2022 HYBRID SPRING ADRC MEETING
May 13th-14th

Tau PET harmonization strategies for multicenter natural history and/or interventional studies

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Pitt ADRC

Disclosures

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  - Life Molecular Imaging
  - Eli Lilly
  - Hospicom
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  - Life Molecular Imaging
  - Eli Lilly
  - ACE Barcelona
  - International Atomic Energy Agency
- **Editorial Boards**:
  - Alzheimer's Research & Therapy
  - J Neurochemistry
  - Eur J Nucl Med Mol Imaging
- **Fees > $10,000**
  - N/A. Not that lucky (*but open to offers)*

(Please see me at the end of the presentation, or email me an offer I can't refuse to victor.villemagne@gmail.com)

Background

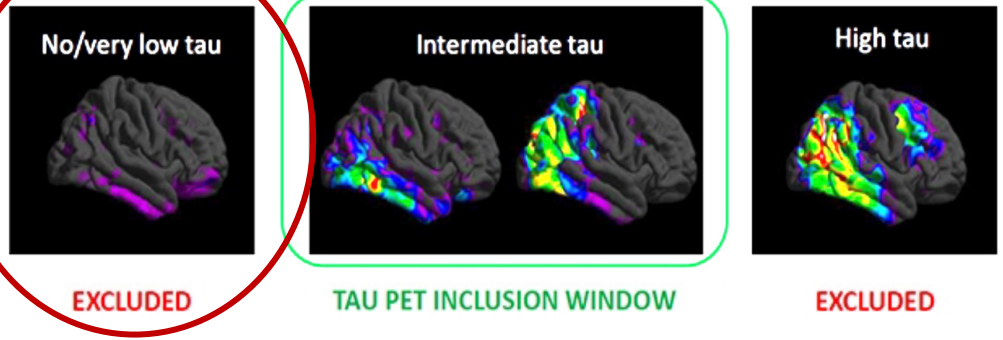
- Over the past decade, several PET tracers have been developed to visualise and quantify brain tau pathology in vivo.
- However, all these tracers have distinct off-target signal, different dynamic ranges and likely different levels of non-specific binding resulting in large variability in their semiquantification.
- We propose to standardise the sampling and the quantification across all available tau tracers using a universal mask and scale.

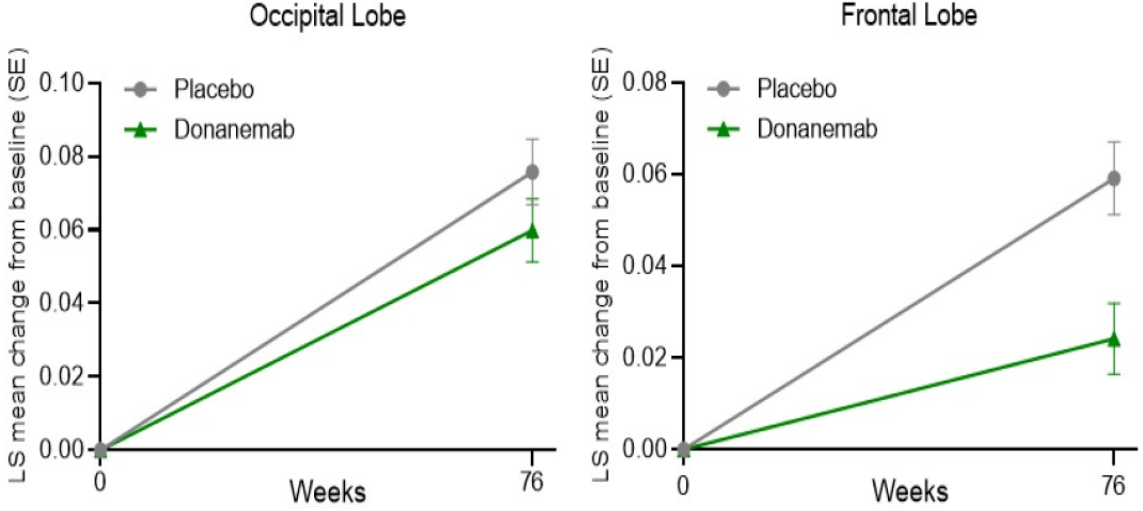
Aims

Develop and implement a stereospecific universal standard approach to generate both continuous and categorical [AT(N)] measures enabling direct data comparisons and/or data pooling across sites and studies using differing tracers, acquisitions, scanners, or analysis methods, aimed at improving the *early detection of tau deposition as well as its progression over time and its use in disease-specific anti-Aβ and/or ant-tau therapeutic trials.*

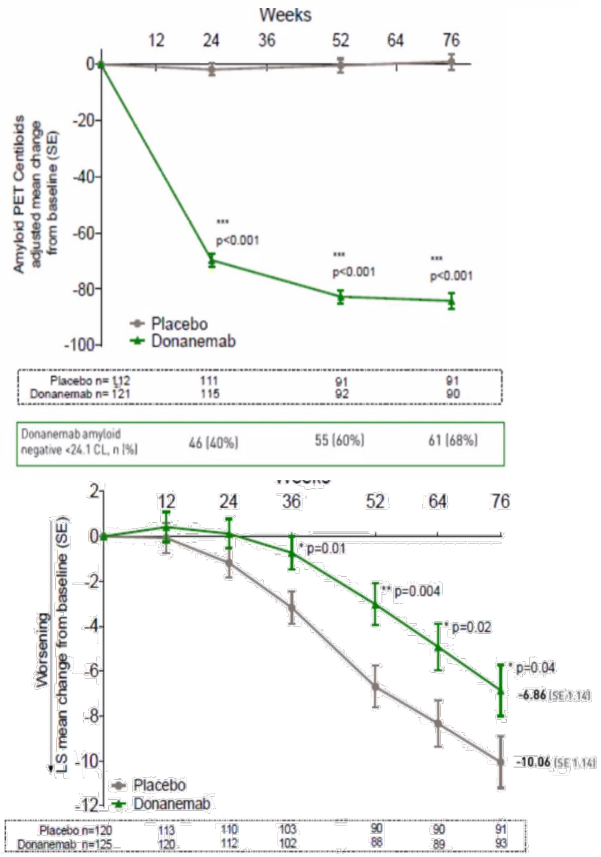
TRAILBLAZER-ALZ iADRS

DONANEMAB IS THE FIRST PLAQUE CLEARING AGENT TO ACHIEVE A DISEASE MODIFICATION PRIMARY ENDPOINT





AVERAGE AMYLOID PLAQUE REDUCTION OF 85 CENTILOIDS AT 76 WEEKS



AT(N) biomarker staging

ELSEVIER
CrossMark
Alzheimer's & Dementia 14 (2018) 535-562
Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

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 Dunn[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], Reisa Sperling[s]
Contributors[t]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

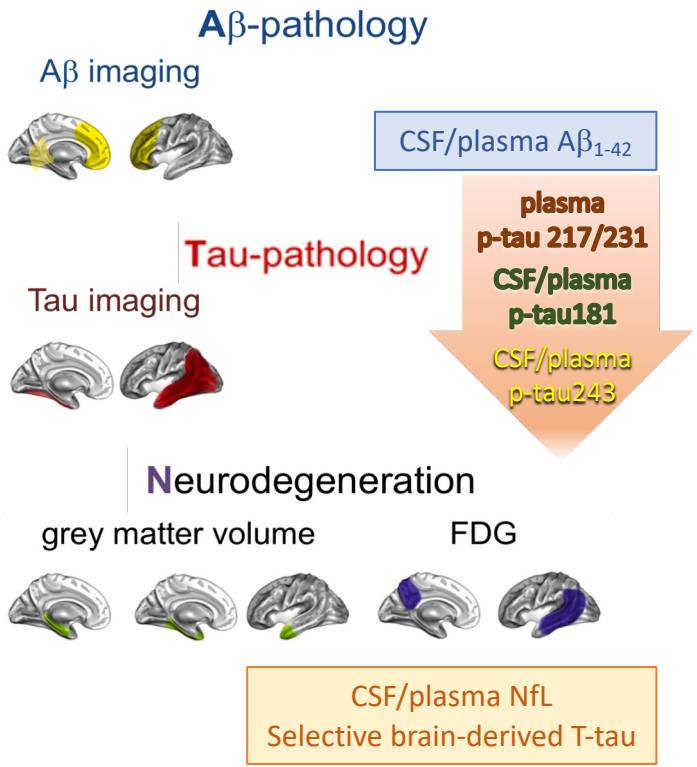
AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum*
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	

AT(N) profiles	Biomarker category
A-T+(N)-	Non- AD pathologic change
A-T-(N)+	Non- AD pathologic change
A-T+(N)+	Non- AD pathologic change

Aβ=beta-amyloid; CSF=cerebrospinal fluid; FDG=fluorodeoxyglucose

Adapted from: La Joie et al. J Neurosci 2012;32(46):16265–16273; Jack et al. Neurology 2016;87(5):539–547

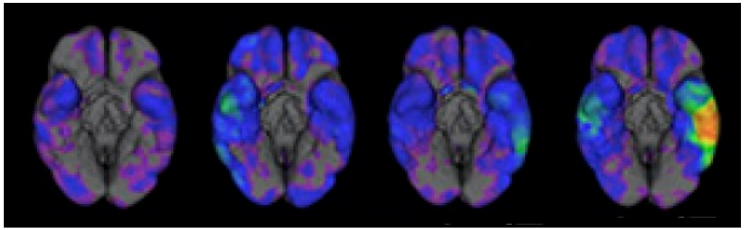
A/T/(N): Three-marker neuroimaging/biofluid signature



What Is T+? A Gordian Knot of Tracers, Thresholds, and Topographies

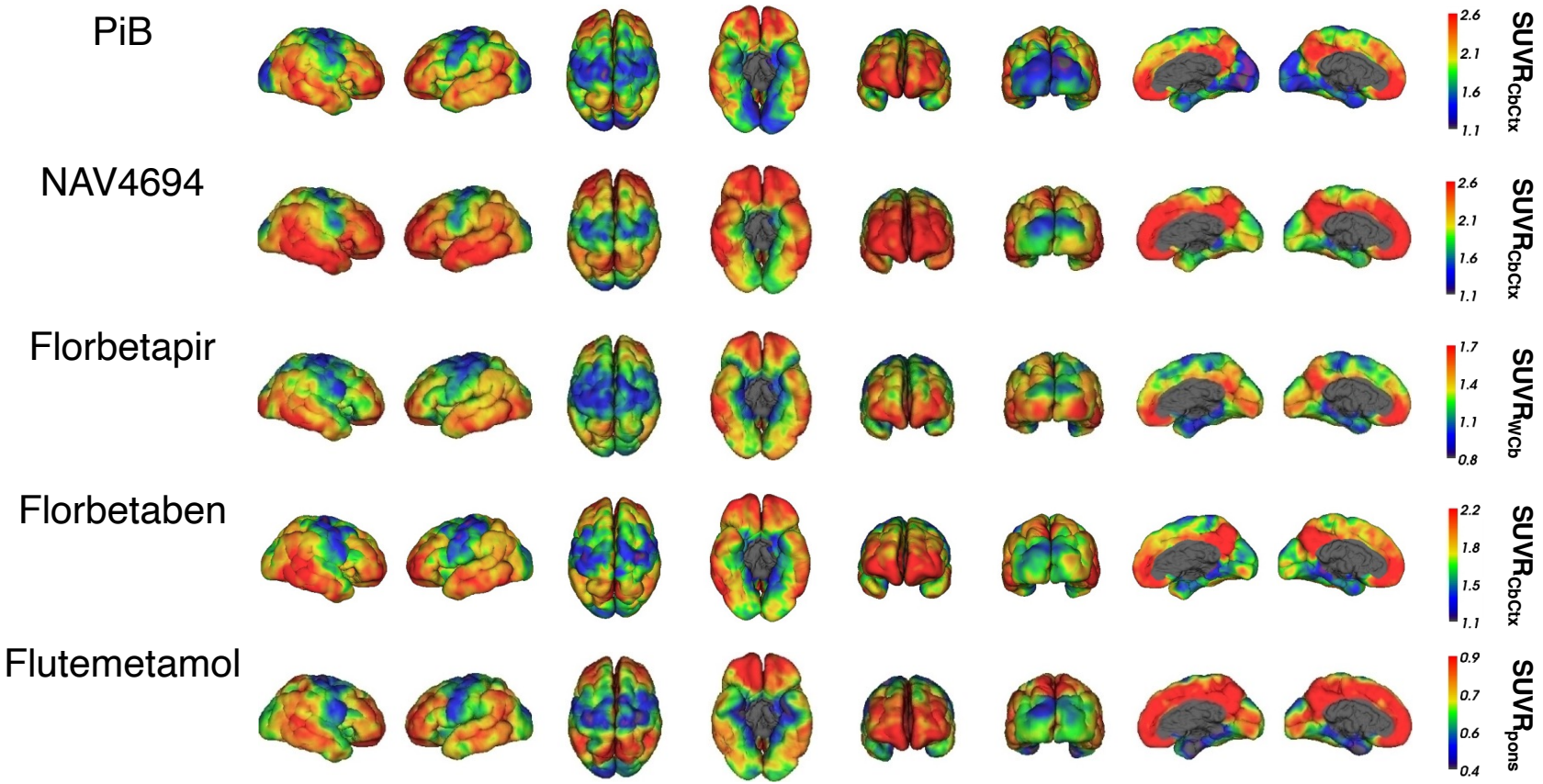
Victor L. Villemagne[1–3], Brian J. Lopresti[4], Vincent Doré[5,6], Dana Tudorascu[1], Milos D. Ikonomovic[1,7], Samantha Burnham[6,8], Davneet Minhas[4], Tharick A. Pascoal[1], N. Scott Mason[4], Beth Snitz[1], Howard Aizenstein[1], Chester A. Mathis[4], Oscar Lopez[1], Christopher C. Rowe[2,5], William E. Klunk[1,7], and Ann D. Cohen[1]

J Nucl Med. 62:614-619, 2021



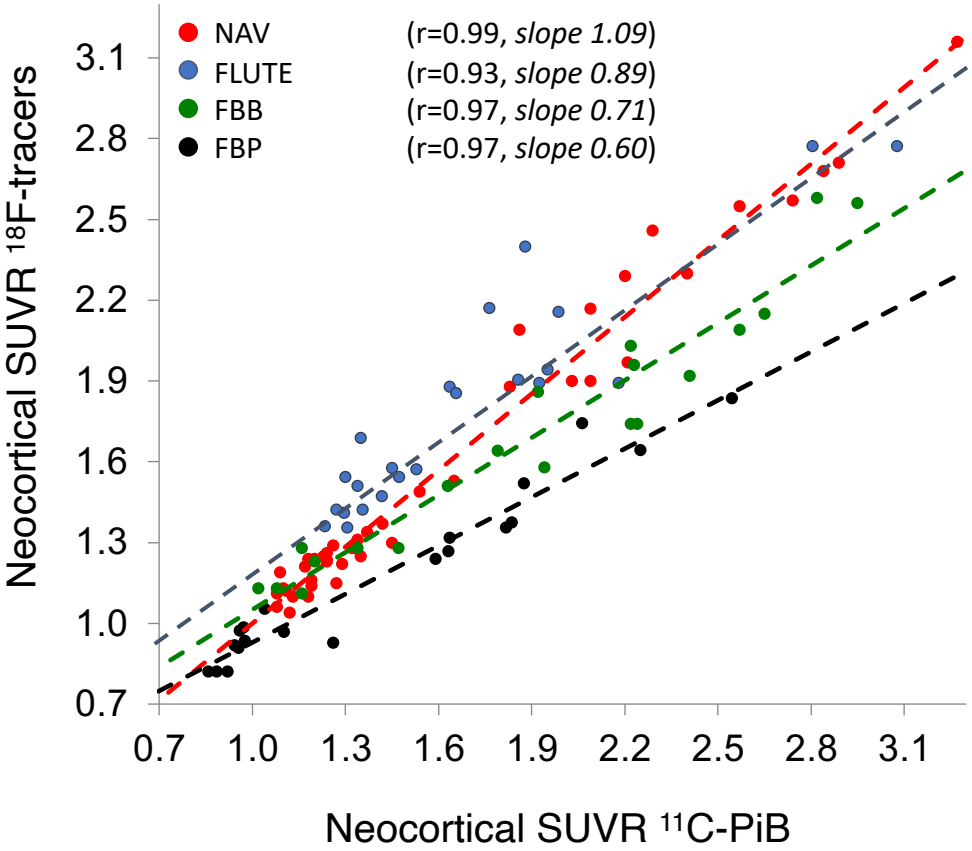
- ***WHERE TO LOOK?***
  - What are the optimal regions for the ***early*** and ***longitudinal*** detection of tau deposition?
  - Regions based on neuropathology or data driven approaches?
  - Braak-like ROI? Temporal composite region? Entorhinal and Inf Temporal? MeTeR scale? Voxelwise approaches?
  - What is considered Tau+? Just cortical tau? MTL? Cortical and MTL?
  - What is the meaning/relevance of MTL tau?, what MTL tau level is considered part of aging (PART) and what MTL tau level is considered part of AD?
- ***HOW TO ESTABLISH THRESHOLDS? – (and for what PURPOSE and for what APPLICATION?)***
  - Young or elderly controls? CSF p-tau (which one?)? Visual? Risk of progression? Reliable worsening method? Specificity threshold? Multiple thresholds?
- ***BETTER TRACER CHARACTERIZATION***
  - Idiosyncrasies/differences. Stability of reference regions.
  - Degree of non-specific binding.
  - Neuropathology/pathophysiological approach.

Why do we need harmonization? Aβ imaging

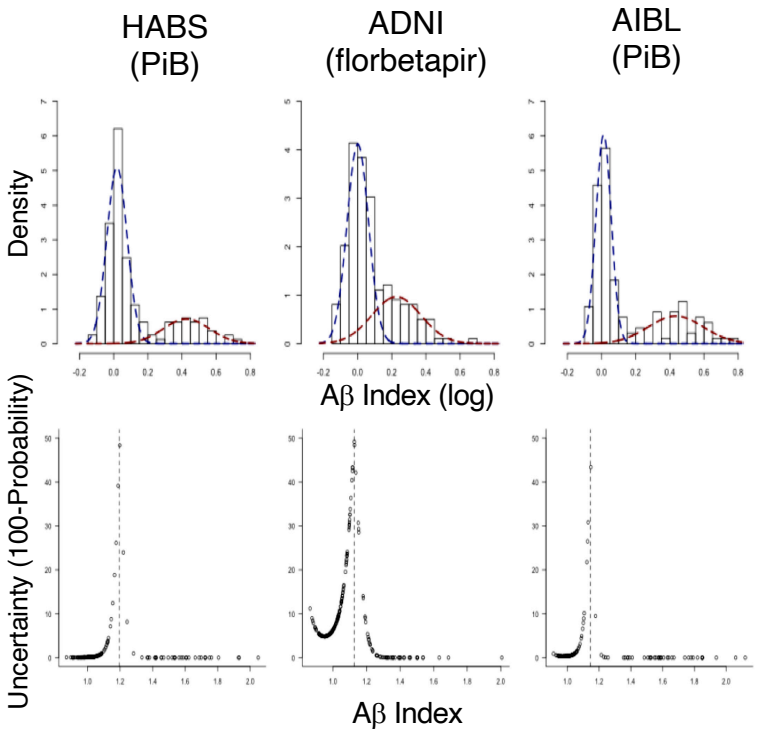


Images generated with CapAIBL® (capaibl-milxcloud.csiro.au)
CSIRO Biomedical Imaging Group

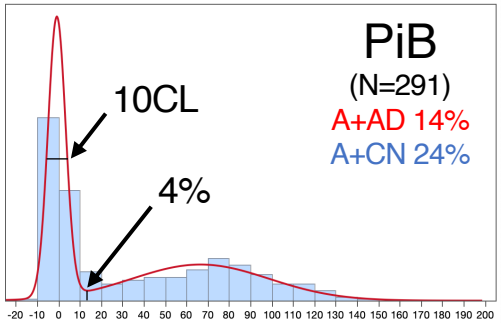
Comparison of ^{18}F-amyloid ligands vs ^{11}C-PiB

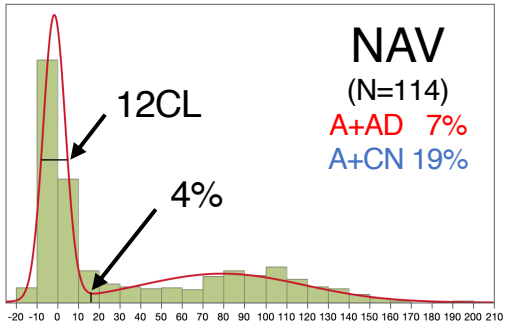


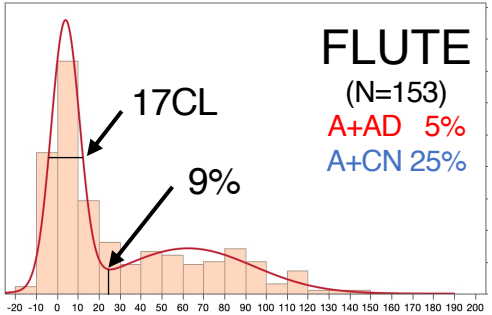
Discriminatory power of Aβ tracers

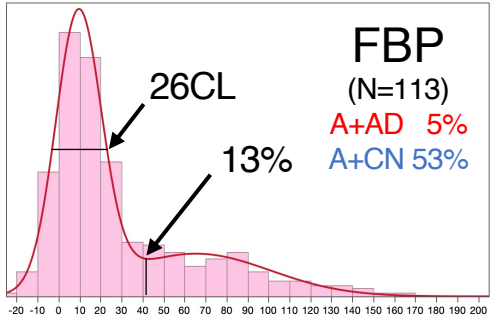


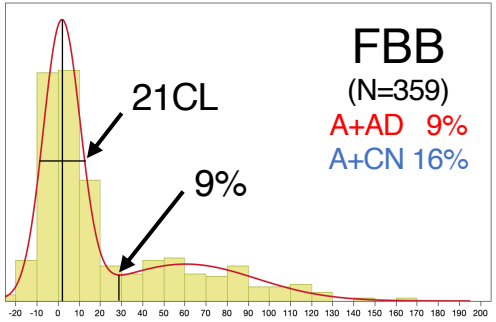
adapted from Mormino et al., Neurology, 2014











Centiloid transformation

ELSEVIER

The centiloid project: Standardizing quantitative amyloid plaque estimation by PET

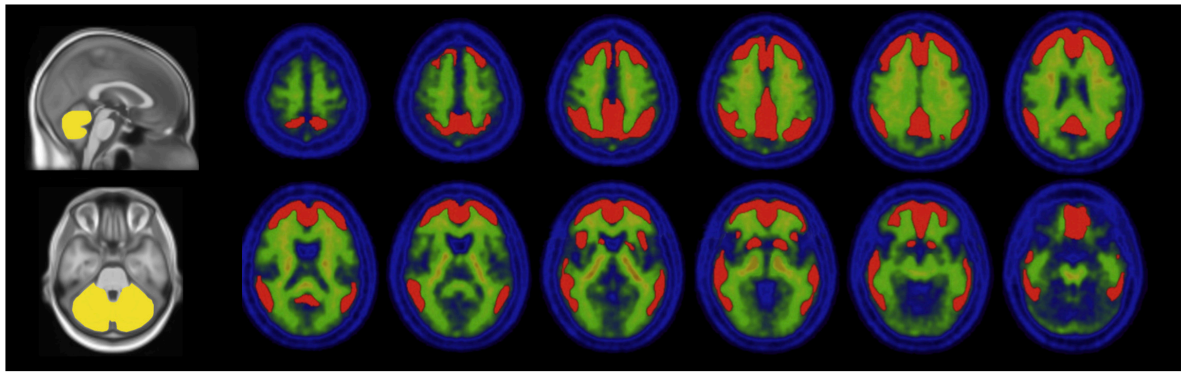
Alzheimer's & Dementia

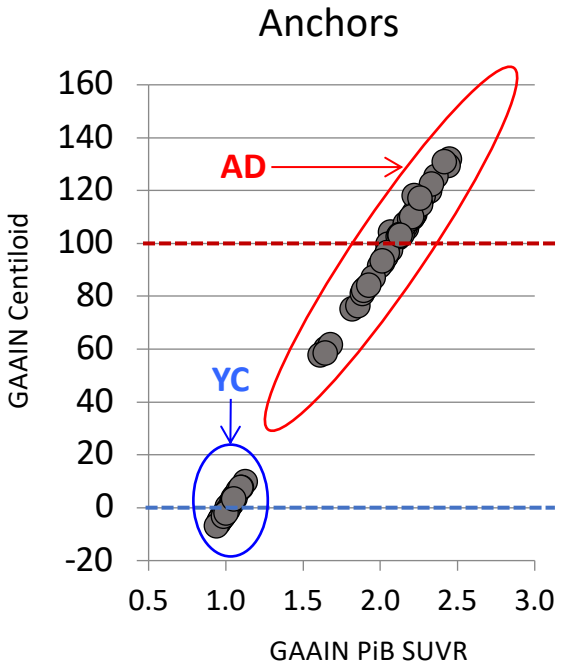
William E. Klunk[a,b,*], Robert A. Koeppe[c], Julie C. Price[d], Tammie L. Benzinger[e,f], Michael D. Devous, Sr.,[g,h], William J. Jagust[i], Keith A. Johnson[e,j], Chester A. Mathis[k], Davneet Minhas[d], Michael J. Pontecorvo[l], Christopher C. Rowe[m], Daniel M. Skovronsky[l], Mark A. Mintun[l]

Defines the *0* (young controls) and *100* (mild AD+) anchor points
Spatial normalization w/ SPM8 of MRI and co-registered PET into MNI-158

- Standard VOIs

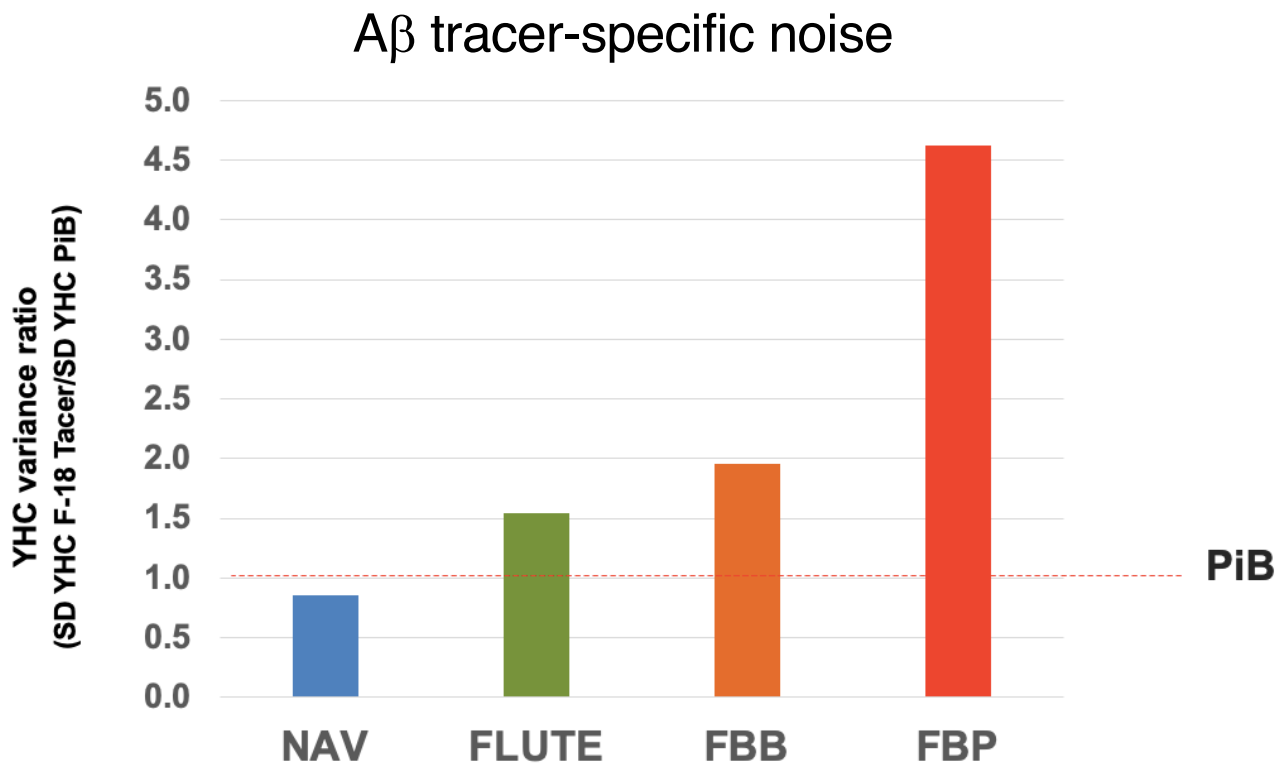
One Cortical VOI (Aβ+ areas after subtracting EC from AD)
Four reference regions: **WCB** – CBGREY - WCB+PONS - PONS





Images & VOI available at the Global Alzheimer's Association Information Network (GAAIN; http://www.gaain.org)

Aβ imaging in Alzheimer's disease



PiB: Klunk et al., Alzheimer Dement, 2015.
NAV: Rowe et al., J Nucl Med, 2016.
FBB: Rowe et al., EJNMMI, 2017.
FBP: Navitsky et al., Alzheimer Dement, 2018.
FLT: Battle et al., EJNMMI Research, 2018.

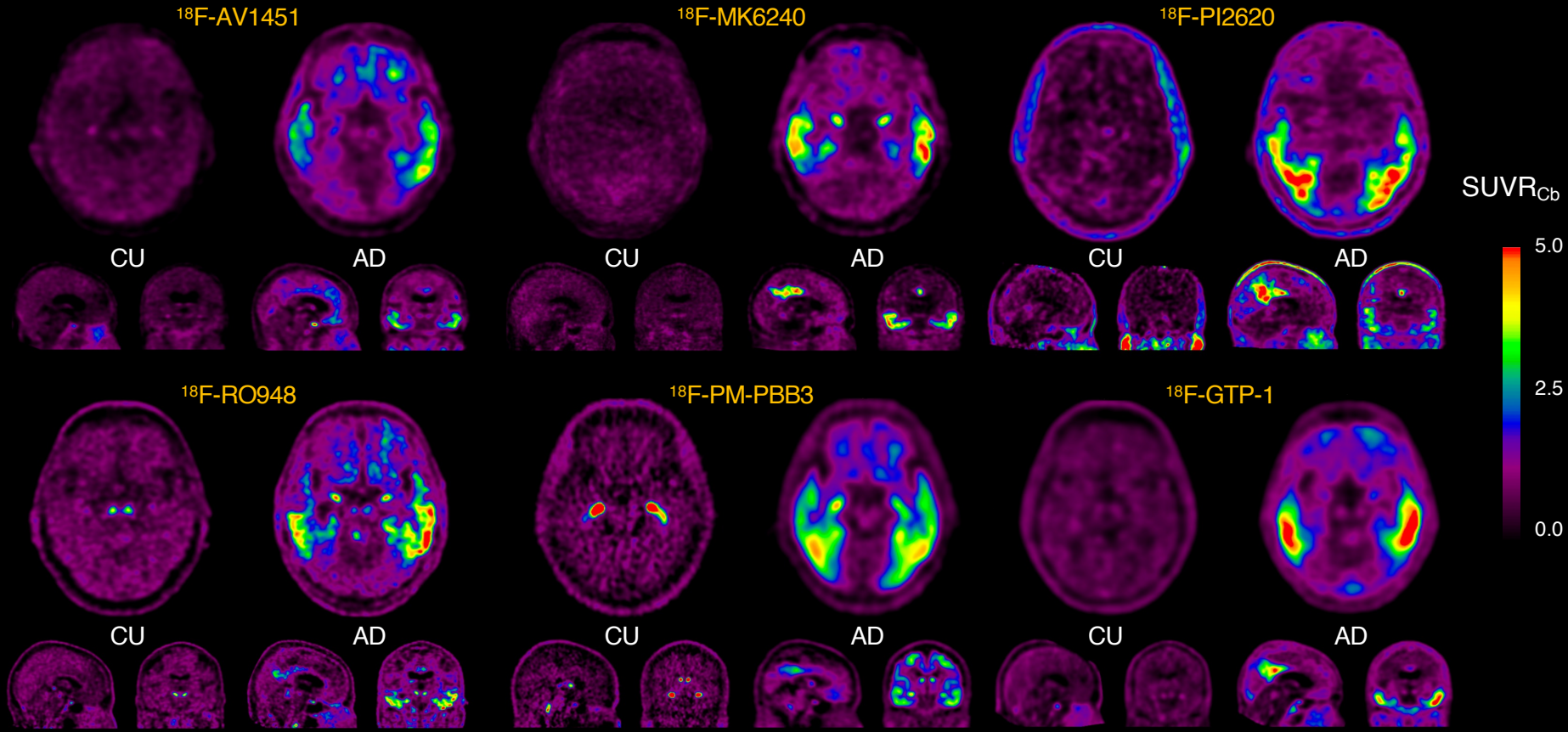
Centiloid Thresholds

Neuropathology		
PiB	(*La Joie et al., Alzheimers Dement. 2019*)	12-24 CL
Florbetaben	(*Doré et al., Alzheimers Dement.. 2019, Bullich et al., AR&T, 2021*)	13-21-36 CL
Florbetapir	(*Navitsky et al., Alzheimers Dement. 2018*)	24 CL
Flutemetamol	(*Battle et al., EJNMMI Res. 2018*)	(25-30 CL)*
Specificity threshold (95%ile YC)		
PiB	(*Su et al., Neuroimage: Clinical. 2018*)	6-12 CL
Reliable worsening method		
PiB	(*Jack et al., Alzheimers Dement. 2017*)	19 CL
PiB	(*Su et al., Neuroimage: Clinical. 2018*)	11 CL
CSF		
Flutemetamol	(*Salvadó et al, Alzheimers Res Ther. 2019*)	12-30 CL
Tipping point		
PiB	(*Schindler et al, Neurology, 2021*)	7 CL
Clustering		
ALL	(*Cox & Villemagne, ADOPIC, 2022*)	18 CL
Risk of cognitive decline/clinical progression		
PiB	(*extended from Rowe Ann Neurol, 2013*)	20 CL
PiB-FBP	(*Farell et al., Neurology, 2021*)	15-18.5 CL

Tau Harmonization

Universal masks

Tau imaging


^{18}F-AV1451
^{18}F-MK6240
^{18}F-PI2620
CU
AD
CU
AD
CU
AD
^{18}F-RO948
^{18}F-PM-PBB3
^{18}F-GTP-1
CU
AD
CU
AD
CU
AD
SUVR$_{Cb}$
5.0
2.5
0.0

Towards a universal cortical tau mask

Vincent Doré

Tracer-specific masks

(Aβ+ AD - Aβ- HC)

MK6240
Aβ- HC = 157
Aβ+ AD = 22

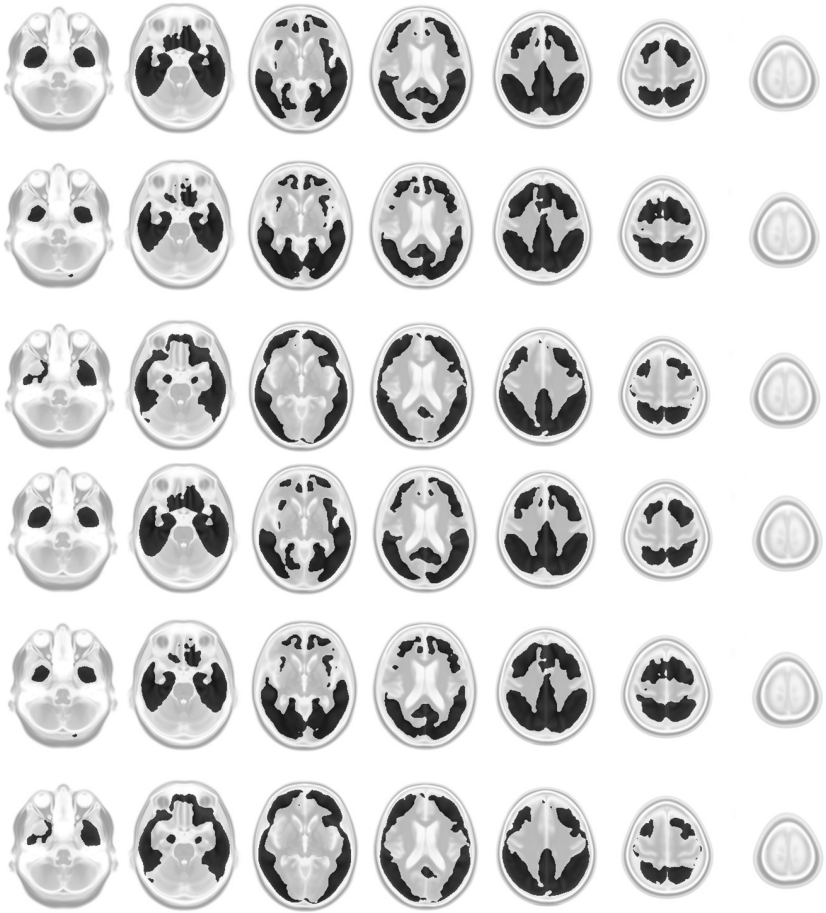
AV1451
Aβ- HC = 54
Aβ+ AD = 24

PI2620
Aβ- HC = 10
Aβ+ AD = 21

RO948
Aβ- HC = 35
Aβ+ AD = 30

GTP-1
Aβ- HC = 15
Aβ+ AD = 38

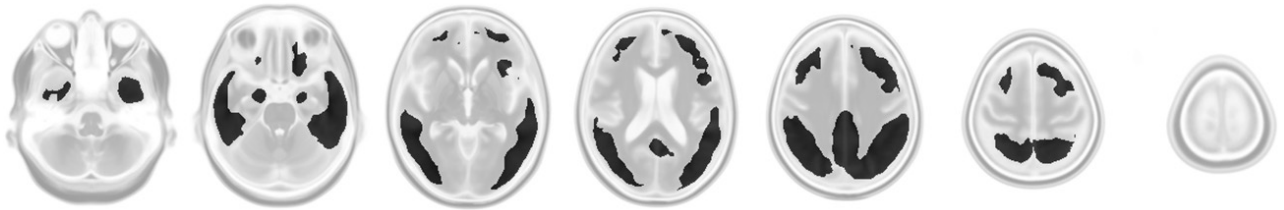
PM-PBB3
Aβ- HC = 30
Aβ+ AD = 28



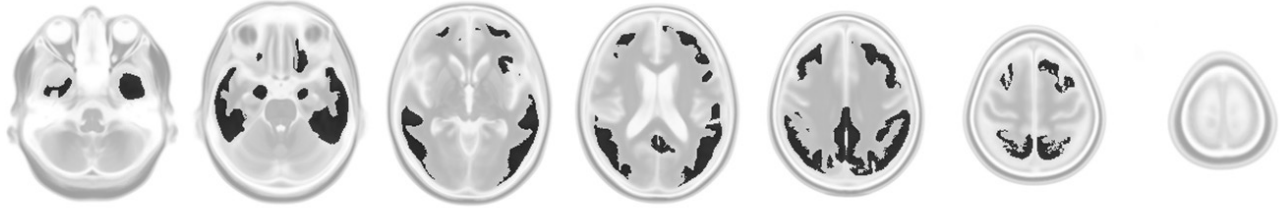
Doré & Villemagne, 2022

Towards a universal cortical tau mask

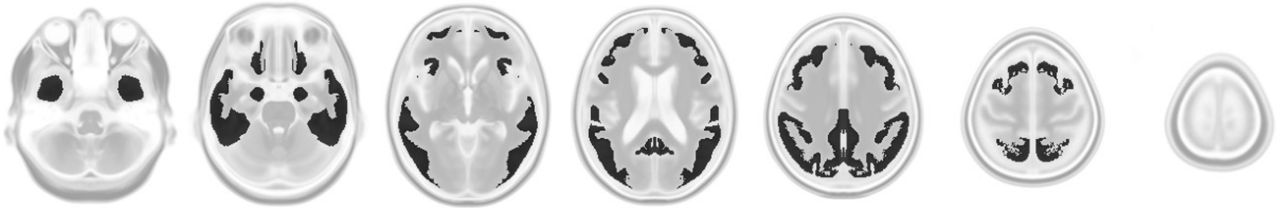
Composite mask
(intersection of 6 tracers)



Composite cortical



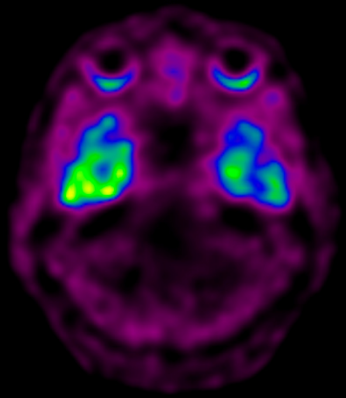
Composite & mirrored cortical



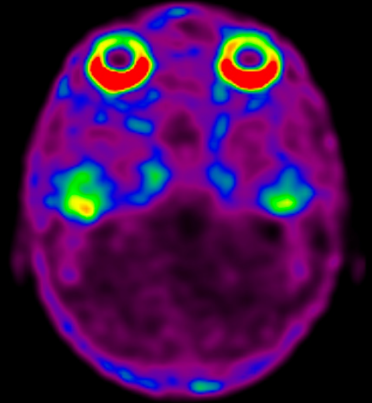
Doré & Villemagne, 2022

Towards a universal tau cerebellar mask

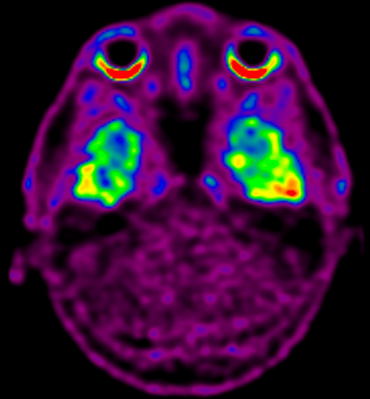
^{18}F-MK6240



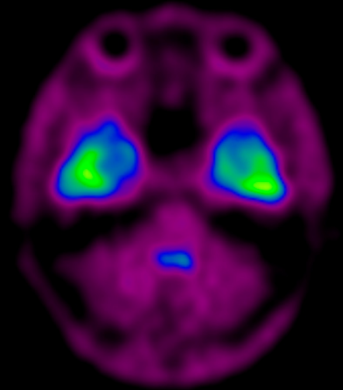
^{18}F-PI2620



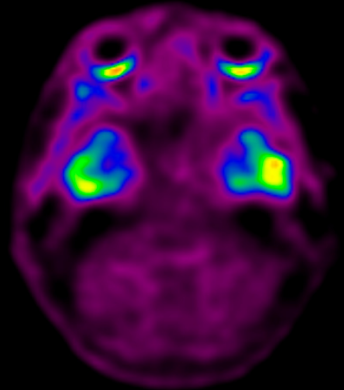
^{18}F-RO948



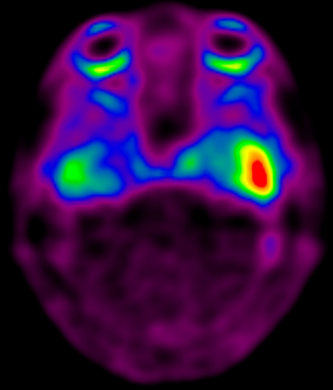
^{18}F-PM-PBB3



^{18}F-AV1451

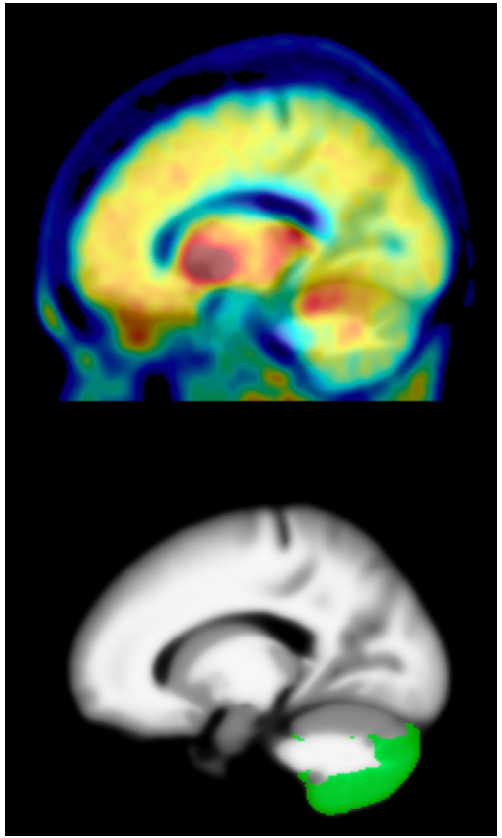


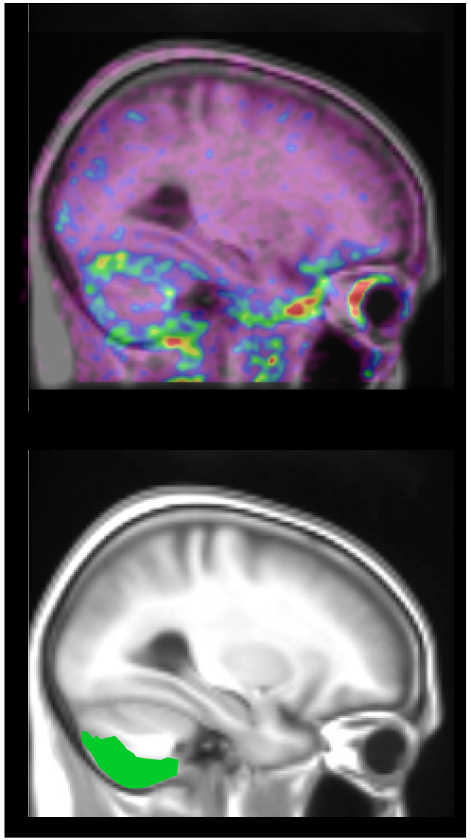
^{18}F-GTP-1



Towards a universal tau cerebellar mask

^{18}F-FTP

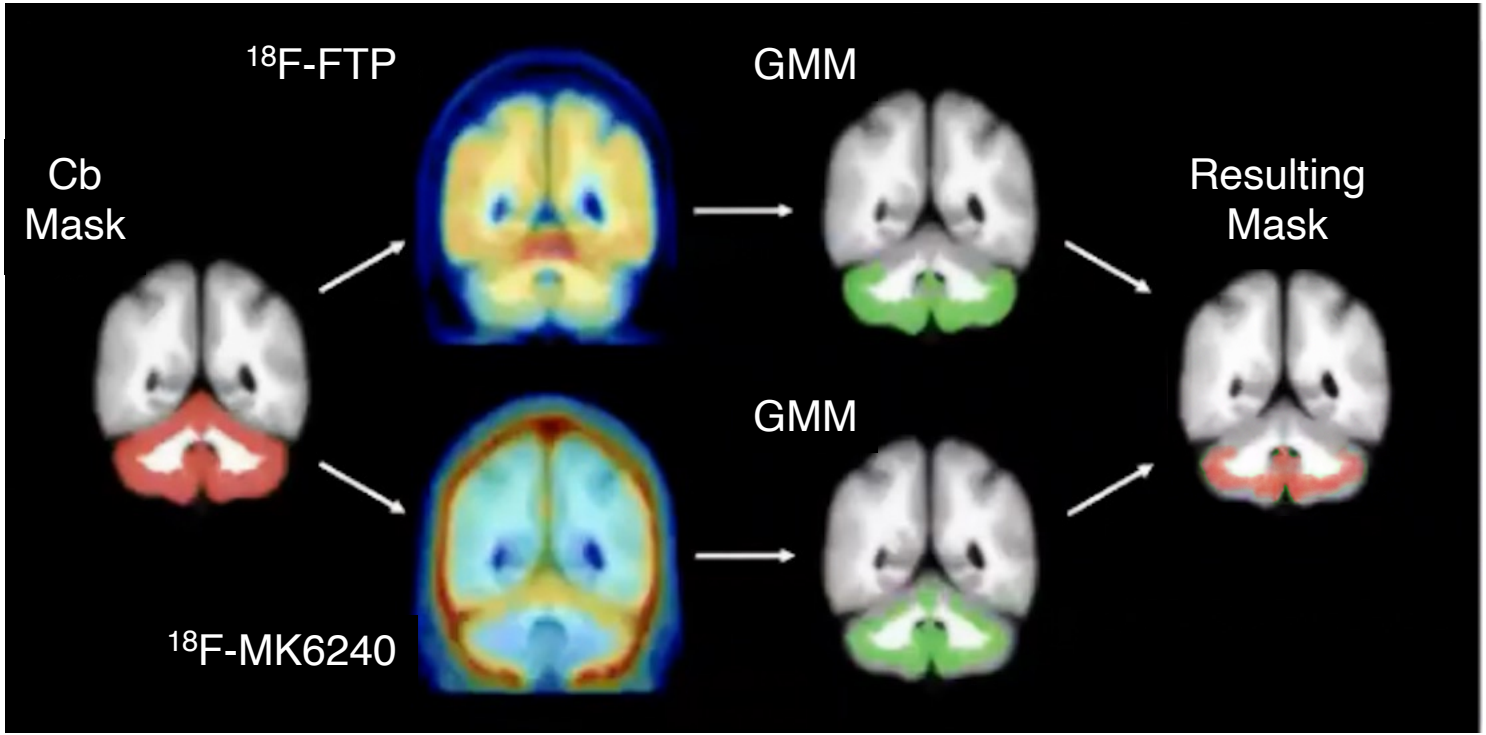




^{18}F-MK6240

Minhas, Lopresti & Villemagne, 2022

Towards a universal tau cerebellar mask



Davneet Minhas

Brian Lopresti

Tau Harmonization

Universal scale

A tale of CenTauRs

Can we combine results from different tau radiotracers?
Can this universal scale be used for longitudinal studies?

1. Measures of amplitude/degree of tracer binding/retention
   a. BP_{ND}/DVR/SUVR (≠tracers w/≠dynamic ranges and thresholds, only categorical -high/low- can be combined)
   b. Z-score (amenable to combine results from ≠tracers) = $CenTauR_Z$© (Villemagne and Doré)

1. Metrics of extent/progression of tracer retention

%Area>threshold	(S Sanabria, *Genentech;* J Seibyl, *Invicro*)
Overlap Index	(Lee et al., J Nucl Med, doi:10.2967/jnumed.121.263136, 2022)

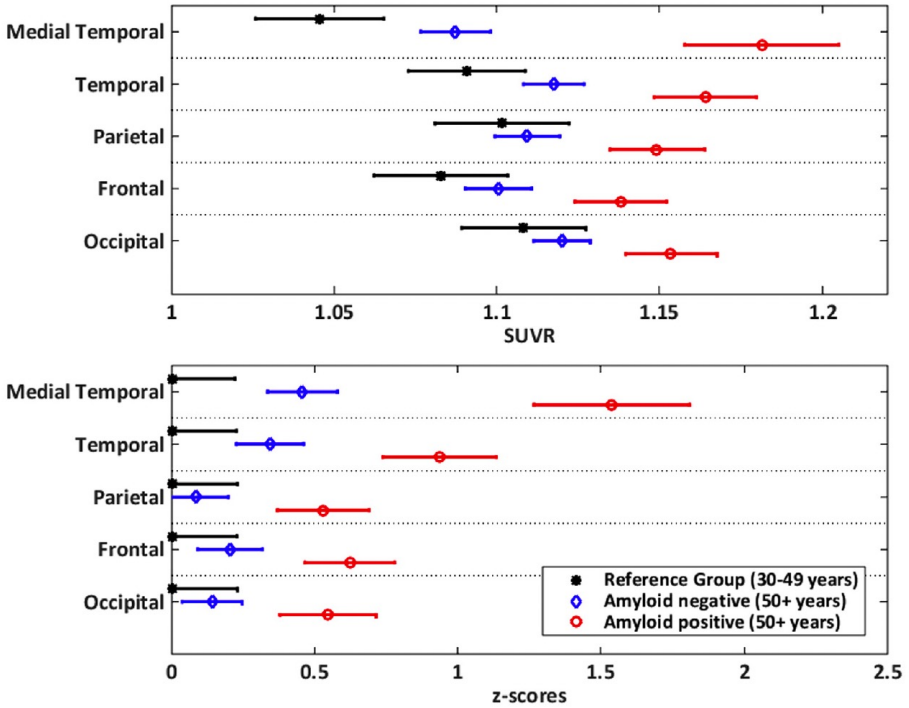
3. Combination of *1.* and *2.* (Villemagne and Doré)
   a. *Regio*-$CenTauR_S$© (BP_{ND}/DVR/SUVR x [1+%Area>threshold])

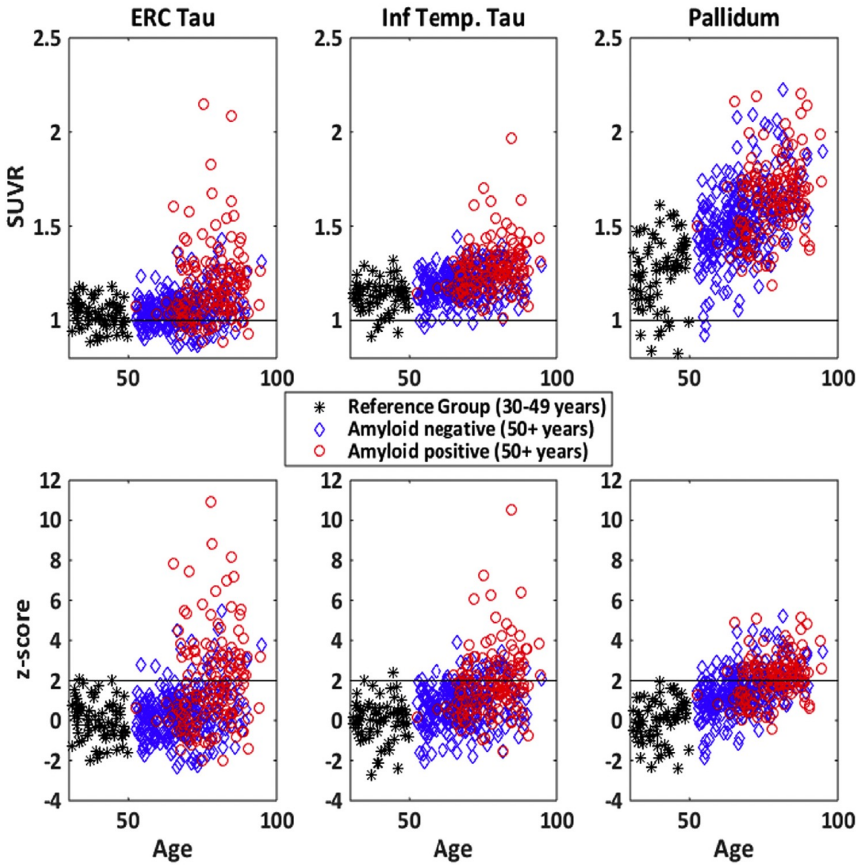
   b. *Regio*-$CenTauR_Z$© (z-score x [1+%Area>threshold] / or x [1+Overlap Index])

ELSEVIER
CrossMark
Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 6 (2017) 21-30
Alzheimer's & Dementia

Tau-PET uptake: Regional variation in average SUVR and impact of amyloid deposition

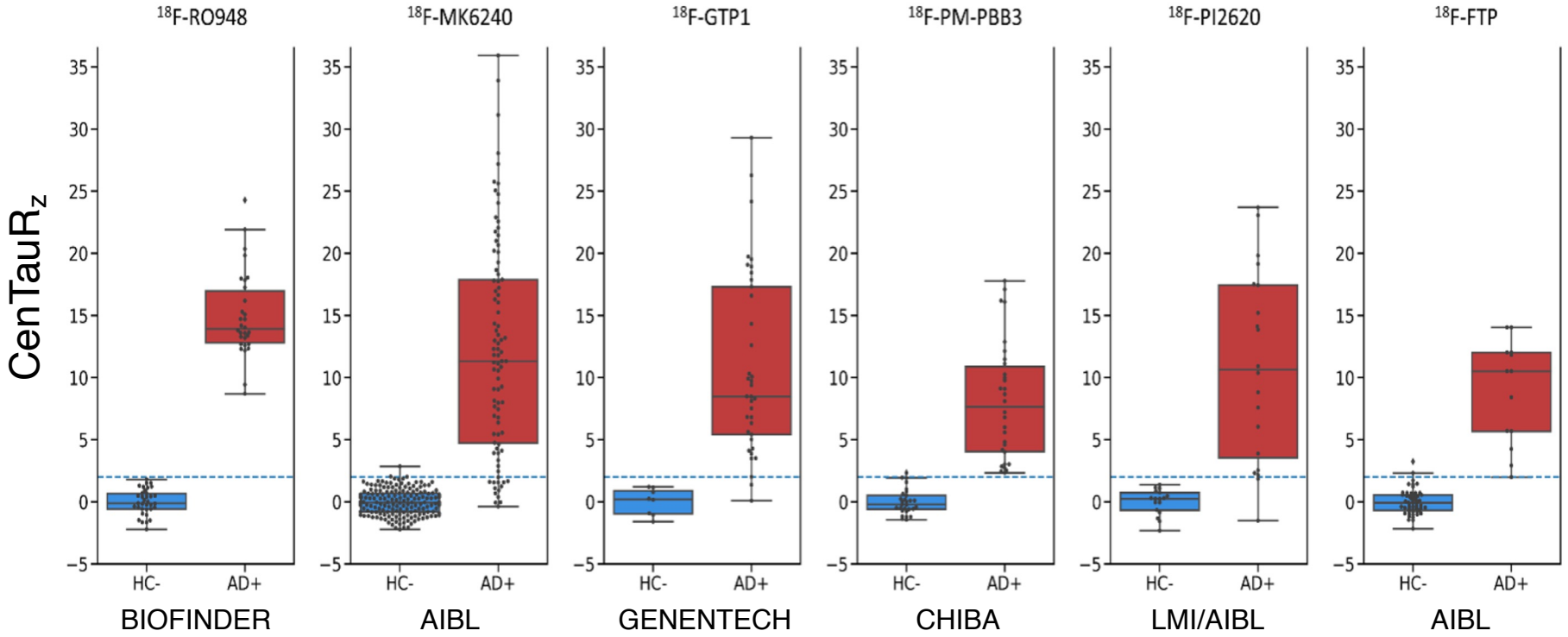
Prashanthi Vemuri[a,*], Val J. Lowe[a], David S. Knopman[b], Matthew L. Senjem[a], Bradley J. Kemp[a], Christopher G. Schwarz[a], Scott A. Przybelski[c], Mary M. Machulda[d], Ronald C. Petersen[b], Clifford R. Jack, Jr.[a]





Towards a universal tau scale

Meta-temporal region



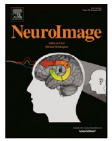
Doré & Villemagne, 2022

Longitudinal analysis

Contents lists available at ScienceDirect

NeuroImage

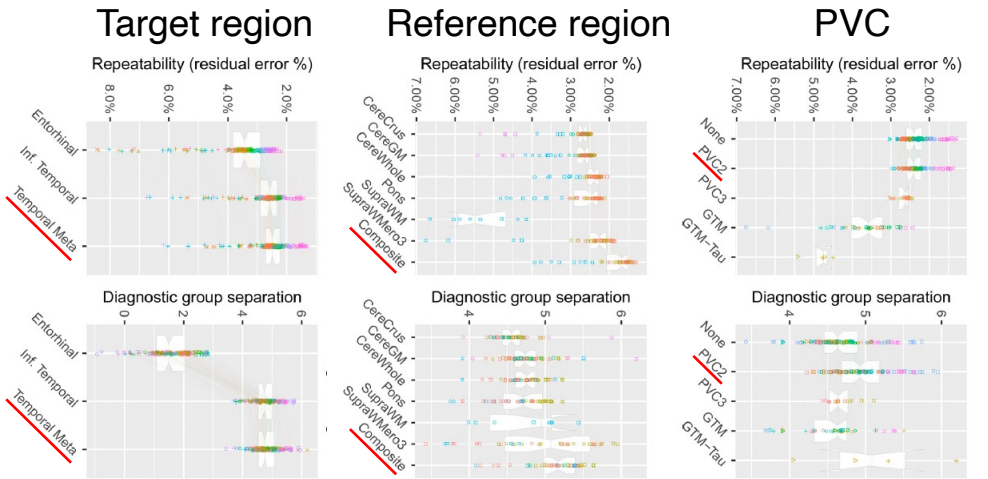
journal homepage: www.elsevier.com/locate/neuroimage



Selecting software pipelines for change in flortaucipir SUVR: Balancing repeatability and group separation

Christopher G. Schwarz[a,*], Terry M. Therneau[b], Stephen D. Weigand[b], Jeffrey L. Gunter[a,c], Val J. Lowe[a], Scott A. Przybelski[b], Matthew L. Senjem[a,c], Hugo Botha[d], Prashanthi Vemuri[a], Kejal Kantarci[a], Bradley F. Boeve[d], Jennifer L. Whitwell[a], Keith A. Josephs[d], Ronald C. Petersen[d], David S. Knopman[d], Clifford R. Jack Jr[a]

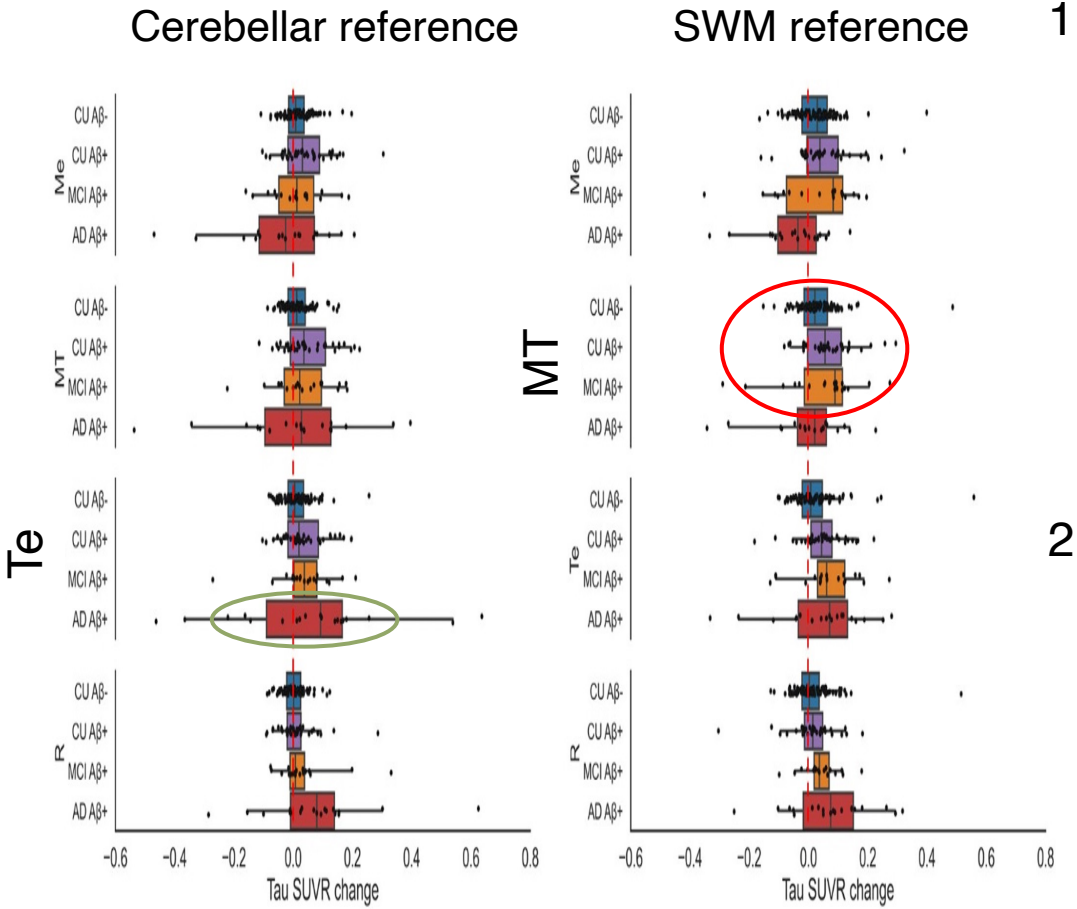
NeuroImage 238 (2021) 118259



Best performance:

1. SUVR approach,
2. temporal-lobe meta-ROI that includes adjacent (juxtacortical) WM
3. an eroded WM + pons + whole cerebellum reference region
4. 2-class voxel-based PVC, and
5. median statistics.

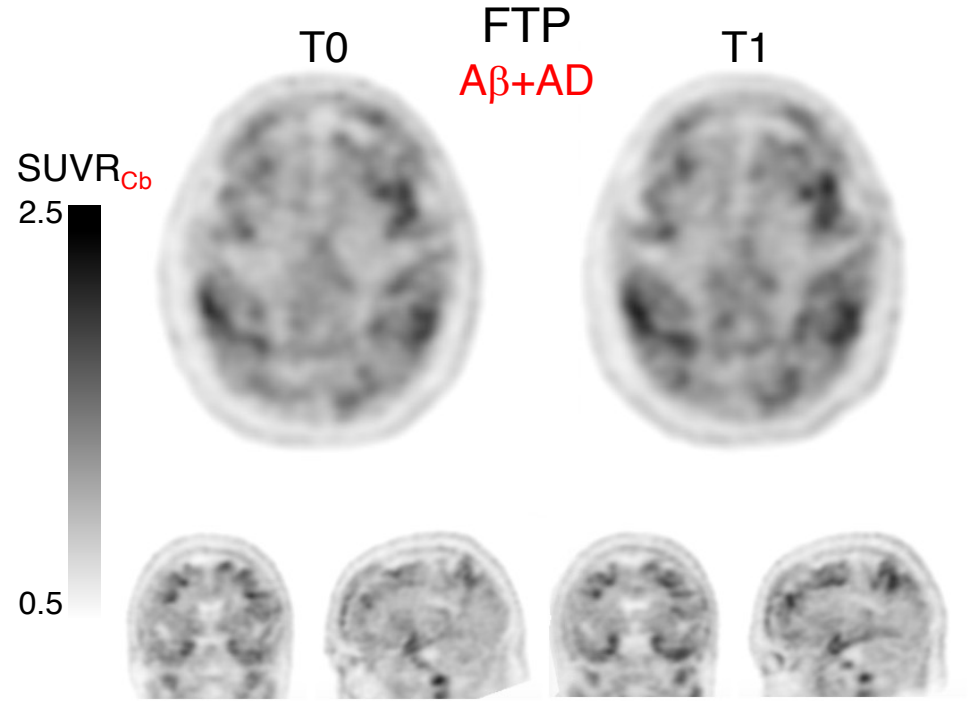
Longitudinal analysis

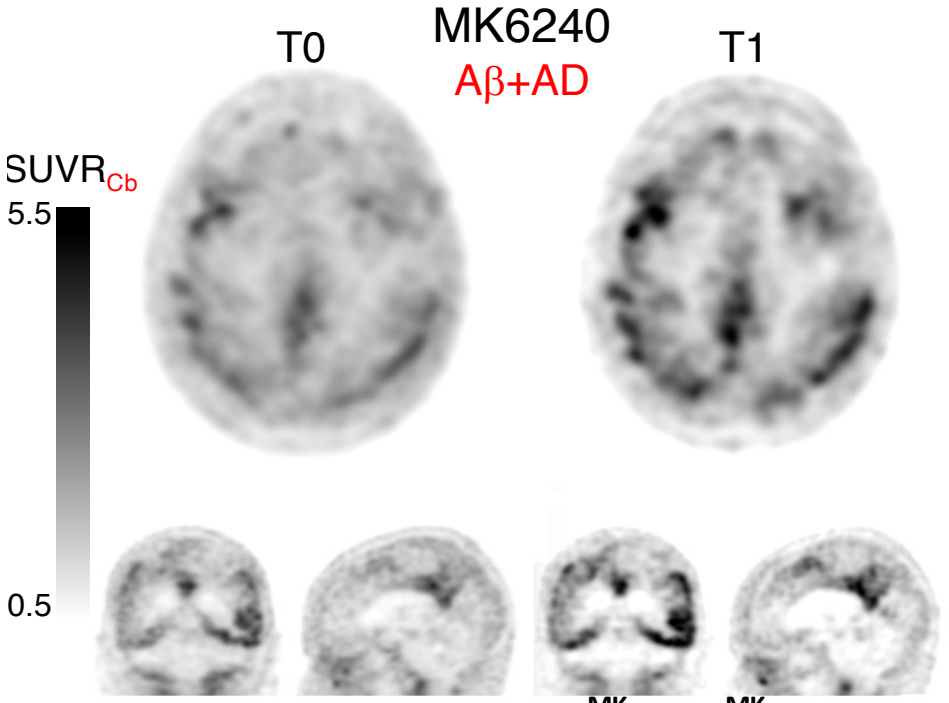


1. a *meta-temporal composite* with an eroded subcortical *white matter reference* is ideal for early detection and assessment of tau accumulation at the preclinical /prodromal stages of the disease
2. a *temporoparietal composite* with a *cerebellar cortex reference* would be preferred for trials at the symptomatic AD stages of disease.

Krishnadas et al. (submitted), 2022

A tale of longitudinal CenTauR$_z$





	FTP SUVR T0	FTP SUVR T1	Δ%	FTP CENTAUR$_z$ T0	FTP CENTAUR$_z$ T1	Δ%
Me	1.56	1.58	*2%*	3.42	3.56	*4%*
Te	1.65	1.78	*8%*	4.93	5.92	*20%*
R	1.26	1.32	*4%*	2.15	2.69	*26%*
MetaT	1.63	1.68	*3%*	4.42	4.78	*8%*
GLOBAL	1.49	1.58	*7%*	3.74	4.54	*21%*

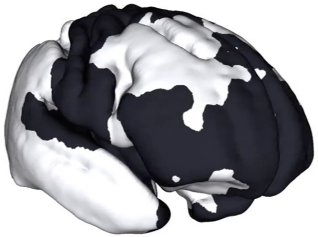
	MK SUVR T0	MK SUVR T1	Δ%	MK CENTAUR$_z$ T0	MK CENTAUR$_z$ T1	Δ%
INF TEMP	2.77	3.57	*29%*	10.17	14.61	*44%*
LAT OCC	1.36	1.58	*16%*	2.73	4.35	*60%*
PVC	1.17	1.18	*1%*	2.48	2.57	*4%*
MetaT	2.76	3.56	*29%*	12.08	17.81	*47%*
GLOBAL	2.29	3.03	*32%*	10.84	16.86	*55%*

Tau Harmonization

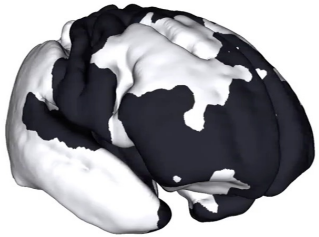
Topologies

(where to look?)

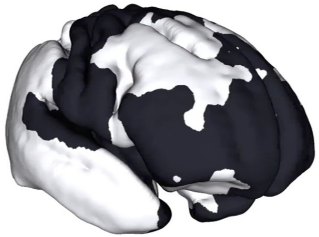
Towards a universal tau cortical mask & scale



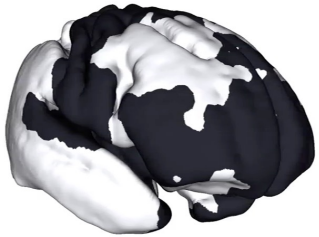
entorhinal/Inf Temporal



Braak&Braak



Temporal composite



MeTeR scale

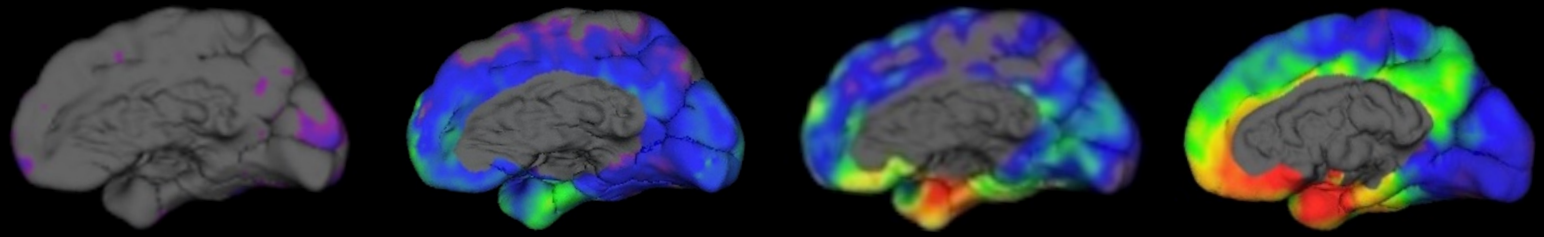
The “universal” tau mask for the AD continuum defines the common “tau space” for most tau tracers, not to obtain a ”global” tau measure as with Aβ, but to use a common space over which several different global/regional sampling VOI or composites can be applied, customized for purpose: *early tau detection, clinical trials, etc.*

Results obtained with different tracers from the same global/regional sampling can be expressed together under the term CenTauR$_z$ (if expressed as z-scores (*Vemuri et al, Neurology, 2017*))

Doré & Villemagne, 2022

Tau imaging across the AD spectrum

(typical cases)

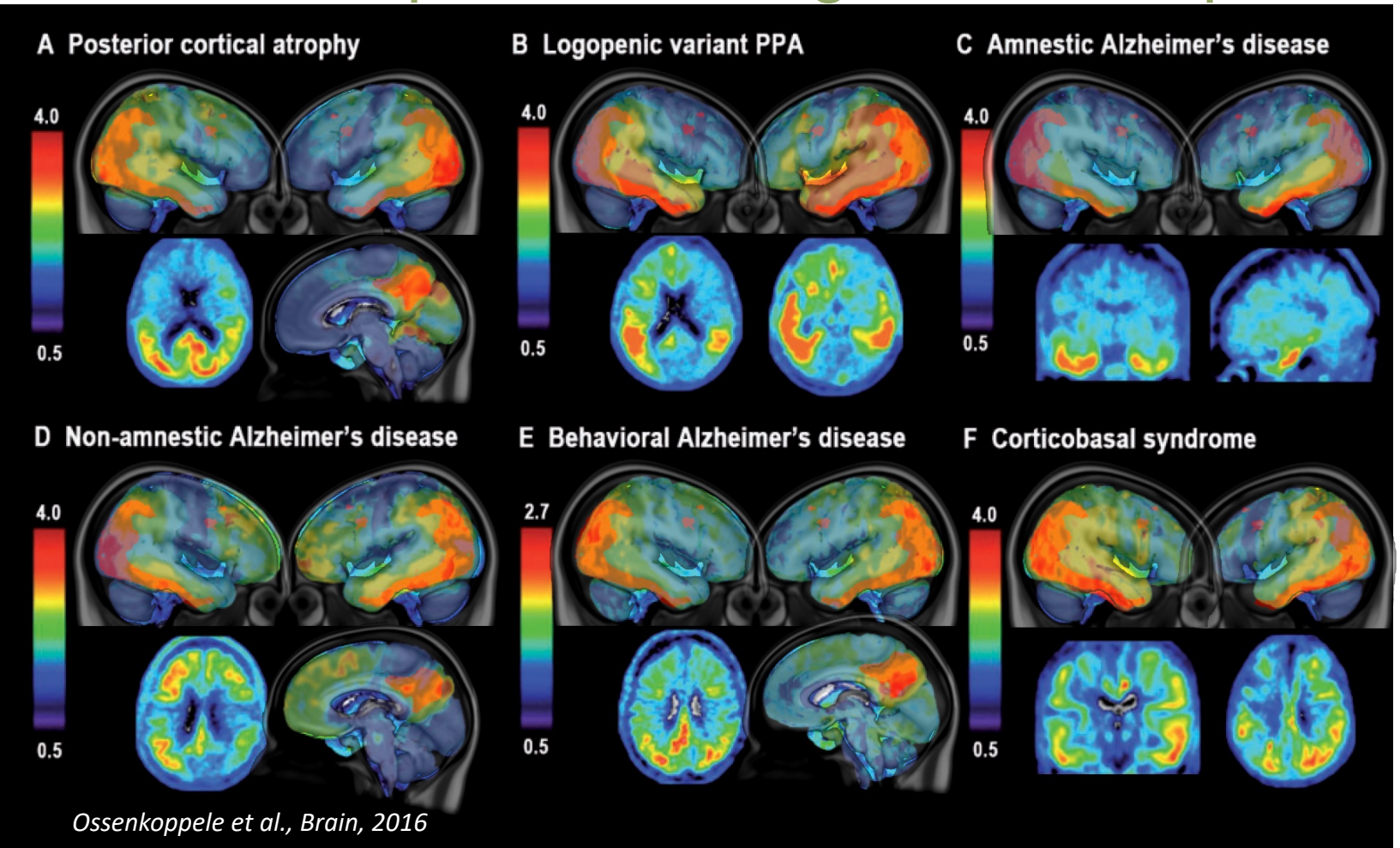


Stage I & II | Stage III & IV | Stage V & VI

A- HC-MCI | A+ HC | A+ Prodromal AD - AD

The temptation of the neuropathological "corset"

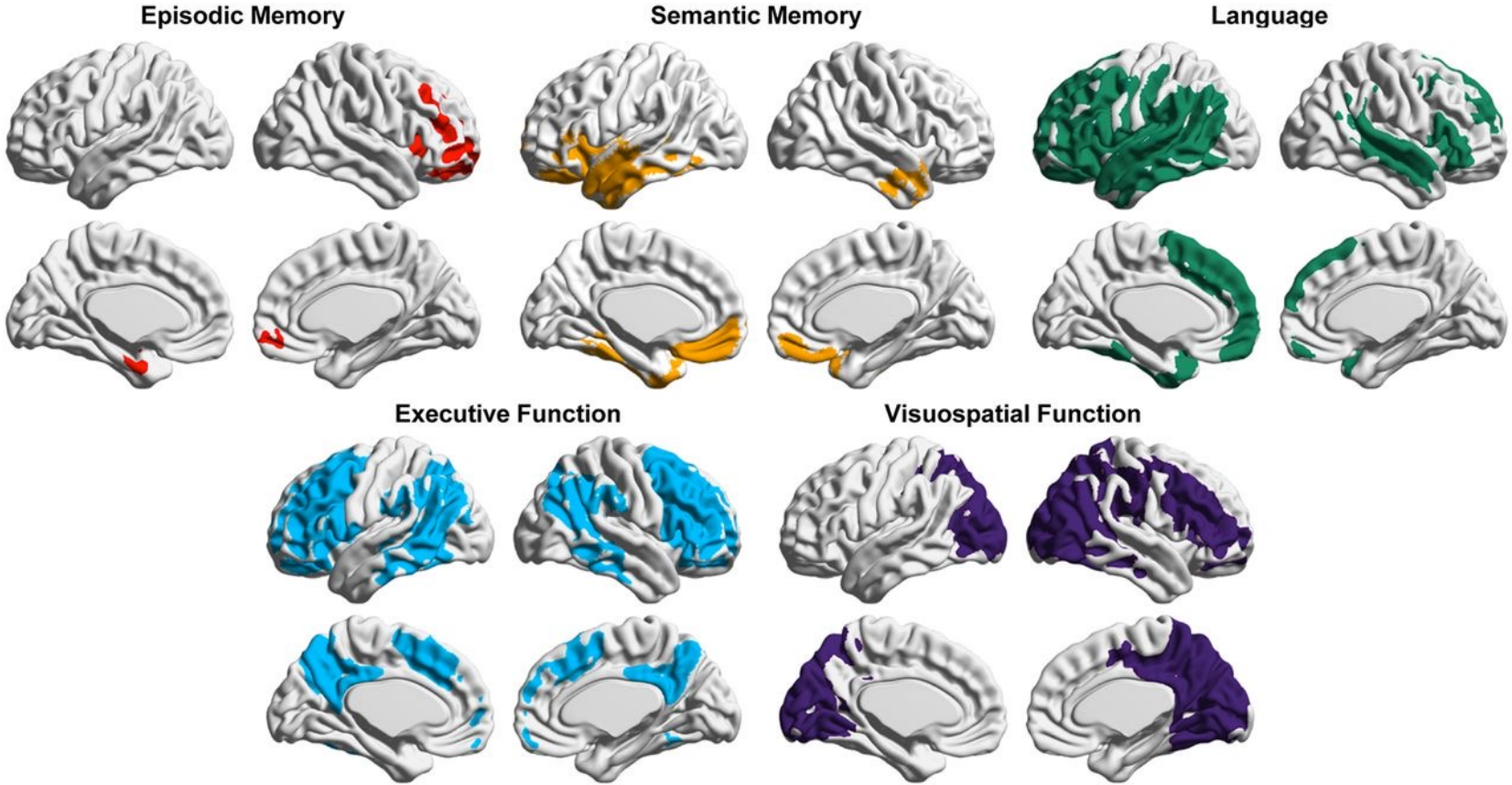
Different patterns of regional tau deposition



Ossenkoppele et al., Brain, 2016

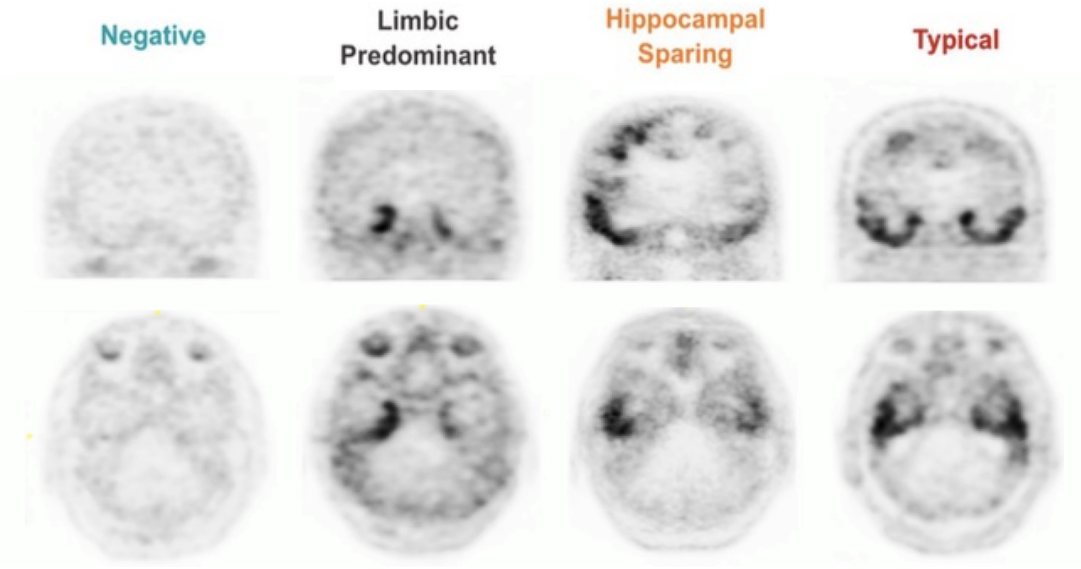
^{18}F- AV1451

Tau correlation with cognitive domains



Tanner and Rabinovici, J Nucl Med 2021

Tau pathological subtypes in AD

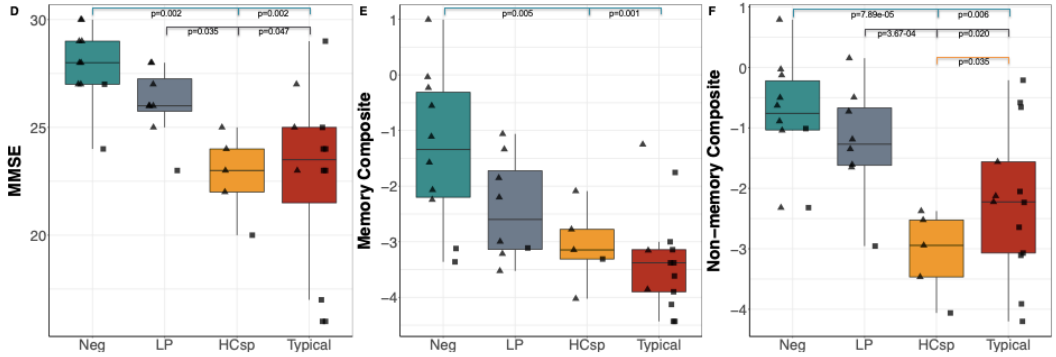


^{18}F-MK6240

MCI/AD

31% Negative
20% Limbic Predominant
14% Hippocampal Sparing
35% Typical

Only 50% of T+ are Typical

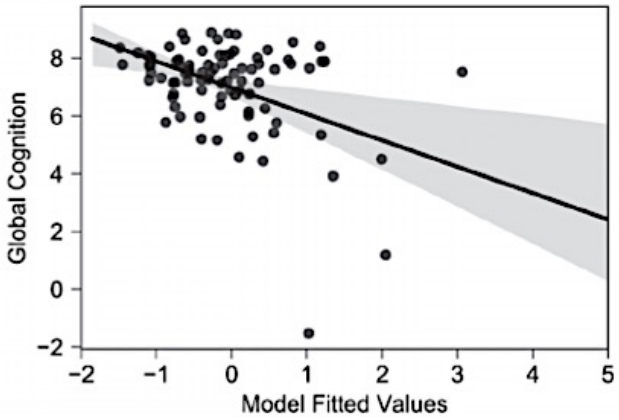


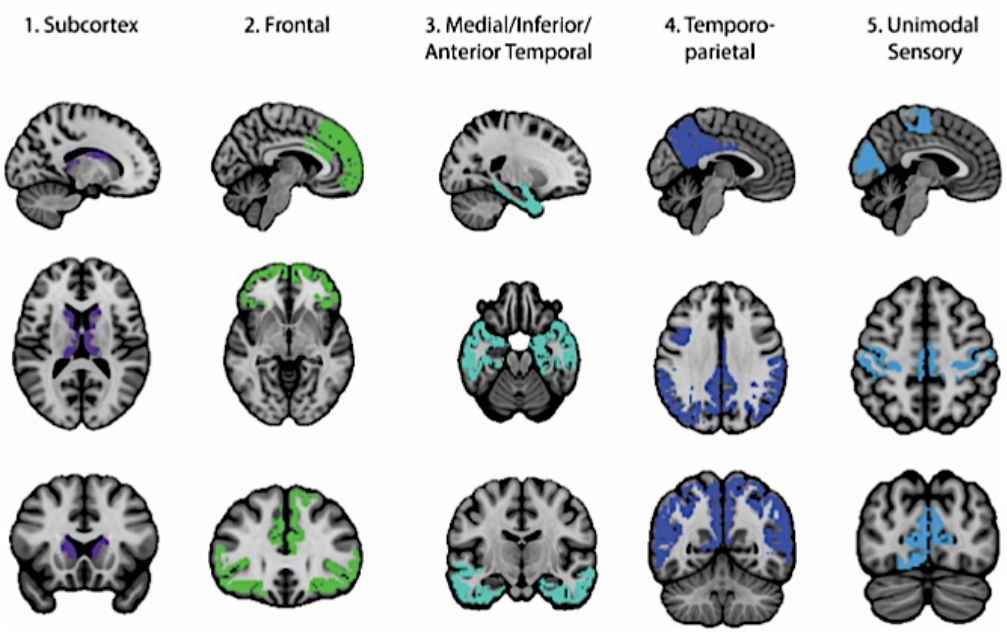
Krishnadas, Doré, Rowe (submitted)

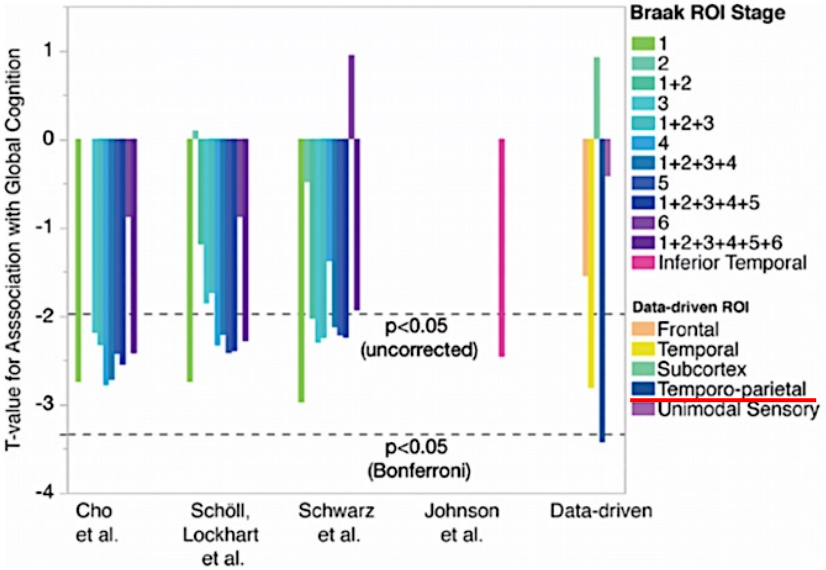
Data-driven approaches for tau-PET imaging biomarkers in Alzheimer's disease

Jacob W. Vogel[1,2] | Niklas Mattsson[3,4,5] | Yasser Iturria-Medina[1] | Olof T. Strandberg[3] | Michael Schöll[3,6] | Christian Dansereau[7,8] | Sylvia Villeneuve[1,9] | Wiesje M. van der Flier[2,10] | Philip Scheltens[2] | Pierre Bellec[7,8] | Alan C. Evans[1] | Oskar Hansson[3,4#] | Rik Ossenkoppele[2,3#] | The Alzheimer's Disease Neuroimaging Initiative[†] | The Swedish BioFINDER Study

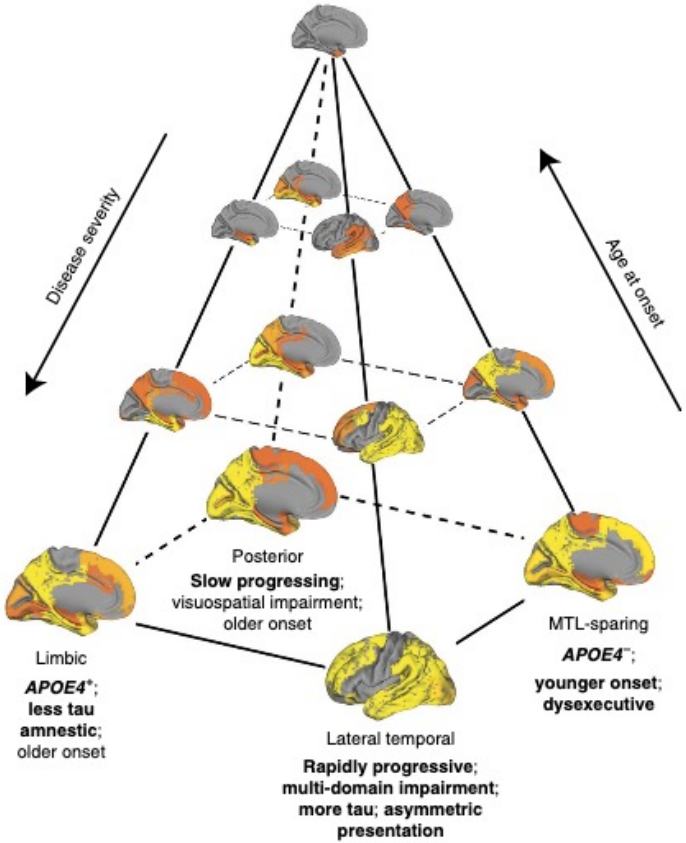
Hum Brain Mapp. 2019;40:638–651.







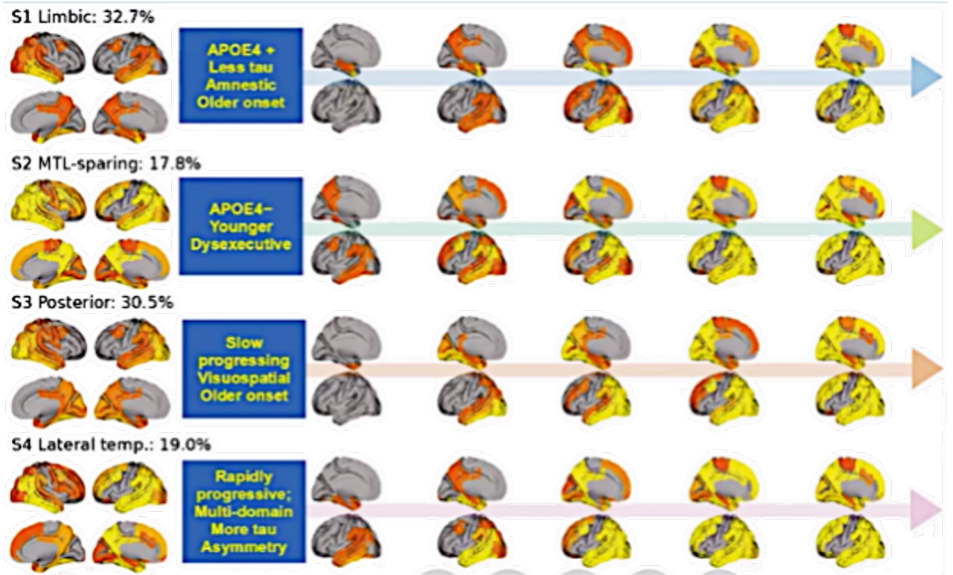
Imaging data-driven classification



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

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✉]



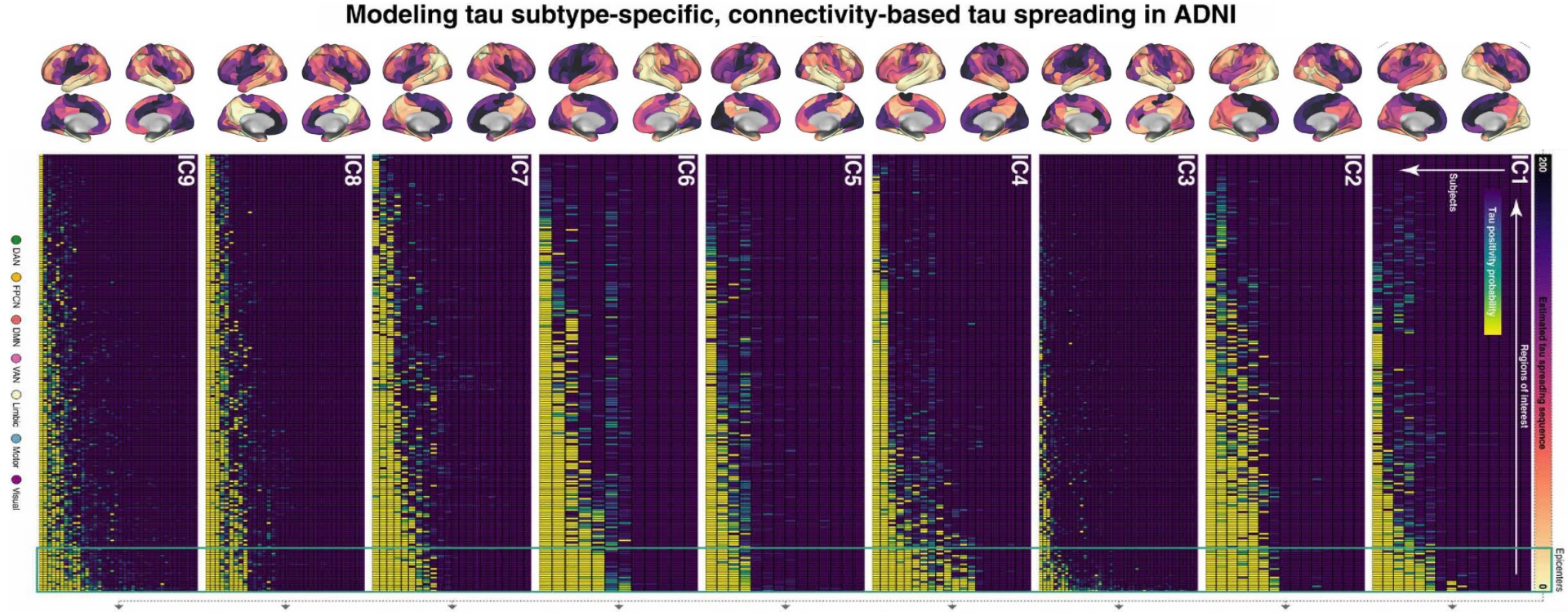
Brain connectivity data-driven classification

SCIENCE ADVANCES | RESEARCH ARTICLE

DISEASES AND DISORDERS

Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease

Nicolai Franzmeier[1]*, Anna Dewenter[1], Lukas Frontzkowski[1], Martin Dichgans[1,2,3], Anna Rubinski[1], Julia Neitzel[1], Ruben Smith[4,5], Olof Strandberg[5], Rik Ossenkoppele[5,6], Katharina Buerger[1,3], Marco Duering[1], Oskar Hansson[5,7], Michael Ewers[1,3]*



adapted from Franzmeier et al., Sci Adv, 2020

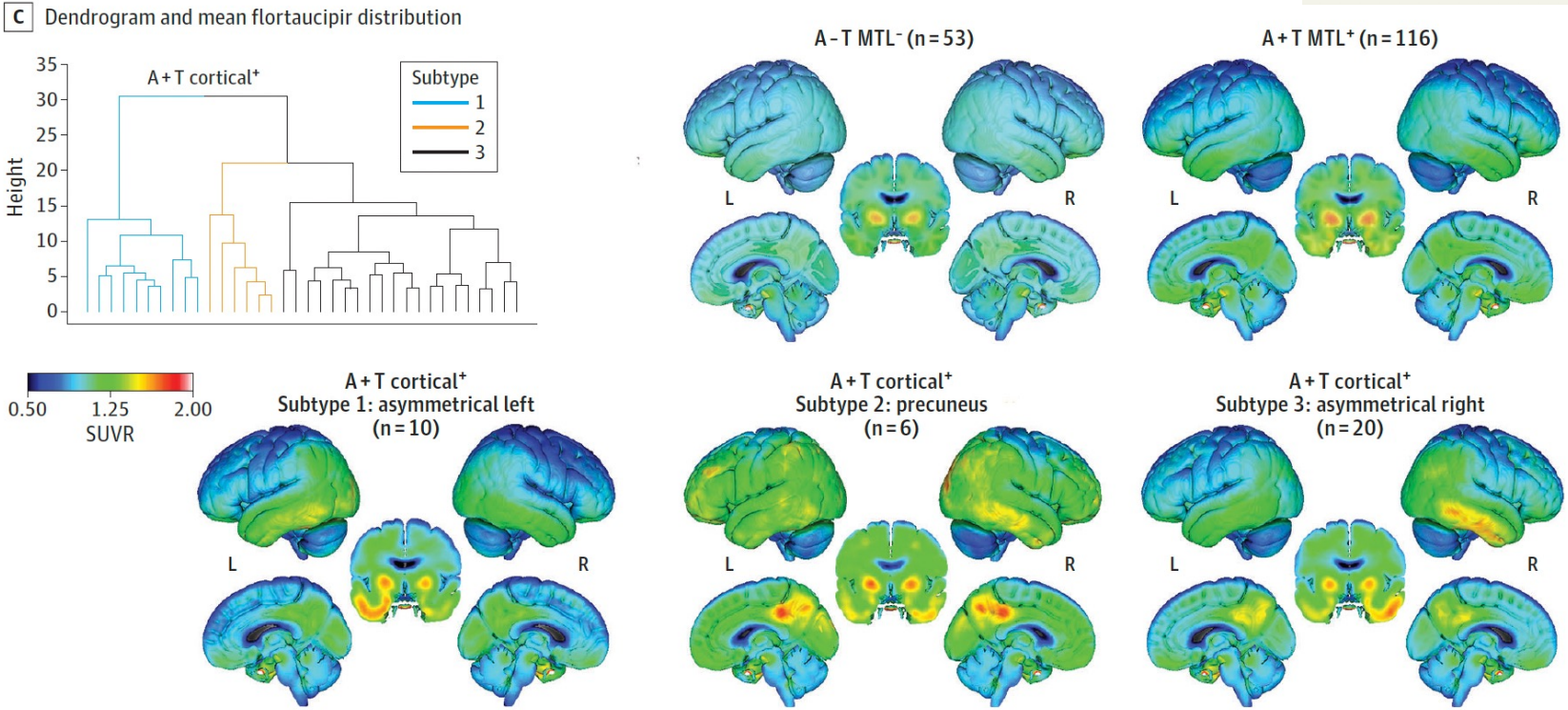
Imaging data-driven classification

JAMA Neurology | Original Investigation

Divergent Cortical Tau Positron Emission Tomography Patterns Among Patients With Preclinical Alzheimer Disease

Christina B. Young, PhD; Joseph R. Winer, PhD; Kyan Younes, MD; Karly A. Cody, BS; Tobey J. Betthauser, PhD; Sterling C. Johnson, PhD; Aaron Schultz, PhD; Reisa A. Sperling, MD; Michael D. Greicius, MD, MPH; Inma Cobos, MD, PhD; Kathleen L. Poston, MD, MS; Elizabeth C. Mormino, PhD; for the Alzheimer's Disease Neuroimaging Initiative and the Harvard Aging Brain Study

JAMA Neurol. doi:10.1001/jamaneurol.2022.0676
Published online April 18, 2022.



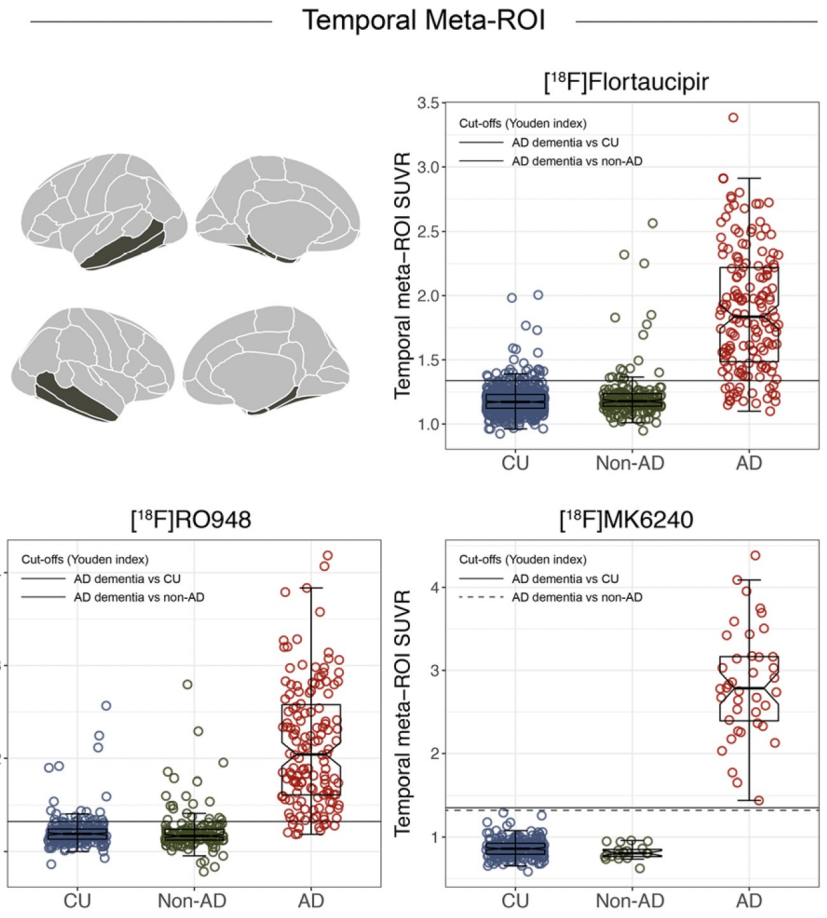
A multicenter comparison of [^{18}F]flortaucipir, [^{18}F]RO948, and [^{18}F] MK6240 tau PET tracers to detect a common target ROI for differential diagnosis

Antoine Leuzy[1] · Tharick A. Pascoal[2,3] · Olof Strandberg[1] · Philip Insel[1,4] · Ruben Smith[1,5] · Niklas Mattsson-Carlgren[1,5,6] · Andréa L. Benedet[2,7] · Hannah Cho[8] · Chul H. Lyoo[8] · Renaud La Joie[9] · Gil D. Rabinovici[9,10] · Rik Ossenkoppele[1,11] · Pedro Rosa-Neto[2,12,13] · Oskar Hansson[1,14]

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2295–2305

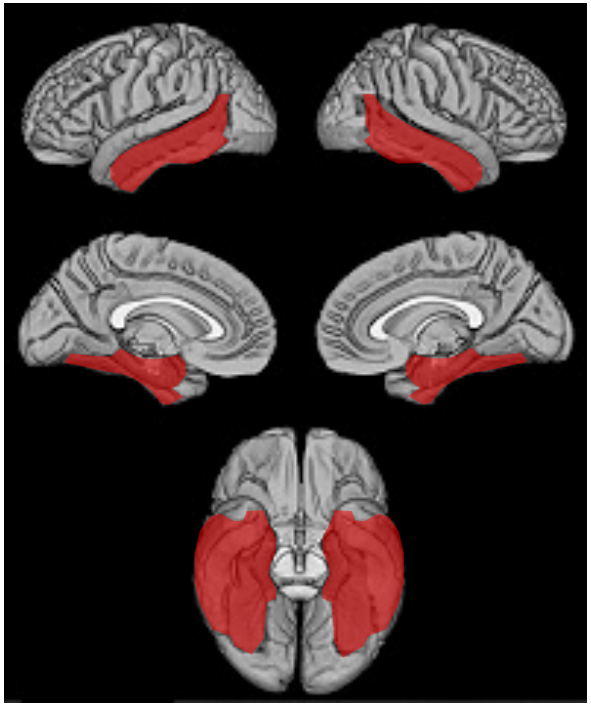
"The temporal meta-ROI can be used for differential diagnosis of dementia patients with ^{18}F-flortaucipir, ^{18}F-RO948, and ^{18}F-MK6240 tau PET with high accuracy, and that using very similar cut-offs of around 1.35 SUVR.

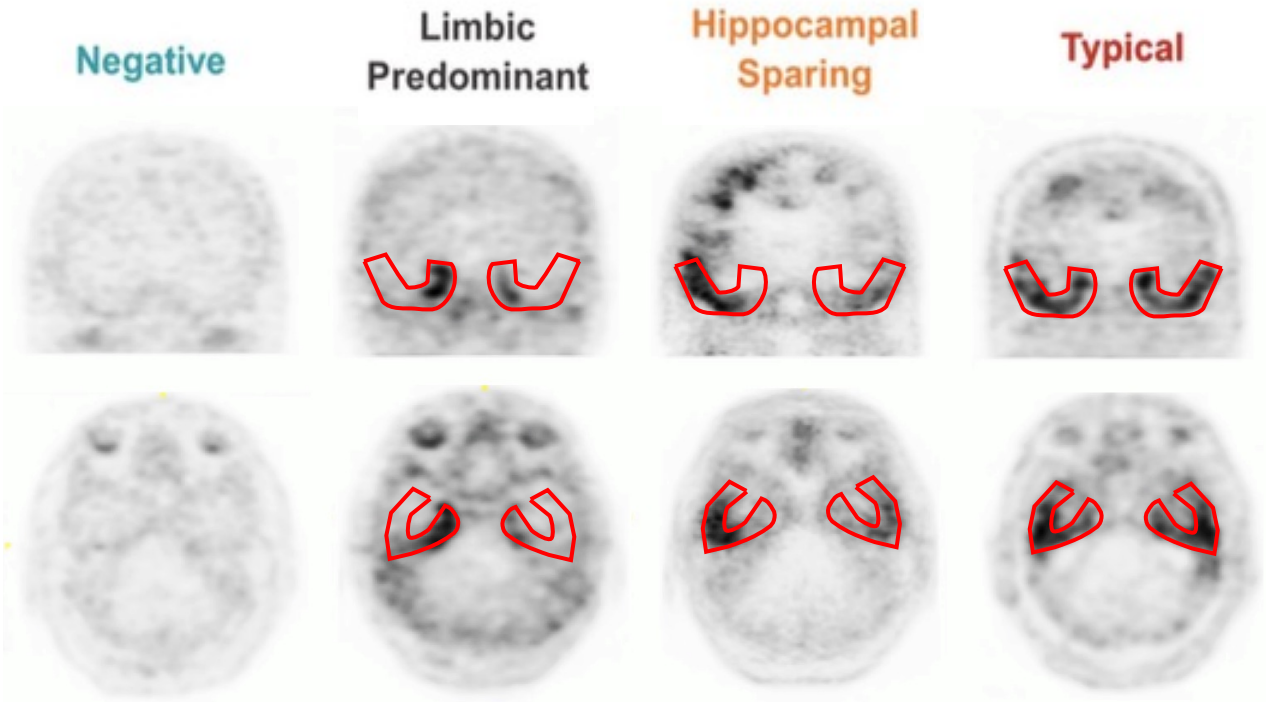
This ROI/SUVR cut-off can also be applied across tracers to define tau positivity."



How to capture early tau, PART, AD subtypes?

MetaTemporal composite





adapted & modified from Jack et al., Brain, 2018

Krishnadas, Doré, Rowe (submitted)

Summary

TO ENSURE CONSISTANT AND REPRODUCIBLE T+ CLASSIFICATION ACROSS CENTERS AND STUDIES

Summary

TO ENSURE CONSISTANT AND REPRODUCIBLE T+ CLASSIFICATION ACROSS CENTERS AND STUDIES

- ***WHAT TO SAMPLE?*** ***Use of a universal tau mask derived from the intersection of six tau tracers to constrain sampling to areas common to all tracers***

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- ***WHERE TO SAMPLE?***
  - What are the optimal regions for ***early*** detection of tau deposition?

    Meta-Temporal composite *(with Cb cortex reference)* *(used to define T+)*

    (captures early cortical tau, PART, as well as three pathological subtypes, and most of the atypical presentations)

Meta-temporal region

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Meta-temporal region

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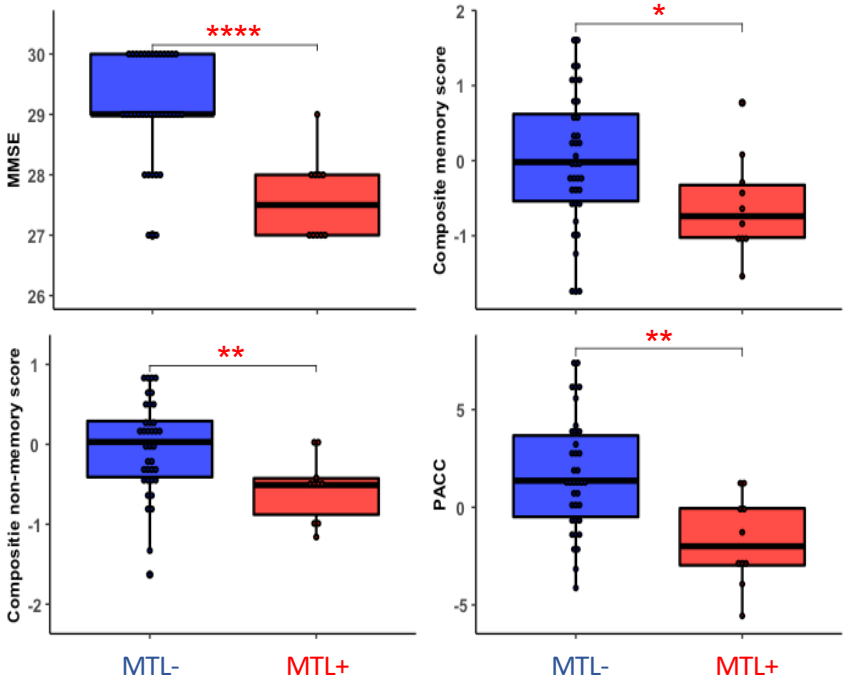
- ***WHAT IS T+?*** **Cortical tau with/without MTL** (*High MTL tau alone does not constitute T+, but it should be recorded**)

Meta-temporal region

*How innocent is MTL+?

^{18}F-FTP

High MTL tau vs. low MTL tau in **Aβ-** elderly controls
(*performing cognitively within normal limits*)

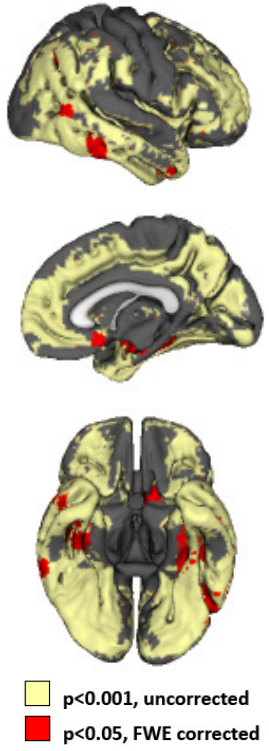


* *significant p<0.05*
** *significant p<0.01*
**** *significant p<0.0001*

Adjusted for age and sex

Is MTL tau a harbinger of future cortical tau deposition?

MTL+ – MTL-



adapted from Groot et al. Neurobiol Aging, 2021

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- ***WHAT IS T+?*** **Cortical tau with/without MTL** (*High MTL tau alone does not constitute T+, but it should be recorded**)
- ***HOW TO ESTABLISH/VALIDATE THRESHOLDS? – (for what PURPOSE?: INCREASE SENSITIVITY)***
  - **Young controls (***20-45 yo***)**
  - **Risk of clinical progression**

Meta-temporal region

Acknowledgements

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Annie Cohen
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Oscar Lopez

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Fiona Lamb
Kung Huang
Christopher C Rowe

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Mike Devous
Mike Navitsky
Mike Pontecorvo

Lifetime Molecular Imaging
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Santi Bullich
André Müeller
Audrey Perrotin

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Cerveau
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