Harmonizing PET Data Symphony or Cacophony?

ADRC Imaging Core
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Harmonization Starts with Acquisition
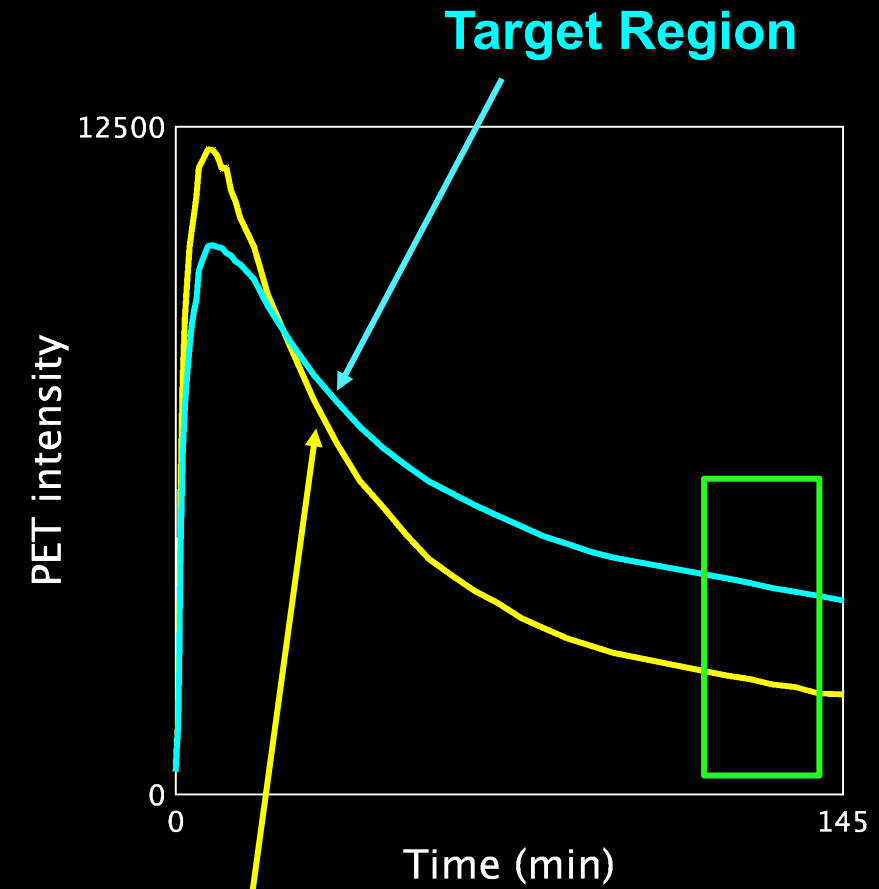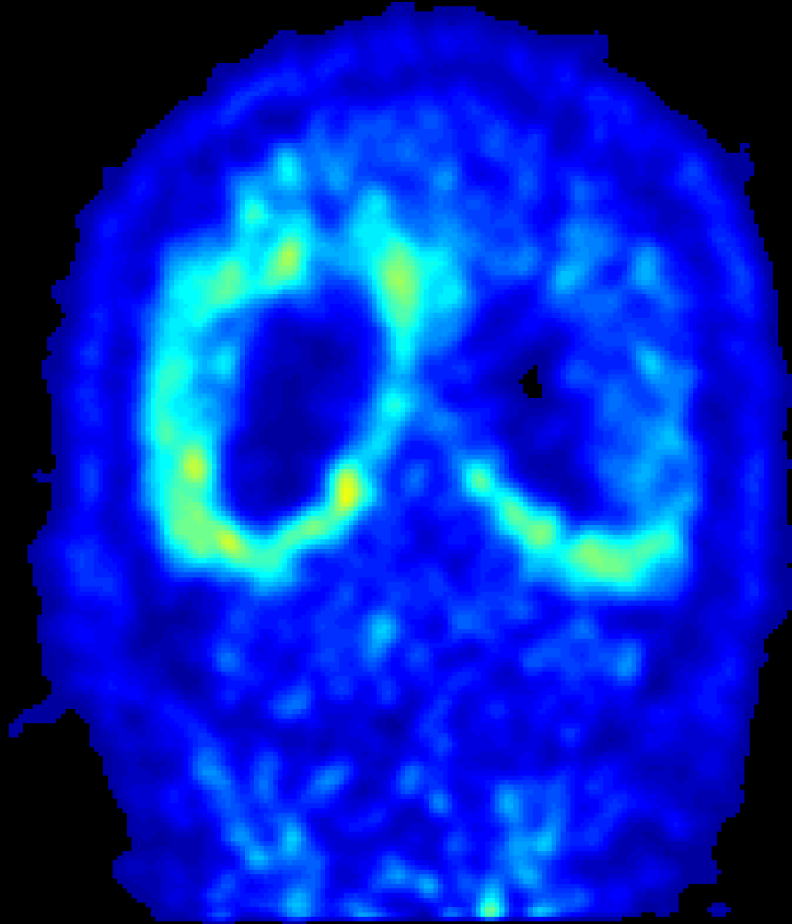
Tracer pharmacokinetics: standardize acquisition times for each tracer

Signal to noise: standardize injection doses

Instrument resolution: smooth data to common resolution

Instrument reconstruction: standardize for each scanner

Different Brain Regions Show Different Kinetics

Target Region

Reference region

Image SUVR

Harmonizing the Image Readout

Visual Reads

Pro: **Can be standardized, reliable**

Con: **Results dichotomous (+/-), quantitative observation may be important for monitoring**

Quantitation

Pro: **many advantages to continuous measures, parallels the biology, good for monitoring**
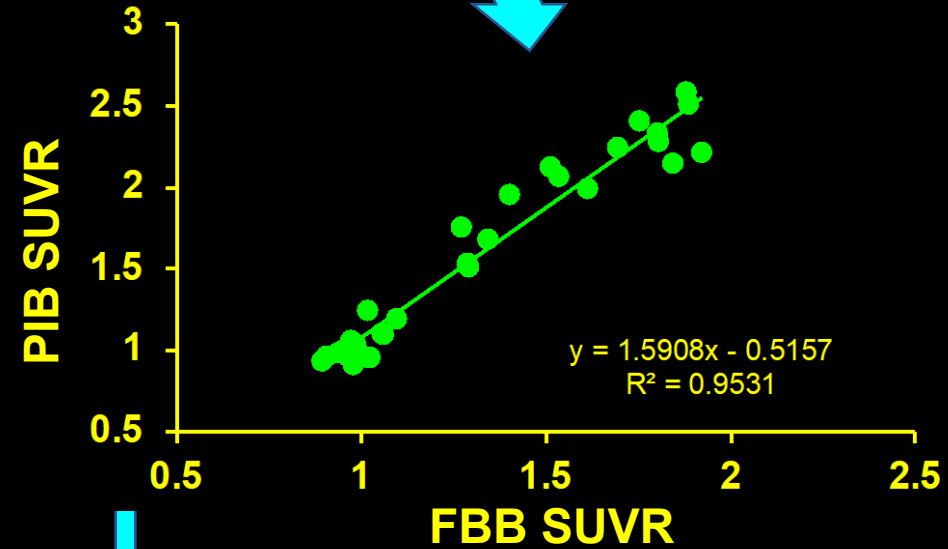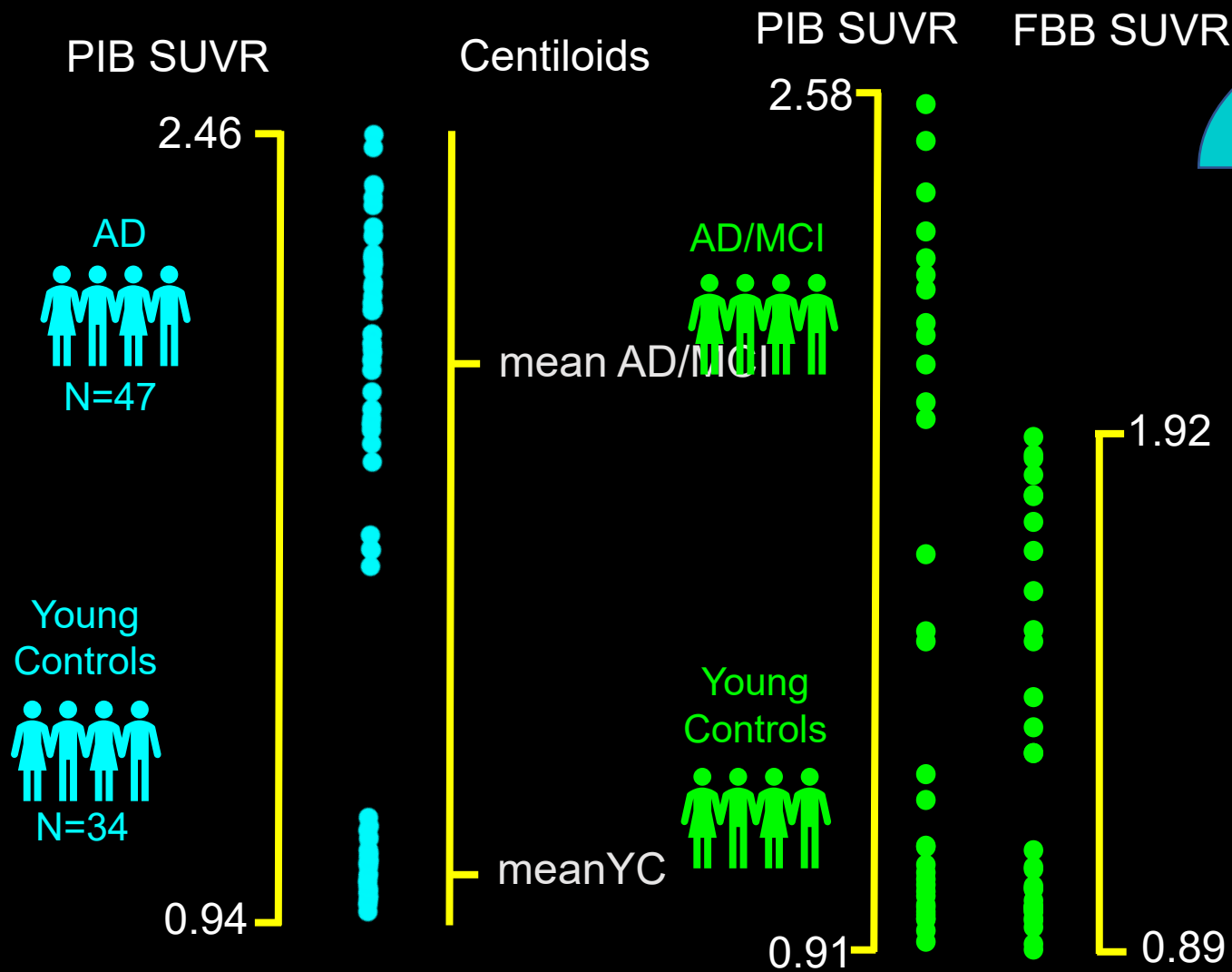
Con: **Can be complex**

Standardize the ROIs for reporting and standardize the scale

Centiloids

GAAIN Data Set

New Pipeline/Tracer (GAAIN ^{18}F Data)

PIB processed with GAAIN method

PIB SUVR | Centiloids

PIB SUVR | FBB SUVR

2.46

AD

N=47

Young Controls

N=34

0.94

2.58

AD/MCI

mean AD/MCI

Young Controls

0.91

1.92

meanYC

0.89

$$y = 1.5908x - 0.5157$$
$$R^2 = 0.9531$$

PIB SUVR

FBB SUVR

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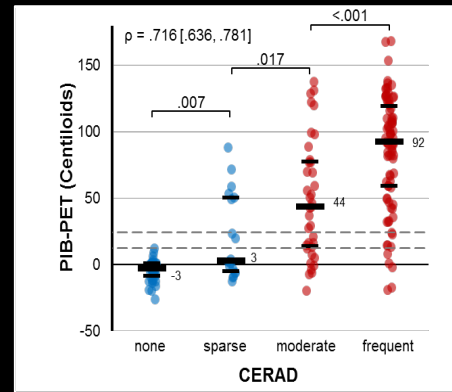1. Requires the GAAIN data to scale 0-100 anchors
2. Creates a new conversion equation for every tracer and processing pipeline

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

Amyloid PET Thresholds

PIB (5 centers N=179 autopsies)
CERAD non/sparse vs mod/freq: 12 CL
AD neuropathologic change:
24 CL

La Joie et al *Alzheimer's & Dementia* 2019

Florbetapir (FBP, ADNI)
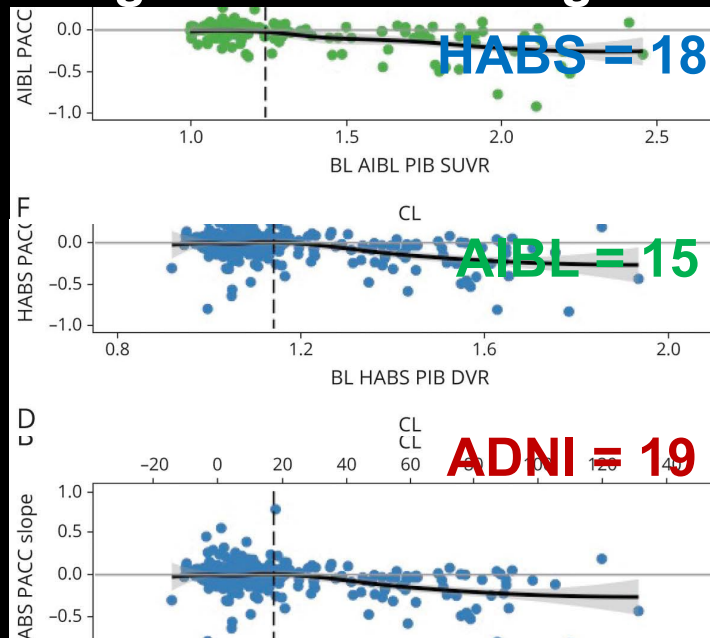**2 SDs above young controls**
1.11 = 20 CL

Joshi et al *J Nucl Med,* 2012

PIB (ALFA+ study)
ROC for CSF Aβ_{42}
12 CL

Salvado et al *Alz Res & Ther* 2019
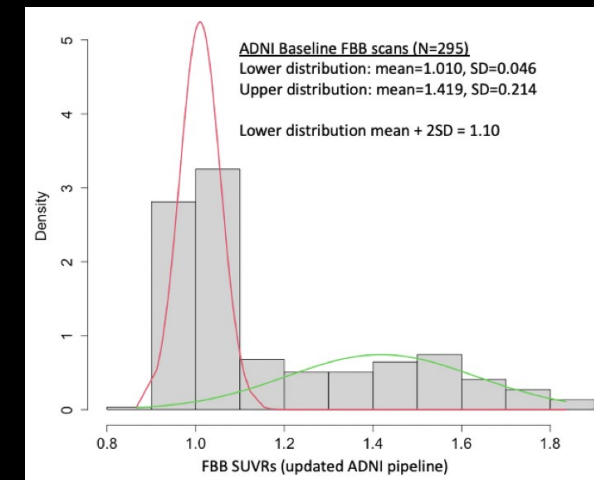
FBP (Avid data)
2 SDs above young controls
1.10 = 24 CL

Navitsky et al *Alz & Dem* 2018

PIB, FBB: level where cognitive decline begins

HABS = 18

AIBL = 15

ADNI = 19

Farrell et al *Neurology* 2021

Florbetaben (FBB, ADNI)
2 SDs above young controls
= 18 CL
GMM = 21 CL

Royse et al *Alz Res & Ther* 2021

iDEAS
Imaging Dementia—Evidence
For Amyloid Scanning

- ~18,000 patients from ~600 memory clinics scanned at ~350 PET facilities
- FDA-approved ^{18}F Aβ ligands: Florbetapir, Florbetaben, Flutemetamol
- Flexible protocol for image acquisition per published guidelines
- Local reads as positive/negative per FDA approved criteria

Post-acquisition processing to the centiloid scale without MRI
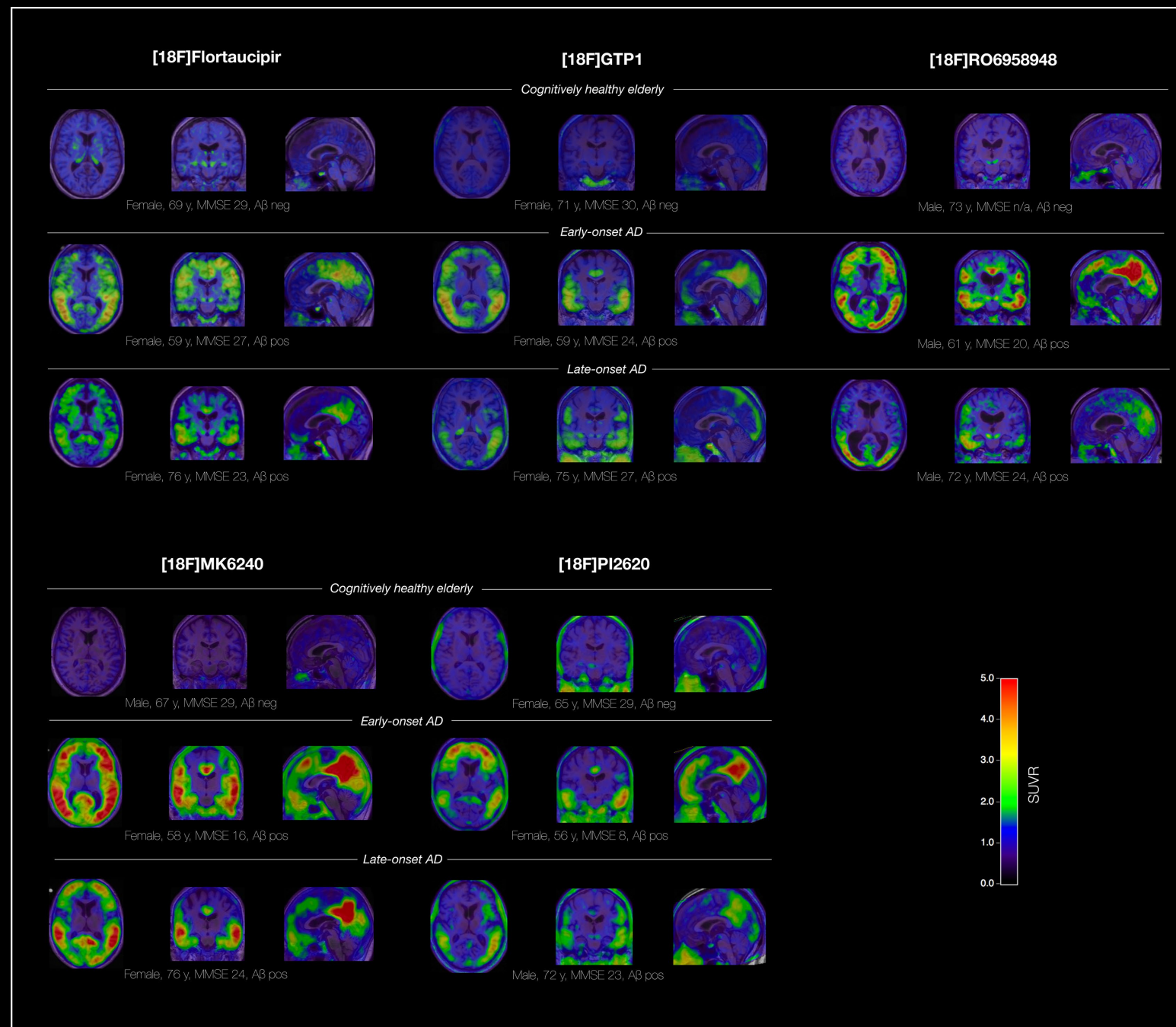
Prespecified threshold of 24 CL separates 2 populations

Most positive visual interpretations > 24 CL

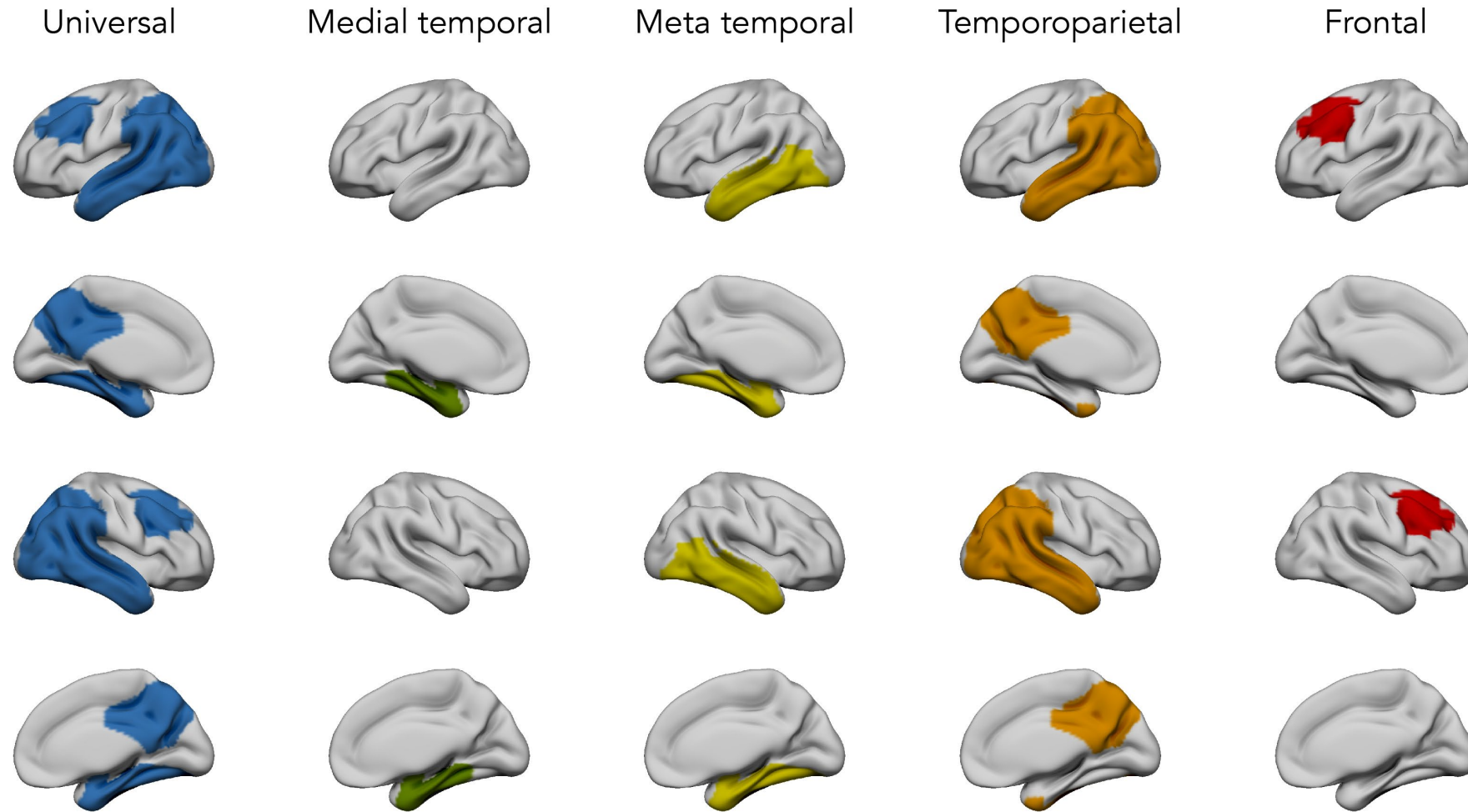**High visual/quantitative concordance with 24 CL threshold**

Most discordant cases near threshols

Tau PET Radiotracers

# Universal Tau PET ROI and Subregions

Universal • Medial temporal • Meta temporal • Temporoparietal • Frontal

Villemagne et al., medRxiv 2023

CenTauRs – Methods

- o Centiloid-like approach
    - ➢ One tracer is selected as reference (PIB equivalent); convert other tracer to equivalent units.
    - ➢ Convert that measure to CenTauRs using equation that maps SUVR to CenTauRs for reference tracer (set using anchor points)

- o Joint Propagation approach
    - ➢ Uses CenTauR as a common latent anchor scale for all observations
    - ➢ No need for a reference tracer; single step analysis where everything is estimated at once based on the full data set

[^{18}F]RO948 vs [^{18}F]Flortaucipir – CenTauRs (CL)
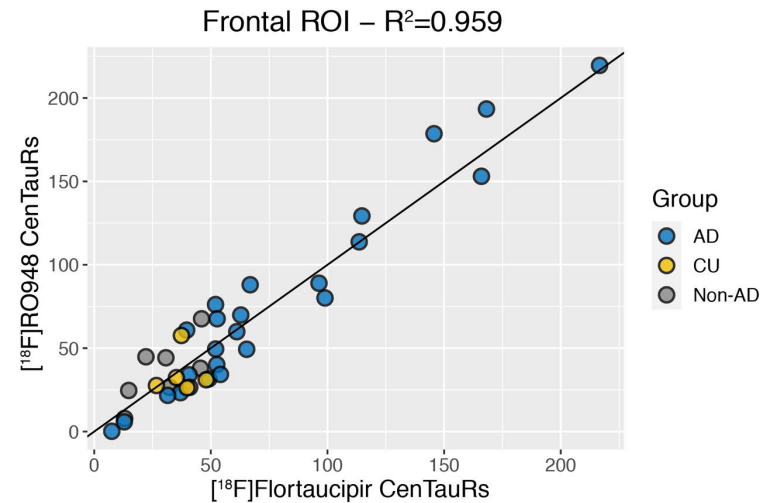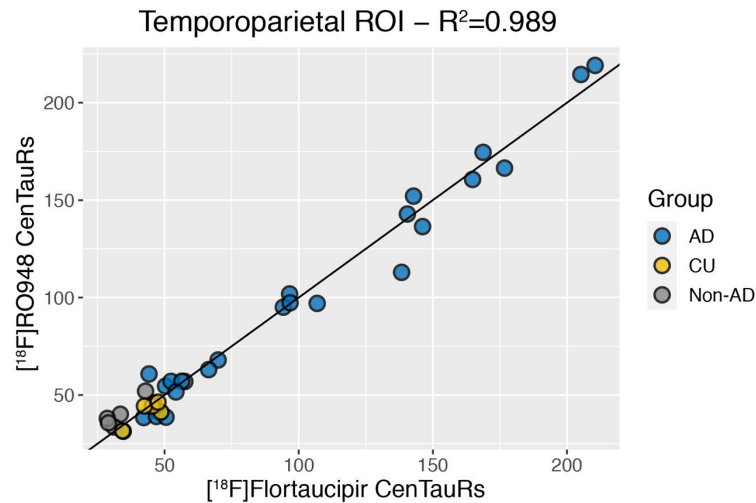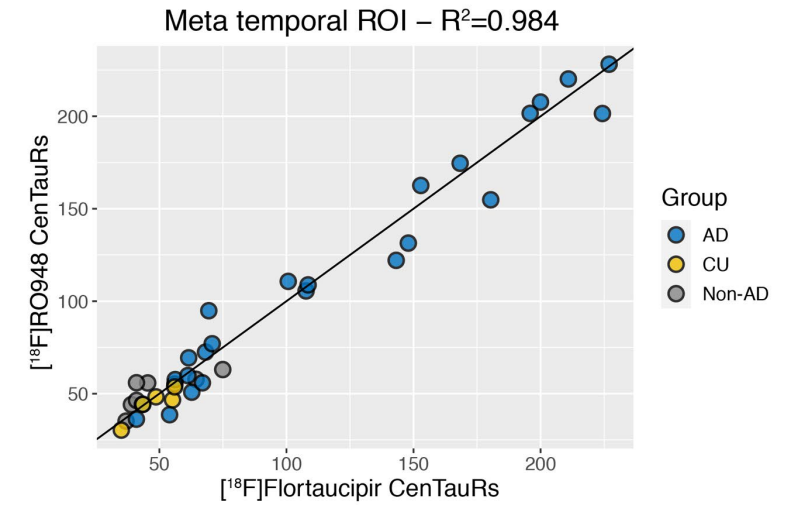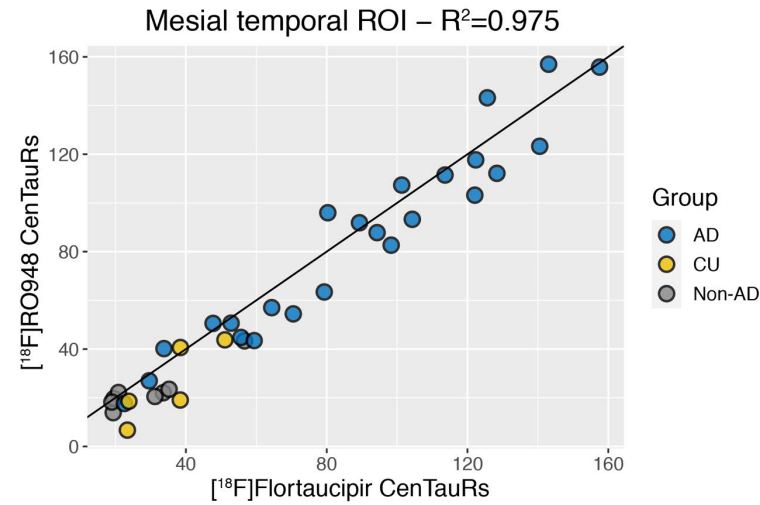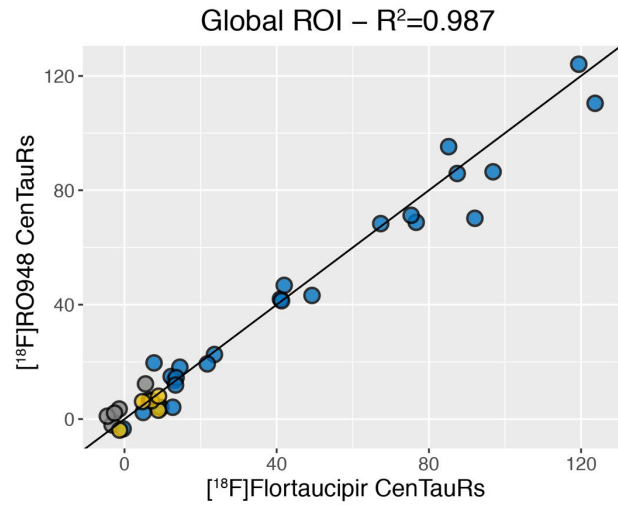
[¹⁸F]RO948 vs [¹⁸F]Flortaucipir – CenTauRs (JPM)
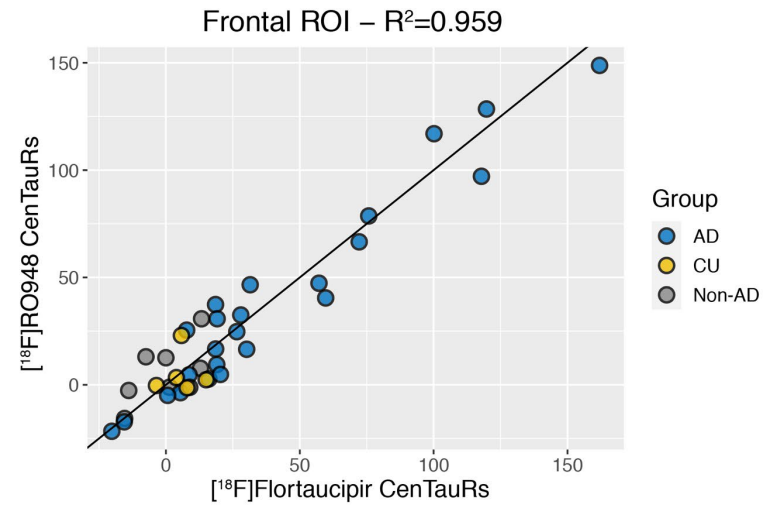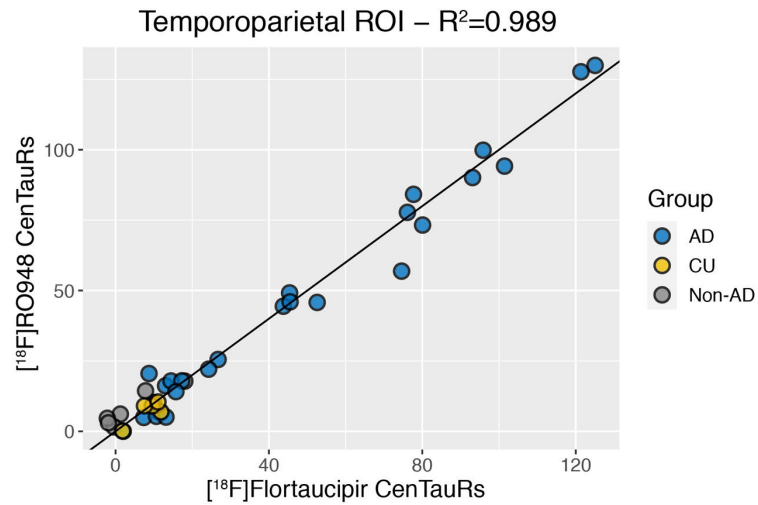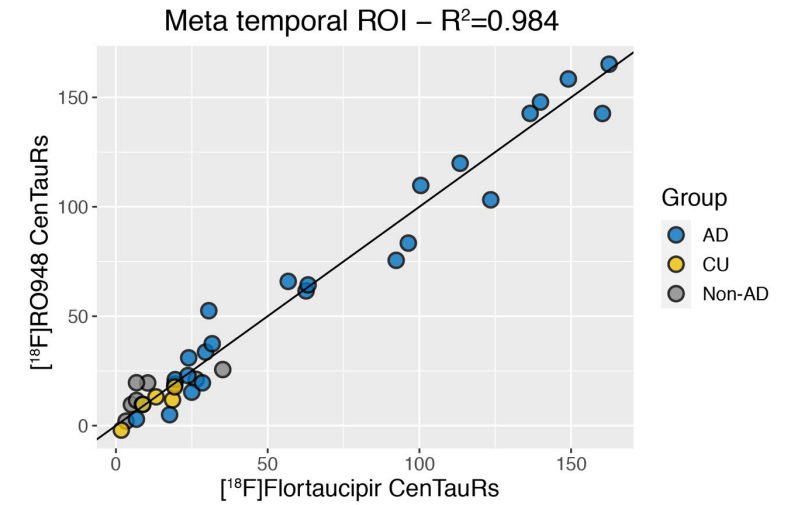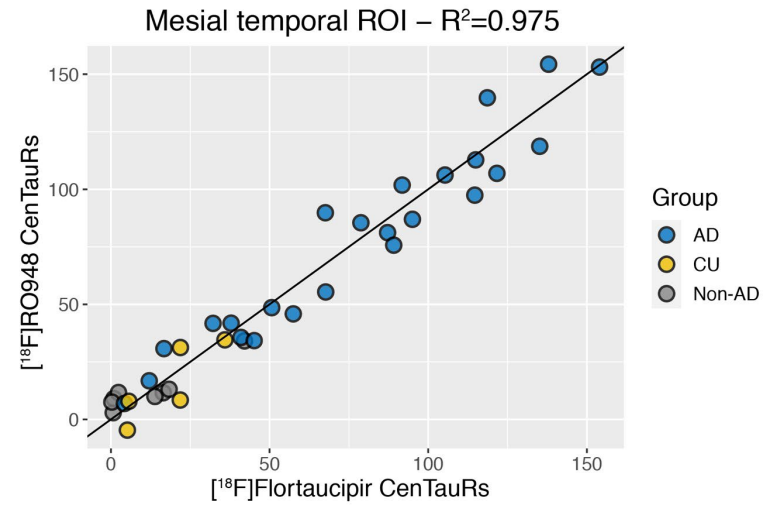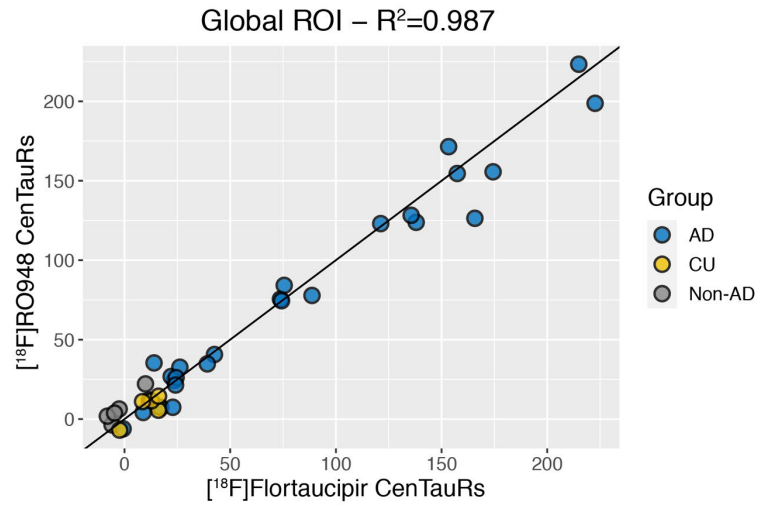
PET Harmonization in ADNI and SCAN

Data acquisition using standard dose of tracer and imaging times

Smooth data to 6mm resolution

Standard ROIs (Desikan-Killiany atlas/FreeSurfer)

For amyloid: SUVRs and centiloids

For tau: CenTauRs

Final Thoughts

No harmonization method is perfect

The tradeoff is usually accuracy/reliability vs cost
  Cost is time and money

What is necessary for the goals of the study?
  Thresholds for A+ or T+?
  Continuous measures of pathology – biological or intervention effects?
  Treatment initiation?