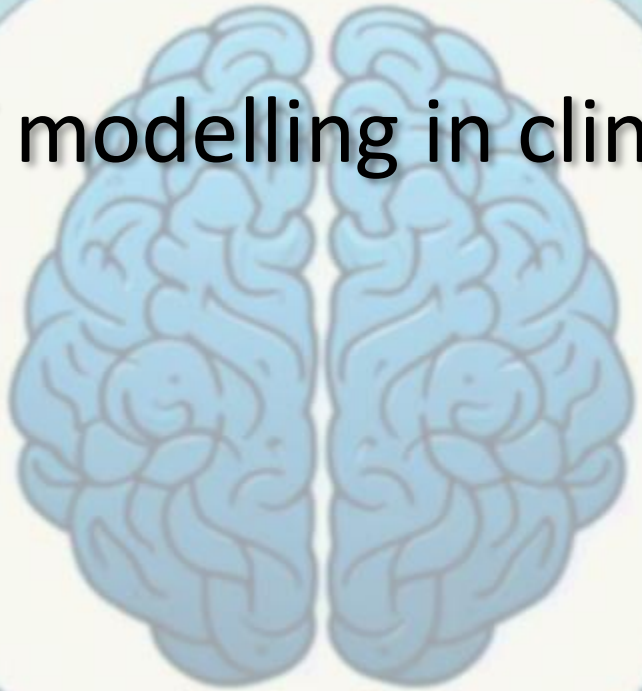
Brain-PET modelling in clinical studies



Marco Bucci, PhD, Docent
Turku PET Centre and Karolinska Institutet

Outline

- Modelling (methods)
  - Kinetic modelling vs Statistical modelling
  - From visual to quantitation
  - Input function modelling

- Brain FDG in research and clinic
  - Metabolic field – Obesity and Diabetes

- Amyloid PET in dementia research and tertiary memory clinic
  - VR vs SUVR

- Tau PET (and Amyloid PET) in research and tertiary memory clinic
  - ATN paper – metaROI and LMM
  - VR and Plasma Biomarkers and LASSO
  - SuStaIn
  - ML Clustering

Modelling methods in Brain PET imaging: Kinetic vs Statistical models

Kinetic models

- designed to describe and quantify the underlying biological processes that govern the behaviour of the radiotracer within the brain.
- based on physiological and biochemical principles and involve the estimation of parameters related to these processes.
- Examples: Compartmental models, Receptor Binding models, Graphical Models, Spectral Analysis

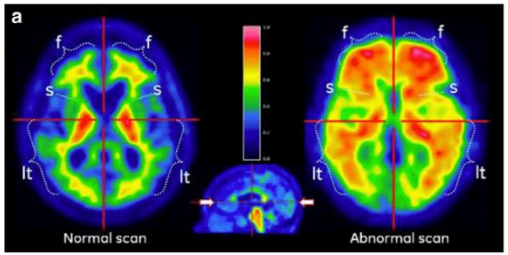
Statistical models

- focused on the statistical properties of the PET signal, often using data-driven approaches to analyze or interpret the imaging data.
- they may not directly describe the underlying biological processes but are useful for extracting patterns, trends, and significant differences in the data.
- Examples: Statistical Parametric Mapping (Atlas ROIs or Clusters), Machine Learning (ML) models (supervised, unsupervised, deep learning, LASSO), Bayesian models

Modelling methods in Brain PET imaging

Modelling: the process of creating mathematical or computational representations that describe and quantify the underlying biological, physiological, or biochemical processes that govern the distribution, kinetics, and interaction of a radiotracer within the brain.

Visual reading

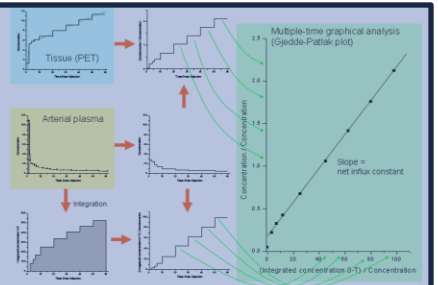


(Non-compart.) Semi-quantitative methods

$$SUV = \frac{[radioph.](kBq/mL)}{\frac{injected\ activity\ (MBq)}{normalizing\ fct\ (BW,BSA,LBM,..)}}$$

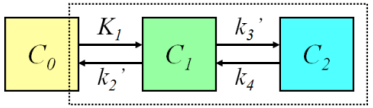
$$SUVR = \frac{SUV\ Target\ region\ (brain\ ROI)}{SUV\ Reference\ region\ (brain\ ROI)}$$

Input-function indep.



Input-function dep.

Fully quantitative methods



Dynamic PET and Input-function dep.

Input recovery method: improve quality of sampled input functions

metabolites

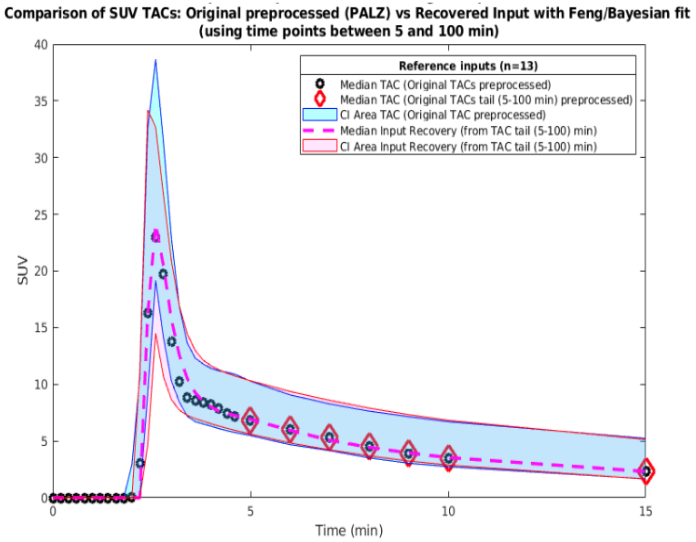
MDPI

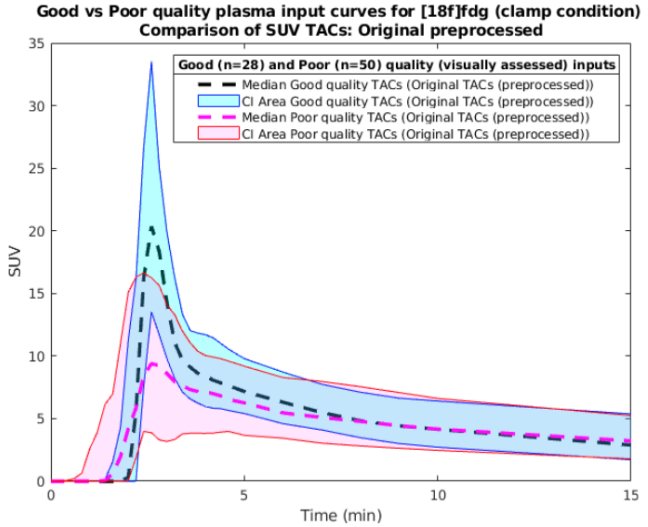
Article

Kinetic Modelling of Brain [18-F]FDG PET time activity curves with Input Function Recovery (IR) method

Marco Bucci [1,2,3,4,5,*], Eleni Rebelos [2], Vesa Oikonen [2], Juha Rinne [1], Lauri Nummenmaa [2,6], Patricia Iozzo [7] and Pirjo Nuutila[2,8]

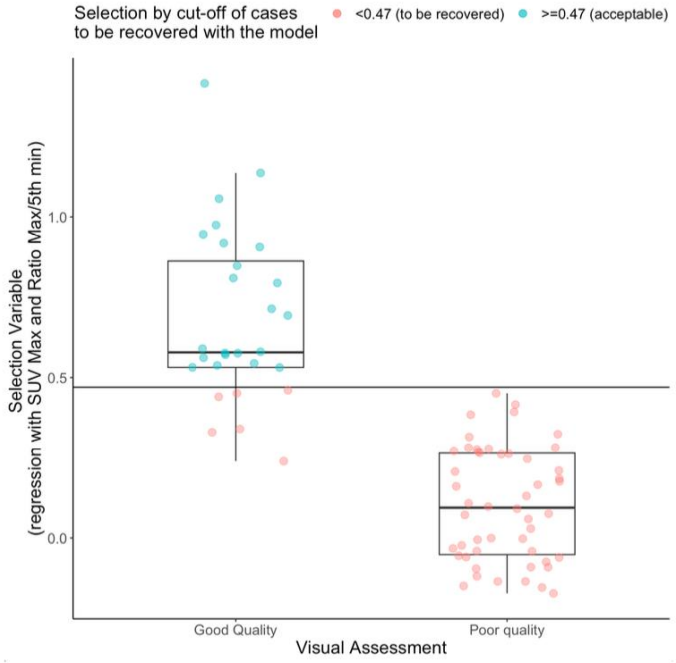
Validation of IR method

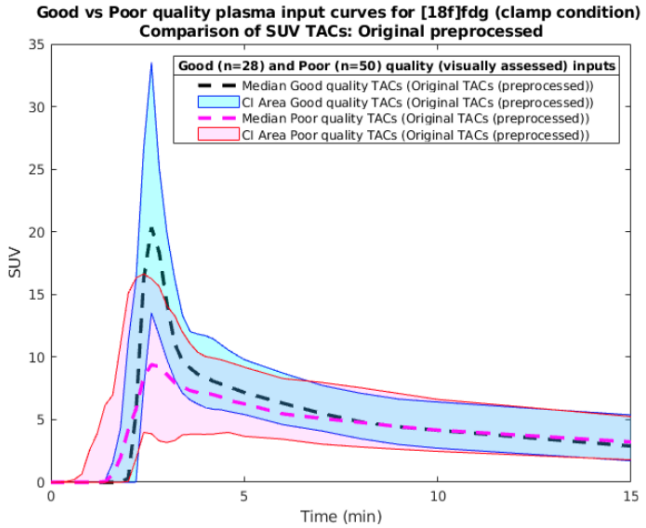




Bucci et al. Metabolites 2024

Validation of IR method





Bucci et al. Metabolites 2024

Validation of IR method

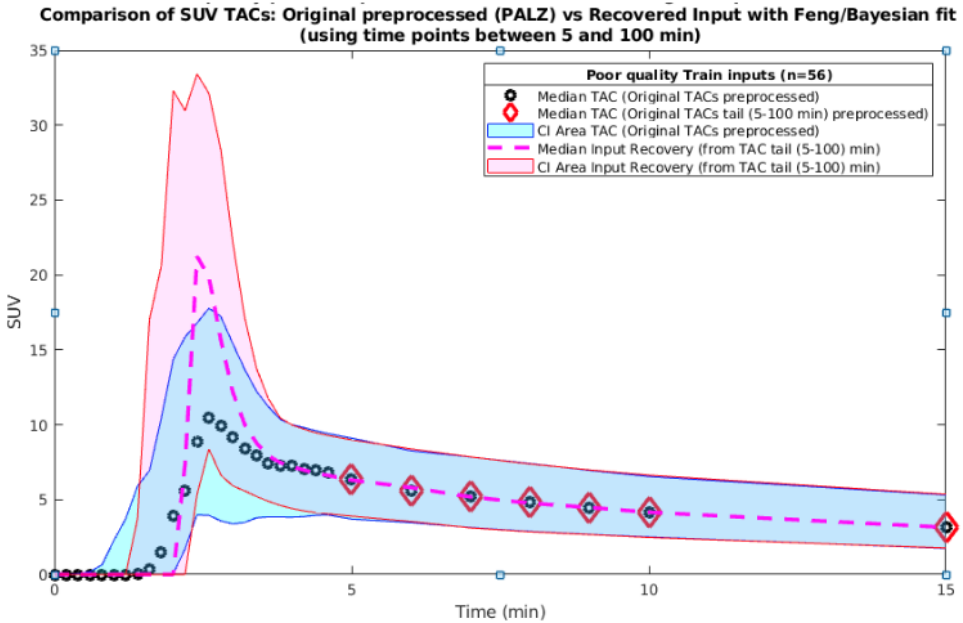
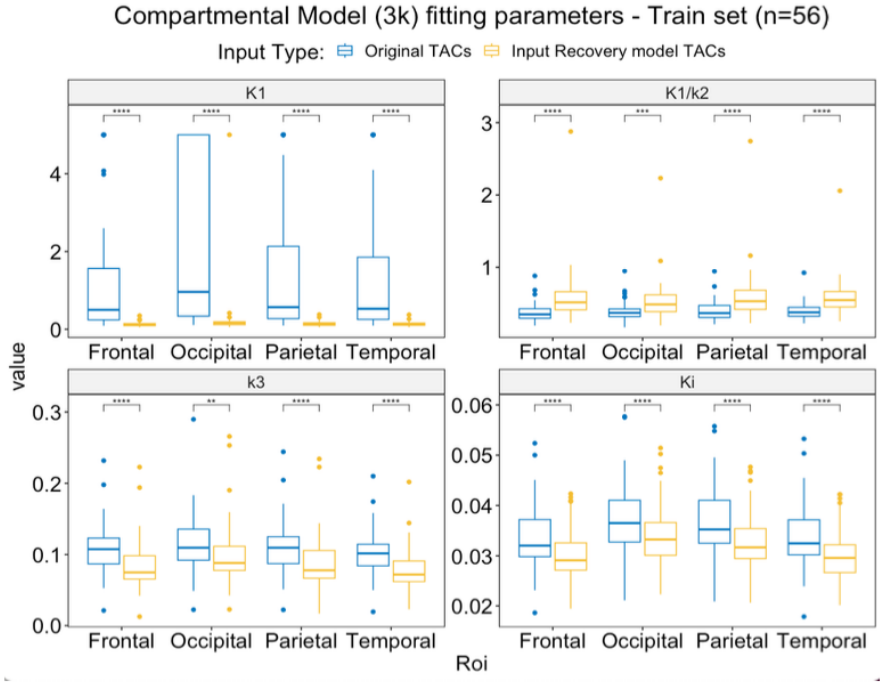


Figure 6. Poor-quality Input TACs (Train set, n = 56) – Original and Recovered by the Feng-Bayes model. The peak is recovered while the tail is kept similar to the original curves.

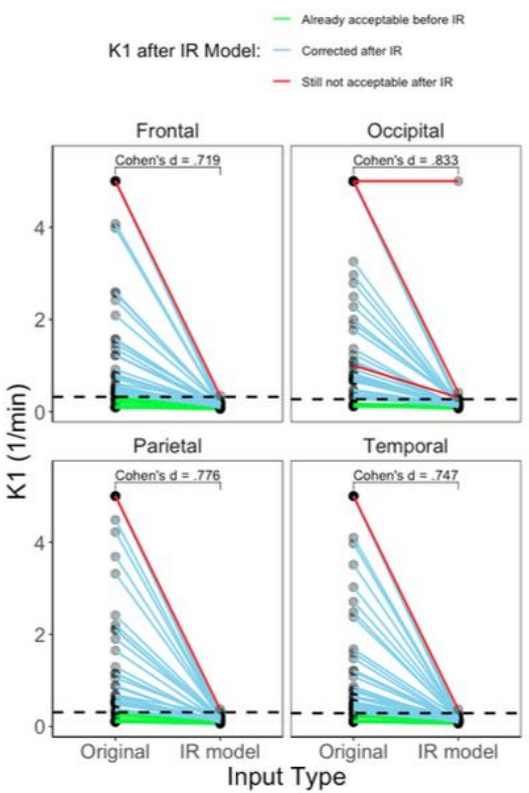
Bucci et al. Metabolites 2024

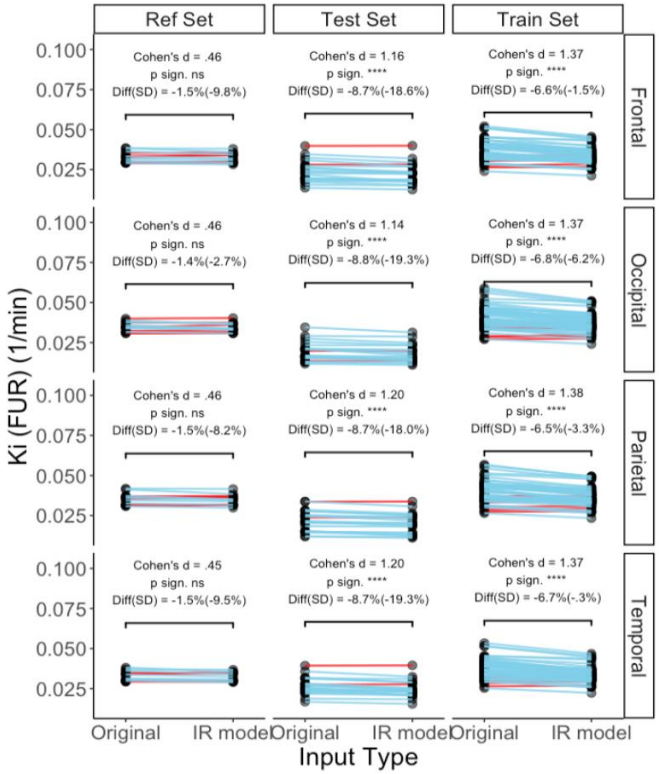
Results (1) from IR method applied to the train set



Bucci et al. Metabolites 2024

Results (2): K1 of train set and FUR of all sets





Bucci et al. Metabolites 2024

Methods in Brain PET imaging: Input modelling conclusions

- Input function quality affects modelling parameters and should be corrected when possible
- Input recovery from samples of the tail of the time activity curve in the plasma is a feasible method of correction
- There are also different ways to derive input from image but good quality images (not suitable for old scans) and arteries should be in the Field Of View. (not shown)

Brain PET: FDG

Brain FDG: Example of Metabolic Study

Insulin Resistance Is Associated With Enhanced Brain Glucose Uptake During Euglycemic Hyperinsulinemia: A Large-Scale PET Cohort

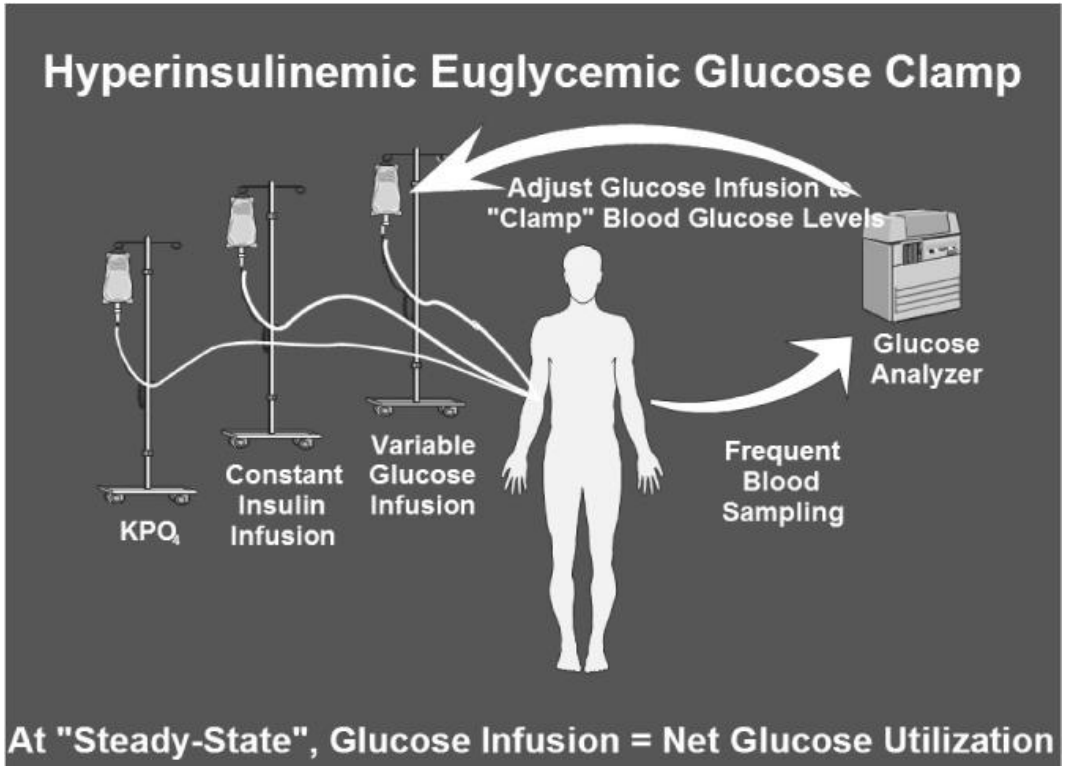
Eleni Rebelos,[1] Marco Bucci,[1] Tomi Karjalainen,[1] Vesa Oikonen,[1] Alessandra Bertoldo,[2] Jarna C. Hannukainen,[1] Kirsi A. Virtanen,[1,3] Aino Latva-Rasku,[1] Jussi Hirvonen,[4] Ilkka Heinonen,[1,5] Riitta Parkkola,[4] Markku Laakso,[6] Ele Ferrannini,[7] Patricia Iozzo,[1,7] Lauri Nummenmaa,[1,8] and Pirjo Nuutila[1,9]

Diabetes Care 2021;44:788–794 | https://doi.org/10.2337/dc20-1549

- Type of modelling: semiquantitative (BGU, brain glucose uptake (graphical analysis (FUR, fractional uptake rate))
- Type of statistical inference: Bayesian

HYPERINSULINEMIC EUGLYCEMIC GLUCOSE CLAMP TECHNIQUE

TO MEASURE THE WHOLE BODY GLUCOSE DISPOSAL DURING INSULIN STIMULATION

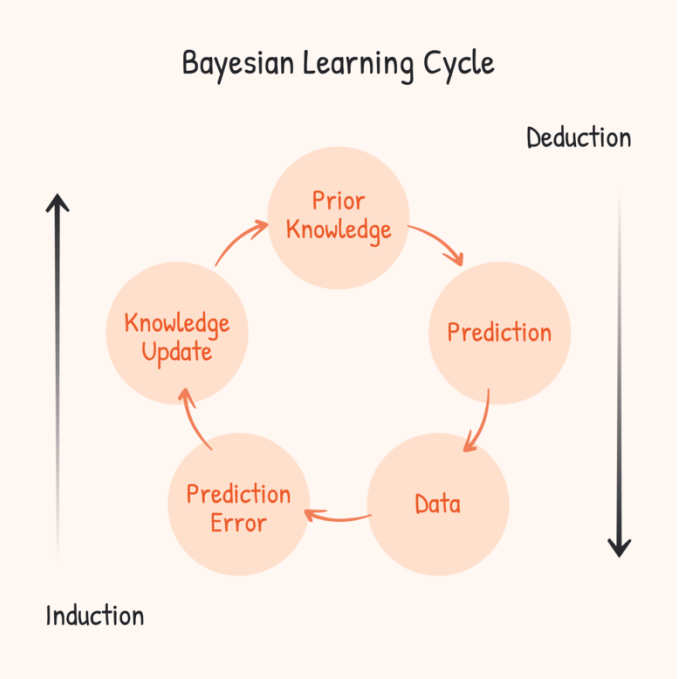


The **m-value** (or **glucose infusion rate, GIR**) represents the amount of glucose that needs to be infused per minute to maintain a constant euglycemic state (normal blood glucose level) during a hyperinsulinemic-euglycemic clamp study. The higher the m-value, the more insulin-sensitive the subject is, as it indicates that more glucose needs to be infused to maintain blood glucose levels in the presence of high insulin.

Figure from: [Kim et al., J Korean Endocr Soc. 2009 Jun;24(2):75-83]

Statistical inferences: Bayesian vs frequentist

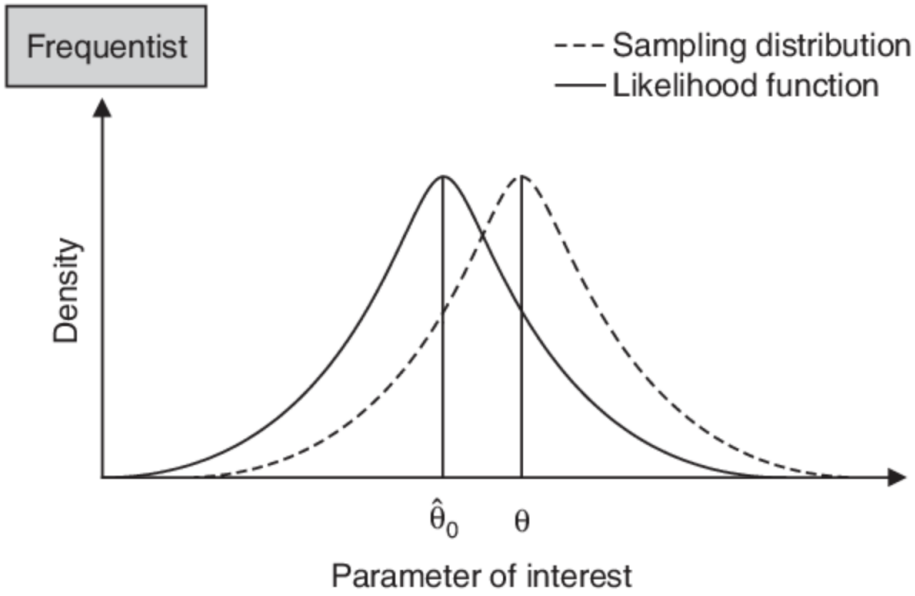
- Bayesian modelling

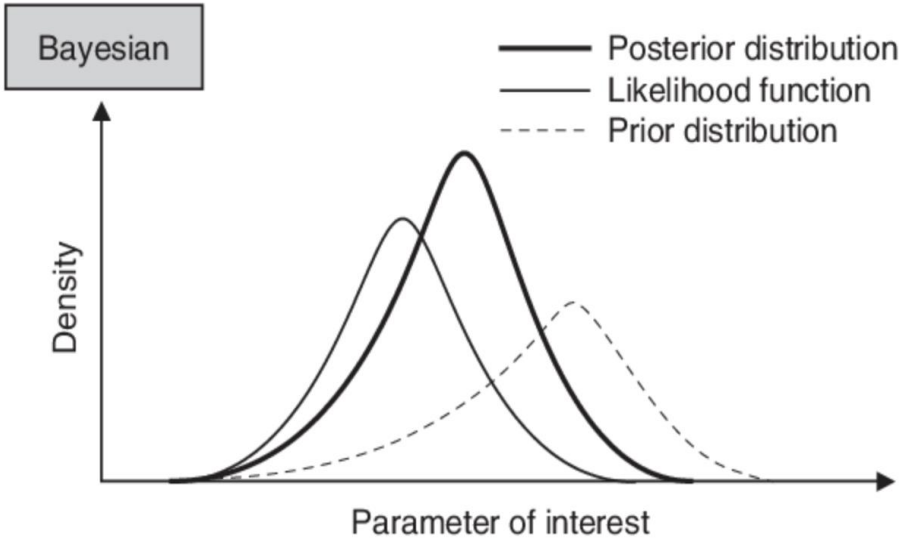


Bayesian vs. Frequentist Summary

Attributes:	Bayesian:	Frequentist:
What is it?	Probability distribution around the parameters	Parameters are fixed and a single point
What does it question?	Given the data, what is the probability of the hypothesis?	Is the hypothesis true or false?
What does it require?	Prior knowledge/information and any dataset.	A stopping criterion
What does it output?	A for or against probability about the hypothesis.	point estimate (p-value)
Main advantage	Backed up with evidence and can apply new information	They are simple and easy to use, and does not need prior knowledge
Main disadvantage	Requires advanced statistics	Highly dependent on the sample size, and only give a yes or no output
When should I use it?	Limited your data when you have priors Uses more computing power	With a large amount of data

Statistical inferences: Bayesian vs frequentist





Source: Skrepnek, G.H. (2007) Pharmaeconomics, 25(8): 649-64

Brain FDG: Posterior distributions predicting BGU

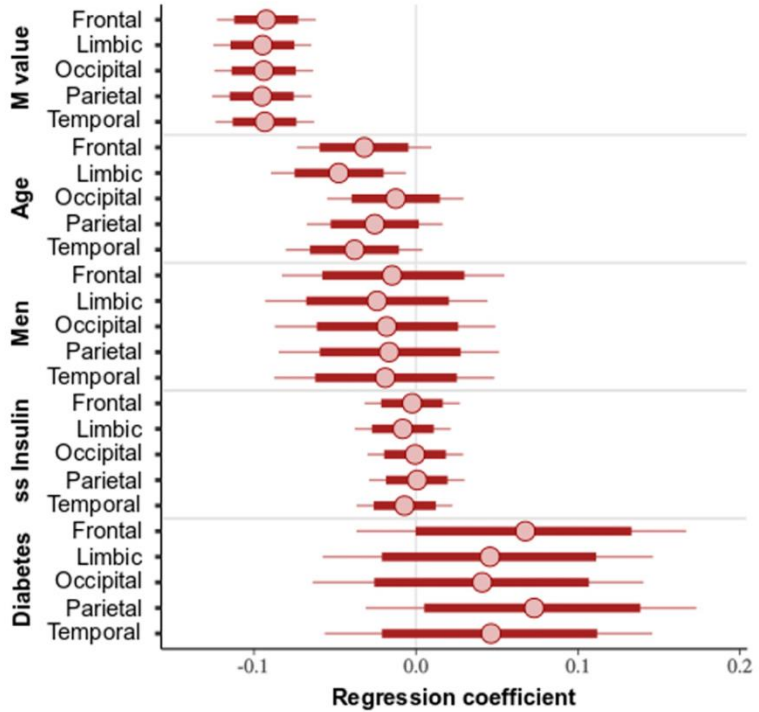


Figure 2—Posterior intervals of the regression coefficients for the variables of interest predicting BGU. The thick lines represent the 80% posterior intervals, the thin lines represent the 95% posterior intervals, and the circles represent posterior means. ss, steady state.

Table 1—Anthropometric and biochemical characteristics of the study participants

	Men (n = 63)			Women (n = 131)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	56	11	20–69	56	14	23–80
BMI (kg · m^{-2})	29	6	22–48	30	7	19–51
HbA_{1c}						
%	5.6	0.3	5.1–6.3	5.6	0.4	4.9–7.1
mmol/mol	38	4	32–45	38	8	30–54
M value (μmol · kg_{FFM}^{-1} · min^{-1})	40.2	24.5	7.9–130.8	49.1	25.3	10.3–138.2
Type 2 diabetes, n (%)	7 (11)			20 (15)		

The **m-value** (or **glucose infusion rate, GIR**) represents the amount of glucose that needs to be infused per minute to maintain a constant euglycemic state (normal blood glucose level) during a hyperinsulinemic-euglycemic clamp study. The higher the m-value, the more insulin-sensitive the subject is, as it indicates that more glucose needs to be infused to maintain blood glucose levels in the presence of high insulin.

Rebelos et al., Diabetes Care, 2021

Brain FDG: Posterior distributions predicting BGU

Higher BGU is associated with lower M-Value (insulin resistance)) probably due to increased brain inflammation

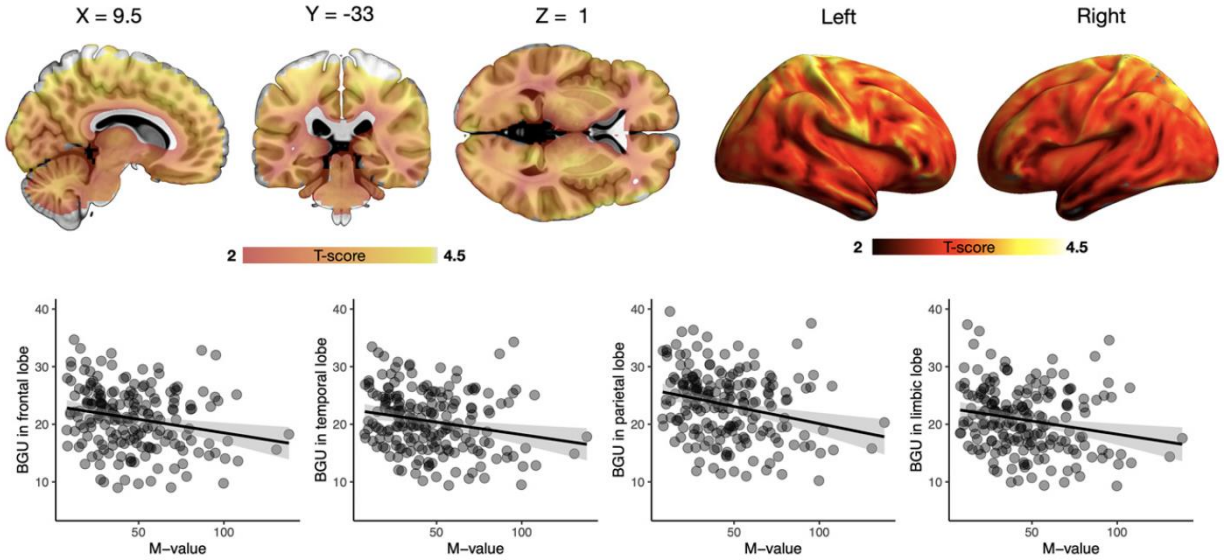


Figure 3—Brain clusters (as defined by false discovery rate–corrected statistical parametric mapping one-sample *t* test) for the association between BGU during clamp and M value and the corresponding scatterplots.

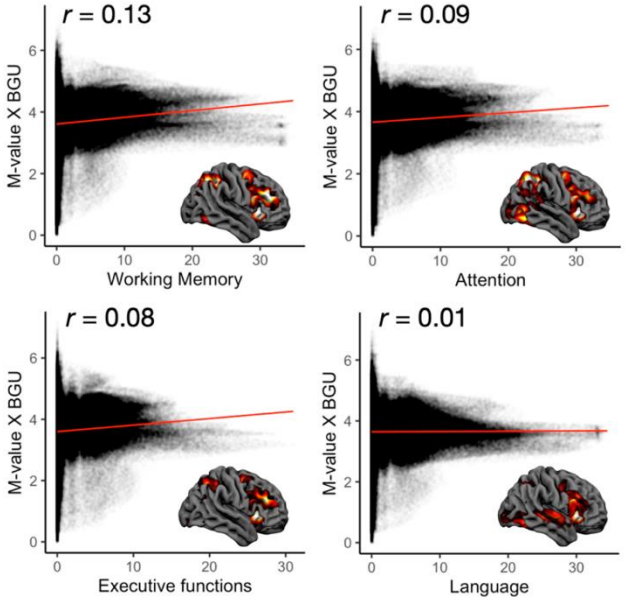


Figure 4—Spatial correlation between the regional M value–dependent insulin-stimulated BGU (*y*-axis) and meta-analytic blood oxygenation level–dependent functional MRI activation patterns for four basic cognitive functions retrieved from the Neurosynth database (https://www.neurosynth.org). These results show how well the M value–dependent BGU effects correspond with cerebral localization of different cognitive functions.

Rebelos et al., Diabetes Care, 2021

Brain PET: Amyloid (Flutemetamol)

Pathological mechanisms involved in AD

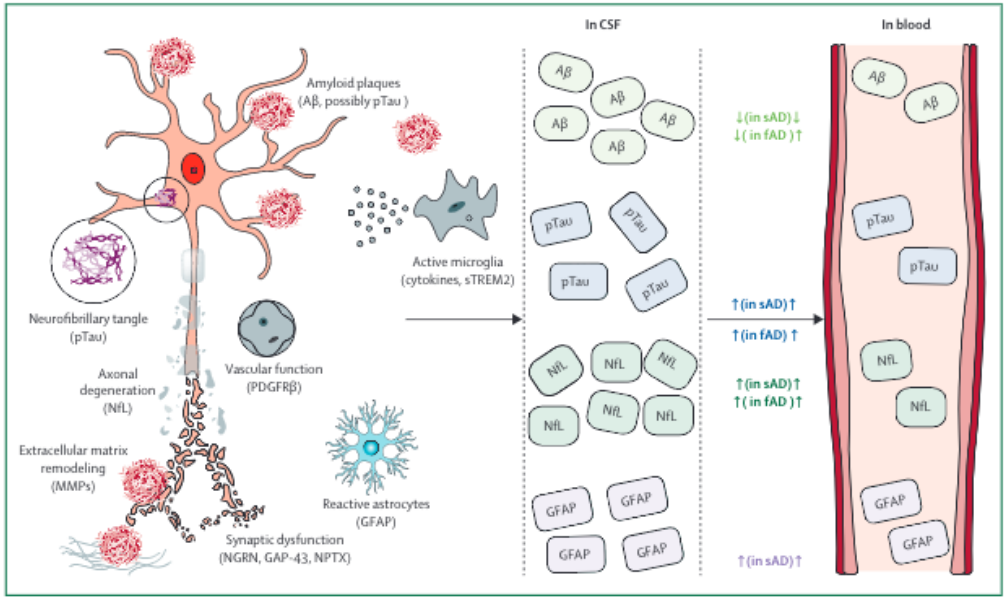


Figure 1: **Pathological mechanisms involved in Alzheimer's disease and their associated biofluid-based biomarkers**
Alzheimer's disease has a complex pathophysiology. Biofluid-based biomarkers that can be reliably measured in both blood and CSF are: Aβ, pTau, NfL, and GFAP. Biomarkers with strong potential in CSF only include: cytokines, sTREM2, PDGFRβ, MMPs, NGRN, GAP-43, and NPTX. Aβ=amyloid β. NfL=neurofilament light chain. pTau=phosphorylated tau. GFAP=glial fibrillary acidic protein. MMP=matrix metalloproteinase. sAD=sporadic Alzheimer's disease. fAD=familial Alzheimer's disease.

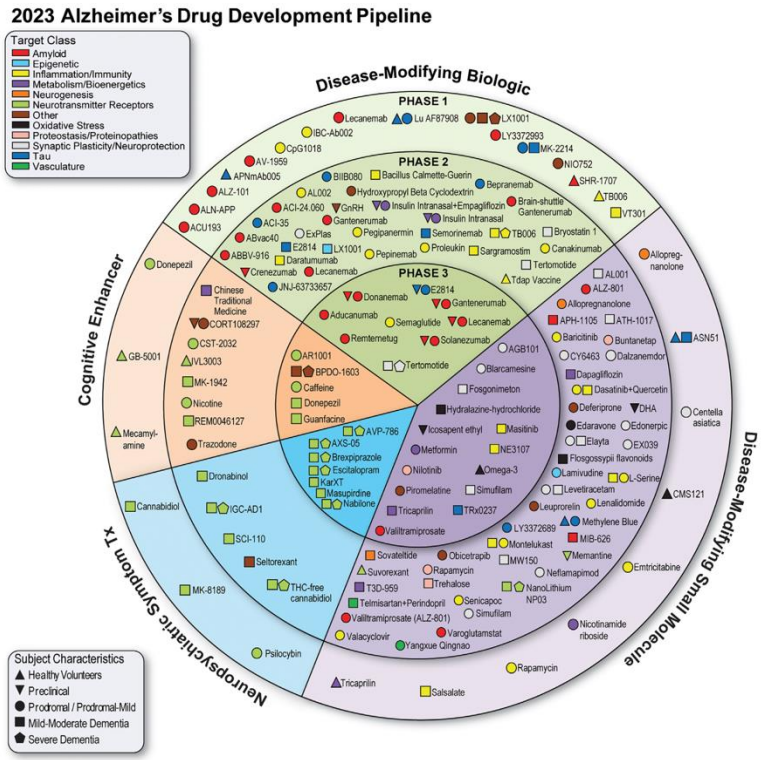


Figure from Teunissen et al., Lancet Neurol., 2022; Cummings et al., A&D, 2023

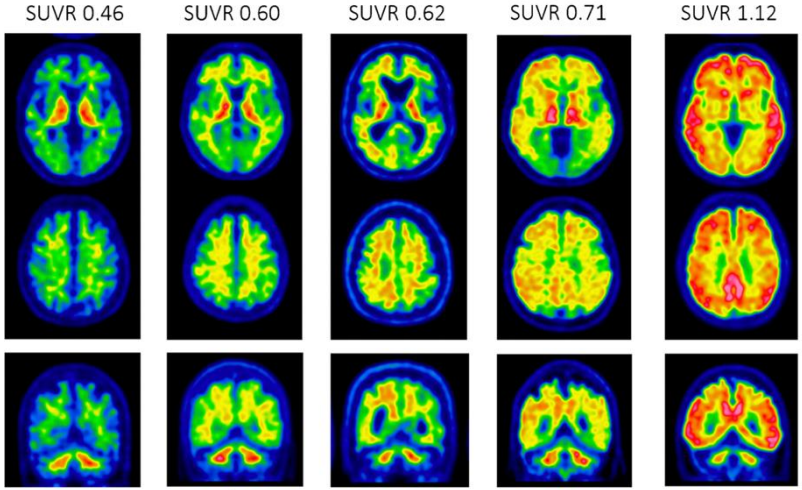
Brain Amyloid PET: VR vs SUVR discordance

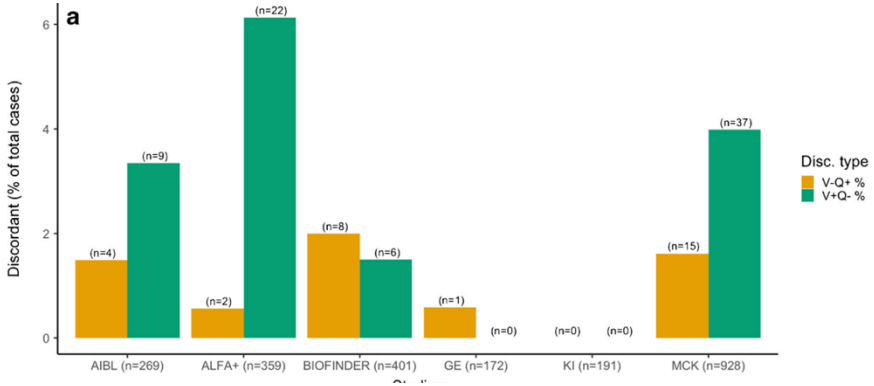
European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2183–2199
https://doi.org/10.1007/s00259-021-05311-5

ORIGINAL ARTICLE

A multisite analysis of the concordance between visual image interpretation and quantitative analysis of [^{18}F]flutemetamol amyloid PET images

Marco Bucci[1] · Irina Savitcheva[2] · Gill Farrar[3] · Gemma Salvadó[4,5] · Lyduine Collij[6] · Vincent Doré[7,8] · Juan Domingo Gispert[4,5,9,10] · Roger Gunn[11,12] · Bernard Hanseeuw[13,14] · Oskar Hansson[15] · Mahnaz Shekari[4,5,9] · Renaud Lhommel[13] · José Luis Molinuevo[4,5,9,16] · Christopher Rowe[7,17] · Cyrille Sur[18] · Alex Whittington[11] · Christopher Buckley[3] · Agneta Nordberg[1,19]





	V+Q- (n=37)	V-Q+ (n=14)	Total (n=51)	p value
Diagnosis				0.014
HC	7 (50 %)	7 (50 %)	14	
HC(ADO)	22 (91.7 %)	2 (8.3 %)	24	
SCD	2 (40 %)	3 (60 %)	5	
MCI	4 (66.7 %)	2 (33.3 %)	6	
AD	1 (100 %)	0 (0 %)	1	
nonAD	1 (100 %)	0 (0 %)	1	

Brain Amyloid PET: VR vs SUVR paper discordance: sensitivity analysis

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2183–2199
https://doi.org/10.1007/s00259-021-05311-5

ORIGINAL ARTICLE

A multisite analysis of the concordance between visual image interpretation and quantitative analysis of [^{18}F]flutemetamol amyloid PET images

Marco Bucci[1] · Irina Savitcheva[2] · Gill Farrar[3] · Gemma Salvadó[4,5] · Lyduine Collij[6] · Vincent Doré[7,8] · Juan Domingo Gispert[4,5,9,10] · Roger Gunn[11,12] · Bernard Hanseeuw[13,14] · Oskar Hansson[15] · Mahnaz Shekari[4,5,9] · Renaud Lhommel[13] · José Luis Molinuevo[4,5,9,16] · Christopher Rowe[7,17] · Cyrille Sur[18] · Alex Whittington[11] · Christopher Buckley[3] · Agneta Nordberg[1,19]

Different sites, maybe necessary harmonization (ComBat) or CL scaling

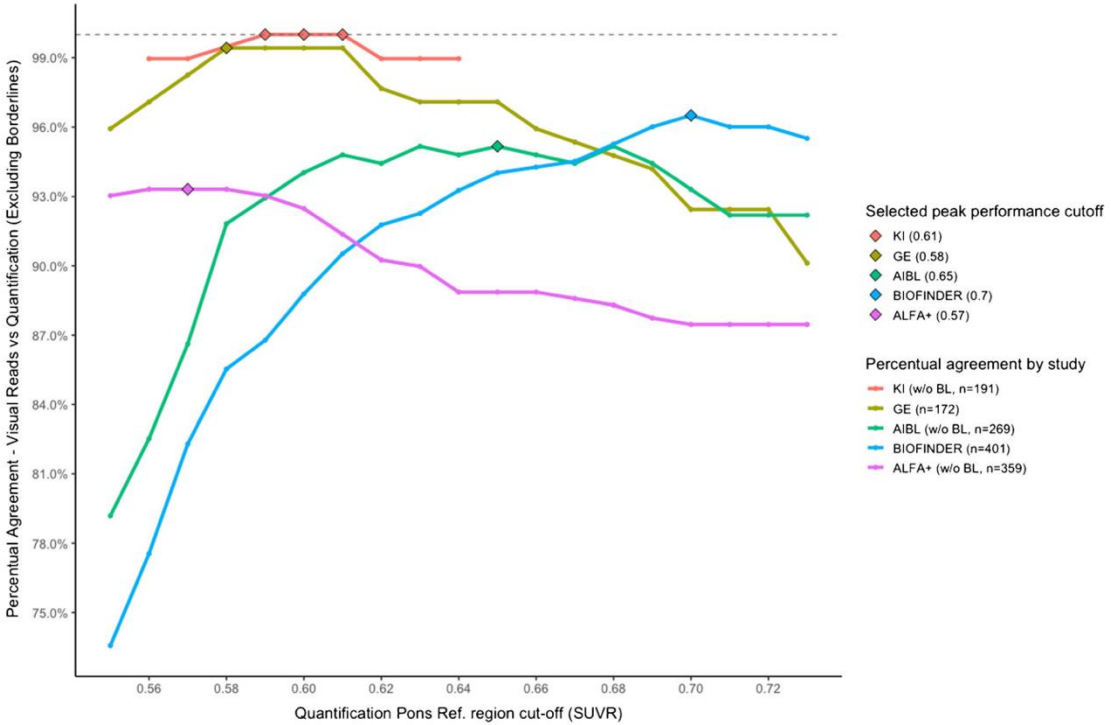


Fig. 1 Change in % agreement between visual and quantitative image interpretation around the SUVr pons threshold of 0.55 to 0.74 (with borderlines (BL) excluded). Note: The number of BL cases excluded is 21, 2 and 7 for KAROLINSKA, ALFA+ and AIBL, respectively

Brain Amyloid PET: VR vs SUVR paper discordance: sensitivity analysis

	V-Q+ (N=21)	V+Q- (N=4)	Total (N=25)	p value
Progression to any clinical diagnosis				0.524
Clinical progression	14 (66.7%)	2 (50.0%)	16 (64.0%)	
stable	7 (33.3%)	2 (50.0%)	9 (36.0%)	
Progression to AD/Other Diagnosis				0.322
Progression to AD	8 (38.1%)	0 (0.0%)	8 (32.0%)	
Progression to Other Diagnosis	6 (28.6%)	2 (50.0%)	8 (32.0%)	
stable	7 (33.3%)	2 (50.0%)	9 (36.0%)	
Progression in detail				0.206
HC to SCD	1 (4.8%)	1 (25.0%)	2 (8.0%)	
MCI to AD	4 (19.0%)	0 (0.0%)	4 (16.0%)	
MCI to Parkinsonian	2 (9.5%)	0 (0.0%)	2 (8.0%)	
SCD to AD	4 (19.0%)	0 (0.0%)	4 (16.0%)	
SCD to MCI	0 (0.0%)	1 (25.0%)	1 (4.0%)	
SCD to Parkinsonian	1 (4.8%)	0 (0.0%)	1 (4.0%)	
SCD to Vascular	2 (9.5%)	0 (0.0%)	2 (8.0%)	
stable	7 (33.3%)	2 (50.0%)	9 (36.0%)	

- Performing **Competing Risk Regression** analysis that took advantage of the full follow-up data (up to 7 years), using censoring similar to a survival analysis and discounting the contribution of the competing events (AD and OD progression):
- the **V-Q+ discordant cases were 11%** (CI 95%: 4%-34%) **more likely to progress to AD than V+Q- discordant cases** ($p<0.001$).

Table from Bucci et al., EJNMMI 2021 (https://doi.org/10.1007/s00259-021-05311-5)

Brain PET: Amyloid (Flutemetamol) + Tau (Fluortaucipir)

AD biomarkers: the AT(N) framework

- Some of the AD biomarkers are designed to target AD-specific changes, such as the deposition of amyloid-β (A) and tau (T), while others the downstream neurodegeneration (N).

- The AT(N) framework from Jack et al (2018):
  - A - Amyloid-β (PET or CSF)
  - T – Tau (PET or CSF p-tau)
  - (N) – Neurodegeneration (MRI, CSF t-tau, FDG PET)

- Note that in the original formulation the biomarkers in the same category (A,T or N) can be used indistinctively!

ATN paper: aims

a) to assess the agreement/concordance of the imaging and CSF biomarkers across the ATN components and as ATN profiles;

b) to evaluate which of the investigated biomarkers proves better in predicting prospective cognitive decline.

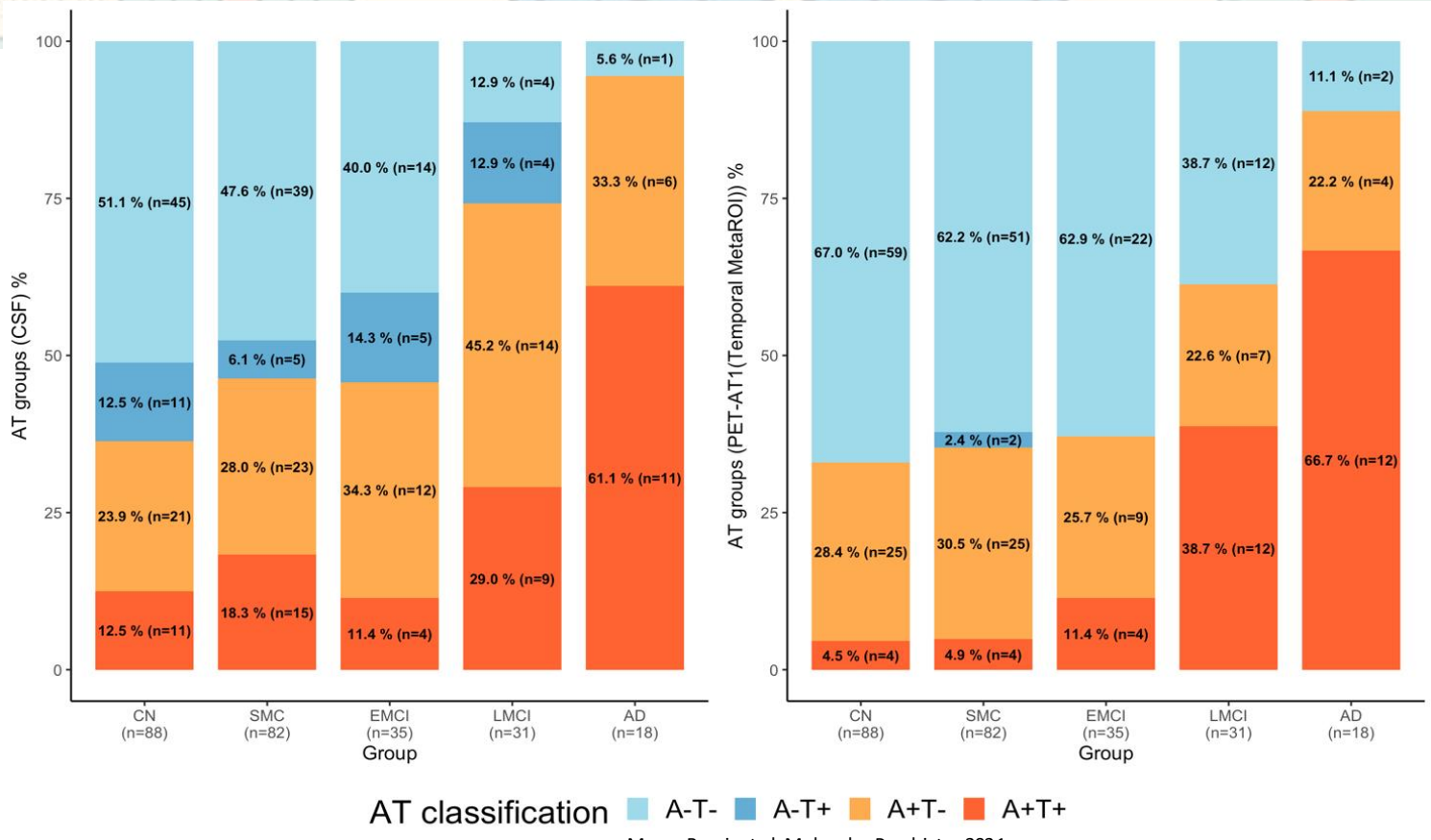
ATN paper: General characteristics

	CN (N=88)	SMC (N=82)	EMCI (N=35)	LMCI (N=31)	AD (N=18)	Total (N=254)	p value
Age, years							0.556[1]
Mean (SD)	72.9 (7.4)	71.3 (6.5)	72.3 (7.8)	73.6 (8.4)	72.1 (9.7)	72.3 (7.5)	
Range	56.0 - 90.4	57.1 - 90.4	57.8 - 88.1	55.9 - 88.2	55.5 - 87.8	55.5 - 90.4	
Sex							< 0.001[2]
M	37 (42.0%)	25 (30.5%)	21 (60.0%)	19 (61.3%)	14 (77.8%)	116 (45.7%)	
F	51 (58.0%)	57 (69.5%)	14 (40.0%)	12 (38.7%)	4 (22.2%)	138 (54.3%)	
Education, years							0.074[1]
Mean (SD)	17.1 (2.0)	16.5 (2.1)	16.3 (2.9)	15.9 (2.4)	16.2 (2.7)	16.6 (2.3)	
Range	12.0 - 20.0	12.0 - 20.0	12.0 - 20.0	10.0 - 20.0	12.0 - 20.0	10.0 - 20.0	
APOE4 carrier							0.040[2]
Missing (n)	0	1	0	0	0	1	
No	61 (69.3%)	45 (55.6%)	25 (71.4%)	16 (51.6%)	7 (38.9%)	154 (60.9%)	
Yes	27 (30.7%)	36 (44.4%)	10 (28.6%)	15 (48.4%)	11 (61.1%)	99 (39.1%)	
MMSE							< 0.001[1]
Mean (SD)	28.9 (1.2)	29.2 (1.0)	28.4 (1.4)[b]	26.9 (2.6)[a.,b.,c.]	22.3 (1.9)[a.,b.,c.,d.]	28.2 (2.3)	
Range	25.0 - 30.0	26.0 - 30.0	25.0 - 30.0	19.0 - 30.0	17.0 - 26.0	17.0 - 30.0	
CDR							< 0.001[1]
Mean (SD)	0.0 (0.1)	0.0 (0.0)	0.5 (0.1)[a.,b.]	0.5 (0.1)[a.,b.]	0.7 (0.3)[a.,b.,c.,d.]	0.2 (0.3)	
Range	0.0 - 0.5	0.0 - 0.0	0.0 - 0.5	0.0 - 1.0	0.5 - 1.0	0.0 - 1.0	
ADNI mem. comp. score							< 0.001[1]
Mean (SD)	1.1 (0.5)	1.0 (0.5)	0.4 (0.4)[a.,b.]	0.1 (0.5)[a.,b.,c]	-0.8 (0.6)[a.,b.,c.,d.]	0.7 (0.7)	
Range	-0.2 - 2.7	-0.2 - 2.3	-0.3 - 1.4	-1.0 - 0.9	-1.6 - 0.4	-1.6 - 2.7	
Follow up time interval, months							0.002[1]
Missing (n)	43	47	6	1	5	102	
Mean (SD)	20.2 (6.7)	17.3 (6.3)	17.1 (8.0)	14.4 (5.3)[a]	14.4 (5.1)[a]	17.3 (6.8)	
Range	0.0 - 28.2	10.7 - 28.4	3.9 - 36.6	4.1 - 26.3	10.4 - 28.2	0.0 - 36.6	

1) Linear Model ANOVA; 2) Pearson's Chi-squared test ; a,b,c,d denote significant differences respectively with CN, SMC, EMCI and LMCI with Tukey Post Hoc. $p < 0.05$. a.,b.,c.,d. $p < 0.001$

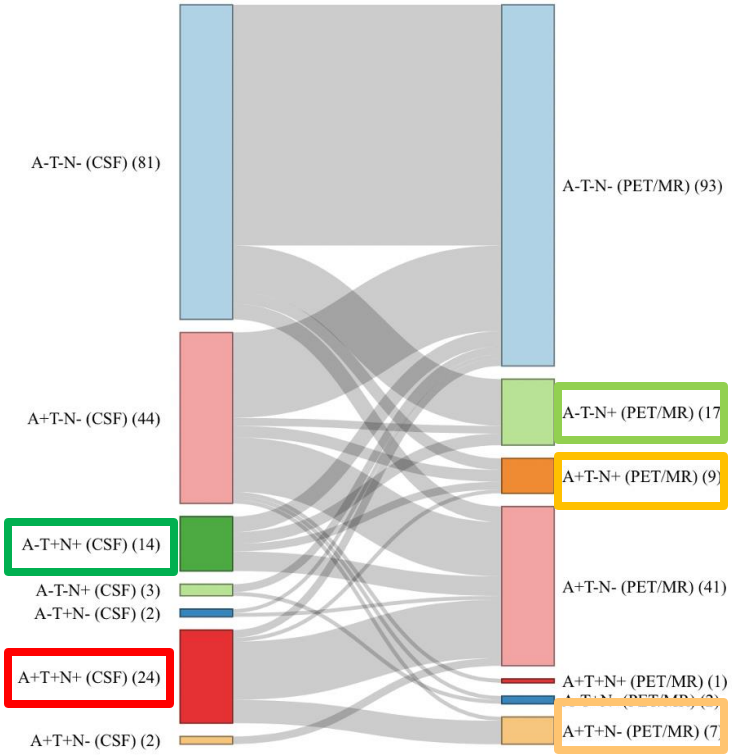
Marco Bucci, et al, Molecular Psychiatry 2021

ATN paper: A/T Profiles – CSF A-T+ > PET

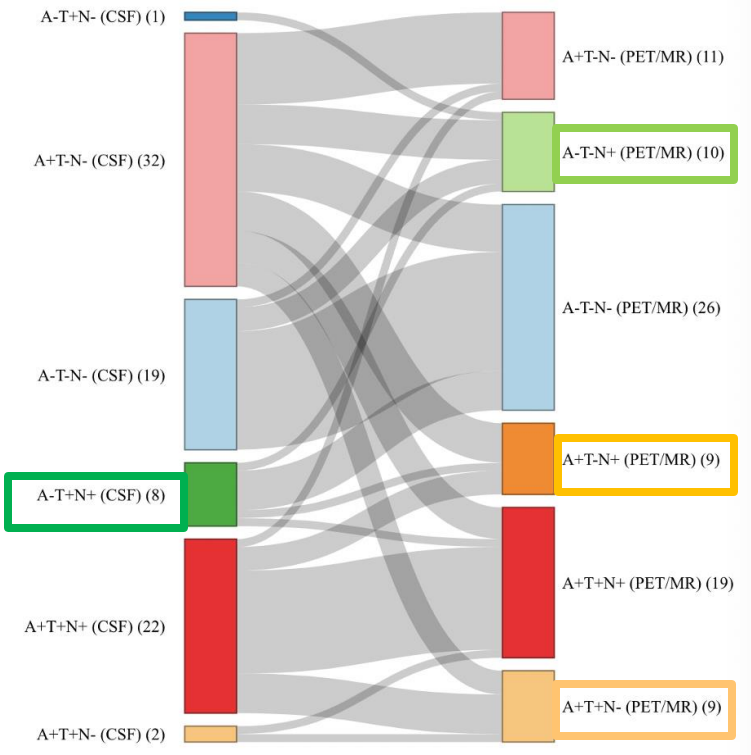


Marco Bucci, et al, Molecular Psychiatry 2021

Results – AT(N) profiles
Discordance between biomarkers



CU (CN,SMC)

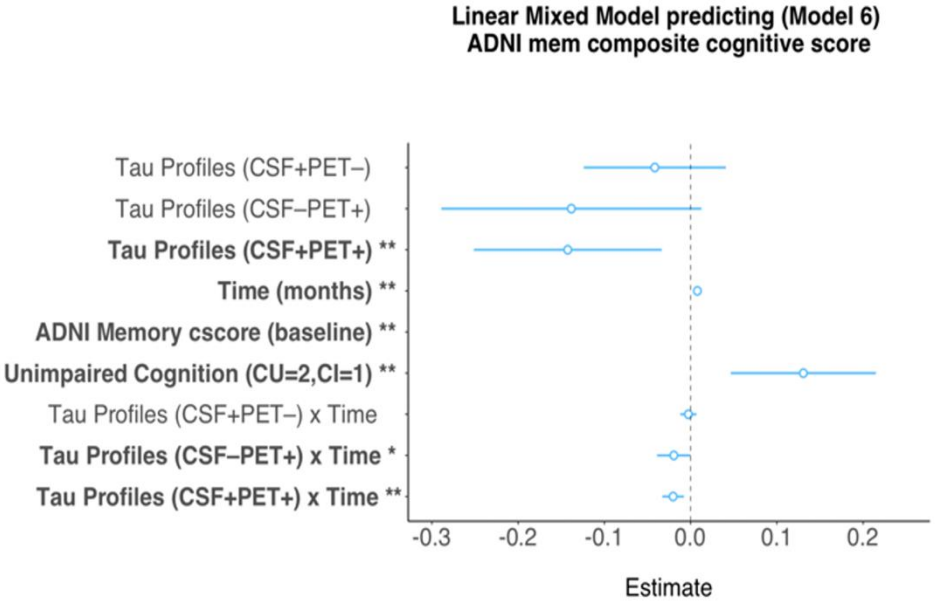


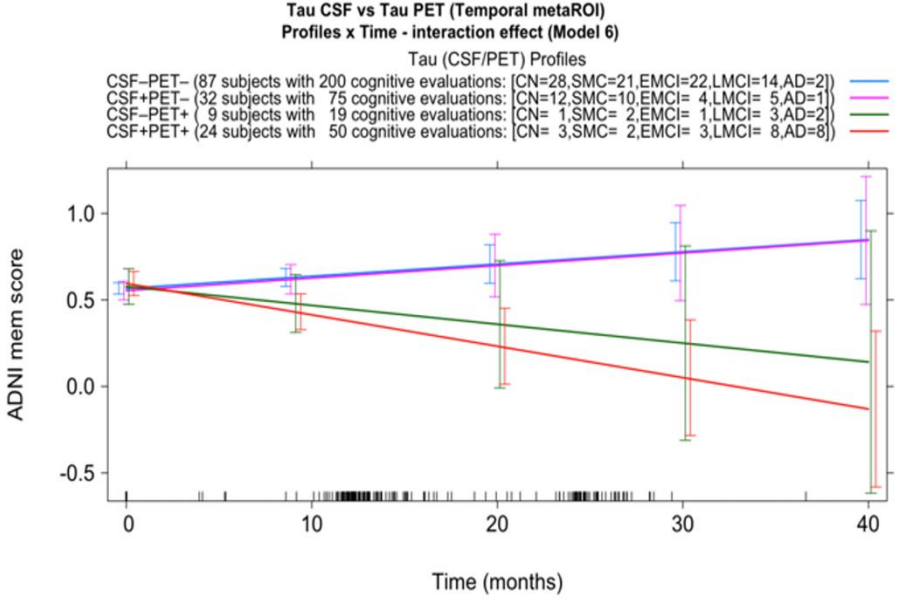
CI (EMCI,LMCI,AD)

Marco Bucci, et al, Molecular Psychiatry 2021

Aim 2 – Prediction of cognitive decline via LMM (Linear Mixed Models)

Results – CSF/PET Tau profiles to predict Cog. Decline: Tau PET better than CSF for prediction

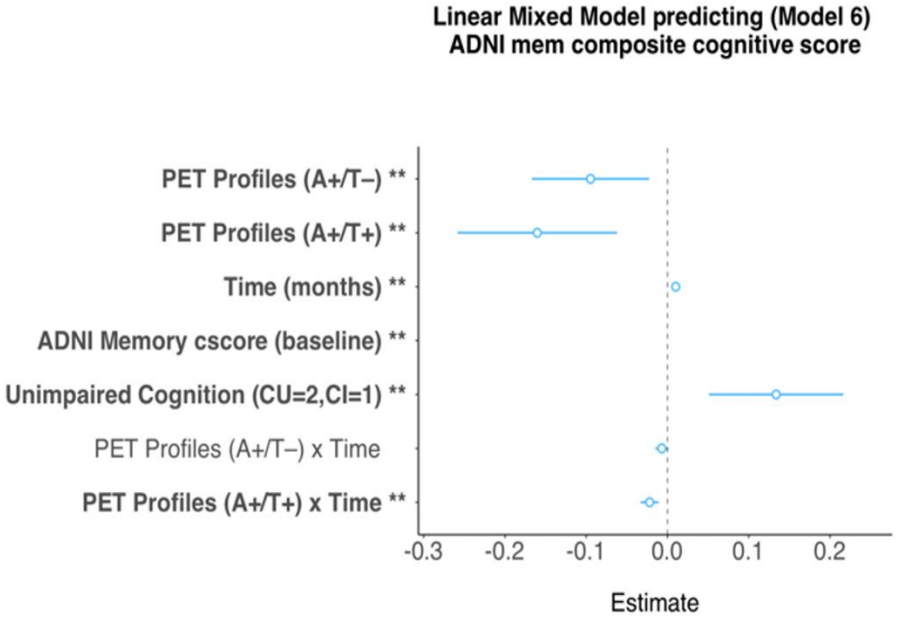


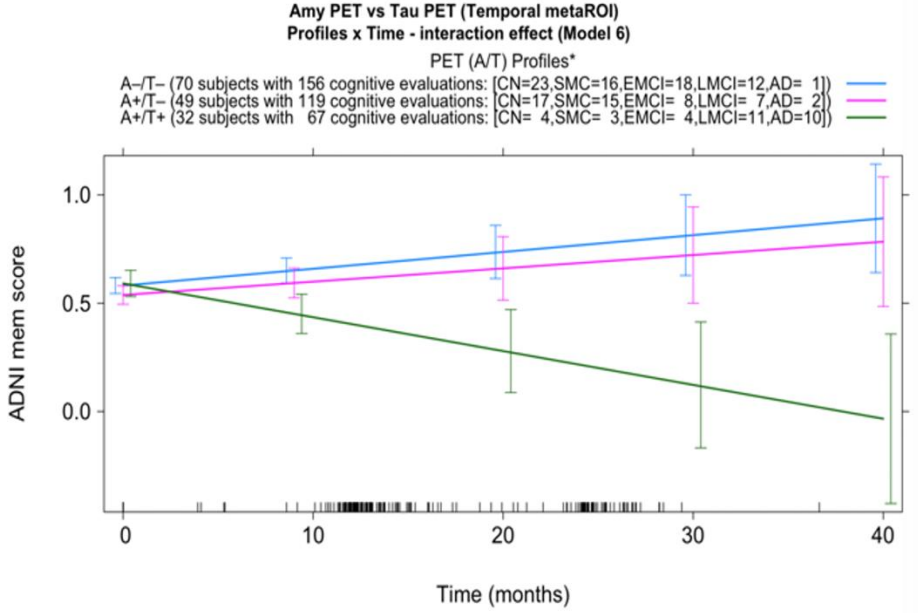


Note: Gender and ApoE4 carrier status were not significant or did not improve the model

** p ≦ 0.01, * p ≦ 0.05

Results – A/T PET profiles to predict Cog. decline
Tau PET is a preferrable predictor to Amy PET





Note: Gender and ApoE4 carrier status were not significant or did not improve the model

** p ≦ 0.01

* PET (A-/T+) profile included only 1 subject (with bordeline values) and was dropped from the analysis

Marco Bucci, et al, Molecular Psychiatry 2021

Conclusions

- While biomarkers for amyloid-beta in CSF and imaging agree considerably, CSF and imaging biomarkers for tau and neurodegeneration proved not to be interchangeable.

- Tau PET positivity was superior to phosphorylated tau and amyloid-β PET in predicting a cognitive decline in the Alzheimer´s disease continuum.

Background

- Plasma biomarkers have shown promising performance in research cohorts in discriminating between different stages of Alzheimer's disease (AD).
  - ⇧ Plasma GFAP, in elderly individuals at high risk of AD (Chatterjee et al, 2021) and in carriers of autosomal dominant AD mutations before symptoms manifestation (Chatterjee et al, 2022).
  - Plasma pTau181 and pTau231, in autopsy studies, had the highest sensitivity and specificity in detecting AD neuropathological changes compared to pathology diagnoses (Smirnov et al, 2022).

Research cohorts tend to have strict inclusion and exclusion criteria, which lead to a higher degree of patient homogeneity, facilitating interpretability of results.

Clinical cohorts should provide valuable insights on the clinical utility of plasma biomarkers ahead of their incorporation in a real-world setting.

- Amyloid-β PET when used clinically has an added diagnostic value, especially in patients with unclear diagnosis (Leuzy et al, 2019).
  - It is of interest to investigate whether single plasma biomarkers or in combination could predict amyloid-β PET positivity (or negativity) in clinical setting.

Aims

- Evaluate plasma biomarkers in a real-world clinical setting in patients undergoing memory clinical assessment in a tertiary memory clinic:
  - Evaluate plasma biomarkers association to amyloidosis in brain (Amyloid-$\boldsymbol{\beta}$ PET)
  - Test if plasma biomarkers alone or in combination can predict amyloid positivity assessed as visual read of Amyloid-$\boldsymbol{\beta}$ PET

Methods (1)

- Tertiary memory clinic of Karolinska University Hospital
- Extensive clinical assessment
  - neuropsychological testing, CT/MRI, CSF biomarker analysis
- [18F]flutemetamol PET (Aβ-PET) examination
  - visual reads, quantification with Centiloids
- Blood samples taken in the same time frame for plasma biomarker analyses
  - Plasma GFAP, NFL, Aβ42 and Aβ40 (Quanterix, SIMOA)
  - Plasma pTau-231, pTau-181 (in-house assay kits from Gothenburg Univ.)

Methods (2) – Study population

Characteristics of the study population and diagnostic subgroups

126 patients

	MCI Aβ- (N=30)	pAD (N=18)	ADD (N=51)	Non-AD (N=23)	CU (N=4)	Total (N=126)	p value
Age							0.808 (1)
-- Mean (SD)	65.87 (10.66)	66.83 (8.41)	64.12 (7.26)	65.70 (8.74)	64.00 (2.16)	65.21 (8.47)	
Sex							0.186 (2)
-- F	17 (56.7%)	14 (77.8%)	28 (54.9%)	9 (39.1%)	2 (50.0%)	70 (55.6%)	
-- M	13 (43.3%)	4 (22.2%)	23 (45.1%)	14 (60.9%)	2 (50.0%)	56 (44.4%)	
MMSE*							< 0.001 (1)
-- Mean (SD)	25.57 (3.36)	27.50 (1.92)	25.38 (3.38)	23.32 (4.04)	29.50 (0.58)	25.50 (3.53)	
Centiloid**							< 0.001 (1)
-- Mean (SD)	-1.02 (16.15)	72.31 (23.32)	87.95 (24.84)	-1.44 (17.28)	-7.41 (2.24)	45.59 (47.79)	

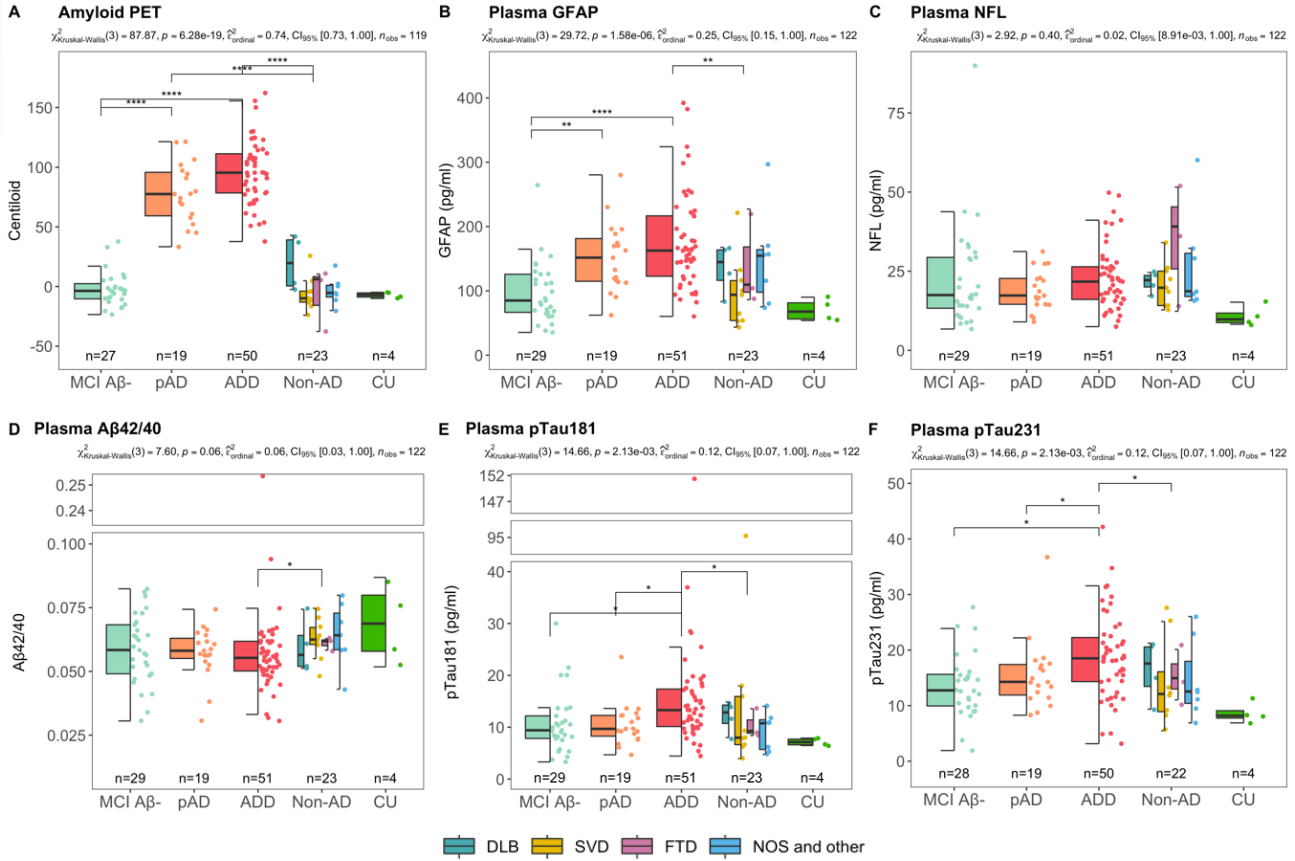
MCI, Mild Cognitive Impairment; **pAD**, Prodromal AD; **ADD**, Alzheimer's Disease Dementia; **Non-AD**, Non-AD dementias, **CU**, Cognitive Unimpaired. (**1**) - Kruskal-Wallis test, (2) – Pearson's χ^2 test

Methods (3) - Statistical analyses

- Group differences, tested with non-parametric tests corrected for multiple comparisons
- Correlation coefficients (Spearman's)
- ROC curves, to predict for Amyloid-β PET positivity
- LASSO regressions to combine multiple variables (and dropping the ones not contributing to the model) for prediction of Amyloid-β PET positivity (cross-validation 10-fold of the models)

Results (1)

- Plasma GFAP levels are different between MCI Aβ- and prodromal AD (MCI Aβ+) groups
- Plasma pTau181 and pTau231 levels were different between prodromal AD and ADD
- Plasma NFL and Aβ42/40 did not differ among AD continuum groups.



MCI, Mild Cognitive Impairment; **pAD**, Prodromal AD; **ADD**, Alzheimer's Disease Dementia; **Non-AD**, Non-AD dementias, **CU**, Cognitive Unimpaired.
DLB, Lewy Body Dementia; **SVD**, Subcortical Vascular Dementia; **FTD**, Fronto-Temporal Dementia; **NOS**, Not Otherwise Specified Dementia.

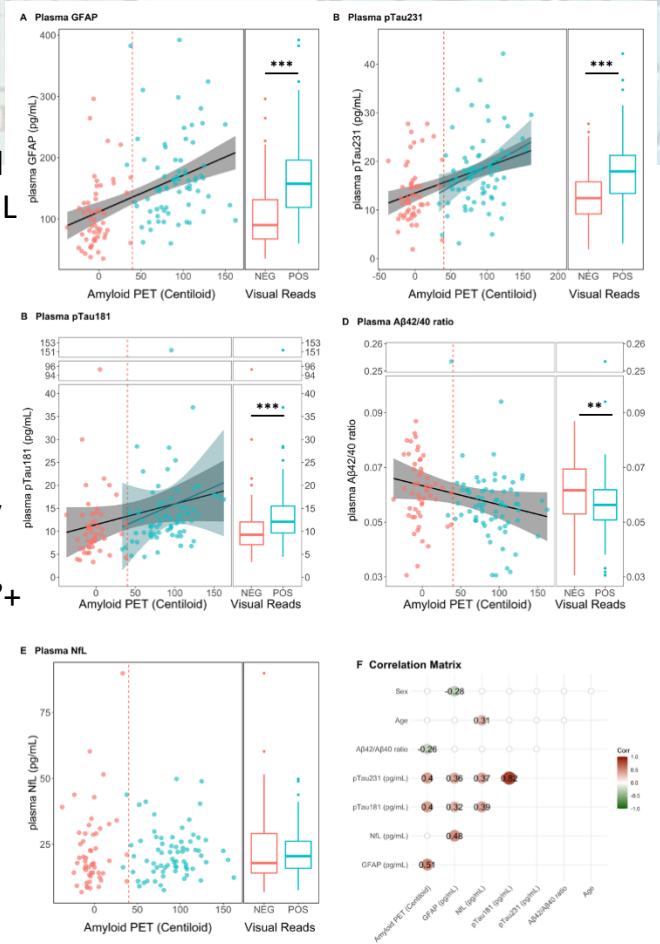
Marco Bucci*, Marina Bluma* et al, Trans. Psychiatry 2024

Results (2)

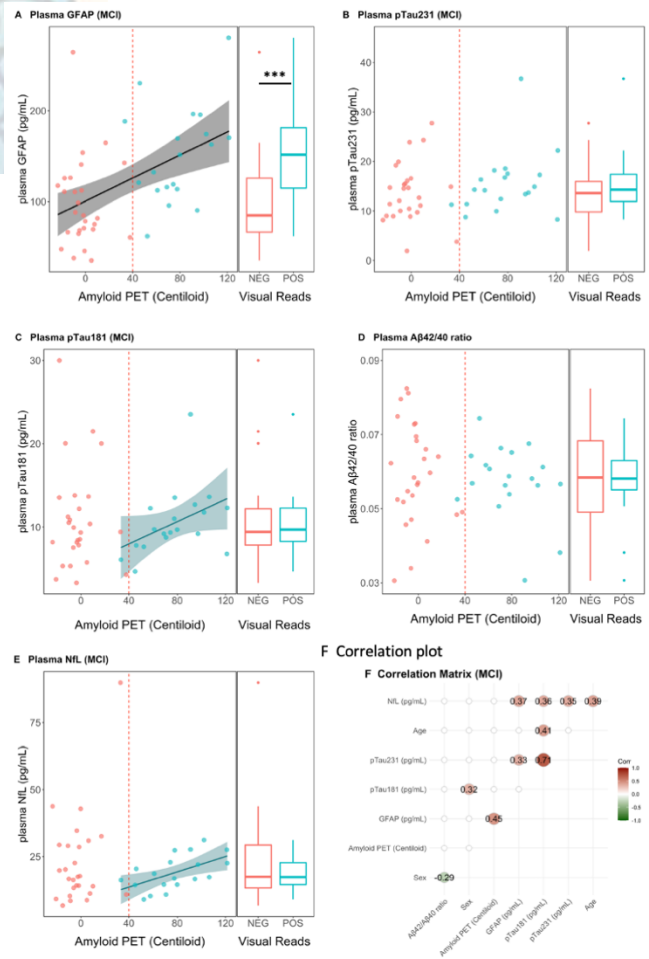
- In the whole group all plasma BM except NFL are increased in the Aβ+ PET group compared to Aβ- and are associated to Aβ PET Centiloids.

- In the MCI group only only plasma GFAP is different between Aβ+ and Aβ– PET groups and associated with Centiloids

Whole group



Mild Cognitive Impairment (MCI) group



Marco Bucci*, Marina Bluma* et al, Trans. Psychiatry 2024

Results (3) In the MCI before PET group:

Plasma BMs combined has 100% Sensitivity and Negative Predictive Value.
Plasma GFAP results superior for AUC to others' biomarkers but with low specificity.

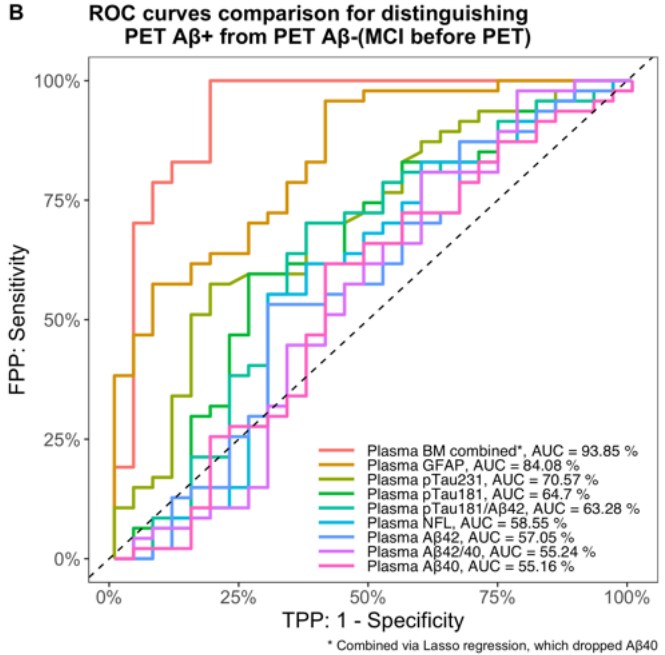


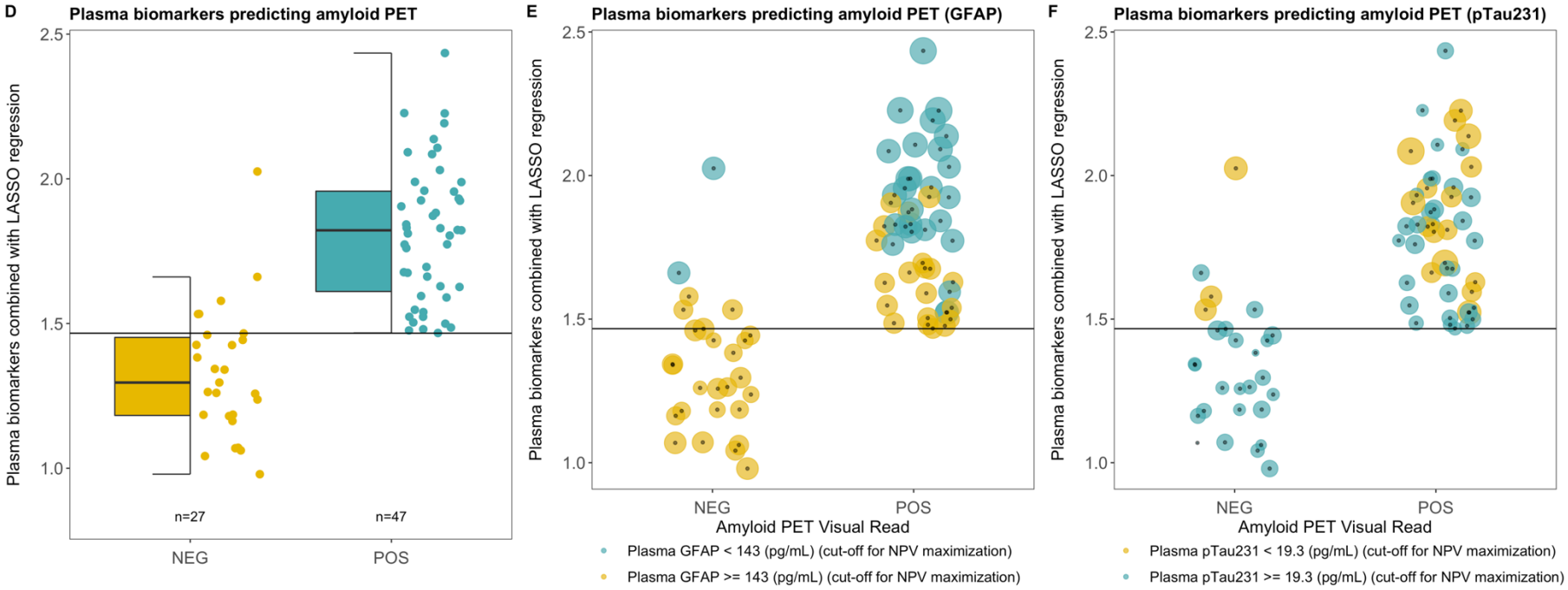
Table 2. Diagnostic performance plasma BM: MCI before PET

Biomarker(s)	AUC (%)	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
Plasma BM combined via Lasso regression (dropped Aβ40)	93.9	81.5	100.0	90	100
Plasma GFAP	84.1	59.3	95.7	80	89
Plasma pTau231	70.6	81.5	57.4	84	52
Plasma pTau181/Aβ42	63.3	63.0	70.2	77	55
Plasma pTau181	64.7	74.1	59.6	80	51
Plasma Aβ42	57.1	70.4	53.2	76	46
Plasma Aβ42/40	55.2	40.7	80.9	70	55
Plasma Aβ40	55.2	59.3	61.7	72	47
Plasma NFL	58.6	70.4	55.3	76	48

Marco Bucci*, Marina Bluma* et al, Trans. Psychiatry 2024

Results (4) In the MCI before PET group:

Plasma biomarkers combined results superior for AUC to others' biomarkers alone and Plasma GFAP and Plasma pTau231 are important contributors to the pooled variable.



Marco Bucci*, Marina Bluma* et al, Trans. Psychiatry 2024

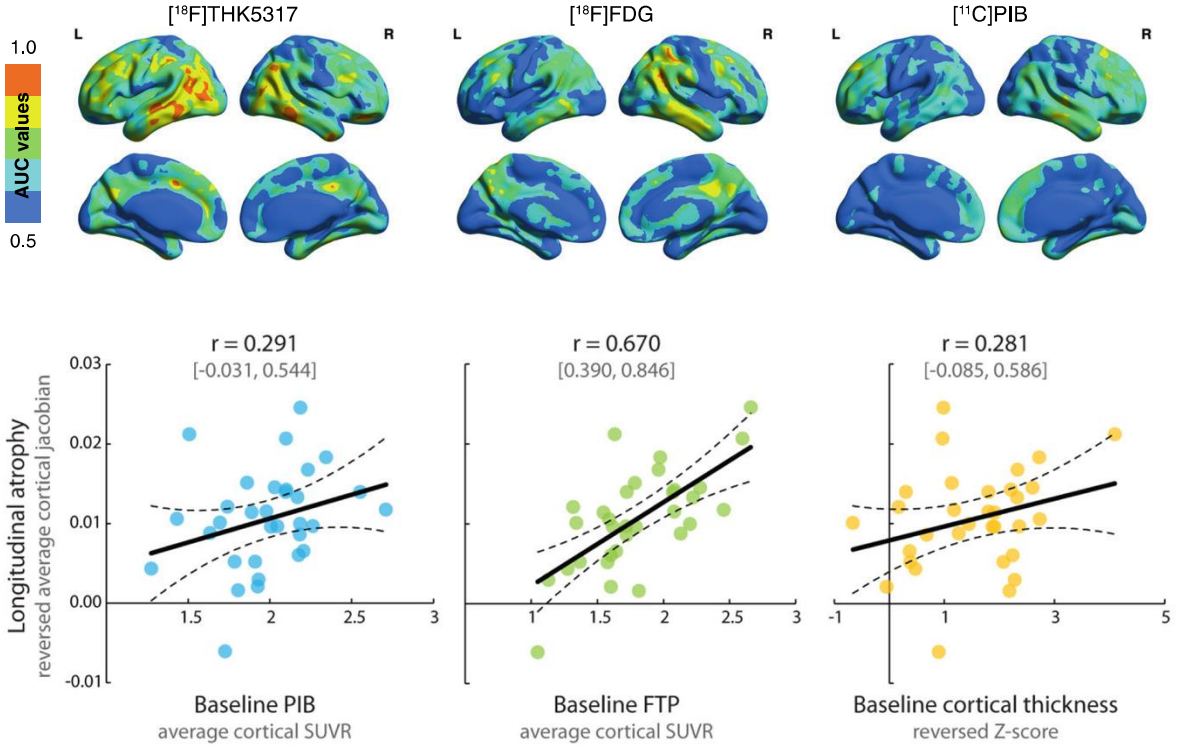
Summary and conclusions

- Plasma BM (especially GFAP) are associated to accumulation of amyloid in the brain in symptomatic clinical cases (especially in MCI)

- Plasma BMs when combined in a pooled variable (with also age and sex) resulted to have the highest negative predictive value (NPP), minimizing the amount of false negatives and being candidate for rule-out rule (if negative no A$\boldsymbol{\beta}$ PET accumulation)

- More studies are needed to confirm these results and evaluate the effect on follow-up data on cognition and conversion to AD (our results on a small sub-sample indicate plasma NFL as a biomarker of interest)

Associations between PET and cognitive decline and atrophy

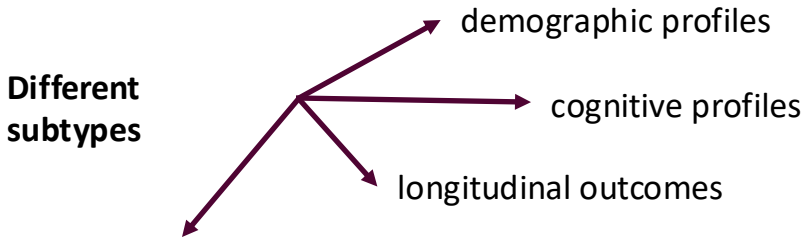


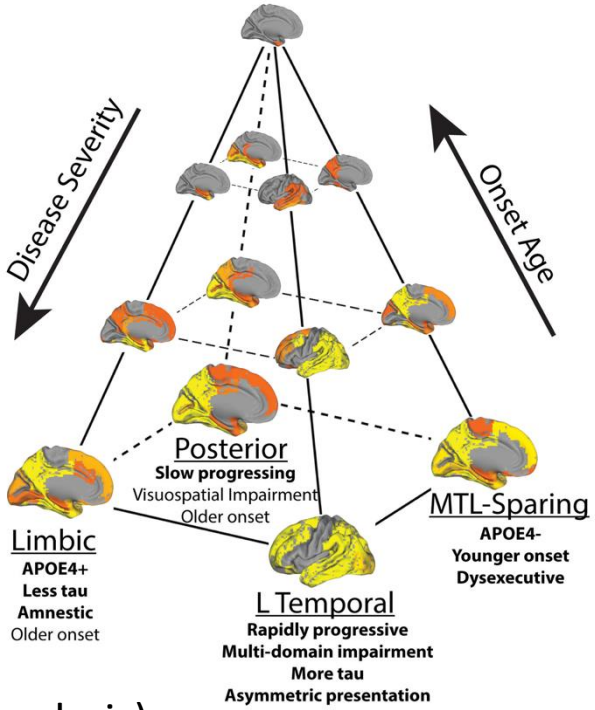
Chiotis K et al. 2020

La Joie et al. 2020

Distinct trajectories of tau deposition in AD

Variation in tau pathology is common and systematic, perhaps warranting a re-examination of the notion of "typical AD", and a revisiting of tau pathological staging





SuStaIN method (Subtype and Stage Inference Model Analysis)

Vogel JW et al. 2021

Brain Tau and Amyloid PET and ML: SuStAin

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01309-6

Check for updates

Four distinct trajectories of tau deposition identified in Alzheimer's disease

Jacob W. Vogel[1✉], Alexandra L. Young[2], Neil P. Oxtoby[3,4], Ruben Smith[5,6], Rik Ossenkoppele[5,7], Olof T. Strandberg[5], Renaud La Joie[8], Leon M. Aksman[3,9], Michel J. Grothe[10,11], Yasser Iturria-Medina[1], the Alzheimer's Disease Neuroimaging Initiative*, Michael J. Pontecorvo[12], Michael D. Devous[12], Gil D. Rabinovici[8,13], Daniel C. Alexander[3,4], Chul Hyoung Lyoo[14], Alan C. Evans[1] and Oskar Hansson[5,15✉]

RESEARCH ARTICLE OPEN ACCESS

Spatial-Temporal Patterns of β-Amyloid Accumulation

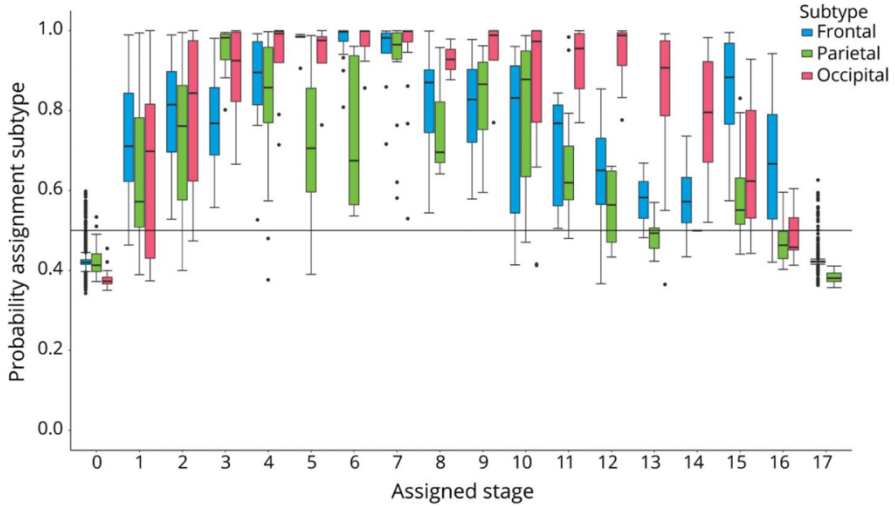
A Subtype and Stage Inference Model Analysis

Lyduine E. Collij, PhD, Gemma Salvadó, PhD, Viktor Wottschel, PhD, Sophie E. Mastenbroek, MSc, Pierre Schoenmakers, BSc, Fiona Heeman, MSc, Leon Aksman, PhD, Alle Meije Wink, PhD, Bart N.M. Berckel, PhD, MD, Wiesje M. van de Flier, PhD, Philip Scheltens, PhD, MD, Pieter Jelle Visser, PhD, MD, Frederik Barkhof, PhD, MD, Sven Haller, PhD, MD, Juan Domingo Gispert, PhD, and Isadora Lopes Alves, PhD, for the Alzheimer's Disease Neuroimaging Initiative; for the ALFA study

Correspondence
Dr. Collij
l.collij@amsterdamumc.nl

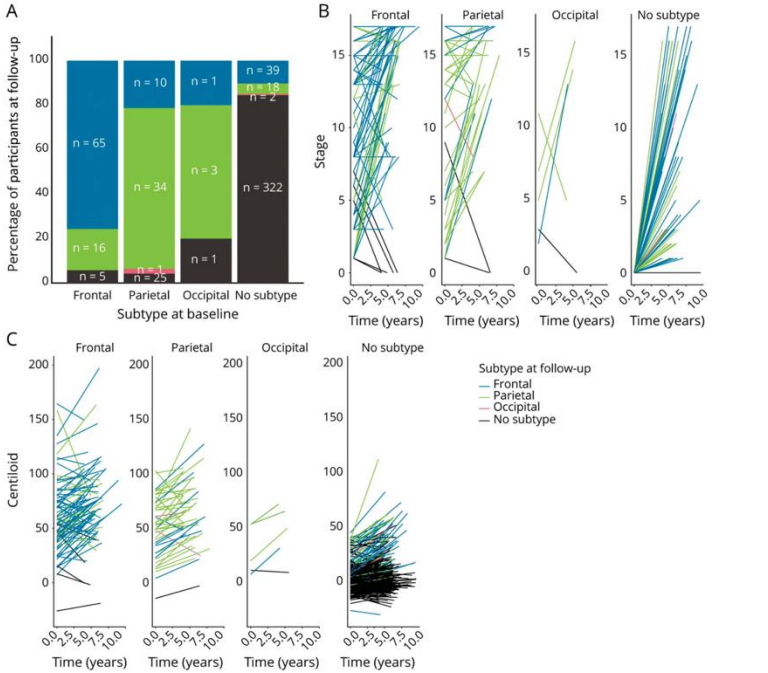
Neurology® 2022;98:e1692-e1703. doi:10.1212/WNL.0000000000200148

Amyloid PET and ML: SuStAin



Collij L et al. 2022

Figure 4 Longitudinal Validation

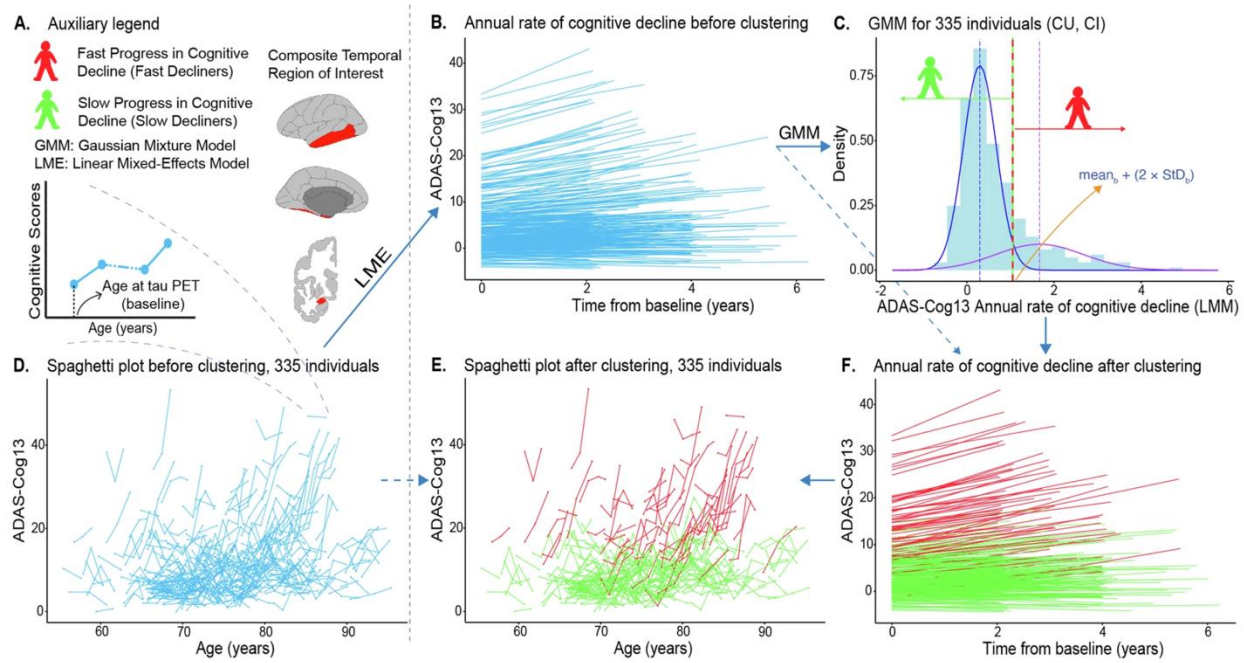


(A) Subtype assignment at baseline vs at follow-up. Spaghetti plots illustrate the change in (B) stage and (C) Centiloid units per subtype as assigned at baseline. Lines are color coded to show changes in subtype assignment at follow-up. Overall, changes in stage are associated with changes in Centiloid and yearly rates of change were lowest for the frontal subtype.

Brain Tau and Cognition: ML clustering pipeline

Fig. 2: The clustering pipeline for the definition of SDs and FDs in the case of the ADAS-Cog13 score.

From: Tau PET positivity predicts clinically relevant cognitive decline driven by Alzheimer's disease compared to comorbid cases; proof of concept in the ADNI study



Molecular Psychiatry www.nature.com/mp

ARTICLE OPEN

Tau PET positivity predicts clinically relevant cognitive decline driven by Alzheimer's disease compared to comorbid cases; proof of concept in the ADNI study

Konstantinos Ioannou[1], Marco Bucci[1,2], Antonios Tzortzakakis[3,4], Irina Savitcheva[4], Agneta Nordberg[1,2], Konstantinos Chiotis[1,2]✉ and for the Alzheimer's Disease Neuroimaging Initiative*

Brain Tau and Cognition

Molecular Psychiatry www.nature.com/mp

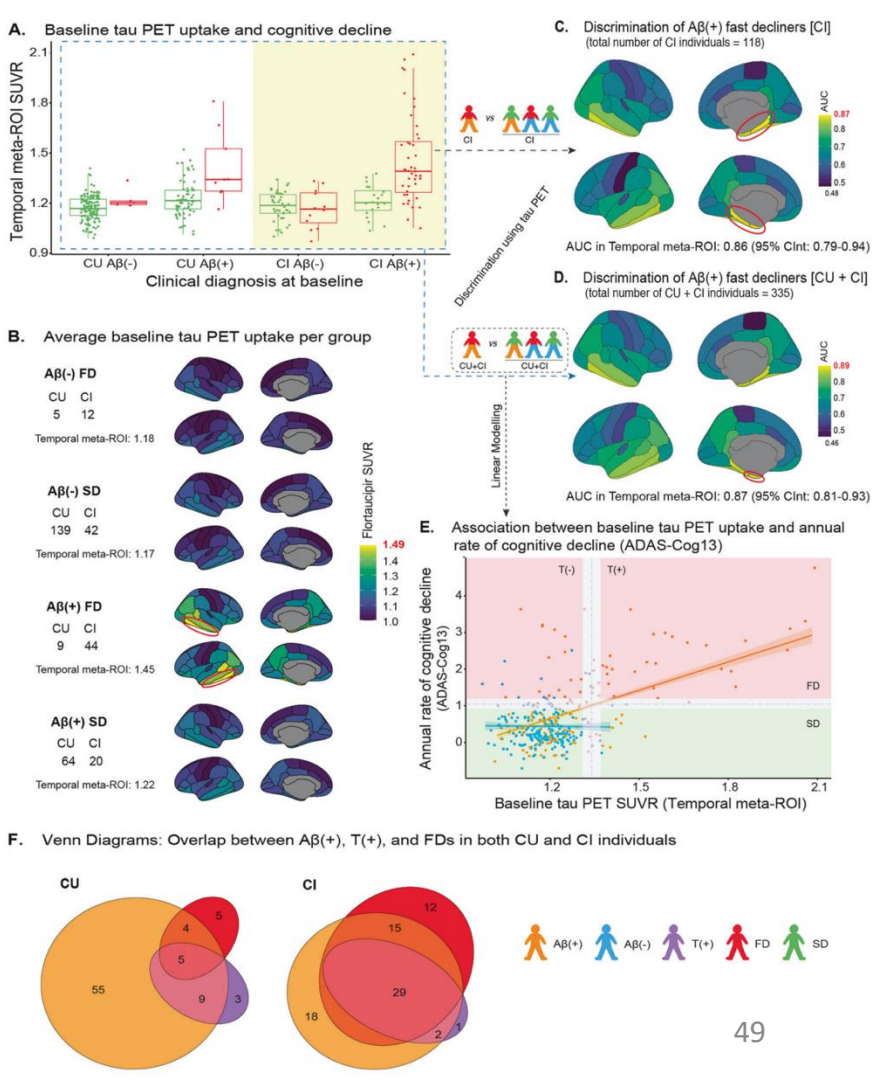
ARTICLE OPEN

Check for updates

Tau PET positivity predicts clinically relevant cognitive decline driven by Alzheimer's disease compared to comorbid cases; proof of concept in the ADNI study

Konstantinos Ioannou[1], Marco Bucci[1,2], Antonios Tzortzakakis[3,4], Irina Savitcheva[4], Agneta Nordberg[1,2], Konstantinos Chiotis[1,5]✉ and for the Alzheimer's Disease Neuroimaging Initiative*

- Tau PET imaging showed high accuracy to predict the subset of Aβ(+) individuals that will show AD-relevant cognitive decline.
- Overall, tau PET can predict a population of high clinical interest and should be considered as a combined diagnostic and prognostic tool with both clinical and research applications for the management of cognitively impaired individuals.



Acknowledgements

Nordberg's Translational Molecular Imaging Lab
Prof. Agneta Nordberg, PhD, MD
Marina Bluma, PhD
Konstantinos Chiotis, PhD, MD
Irina Savitcheva, PhD, MD
Konstantinos Ioannou, MSc

Rinne Lab - ADImaging

Thanks for the attention