Regulatory Perspectives on Technical Characteristics of Drugs for Brain Amyloid PET

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U.S. Food and Drug Administration

FDA Workshop: Quantitative Brain Amyloid PET Imaging-Technical Considerations
November 17, 2022

Disclaimers

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Outline

1. Establishing effectiveness for diagnostic radiopharmaceuticals
2. Brain amyloid PET tracers
3. ^{18}F labeled brain amyloid PET tracers
4. Key points

Medical Imaging Agents: Labeled Indications

Diagnostic radiopharmaceuticals are governed by the same regulations as other drugs or biological products

Labeled Indications

- Structure delineation
- Disease or pathology detection or assessment
- Functional, physiological, or biochemical assessment
- Diagnostic or therapeutic patient management

Medical Imaging Agents: Establishing Effectiveness

- Code of Federal Regulations (CFR) 315
  - 315.5 Evaluation of effectiveness

  (a) The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use.
- Guidance on Developing Medical Imaging Agents – Establishing Effectiveness
  1. Validity and reproducibility
  2. Clinical utility

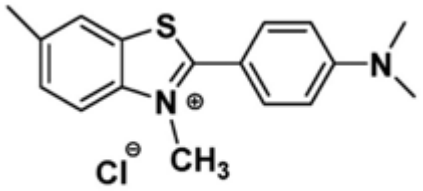
Establishing Effectiveness: Disease or Pathology Detection Claims

1. Validity and Reproducibility
    - Validity - Comparison to truth standard (e.g. histopathology)
    - Reproducibility
        - Test results
        - Interpretation of images obtained using the agent
2. Clinical usefulness
    - *Indication* – Does the image represent what it is designed to measure?
    - *Usefulness* – Is the provided information clinically useful?

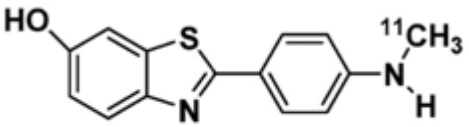
Amyloid PET Tracers

- In 2004, Klunk et al. reported the use of ^{11}C-labeled Pittsburgh compound B (^{11}C-PiB) to image amyloid plaques in patients with AD
- PIB is an analog of thioflavin-T, a dye used for staining amyloid in brain tissue
- In nanomolar concentrations injected for human imaging, ^{11}C-PiB was shown to bind with acceptable affinity to fibrillar Ab aggregates
- Binds to neuritic plaques more than diffuse plaques, and to vascular amyloid in cerebral amyloid angiopathy
- The short half-life of ^{11}C radioisotope of 20 minutes limits the use of ^{11}C-PIB to research PET centers equipped with a cyclotron
- Since the advent of ^{11}C-PiB, PET amyloid tracers labeled with ^{18}F, which has a half-life of 110-min, have been developed and can be distributed more widely from commercial radiopharmacies

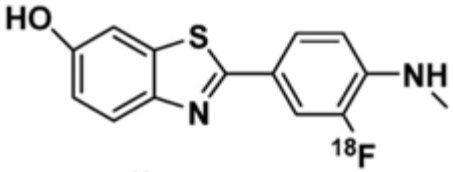
Structures of Amyloid PET Tracers



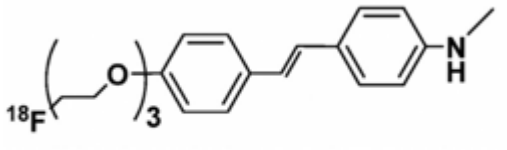
Thioflavin-T



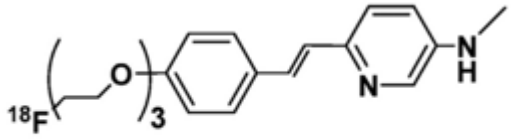
^{11}C-PiB



^{18}F-Flutemetamol



^{18}F-Florbetapir



^{18}F-Florbetaben

Amyloid PET Tracers: Establishing Effectiveness

1. Validity - Comparison to truth standard

Test Result:	Disease: Present (+)	Disease: Absent (-)	
Positive (+)	TP (a) true positive=TP	FP (b) false positive=FP	m1 = a+b =TP+FP total with positive test
Negative (-)	FN (c) false negative=FN	TN (d) true negative=TN	m2 = c+d =FN+TN total with negative test
	n1 = a + c = TP+FN total with disease	n2 = b +d=FP+TN total without disease	N = a+b+c+d =TP+FP+FN+TN total in study

2. Reproducibility – consistency of interpretation of images obtained using the imaging agent

Approved ^{18}F-labeled Brain Amyloid PET Tracers

---------- INDICATIONS AND USAGE ----------

xxxxx is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative **xxxxx** scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive **xxxxx** scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. **xxxxx** is an adjunct to other diagnostic evaluations (1).

Approved ^{18}F-labeled Brain Amyloid PET Tracers

Limitations of Use

- A positive **xxxxx** scan does not establish a diagnosis of AD or other cognitive disorder (1).
- Safety and effectiveness of **xxxxx** have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies (1).

Acquisition and Interpretation of Brain PET Scans Using Approved ^{18}F-labeled Amyloid PET Tracers

Summary Guidelines

Tracer name	Dose and acquisition protocol (clinical)	Visualization	Interpretation criteria for positive scan
^{18}F-florbetaben	~300 MBq; 15- to 20-min acquisition beginning at 45–130 min (research use, 20-min acquisition beginning at 90–110 min)	Gray scale; window images to optimize GM/WM contrast in cerebellum	Increased GM uptake extending to cortical margin involving most slices in at least 1 of 4 target cortical regions: frontal, parietal, precuneus/posterior cingulate, lateral temporal; regional cortical tracer uptake/brain amyloid plaque load scores (*20*)
^{18}F-florbetapir	~370 MBq; 10- to 20-min acquisition beginning at 30–50 min (package insert guidelines) for clinical use or 50–70 min (optimized kinetics for quantification) for research use	Inverse gray scale; window images to optimize GM/WM contrast in cerebellum	Loss of GM/WM contrast due to increased cortical binding in, first, 2 or more brain areas (each larger than single gyrus) with reduced or absent GM/WM contrast or, second, 1 or more areas with intense signal where GM > WM
^{18}F-flutemetamol	~185 MBq; 10- to 20-min acquisition at 60–120 min (research use, 20-min acquisition at 90–110 min)	Color scale (NIH); normalize so that pons is at 90% of activity	Increased GM uptake (>50%–60% peak intensity) or loss of GM matter contrast in at least 1 of 4 cortical regions and 1 subcortical region: frontal, inferolateral parietal, precuneus/posterior cingulate, lateral temporal, striatum

Source- Table modified from Marianne Chapleau et al. J Nucl Med 2022;63

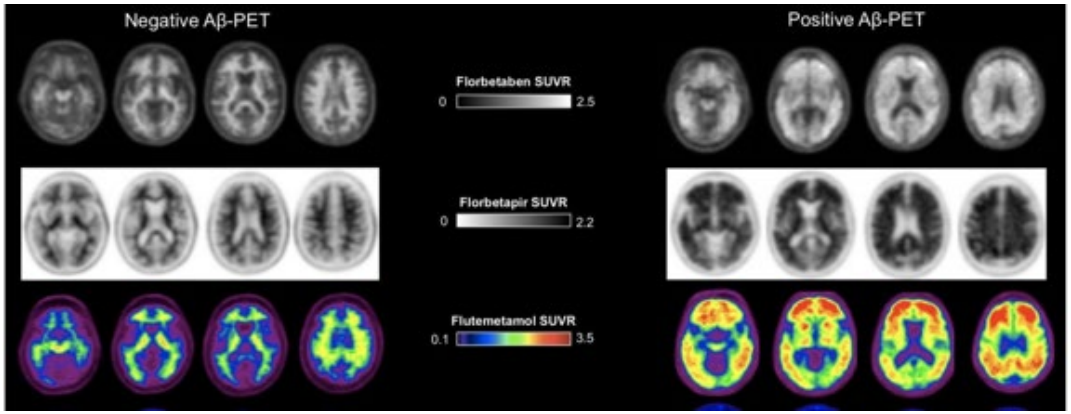
Images should be interpreted only by readers who successfully completed the training program (electronic or in-person) provided by the manufacturer

Objective of the image interpretation is to estimate beta amyloid neuritic plaque density in gray matter and label the images as beta-amyloid positive or beta-amyloid negative but not to make a clinical diagnosis

Typical Distribution of Uptake of Approved ^{18}F-labeled Amyloid PET Tracers in the Brain

- The topography of distribution of uptake of amyloid PET tracers is consistent with the known distribution of amyloid pathology in AD
- All amyloid PET tracers show nonspecific retention in the white matter, irrespective of the presence or absence of amyloid pathology
- All amyloid PET tracers bind to fibrillar amyloid and not to the more toxic soluble Abeta oligomers

Negative and positive images using approved amyloid PET tracers



Source- Figure modified from Marianne Chapleau et al. J Nucl Med 2022;63

Key Points

- Three F-18 labelled PET tracers have been approved for assessing cerebral amyloid plaque pathology in diagnostic work-up of suspected Alzheimer's Disease
- Scanning protocols are relatively similar across tracers
- Visual rating protocols differ across the three tracers
- Visual interpretations are currently the standard in clinical practice – objective is not to make a clinical diagnosis but to label images as amyloid positive or negative
- Since FDA approval, quantitative metrics with these tracers are being used in natural history studies for disease staging and monitoring disease progression in patients with Alzheimer's Disease but they are not included in the current FDA Prescribing Information

Thank You!!

Regulatory Perspectives on Devices for Brain Amyloid PET Quantitation

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FDA-CDER-CDRH, SNMMI, and MITA Workshop: Quantitative PET Brain Amyloid
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Disclaimer

- I do not have any conflicts of interest
- The mention of any commercial products, methods, trade names, or organizations does not imply endorsement or recommendation for use by the FDA, the Department of Health and Human Services, or United States Government.

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Outline

- 510(k) pathway (regulatory concerns)
- Devices in imaging assessments
- Intended use/indications for use
- Validation and performance data

Devices in Amyloid Quantitation

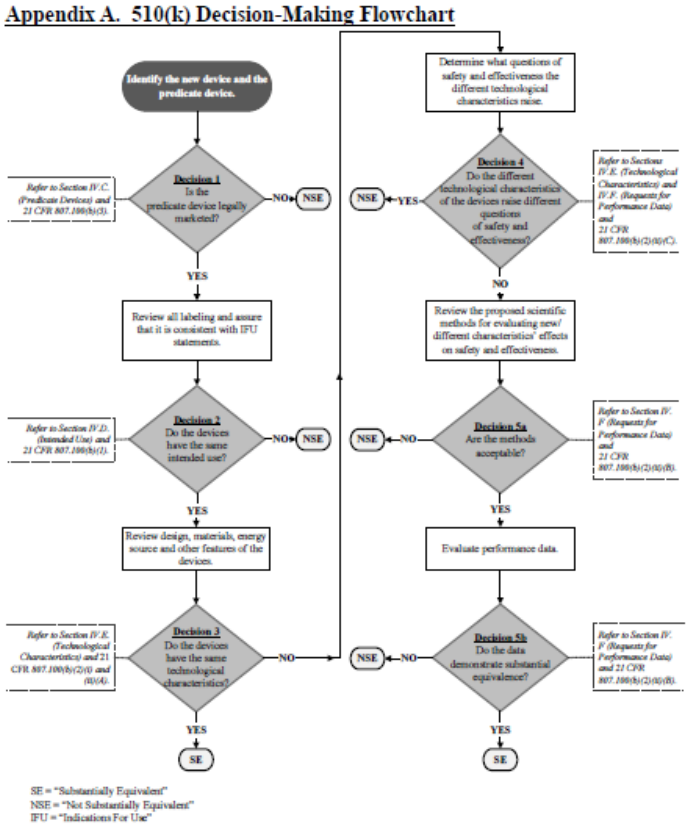
- PET scanner
  - Protocols
  - Corrections
  - Reconstructions
- Analysis software
  - Visualization
  - Preprocessing
  - Co-registration
  - Regions of interest
  - Presentation of images or metrics to the user

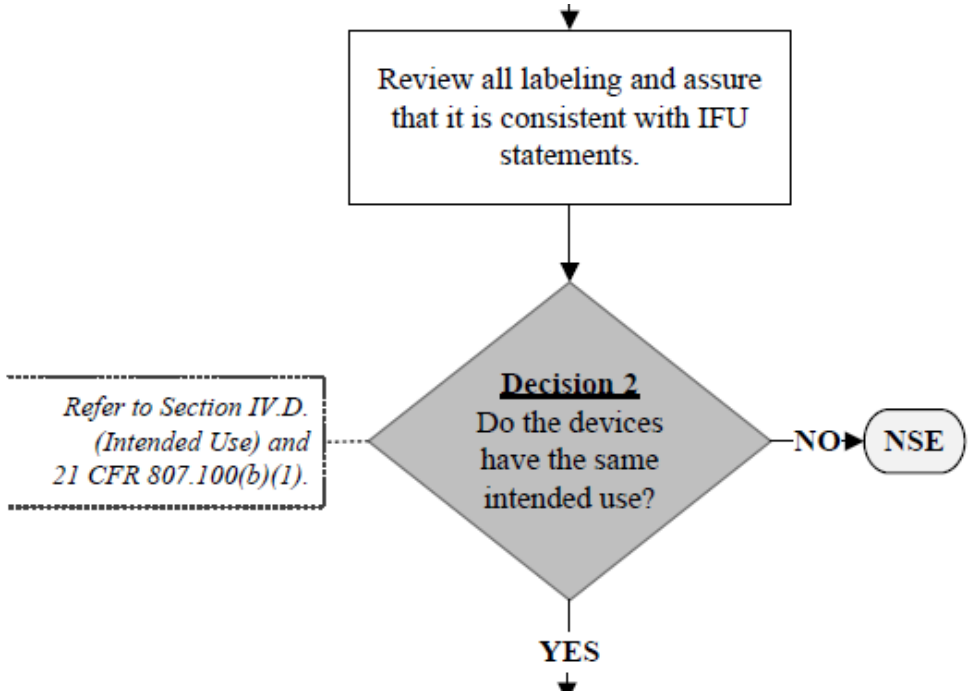
510(k) Premarket Notifications

Substantially equivalent (SE):

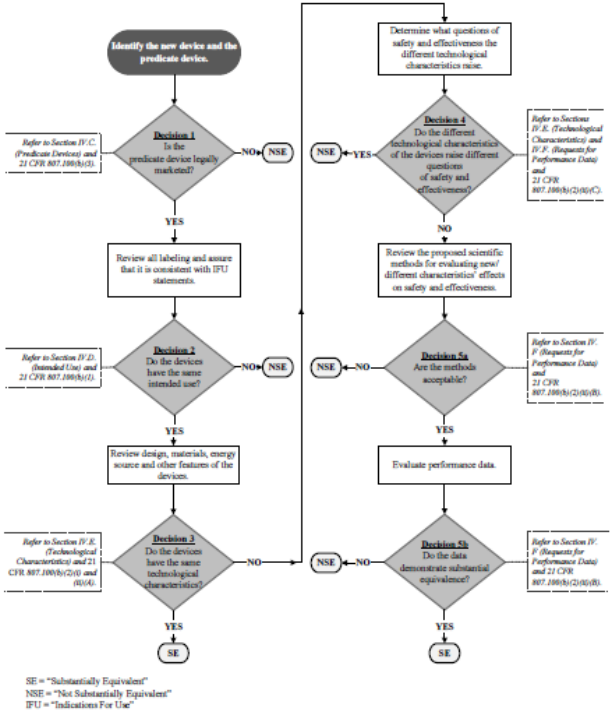
same intended use AND same technological characteristics OR

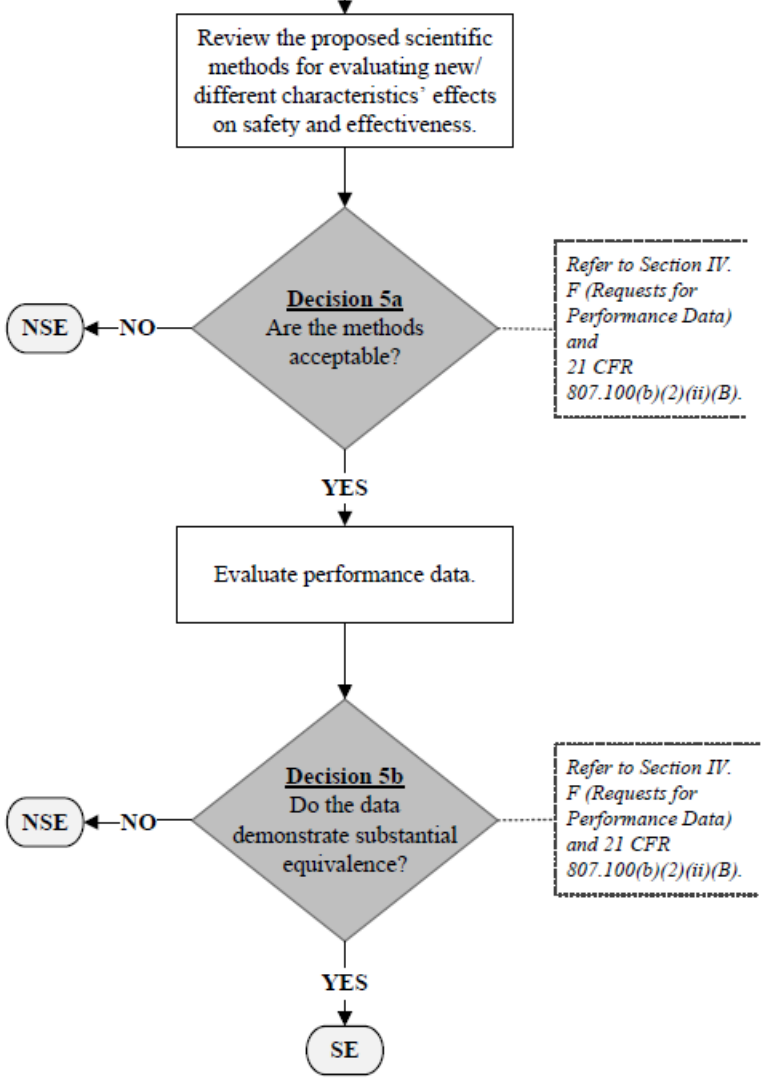
same intended use AND different technological characteristics (e.g., change in material, design, energy source, software) AND these differences do not raise different questions of safety and effectiveness


Appendix A. 510(k) Decision-Making Flowchart
Identify the new device and the predicate device.
Decision 1
Is the predicate device legally marketed?
NO
NSE
YES
Review all labeling and assure that it is consistent with IFU statements.
Decision 2
Do the devices have the same intended use?
NO
NSE
YES
Review design, materials, energy source and other features of the devices.
Decision 3
Do the devices have the same technological characteristics?
NO
YES
SE
Determine what questions of safety and effectiveness the different technological characteristics raise.
Decision 4
Do the different technological characteristics of the devices raise different questions of safety and effectiveness?
YES
NSE
NO
Review the proposed scientific methods for evaluating new/ different characteristics' effects on safety and effectiveness.
Decision 5a
Are the methods acceptable?
NO
NSE
YES
Evaluate performance data.
Decision 5b
Do the data demonstrate substantial equivalence?
NO
NSE
YES
SE
SE = "Substantially Equivalent"
NSE = "Not Substantially Equivalent"
IFU = "Indications For Use"


Review all labeling and assure that it is consistent with IFU statements.
Refer to Section IV.D. (Intended Use) and 21 CFR 807.100(b)(1).
Decision 2
Do the devices have the same intended use?
NO
NSE
YES

Appendix A. 510(k) Decision-Making Flowchart





Intended use

The general purpose of the device or its function. The intended use of a device encompasses the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended to be used.

General to specific

Levels of Specificity for diagnostic medical devices:

1. Identification or measurement of a physical parameter (e.g., image, heart rate) or biochemical parameter (e.g., analyte)
2. Identification of a new or specific target population (e.g., women, children of a certain age range) or anatomical location (e.g., MR of the brain)
3. Identification of the clinical use of the measurement (e.g., diagnosis, screening)
4. Identification of or implication of an effect on the clinical outcome (e.g., screening mammography reduces breast cancer mortality)

Evidence depends

- On the regulatory pathway (e.g., 510k, PMA)
- Statutory standards
  - "least burdensome" – the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.
  - Substantial equivalence
  - Reasonable assurance of safety and effectiveness

Examples of Indications

- Visualization of images
- Tools for quantitative analyses (including segmentation)
- Tools for quantitation associated with amyloid
- (not cleared today) Tools for diagnosing disease (e.g., Alzheimer's Disease)

Evidence and indications

- Evidentiary expectations are linked to the indications, technological characteristics, and regulatory pathway
- In general, more specificity in the diagnostic claims leads to a greater expectation for performance data to demonstrate a reasonable assurance of safety and effectiveness

Qualitative vs. Quantitative

Qualitative

From flutemetamol and florbetapir, florbetaben, “Images are designated as **positive or negative** either by comparing radioactivity in cortical grey matter with activity in adjacent white matter

Florbetaben – “the PET image assessment is categorized as “beta-amyloid-**positive**” or “beta-amyloid-**negative**”

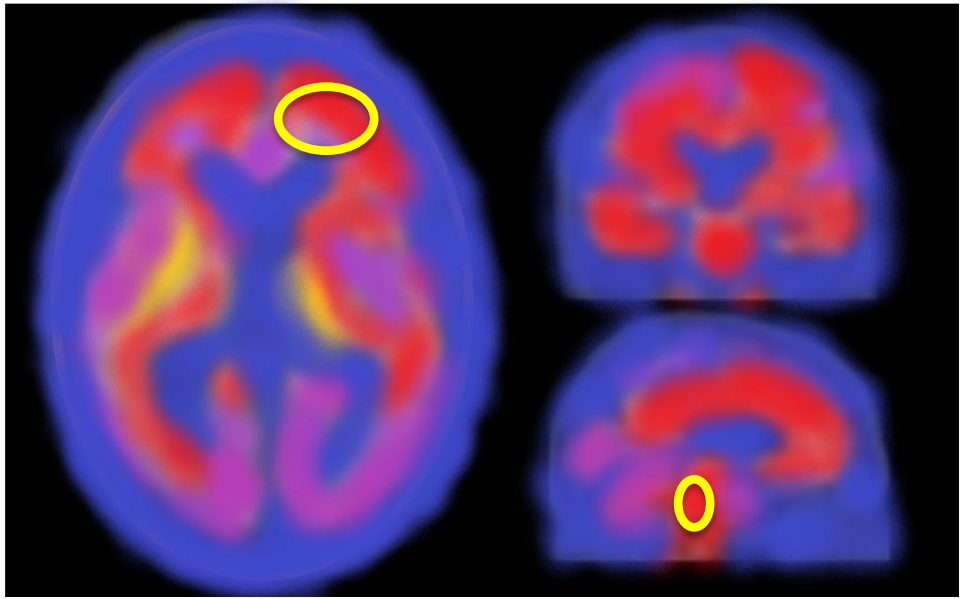
Quantitative

- An objective characteristic derived from a medical image measured on a ratio or interval scale (e.g., mL, cm, m/s, m^3)
- SUVr comparing pons region to medial parietal cortex region based on the average intensity in two regions bounded by segmentation

Cleared devices

- Search of internal 510k for “amyloid” and product code LLZ, KPS found more the 20 devices
- Any device with SUVr capabilities “could” be used to do some type of quantitative analysis
- Many devices have semi-automated segmentation capabilities for various brain structures
- Devices may include statistical comparisons to a normative dataset (especially for anatomical segmentation based on MRI)

Cleared devices



Example:

- Input images
- Draw ROIs (target/reference)
- Average
- Divide target/reference

Many flavors within and between FDA-cleared software packages

Validation

- **Definition[1] –** establishing that the performance of a test, tool, or instrument is acceptable for its intended purpose
- **Type/extent of validation data required depends on the claims**
  - Intended use/Indications for use for medical devices

1. BEST glossary - PMID: 27010052

Software validation and performance data

- **Validation** - establishing that the performance of a test, tool, or instrument is acceptable for its intended purpose (BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet] - PubMed (nih.gov))
- **Design validation** - "means establishing by objective evidence that device specifications conform with user needs and intended use(s)." 21 CFR 820.3(z)(2)
- **Performance data** – Performance data can be any data, including non-clinical (e.g., data from engineering testing, such as fatigue, wear, corrosion, etc., biocompatibility, functional animal studies, cadaver, etc.) and/or clinical, that are provided to support the substantial equivalence of a device that is intended to be marketed. (The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] | FDA)

Quantitative Imaging Guidance

Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions: Guidance for Industry and Food and Drug Administration Staff (June 2022)

- Definitions
- Potential sources of measurement error
- Information to include in a premarket submission
  - Function description
  - Technical performance assessment
  - Labeling

Understanding uncertainty

- Uncertainty information should be communicated in labeling
- Technical performance assessment may be used to investigate potential sources of measurement error and expected uncertainty
- Primary sources of variability should be described in labeling, if specific performance metrics related to uncertainty cannot be provided

Uncertainty of quantitative (or qualitative) metrics

- Under controlled conditions, pathology changes may be reliably and accurately measured with quantitative techniques or assessed qualitatively
- Understanding the effect size in terms of measurement error
  - How much change is meaningful?
  - How much might be measurement error?
  - How much physiologic variation is anticipated (e.g., topography of amyloid burden)?
  - Confounds/interference (e.g., measurement specificity/sensitivity)?

Summary

- 510(k) pathway and other regulatory pathways
- Explored existing devices in imaging assessments of amyloid
- General-to-specific indications for use
- Validation and performance data

THANKS!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ADMINISTRATION

Amyloid quantitation methodologies

Susan M Landau, PhD

Helen Wills Neuroscience Institute
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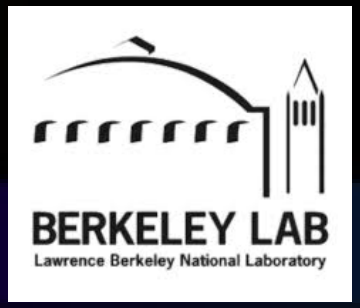
Molecular Biophysics and Integrated Bioimaging
Lawrence Berkeley National Lab



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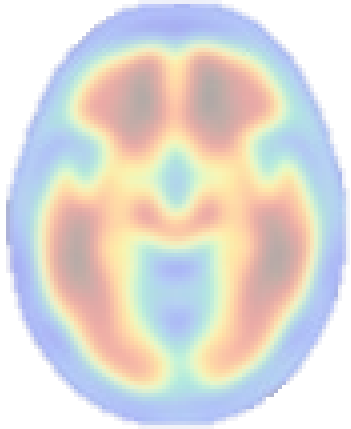
U24 AG067418



SUVrs and CLs: Which quantitation issues matter?

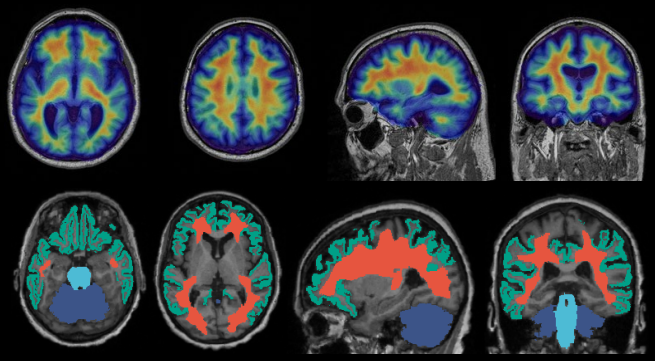
+/- status: Are visual reads as good as quantitation?

When is +/- status not sufficient?

Challenges and unresolved problems in Aβ quantitation

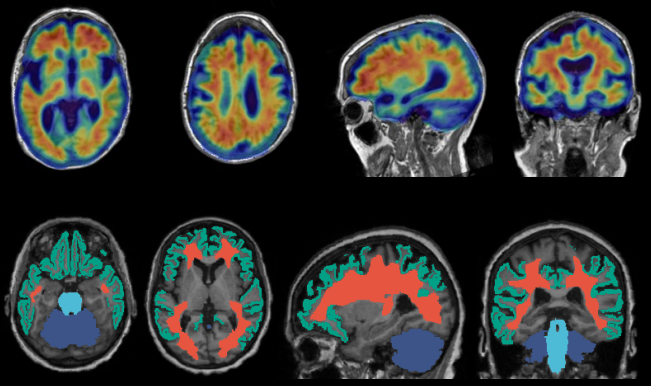
Quantitation of Aβ PET

Aβ- Cognitively normal



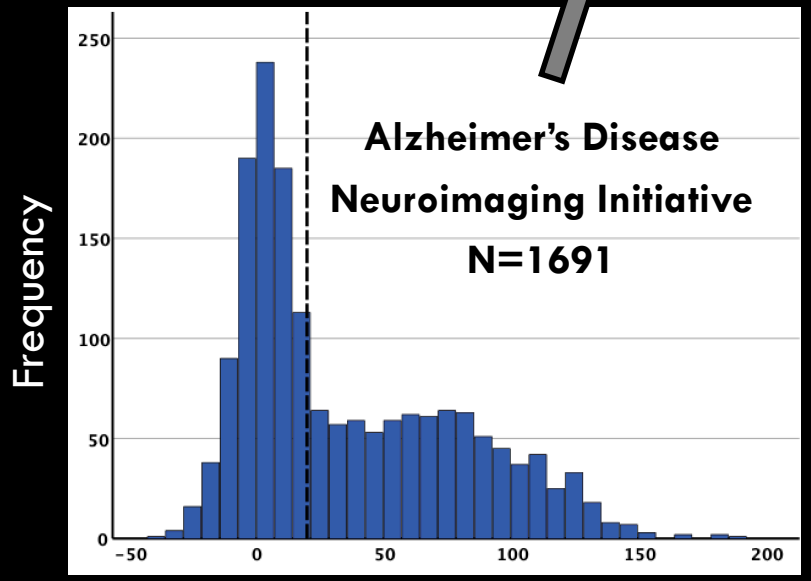
coregister

Aβ+ Alzheimer's patient



coregister

Multisite Aβ image dataset available to the scientific community for evaluating pipelines



Factors related to quantitation of Aβ PET

Image acquisition / reconstruction

Injected dose

Post-injection acquisition time, # of frames

Frames realigned / participant motion

Scanner-specific factors: reconstruction, spatial resolution

Processing and Analysis

Common image resolution

ROIs/ref region definition:

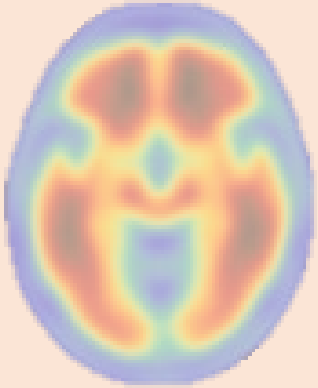
Native vs template space

Anatomical vs statistical

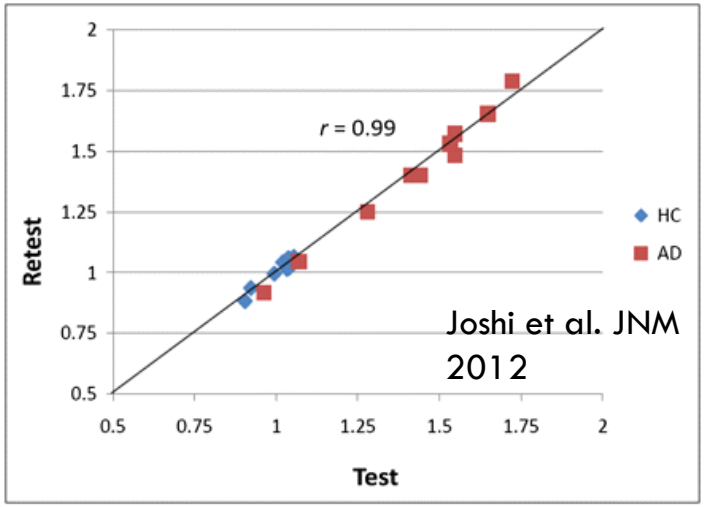
Standardized units (Centiloids)

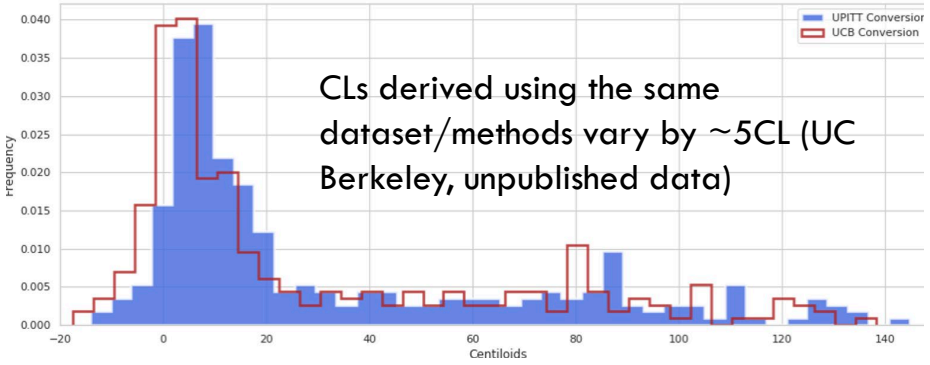
Partial volume correction

Longitudinal analysis



Aβ PET SUVr test-retest variability is ~5%





PiB

~5% (LoPresti et al. JNM 2005)

~3.5% (Villemagne et al. Ann Neurol 2011)

Florbetapir

AD: 2.4% ± 1.4%

Young controls: 1.5% ± 0.8%

(Joshi et al. JNM 2012)

Florbetaben

AD: 6.8% (0.6-12.2%) (AD)

Older controls: 2.9% (0.1-9%)

(Rowe et al. JNM 2009)

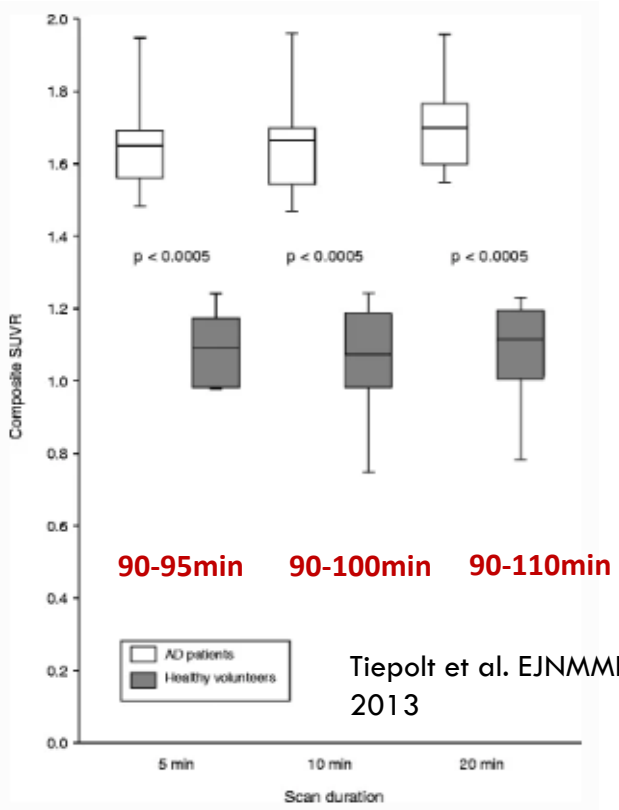
Flutemetamol

~1-4%

(Vandenberghe et al. Ann Neurol 2010)

Methodological factors that affect SUVRs/CLs within the test-retest range probably have minimal influence on quantitation

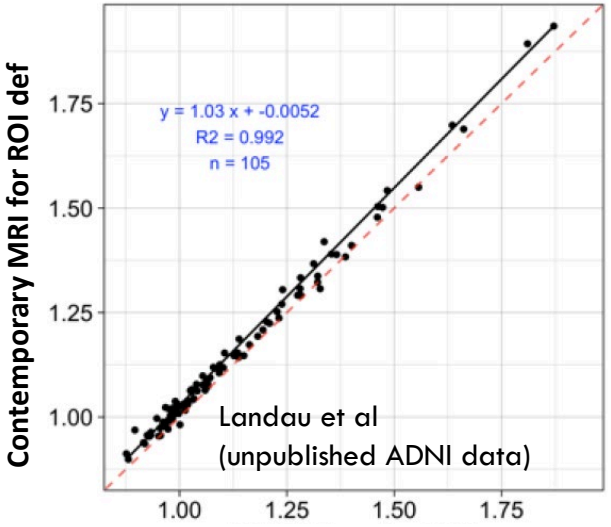
Acquisition time



90-95min **90-100min** **90-110min**

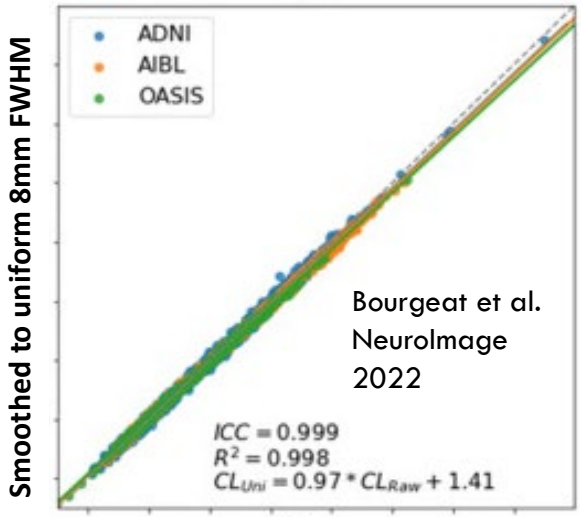
Tiepolt et al. EJNMMI 2013

Contemporary MRI



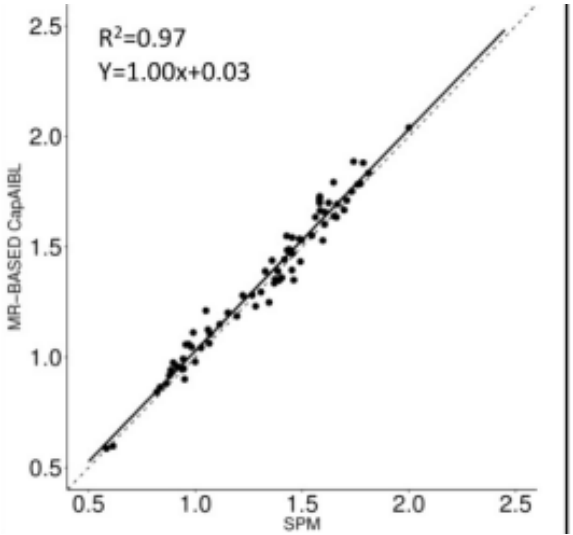
MRI ≤10yrs prior to PET for ROI def

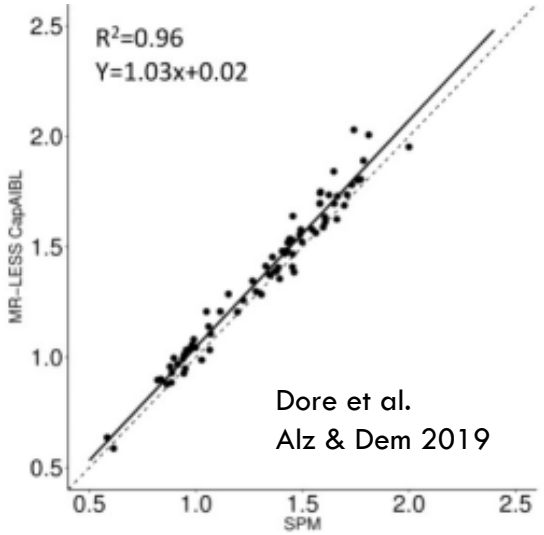
Uniform smoothing



No uniform smoothing

Modifications to Centiloid pipeline

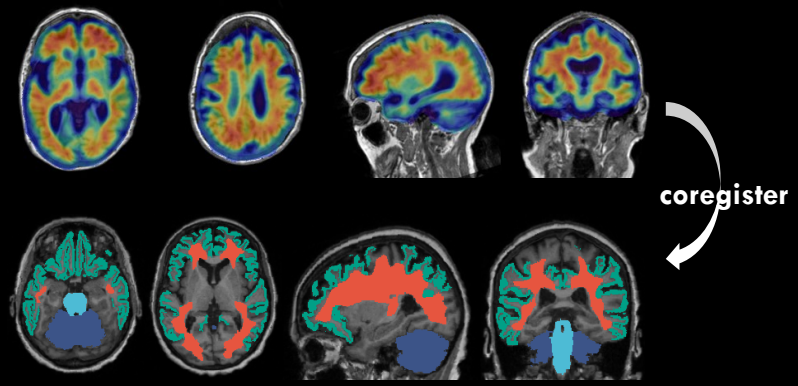




Region of interest definition

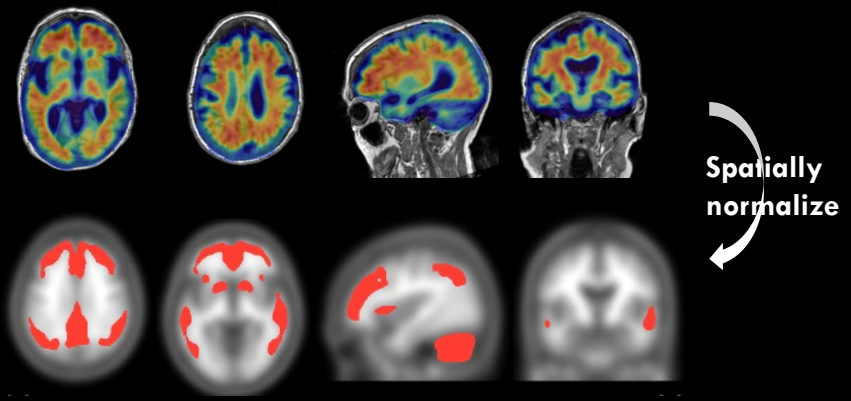
Processing using MRI-defined regions

"MRI-dependent"

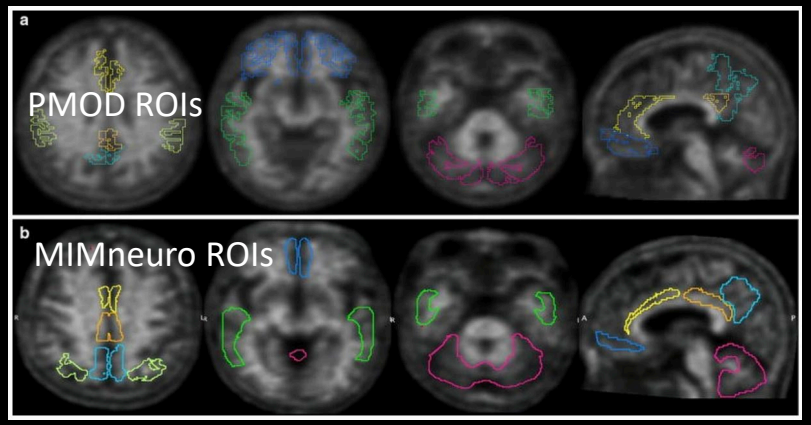


Processing using template-defined regions

"MRI-free"



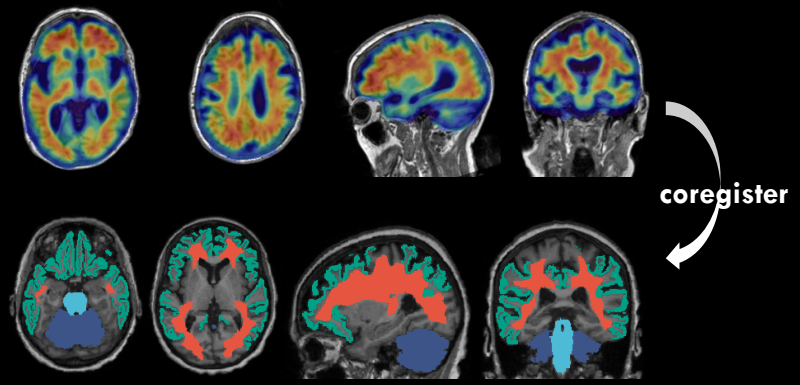
GAAIN ROIs used for centiloid standardization
(Klunk et al. Alz & Dem 2014)



Choi et al. Ann Nucl Med 2016

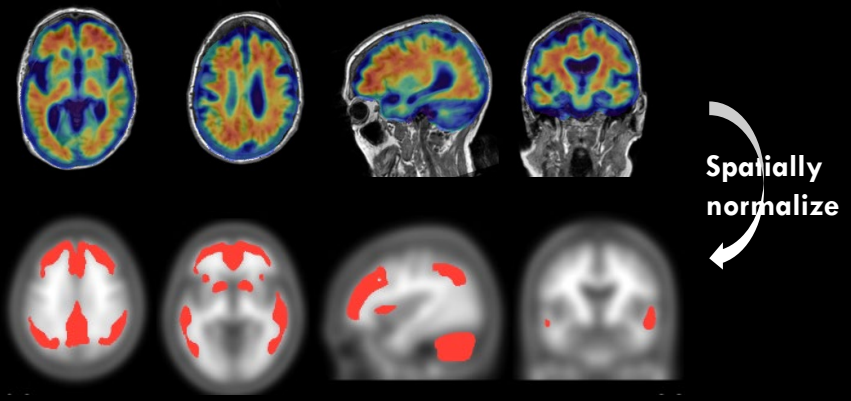
Processing using MRI-defined regions

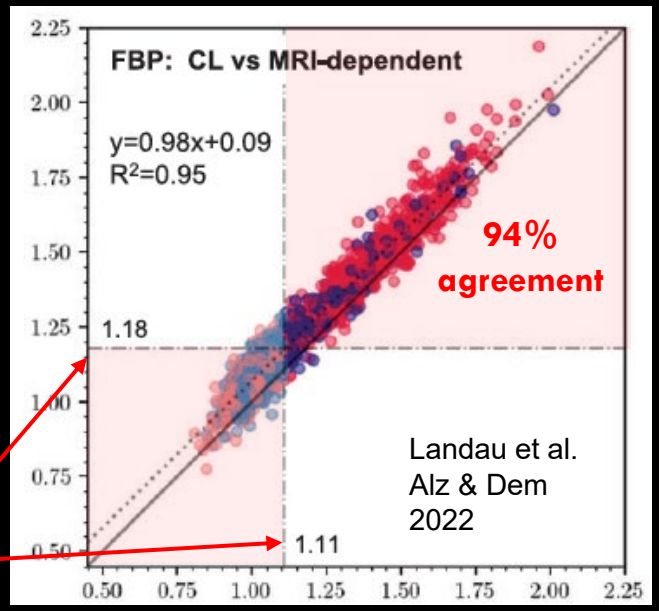
"MRI-dependent"



Processing using template-defined regions

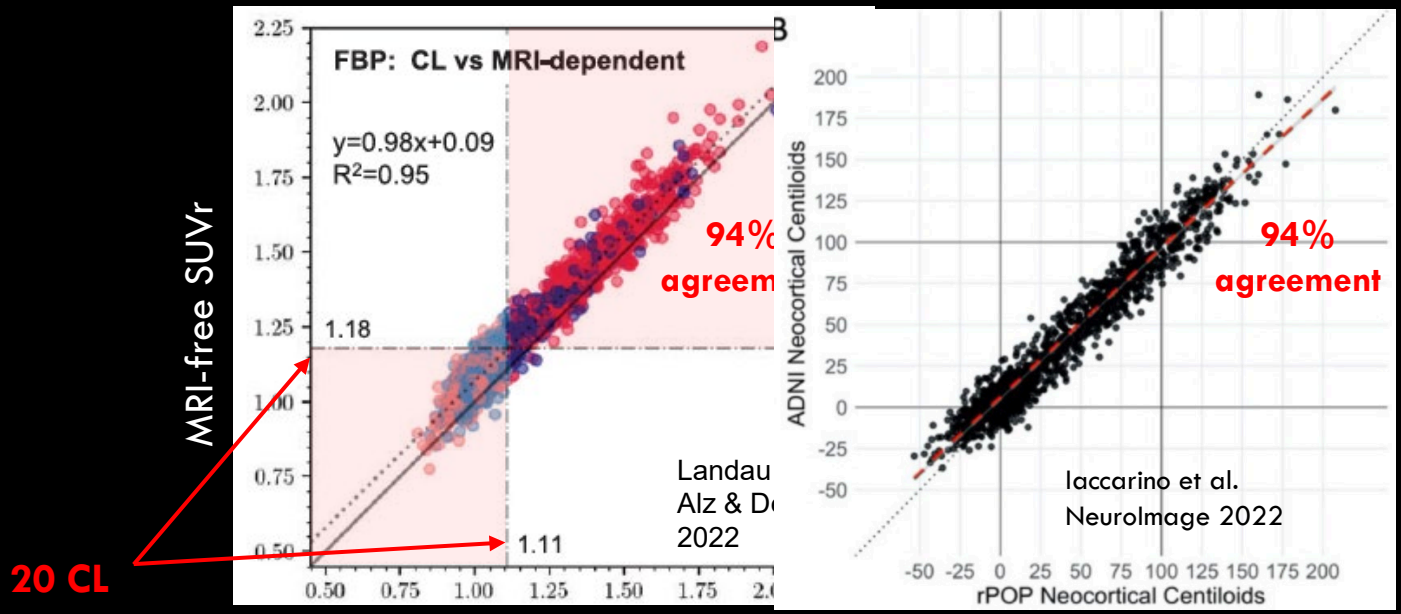
"MRI-free"



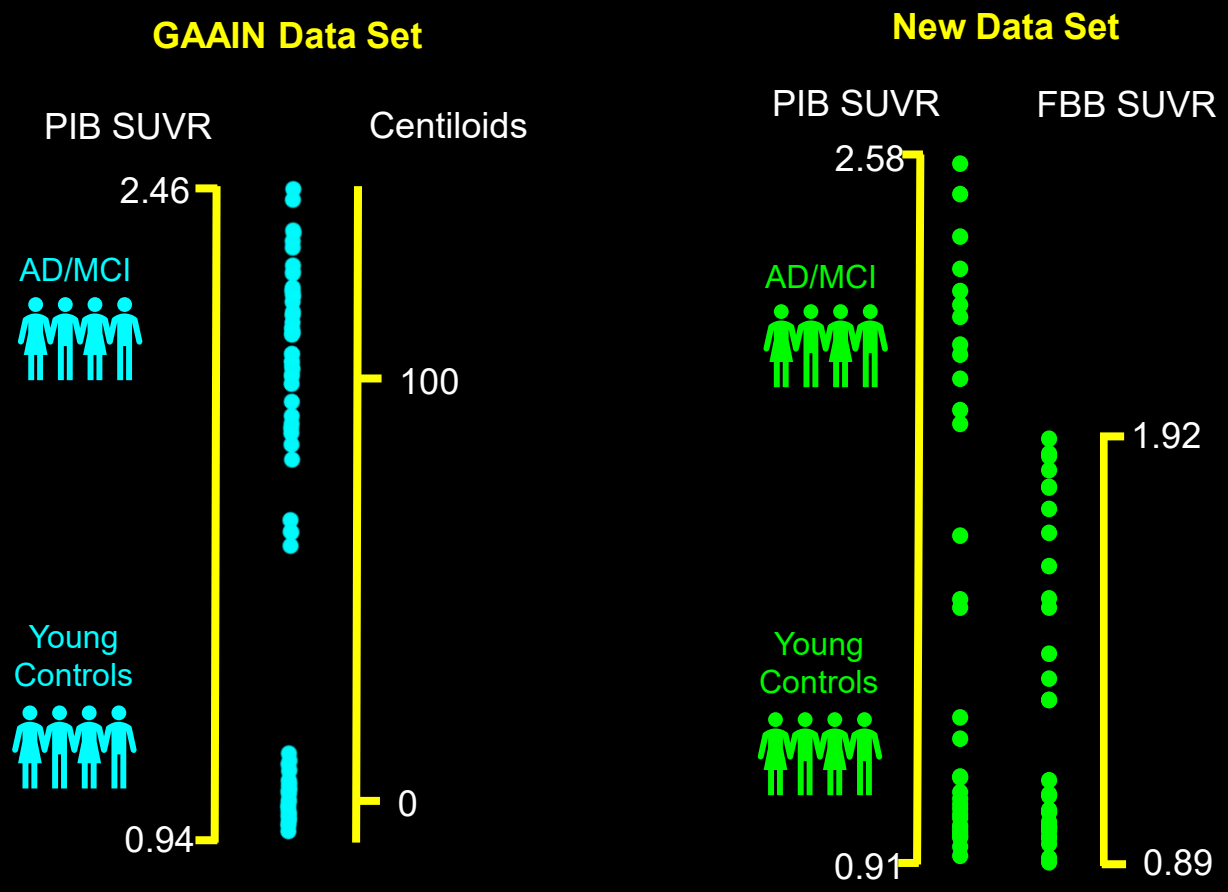


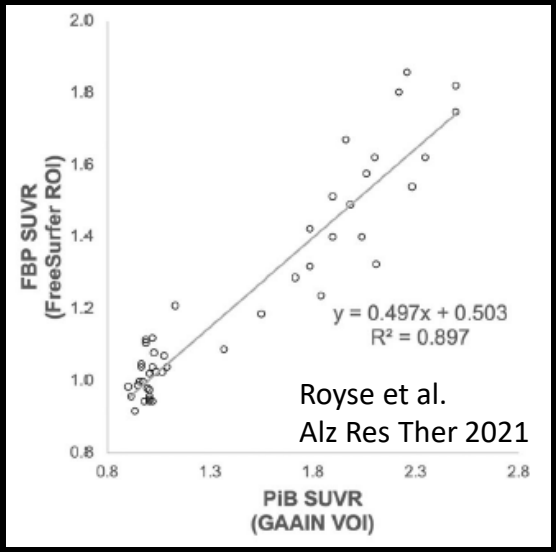
20 CL

94% agreement for MRI-free processing vs MRI-dependent standard of truth

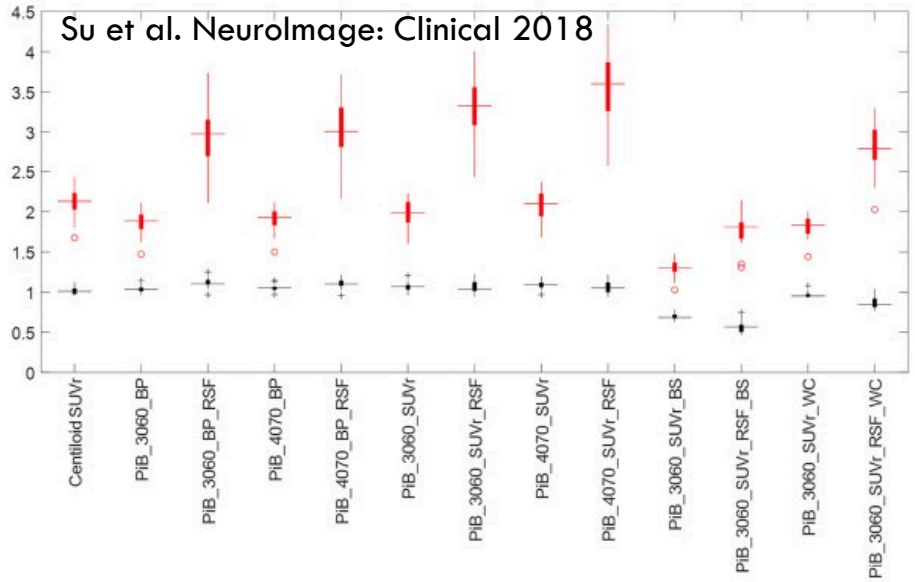


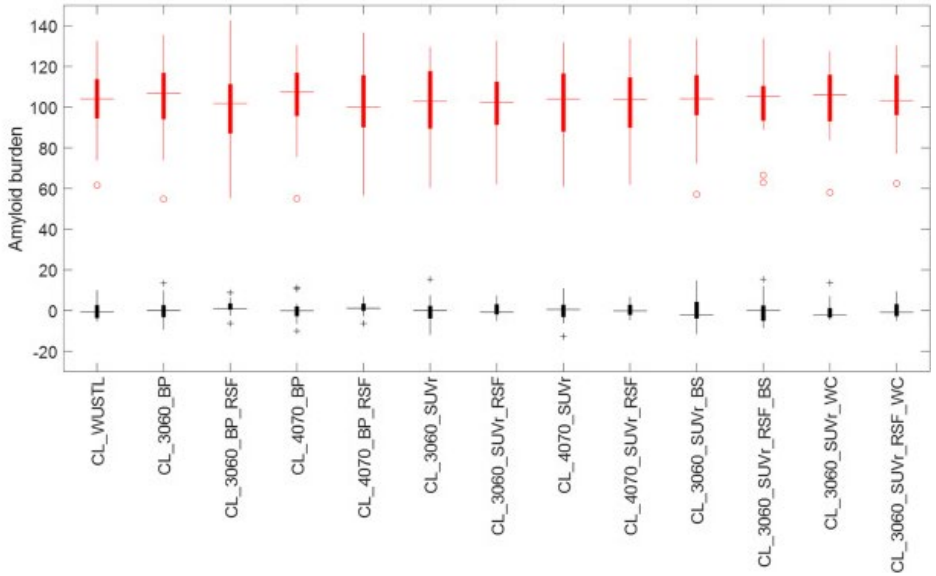
Standardization: Centiloids





Centiloid standardization accounts for sources of variability



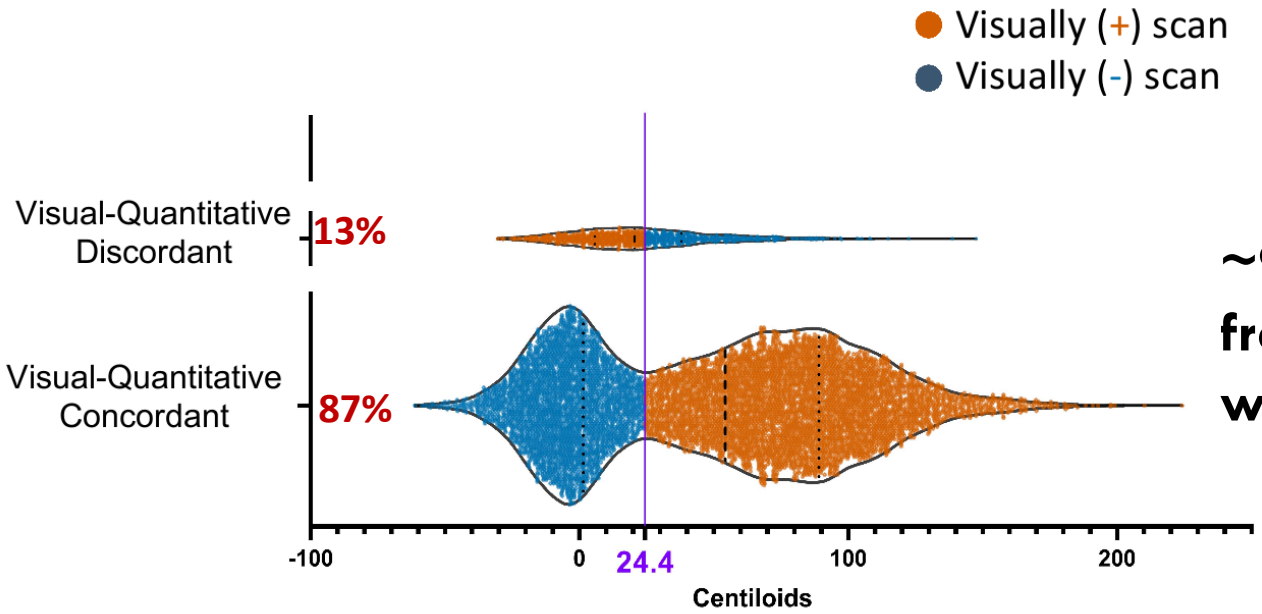


13 different pipelines in 34 YCs and 45 ADs:

DVR vs SUVr
native space vs template space
acquisition times

Centiloid standardization accounts for this variability

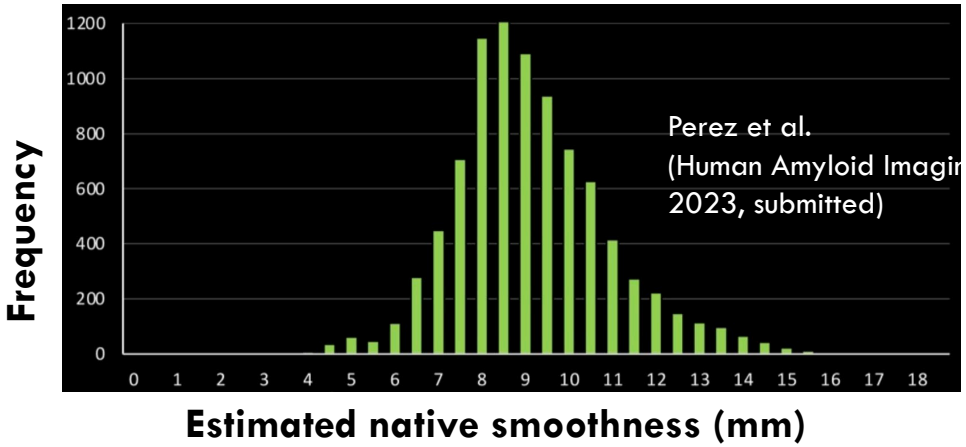
Quantitative/visual assessments in a real-world clinical setting align and are robust to variability in acquisition



(Zeltzer et al. Human Amyloid Imaging 2023, submitted)

~9000 amyloid PET scans from IDEAS participants with MCI or AD

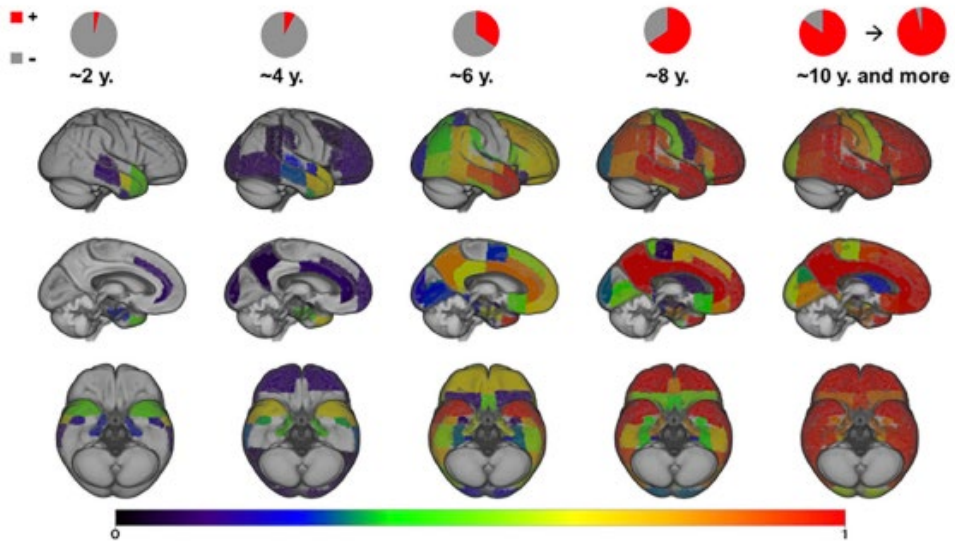
FBB: 94% agreement
(Bullich et al. NeuroImage:Clinical 2017)



When is Aβ +/- status not sufficient?

Regional Aβ information

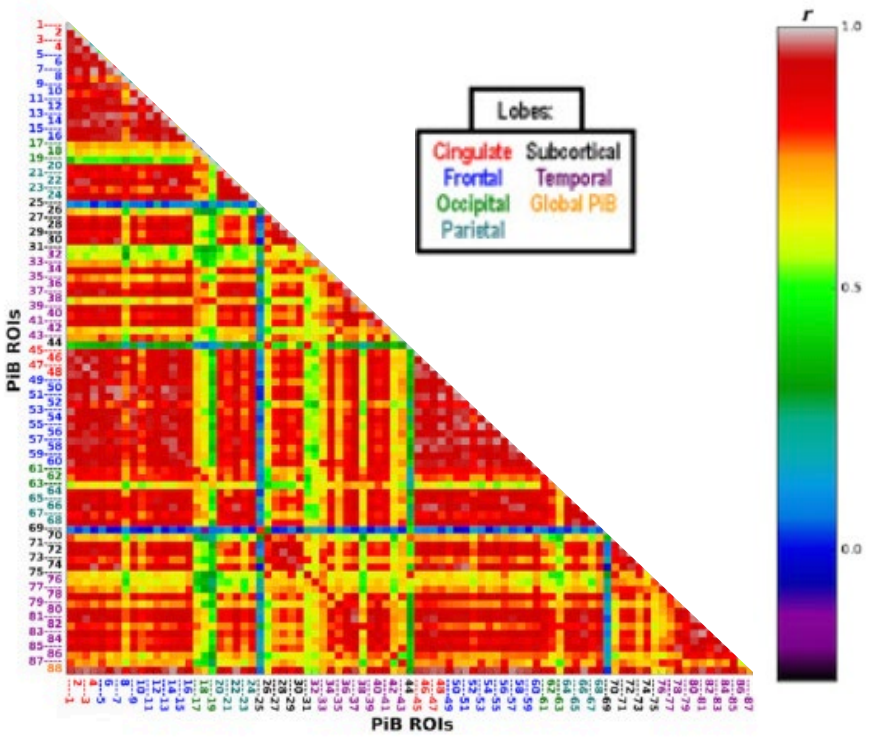
Some research has shown subtle regional differences in Aβ accumulation in the earliest phases



Jelistratova et al. Hum Br Mapp 2020

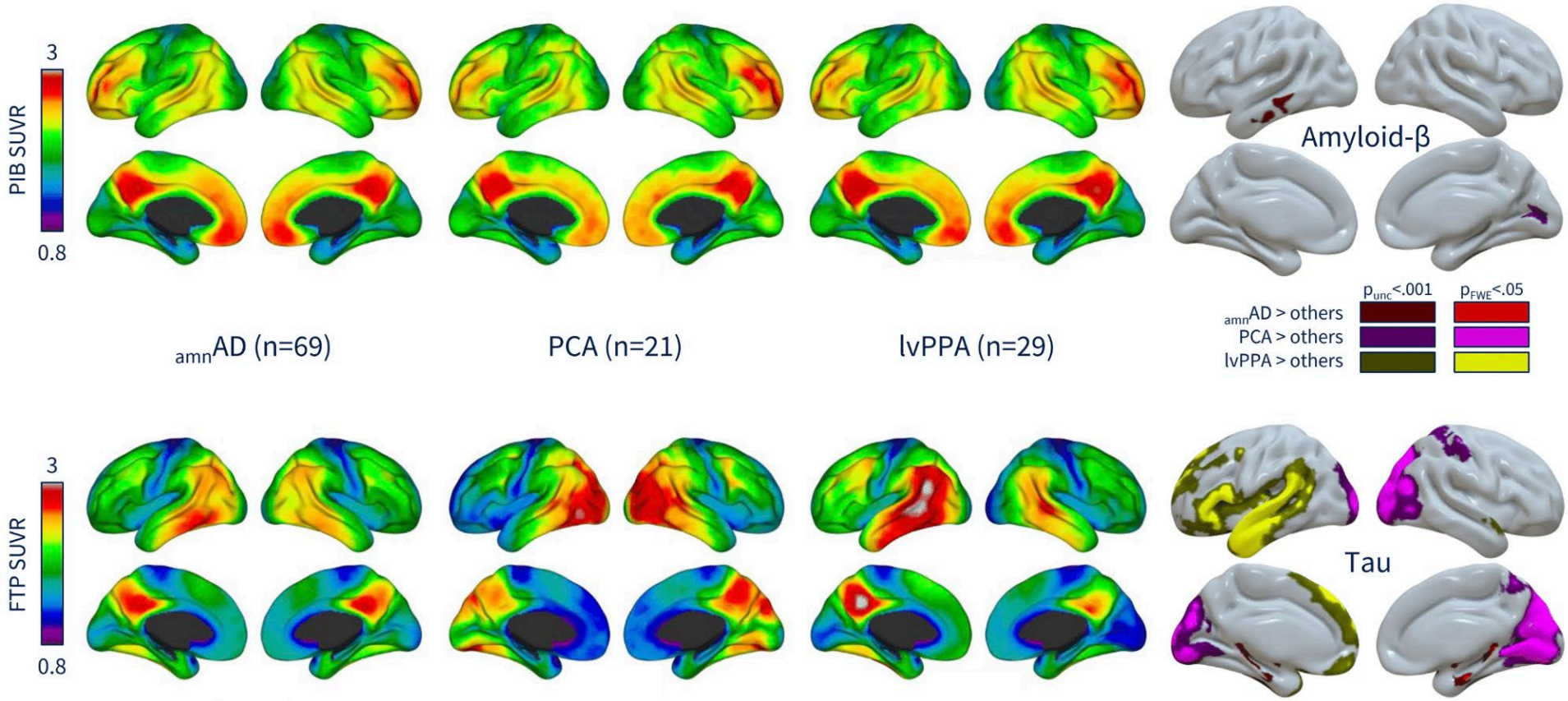
Mattsson et al. JAMA Neurol 2019
Villeneuve et al. Brain 2015
Guo et al. Neurology 2020

But overall regional Aβ is highly inter-correlated



Lockhart et al. NeuroImage 2017

Spatial distribution of Aβ is similar across clinical phenotypes

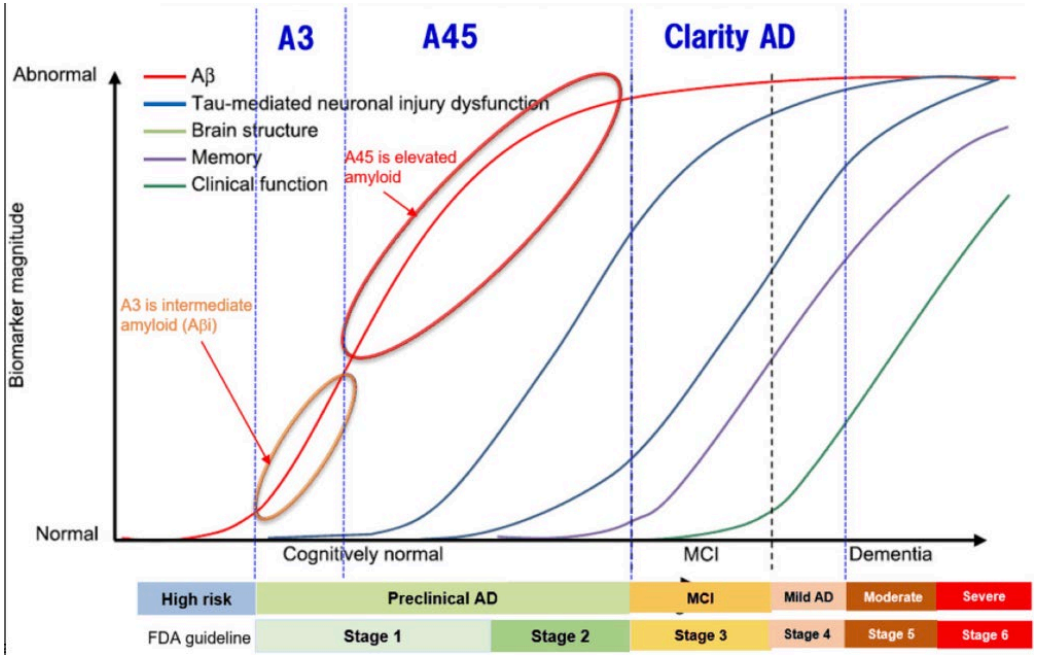


La Joie et al. Neurology 2021

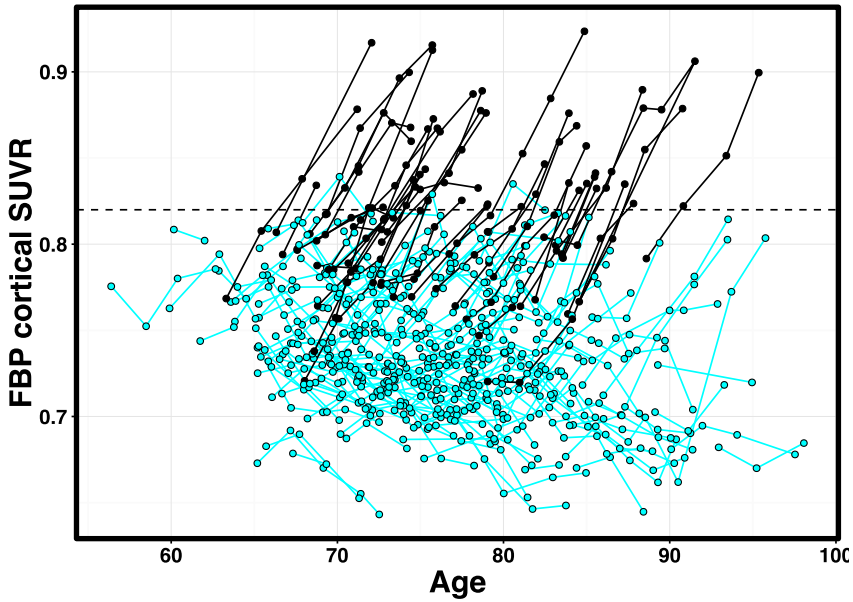
La Joie et al Sci Trans Med 2020
Ossenkoppele et al. Alz & Dem 2020

Aβ burden in an “at-risk” range

20-40 CL in unimpaired individuals
A3 study from AHEAD



Rafii et al. Alz & Dem 2022

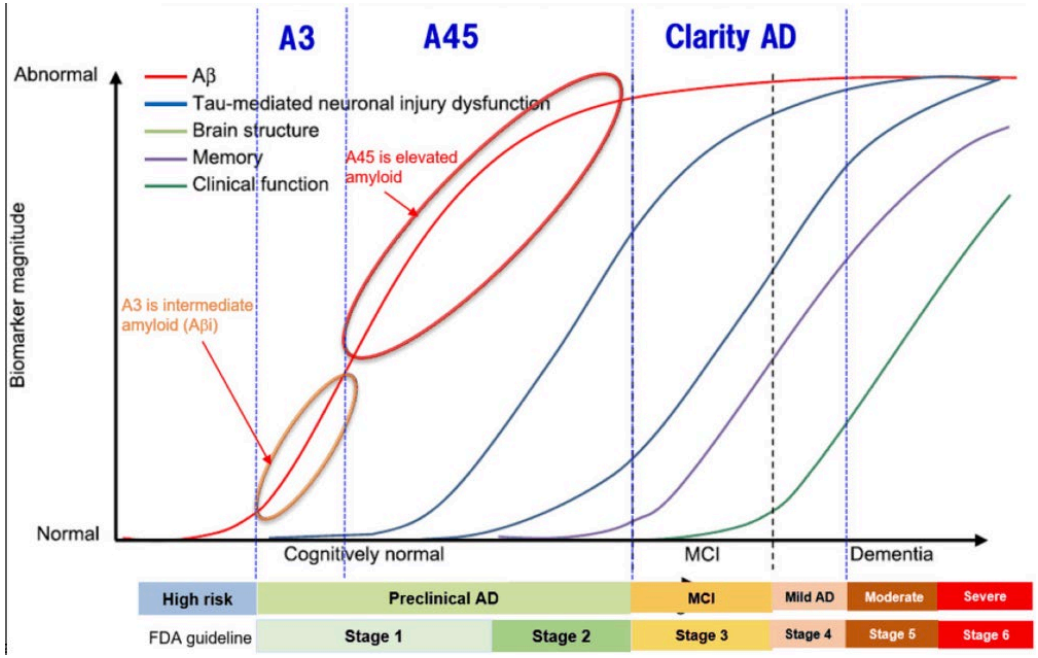


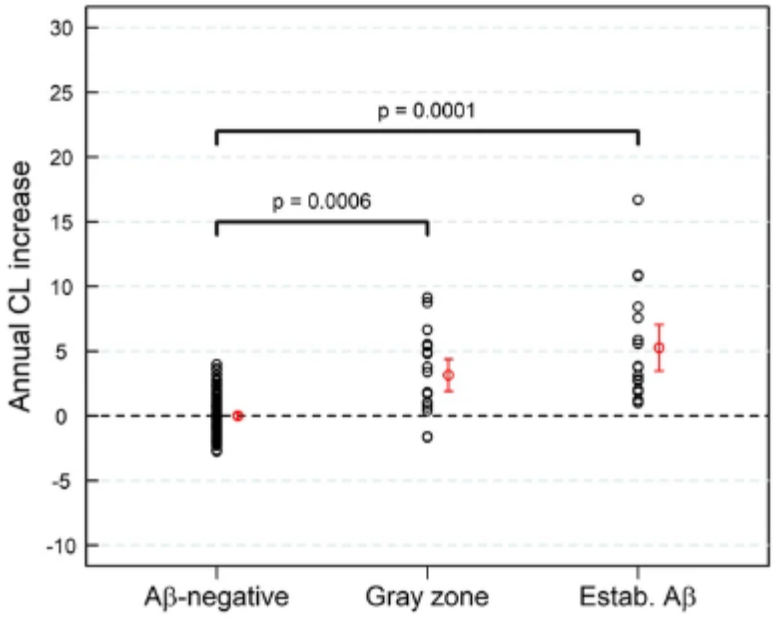
Jagust & Landau Neurology 2021

Aβ burden in an “at-risk” range

20-40 CL in unimpaired individuals
A3 study from AHEAD

“Grey zone”: 14 – 36 CL



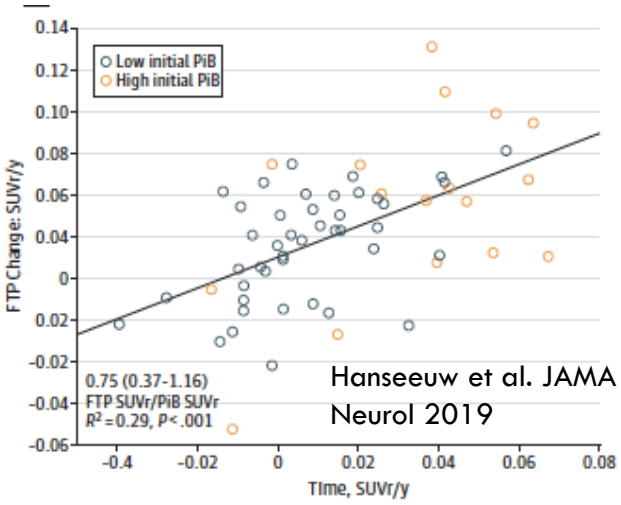


Rafii et al. Alz & Dem 2022

Bullich et al. Alz Res Ther 2021

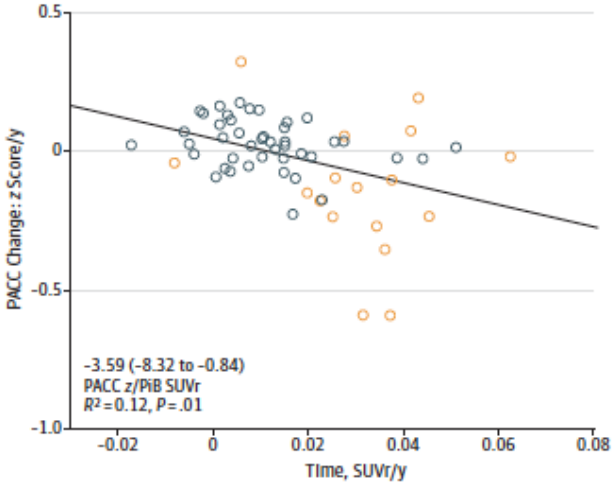
Clinical relevance of longitudinal quantitative Aβ PET

Increases in Aβ are related to increases in tau

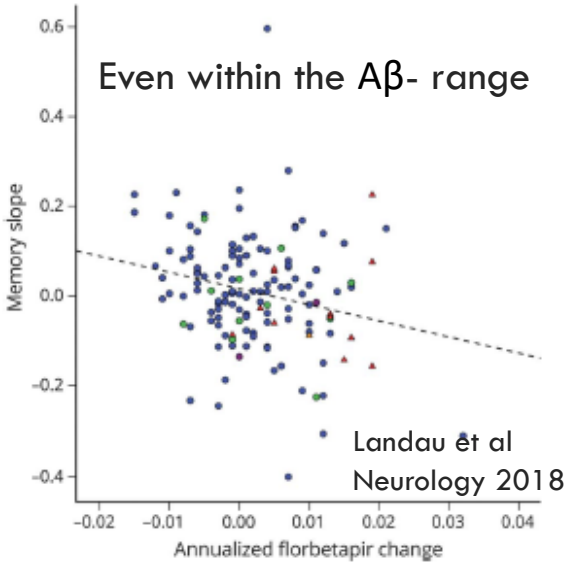


Hanseeuw et al. JAMA Neurol 2019

Increases in Aβ are related to cognitive decline

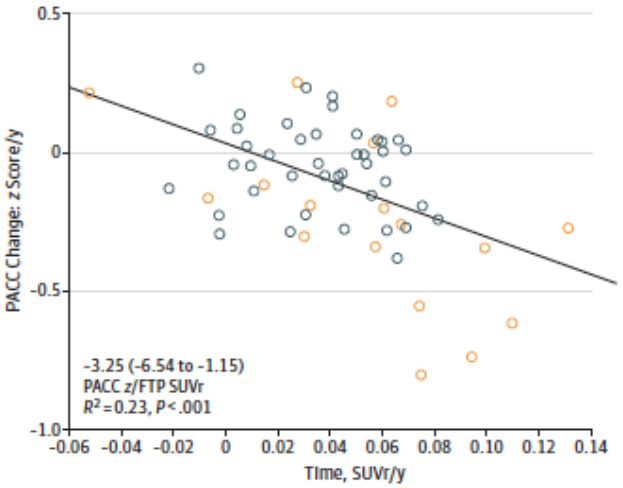


Even within the Aβ- range



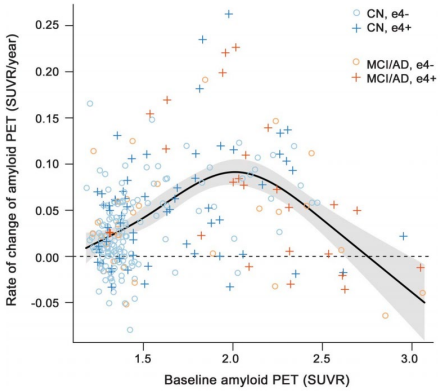
Landau et al Neurology 2018

Tau increases are more closely linked to cognitive decline



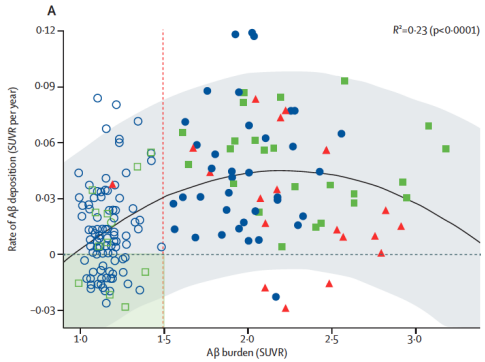
The rate of Aβ accumulation is not constant over the course of disease

Mayo



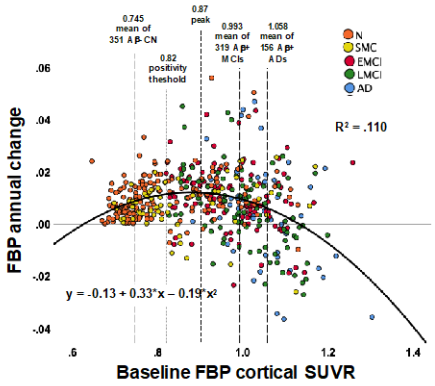
Jack et al. Neurology (2013)

AIBL



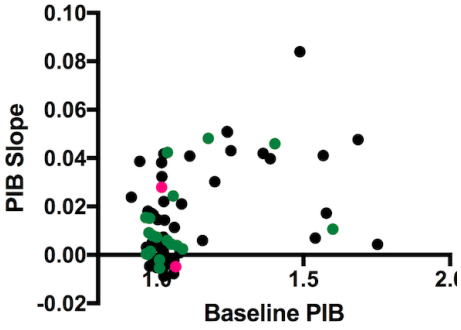
Villemagne et al. Lancet Neurol (2013)

ADNI



Jagust & Landau Neurology (2021)

Berkeley

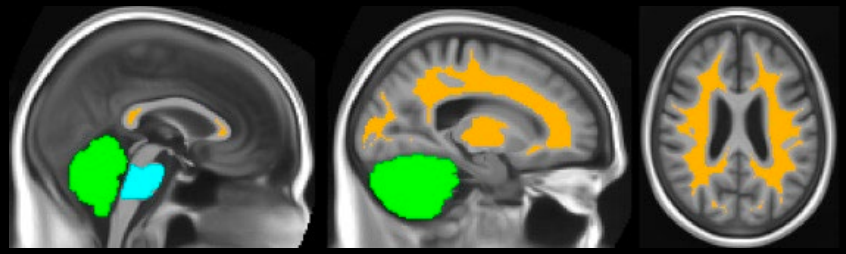


Leal et al. eLife (2017)

Aβ accumulation slows at high levels, even in cognitively normal people

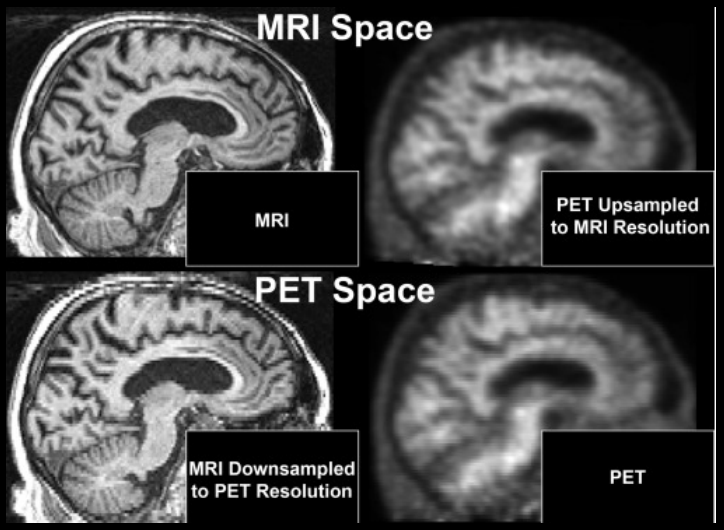
Longitudinal quantification is more vulnerable to variations in processing

Reference region selection

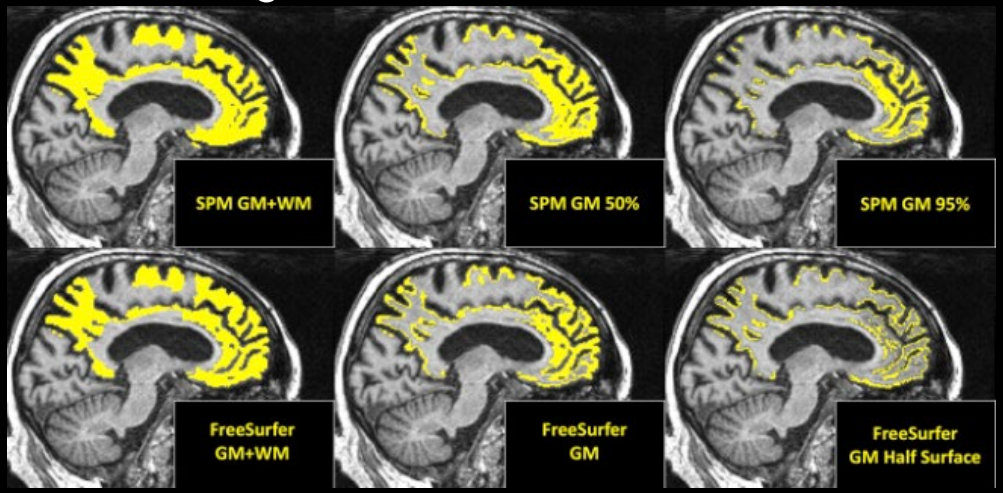


Schwarz et al. NeuroImage 2017

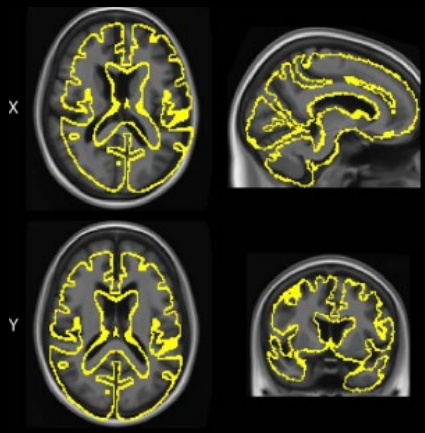
PET vs MRI resolution



Degree of ROI erosion

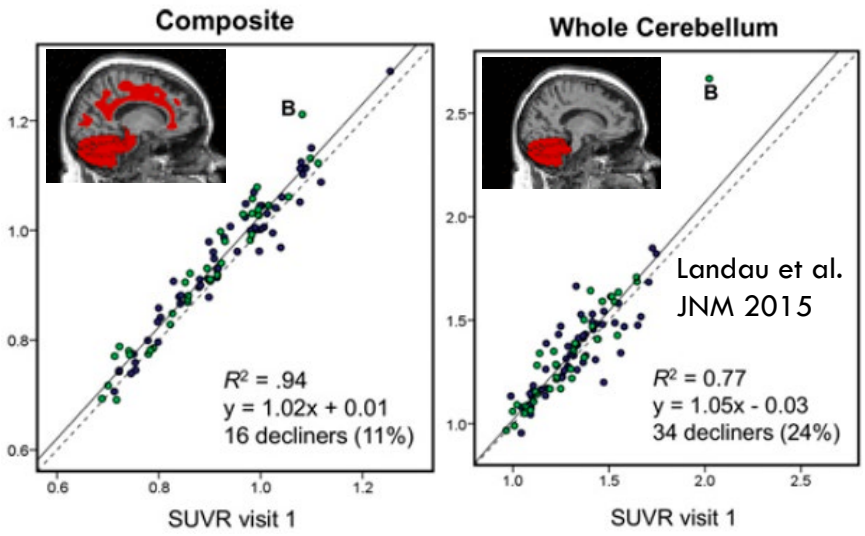


Coregistration



Schwarz et al. Hum Br Mapp 2017

Longitudinal quantification is more vulnerable to variations in processing



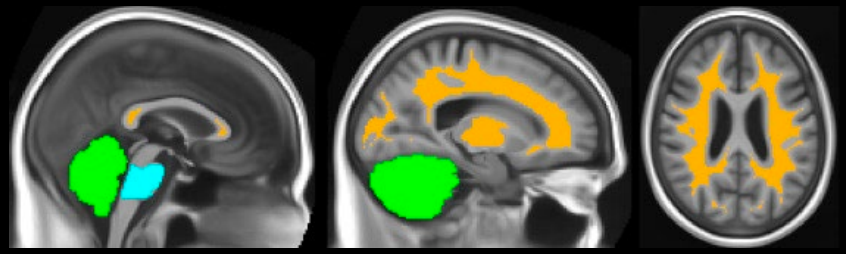
Use of a reference region containing WM improves signal to noise for longitudinal measures

FBP: Chen et al. JNM 2015, Brendel et al. Neuroimage 2015

PiB: Schwarz et al Neuroimage 2017

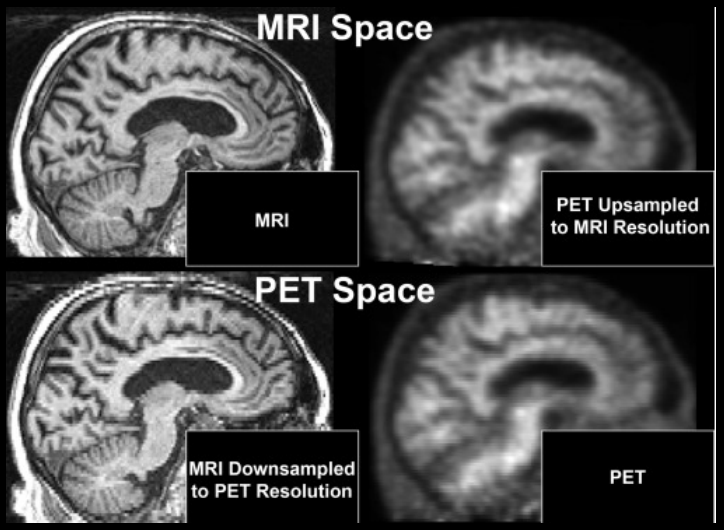
Longitudinal quantification is more vulnerable to variations in processing

Reference region selection

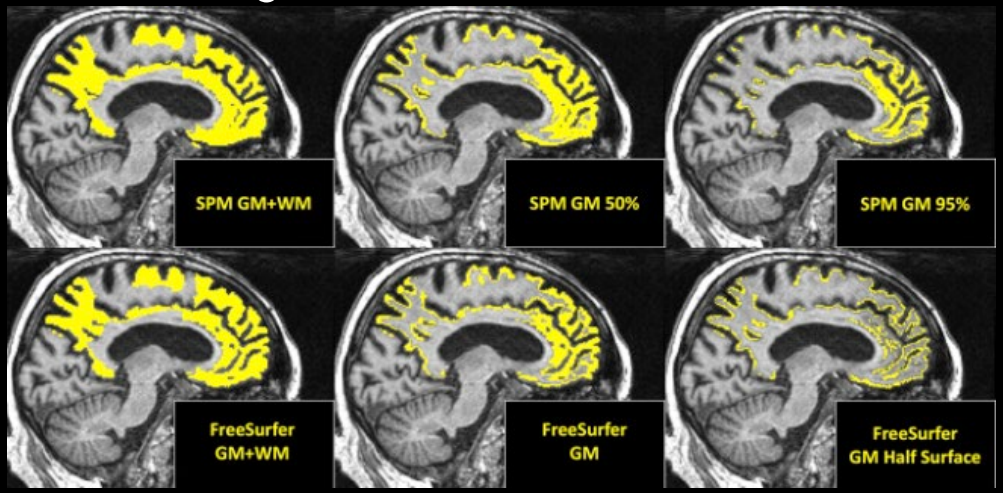


Schwarz et al. NeuroImage 2017

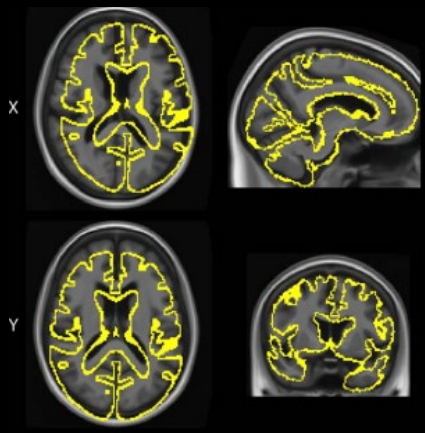
PET vs MRI resolution



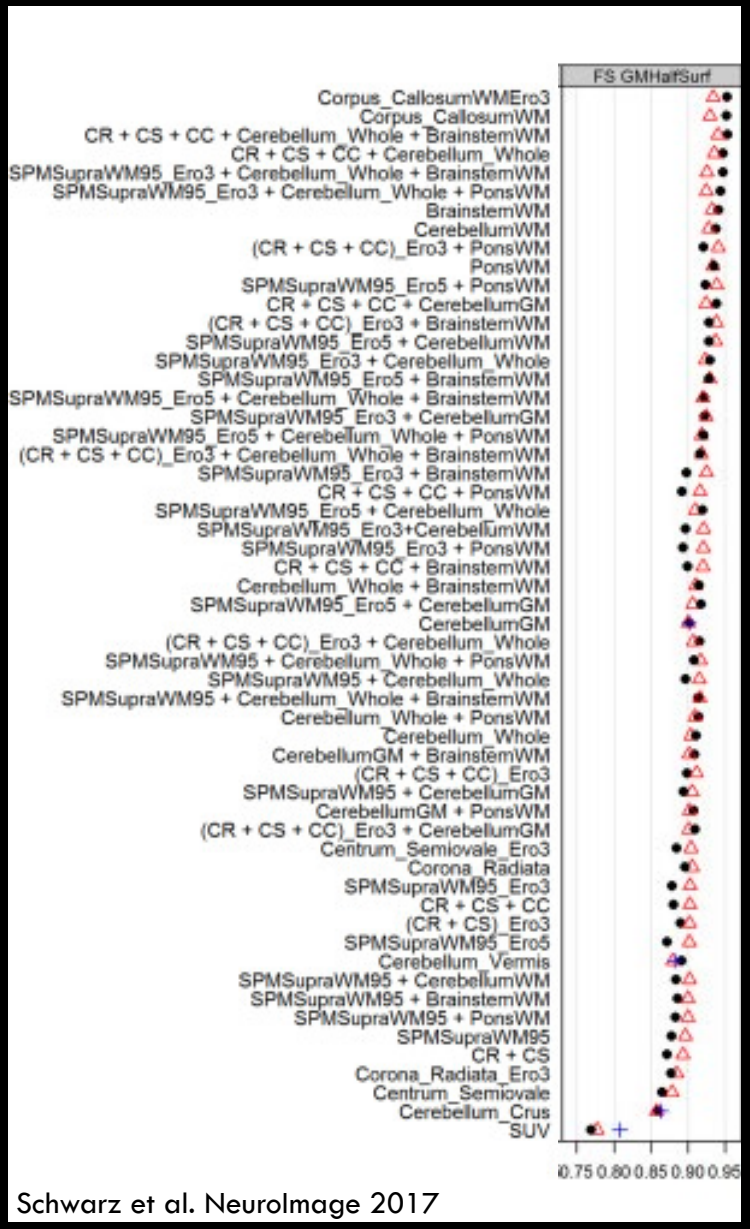
Degree of ROI erosion



Coregistration



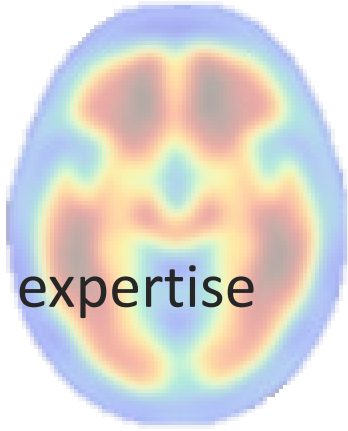
Schwarz et al. Hum Br Mapp 2017



Schwarz et al. NeuroImage 2017

Testing ~1000 pipeline permutations resulted in AUROCs ~0.85-0.95 for detecting longitudinal change in high vs low baseline **Aβ groups**

Unresolved problems in Aβ quantitation



Pipelines are not fully automated; QC involves specialized expertise

Thresholds

Most studies have converged on ~20CL, but implementation is use dependent

No consensus on at-risk/intermediate range

Longitudinal quantitation

More vulnerable to acquisition/processing influences

Validation is challenging (no standard of truth)

PET-fluid biomarker slopes are unrelated

Conclusions

Effects of acquisition/processing factors within the test-retest range (~5%) are unlikely to substantially influence quantitation

CLs can account for effects of acquisition/processing, enabling standardization across heterogeneous datasets

Global, binary Aβ+/- status is often sufficient, but continuous Aβ measures are critical in specific situations:

- Detection of intermediate accumulation
- Longitudinal change

NeuroQ™, Syntermed

C. David Cooke, Director of Clinical Applications

- Monitoring
  - Availability of Standardized Templates.
  - Standardized registration algorithm?
- Standardization
  - Standardized datasets, available to software companies for creating normal files.
  - How do camera specifics play into this? ie, newer cameras have better imaging characteristics then older cameras (resolution, sensitivity, reconstruction method, …)
  - Do the normal files need to be re-created with each new generation of camera?

Quantitative PET Brain Amyloid Imaging FDA Workshop

SATOSHI MINOSHIMA, MD, PHD

ANNE G. OSBORN CHAIR AND PROFESSOR

DEPARTMENT OF RADIOLOGY AND IMAGING SCIENCES

UNIVERSITY OF UTAH

Quantitative Amyloid PET

- Implementation: Inter-subject (cross sectional) vs intra-subject (longitudinal) analysis
- Interpretation: Discordance between visual interpretation & quantitative analysis. Which one to trust in the clinic?
- Regulatory Approval: 510(k) good enough? More stringent validation? Gold standard? Fluid biomarkers vs quantitative PET
- Implications: Quantitative analysis for other approved brain MI tracers

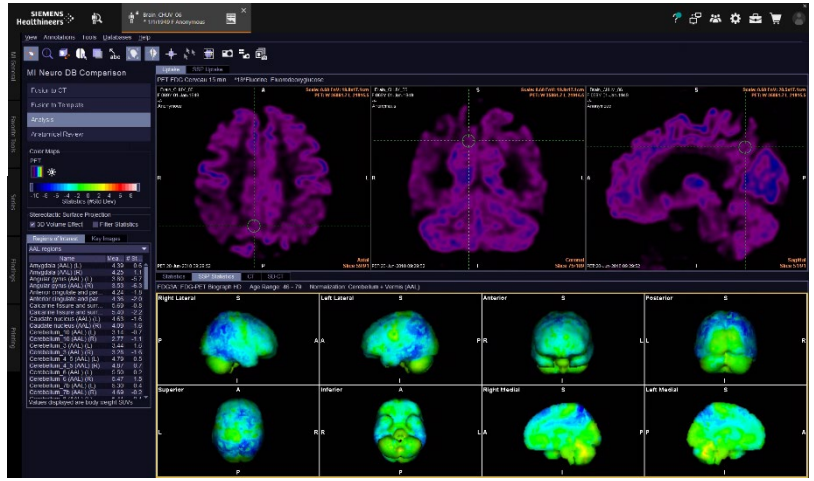
SIEMENS Healthineers

Quantitative PET Brain Amyloid Imaging

Marcus Steward
November 2022

MI Neurology Clinical Applications Portfolio

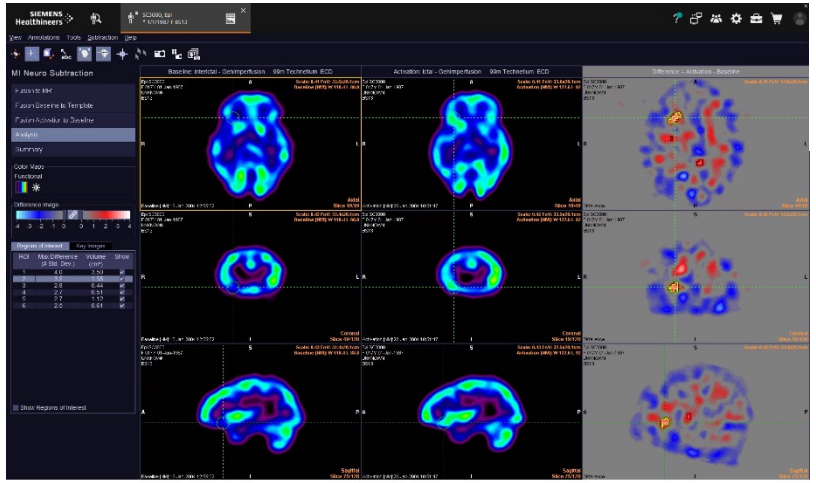
syngo.MI Neuro Database Comparison



syngo.MI Neuro Striatal Analysis

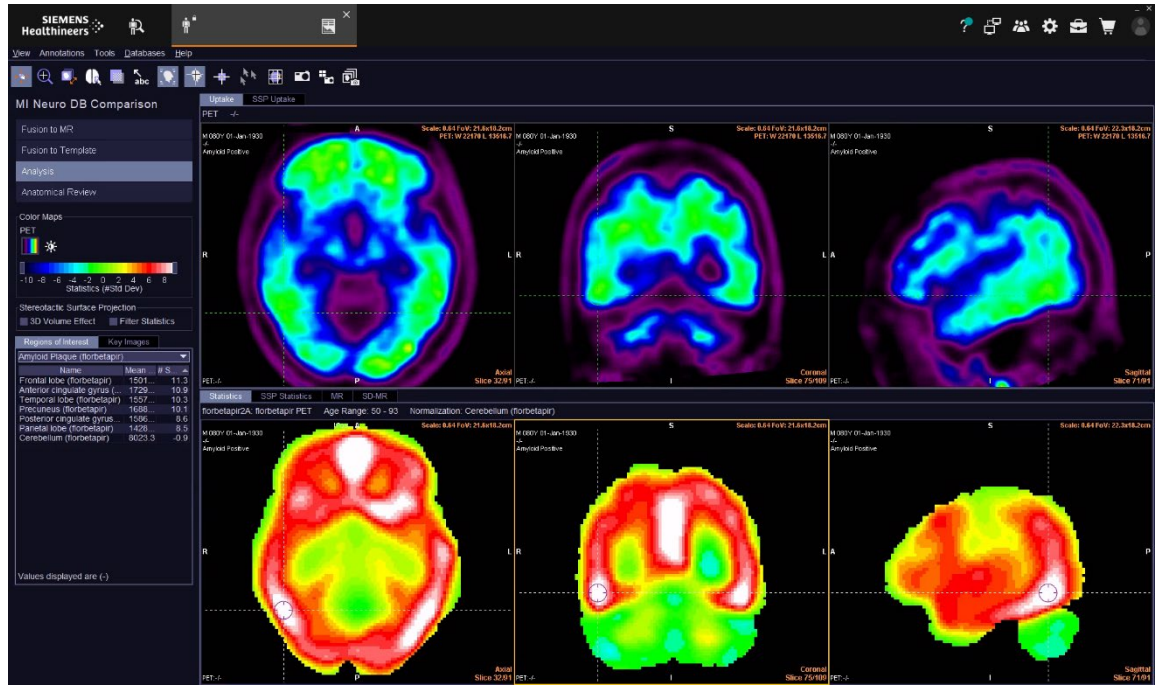
syngo.MI Neuro Cortical Analysis

syngo.MI Neuro Subtraction



syngo.via MI Neuro Database Comparison

- Automatic correlation of the patient's study (PET or SPECT with an optional CT and/or MR) with an average normal brain for identification and quantification of abnormalities
- Voxel-wise evaluation of abnormal regions and automatic positioning of anatomical regions of interest optimized for evaluation of dementia
- Color-coded statistical analysis highlighting patterns of amyloid deposits as number of standard deviations from the norm
- Tracer-specific normal databases are included



Data courtesy of University of Tennessee Medical Center, Knoxville, Tennessee, USA.

The listed application features are medical products in their own rights and necessary country specific approvals might not yet be available (e.g., 510(k), CE Mark).
Intended for use only with approved Amyloid radiopharmaceuticals in the country of use. Users should review the drug labeling for approved uses.

syngo.via MI Neuro Cortical Analysis

- Regions of interest (ROI) tailored for amyloid tracers or from the AAL atlas
- SUVr of each ROI to quantify amyloid deposits

Data courtesy of University of Tennessee Medical Center, Knoxville, Tennessee, USA.

The listed application features are medical products in their own rights and necessary country specific approvals might not yet be available (e.g., 510(k), CE Mark).
Intended for use only with approved Amyloid radiopharmaceuticals in the country of use. Users should review the drug labeling for approved uses.

Questions

- How to avoid a proliferation of normal databases?
- How to derive additional clinical benefit from improved scanner characteristics?
- Is Centiloid ready for routine clinical use?

Thank you

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Phone: +1 847-304-7700

siemens-healthineers.com/mi

Marcus Steward
Product Manager, Clinical Applications
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Session II:
Products for Brain Amyloid Imaging

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

Quantitative PET Brain Amyloid

November 17, 2022

Disclaimer

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

Session II: Discussion

- What are some of challenges to advancing quantitative amyloid analysis in clinical practice? For software developers?
- What are the needs of software device developers to advance quantitative amyloid analysis in research? In clinical practice? (e.g., data sharing, standardization)
- How do software developers balance the desire for tools that enable flexibility for site-specific methods with the need for clinicians to be able to compare results across sites and across time?
- What are the clinicals need to advance “newer” analysis methods such as Centiloids? Are existing metrics based on reference regions adequate?
- Are there examples in other fields for advancing quantitative methods that address sources of variability from image acquisition, tracer selection, image reconstruction, user-selected reference region, target region of interest, image co-registration, etc.?
- What tools are available for clinicians to compare analysis methods and various software packages?
- What are barriers to the adoption of quantitative analyses and the tools that facilitate these methods?
- What is the added value of quantitation in clinical practice?


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