UPDATE

Amyloid PET: quantification, classification and clinics

Enrico Peira

AIM general meeting

Pisa - February 3rd, 2020

Aim

“to develop and validate new approaches for quantification and classification of amyloid PET that can be integrated into the clinical practice“

Concluded projects:

quantification & grading
a kinetic based approach to quantification

Ongoing studies:

further validation of our methodologies
regional accumulation: does it make sense?
regional accumulation: how?
EEG to amyloid

Quantification & grading

study design & objectives

175 cases
symptomatic outpatients
age [62 - 88]
MMSE μ = 26.1

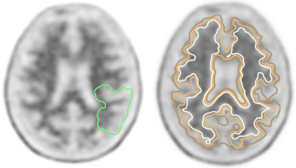
multicentric
6 EADC centers, **population matching**
cross-sectional data

3 fluorinated **tracers**
62 F-mol, 53 F-ben, 60 F-pir
no shared protocol

5 independent **expert readers**
quality, n/p and 5-step* classification

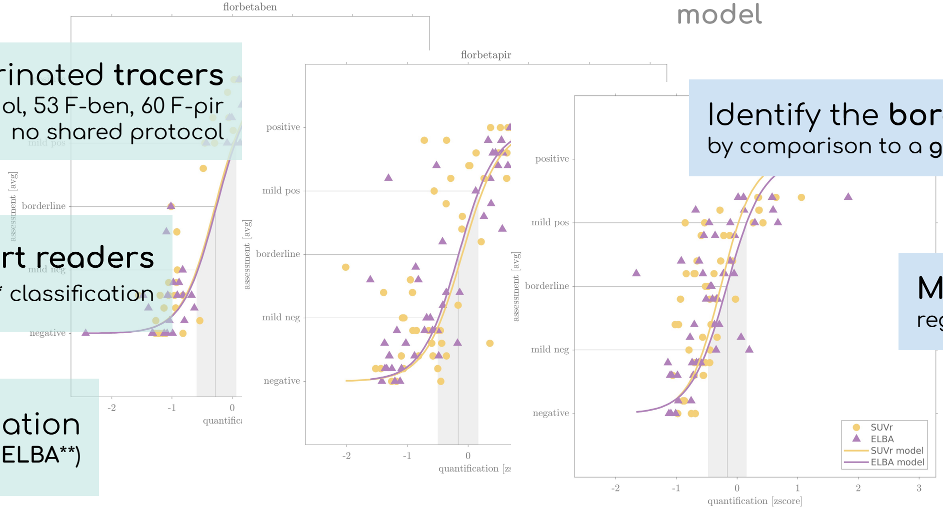
2 quantification
(cortico-cerebellar **SUVr**, **ELBA****)

visual inspection



quantitative analysis

model



Test a more complex visual scale*
across different tracers

Identify the **borderline** zone and **cut-off**
by comparison to a **graded*** visual assessment

Map function (SUVr, ELBA)
regardless of tracer

---

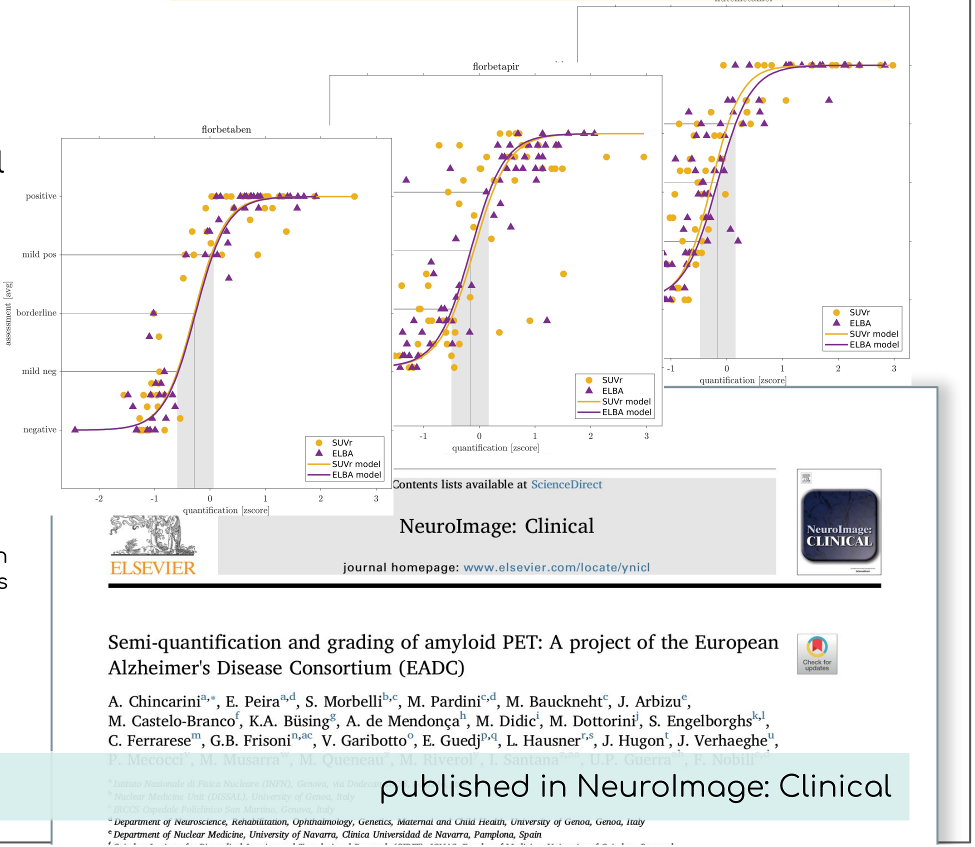
* *Paghera et al. Comparison of visual criteria for amyloid Positron Emission Tomography reading: could their merging reduce the inter-raters variability. Q. J. Nucl. Med. Mol. Imaging. 2019*
** *Chincarini et al. Standardized uptake value ratio-independent evaluation of brain amyloidosis. J. Alzheimers Dis. 2016*

Quantification & grading

results

- Thanks to a sigmoid model and to the 5-step visual scale it was possible to define **cut-offs** and **transition regions** (borderline) on all tracers
- It is possible to construct a **map** between different **tracers** and different **quantification** methods without resorting to ad-hoc acquired cases
- No **tracer** is the winner here, all are **equivalently discriminating** (means: equivalent contrast)

very little literature on tracer comparison
with evaluation from the same set of readers



Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Semi-quantification and grading of amyloid PET: A project of the European Alzheimer's Disease Consortium (EADC)

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published in NeuroImage: Clinical

A kinetics-based approach to quantification

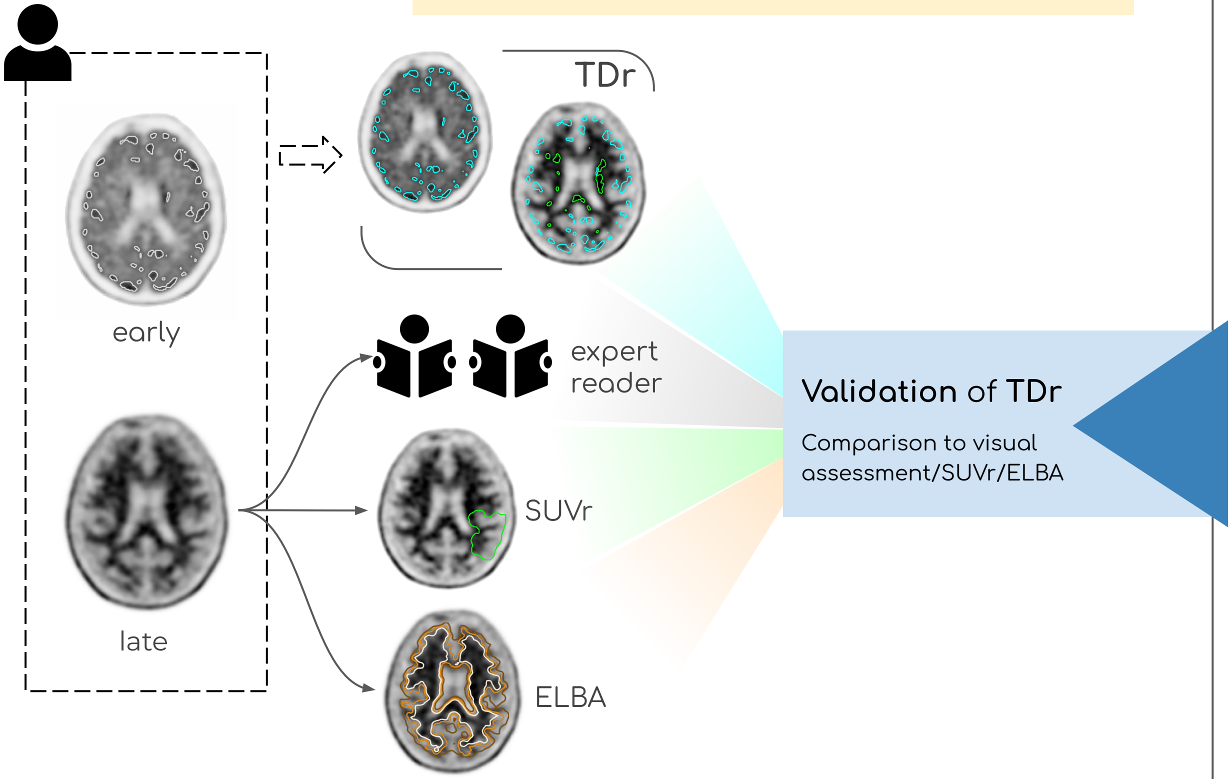
study design & objectives

143 cases
symptomatic outpatients
age [54-87]

2 acquisitions per patient
early (0-5 min.) + **late** (50-70 min.)

1 tracer
^{18}F-florbetapir

multicentric
4 EADC centers
cross-sectional data



Validation of TDr

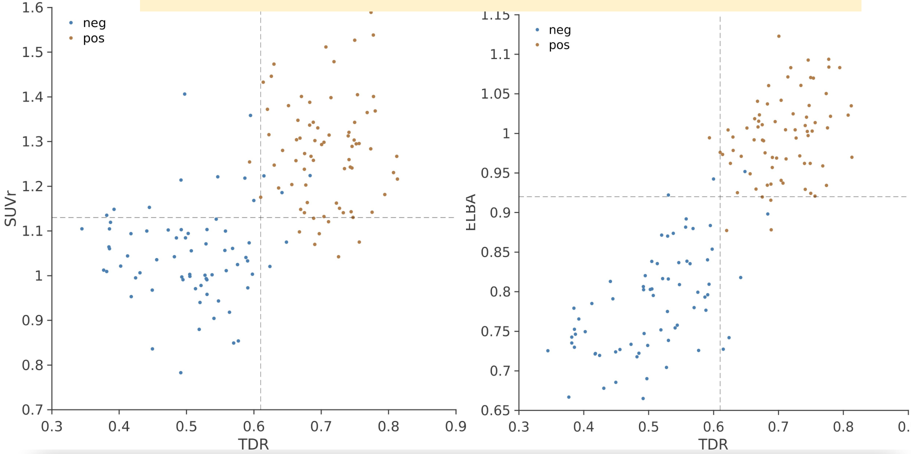
Comparison to visual assessment/SUVr/ELBA

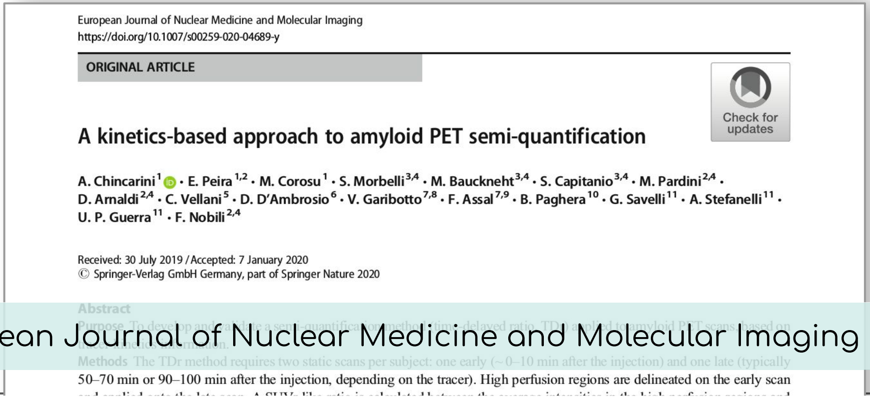
A kinetics-based approach to quantification

results

- **Novel** kinetic-based **approach** to quantification of amyloid PET, **tested** on **naturalistic population**
- Based on **dual-time point** acquisition, **tailored** on individual patient **anatomic** and **pathophysiological** characteristics
- Excellent **agreement** with **visual assessment**
- Significantly **correlates** with the two validated methods (**ELBA, SUVr**)

TDr is a patented method




European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-04689-y

ORIGINAL ARTICLE

Check for updates

A kinetics-based approach to amyloid PET semi-quantification

A. Chincarini[1] · E. Peira[1,2] · M. Corosu[1] · S. Morbelli[3,4] · M. Bauckneht[3,4] · S. Capitanio[3,4] · M. Pardini[2,4] · D. Arnaldi[2,4] · C. Vellani[5] · D. D'Ambrosio[6] · V. Garibotto[7,8] · F. Assal[7,9] · B. Paghera[10] · G. Savelli[11] · A. Stefanelli[11] · U. P. Guerra[11] · F. Nobili[2,4]

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Abstract

Purpose To develop and validate a semi-quantification method (time-delayed ratio, TDr) applied to amyloid PET scans, based on tracer kinetics information.

Methods The TDr method requires two static scans per subject: one early (~ 0–10 min after the injection) and one late (typically 50–70 min or 90–100 min after the injection, depending on the tracer). High perfusion regions are delineated on the early scan

published in European Journal of Nuclear Medicine and Molecular Imaging

Further validation of our methodologies

90 cases

symptomatic outpatients
age [67 - 82]

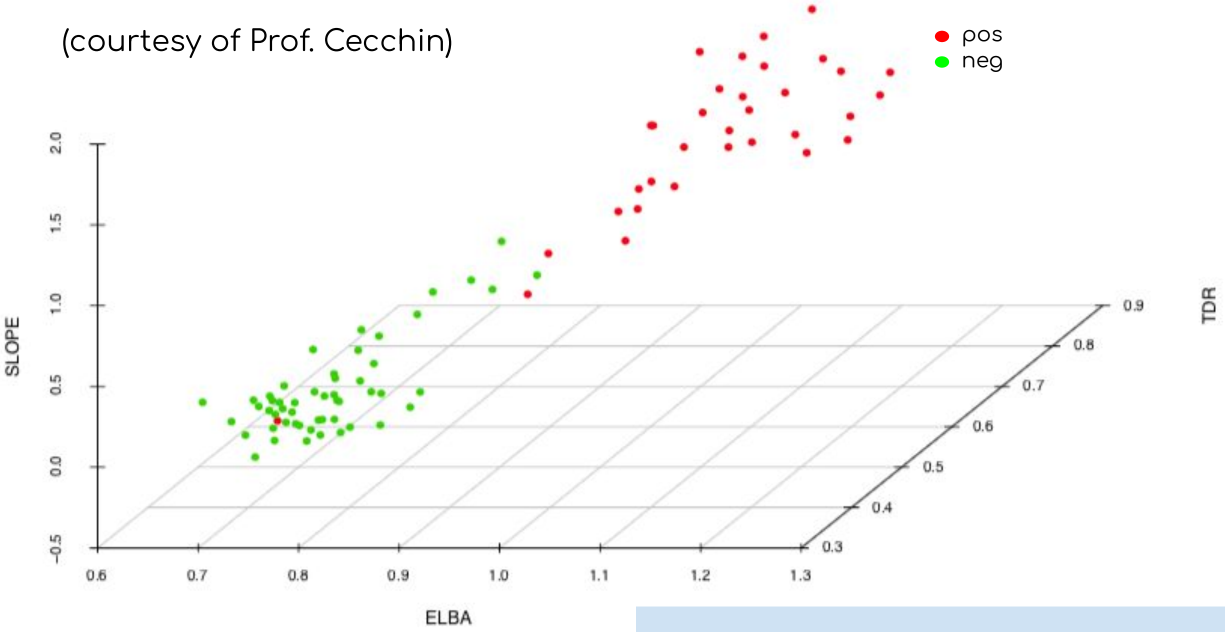
2 acquisitions per patient

early (0-5 min.) + **late** (50-70 min.)
1 Tracer (^{18}F-florbetaben)

2 quantification
(TDr, ELBA, SLOPE)

2 independent
expert readers

(courtesy of Prof. Cecchin)



Compare ELBA and **TDr** to **SLOPE***

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* *Cecchin et al. A new integrated dual time-point amyloid PET/MRI data analysis method. EJNMMI. 2017*

Regional amyloid accumulation: does this make sense?

84 cases

symptomatic outpatients

age [54 - 87]

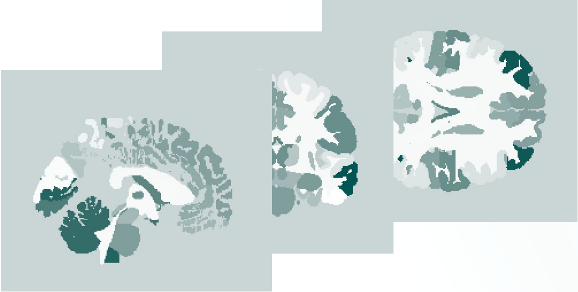
Amyloid PET

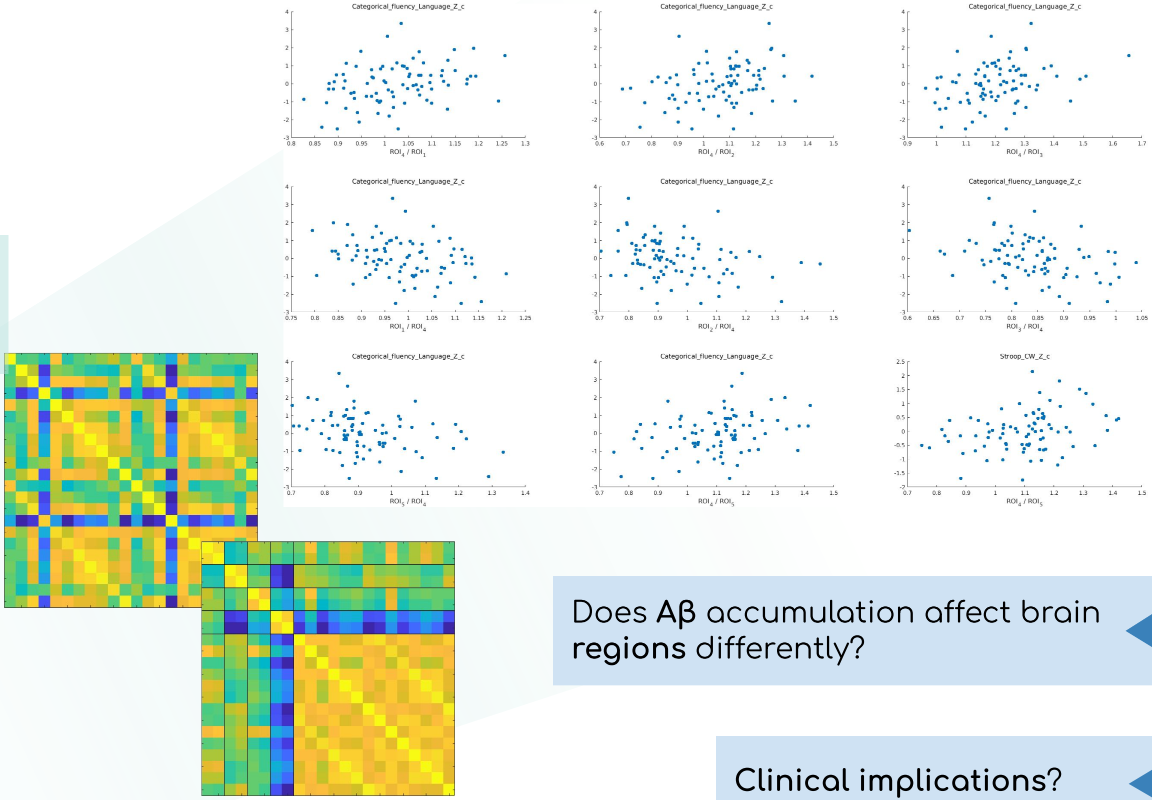
Neuropsychological assessment

[MMSE, RAVLT, TMT-A, TMT-B, Stroop, ...]

ELBA + SUVr quantification

[template 11 ROI]





Does **Aβ** accumulation affect brain **regions** differently?

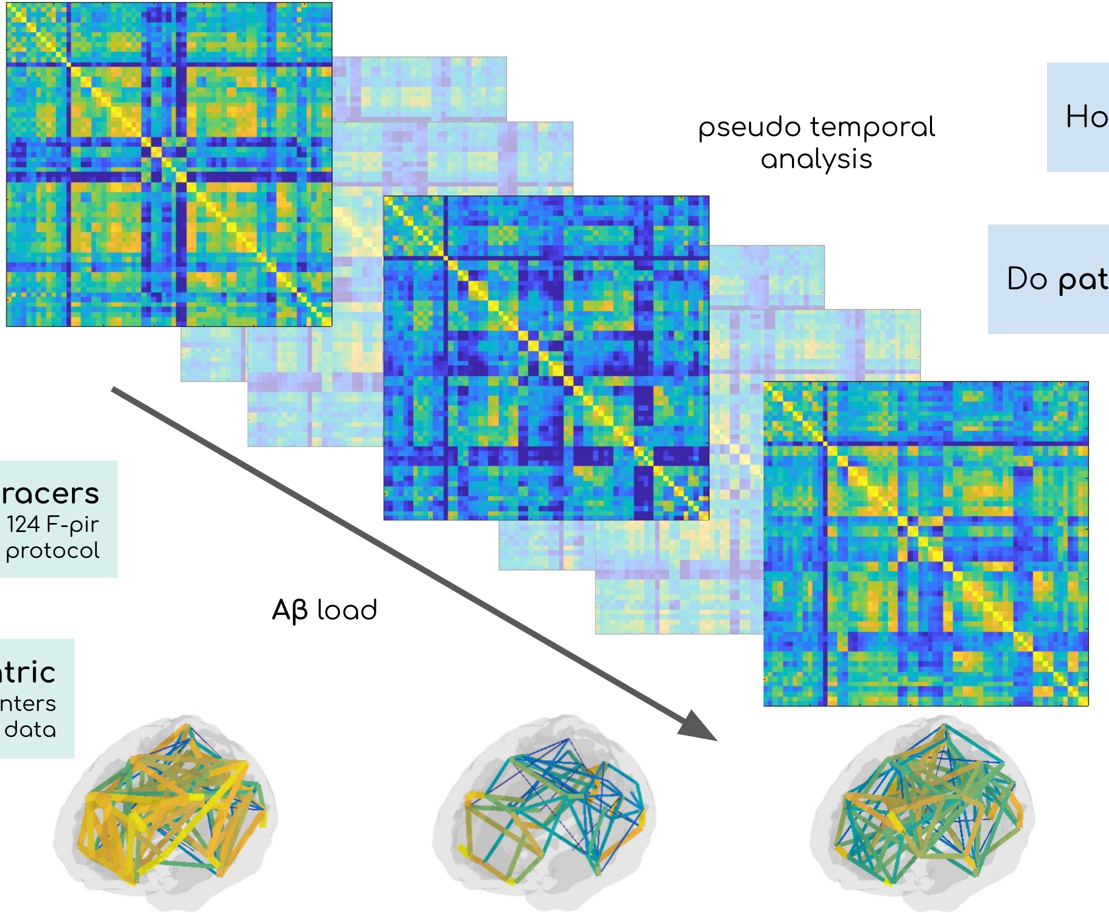
Clinical implications?

Regional amyloid accumulation: how it happens?

341 cases
symptomatic
outpatients

3 fluorinated **tracers**
62 F-mol, 155 F-ben, 124 F-pir
no shared protocol

multicentric
9 centers
cross-sectional data



pseudo temporal
analysis

Aβ load

How does **Aβ** spread?

Do **patterns** exist?

validation on
longitudinal data ..

Fundació ACE

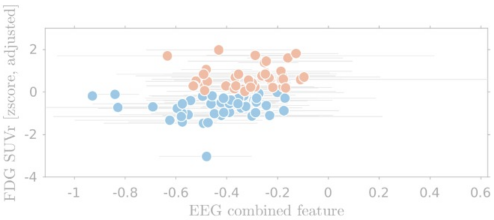
from EEG to amyloid

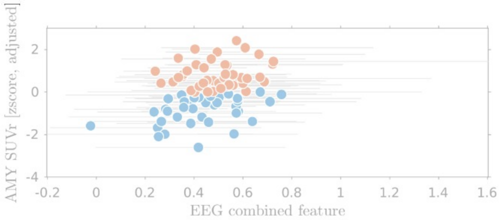
89 cases
symptomatic outpatients
age [50 - 82]

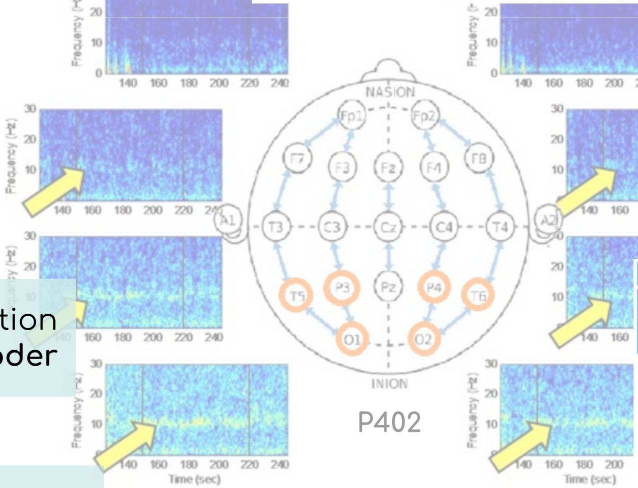
1 **amyloid** PET
1 **FDG** PET
low-density **EEG**
per patient

EEG features selection
with **deep autoencoder**

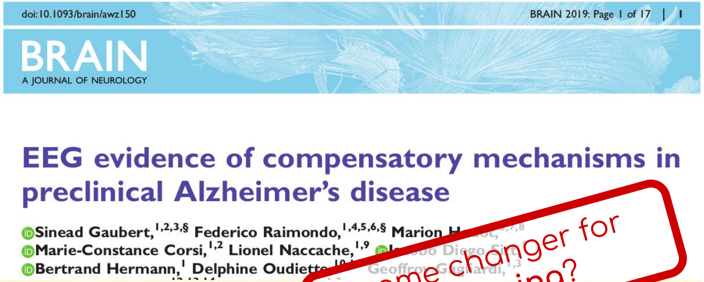
EEG features are **corrected**
for **neurodegeneration**







Investigate possible **relation** between **Aβ** and EEG **signal**

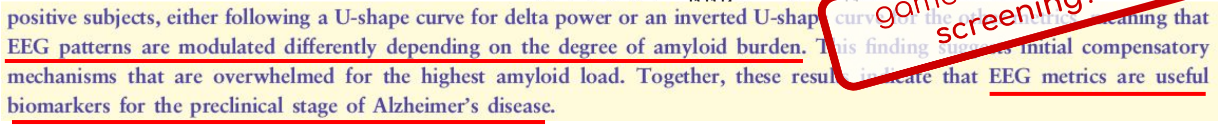


doi:10.1093/brain/awz150 BRAIN 2019: Page 1 of 17 | 1

BRAIN
A JOURNAL OF NEUROLOGY

EEG evidence of compensatory mechanisms in preclinical Alzheimer's disease

Sinead Gaubert,[1,2,3,§] Federico Raimondo,[1,4,5,6,§] Marion H
Marie-Constance Corsi,[1,2] Lionel Naccache,[1,9] Jacobo Diego Sitt,
Bertrand Hermann,[1] Delphine Oudiette,[10] Geoffroy Gagliardi,[1,3]



positive subjects, either following a U-shape curve for delta power or an inverted U-shape curve for the other metrics, meaning that EEG patterns are modulated differently depending on the degree of amyloid burden. This finding suggests initial compensatory mechanisms that are overwhelmed for the highest amyloid load. Together, these results indicate that EEG metrics are useful biomarkers for the preclinical stage of Alzheimer's disease.

game changer for screening?

Flavio Nobili, Matteo Pardini, Silvia Morbelli, Dario Arnaldi, Matteo Bauckneht, Matteo Grazzini

The group

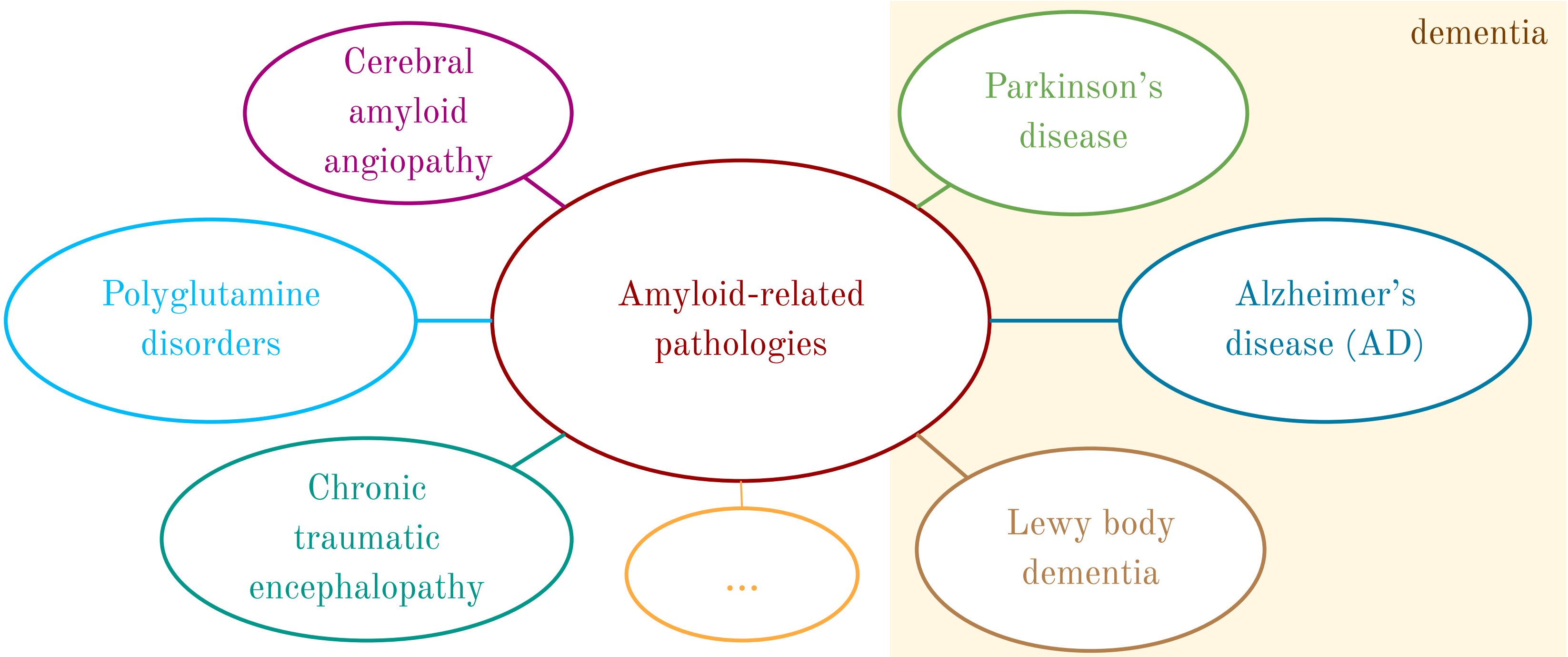
Thank you!

Andrea Chincarini, Francesco Sensi, Enrico Peira, Nicola Alchera, Gloria Pedemonte

special thanks to Ugo Paolo Guerra

Brain amyloidosis

- Amyloidosis is a general term that describes a **wide spectrum of diseases** characterized by a **deposit** of a neurotoxic peptides (β-Amyloid, **Aβ**) in different organs
- Aβ deposit in the central nervous system represents the most frequent form of amyloidosis in humans



dementia

Amyloid-related pathologies

Cerebral amyloid angiopathy

Polyglutamine disorders

Chronic traumatic encephalopathy

...

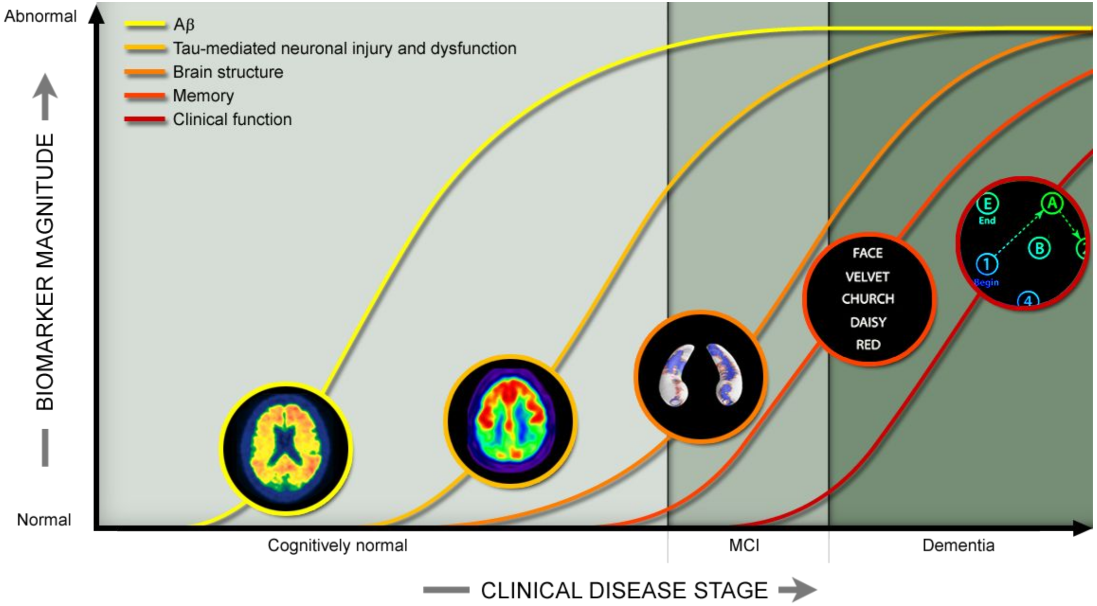
Parkinson's disease

Alzheimer's disease (AD)

Lewy body dementia

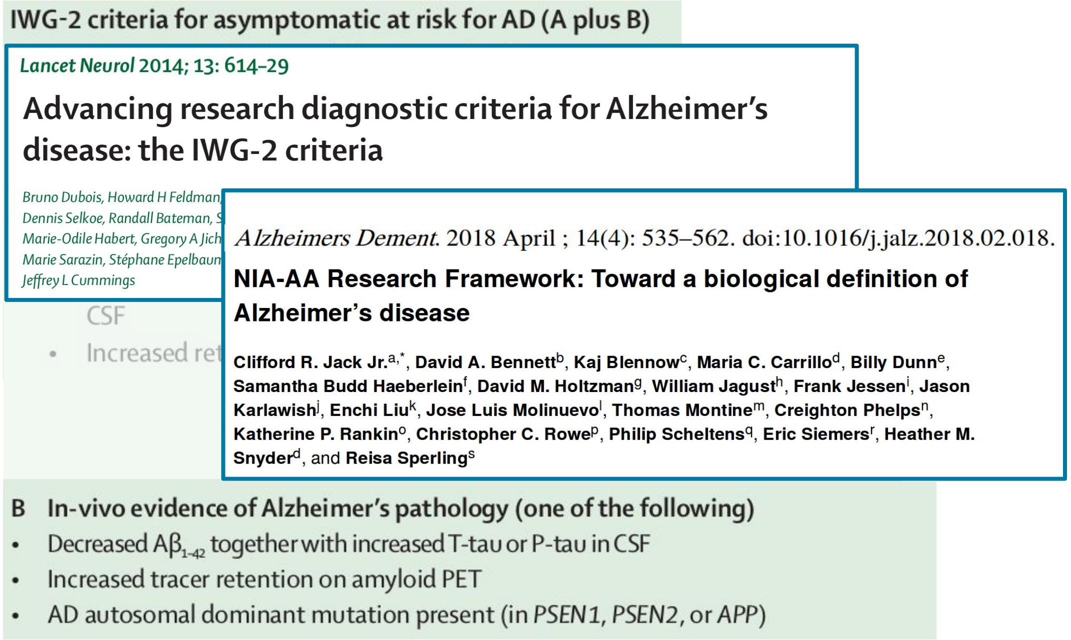
Amyloid: why?

The **increase of Aβ** is a key event in **AD**: its aggregation **precedes clinical symptoms** by many years (Jack 2010)



The **in-vivo assessment** of cerebral amyloid is taking a leading role in the **early differential diagnosis** becoming a biomarker of prime importance for **AD**

Amyloid: a watershed in the AD diagnosis



IWG-2 criteria for asymptomatic at risk for AD (A plus B)

Lancet Neurol 2014; 13: 614–29

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman,
Dennis Selkoe, Randall Bateman, S
Marie-Odile Habert, Gregory A Jich
Marie Sarazin, Stéphane Epelbaum
Jeffrey L Cummings

CSF

- Increased ret

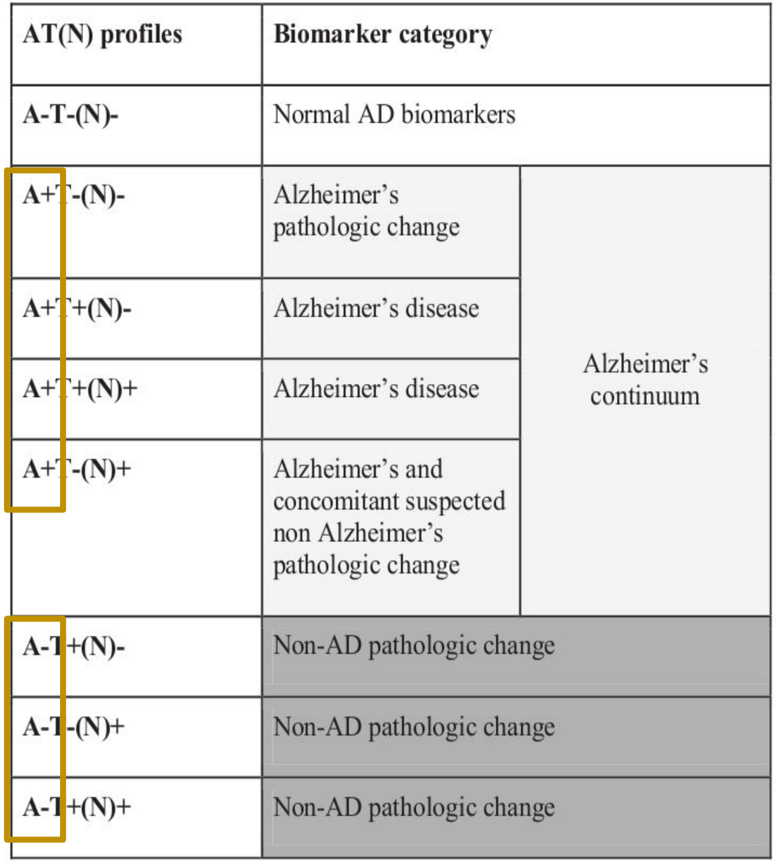
Alzheimers Dement. 2018 April ; 14(4): 535–562. doi:10.1016/j.jalz.2018.02.018.

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

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

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1\text{-}42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)



AT(N) profiles	**Biomarker category**	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Aβ **negativity excludes** the **AD !**

In-vivo amyloid assessment

PET

cons

radiation dose to patient, a-specific sites (WM), ...

pro

routine technique, reliable, easier quantification, tracer availability, ...

CSF

cons

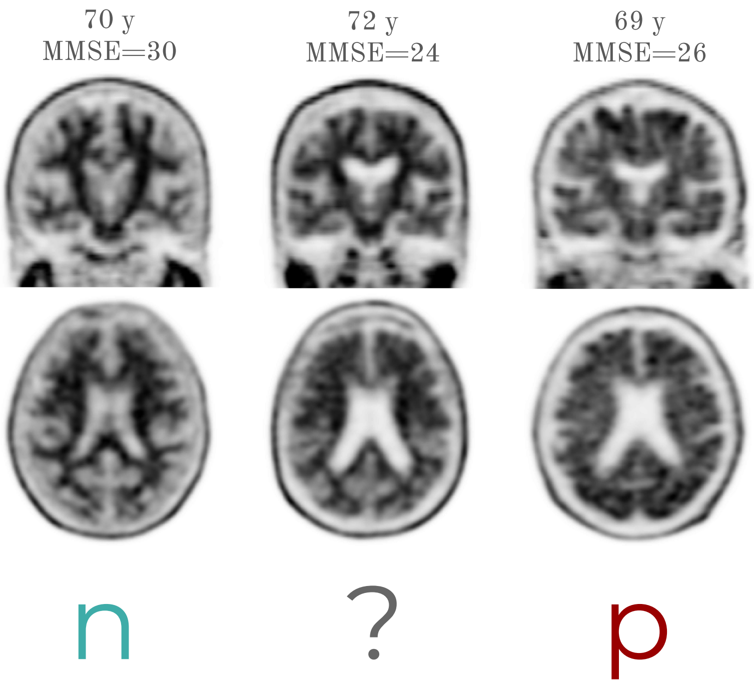
lumbar puncture: invasive, results sensitive to procedure, ...

pro

$A\beta_{40}/A\beta_{42}$, phosph-τ / tot-τ, higher clinical content, ...

With the hopefully near introduction of disease-modifying drugs, we expect a **paradigm shift** in the current **diagnostic pathway** with an unprecedented surge in the request of exams and detailed analysis

Amyloid PET: binary classification



binary reading rules of thumb

a. visually inspect image for quality and artifacts
b. review ligand-specific criteria for positivity (e.g: positive if contrast reduction at least in two lobes)
c. inspect and evaluate on all cross-sections

Recommendations from the Italian Interdisciplinary Working Group (AIMN, AIP, SINDEM) for the utilization of amyloid imaging in clinical practice

**Ugo Paolo Guerra · Flavio Mariano Nobili · Alessandro Padovani ·
Daniela Perani · Alberto
Marco Trabucchi**

It is common wisdom that a dichotomous classification (positive/negative exam) is inadequate for a thorough interpretation and reporting procedure. The amyloid accumulation period can last for up to 15 years and during this positivity level gradually increases [22, 23].

Therefore, a quantification or semi-quantification of the PET exam providing information about the level of positivity is advisable and should be strongly encouraged.

TDr validation - Data & Study Design

Cross-sectional data

- **Symptomatic outpatient**
- **143** patients (age [54-87])
- **Clinical suspicion:** FTD, AD, MCI, MCIAD, Dep, SMC, VCI, CBS, MSA, SNAP
- **Amyloid PET**, 2 acquisitions per patient
  - **early** (0-5 min. after injection)
  - **late** (50-70 min. after injection)
- **^{18}F-florbetapir**
- **4 centers**
  - IRCCS Maugeri (Pavia)
  - IRCCS S.Martino (Genoa)
  - Fondazione Poliambulanza (Brescia)
  - HUG (Geneva)

Late scans:

1. **Visually** inspected & **labeled** (blind & open visual assessment session)

   70 negatives / 73 positive

   \+ 5 yr scan reporting (NM)

2. Processed with **SUVr** & **ELBA** (Chincarini 2016)

Early and late scans:

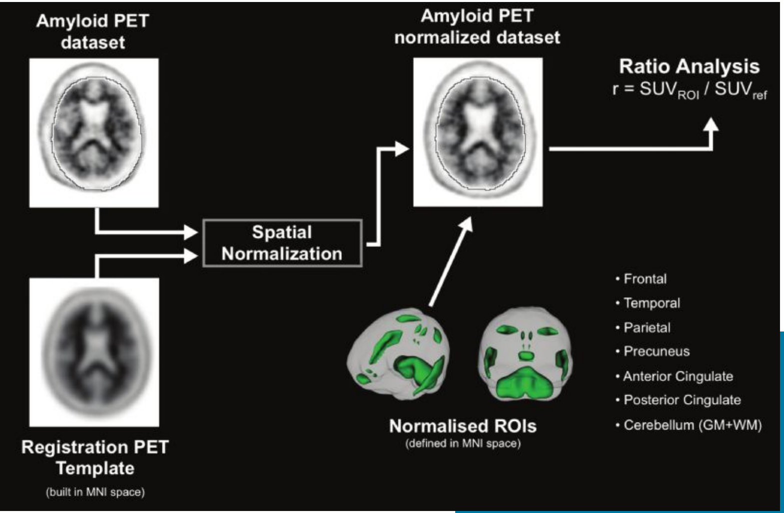
- **TDr** calculation

Comparison:

- TDr vs. visual assessment
- TDr vs. SUVr & ELBA

SUVr [**S**tandardized **U**ptake **V**alue **r**atio]

- register on a reference spatial frame (i.e. MNI)
- select reference (cerebellum, brain stem, ...) & target ROI (cortical)
- average counts (single/all ROI) and take the ratio

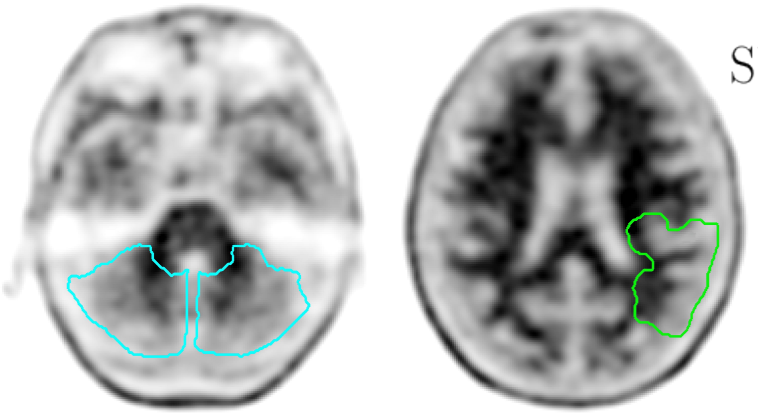


ratio of raw (mean) intensities
segmentation dependence
fixed target *ROI*
fixed ***reference*** *ROI*

very common quantification approach (Kinahan 2010)

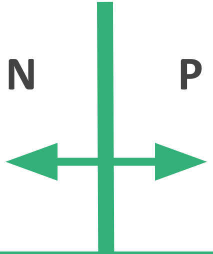
automatic analysis software **available**

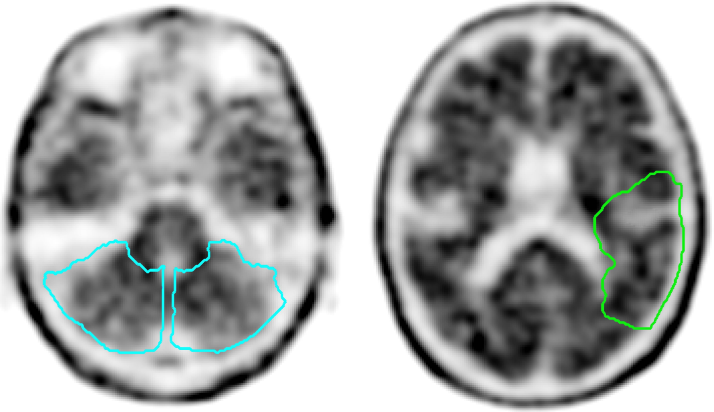
SUVr values/outcome critically depend on ROI **definitions** and **positioning**



Cerebellum as reference ROI

$$\mathrm{SUVR} = \frac{C_{\mathrm{ROI}}}{C_{\mathrm{ref}}} = \frac{\text{🟩}}{\text{🟦}}$$





SUVr method

- Acquisition noise
  - Poor image quality, arbitrarity in acq. parameters
- Physiological noise
  - To some extent canceled by the pathology
  - Issues with severe atrophy (e.g., ventricles enlargement)
- Gold-standard noise
  - Expert reader evaluated images
  - “Weak” gold standard (P/N)
- Data processing noise
  - Implement two other methodologies..

noises & assumptions

- Additivity
  - Pathologic Aβ deposit adds to aging-related (incidental) effect
- Linearity
  - Common & significative contribution in all the affected subjects
- Isolation
  - Slow time-scale
- Derivative
  - Smooth transition between N/P

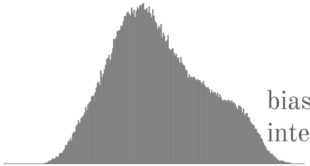
ELBA [Evaluaton of Brain Amyloidosis]

equal mix of geometric properties (sphericity) of iso-intensity surfaces & intensity statistics

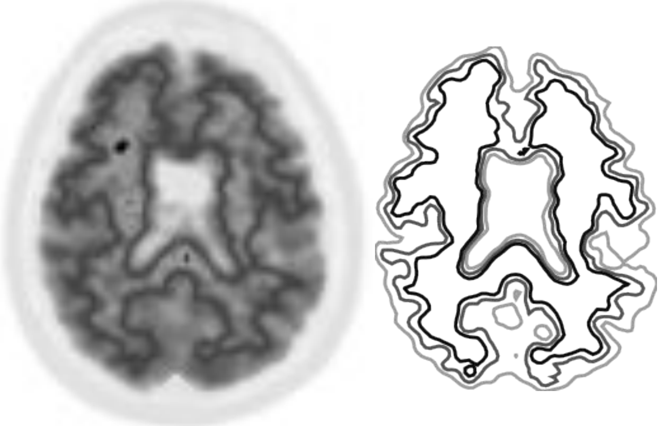
no need for ROIs, no need for reference uptake!

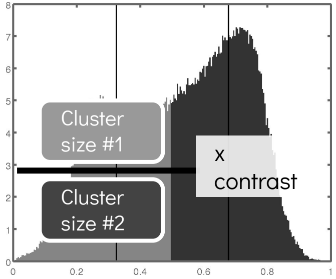
[1] ***SUVr-independent evaluation of brain amyloidosis***, Journal of Alzheimer's Disease, Vol. 54-4 (2016)

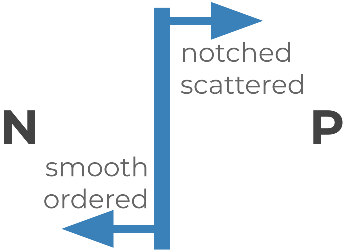
[2] ***Approaches to semi-quantification: beyond SUVr in amyloid imaging***, European Conference on Clinical Neuroimaging, Roma (2016)



bias on lower intensities

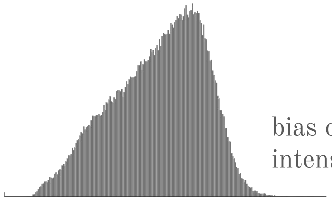




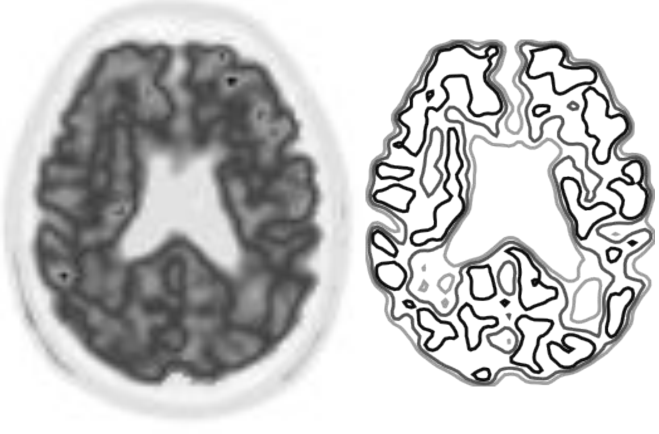


notched scattered

smooth ordered

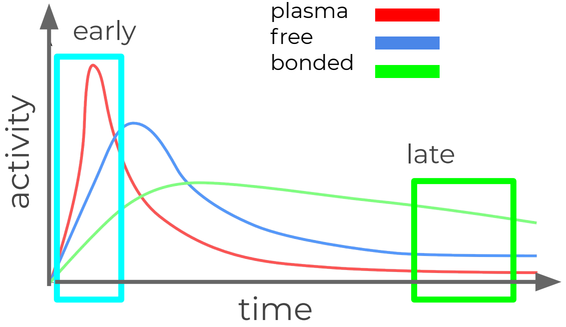


bias on higher intensities



TDr [Time-Delayed ratio]

REQUIREMENT: **early** acquisition, **proxy** of brain blood **perfusion** (Contractor 2012)



Target

highest uptake in
the **early** scan (CBF)

(Osch 2009)

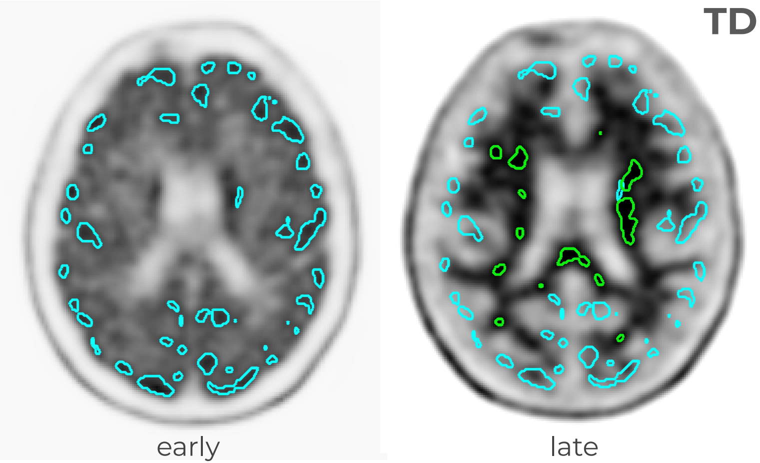
Reference

highest uptake in the
late scan (hot spot)

(Fleisher 2017)

ratio of raw (mean) intensities
no segmentation
***subject-dependent uptake** ROI*
*subject-dependent **reference ROI***

$$\textbf{TDr} = \frac{\langle I_{late} \rangle_{\text{Target}}}{\langle I_{late} \rangle_{\text{Reference}}} = \frac{🟦}{🟩}$$



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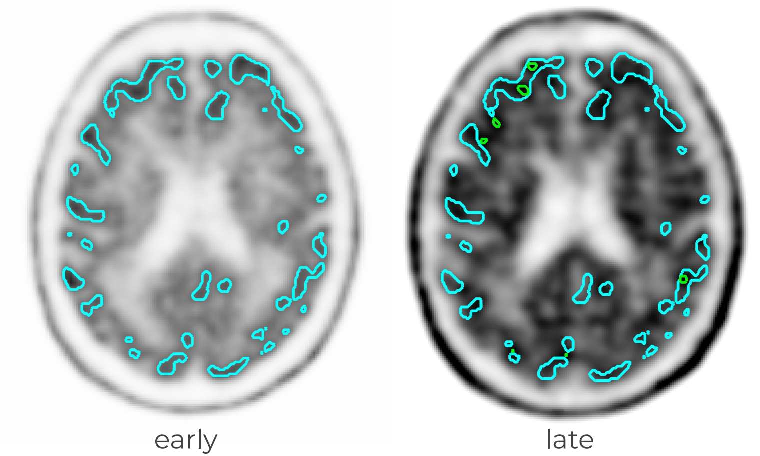


ROI definition

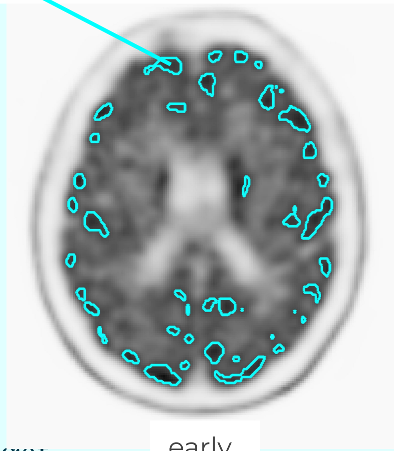
Target region (D_E)

$$\boxed{D_E} = (v \in E | I_v \geq I_0^E) \quad I_0^E = 0.85$$

Reference region (D_E)

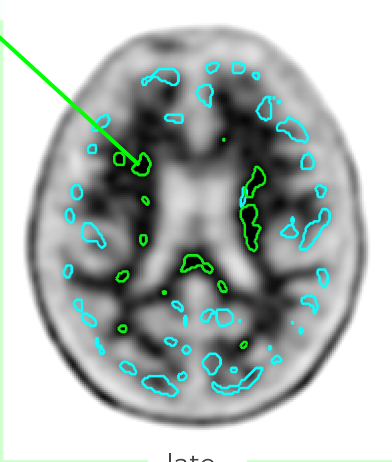
$$\boxed{D_L} = (v \in L | I_v \geq I_0^L) \quad I_0^L = 0.99$$

percentile on **early** (I_0^E) and **late** (I_0^L) scan intensity distribution



early

average target ROI **thickness** $\mu = 3.1\pm1.4$ mm, **comparable** to the **cortical GM** thickness (Hutton 2008, Lerch 2004)



late

hot spot on the late scan
(**non negligible volume,** $\mu = 13.47\pm1.2$ ml)

Concordance with visual assessment

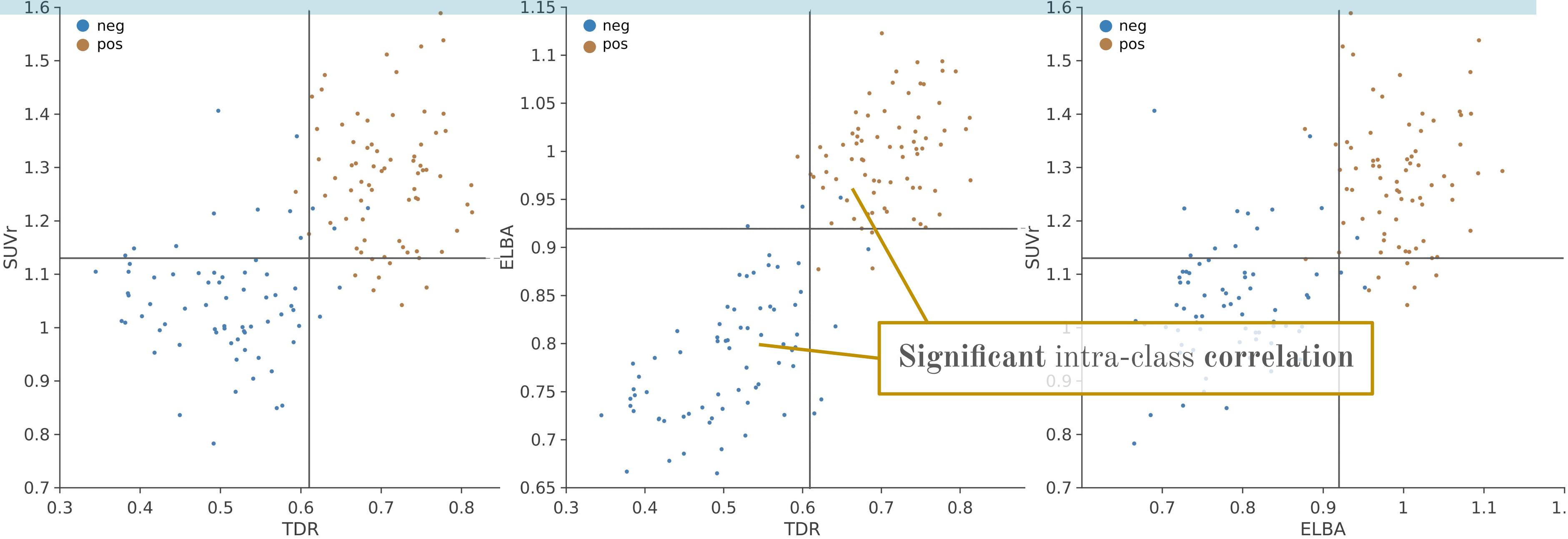
Site	TDr	SUVr	ELBA
Brescia	1.00	0.99	1.00
Geneva	1.00	0.95	1.00
Genoa	0.99	0.76	0.99
Pavia	1.00	0.94	0.98
Whole set	0.99	0.92	0.99

- **AUC** (Area Under ROC curve)
- TDr: **discriminating** power (single site, overall)

- Leave-10-out **cross validation**
- **500** repetition
- cut-off ($c_{TDr} = 0.611$)
- TDr: **excellent performances**

	Accuracy	Specificity	Sensitivity
		[95% CI]	
TDr	0.945 [0.937 0.951]	0.933 [0.931 0.934]	0.957 [0.928 0.970]
SUVr	0.862 [0.853 0.874]	0.836 [0.831 0.848]	0.893 [0.864 0.906]
ELBA	0.955 [0.944 0.958]	0.958 [0.958 0.959]	0.953 [0.930 0.957]

TDr versus SUVr and ELBA



Significant intra-class **correlation**

	Methods	whole set	negative	positive
Correlation Pearson r	TDr/SUVr	0.61 ($<10^{-3}$)	0.08 (<0.517)	0.002 (<0.980)
	TDr/ELBA	0.86 ($<10^{-3}$)	0.57 ($<10^{-3}$)	0.314 (<0.006)
	SUVr/ELBA	0.66 ($<10^{-3}$)	0.21 (<0.082)	0.03 (<0.801)

TDr significantly **correlates** with SUVr & ELBA

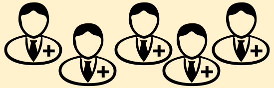
Quantification and grading - Data & Study Design

Cross-sectional data

- **Symptomatic outpatient**
- **175** patients (age [62-88])
- **Clinical suspicion:** MCIAD, possAD, probAD, probFTD, possDLB, probVaD, pseudoDD, aMCI, naMCI, SCI
- **6 centers**
  - HUG (Geneva)
  - IRCCS S.Martino (Genoa)
  - Fondazione Poliambulanza (Brescia)
  - Institute of Mental Health (Mannheim)
  - University of Paris Diderot (Paris)
  - University of Antwerp (Antwerpen)
- **No shared** acquisition **protocol**

Late scans:

1. **Visually** inspected & **labeled** (5 readers, 2 scales) (no consensus reached)



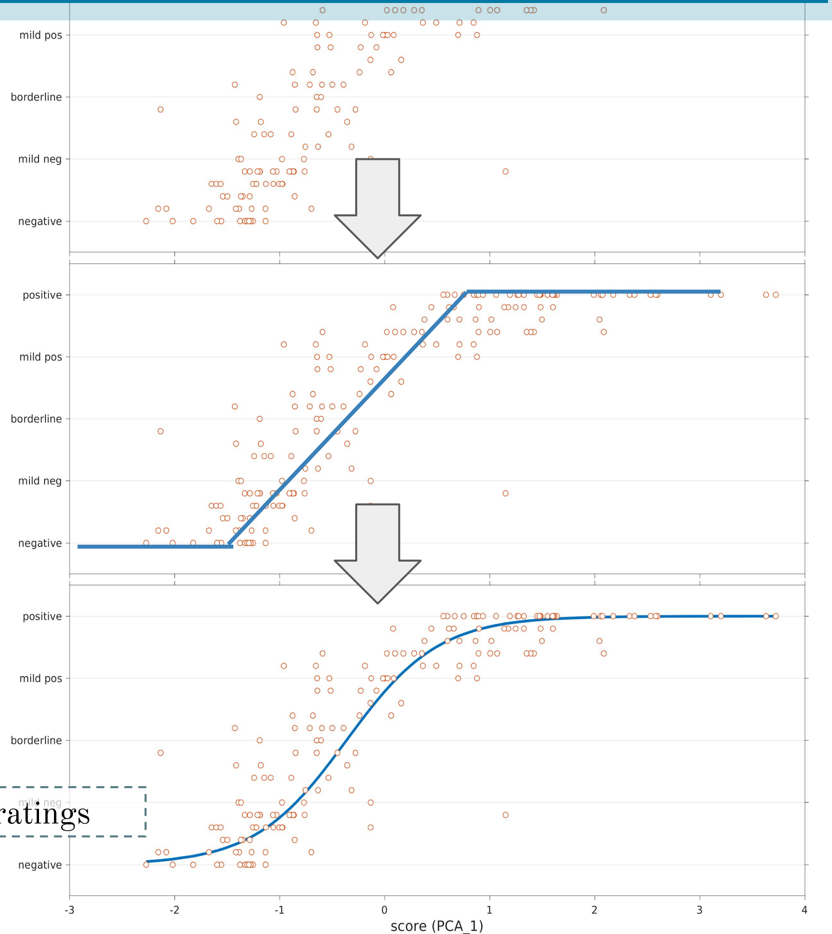
+ 5 yr scan reporting (NM)

2. Processed with **SUVr** & **ELBA** (Chincarini 2016)
3. Investigate link between quantification and 5-step scale
4. Study the “latitude”: the discrepancies of 5-step classification among evaluators

Quantification and grading - Link with quantification

The *natural* function to link semi-quantification to grading is the **sigmoid**.

It follows from the floor/ceiling effect on the visual reading and the necessity of a [smooth] transition (accumulation is gradual)



mean value of the visual ratings

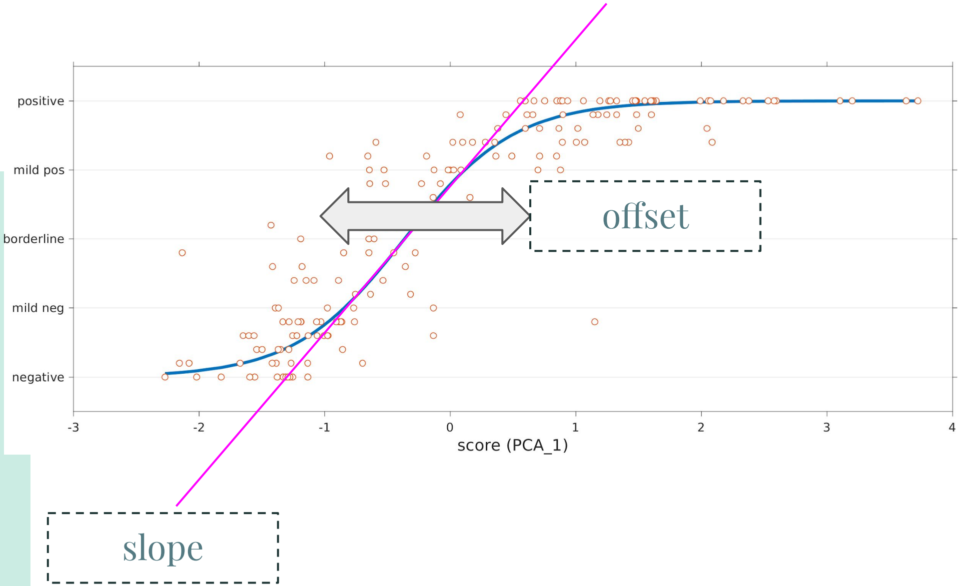
Quantification and grading - Free parameters

$$Gr(n,p,s,o) = p - \frac{p-n}{1+e^{-s(q-o)}}$$

p & **n** values are set by limiting conditions

Only the slope ***s*** and the offset ***o*** are free parameters.

Only 2 d.o.f. to fit ~60 data points



Quantification and grading - What can we measure?

the model can be used to study:

Contrast on tracers

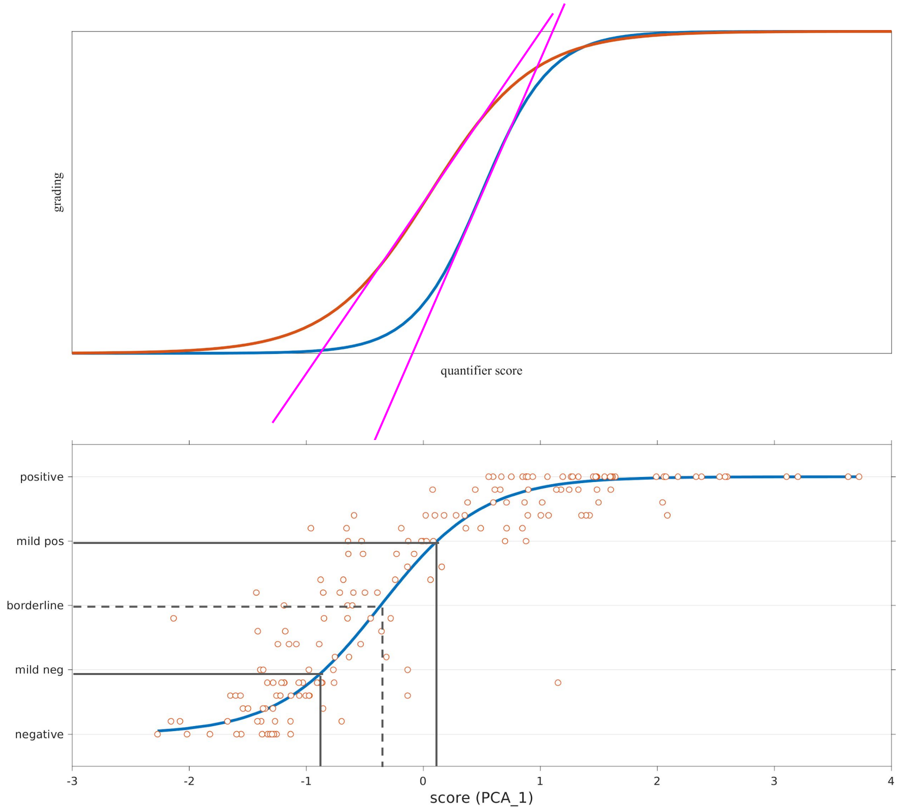
- Different slopes on different quantifiers hint to the degree of neg/pos discrimination of the tracer

Equivalence of quantifiers

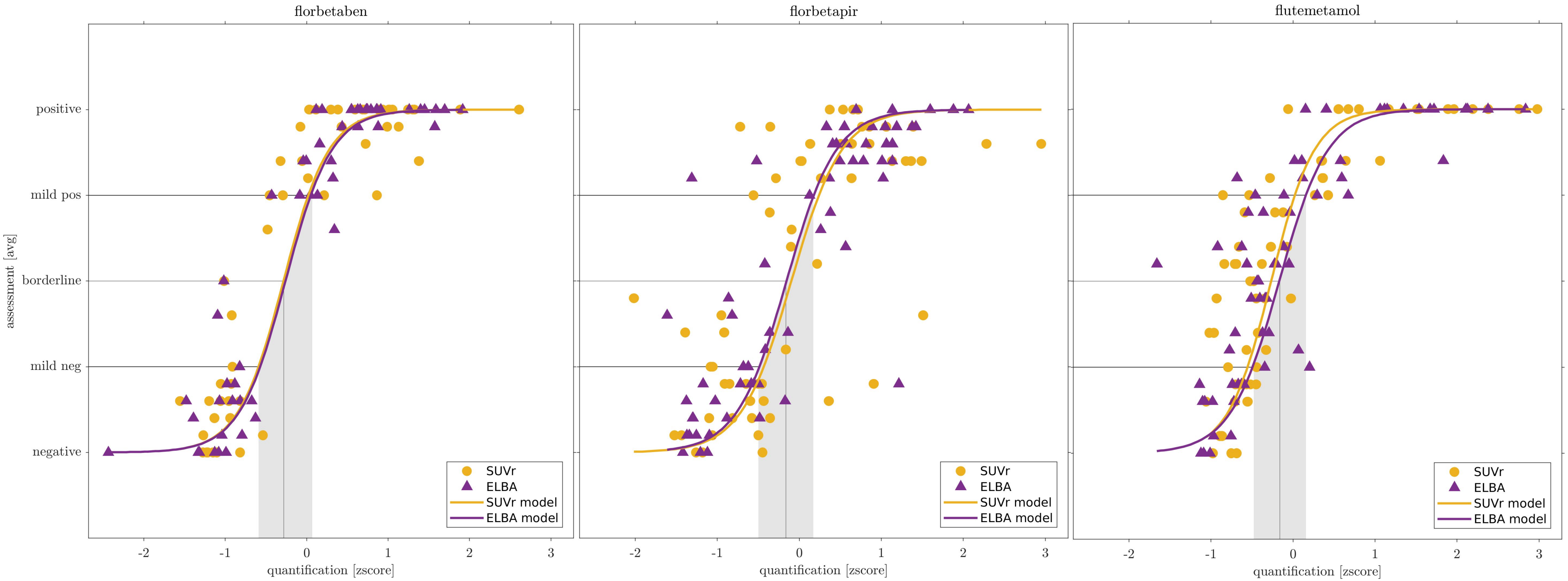
- Similarity of slope and offset for different quantifiers show equal ability to match the visual rating

Cutoff & Transition region

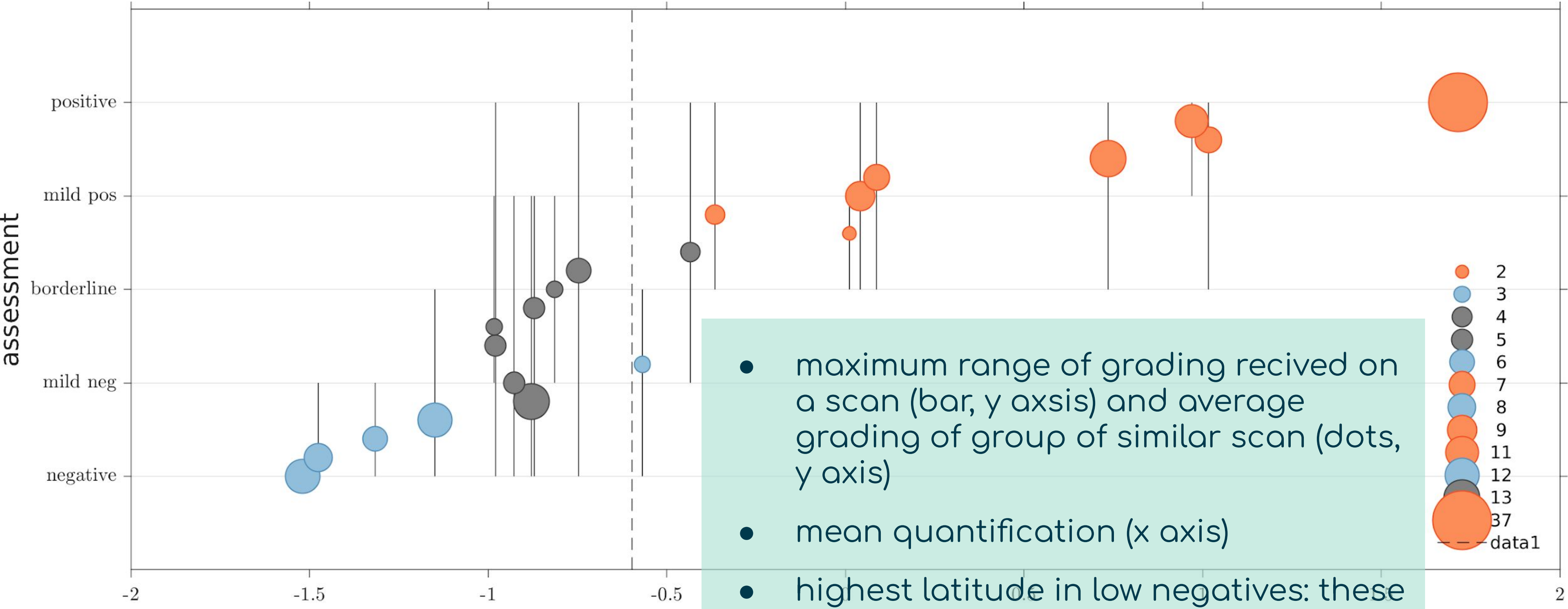
- model-driven cutoff allow a [almost] population-independent value



Quantification and grading - Sigmoid models by tracer



Quantification and grading - Latitude



- maximum range of grading recived on a scan (bar, y axsis) and average grading of group of similar scan (dots, y axis)
- mean quantification (x axis)
- highest latitude in low negatives: these scans are most at risk of misclassification