CN/SCD/MCI)	28/24/46	24/19/15	2/0/0	2/5/31 **
Centiloids	36.1 ± 41.2 (−32–140)	5.4 ± 12.3 (−32–44)	31.1 ± 3.3** (29–33)	83.2 ± 21.6** (49–140)
Number of patients demented after follow-up (%)	46 (47%)	10 (17%)	1 (50%)	35 (92%)
Clinical follow-up duration (years) [$]	4.8 ± 1.9 (1.1–8.0)	5.8 ± 1.6 (1.1–8.0)	5.7 ± 2.1 (4.2–7.2)	3.2 ± 1.3 ** (2.0–6.4)
Number followed using PET	34	33	1	0
PET follow-up duration (years)	3.1 ± 0.9 (1.5–6.2)	3.1 ± 0.9 (1.5–6.2)	2.8	/
Number of patients visually positive after follow-up (%)	4 (12%)	3 (9%)	1 (100%)	/

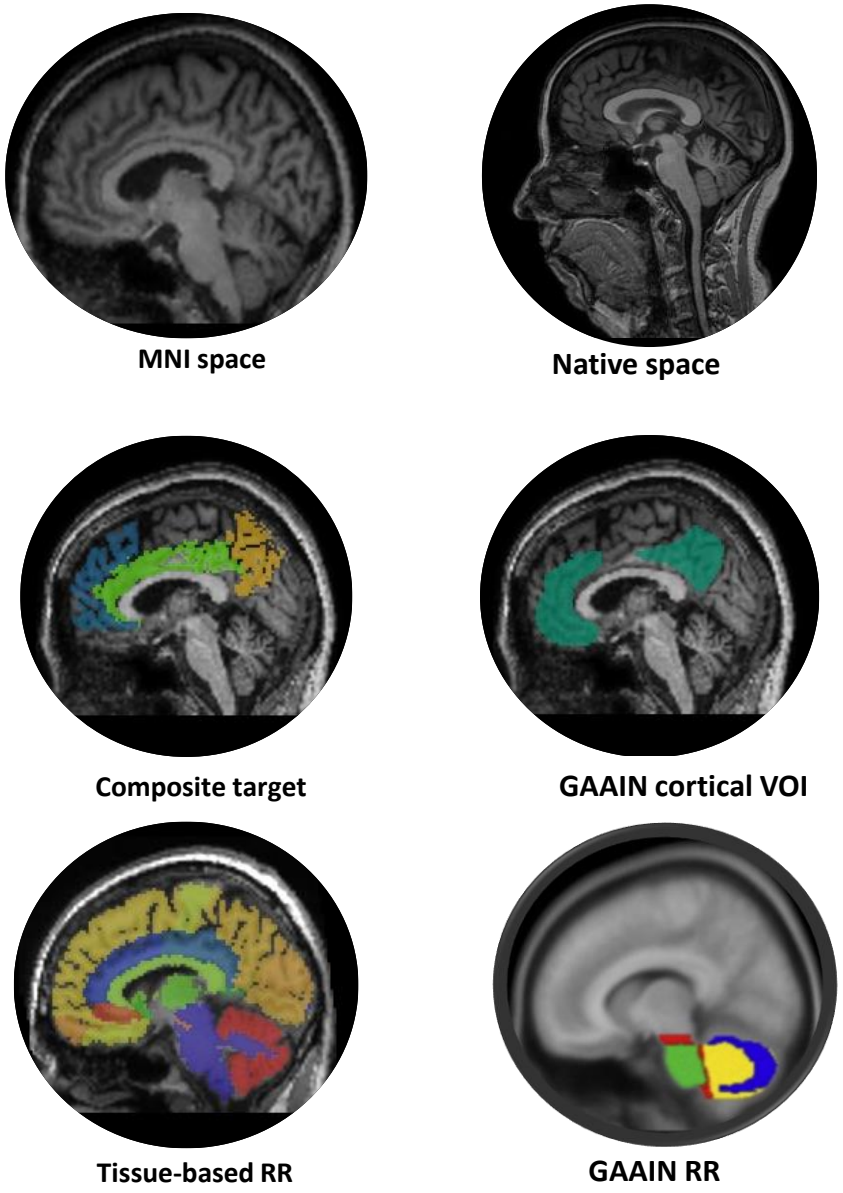
Mean ± SD (min-max), *$p < 0.05$, **$p < 0.001$ compared to the visually negative group. One patient was recruited but excluded from the study because of a presenilin 1 mutation



Hanseeuw *et al.* Eur J Nucl Med Mol Imaging 2021

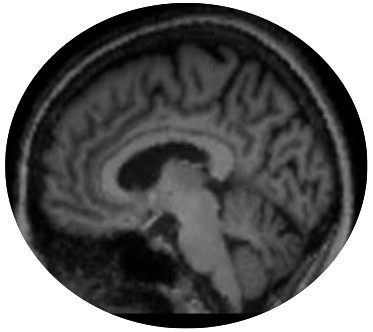
Aim: Impact of Pipeline Choices on Centiloid Units

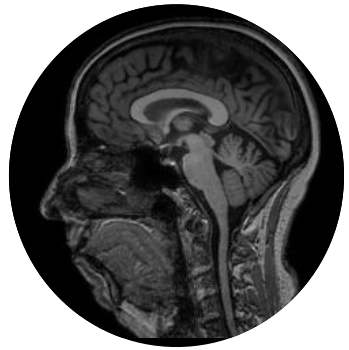
- CL enables the derivation of universal reference values
- **Aim: Quantifying the impact of pipeline design options in absolute Centiloid units**
  - **Bias**
  - **Uncertainty**
- Is it tracer-dependent?

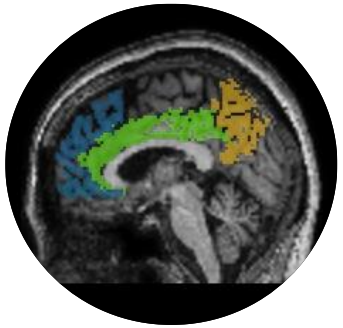


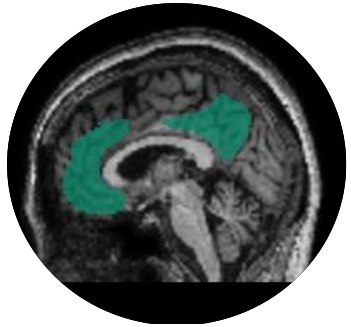
Aim: Impact of Practical Pipeline Choices on Centiloid Units

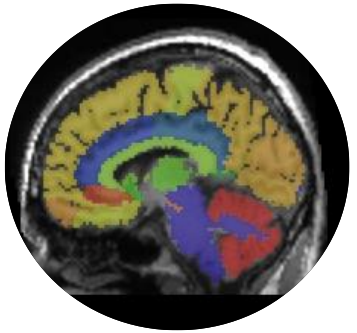
- Typical choices for a Centiloid (CL) pipeline
  - Space
    - **MNI**, Native
  - Definition of Target and Reference Regions
    - **GAAIN**, AAL composite + Tissue segmentation
  - Reference Region
    - **Whole Cerebellum**, Cerebellar Grey, Pons, Brainstem+Cerebellum, etc…

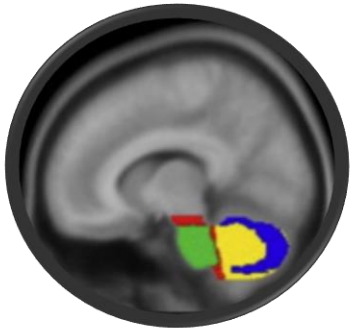

MNI space


Native space


Composite target

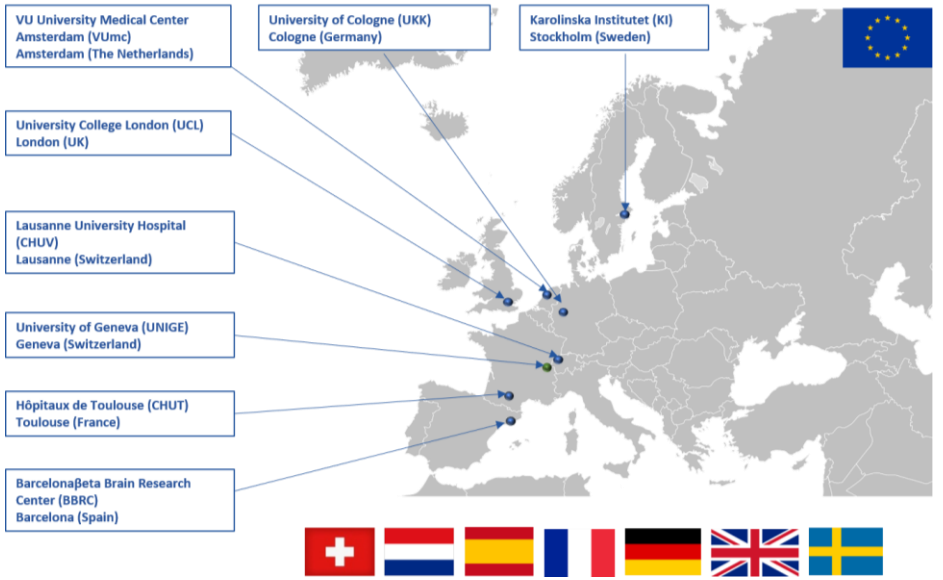

GAAIN cortical VOI

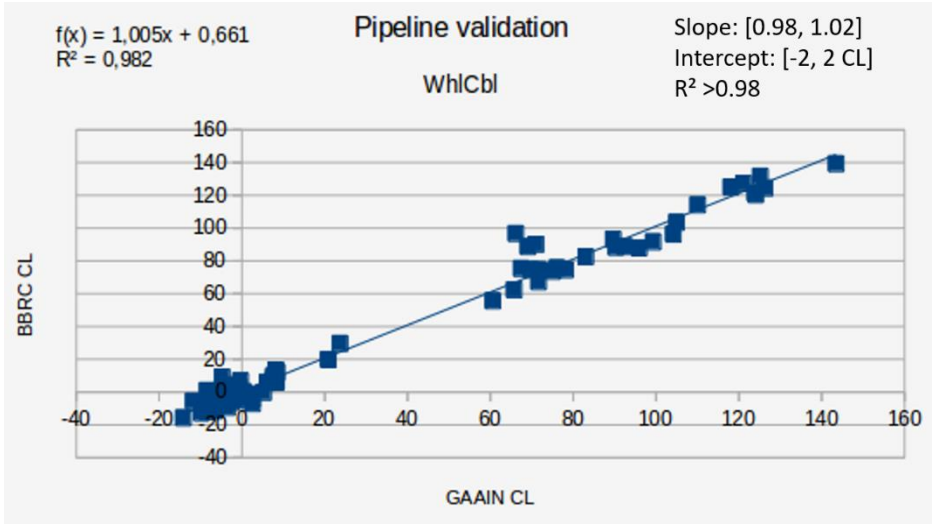

Tissue-based RR


GAAIN RR

Material and Methods: Subjects, Scans and CL Pipelines

- Participants (N=330) from the AMYPAD Diagnostic and Patient Management Study (DPMS)[1]
  - Subjective Cognitive Decline plus (SCD+)
  - Mild Cognitive Impairment (MCI)
  - Dementia
- With T1w MRI and PET available
  - 18F-Flutementamol
  - 18F-Florbetaben
- 32 Centiloid (MR-aided; SPM12) pipelines were deployed, calibrated and **validated**:
  - 4 Reference Regions (WC, CG, Pons, WCB)
  - 2 Reference Region Type (GAAIN, Atlas Composite + Tissue segmentation)
  - 2 Target Region Types (GAAIN, Atlas Composite + Tissue segmentation)
  - 2 Spaces (MNI and Native)





[1]Altomare *et al.* Alz & Dement 2022

Material and Methods: Statistical Analysis

- Repeated-measure model estimated with Generalized Estimating Equations (GEE)

Centiloid ~ Intercept + visual read + MMSE + Tracer + Space + Target Type + Reference Region + Reference Region Type

Tracer	Space	Target Type	Reference Region	Reference Region Type
FTM	MNI	GAAIN	WC	GAAIN
FBB	Native	Composite	CG	Tissue-based
			Pons	
			WCB	

- Factor types:
  - Modeling CL distribution
  - Does Tracer introduce a bias in CL quantification?
  - Pipeline design factors of interest

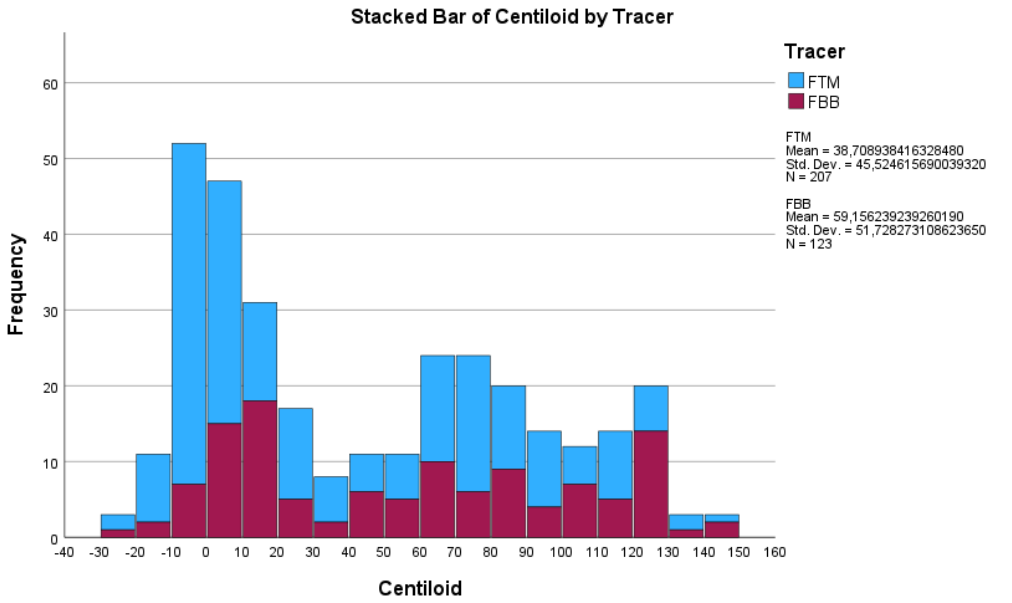
Material and Methods: Statistical Analysis

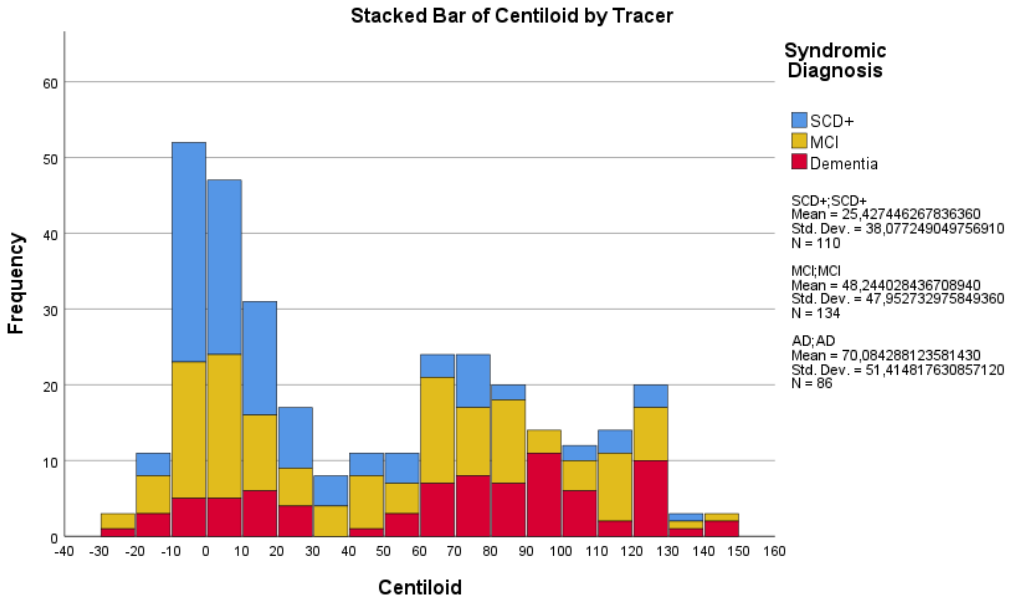
- Measures of interest:
  - Difference in marginal means (bias)
  - 95%CI of marginal means (uncertainty)

Reference CL Values	
2.5-3.5	Test-Retest variability
5-7	Biological variability (SD, YC)
10-12	Absence of pathology Cut-off of abnormality
24-26	Sparse pathology Cut-off of Positive Visual Read
50	Likely to meet ADNC criteria
60-85	Changes associated with experimental anti-amyloid monoclonal antibodies
100	Typical of mild or moderate AD

Results: Sample

Demographics	N=330
Age (Mean±SD)	70.52±7.23
Sex (Female%)	138 (41.8%)
MMSE (Mean±SD)	25.67±4.14
Clinical status	SCD+: 110 (33.0%) MCI: 134 (40.6%) Dementia: 86 (26.1%)
Tracer	FTM: 207 (62.7%) FBB: 123 (37.3%)
Visual Read	Negative: 148 (44.8%) Positive: 182 (55.2%)
Centiloid (Mean±SD)	46.33±48.86



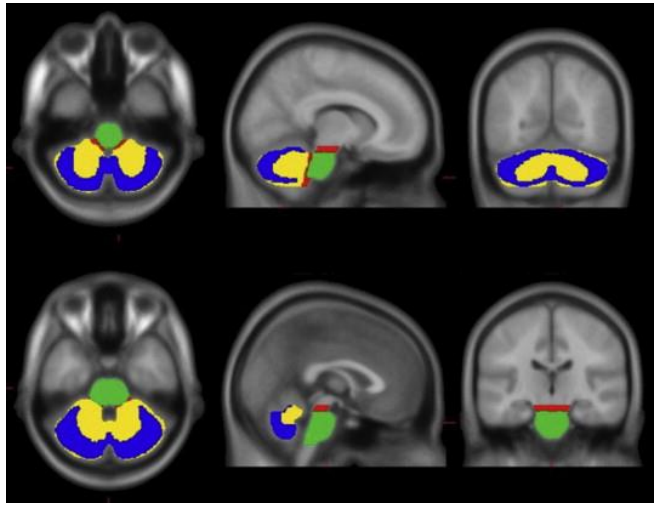


Results: Overview

Tests of Model Effects			
Source	Type III		
	Wald Chi-Square	df	P-value
(Intercept)	71.684	1	**<0.001**
Visual read	516.25	1	**<0.001**
MMSE	19.076	1	**<0.010**
Reference region	164.191	3	**<0.001**
Reference region type (GAAIN vs tissue-based)	84.601	1	**<0.001**
Target (GAAIN vs AAL-composite)	36.668	1	**<0.001**
Space (MNI vs Native)	9.564	1	**0.002**
Tracer	0.321	1	0.571
Dependent Variable: Centiloid Model: (Intercept), Visual read, MMSE, Target Type, Reference region, Reference region type, Space, Tracer			

Results: Reference Region

Reference region	Mean Diff	Std. Error
Whole cerebellum	**Ref**	**Ref**
Cerebellum grey matter	3.365	0.388
Whole cerebellum+Brainstem	-3.048	0.238
Pons	-12.427	0.981



Reference VOIs:

- Cerebellar gray (blue)
- Whole cerebellar (blue+yellow)
- Pons (green)
- Whole cerebellum plus brainstem (all colors combined)

(*) the red area represents that part of the WC+B that does not overlap either the WC or the Pons

Reference region	Mean	Std. Error	95% Wald Confidence Interval		
			Lower	Upper	**Diff**
Whole cerebellum	42.115	1.504	39.167	45.063	**5.896**
Cerebellum grey matter	45.480	1.590	42.362	48.598	**6.236**
Whole cerebellum+Brainstem	39.066	1.467	36.190	41.942	**5.752**
Pons	29.688	1.612	26.527	32.848	**6.321**

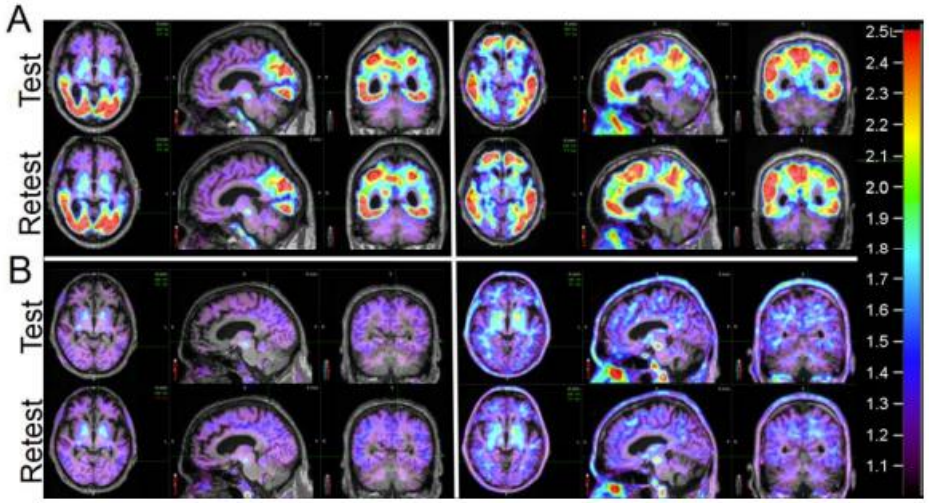
95% Confidence Interval

(Repeated Measures) ~ **6 CL**

Klunk *et al.* Alz & Dement 2015; http://gaain.org/centiloid-project

What happens with the pons?

- Low correlation between 11C-PIB and 18F-tracers
- Smallest Ref Region: Low test-retest variability



Devous *et al.* JNM. 2018

Table 3 Regional correlation coefficients for PiB and FBB SUVRs

Region	*r*	*p*
Dorsolateral prefrontal	0.94	<0.0001
Ventrolateral prefrontal	0.96	<0.0001
Orbitofrontal	0.96	<0.0001
Gyrus rectus	0.94	<0.0001
Anterior cingulate	0.94	<0.0001
Posterior cingulate	0.96	<0.0001
Parietal	0.94	<0.0001
Lateral occipital	0.92	<0.0001
Lateral temporal	0.96	<0.0001
Mesial temporal	0.82	<0.0001
Caudate nuclei	0.98	<0.0001
Putamen	0.95	<0.0001
Thalamus	0.84	<0.0001
Pons	0.50	0.03
White matter	0.63	0.003
Neocortex[a]	0.97	<0.0001

[a]Values for the neocortex comprise the average SUVRs for the frontal, parietal, cingulate, lateral occipital and lateral temporal cortices.

Villemagne *et al.* EJNMMI. 2012

TABLE 3: Region-Wise Slope, Linear Fit, and Test-Retest Variability

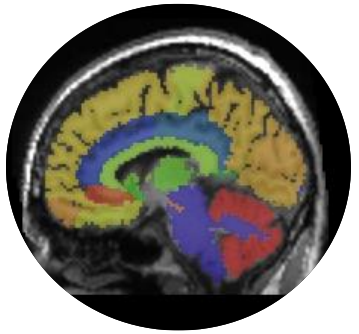
VOI	^{18}F-Flutemetamol			
	Versus ^{11}C-PIB		Test-Retest, %	
	m	*r*	Mean	SD
COM	0.99	0.91	1.5	0.7
FRO	1.00	0.92	1.4	0.4
PAR	1.01	0.92	2.1	1.8
LTC	0.99	0.91	1.8	0.8
POC	1.01	0.91	1.2	0.5
ANC	0.91	0.88	2.0	0.9
MTC	0.74	0.83	3.8	2.4
OCC	1.03	0.89	0.9	0.5
STR	0.88	0.84	0.9	0.5
SWM	0.22	0.36	3.2	2.1
PON	0.50	0.63	3.1	2.7

Second and third columns: region-wise slope (*m*) of the linear fit and the Pearson correlation coefficient (*r*) from the correlation between SUVR from ^{11}C-PIB and ^{18}F-flutemetamol scan data from 20 Alzheimer disease and 20 mild cognitive impairment subjects. Fourth and fifth columns: mean test-retest variability (percentage) and SD over 5 Alzheimer disease subjects for each brain region when using ^{18}F-flutemetamol positron emission tomography.
^{11}C-PIB = ^{11}C-Pittsburgh compound B; SD = standard deviation; COM = composite cortical volume of interest; FRO = lateral frontal cortex; PAR = lateral parietal cortex; LTC = lateral temporal cortex; POC = posterior cingulate; ANC = anterior cingulate; MTC = medial temporal cortex; OCC = occipital; STR = striatum; SWM = subcortical white matter; PON = pons.

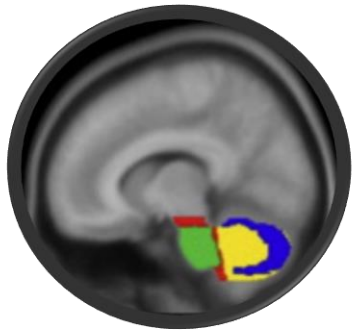
Vandenberghe *et al.* Ann. Neurol. 2010

Results: Reference Region Type

Reference region	Mean Diff	Std. Error
GAAIN VOI	**Ref**	**Ref**
Tissue-based	-3.576	0.389



Tissue-based RR

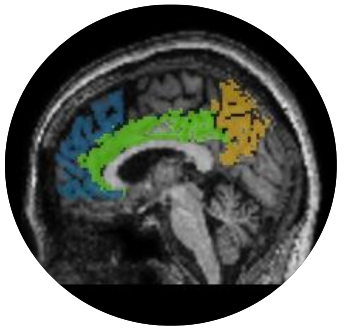


GAAIN RR

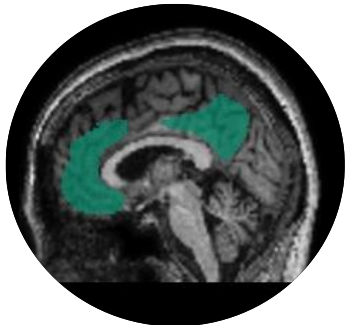
Reference region type	Mean	Std. Error	95% Wald Confidence Interval		
			Lower	Upper	**Diff**
GAAIN VOI	40.875	1.481	37.972	43.778	**5.806**
Tissue-based	37.299	1.479	34.398	40.200	**5.802**

Results: Target Type

Reference region	Mean Diff	Std. Error
GAAIN CRTX	**Ref**	**Ref**
AAL composite	2.484	0.410



Composite target

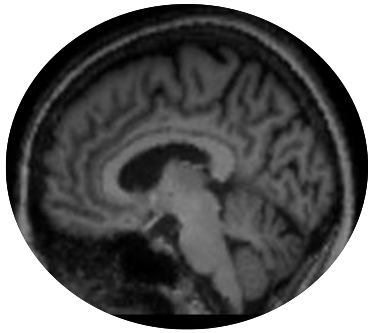


GAAIN cortical VOI

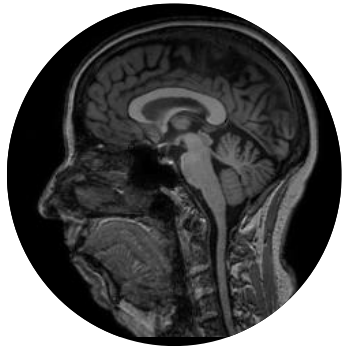
Target type	Mean	Std. Error	95% Wald Confidence Interval		
			Lower	Upper	**Diff**
GAAIN CRTX	37.845	1.456	34.991	40.699	**5.708**
AAL composite	40.329	1.507	37.375	43.283	**5.908**

Results: Target Type

Reference region	Mean Diff	Std. Error
MNI	**Ref**	**Ref**
Native	-1.212	0.392



MNI space

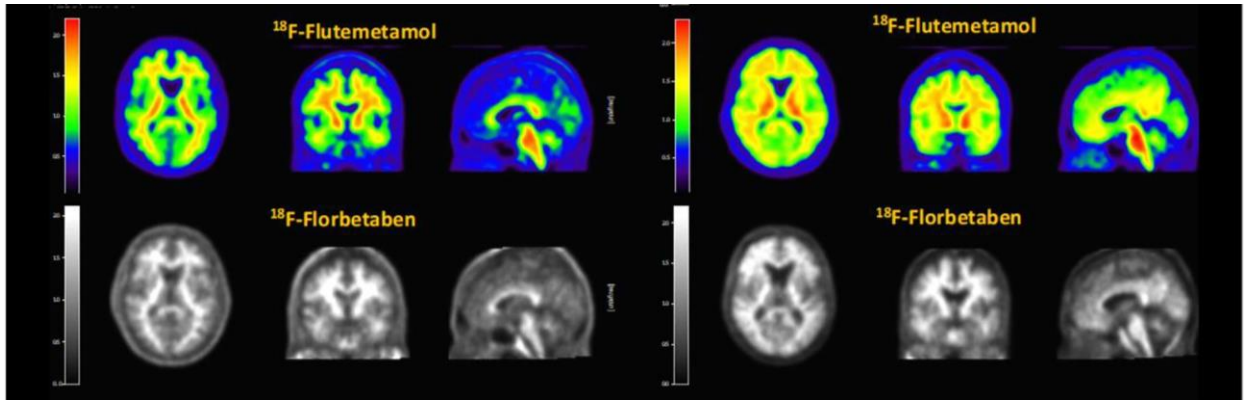


Native space

Quantification space	Mean	Std. Error	95% Wald Confidence Interval		
			Lower	Upper	**Diff**
MNI	38.481	1.415	35.707	41.255	**5.548**
Native	39.693	1.543	36.669	42.718	**6.049**

Results: Tracer

Reference region	Mean Diff	Std. Error
FTM-FBB	-1.857	3.276
FBB-FTM	1.857	3.276



Tracer	Mean	Std. Error	95% Wald Confidence Interval		
			Lower	Upper	**Diff**
Flutemetamol	25.830	1.945	22.017	29.644	7.627
Florbetaben	26.825	3.859	19.260	34.390	15.130

Centiloid Sensitivity to Effective Image Resolution

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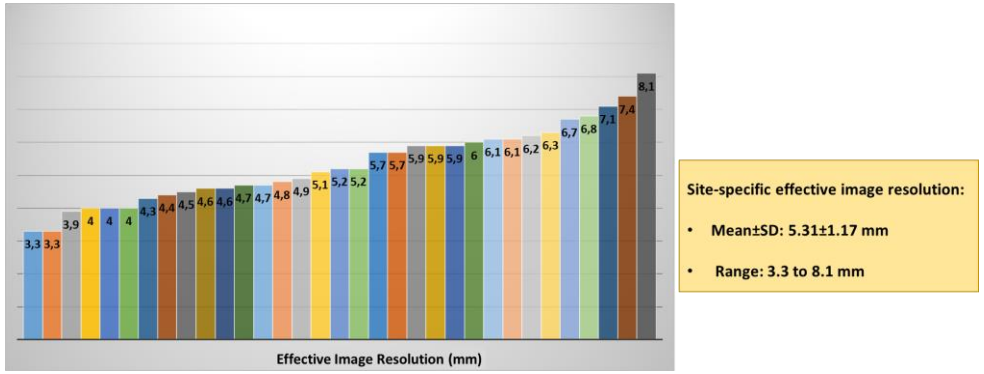
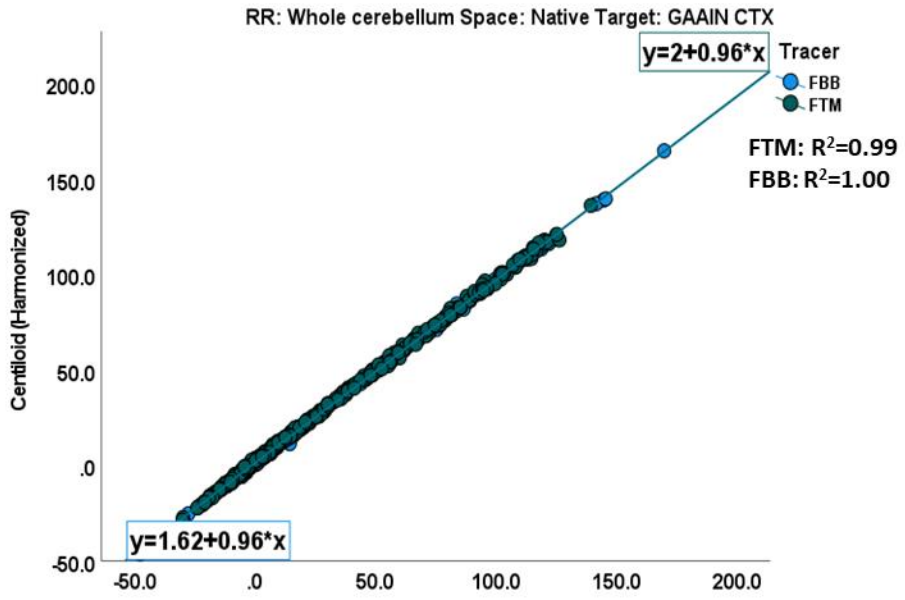
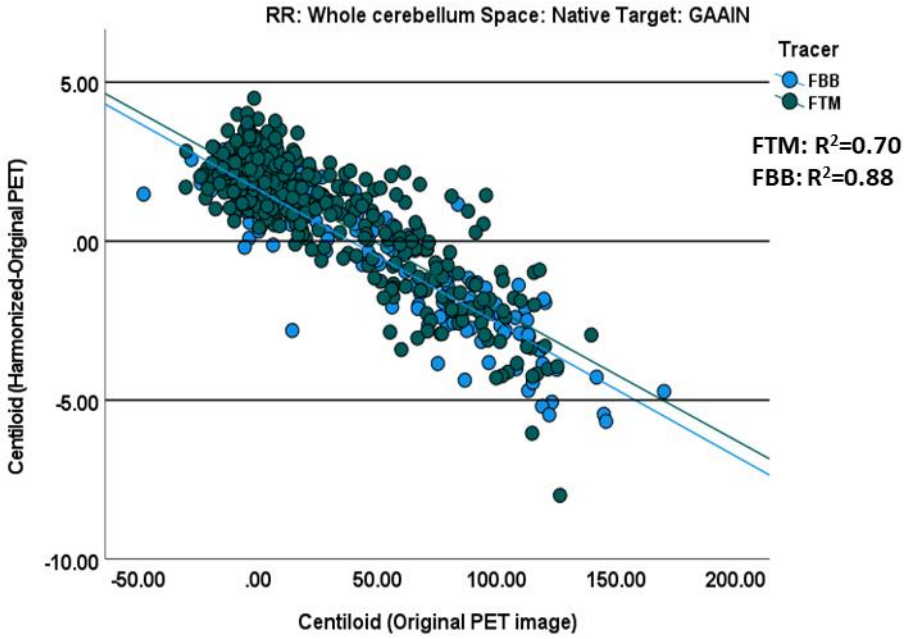
- 659 scans from AMYPAD DPMS & PNHS
  - FBB: 158, FTM: 501
- 22 sites, 30 different PET scanners



- Image resolution harmonized[8] to 8 mm FWHM
- CL calculated with Standard Pipeline (WC)
- Difference in CL pre-post harmonization
  - FTM: Mean: **1.12** CL (95%CI: -2.25, 4.48)
  - FBB: Mean: **-0.35** CL (95%CI: -3.88, 4.57)

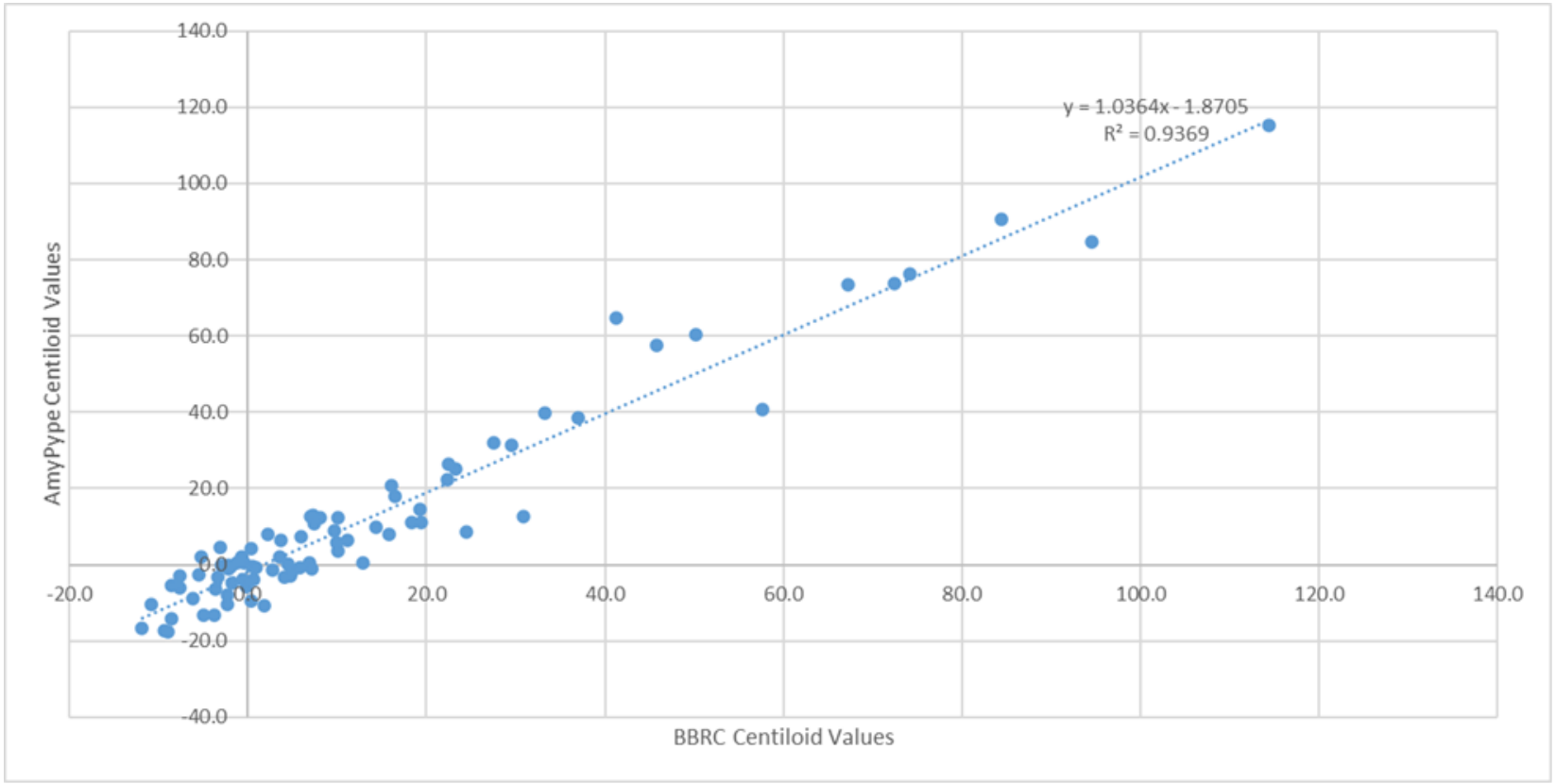




[8]Shekari *et al.* EANM 22

Between-Pipeline Comparison

- Standard Centiloid Pipeline @ BBRC (PET+MR) vs AMYPYPE (PET-Only)

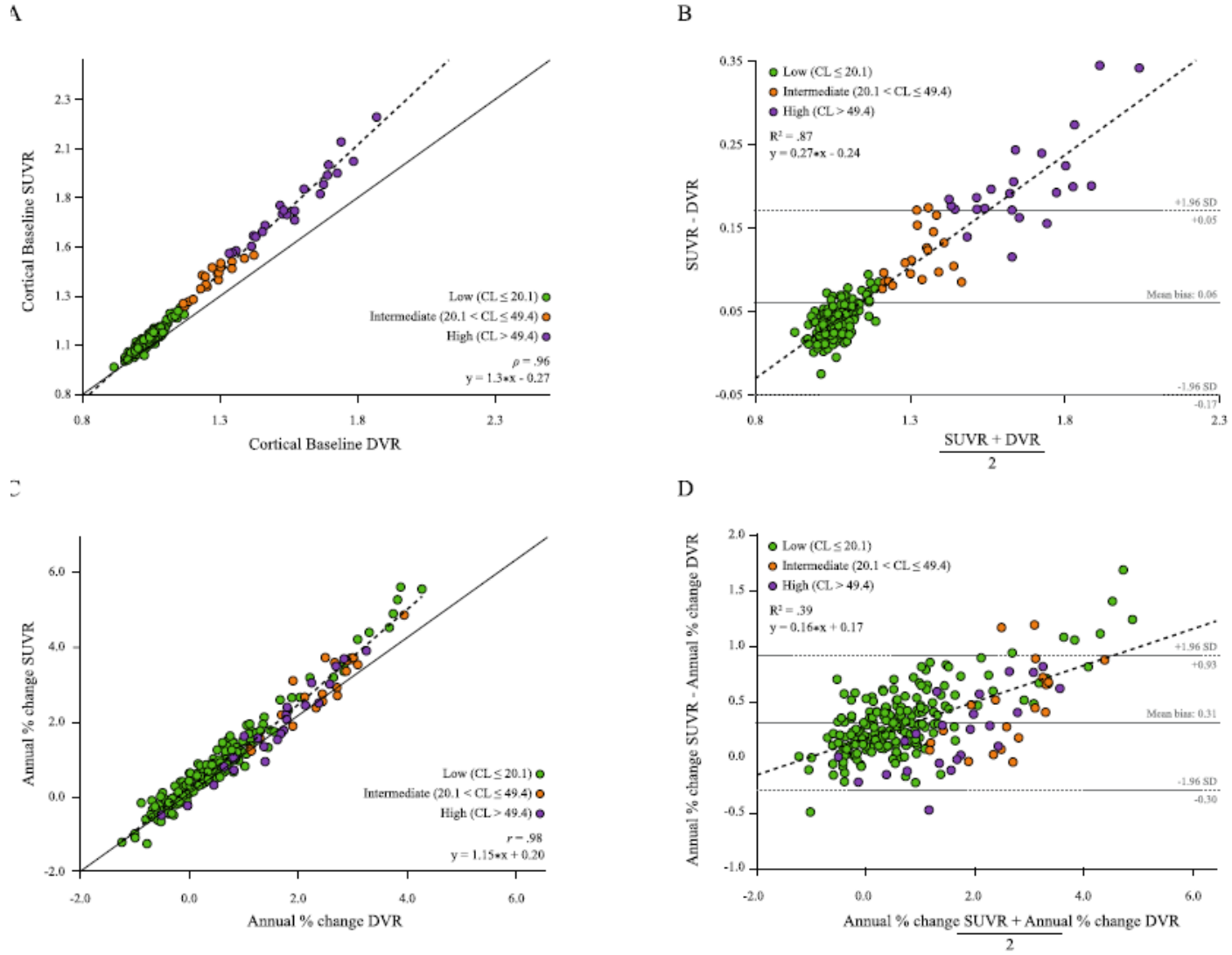


R^2: 0.9369
Mean difference (bias): 1.4 CL
Mean absolute difference: 5.4 CL
95% CI Diff: ±13.2 CL

Buckley *et al.* EANM 2019

Other metrics: BPnd / DVR

- Pros:
  - **More accurate measure of amyloid burden**
  - Lower (~30%-50%) test-retest variability
  - Insensitive to time window for PET imaging
  - Account for variability in cerebral blood flow
- Cons:
  - Require dynamic acquisitions
    - Longer scanner time, higher cost, more participant burden
  - Not possible to convert to standard units (i.e. Centiloids)
    - Lack of Head-to-Head dynamic acquisitions btw 11C-PIB and 18F-Tracers



Lopes-Alves *et al.* Alz Res & Ther. 2021

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    - Lack of Head-to-Head dynamic acquisitions btw 11C-PIB and 18F-Tracers

Table 2. Correlations and test–retest results between 2T4k_V_B-derived DVR values and those seen with the tested parametric methods.

Parametric methods	All subjects r^2 (slope)	Controls r^2 (slope)	TRT (%)	AD r^2 (slope)	TRT (%)
$SUVr_{50-70}$	0.92	0.84	3.35	0.85	7.78
	1.16	1.06		1.12	
90 min					
RPM	0.95	0.84	1.09	0.92	3.05
	0.92	0.88		0.91	
SRTM2	0.91	0.61	1.12	0.88	2.07
	0.83	0.61		0.83	
rLogan	0.94	0.77	0.85	0.90	3.33
	0.88	0.75		0.85	
SA	0.91	0.70	8.12	0.92	18.19
	0.88	0.83		0.92	
Logan	0.95	0.86	9.43	0.93	16.25
	0.84	0.79		0.80	
MRTM0	0.92	0.76	0.88	0.86	3.17
	1.03	1.01		1.00	
MRTM1	0.93	0.83	0.62	0.87	3.8
	0.97	0.95		0.93	
MRTM2	0.83	0.47	2.04	0.74	3.29
	0.96	0.76		0.89	
MRTM3A	0.91	0.74	0.58	0.91	2.88
	1.01	0.93		1.00	
MRTM3B	0.85	0.53	1.62	0.77	2.69
	0.98	0.84		0.94	
60 min					
RPM	0.90	0.73	0.69	0.84	2.58
	0.92	0.86		0.92	
SRTM2	0.88	0.51	1.10	0.83	1.88
	0.81	0.54		0.79	
rLogan	0.90	0.64	0.77	0.84	2.15
	0.84	0.66		0.81	
SA	0.79	0.70	7.73	0.65	17.46
	0.85	0.72		0.80	
Logan	0.88	0.75	8.22	0.82	14.57
	0.78	0.65		0.71	

Note: Parametric methods in comparison to plasma input-derived 2T4k_V_B (V_T or DVR values) using 90 min scan data. The following optimized settings were used for each parametric method (RPM= 0.01–0.1, 50 basis functions; SRTM2 = 0.01–0.1, 50 basis functions; rLogan = 30–90 min; Logan = 30–90 min; Spectral analyses = 0.000167–0.008 (start-end), 50 basis functions. Test–retest results were based upon the average variation of all regions of interest.

Verfaillie *et al.* JCBF&M 2021

Other metrics: BPnd / DVR

- Pros:
  - More accurate measure of amyloid burden
  - Lower (~30%-50%) test-retest variability
  - **Insensitive to time window for PET imaging**
  - Account for variability in cerebral blood flow
- Cons:
  - Require dynamic acquisitions
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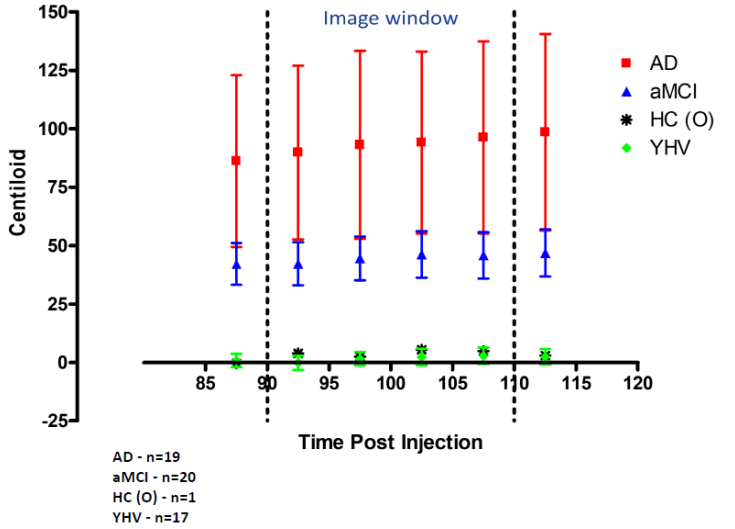

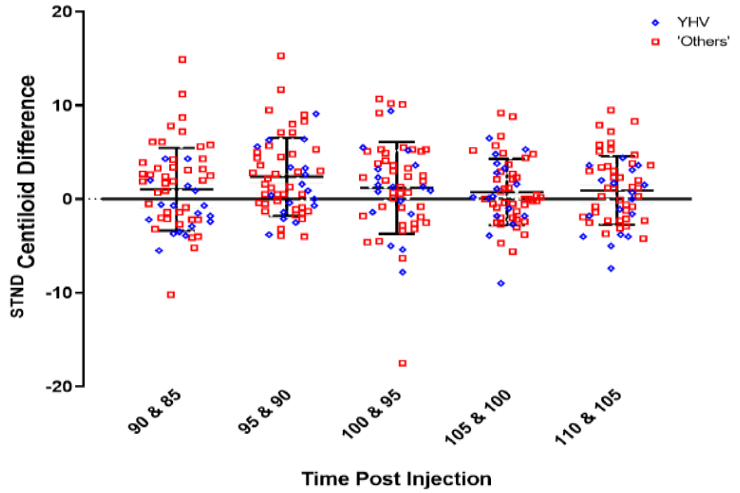

The average difference between the last and first frames (115&85min) was 6(±8) CL in the AD group

Battle *et al.* AAIC 2019

Other metrics: BPnd / DVR

- Pros:
  - More accurate measure of amyloid burden
  - Lower (~30%-50%) test-retest variability
  - Insensitive to time window for PET imaging
  - **Account for variability in cerebral blood flow**
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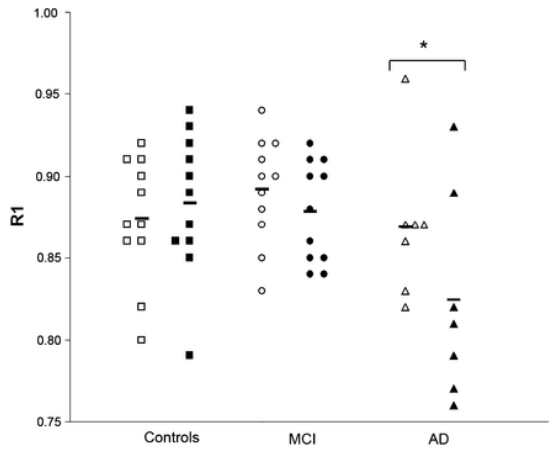
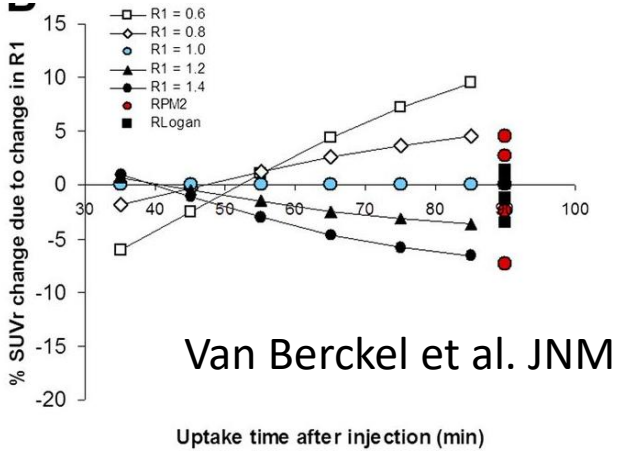
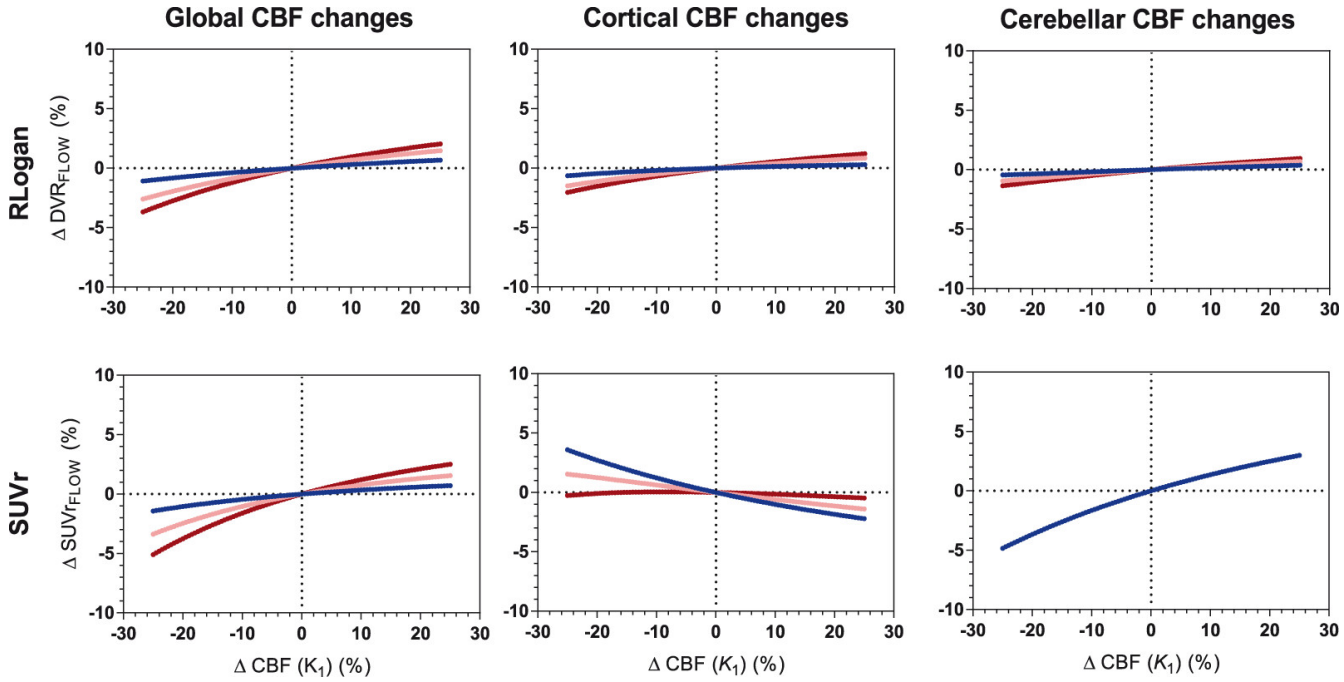




Van Berckel et al. JNM 2013



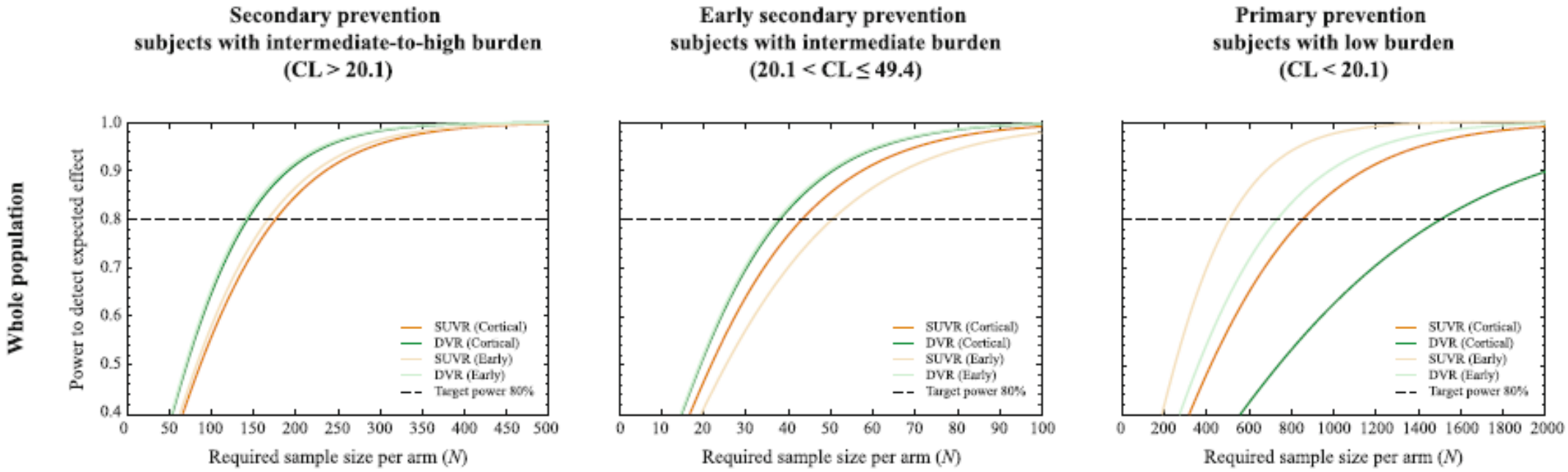
Heeman et al. EJNMMI Res 2022

Other metrics: BPnd / DVR

- Suited for detecting small differences in amyloid rates of accumulation
  - E.g. primary prevention

Table 2 Sample size requirements per trial arm, for three hypothetical trial scenarios, comparing differences between using DVR/SUVR, a cortical/early composite ROI, and restricting the inclusion to *APOE*-ε4 carriers or not

	Whole population				*APOE- ε4 carriers only*			
	SUVR		*DVR*		*SUVR*		*DVR*	
	Cortical ROI	*Early ROI*	*Cortical ROI*	*Early ROI*	*Cortical ROI*	*Early ROI*	*Cortical ROI*	*Early ROI*
Secondary prevention to detect 20% reduction in accumulation (CL > 20.1)	176	167	143	140	116	125	83	97
Early secondary prevention to detect 20% reduction in accumulation (20.1 < CL ≤ 49.4)	44	51	39	38	52	56	47	43
Primary prevention to detect 20% reduction in accumulation (CL ≤ 20.1)	855	509	1508	734	724	455	1162	630



Lopes-Alves *et al.* Alz Res & Ther. 2021

Other ratio methods

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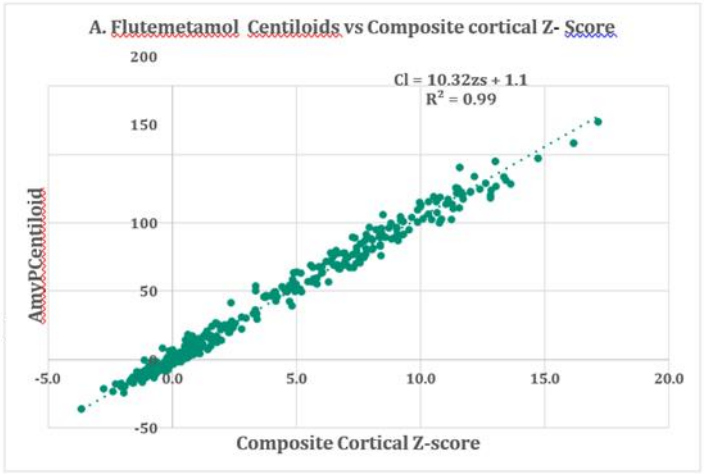
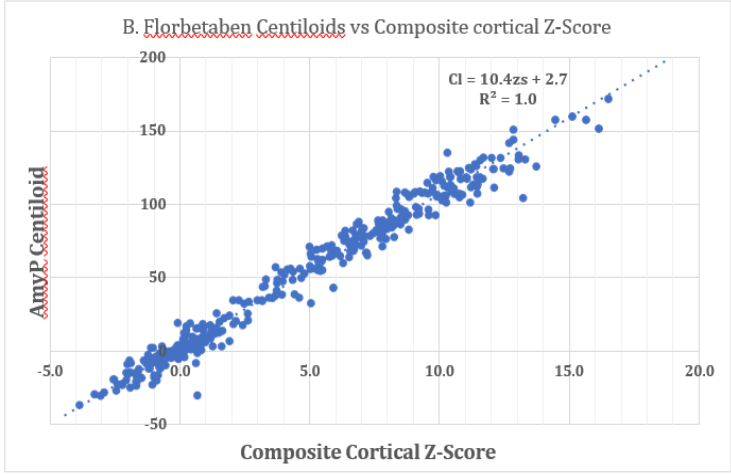
- Other ways to express the ratio between the target and reference regions exist:
  - Z-score:
    - SUVR normalized to the mean and SD of a reference group
    - Since are linear mappings, they SUVR, CL and Z-scores all share the same statistical properties





- Other methods to define the target and reference regions

Jovalekic *et al.* CTAD 22

Other ratio metrics

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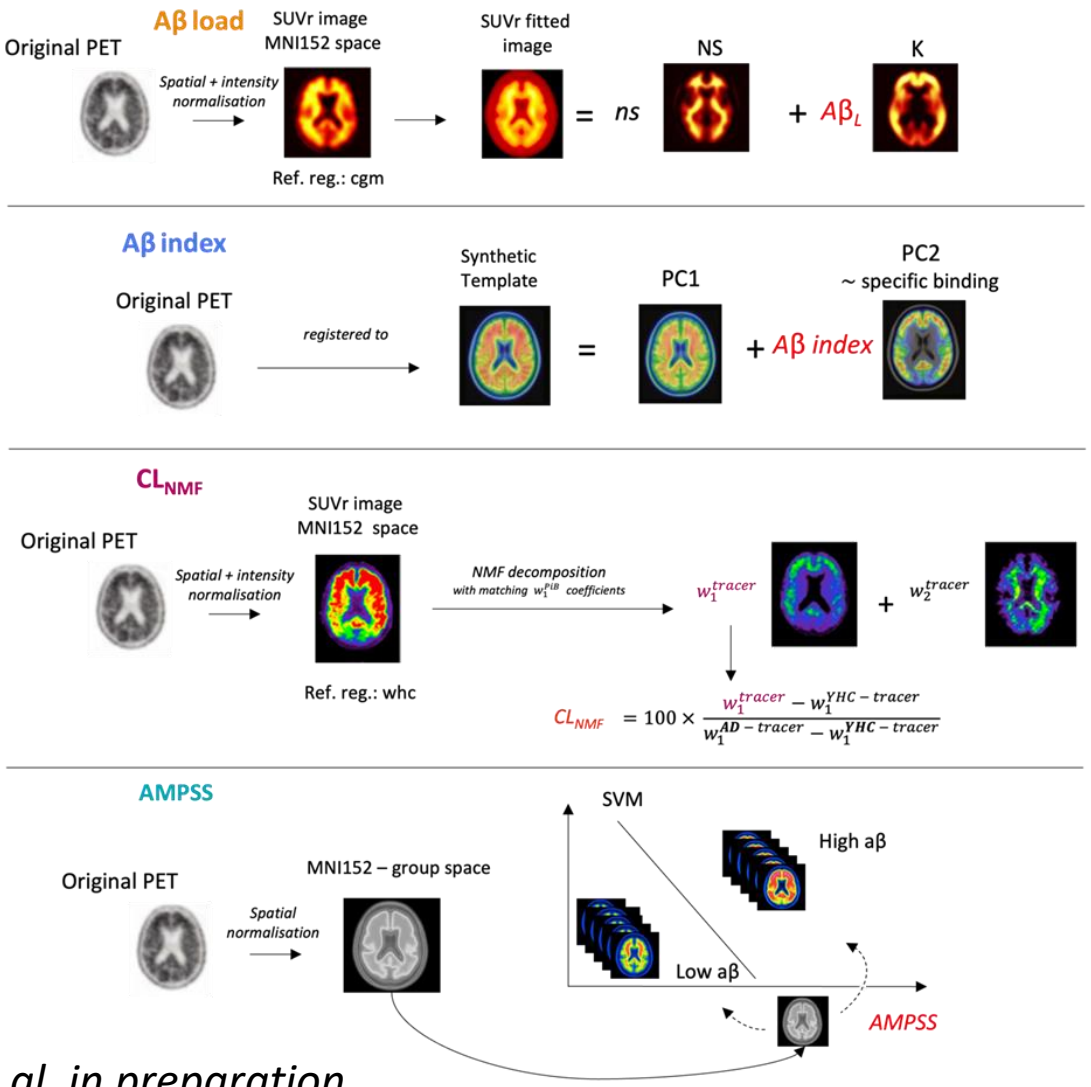

Bollack *et al. in preparation*

$Aβ_L$ = Aβ load (Whittington and Gunn, *J Nucl Med*, 2019)
Aβ index = Aβ pathology accumulation index (Leuzy et al., *Neurology*, 2020)
CL_{NMF} = Centiloid derived from non-negative matrix factorisation (Bourgeat et al., *Neuroimage*, 2021)
AMPSS = amyloid pattern similarity score (Prosser et al., *AAIC*, 2020)

Main characteristics	Aβ load *Whittington et al., 2019*	Aβ index *Leuzy et al., 2020*	CL_{NMF} *Bourgeat et al., 2021*	AMPSS *Prosser et al.*
Key idea	Image decomposition into 2 components: non-specific binding and Aβ carrying capacity determined *via* logistic growth model	Image decomposition *via* principal component analysis isolates specific binding	Image decomposition *via* non-negative matrix factorisation (NMF)	Support vector machine to produce probabilities score from little to no specific binding through to AD-like scans
Assumptions	Spatially synchronised accumulation according to the maximum amyloid carrying capacity of each region	Second principal component represents specific binding	First component represents specific binding	-
Range	% unbounded	-1 to 1 unbounded	0 to 100 0 and 100 are anchor points	% bounded (or unbounded using a logit transform)
Reference region independent	No	No	No	Yes
MR independent	No	Yes (but No for training)	No	No
Specificity when processing scans from different tracers	Needs to match NS_K image scale [40]	Principal components specific to each tracer	NMF components specific to each tracer	Training on tracer specific datasets
Possible application for tau	Implemented [41]	Not implemented, comparable approach by Cho *et al.* [42]	N/A	Not implemented
Validation	Against SUVr on ADNI [35] and GAAIN data [40]	Against SUVr, CSF, visual read and neuropathology on BioFINDER and ADNI data [36,39]	Against standard CL on GAAIN and AIBL data [37]	Against SUVr and CSF Aβ42 using ADNI data
Availability	Available *via* Invicros's IQ Analytics Platform	Software freely available for research upon request	Open source https://doi.org/10.25919/5f8400a0b6a1e.	Plans to make it open source
Implementation in studies	Zammit et al., 2019, 2021 [43,44]	Haller et al., 2021 [45]	-	-
Main strengths	- Increased sensitivity for longitudinal change in amyloid load - Implemented for all amyloid tracers (PiB [44]; ^{18}F tracers [40]) - Implemented for tau [41]	- MR independent - Reference region independent - Software includes pre-processing - Fully automatic process (~20 seconds)	- Robustness to change in tracer in a longitudinal setting - Improve longitudinal consistency compared to CL - Implemented for all amyloid tracers	Reference region independent
Main limitations	Relies on a reference region	Relies on a reference region for training	- Relies on a reference region - Sub-optimal decomposition for ^{18}F tracers	Sensitivity to training set
Possible improvements	-	Allow for more principal components	Independence from MR using CapAIBL [46]	Independent from MR

Other ratio metrics

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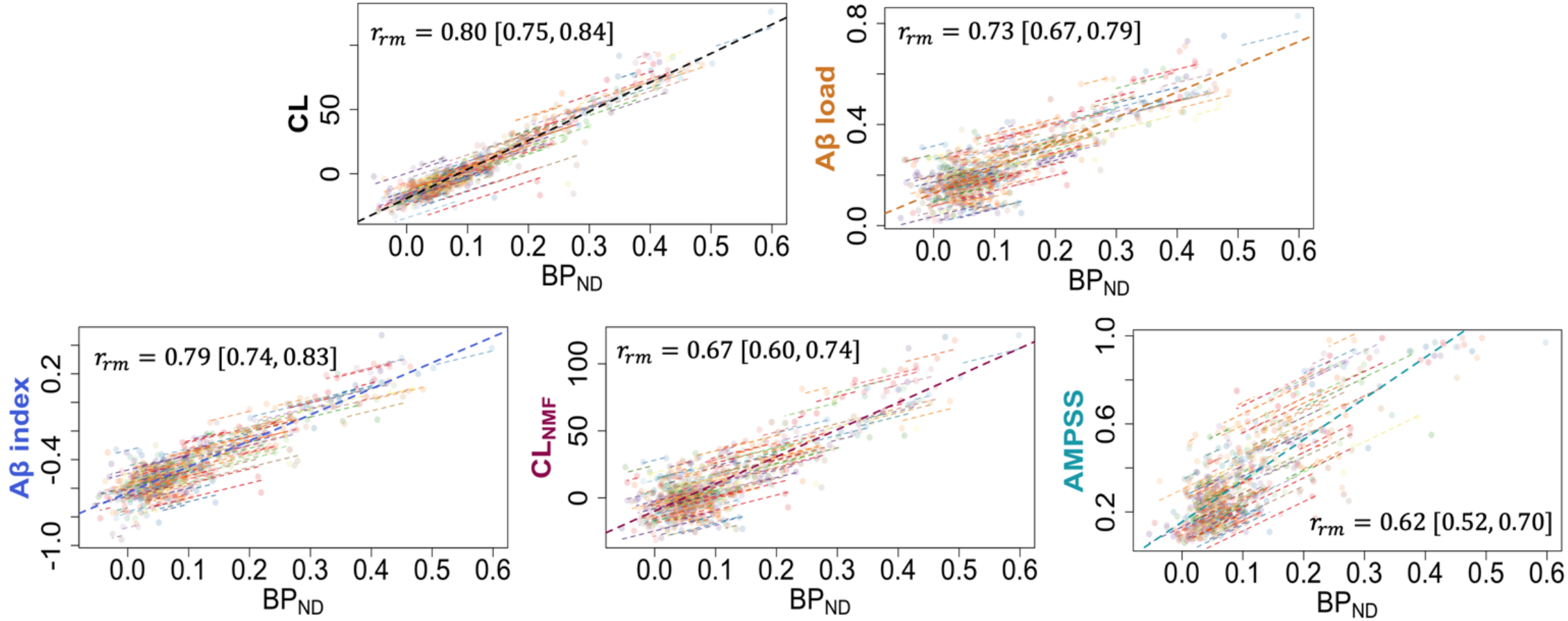

Correlation between amyloid metrics and non-displaceable binding potential BP_{ND}*, evaluated with dynamic acquisition scans from Insight46 data. The 95% confidence interval for* r_{rm} *was built using 2,000 bootstrap replicates. The dotted lines represent the regression for the metrics averaged per subject*

Bollack *et al. in preparation*

Other ratio metrics

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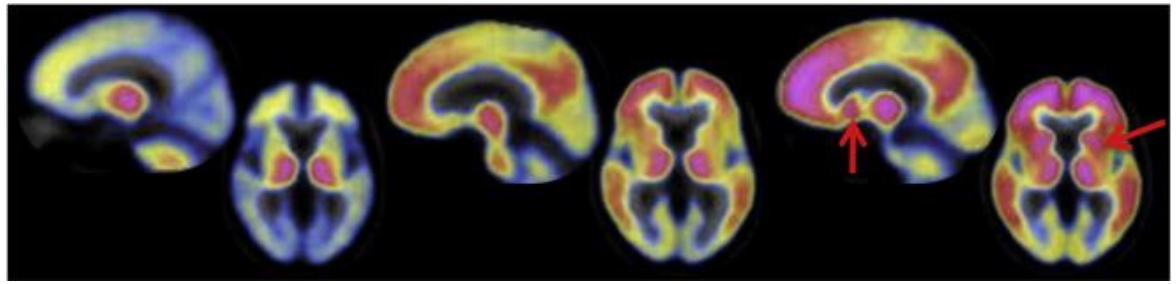
	Insight46	
	20 ≤ CL ≤ 50	CL > 20
N	39	67
BP_{ND}	93 [58, 507]	105 [74,394]
CL	96 [85, 307]	117 [105,348]
Aβ load	81 [83, 218]	111 [110,312]
Aβ index	131 [107, 489]	147 [135,533]
CL_{NMF}	71 [70, 184]	74 [82,173]
AMPSS	558 [334, 4772]	553 [358,4590]

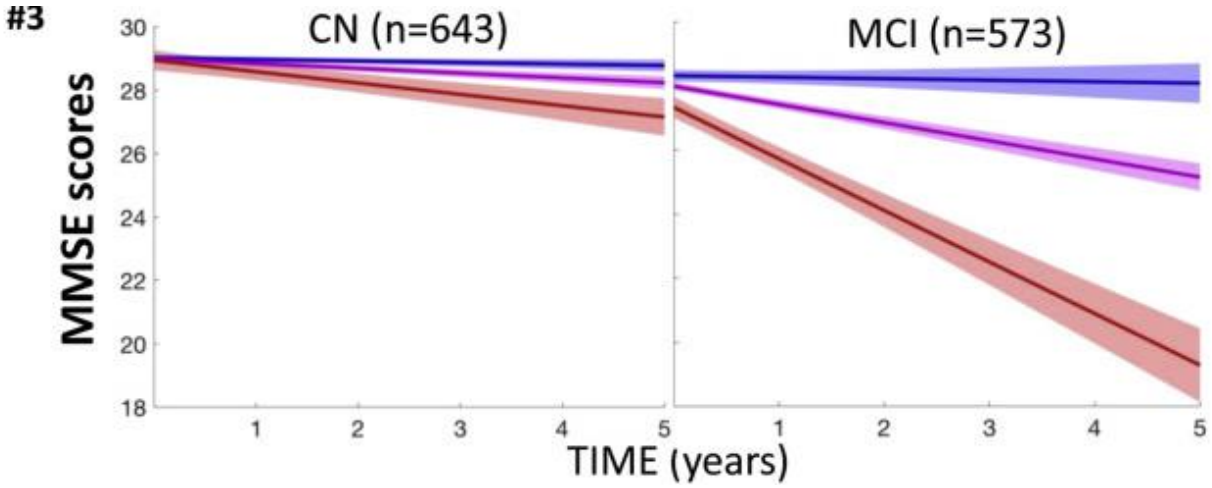
Samples size estimates (α = 0.05; 1-β = 80%) required to detect a 25% decrease in annualized amyloid accumulation. Two scenarios were assessed: a secondary prevention trial focusing on early accumulators (20<CL≤ 50), and a secondary prevention trial for individuals with at least moderate amyloid burden (CL□20).

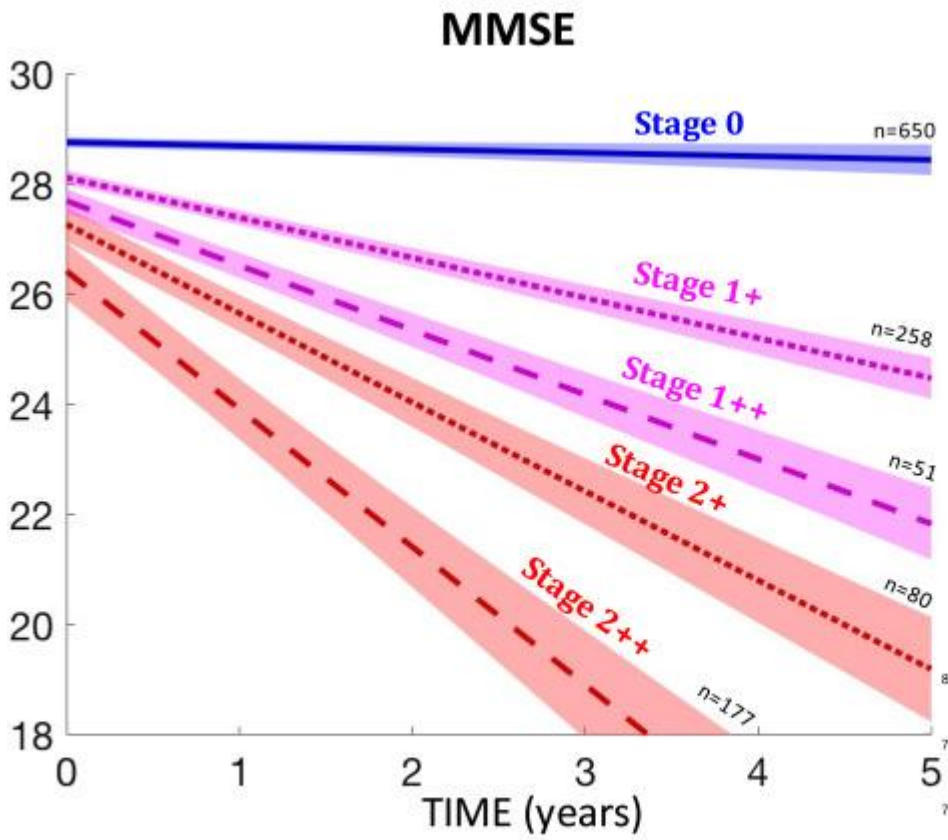
Bollack *et al. in preparation*

Regional Staging Methods

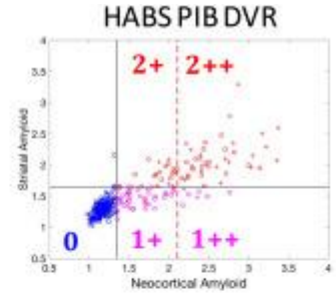
- Visual detection of amyloid in the striatum associated with cognitive decline

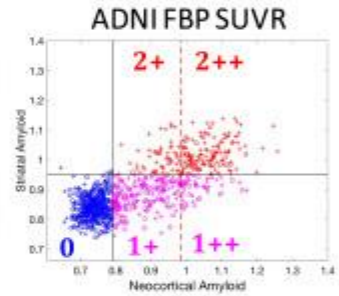


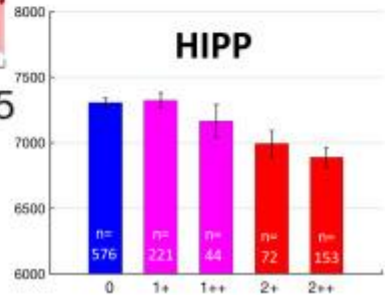




HABS and ADNI, CN and MCI pooled: Total n=1216



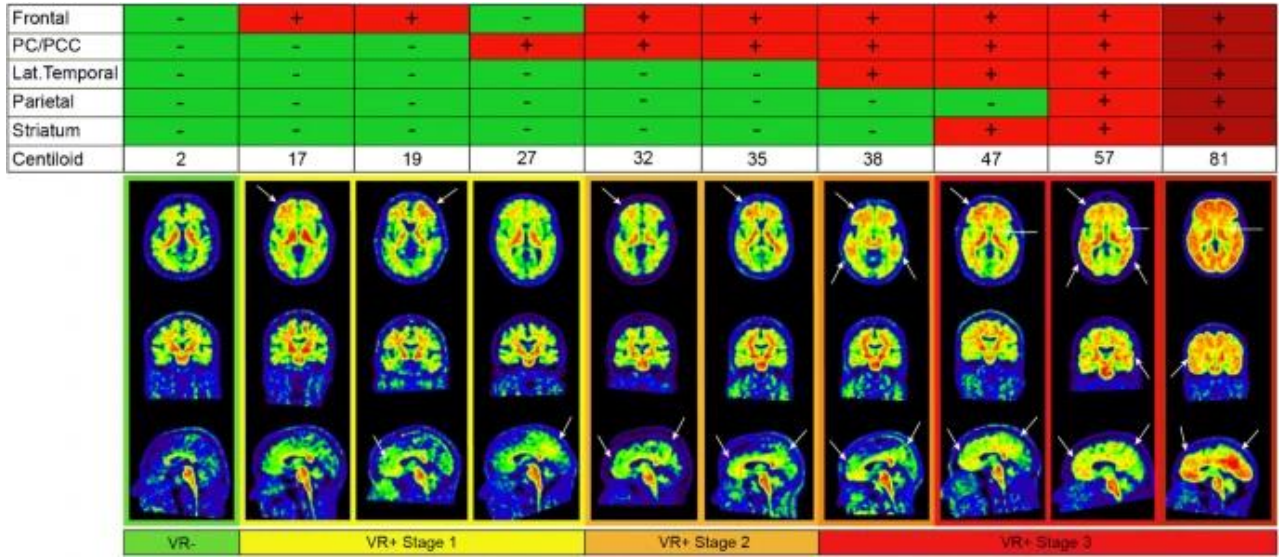


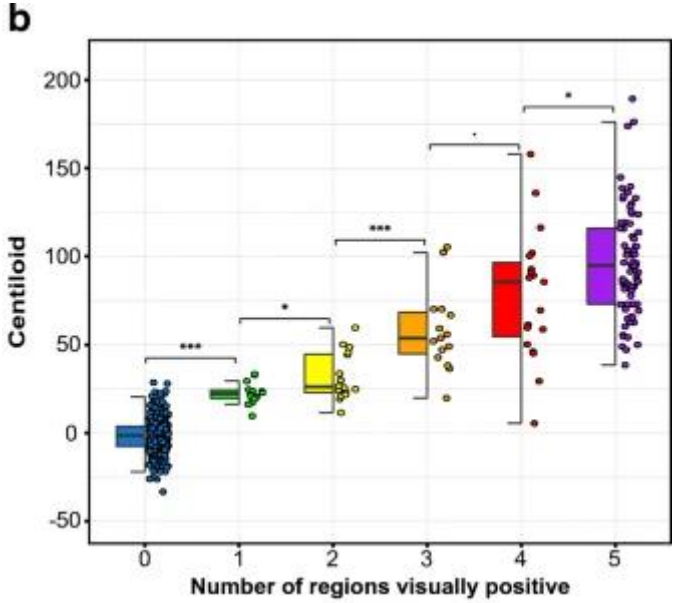


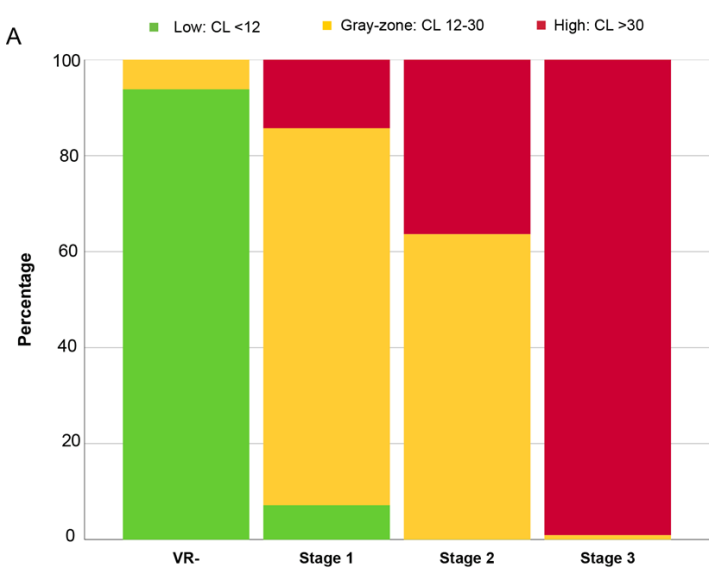
Hanseeuw *et al.* Alzheimers Dement. 2018

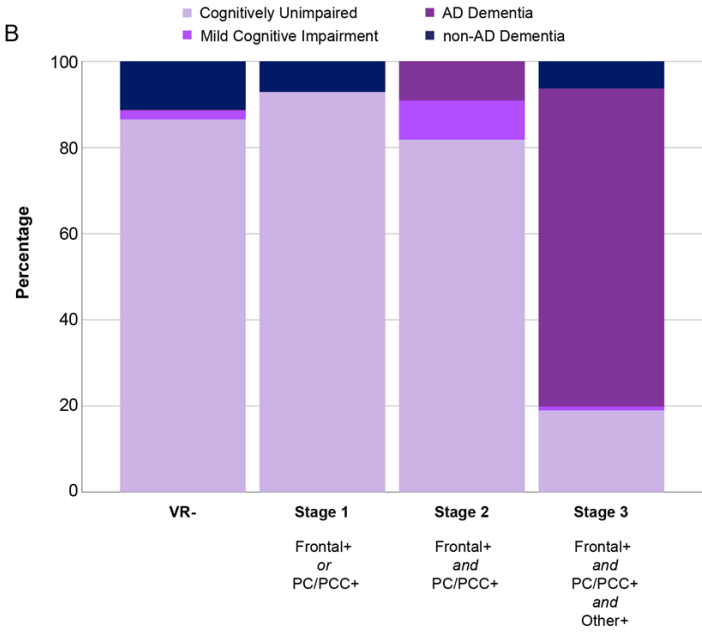
Global vs Regional Amyloid

- Little topographical variability of Amyloid deposition in AD
  - Exception: Occipital uptake in cognitively unimpaired individuals
- Regional positivity can be used to stage amyloid accumulation and disease progression





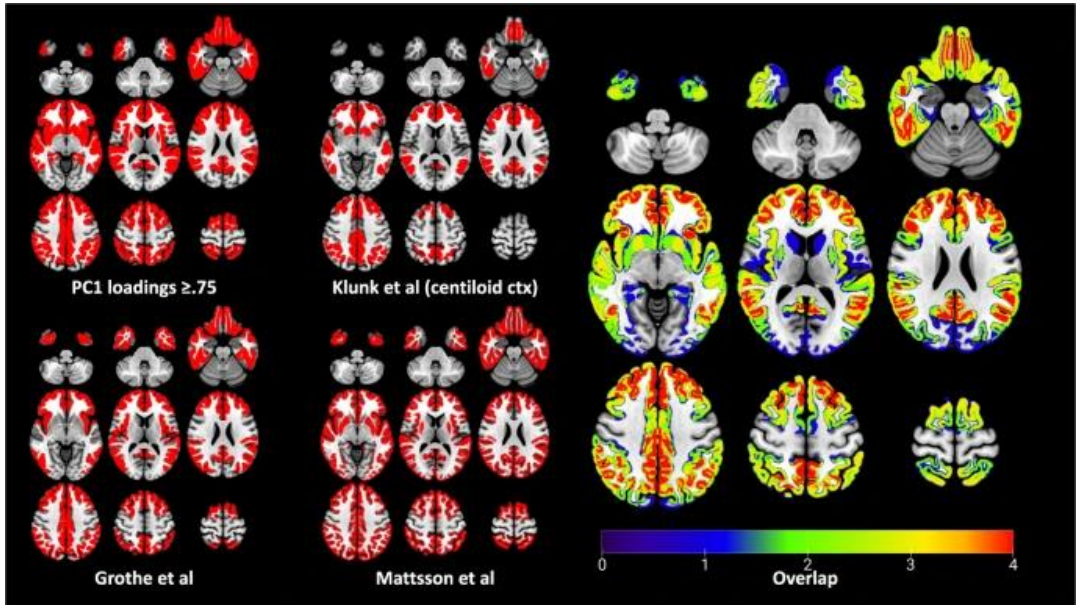




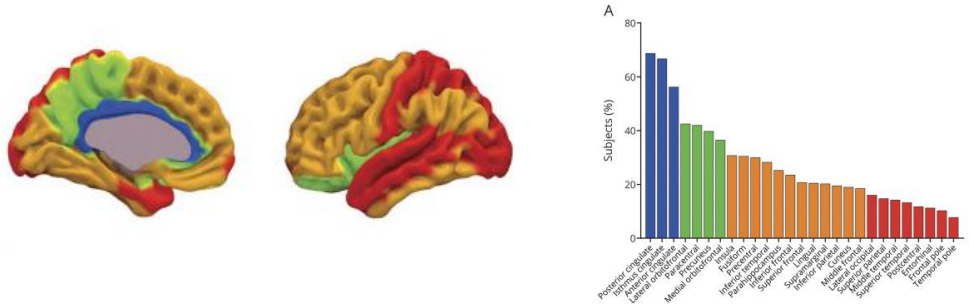
Collij *et al.* EJNMMI 2021

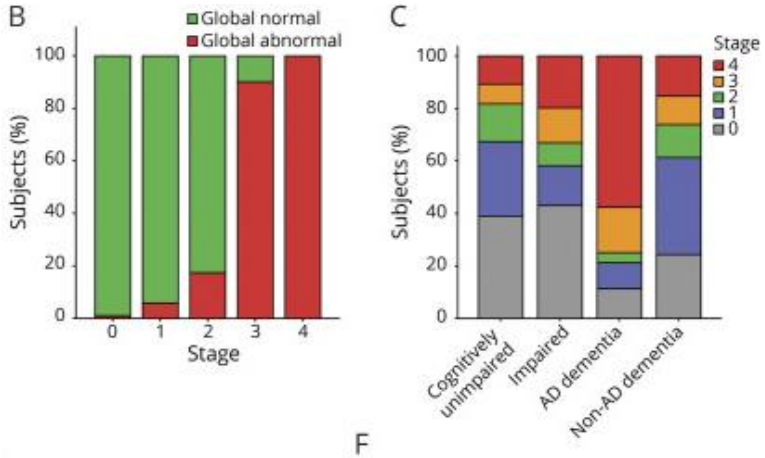
Global vs Regional Amyloid: Regional Staging Methods

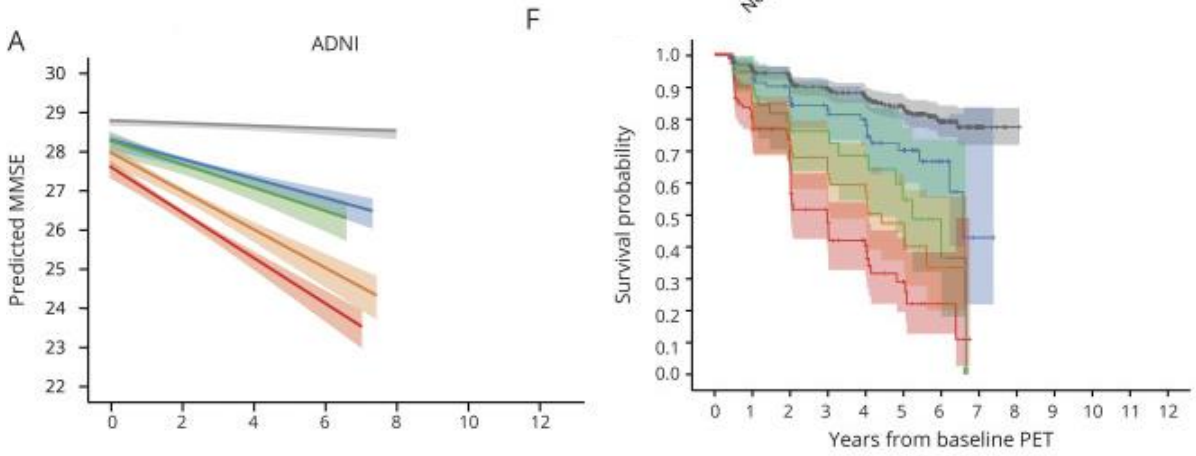
- Little topographical variability of Amyloid deposition in AD
  - Exception: Occipital uptake in cognitively unimpaired individuals
- Regional positivity can be used to stage amyloid accumulation and disease progression



Michalowska *et al.* Mol Psyatr. 2022



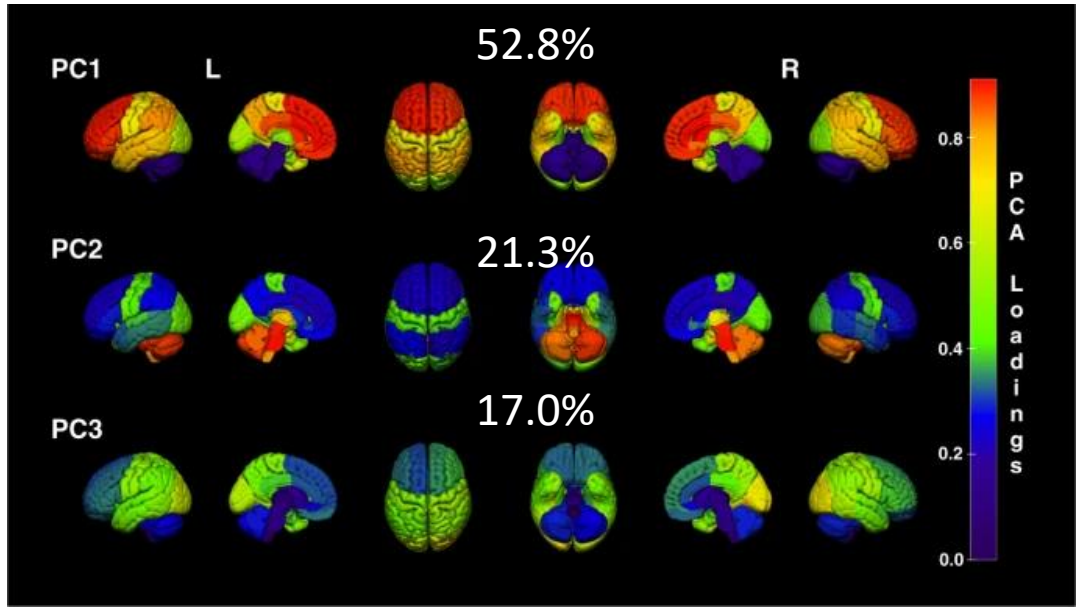




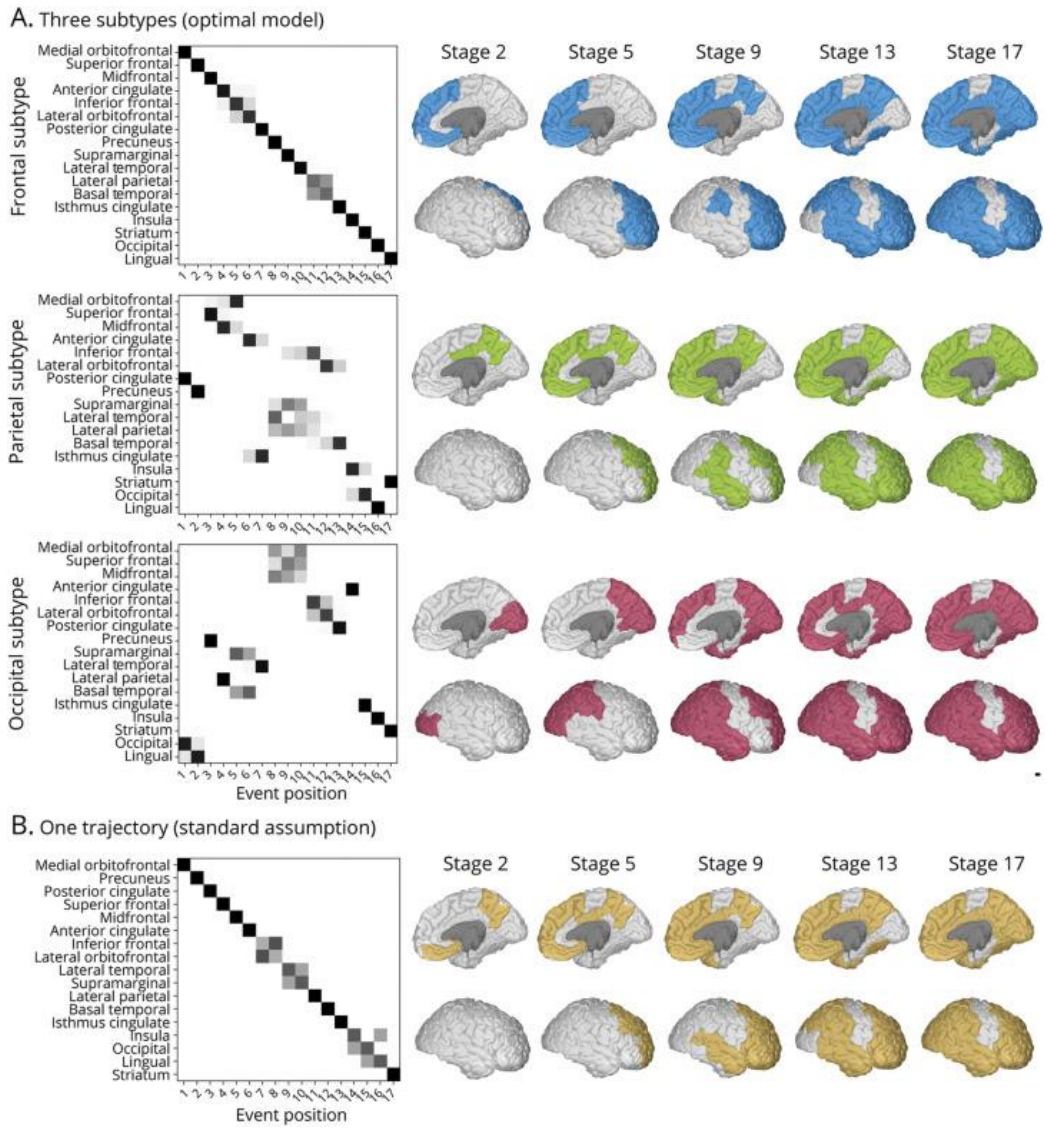
Collij *et al.* Neurology 2021

Global vs Regional Amyloid: Spatial Patterns of Variability

- Little topographical variability of Amyloid deposition in AD
  - Exception: Occipital uptake in cognitively unimpaired individuals
- Regional positivity can be used to stage amyloid accumulation and disease progression



Michalowska *et al.* Mol Psyatr. 2022



Collij *et al.* Neurology 2022

Conclusions

- **Contexts of Use** of quantitative amyloid-β PET are expanding
- The Centiloid concept provides a **universal metric** of amyloid-β load that is **comparable** across quantification methods
- It is therefore important to **identify and quantify sources of error** in Centiloids
- A statistical framework has been developed to quantify the impact of **pipeline design options** in absolute Centiloid units

Conclusions: Centiloid Sources of Variability

- The Centiloid method is **robust to pipeline** design alternatives, as well as **across pipelines**
  - Within-pipeline:
    - **Bias below test-retest variability** (3.5 CL)
      - Sole exception: Pons as reference region (ΔCL = 12 CL)
    - Within-pipeline (95% CI) **uncertainty around 6 CL**
    - Impact of effective **image resolution <5 CL**
  - Between-pipeline:
    - Mean absolute error: 5-8 CL
    - Between-pipeline 95% CI (individual error bound): 13 CL, at the level of thresholds for abnormality
- **Tracer had no impact** on Centiloid values, no matter the pipeline

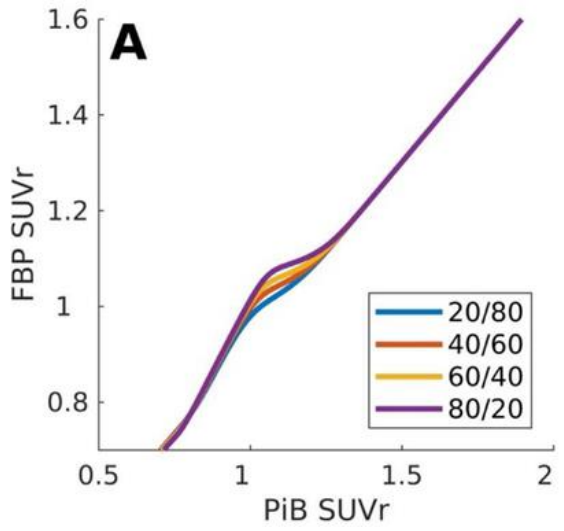
Conclusions: Other Metrics of Aβ burden

- **Kinetic modeling** (BP_{ND}/DVR) brings **moderate improvements** (wrt SUVR/CL) in:
  - Accuracy (bias ~30% cross-sectional; ~15% longitudinal)
  - Precision (test retest ~50%)
  - Robustness to:
    - Technical confounders (10 min delay in imaging window -> ΔCL <3 CL)
    - Physiological confounders (±25% change in global CBF-> 5% change in SUVR/CL)
  - Require dynamic acquisitions
    - Infrequently used in clinical practice and trials
  - Conversion to Centiloids is not possible due to the lack of full dynamic H2H data

- Other 'ratio' metrics (Aβ load, Aβ index, CL_{NMF}, etc…)
  - Moderately improved precision with respect to standard Centiloid pipeline
    - Derived of the optimal definition of target and reference regions
  - **Can be scaled to the Centiloid**

Conclusions: Limitations of Centiloid Method

- **Limitations** of Centiloid:
  - Inherent limitations of 'ratio' methods
  - Need for H2H reference datasets vs 11C-PIB
  - Assumption of linear association with 11C-PIB
    - Non-linear alternatives: NoDim (Properzi et al 2019)
  - Global metric
    - However, there is little regional variability in AD
    - Global CL tracks well regional cerebral spread



- Taken together, limitations have a small impact on accuracy, precision, robustness and utility

- **The Centiloid is a well-established, robust and useful method to render absolute units of Aβ burden**

Acknowledgements

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Quantifying the Variability of Amyloid-β PET in Centiloid Units

Backup Slides

AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

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Quantitative Amyloid Imaging: Context of Use in Clinical Trials (I)

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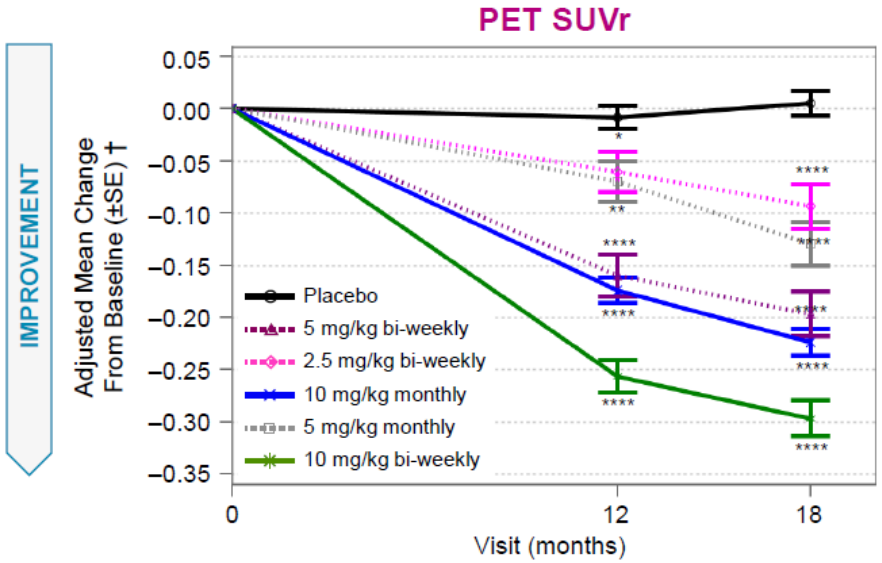
- Assessment of treatment response (phamacodynamic endpoint)
- Surrogate endpoint of efficacy



Global Cortical Average versus Whole Cerebellum Reference

*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. †Adjusted mean change from baseline by Mixed Model Repeated Measures (MMRM).
The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.
For PET analysis N=306 at 12 months and N=277 at 18 months.

https://www.eisai.com/ir/library/presentations/pdf/4523_180726.pdf

Quantitative Amyloid Imaging: Context of Use in Clinical Trials (I)

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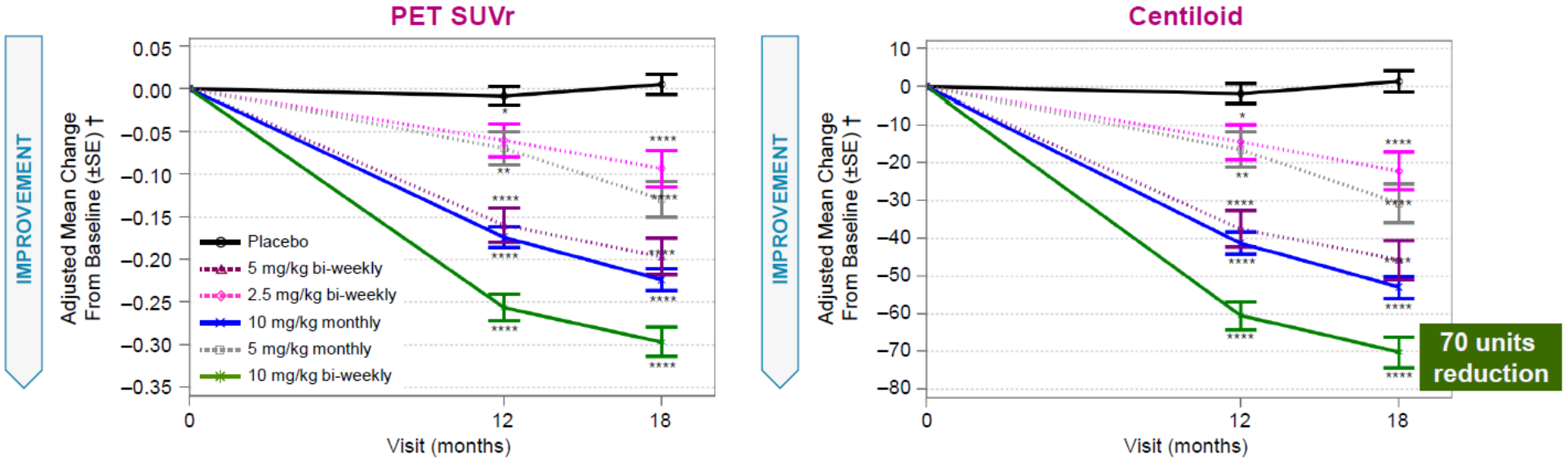
- Assessment of treatment response (phamacodynamic endpoint)
- Surrogate endpoint of efficacy



*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. †Adjusted mean change from baseline by Mixed Model Repeated Measures (MMRM).
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https://www.eisai.com/ir/library/presentations/pdf/4523_180726.pdf

Quantitative Amyloid Imaging: Context of Use in Clinical Trials (II)

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- Inclusion Criterion
  - Trials in Symptomatic Populations: Positive Visual Read (VR)
  - **Prevention Trials (e.g. AHEAD 3-45)**

ACTC ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

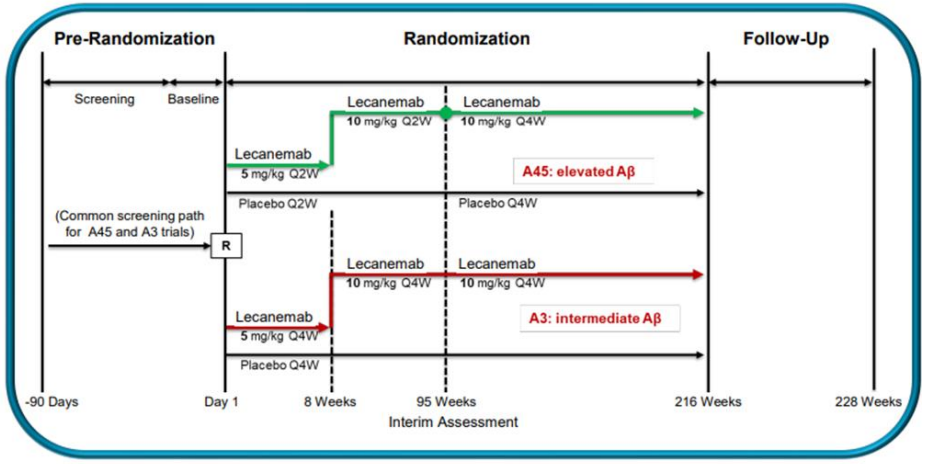
Study Design & Conduct: Dosing Regimens Tailored to Baseline Amyloid PET Levels and Normal Cognition

Eisai

A45 – Elevated amyloid (>40 centiloids) aimed at preventing cognitive decline
- 4-year Phase 3 trial (n=500/arm)
- 5 mg/kg Q2W titration, 10 mg/kg Q2W induction, then 10 mg/kg Q4W maintenance
- Cognitive primary outcome (PACC-5)
- Amyloid and Tau PET key secondary
- Additional cognitive, participant reported, plasma and CSF biomarker outcomes

A3 – Intermediate amyloid (20-40 centiloids) aimed at slowing Aβ accumulation
- 4-year Phase 2 trial (n=200/arm)
- 5 mg/kg Q4W titration, 10 mg/kg Q4W treatment
- Amyloid PET primary outcome
- Tau PET key secondary
- Cognition exploratory (PACC-5 and C3)

Study Conduct
- About 100 sites world-wide planned, 76 activated in US, Japan, UK and Australia
- First participant randomized in US on September 17, 2020



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https://www.bioarctic.se/en/wp-content/uploads/sites/2/2020/11/ctad-2020-sperling-oc2-final.pdf

Quantitative Amyloid Imaging: Context of Use in Clinical Trials (III)

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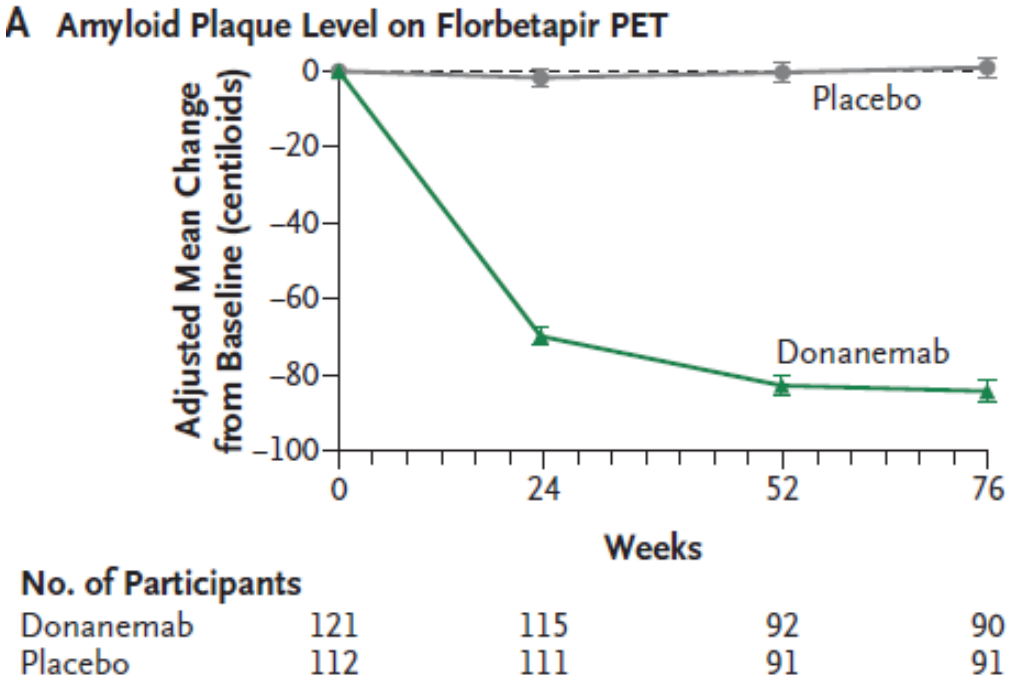
- Support Clinical Dose selection / Cessation of Treatment
  - Donanemab Phase II trial
    - If 11<CL<25: Dose reduced to 700 mg (from 1400 mg)
    - If CL<11 or 2 consecutive scans with CL<25: Participant switched to placebo
      - 27.4% (w28) and 54.7% (w56) of participants



	Difference in Adjusted Mean Change		Amyloid-Negative Status, Donanemab
	Donanemab vs. placebo	95% CI	
	centiloids		*no. (%)*
Wk 24	−67.83±3.16	−74.04 to −61.61	46 (40.0)
Wk 52	−82.30±3.41	−89.02 to −75.59	55 (59.8)
Wk 76	−85.06±3.87	−92.68 to −77.43	61 (67.8)

CL<24.10

Mintun et *et al.* NEJM 2022

Potential Use of Quantitative Amyloid PET in Clinical Practice?

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- Contexts of Use of quantitative amyloid-β PET (in CL) are expanding

    1. Pharmacodynamic / Target Engagement
    2. Surrogate Endpoint of Efficacy
    3. Dose selection / Treatment Cessation
    4. Patient selection (prevention trials)

- Potential clinical utility when anti-amyloid drugs are approved

Potential Use of Quantitative Amyloid PET in Clinical Practice?

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- Contexts of Use of quantitative amyloid-β PET are expanding
- Potential clinical utility when anti-amyloid drugs are approved
- Likely, in combination with blood-based biomarkers

Table 1. Some examples of blood-based markers use in clinical trials

Study	Clinicaltrial.gov identifier	Phase	Population	Therapy	Blood biomarker	Role
AHEAD 3-45	NCT04468659	III	Preclinical AD	Lecanemab	Aβ42/40 ratio	Prescreening
AUTONOMY	NCT04619420	II	Early symptomatic AD	JNJ-63733657	p-tau217	Prescreening
BAN2401-G000-201 Core and Open Label Extension	NCT01767311	II	Early symptomatic AD	Lecanemab	Aβ42/40 ratio p-tau 181	Pharmacodynamic
DIAN-TU	NCT04623242	II/III	Preclinical and early symptomatic AD	Gantenerumab	Aβ42/40 ratio p-tau181	Pharmacodynamic
EMERGE	NCT02484547	III	Early symptomatic AD	Aducanumab	p-tau 181	Pharmacodynamic
ENGAGE	NCT02477800	III	Early symptomatic AD	Aducanumab	p-tau 181	Pharmacodynamic
EVOKE	NCT04777396	III	Early symptomatic AD	Semaglutide	p-tau181, NfL, GFAB	Pharmacodynamic
EVOKE-PLUS	NCT04777409	III	Early symptomatic AD	Semaglutide	p-tau181, NfL, GFAB	Pharmacodynamic
INVOKE-2	NCT04592874	II	Early symptomatic AD	AL002	PrecivityAD™ (algorithm derived from Aβ42/40 ratio, APOE genotype and age)	Prescreening
PROSPECT-ALZ	NCT05063539	II	Early symptomatic AD	LY3372689	p-tau217	Prescreening
TRAILBLAZER-ALZ 2	NCT04437511	III	Early symptomatic AD	Donanemab	p-tau181 p-tau217	Exploratory endpoint
TRAILBLAZER-ALZ 3	NCT05026866	III	Preclinical AD	Donanemab	p-tau217	Exploratory endpoint

Aβ, Amyloid-beta; AD, Alzheimer´s Disease; APOE, Apolipoprotein E; NfL, Neurofilament Light chain; P-tau, phosphorylated tau.

Angioni et *et al.* JPAD 2022

Potential Use of Quantitative Amyloid PET in Clinical Practice?

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- Contexts of Use of quantitative amyloid-β PET are expanding
- Potential clinical utility when anti-amyloid drugs are approved
- Likely, in combination with blood-based biomarkers

Table 3. Appropriate and inappropriate uses of blood-based markers in clinical practice

	Appropriate use	Inappropriate use
What blood-based markers?	1. p-tau, Aβ42/40 alone or in combination with other biomarkers, in individuals with typical amnestic presentation 2. NfL to explore neurodegenerative process	1. Any biomarker quantified in an unregulated, non-certified, non-accredited laboratory
When to use blood-based markers?	1. In individuals with objective cognitive impairment (possible or probable AD, MCI/dementia) 2. If suspicion of AD, as part of the initial diagnostic workup 3. If any contraindication or patient aversion to LP (CSF biomarkers)	1. Instead of the cognitive testing 2. In cognitively unimpaired individuals, except context of clinical research 3. Use to determine disease severity in patients having already received a diagnosis of AD 4. APOE4 carriers with no cognitive impairment
Where to use blood-based markers?	1. In primary care to help PCP referring patients to specialists in memory disorders 2. In primary and specialty care to aid in diagnosis of AD (positive biomarkers along with classical cognitive presentation). 3. In clinical trials (Research Setting)	1. In any facility in the absence of trained physicians
How to interpretate blood-based markers?	1. Holistic approach, model combining blood-based biomarkers and cognitive performance 2. Need to perform CSF biomarkers or PET if clinical presentation, structural imaging or other evaluative tests conflict with the blood-based biomarker test result	1. Interpretation of biomarkers without considering the history, clinical exam, cognitive testing, and patient autonomy

Aβ, Amyloid-beta; AD, Alzheimer Disease; CSF, Cerebrospinal Fluid; LP, Lumbar Puncture; PCP; Primary Care Physician; NfL, Neurofilament light Chain; P-tau, phosphorylated tau.

Angioni et *et al.* JPAD 2022

Other ratio metrics

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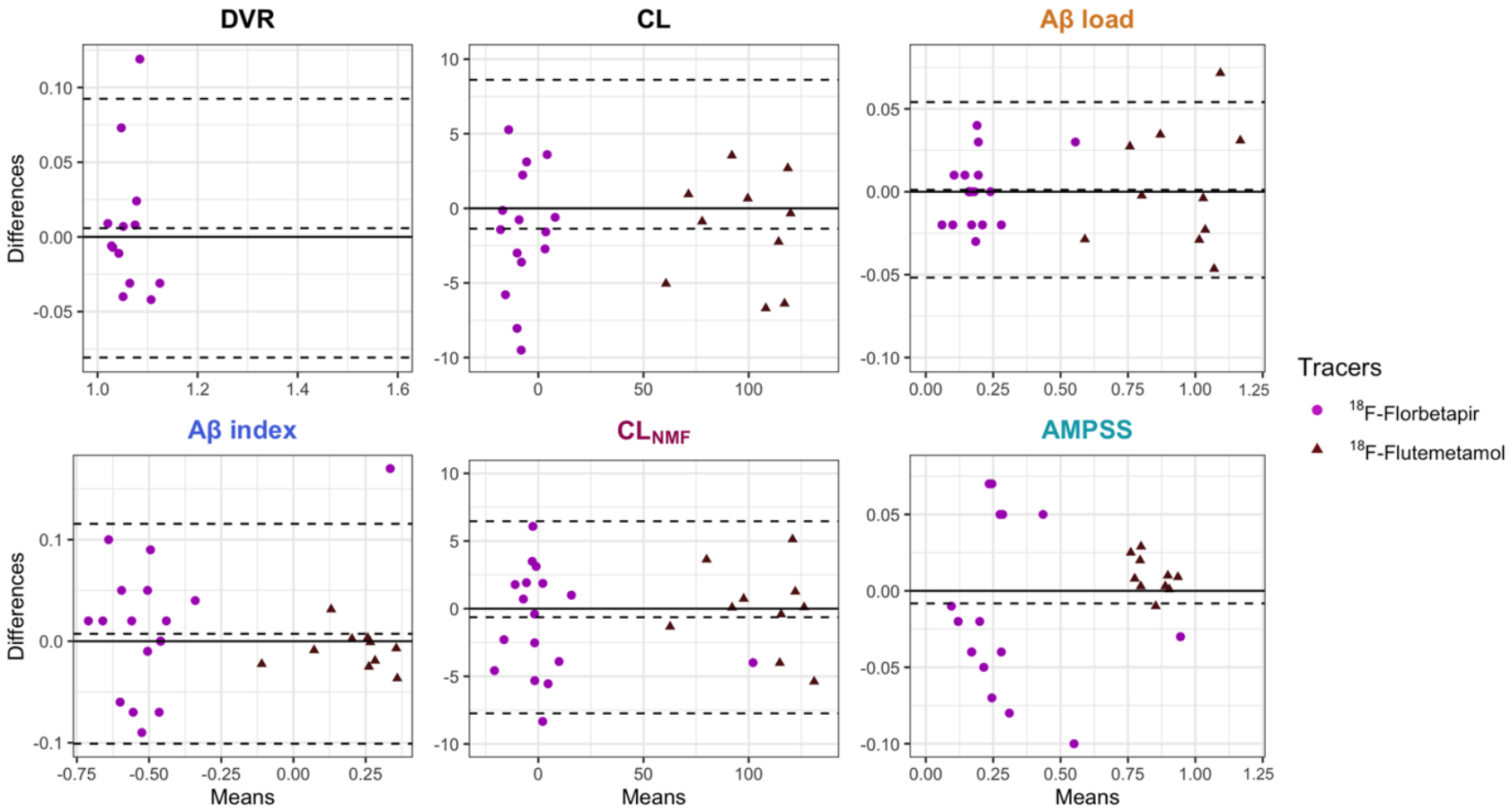

Bland-Altman plots *indicating bias between test and retest measurements. Dashed lines indicate the mean, lower and upper limit of agreement (+/- 1.96 standard deviation from the mean)*

Bollack *et al. in preparation*

Other ratio metrics

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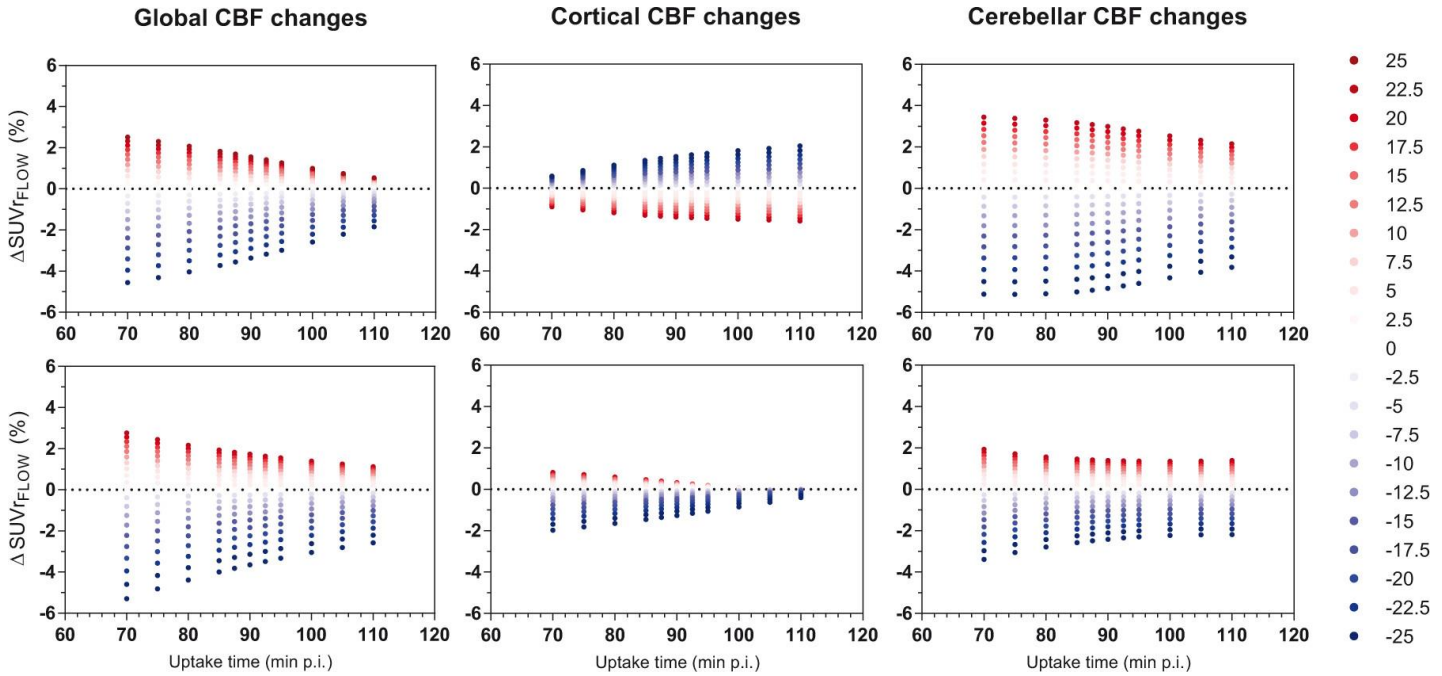
	Insight46					AIBL				
	ARC				CV	ARC				CV
	All	CL ≤ 15	20 ≤ CL ≤ 50	CL > 20	All	All	CL ≤ 15	20 ≤ CL ≤ 50	CL > 20	All
N	438	331	39	67	438	185	100	11	52	185
BP_{ND}	0.011 ± 0.019	0.0079 ± 0.017	0.027 ± 0.016	0.025 ± 0.018	1.63 [1.32, 2.24]	N/A				
CL	2.35 ± 3.47	1.53 ± 2.76	6.10 ± 3.76	5.53 ± 3.52	1.47 [1.27, 1.74]	0.51 ± 13.78	-0.11 ± 12.48	2.95 ± 13.43	2.36 ± 15.71	28.89 [6.62, >100]
Aβ load	0.0091 ± 0.015	0.0052 ± 0.012	0.029 ± 0.016	0.025 ± 0.014	1.68 [1.43, 2.03]	0.013 ± 0.037	0.0090 ± 0.025	0.016 ± 0.022	0.019 ± 0.048	2.85 [3.06, 3.06]
Aβ index	0.013 ± 0.028	0.0077 ± 0.027	0.036 ± 0.026	0.037 ± 0.028	2.23 [1.75, 3.17]	0.021 ± 0.076	0.012 ± 0.044	0.037 ± 0.14	0.032 ± 0.093	3.62 [3.38, 5.03]
CL_{NMF}	2.077 ± 3.036	1.21 ± 2.26	5.94 ± 3.14	5.21 ± 2.79	1.46 [1.27, 1.75]	2.37 ± 5.60	1.62 ± 5.55	3.64 ± 4.20	3.50 ± 5.51	2.36 [2.49, 2.49]
AMPSS	0.021 ± 0.0401	0.0171 ± 0.0366	0.0364 ± 0.0542	0.0375 ± 0.0521	1.91 [1.57, 2.43]	0.0087 ± 0.1132	0.0056 ± 0.11	0.031 ± 0.068	0.015 ± 0.11	12.85 [4.59, >100]

Annualised rates of change in amyloid deposition and coefficients of variation in AIBL and Insight46 datasets. Values are described as mean ± standard deviation. Confidence intervals for the coefficients of variation were built via bootstrap resampling using 2,000 replicates

Bollack *et al. in preparation*

Other metrics: BPnd / DVR

- Pros:
  - More accurate measure of amyloid burden
  - Insensitive to time window for PET imaging
  - Lower (~50%) test-retest variability
  - **Account for variability in cerebral blood flow**
- Cons:
  - Require dynamic acquisitions
    - Longer scanner time, higher cost, more participant burden
  - Not possible to convert to standard units (i.e. Centiloids)
    - Lack of Head-to-Head dynamic acquisitions btw 11C-PIB and 18F-Tracers



Heeman *et al.* J Cereb Blood Flow Metab. 2021

Quantitative Brain Amyloid PET Imaging Methodology, Metrics, Analytical Validity

Amyloid^{IQ}

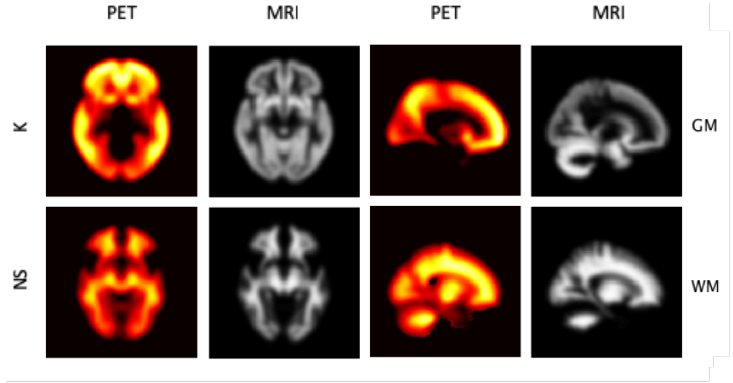
Roger Gunn, Ph.D.

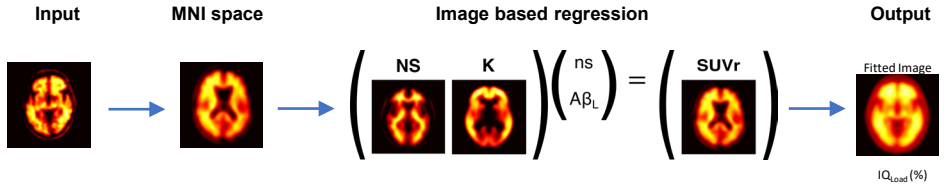
Invicro & Imperial College London

Acknowledgements: Alex Whittington (Invicro)
Neuraceq^{TM} Data (LMI: Santiago Bullich & Andrew Stephens)
Amyvid^{TM} Data (ADNI)

AMYLOID IQ

Canonical Images





Spatiotemporal Distribution of β-Amyloid in Alzheimer Disease Is the Result of Heterogeneous Regional Carrying Capacities

Alex Whittington[1], David J. Sharp[1], and Roger N. Gunn[1–3] for the Alzheimer's Disease Neuroimaging Initiative

2018, JNM

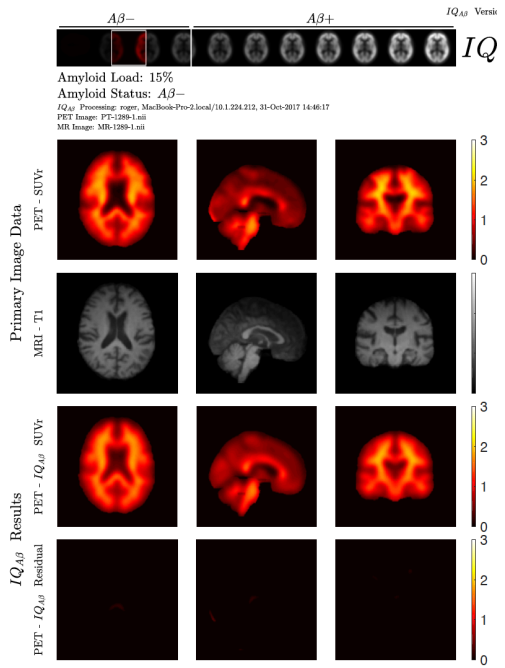
Amyloid Load: A More Sensitive Biomarker for Amyloid Imaging

Alex Whittington[1,2] and Roger N. Gunn[1–3]; for the Alzheimer's Disease Neuroimaging Initiative

2019, JNM

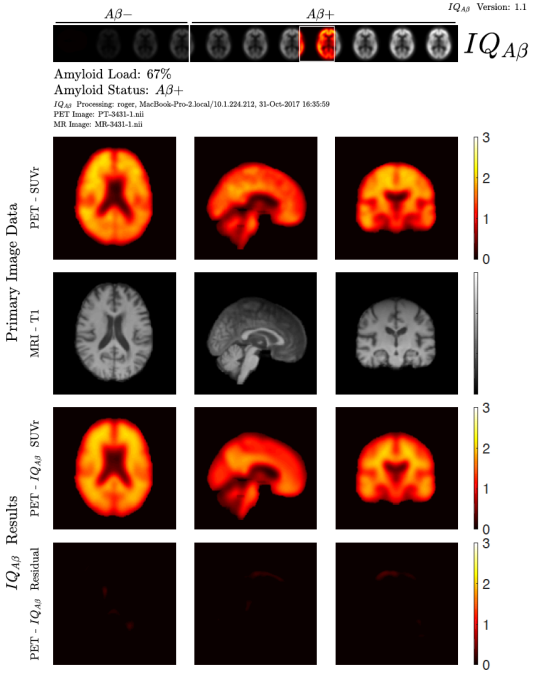
Healthy

Low Aβ



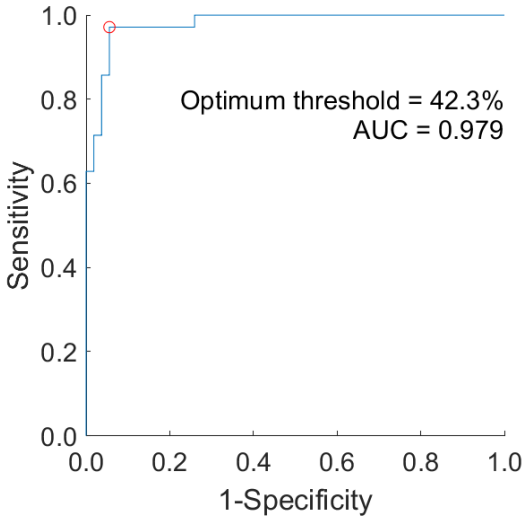
AD

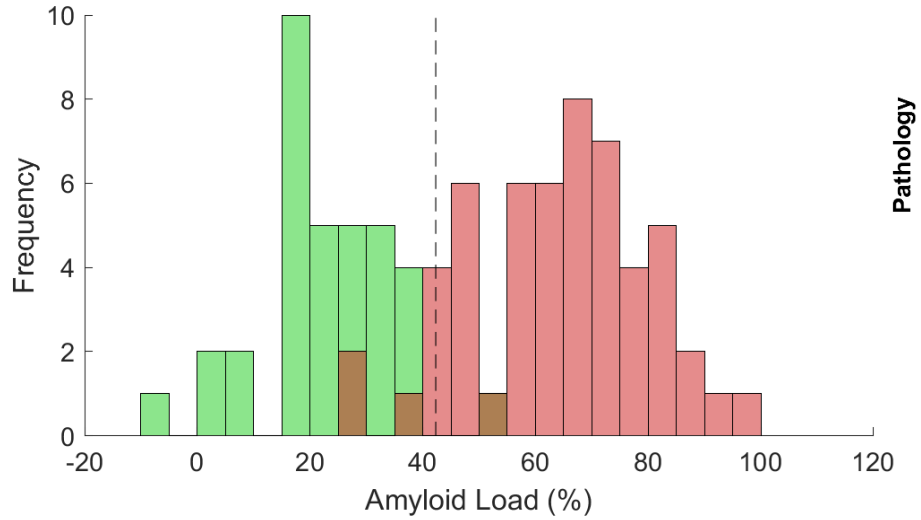
High Aβ



AMYLOID^{IQ} - Neuraceq^{TM}

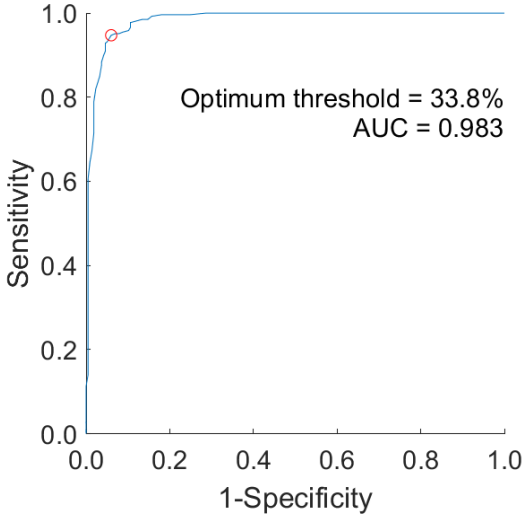
Amyloid^{IQ}
Vs
Pathology
(N=89)

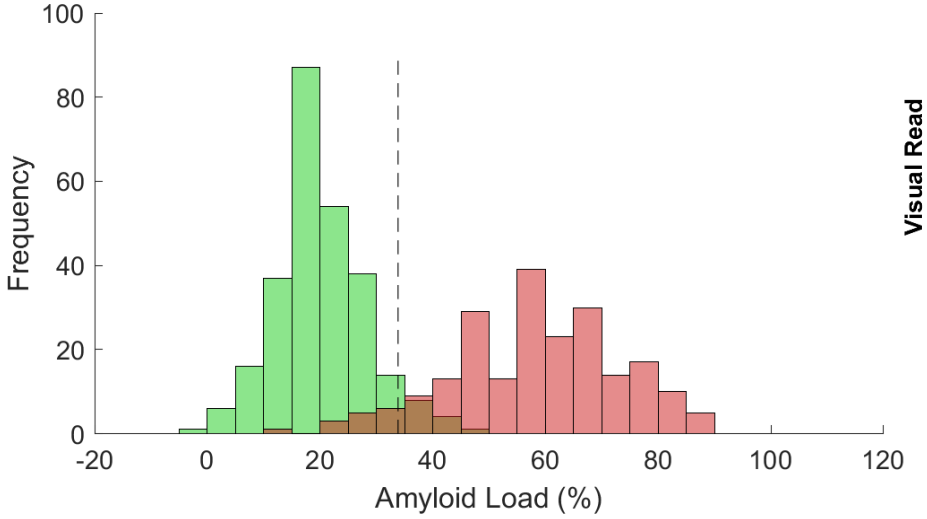




Pathology	Amyloid^{IQ} Positive	Amyloid^{IQ} Negative	
Present	50	4	Sensitivity = 0.926
Absent	1	34	Specificity = 0.971
			Accuracy = 0.944

Amyloid^{IQ}
Vs
Majority Read
(N=483)

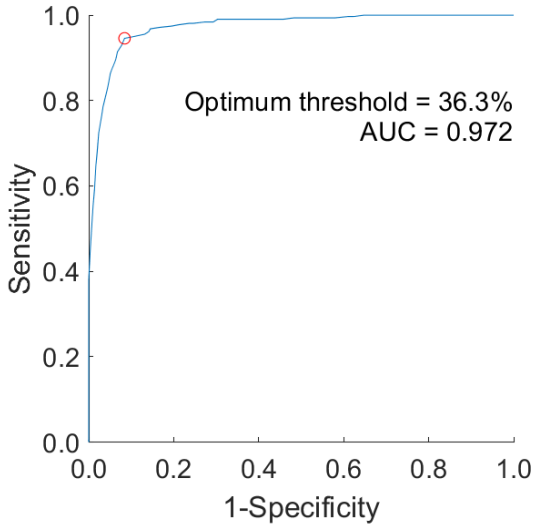


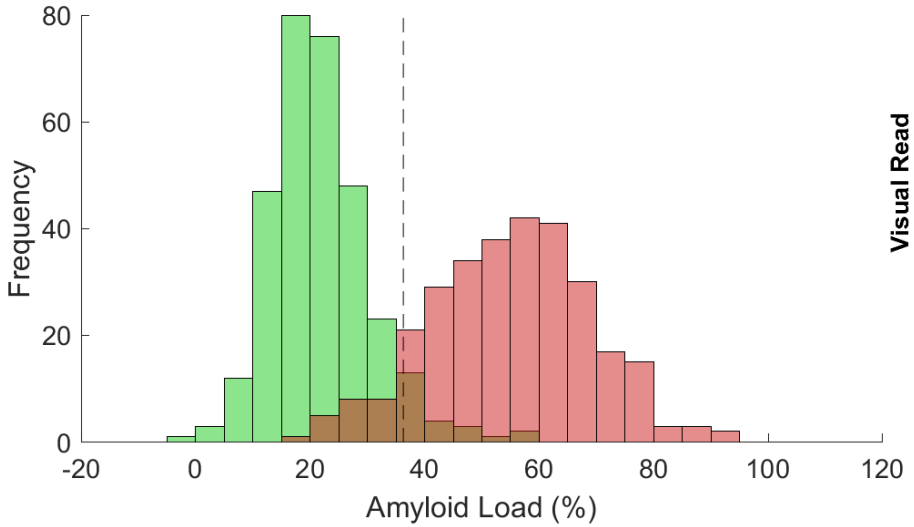


Visual Read	Amyloid^{IQ} Positive	Amyloid^{IQ} Negative	
Positive	204	13	Sensitivity = 0.94
Negative	14	252	Specificity = 0.947
			Accuracy = 0.944

AMYLOID^{IQ} - Amyvid^{TM}

Amyloid^{IQ}
Vs
Majority Read
(N=610)





Visual Read	Amyloid^{IQ} Positive	Amyloid^{IQ} Negative	
Positive	272	25	Sensitivity = 0.916
Negative	17	296	Specificity = 0.946
			Accuracy = 0.931

Sources of Variability in Cross-sectional and Longitudinal Quantitative Aβ PET

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University of Pittsburgh · Austin Health · The University of Melbourne · Australia ECU Edith Cowan University

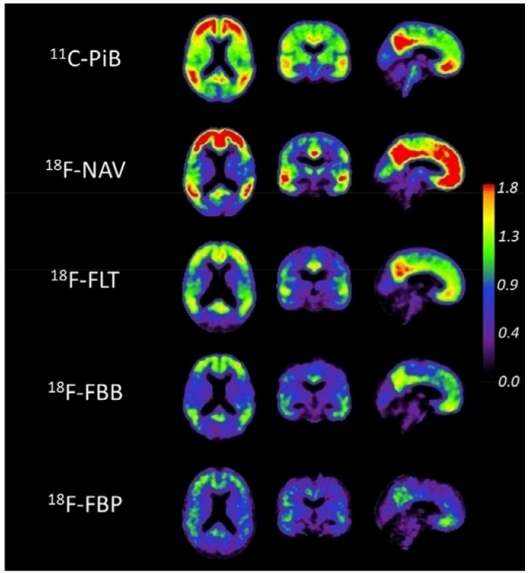
Effect of change of tracer/scanner on longitudinal studies

NeuroImage

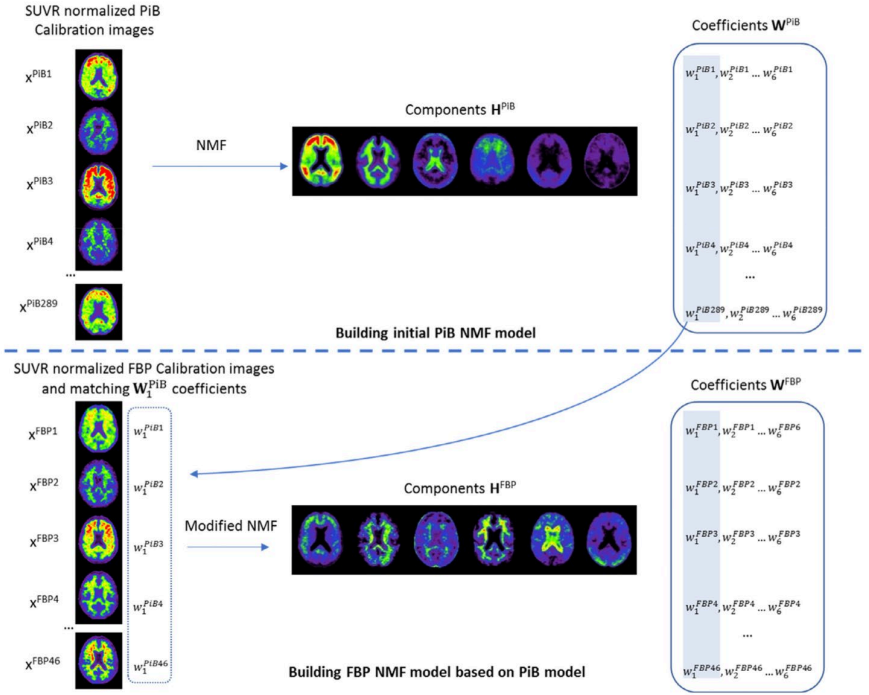
Non-negative matrix factorisation improves Centiloid robustness in longitudinal studies

Pierrick Bourgeat[a,*], Vincent Doré[a,b], James Doecke[a], David Ames[c], Colin L. Masters[d], Christopher C. Rowe[b,e], Jurgen Fripp[a], Victor L. Villemagne[b,e], the AIBL research group

[a] CSIRO Health and Biosecurity, Brisbane, Australia
[b] Department of Molecular Imaging & Therapy, Austin Health, Melbourne, Australia
[c] University of Melbourne, Academic Unit for Psychiatry of Old Age, St George's Hospital, Kew, Australia
[d] The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Melbourne, Australia
[e] Department of Medicine, University of Melbourne, Melbourne, Australia



Aβ PET images can be modeled as a sum of a specific and non-specific binding components. Non-negative matrix factorization is a machine learning technique which is trained to estimate these components. The resulting specific binding component, which represents Aβ burden, can be then transformed into Centiloids.



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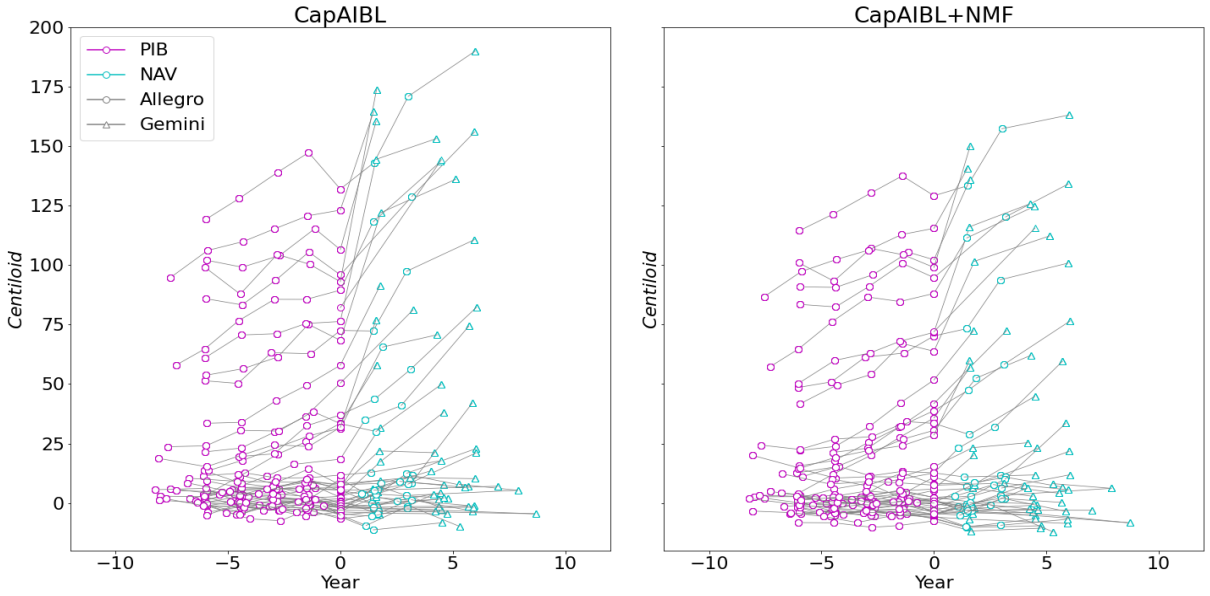
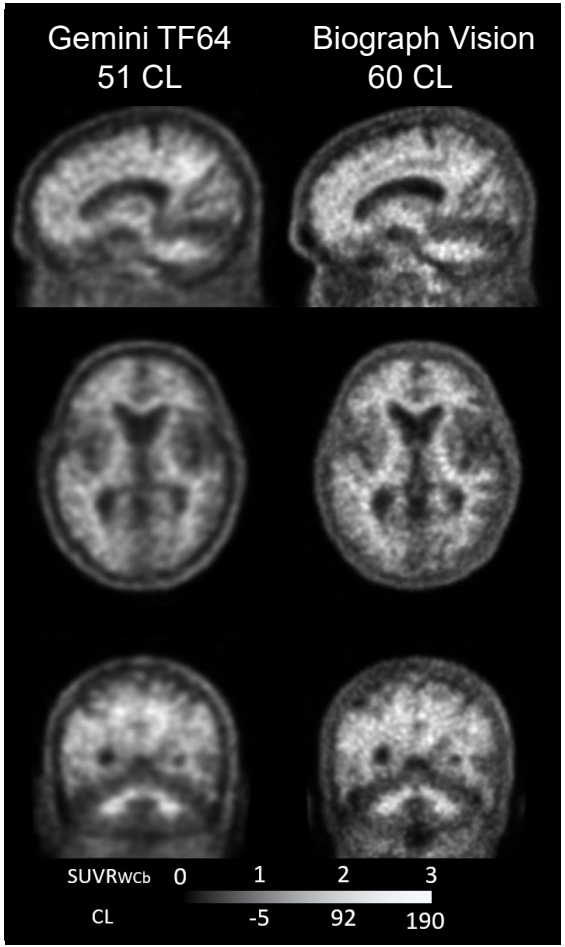
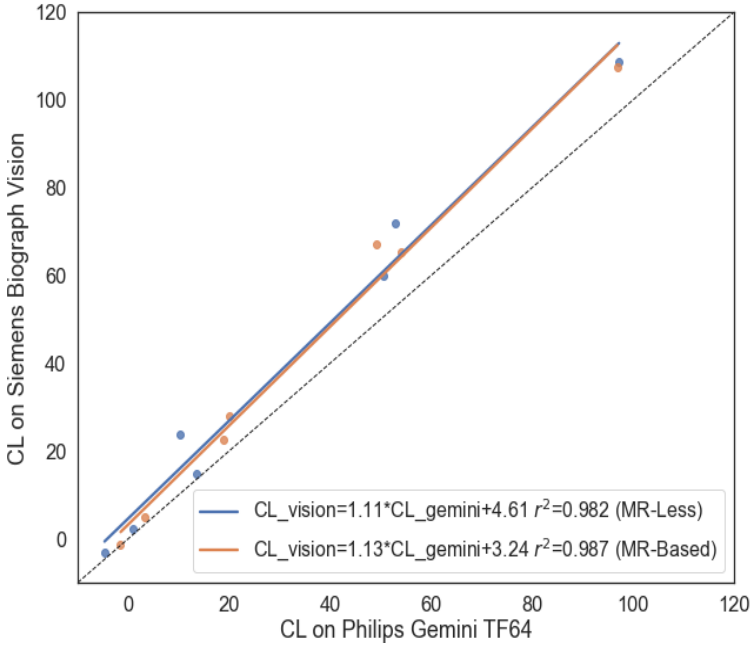


Effect of digital PET scanners



Head-to-Head comparison between Philips Gemini TF64 and Siemens Biograph Vision 600 for brain amyloid Centiloid quantitation

S Li, P Bourgeat, S Bozinovski, K Huang, R Guzman, R Williams, J Fripp, VL Villemagne, CC Rowe, V Dore



Digital PET scanner

- *~15% higher values*
- *Higher resolution*
- *Half the injected dose*

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Session III:
Quantitative Brain Amyloid PET Imaging Methodology, Metrics, Analytical Validity

FDA-CDER-CDRH, SNMMI, and MITA Workshop:

Quantitative PET Brain Amyloid

November 17, 2022

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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.

Session III: Topics for Discussion

- Do you envision AI/ML analysis techniques playing a significant role in amyloid quantitation in the future?
- What factors contribute to the variability with different quantitative metrics? Which factor do you think contributes the most variability?
- How to address variability with longitudinal metrics and best practices for controlling variability?
- Is there enough added value with amyloid quantitation considering the variability introduced?
- Centiloid composite measures vs regional (and what is the usefulness of regional values?)
- Value of z-score when looking at regional data and composite Centiloid thresholds.


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