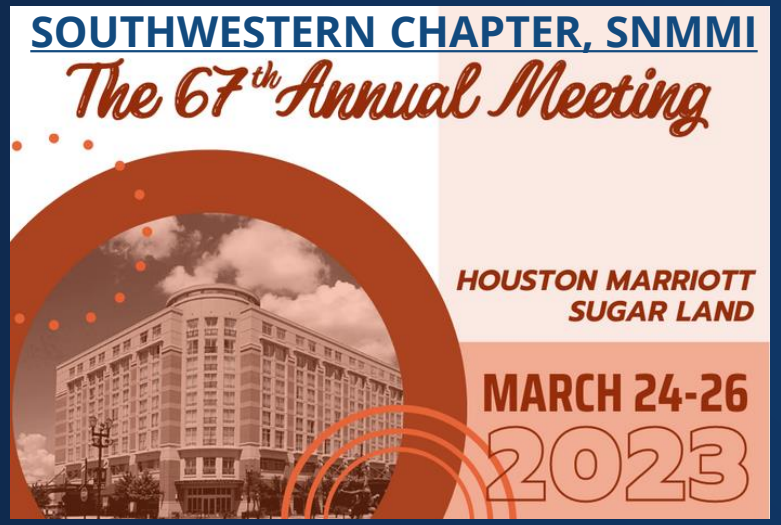
Nuclear Imaging of Diseases Leading to Dementia



Joseph C. Masdeu, MD, PhD

Director, Nantz National Alzheimer Center

Professor of Neurology, Weill Cornell Medicine

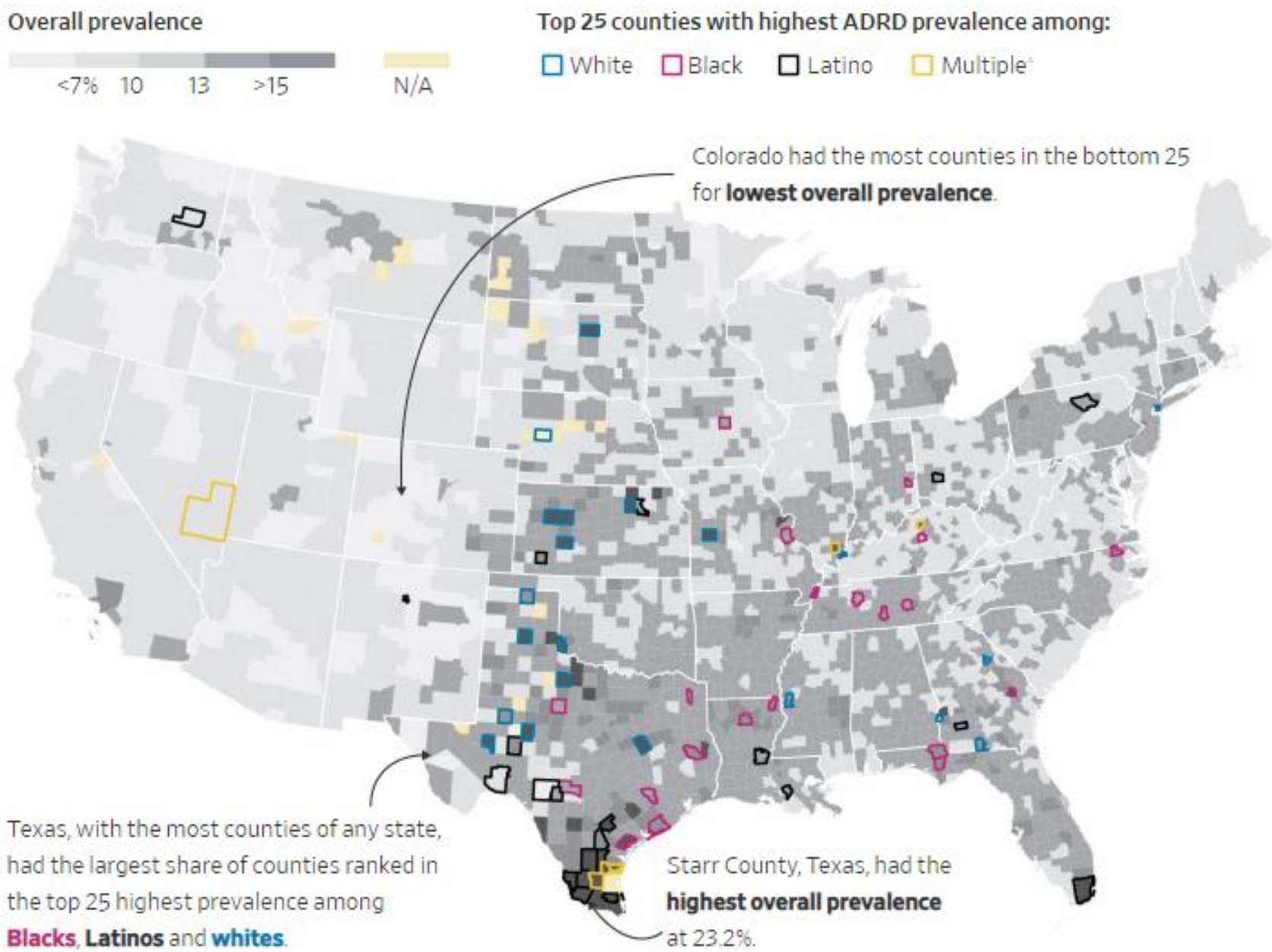
Weill Cornell Medicine

HOUSTON Methodist LEADING MEDICINE

Disclosures

Agency or Company Name	Royalties	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research
Elsevier	X			
Wolters Kluwer Health	X			
Green Valley				X
Alector				X
Alzheimer's Association				X
Biogen		X	X	X
Eisai				X
Eli Lilly		X		X
NIH (NIA)				X
Novartis				X

Alzheimer's disease and related dementias (ADRD) prevalence by county



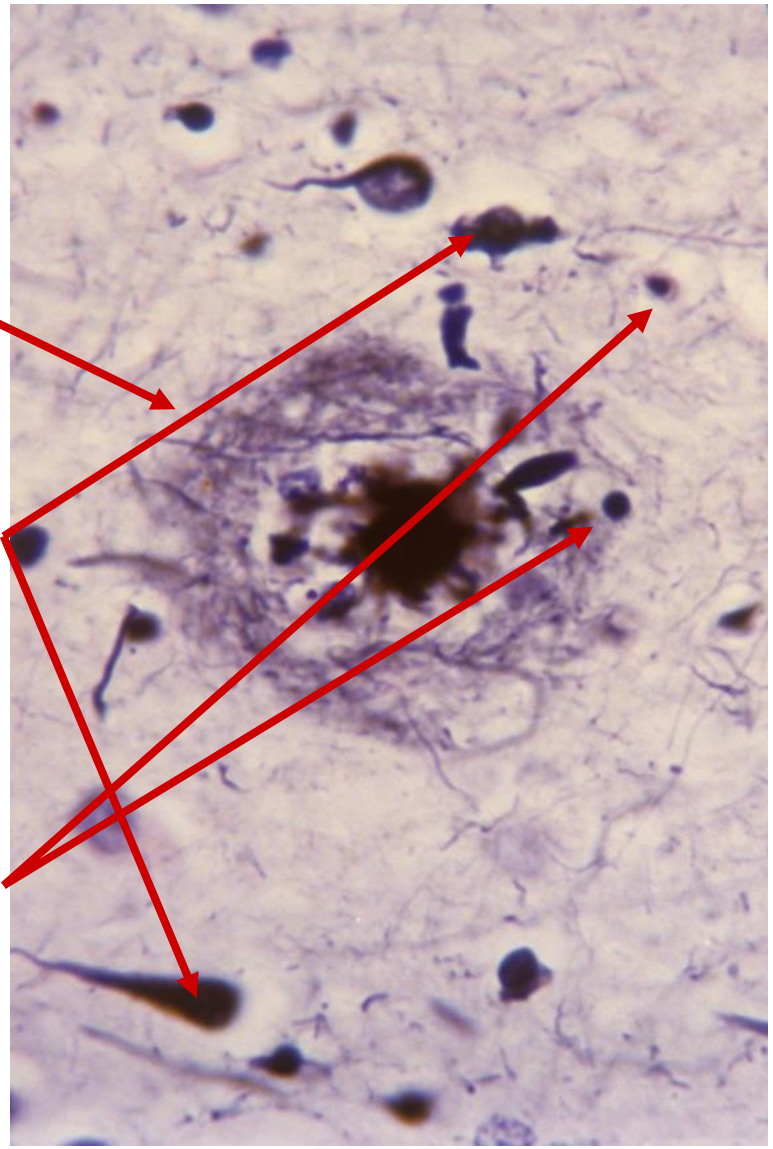
Conventional AD Rx

- Not very effective or well tolerated

2023 Therapeutics for Dementia

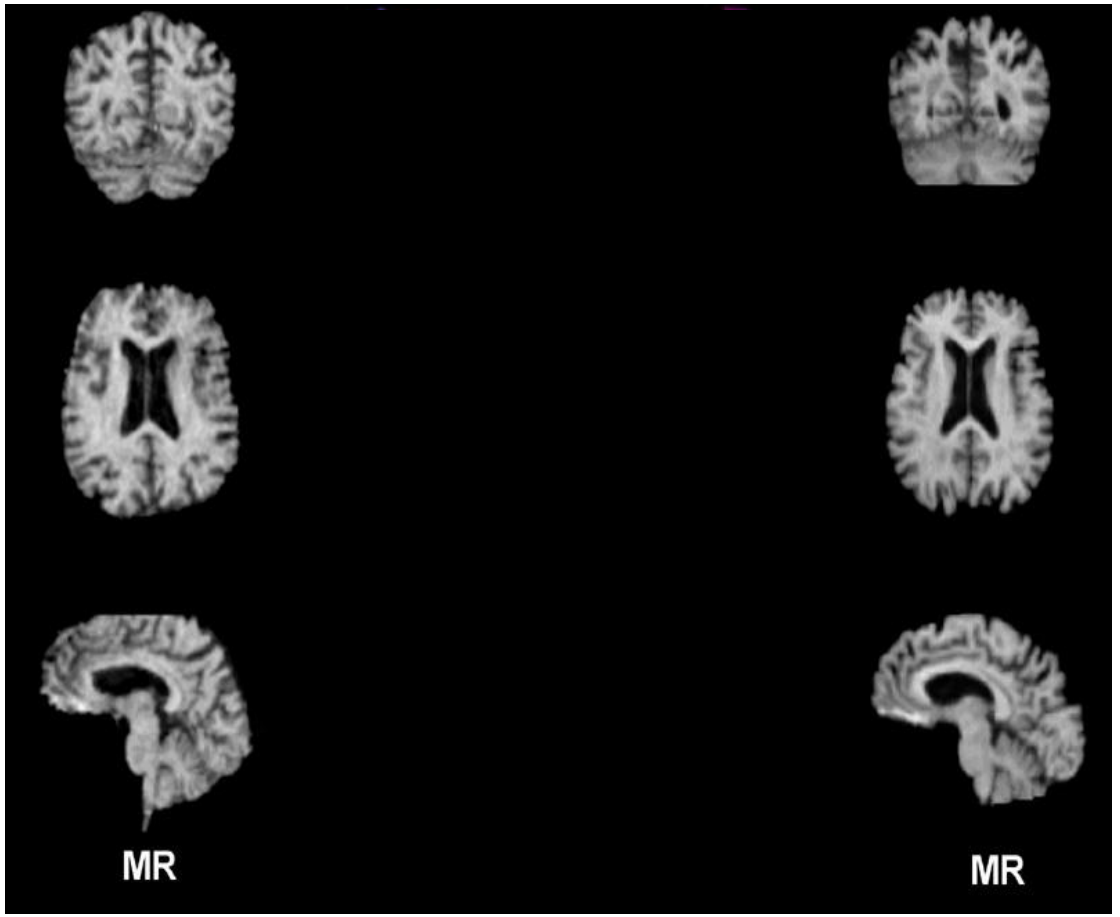
- Linked to Brain Imaging (***Theranostics***)
  - Monoclonal antibodies against beta amyloid
    - Shown by PET to decrease beta-amyloid
    - Lecanemab 2023 FDA approval
      - Slowed down worsening
  - Inflammation PET
    - Has encouraged immunomodulation trials

Multimodal Imaging in Alzheimer's Disease

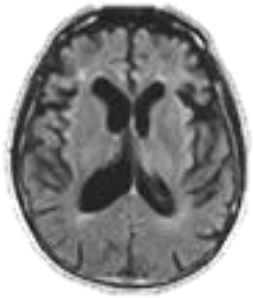


Patient with Alzheimer's Disease

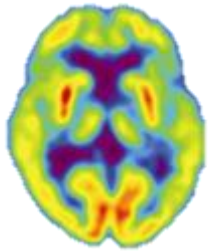
Healthy Elderly



Imaging Modalities for Neurodegenerative Dementias



- MRI
  - Volume (atrophy)
  - Anatomical (DTI) & functional connectivity (BOLD)
  - Blood flow (ASL)

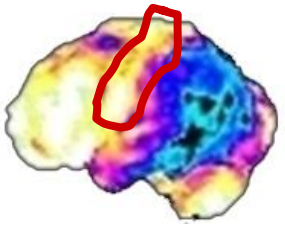


- PET (Positron Emission Tomography)
  - Metabolism
  - β-amyloid load
  - $_{p}$Tau load
  - Inflammation
- SPECT (Perfusion)

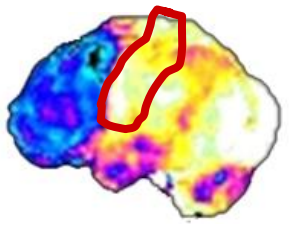
Metabolism (FDG) **PET**

- **Regional pattern** (space)

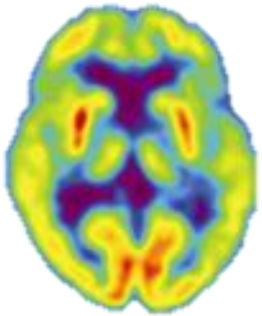
Alzheimer Disease (**AD**)



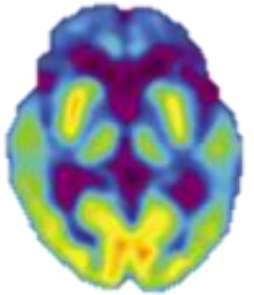
Frontotemporal Dementia (**FTD**)



- **Disease stage** (time)



2 years later



Brain FDG PET: Regional Patterns (Disease Anatomy)

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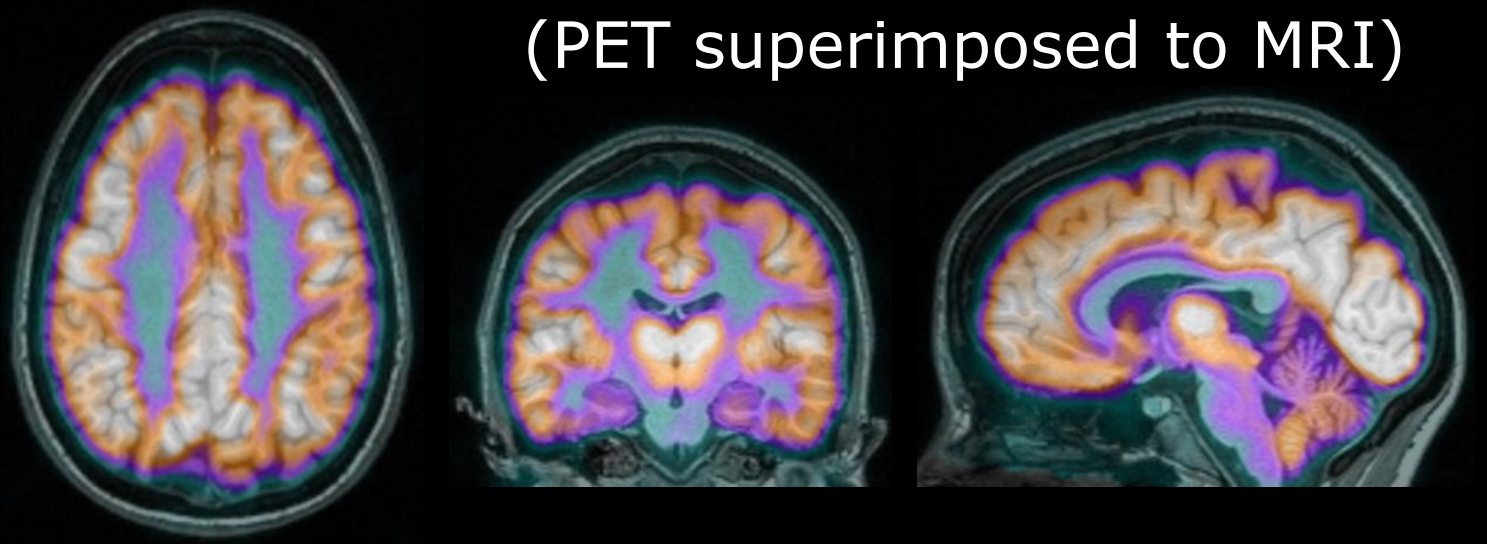
Individual FGD-PET Scan Examples: AD

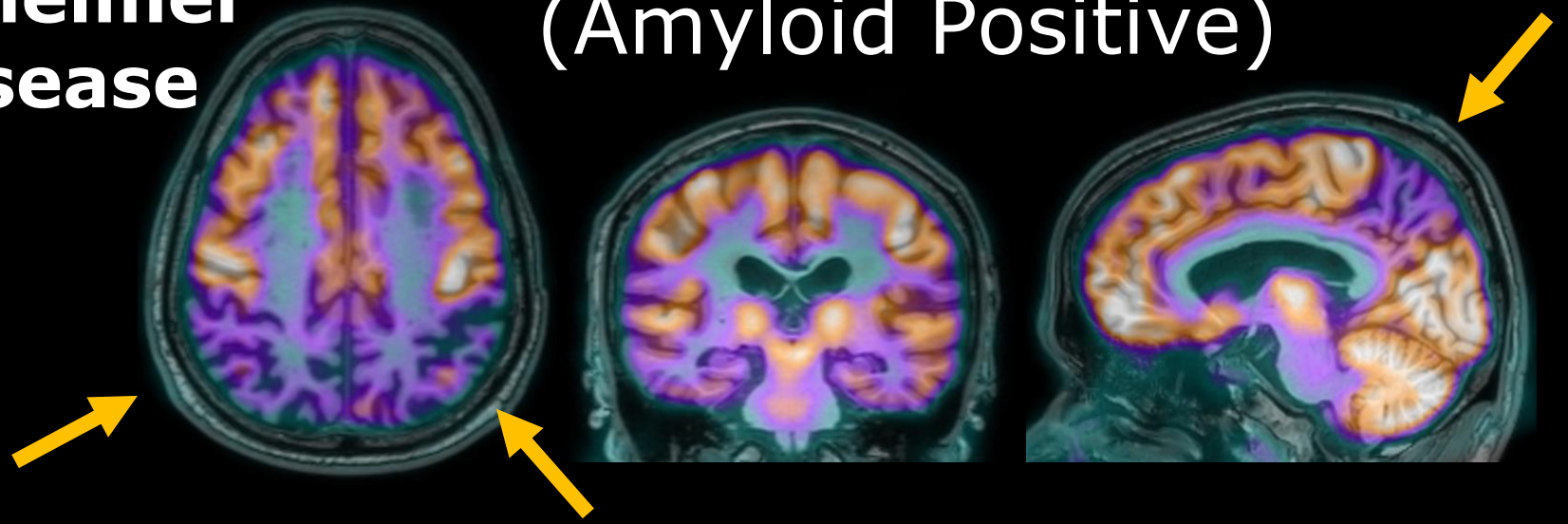
(PET superimposed to MRI)

Healthy Control

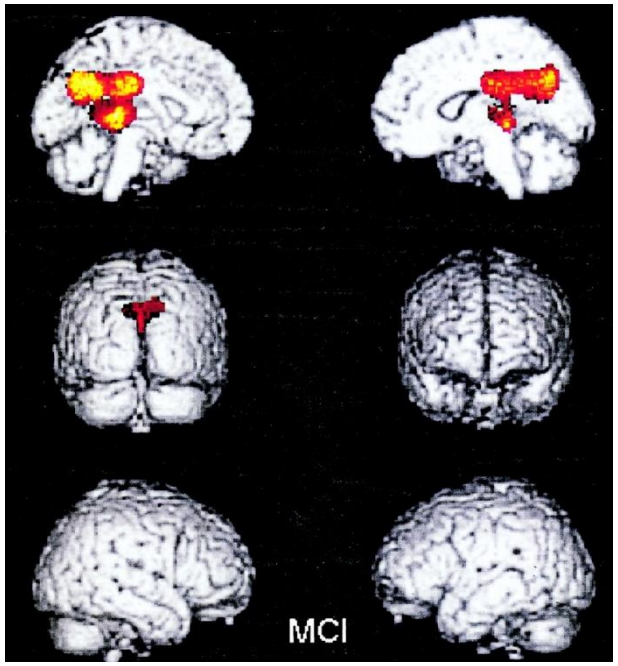


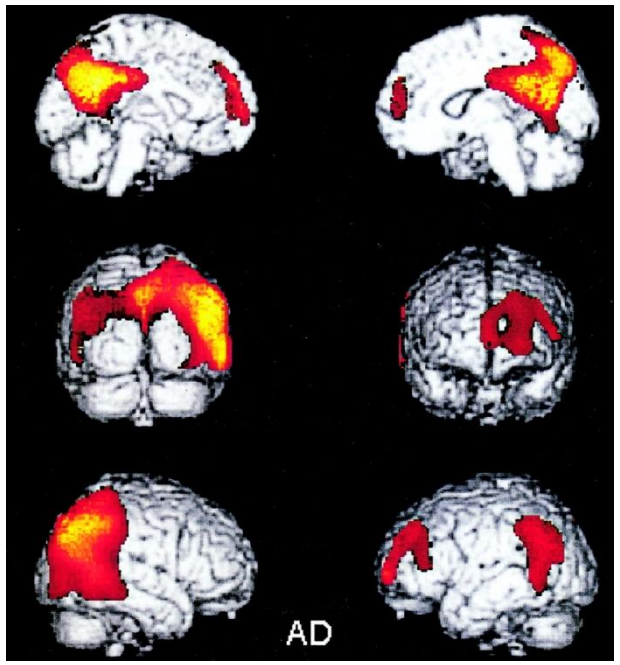
Alzheimer disease

(Amyloid Positive)



Amyloid-Positive Dementias
(FDG-PET is enough!)



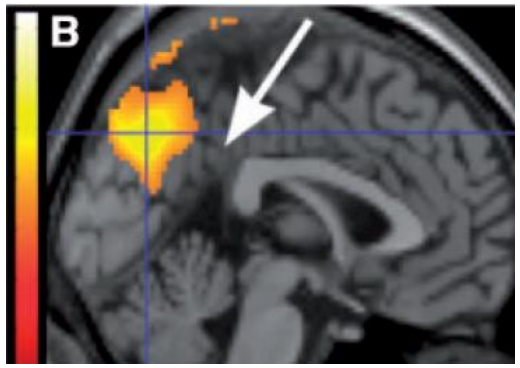


Alzheimer's disease

Affected (in red or yellow above):

- Precuneus and posterior cingulate gyrus
- Parieto-temporal association cortex

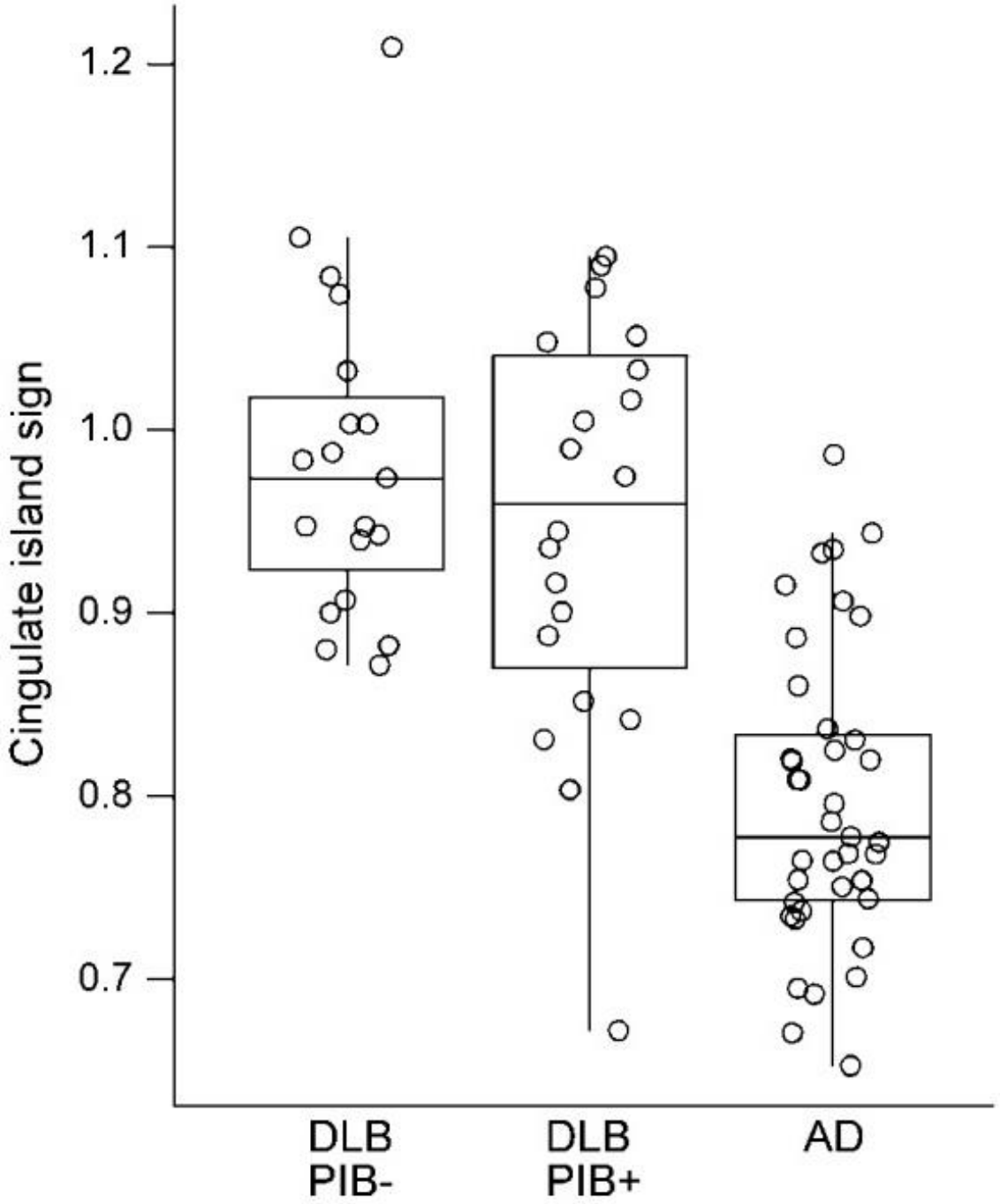
Nestor PJ et al. *Ann Neurol* 2003;54:343



Diffuse Lewy body disease

Similar pattern on the lateral aspect but the posterior cingulate not affected ("cingulate island sign")

Masdeu JC et al. *Brain* 2012;135:2440

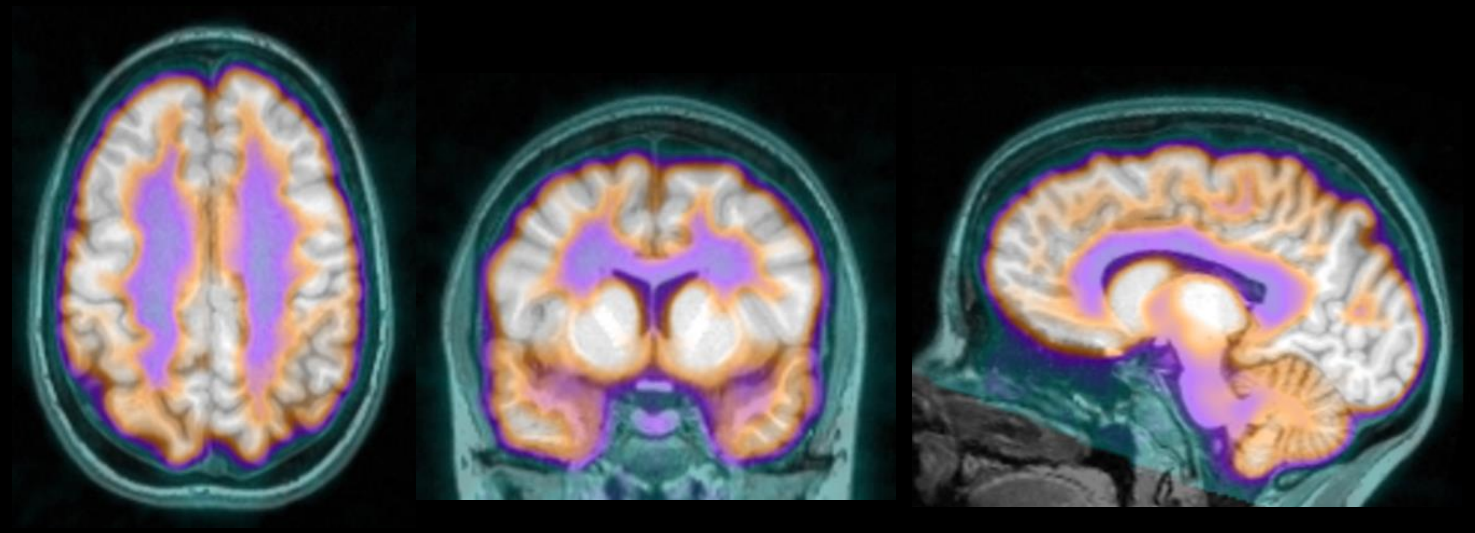


Cingulate island sign

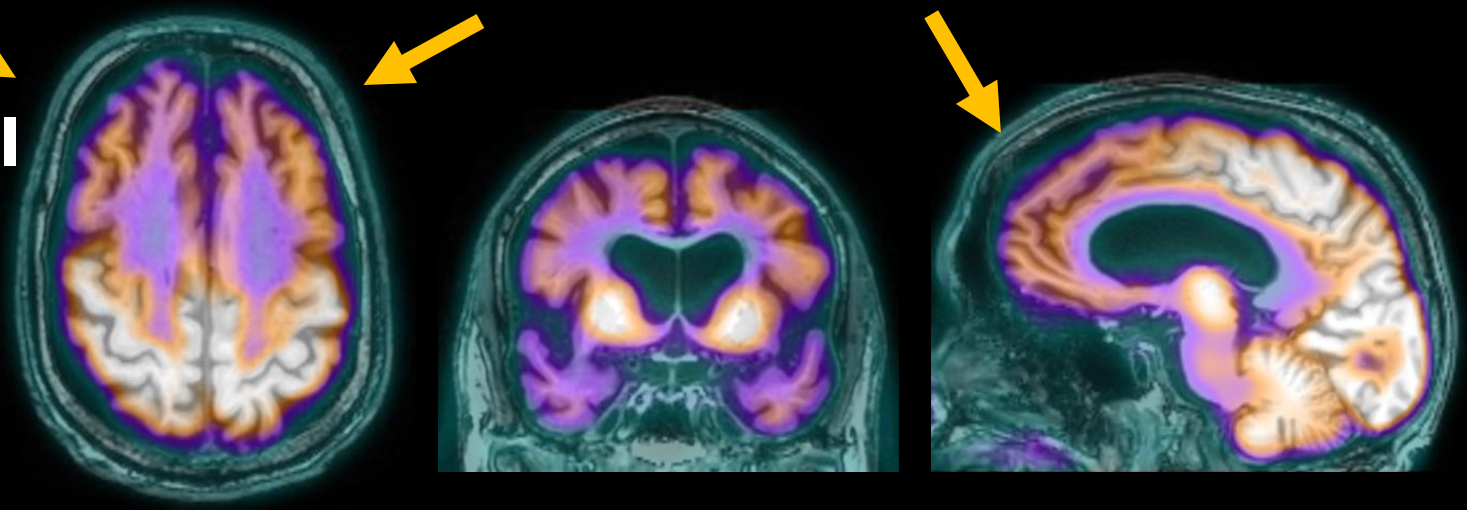
Graff-Radford J, et al. Dementia with Lewy bodies: basis of cingulate island sign. *Neurology* 2014;83:801-809.

Frontotemporal Dementia Variants
(Amyloid Negative)

Healthy Control

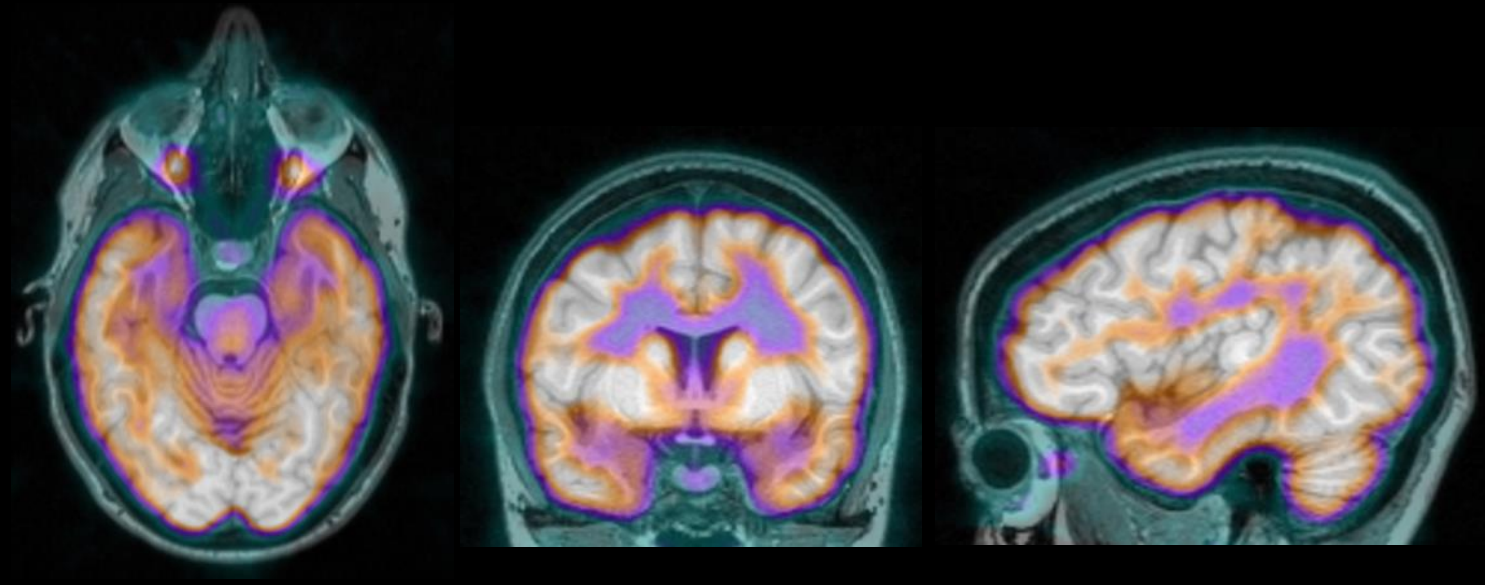


Behavioral
Tau or
TDP43

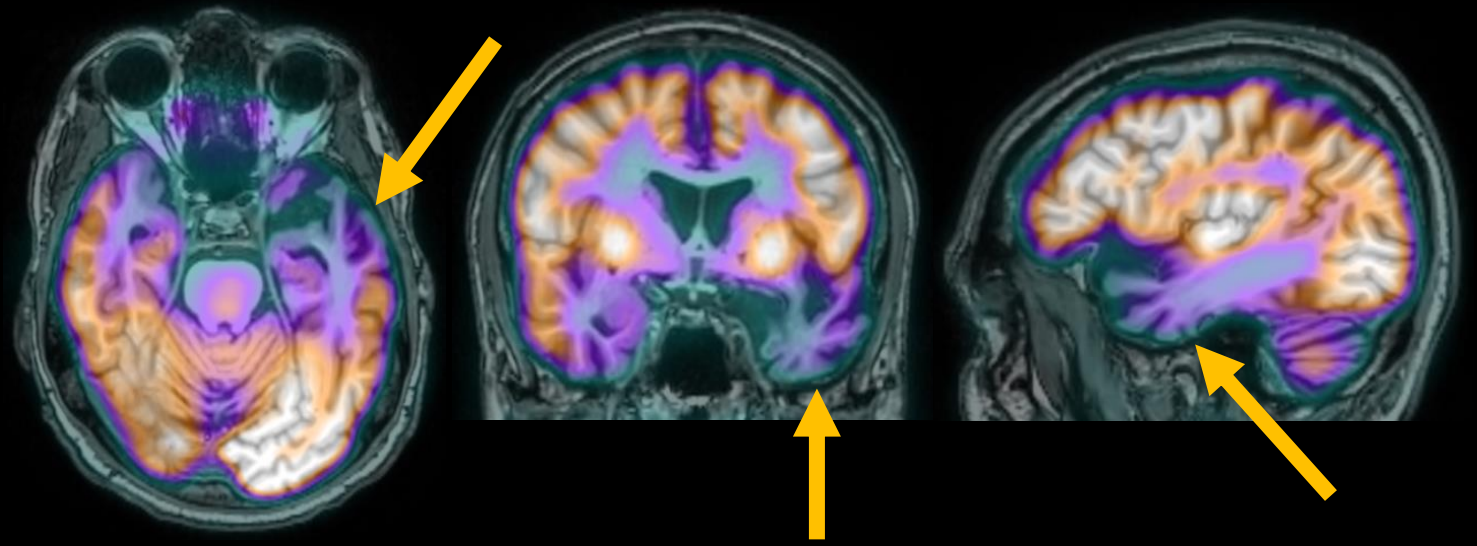


Frontotemporal Dementia Variants

Healthy Control

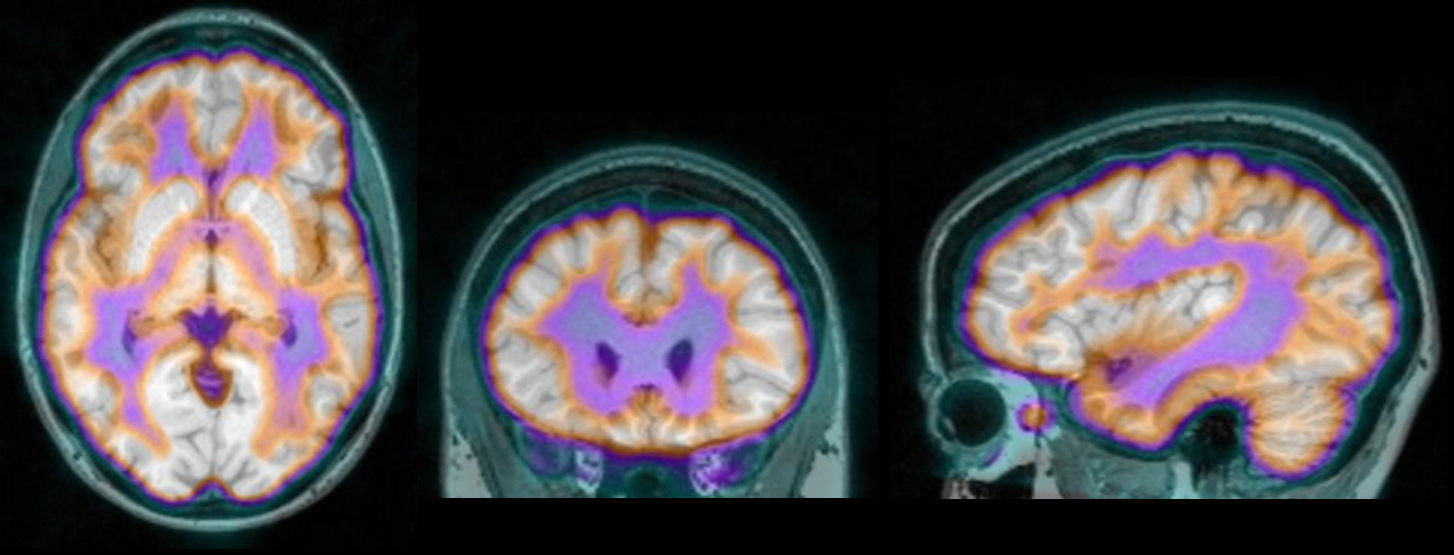


Semantic Dementia
TDP43

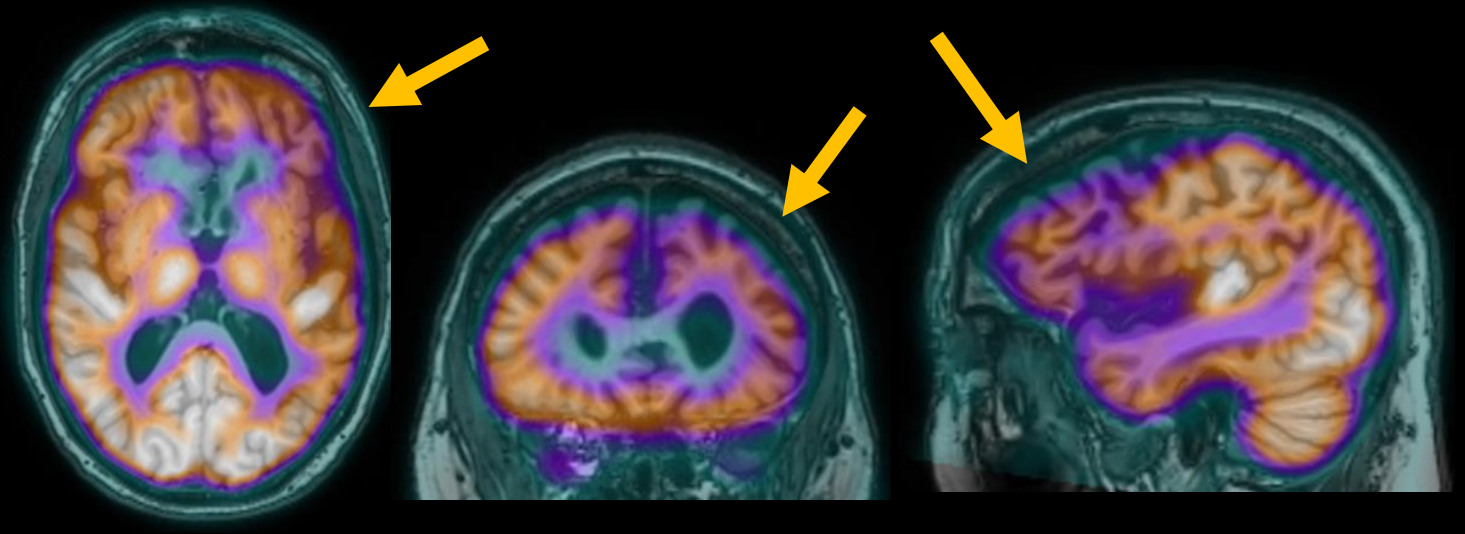


Frontotemporal Dementia Variants

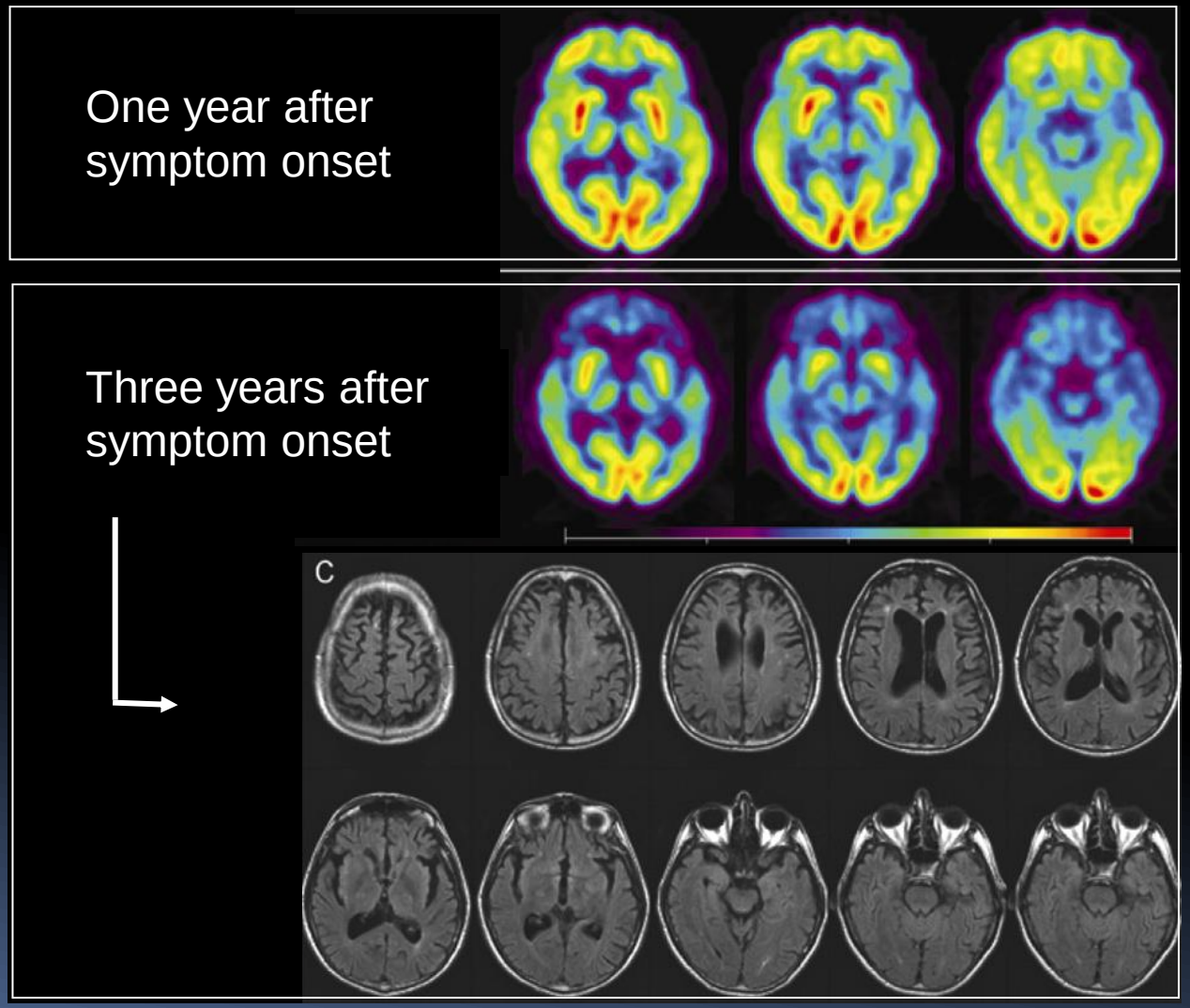
Healthy Control



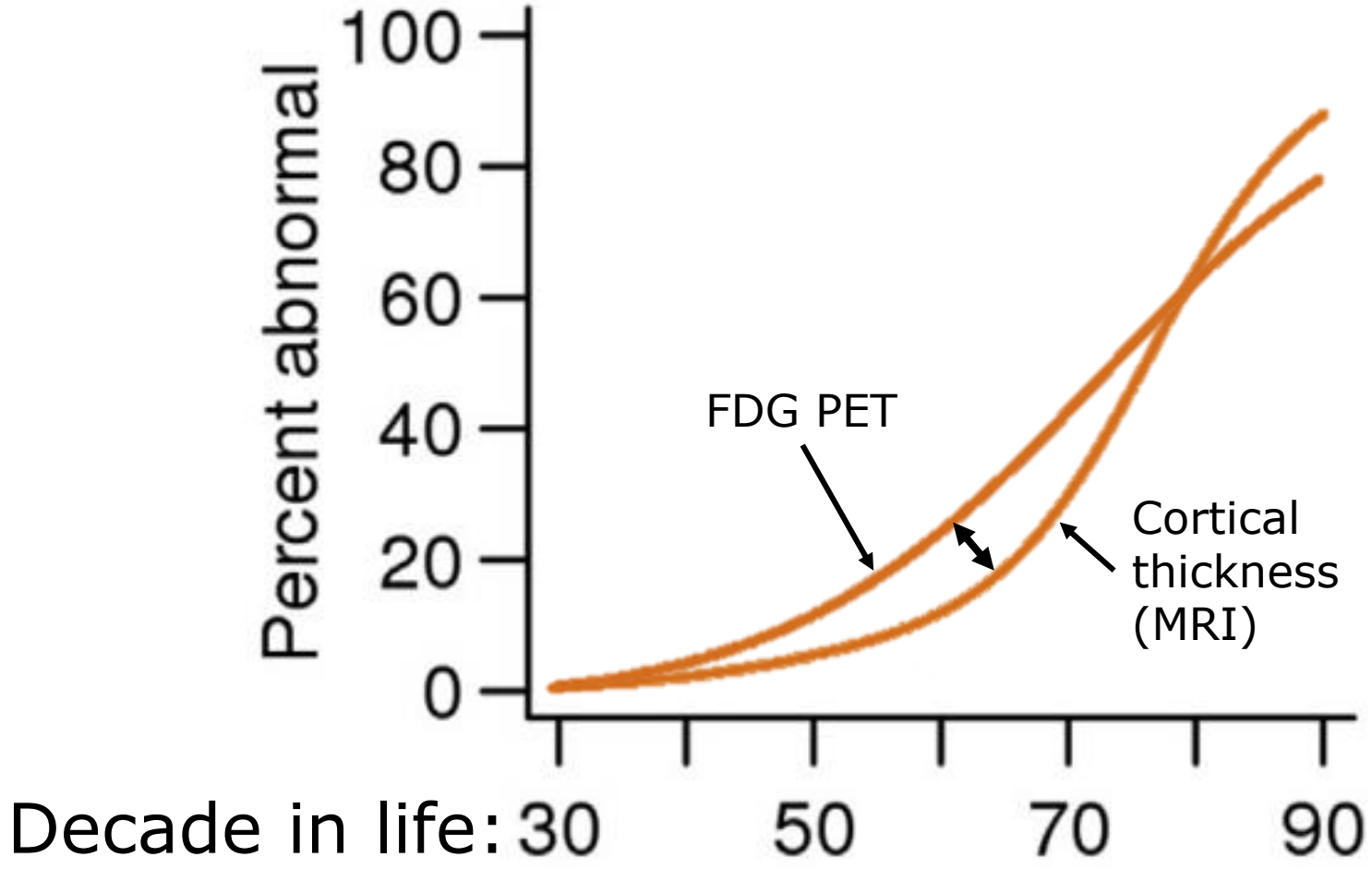
Agrammatic Primary Progressive Aphasia
Tau



FDG Metabolism vs MRI in Fronto-temporal Dementia



FDG PET: Is Abnormal Before **Cortical Thickness** Becomes Abnormal



Jack CR et al. *Alzheimers Dement* 2017;13:205

PET in Alzheimer's Stages (Disease Timing)

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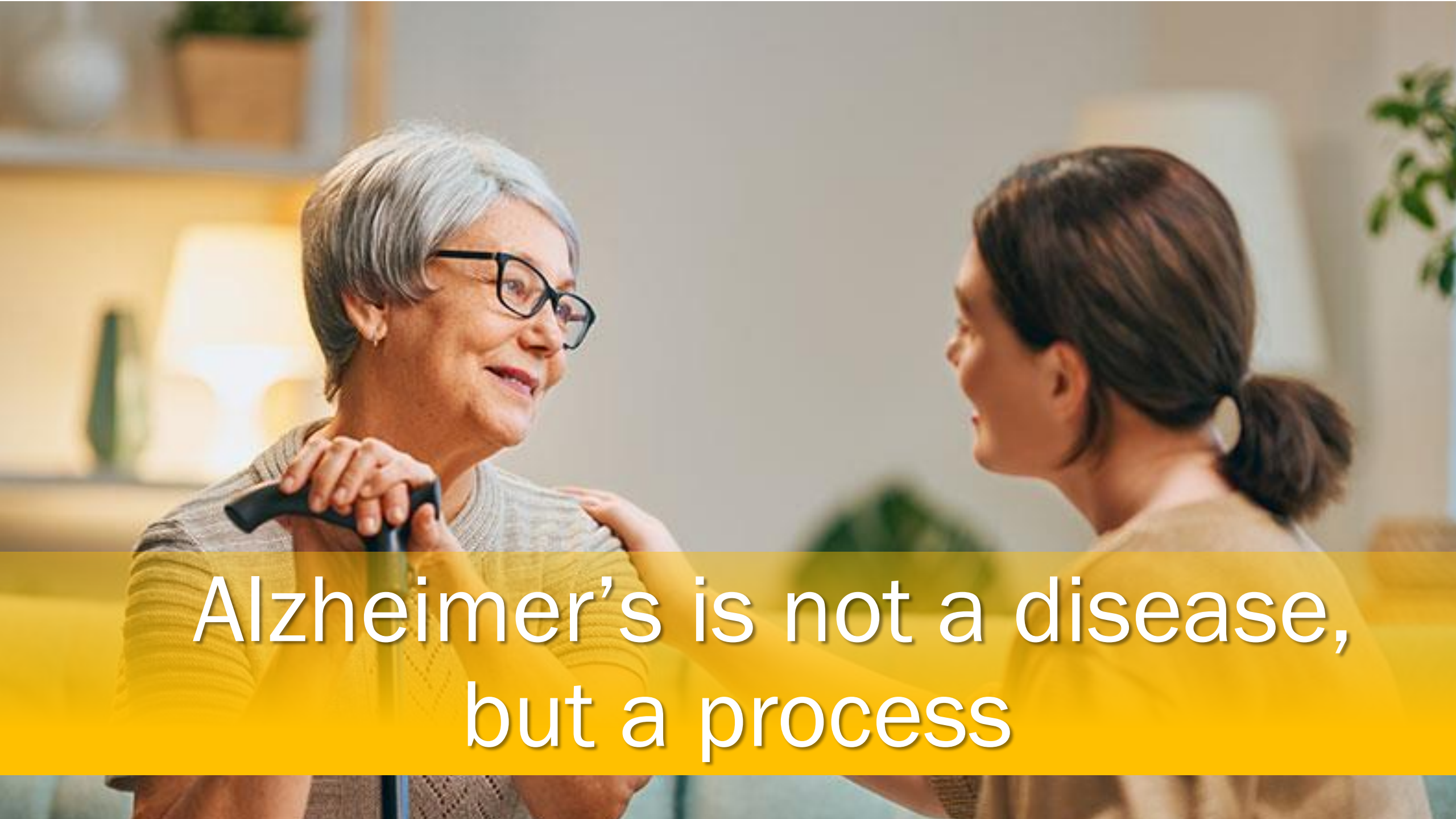
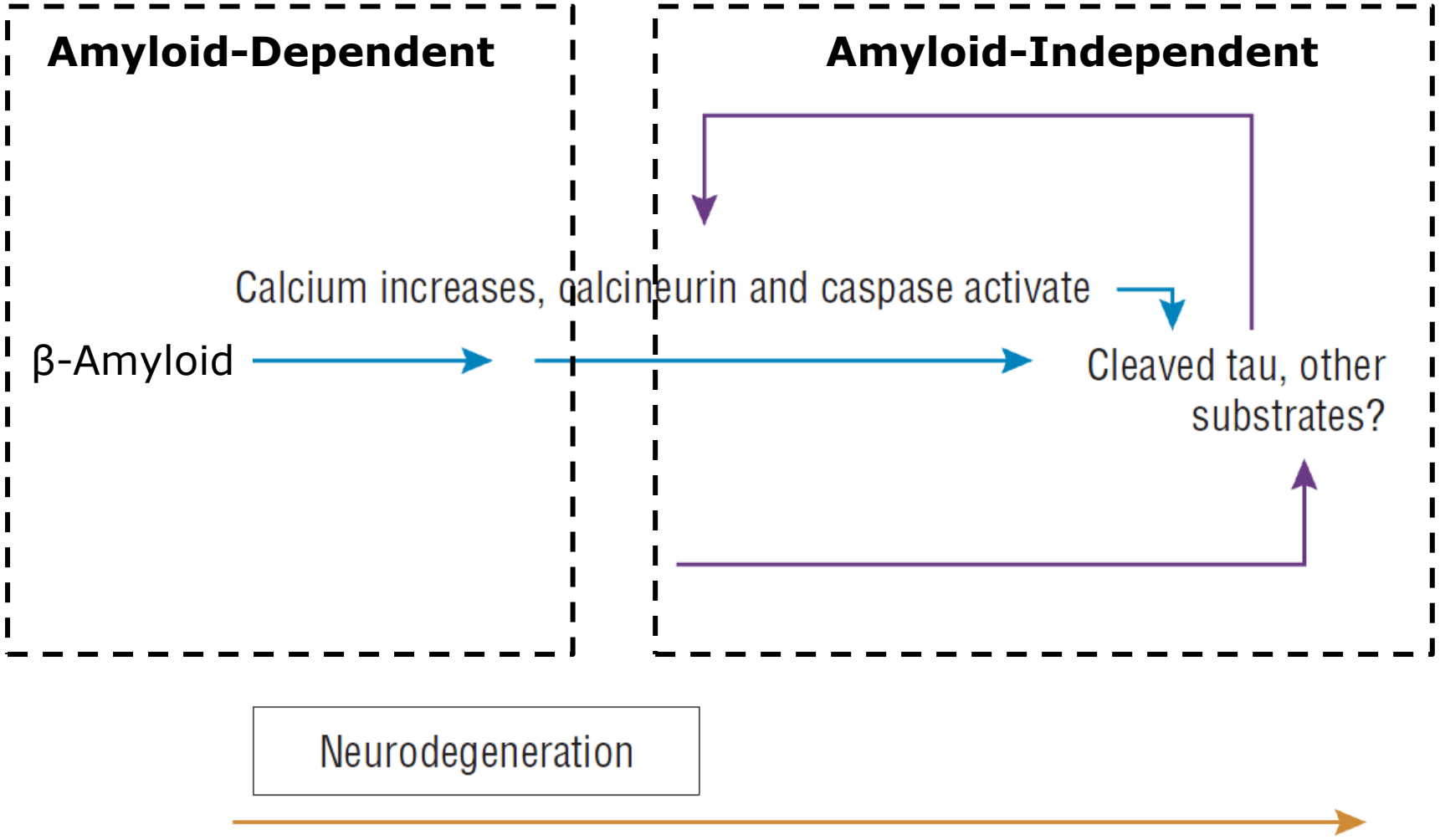
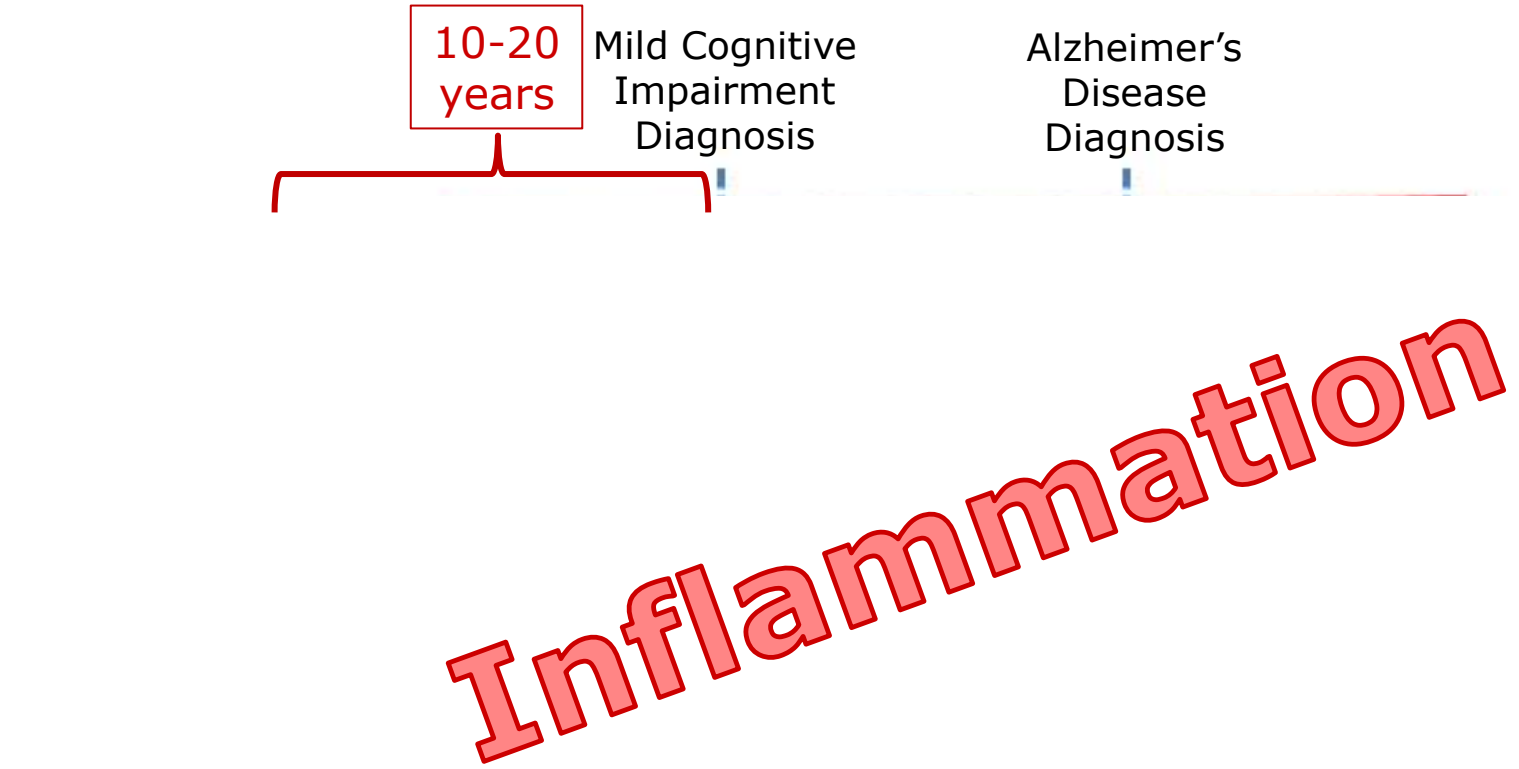

Alzheimer’s is not a disease,
but a process

Stages of AD in Mice



Hyman BT. *Arch Neurol* 2011:68;1062

Stages of AD in Patients (Imaging)



Masdeu JC. *Curr Opin Neurol* 2012

Beta Amyloid Tracers

- F18
  - Commercially available
    - Amyvid™ (florbetapir),
    - Neuraceq™ (florbetaben)
    - Vizamyl™ (flutemetamol)
  - For clinical trials only
    - NAV-4694 (flutafuranol)
- C11
  - PIB

Facts Supporting the Existence of an "Amyloid-Independent" Stage in Humans

1. Cognitive impairment linked to tau, not amyloid
2. Tau spreads in a prion-like fashion across natural brain networks
3. Amyloid trials in the "tau-stage" have failed to slow down progression

(1) Cognitive impairment is linked to tau, not amyloid

Cognitive Impairment is Linked to Decreased Brain Metabolism

Brain Metabolism
Is Depressed Where
Tau is High

Logopenic Aphasia (Alzheimer disease)

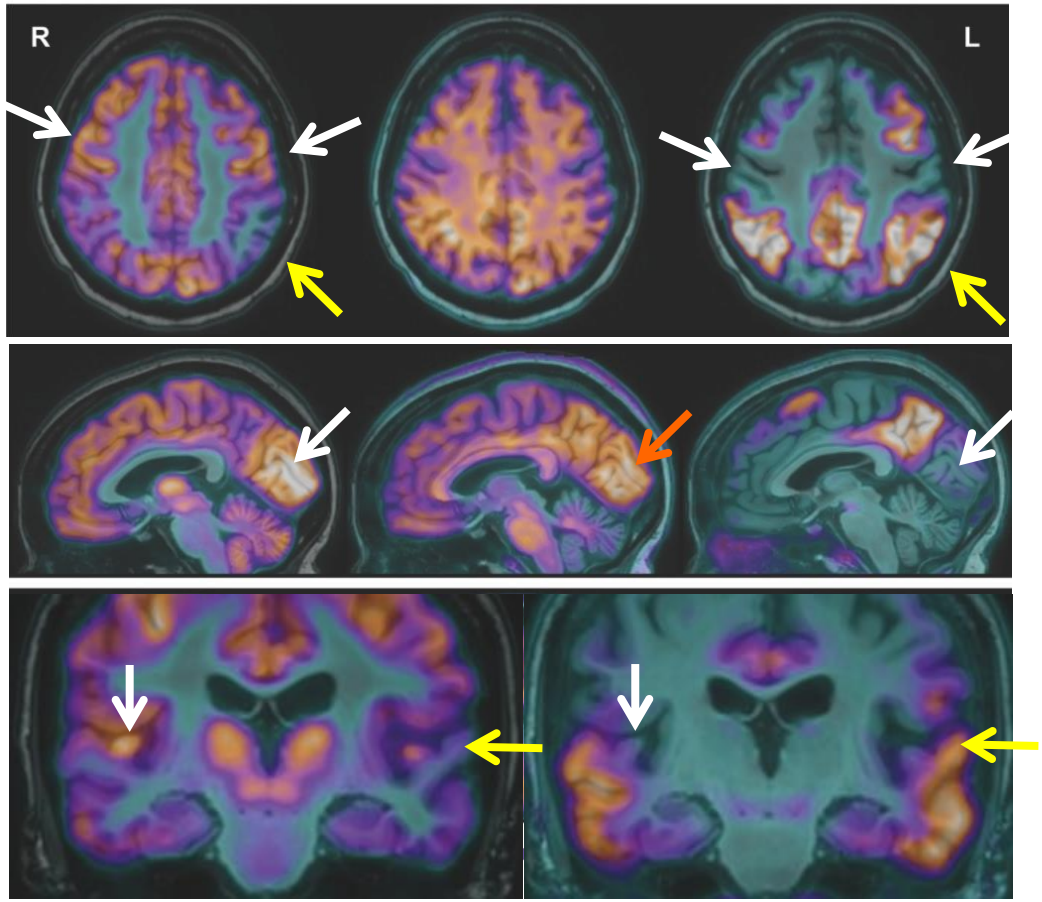
- **Areas of normal metabolism**
- **Have no tau**

- **But areas with high amyloid**
- **May have normal metabolism**

- **Areas with high tau**
- **Have reduced metabolism**

Tau more closely linked to neurodegeneration than amyloid

Metabolism ^{18}F-FDG | **57-year-old woman** | **Amyloid** ^{18}F-florbetapir | **Tau** ^{18}F-flortaucipir



Pascual et al. *Neurology* 2016;85:487

(2) Phosphorylated Tau Propagates Along Natural Brain Networks

Tau deposits in anterior and posterior neuronal nodes of the syntactic network

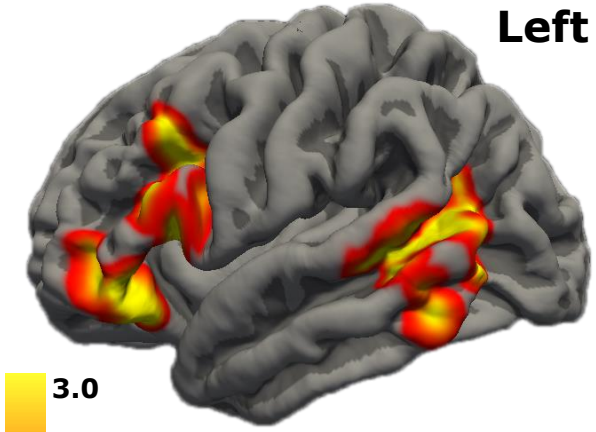
These neuronal nodes are connected by the arcuate fasciculus, abnormal near the anterior node, where the disease begins

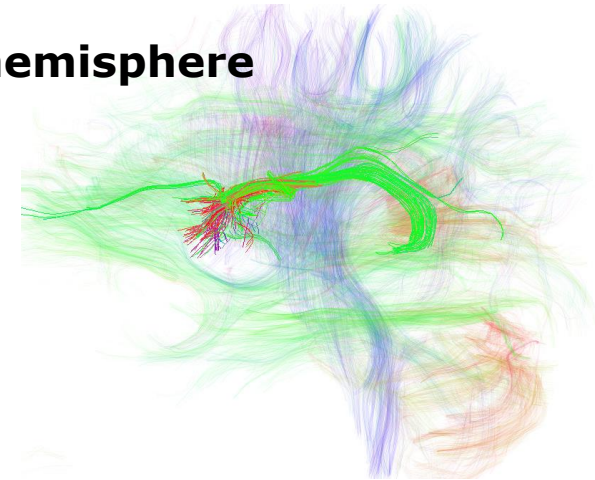
^{18}F-AV1451 Tau PET in Non-fluent Primary Progressive Aphasia (nfvPPA)

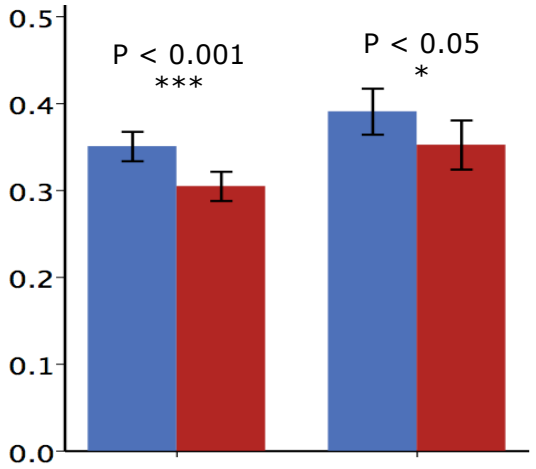
Arcuate Fasciculus Tractography

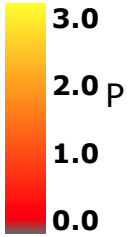
Fractional Anisotropy of Arcuate Fasciculus

Left hemisphere



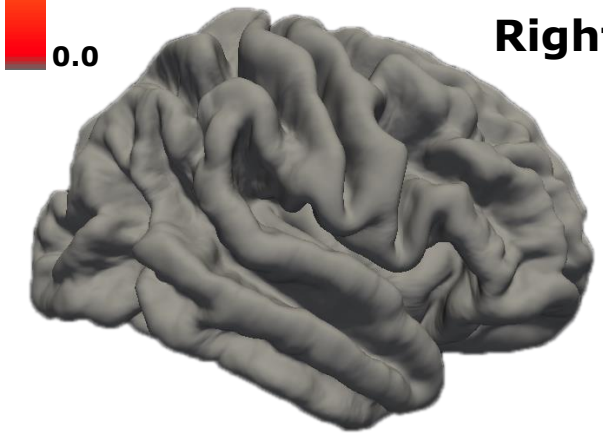


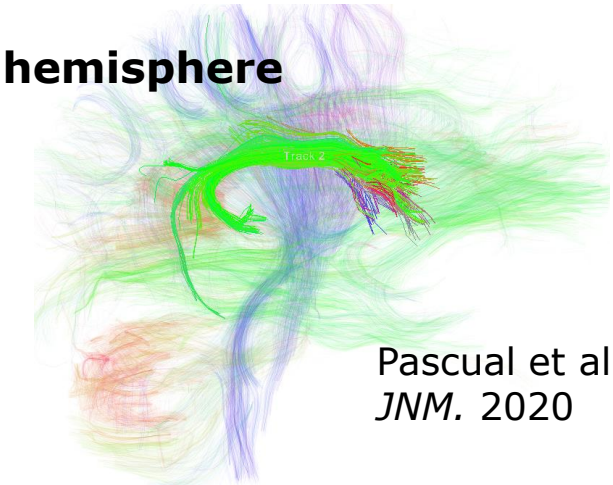


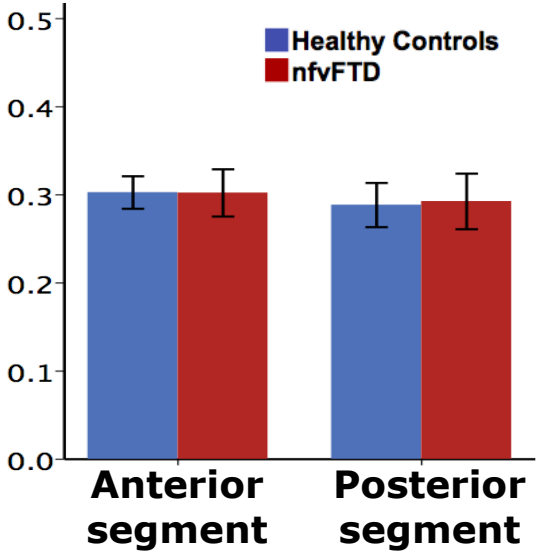


P < 0.05 FWE-corrected cluster-level

Right hemisphere







Pascual et al. *JNM.* 2020

(3) Amyloid trials in the "tau-stage"* have failed to slow down progression, but

*Amyloid-independent stage

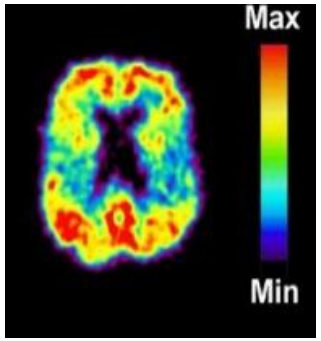
September 27, 2022 The New York Times

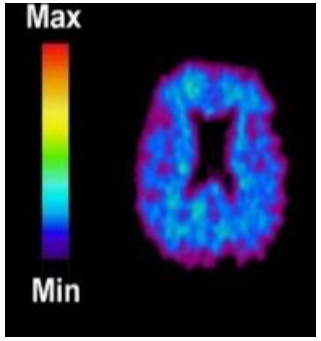
Alzheimer's Drug Slows Cognitive Decline in Key Study

Biogen and Eisai reported the finding from a large late-stage clinical trial of lecanemab, a drug they are developing.

Give this article 70

In January 2023, the FDA approved the first medication that slows the progressive AD worsening

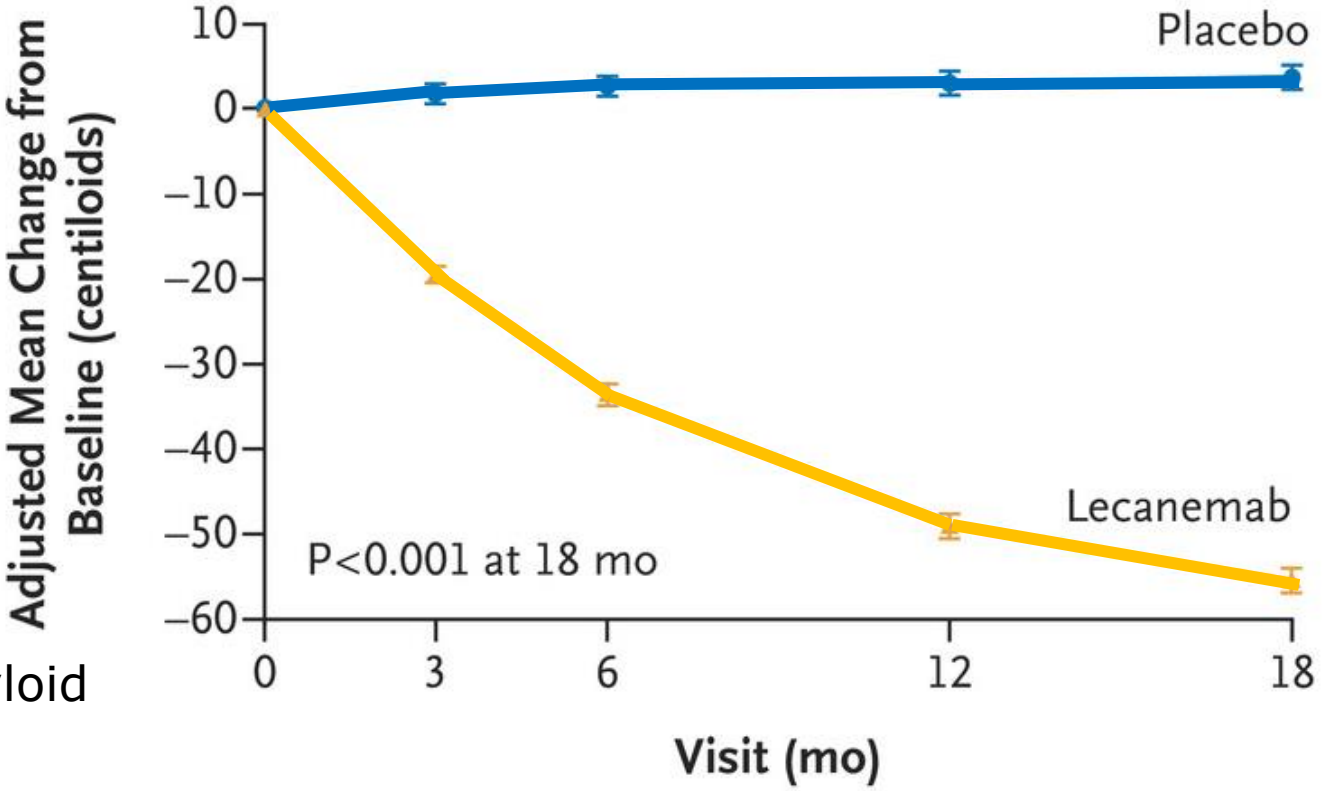




Amyloid Burden on PET

More amyloid

Less amyloid



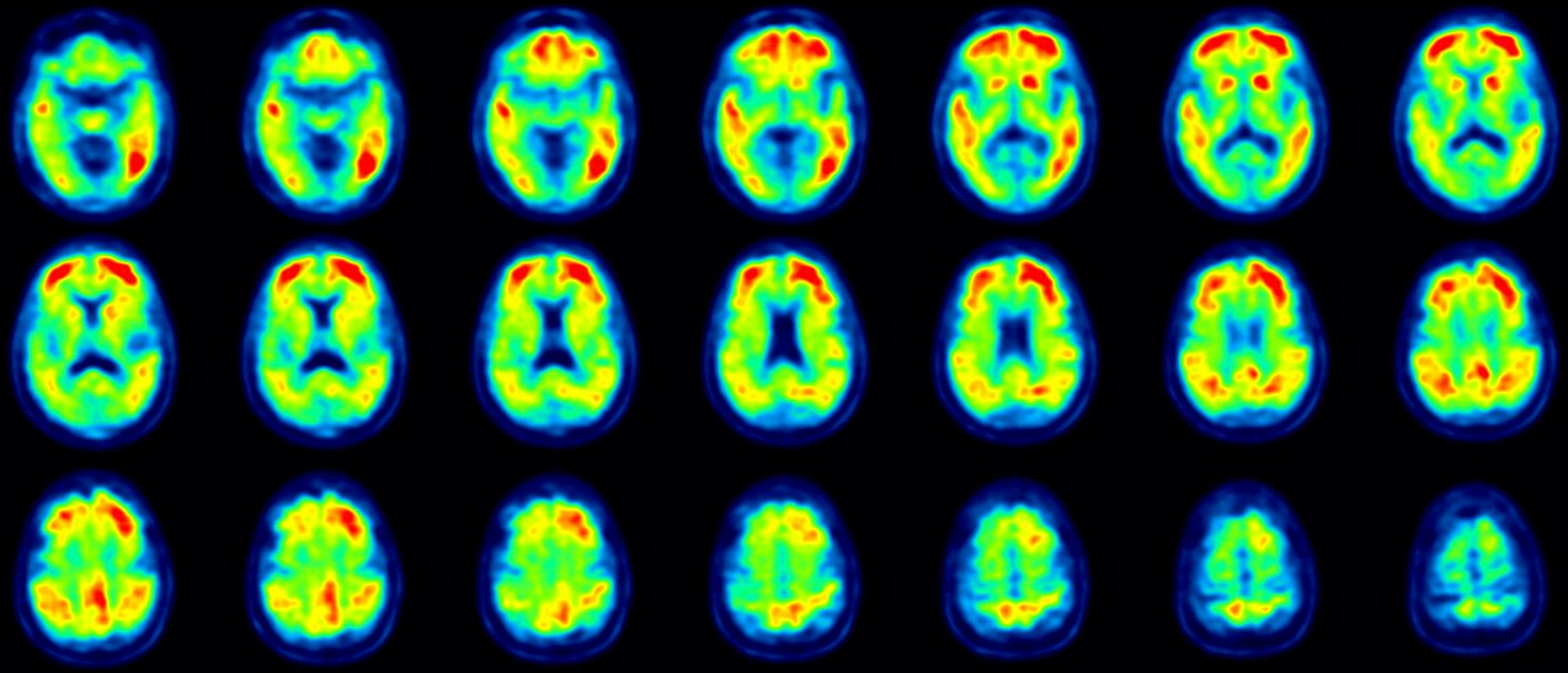
No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

Van Dyck CH et al. *N Engl J Med* 2023;388:9-21

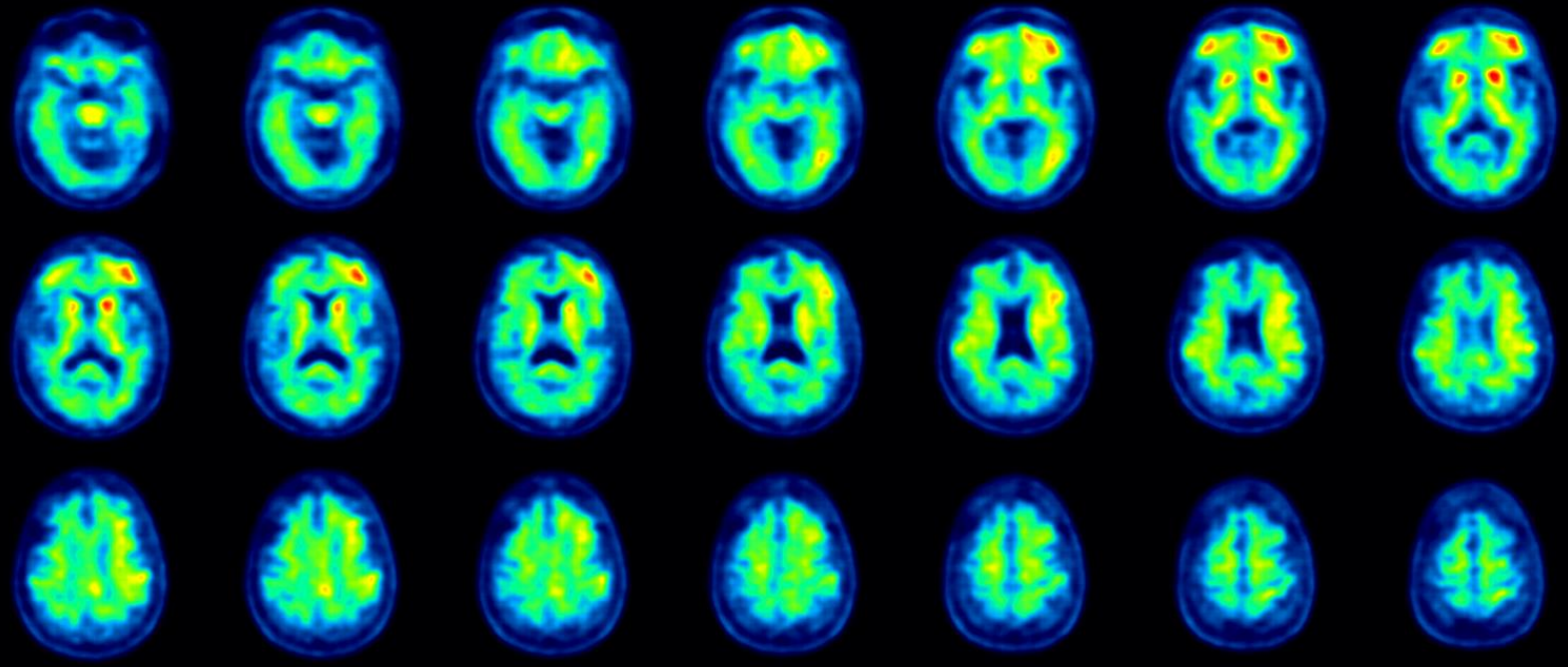
^{18}F-flutafuranol Amyloid PET

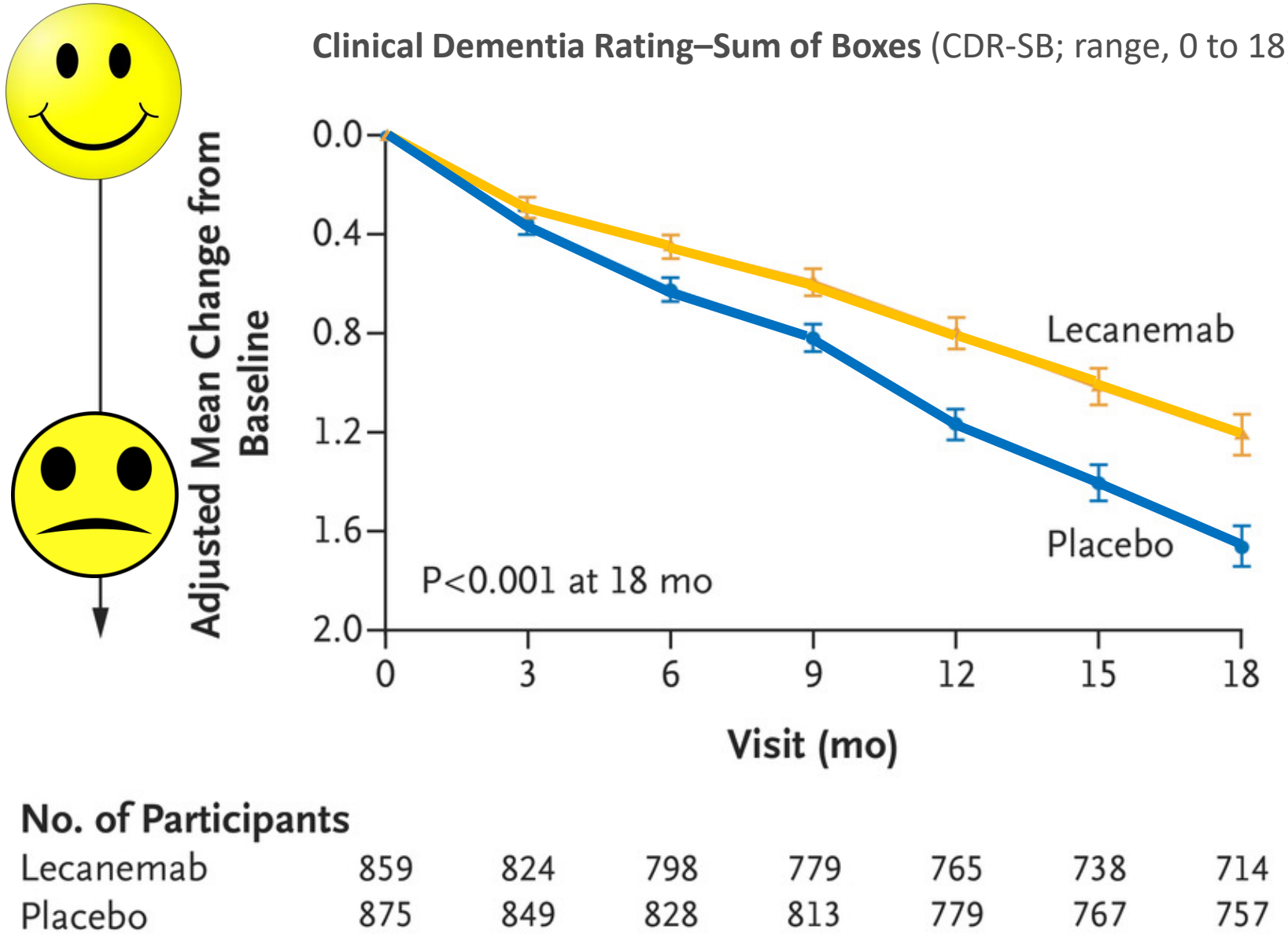
December 2021



Lecanemab

March 2023





No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Van Dyck CH et al. *N Engl J Med* 2023;388:9-21

Brain Edema after Lecanemab Infusion

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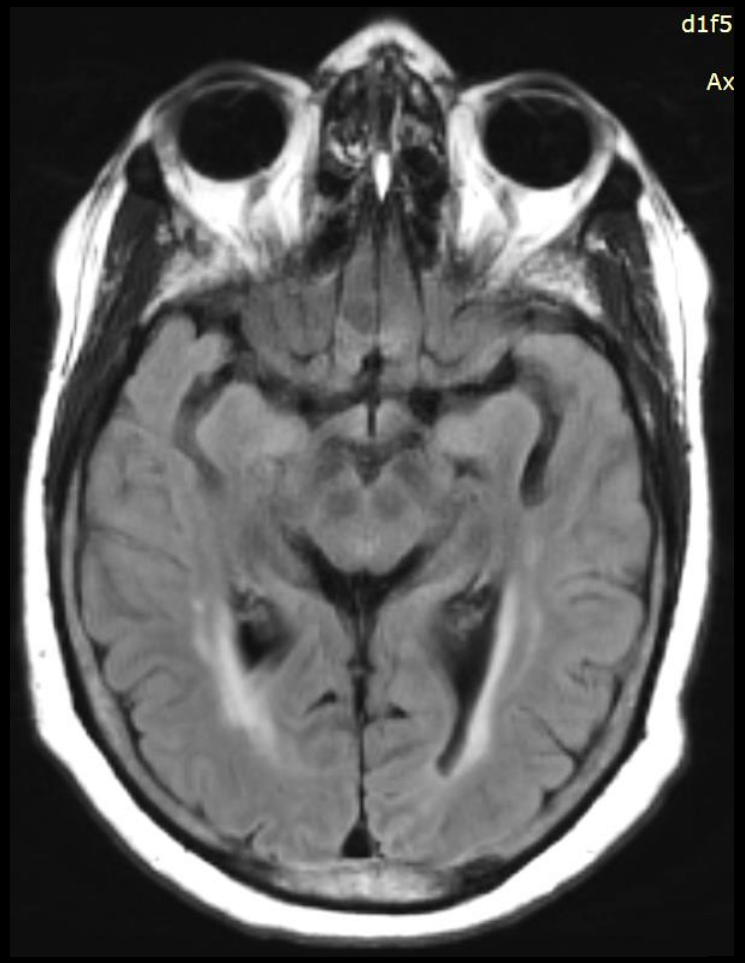
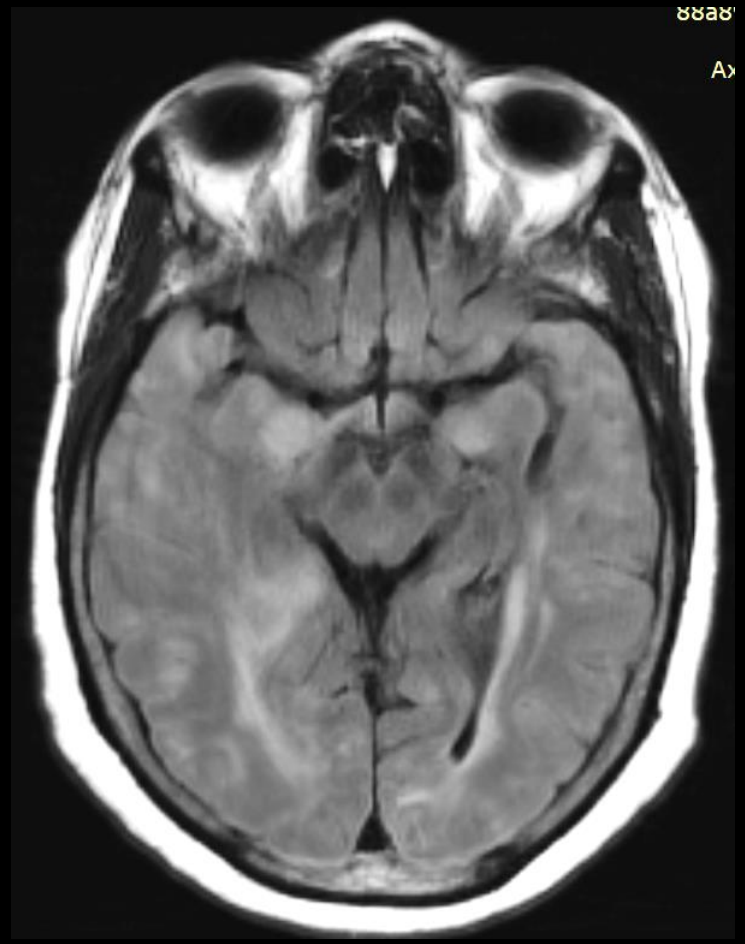
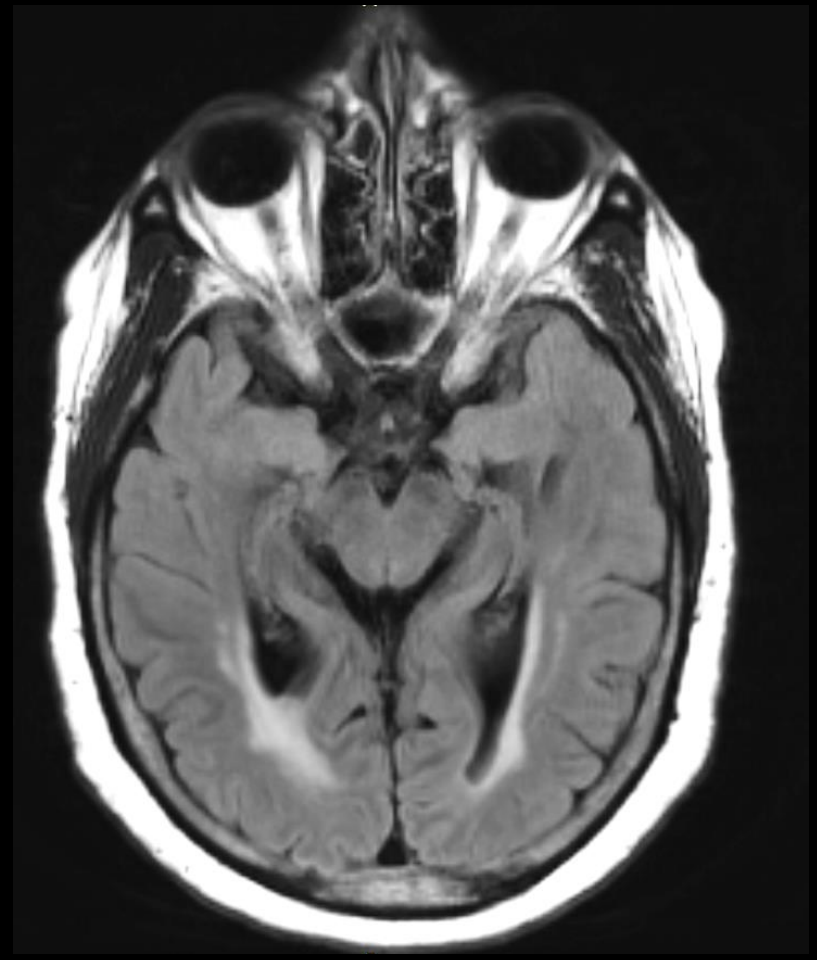


Feb 2022
Baseline

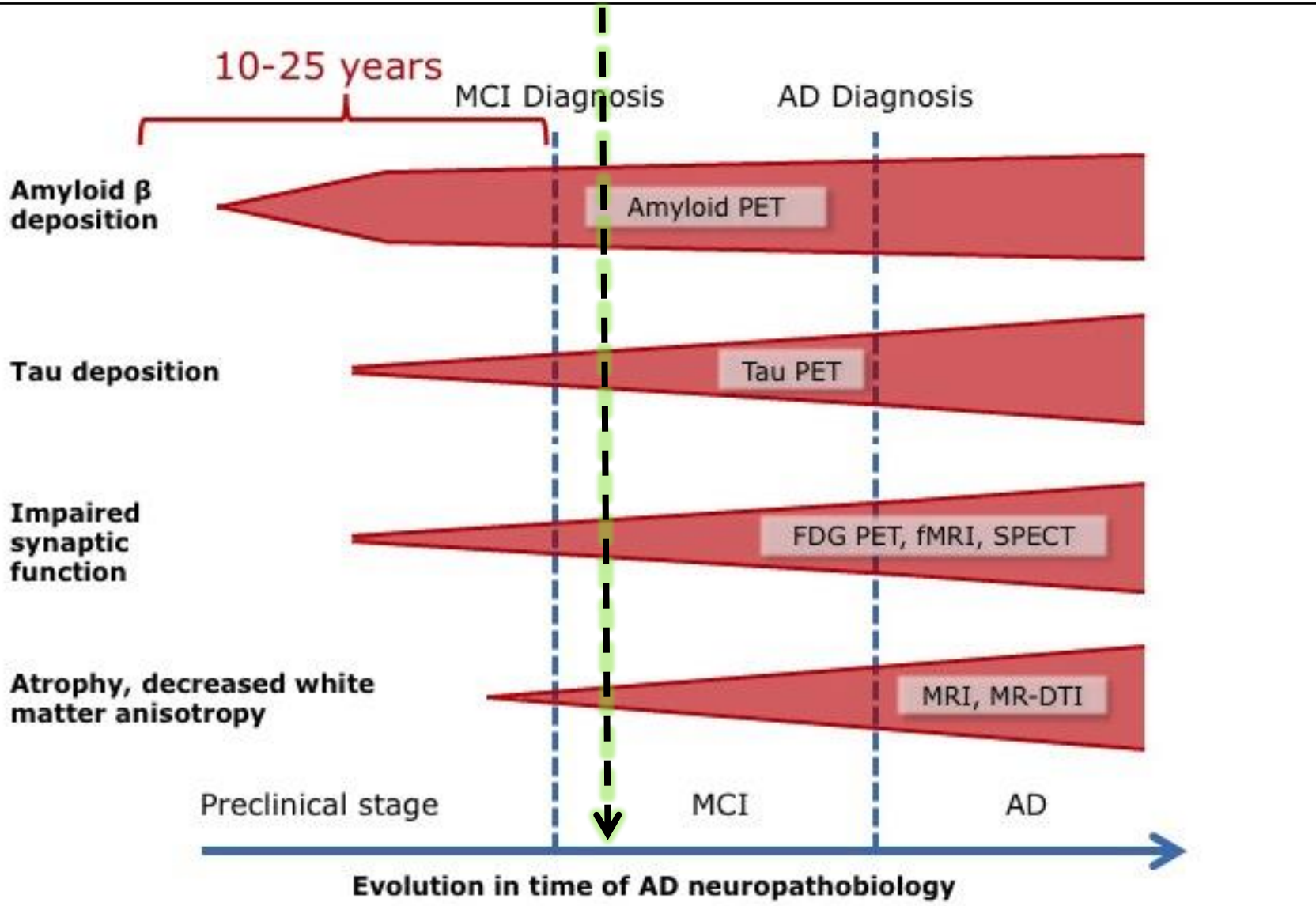


May 2022
After 2 lecanemab infusions



March 2023
Infusions stopped in May 2022

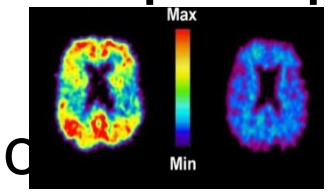
FDA-Approved Lecanemab Immunotherapy



Masdeu JC. *Curr Opin Neurol* 2012;25:411

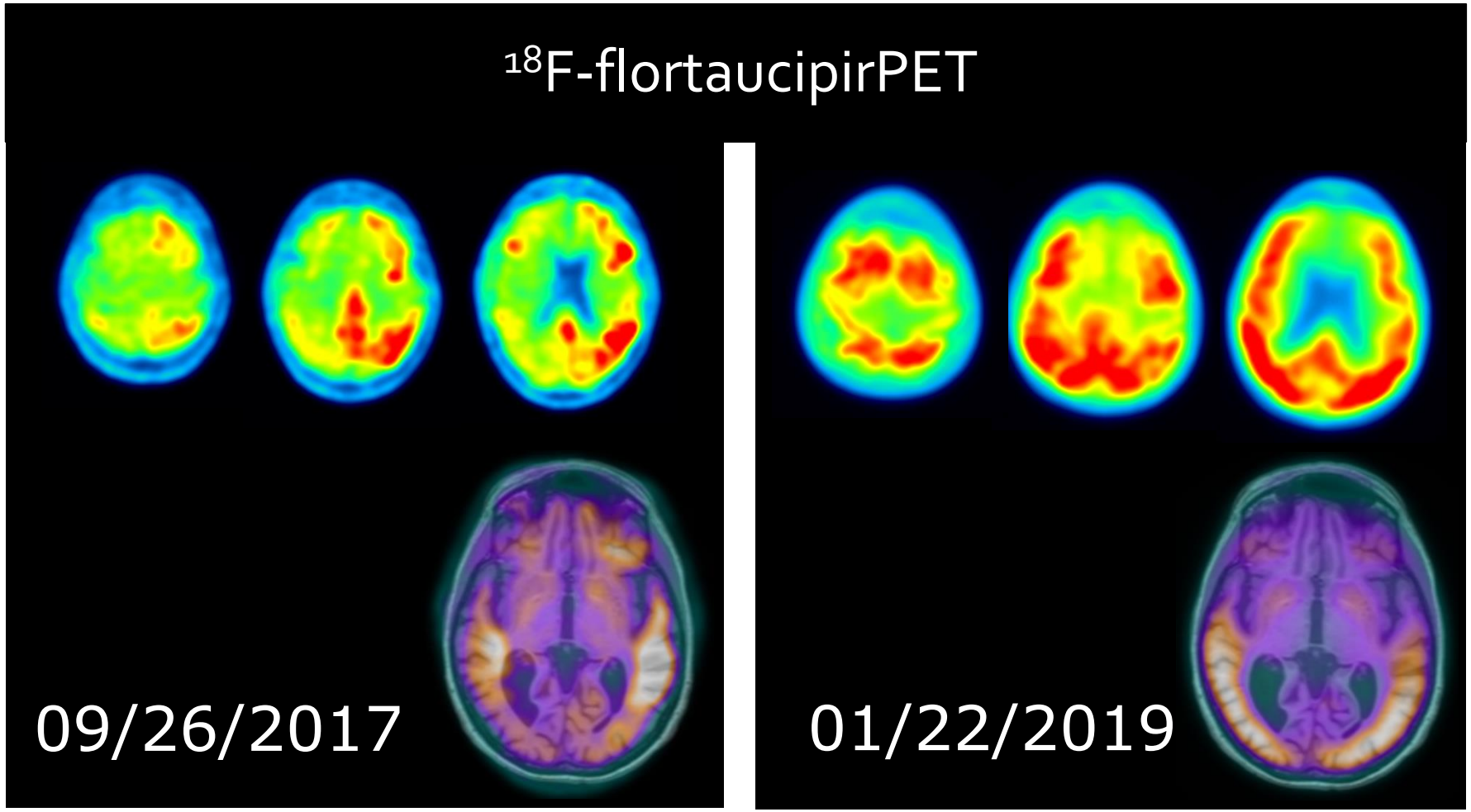
Anti-Amyloid Antibody Alzheimer Rx Trials

- PET: do candidates have abnormal Aβ deposition in the brain?
  - Those having abnormal Aβ are randomized
    - Treatment or placebo
  - PET tau load as a secondary end-point



- People being followed
  - Cognitively normal at risk
    - Solanezumab, IV (A4 trial, for people 65-85): Not effective (March 2023)
    - Lecanemab, IV (AHEAD trial, for people 55-80)
  - Mild cognitive impairment
    - Donanemab, IV (for people 50-85)

Using tau PET as Secondary Outcome

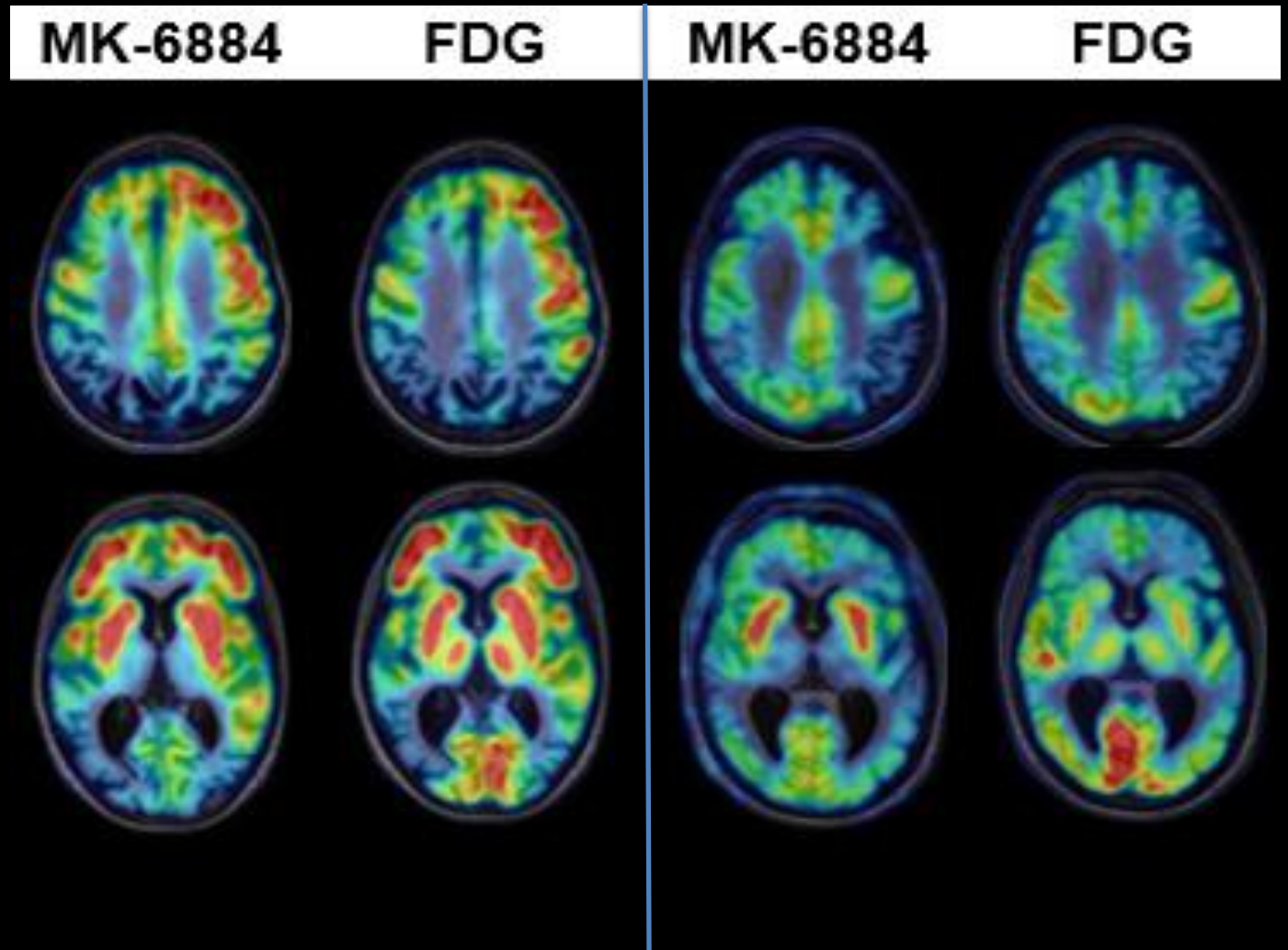


Clear-cut, quantifiable worsening in about 15 months

[^{11}C]MK-6884 PET tracer for M4 muscarinic receptors

First in-human patient study was done at HMRI

PET on MRI



NeuroInflammation Modulation in Alzheimer's Disease (AD) and FrontoTemporal Dementia (FTD)

HOUSTON Methodist
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TSPO: Expressed in Inflammation

- The 18 kDa translocator protein (TSPO) is expressed by
  - **Activated microglia**
  - Astrocytes
  - Endothelial cells
- TSPO: most frequent target of inflammation imaging
  - Using positron emission tomography (PET)

PET Tracers for TSPO

- ^{11}C-(R)-PK11195 (introduced in 1986)
  - Low specific binding to TSPO (BP_{ND}: 0.5-0.8)
- "Second generation" tracers (introduced from 2007)
    - Binding affected by TSPO rs6971 polymorphism (low-binders)
  - ^{11}C-PBR28 (1.2)
  - ^{18}F-DPA-714 and ^{11}C-DPA-714 (7.3, high radiometabolites)
  - ^{11}C-ER176 (4.1)
    - High TSPO affinity, less radiometabolites, low-binders can be imaged

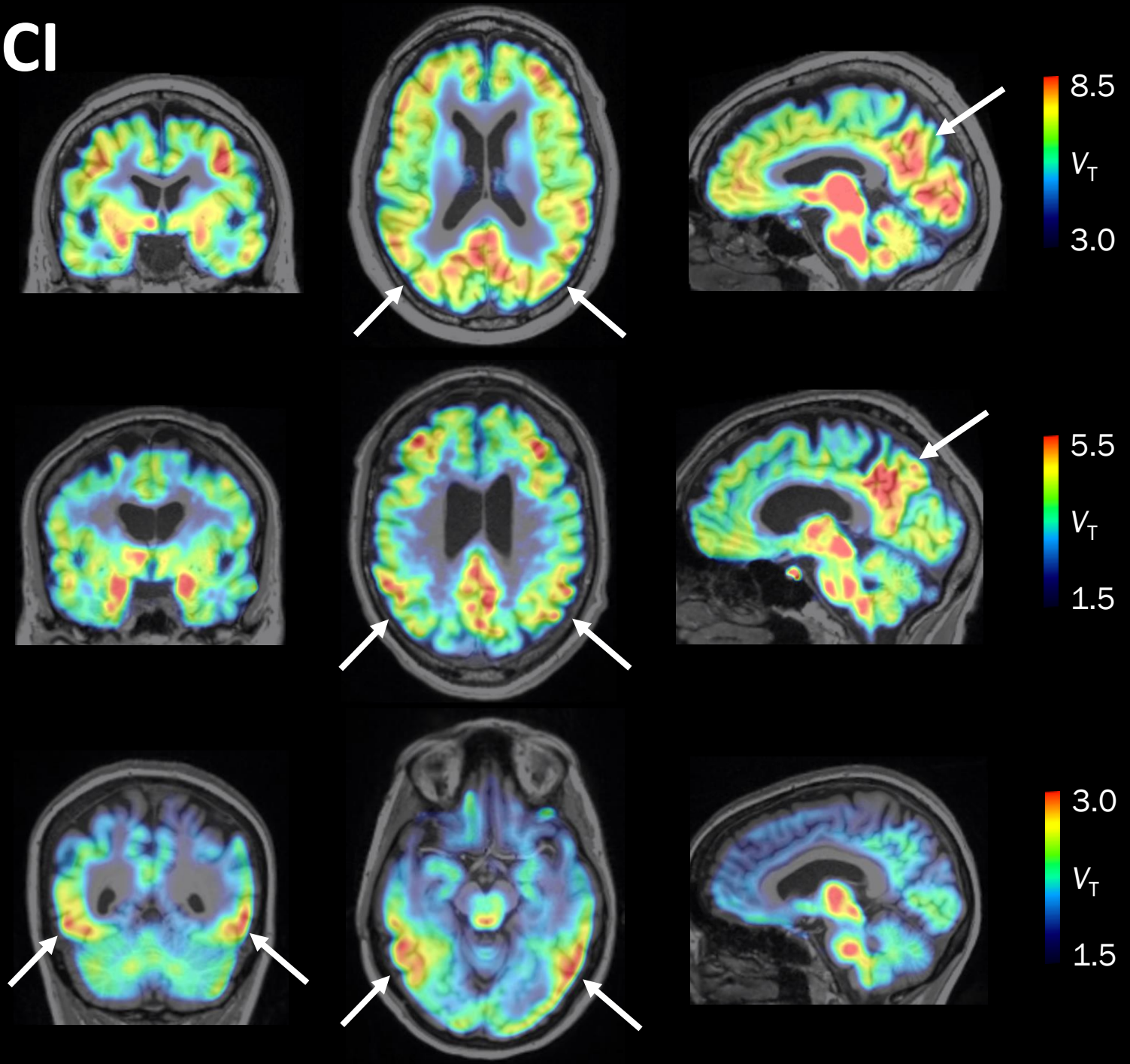
Fujita, M., et al. *EJNMMI Res 2017;7:84.*

^{11}C ER176 PET in MCI

High Affinity (56 y/o man)

Mixed Affinity (62 y/o man)

Low Affinity (52 y/o woman)



NeuroInflammation Imaging in Alzheimer's Disease (AD)

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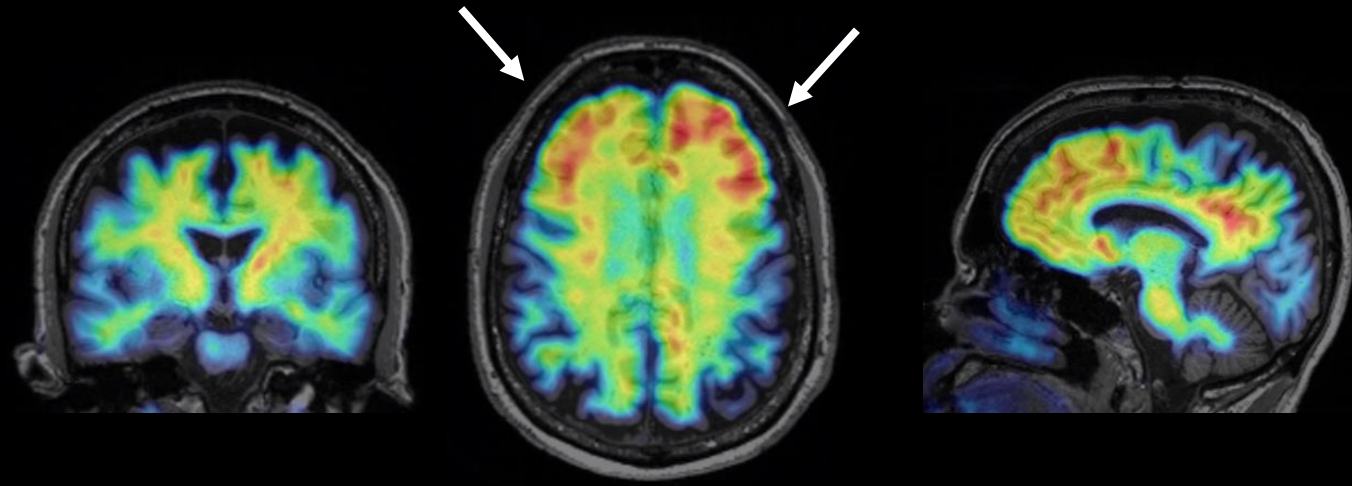
Brain Inflammation in Presymptomatic AD

Weill Cornell Medicine

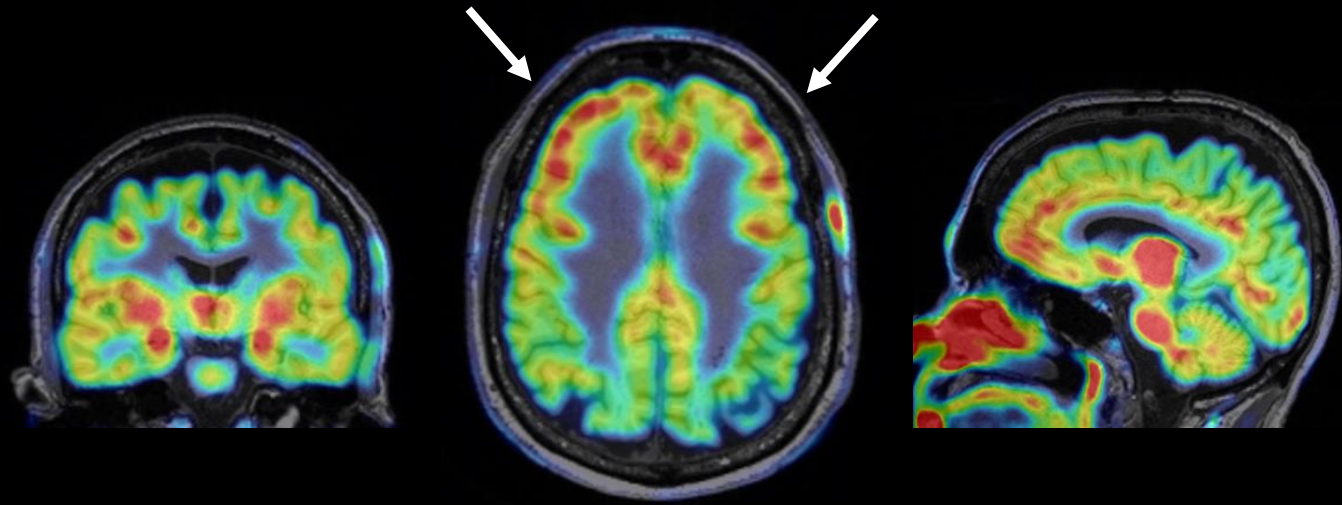
HOUSTON Methodist®
LEADING MEDICINE

Presymptomatic, CDR: 0 67 y/o man

Amyloid
^{11}C PIB PET SUV



Inflammation
^{11}C ER176 PET V_T



Courtesy of B. Pascual, NNAC, Houston Methodist

Brain Inflammation in Mild Cognitive Impairment

Weill Cornell Medicine

HOUSTON Methodist
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While TSPO PET is Positive in AD, it may be Negative in MCI

HOUSTON Methodist LEADING MEDICINE

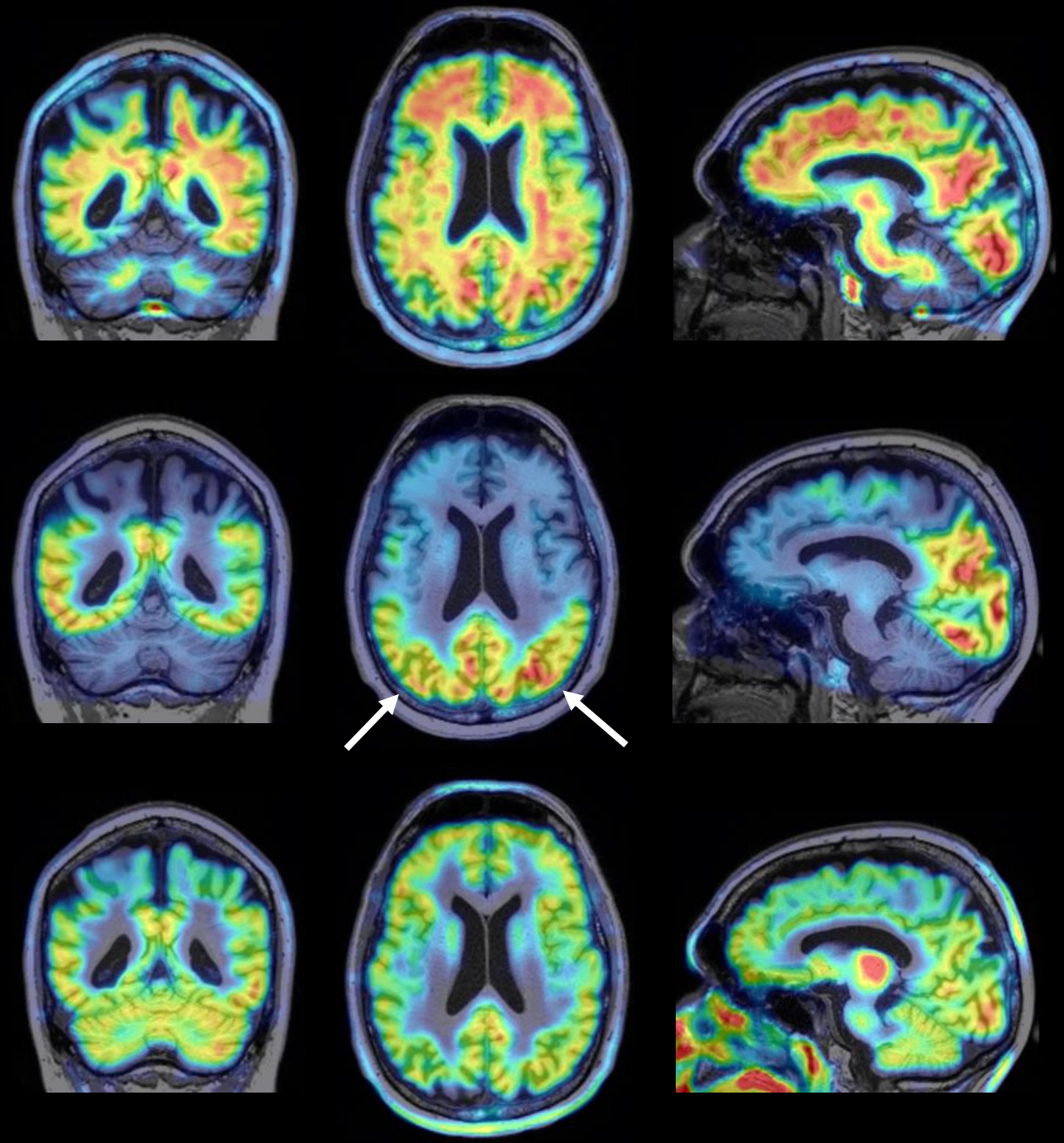
- TSPO PET in MCI
  - Positive (e.g.)
    - Fan, Z. et al. *Eur J Nucl Med Mol Imaging 2018;*45:1432.
    - Hamelin, L. et al. *Brain 2018;*141:1855-1870.
    - Dani M et al. *Brain*. 2018;141:2740-2754.
    - Pascoal TA et al. *Nat Med* 2021;27:1592-1599.
  - Negative (e.g.)
    - Knezevic, D. et al. *J Cereb Blood Flow Metab* 2018;38:1885.
    - Kreisl, W.C. et al. Brain 2013;136:2228.

MCI-CDR 0.5 (56 y/o man)

Amyloid
^{18}F Florbetaben PET SUV

Tau
^{18}F Flortaucipir PET SUVR

Inflammation
^{11}C ER176 PET V_T



Negative Study

MCI-CDR 0.5 (58 y/o man)

Amyloid

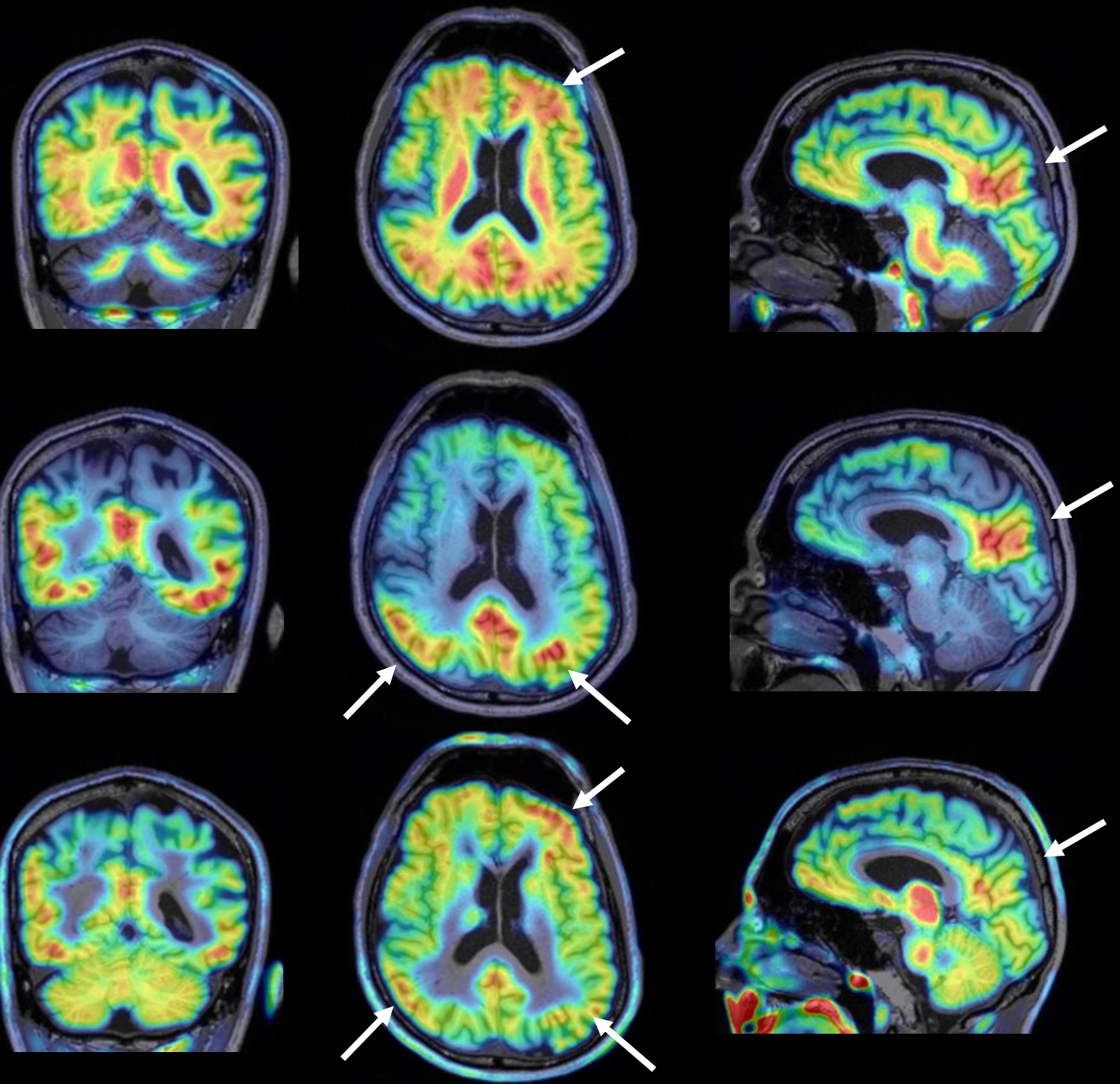
^{18}F Florbetaben PET SUV

Tau

^{18}F Flortaucipir PET SUVR

Inflammation

^{11}C ER176 PET V_T



Our Participants

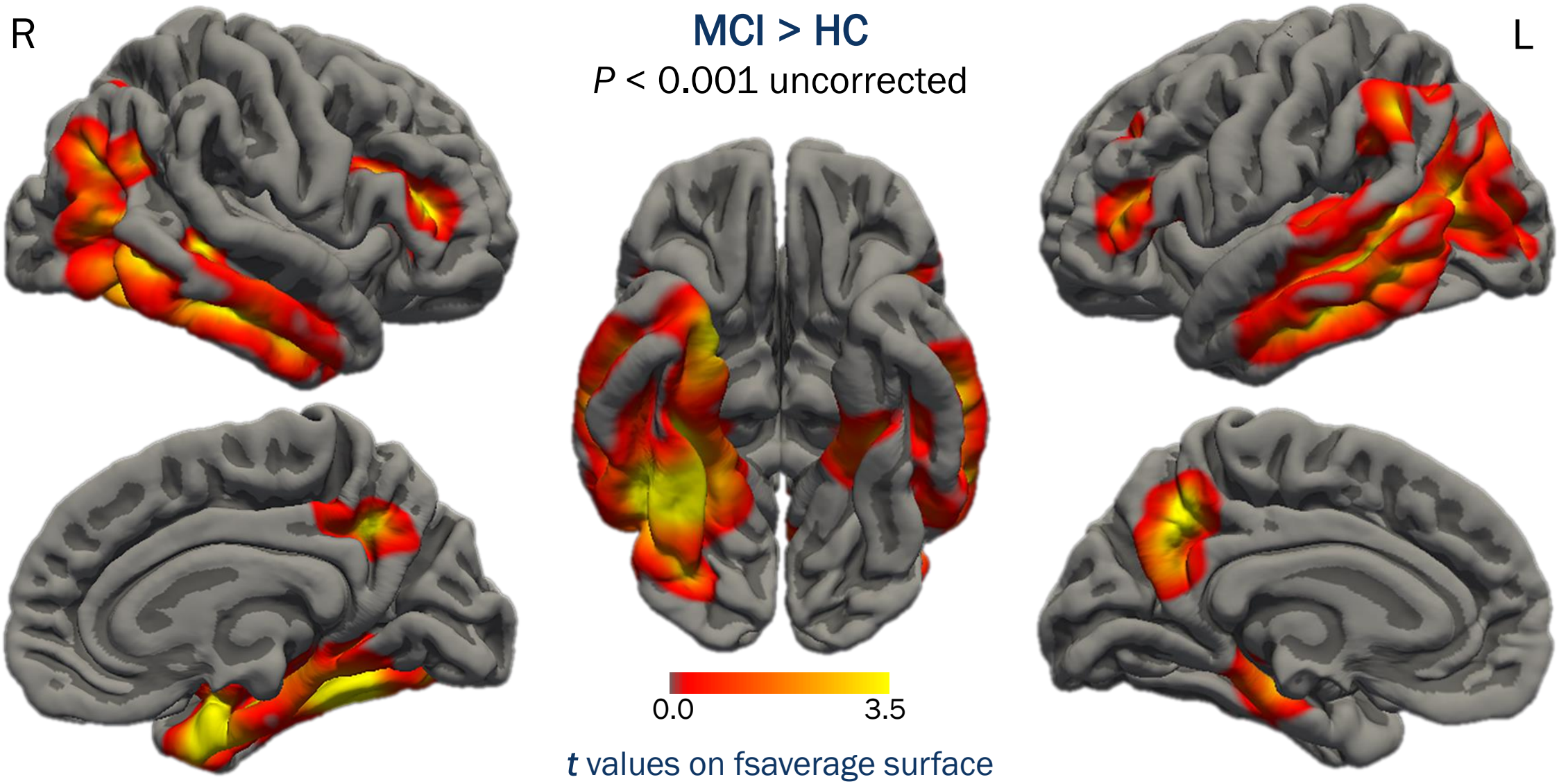
HOUSTON Methodist LEADING MEDICINE

	MCI	HC
N	23	20
Women / Men	10/11	8/7
Age (M±SD)	62±6	65±7
MMSE (M±SD)	22±5	29±1
CDR (M±SD)	0.5	0
^{11}C PIB / ^{18}F Florbetapir / ^{18}F Florbetaben	3/3/12	N/A
^{18}F Flortaucipir	13	N/A
TSPO High/Mixed/Low-Affinity binders*	7/11/3	5/7/3

* Determined by TSPO Ala147Thr (rs6971) polymorphism genotyping

^{11}C ER176 in MCI: Voxel-wise analysis

HOUSTON Methodist LEADING MEDICINE



Brain Inflammation at the Alzheimer Disease Stage

Weill Cornell Medicine

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Mild AD-CDR 1 (57 y/o man)

amnestic syndrome

Amyloid

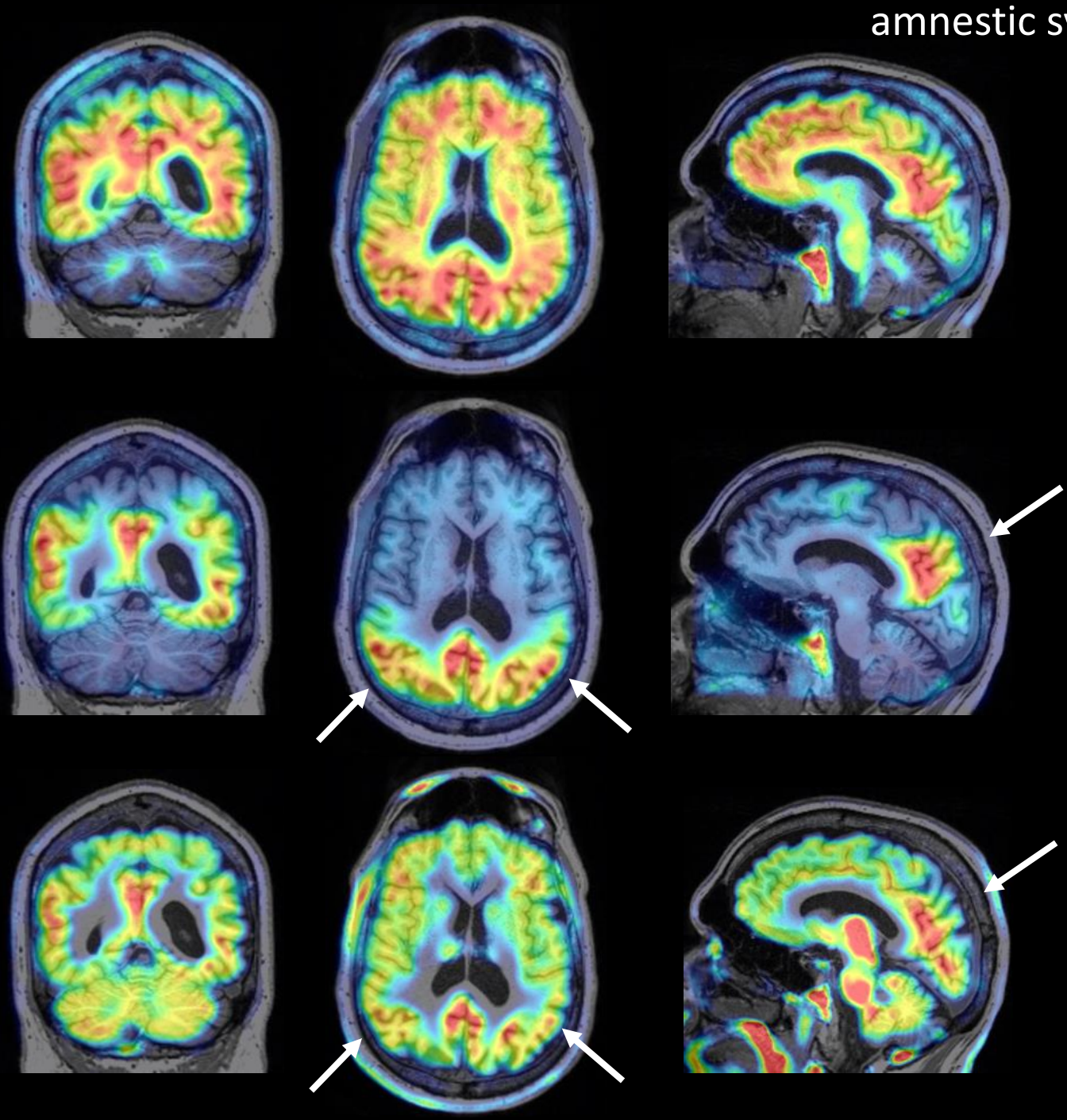
^{18}F Florbetaben PET SUV

Tau

^{18}F Flortaucipir PET SUVR

Inflammation

^{11}C ER176 PET V_T

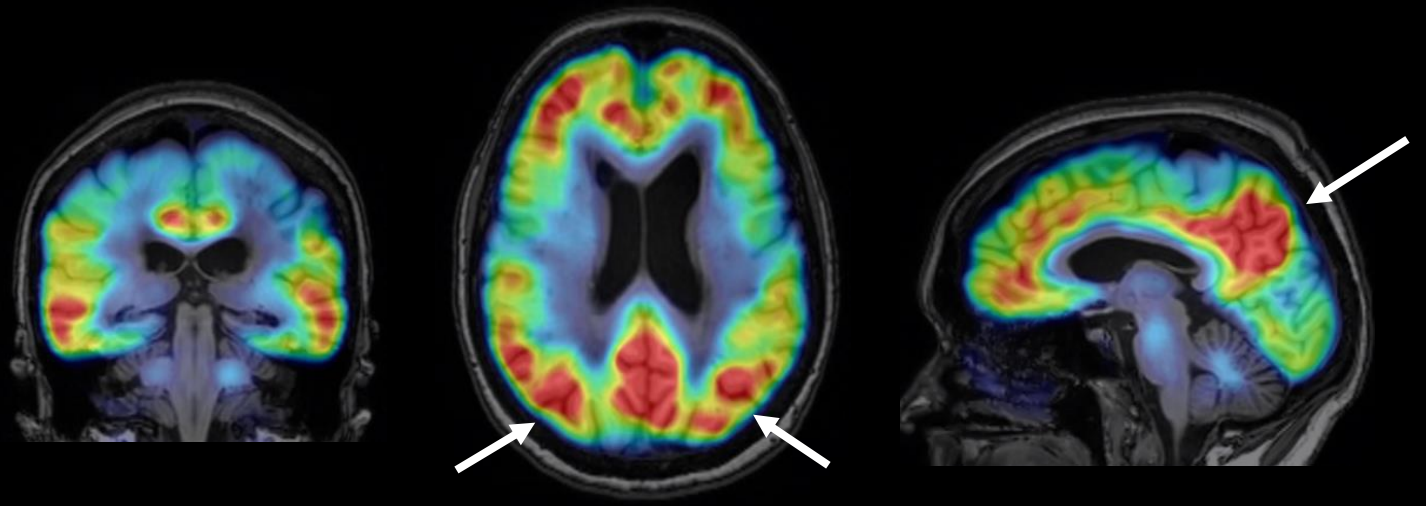


Positive Study

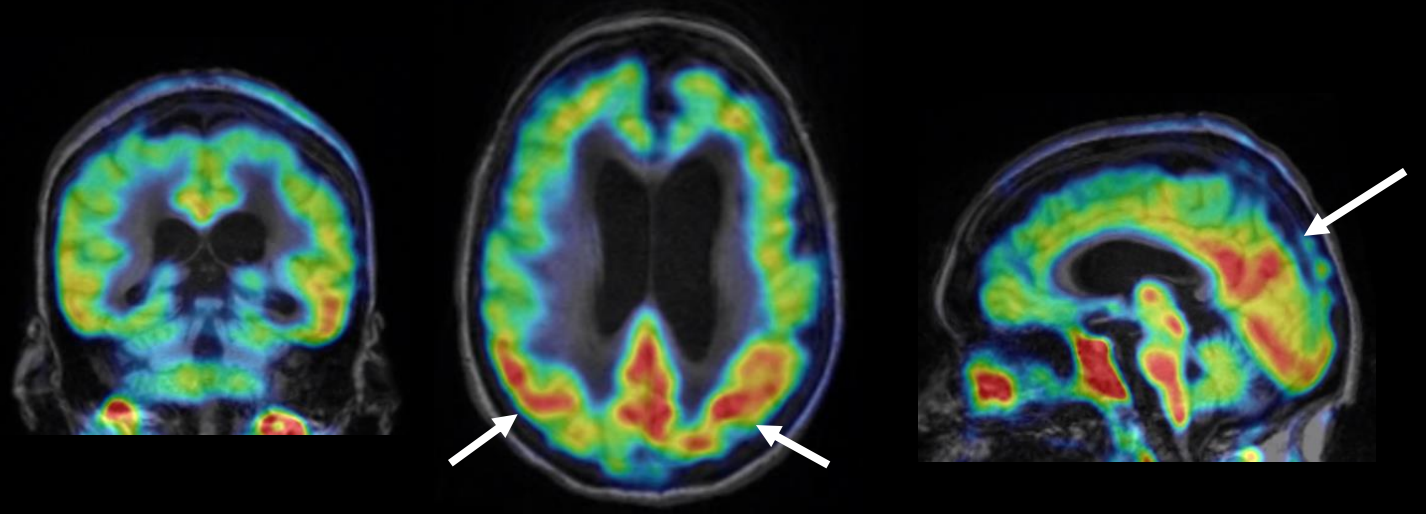
Advanced AD, CDR: 3

72 y/o woman; amnestic syndrome

Amyloid
^{11}C PIB PET SUV



Inflammation
^{11}C ER176 PET V_T

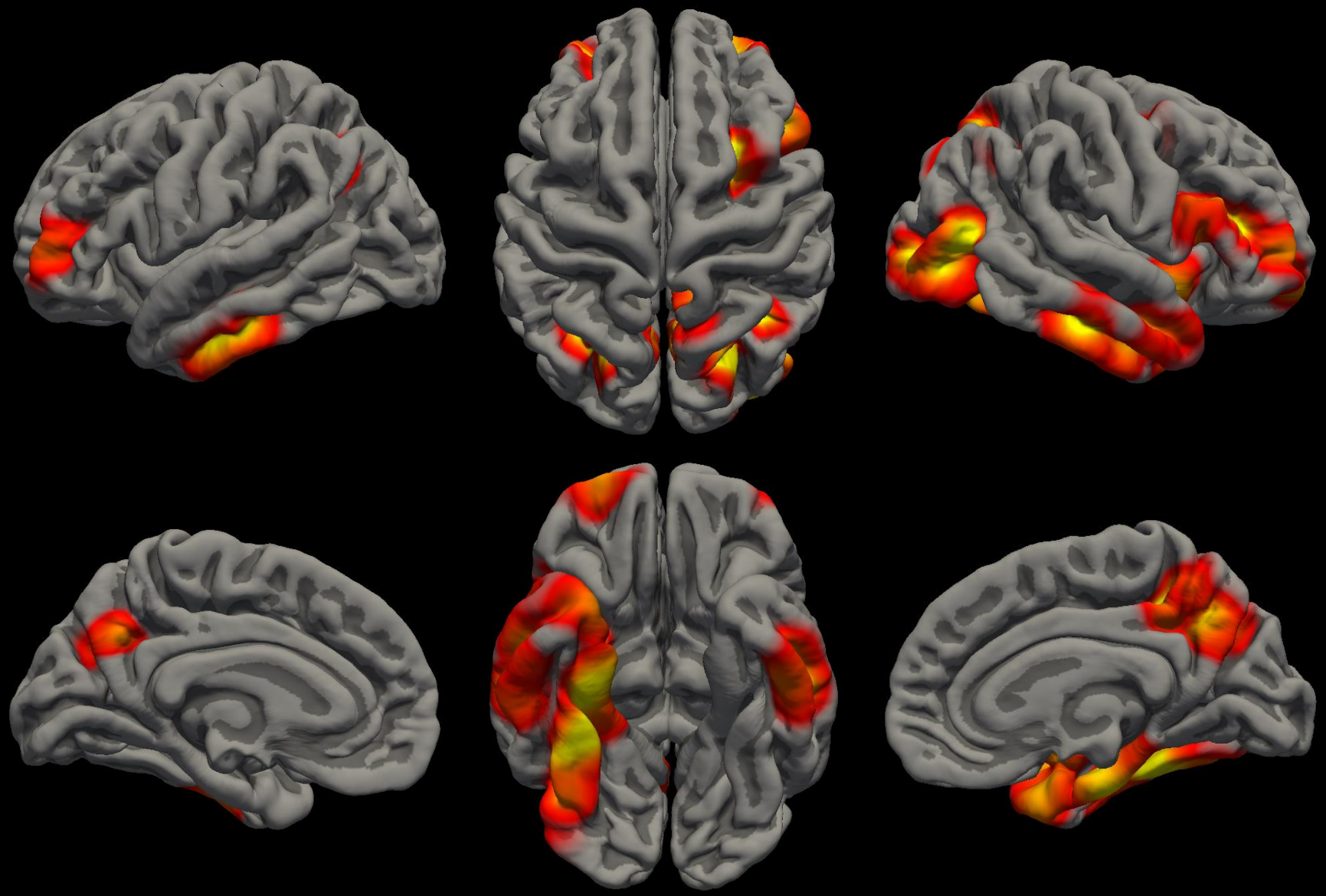


Courtesy of B. Pascual, NNAC, Houston Methodist

Inflammation in Alzheimer's Disease: Group Comparison

AD patients
>
Healthy Controls

Projected t-values
p < 0.005



Inflammation vs { β Amyloid, Tau }

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Our Correlation Method

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Intra-subject Correlation

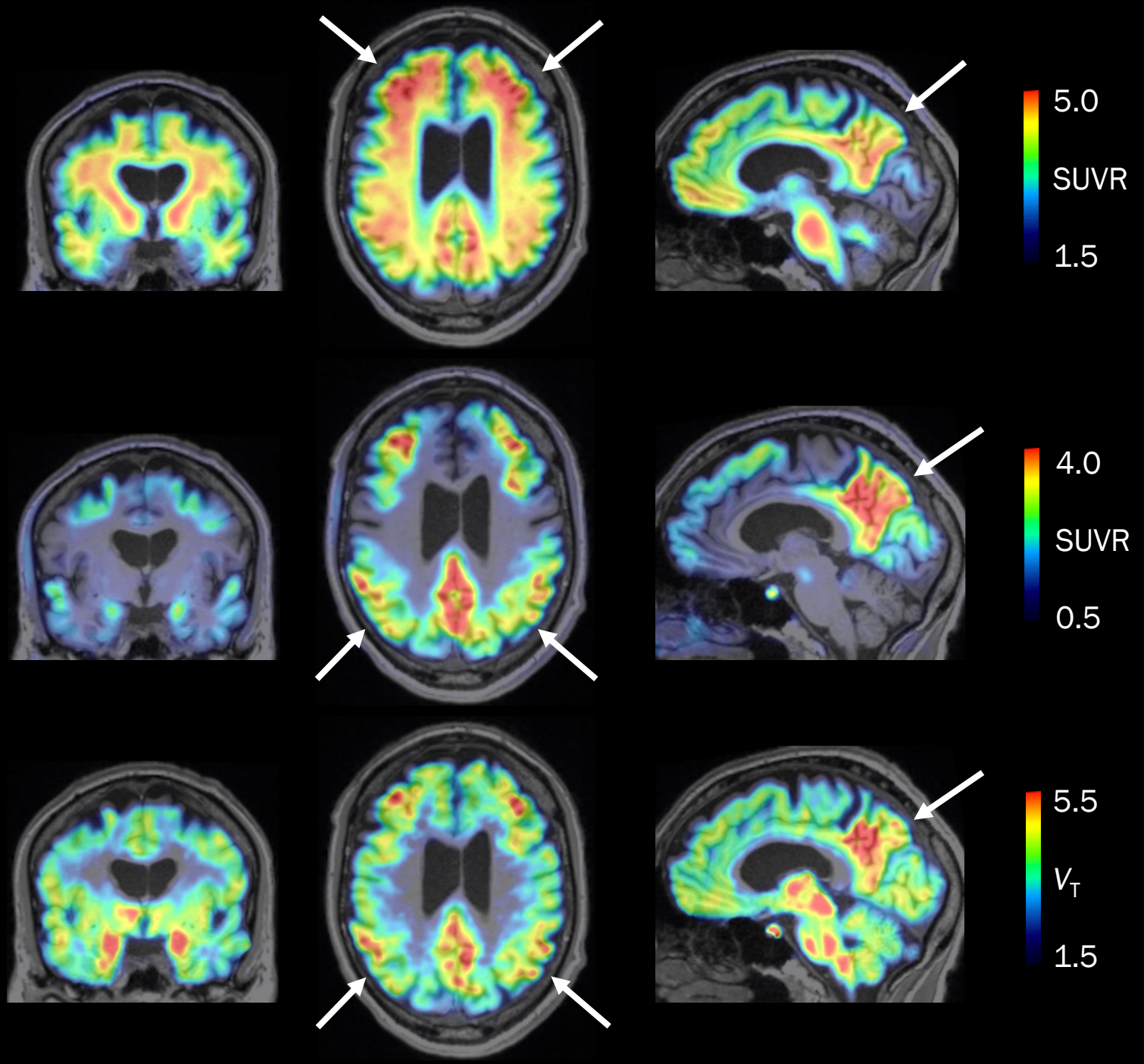
- To account for interindividual variability in the brain topography of
  - Amyloid
  - Tau
  - Inflammation

MCI-CDR 0.5 (62 y/o man)

Amyloid
^{18}F Florbetaben PET SUV

Tau
^{18}F flortaucipir PET SUVR

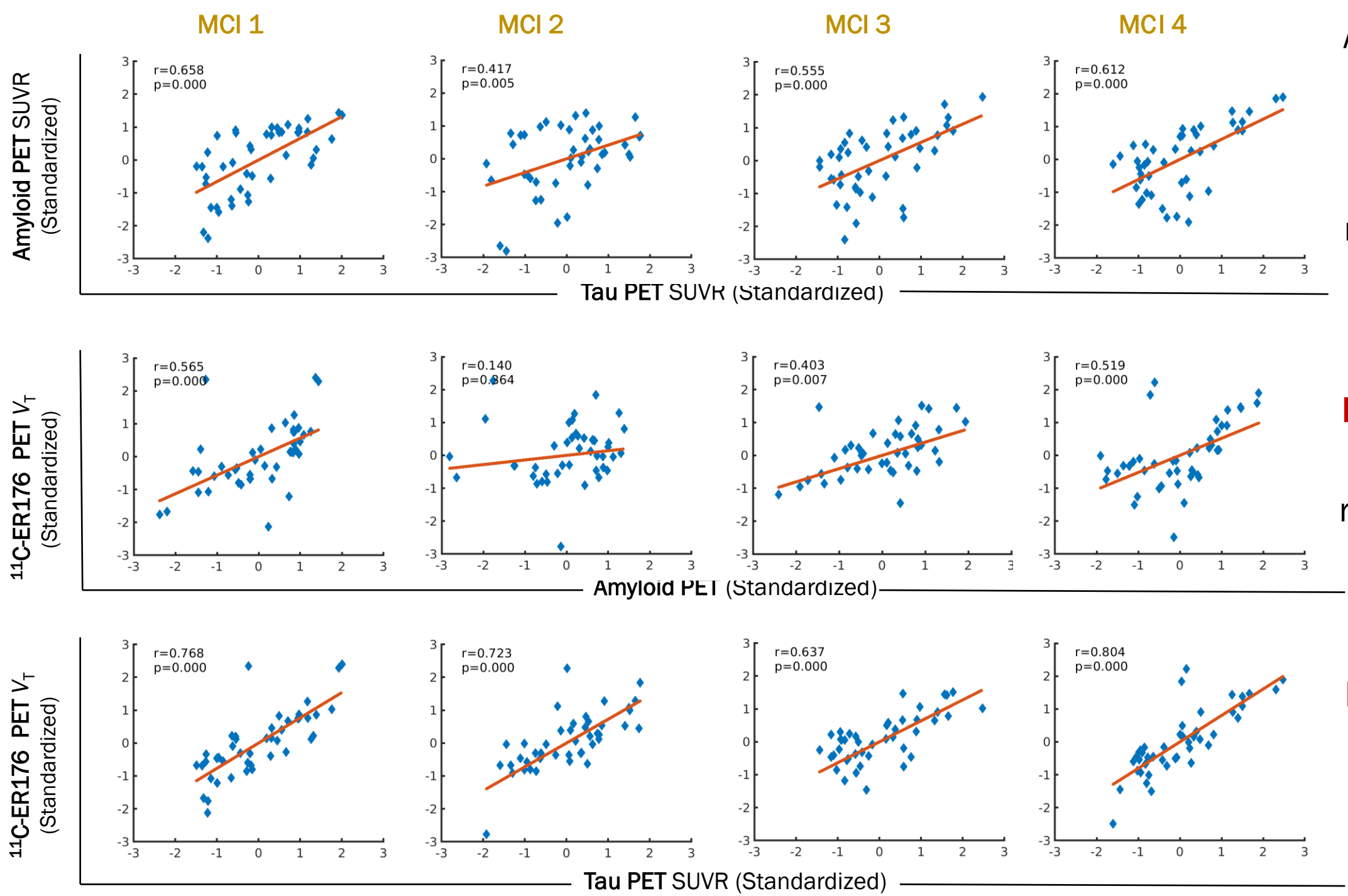
Inflammation
^{11}C ER176 PET V_T
MAB



Correlation Method

Intra-subject Correlation

- To account for interindividual variability in the brain topography of
  - Amyloid
  - Tau
  - Inflammation
- And the variability introduced by the three TSPO binding affinities



Average across MCI subjects

Amyloid *vs* Tau

r = **0.53** ± 0.21

Inflammation *vs* Amyloid

r = **0.43** ± 0.20

Inflammation *vs* Tau

r = **0.60** ± 0.29

Conclusions

- ^{11}C-ER176 PET allows for the identification in MCI patients of neuroinflammation in regions known to be involved in the AD process
- Subjects with any TSPO genotype could be studied
- The co-localization of neuroinflammation with tau was even higher than between amyloid and tau
- This finding highlights the importance of neuroinflammation as a key process in AD and as a potential therapeutic target

NeuroInflammation Imaging in Frontotemporal Dementia (FTD)

Courtesy of Dr. Belen Pascual,
Director, FTD Unit

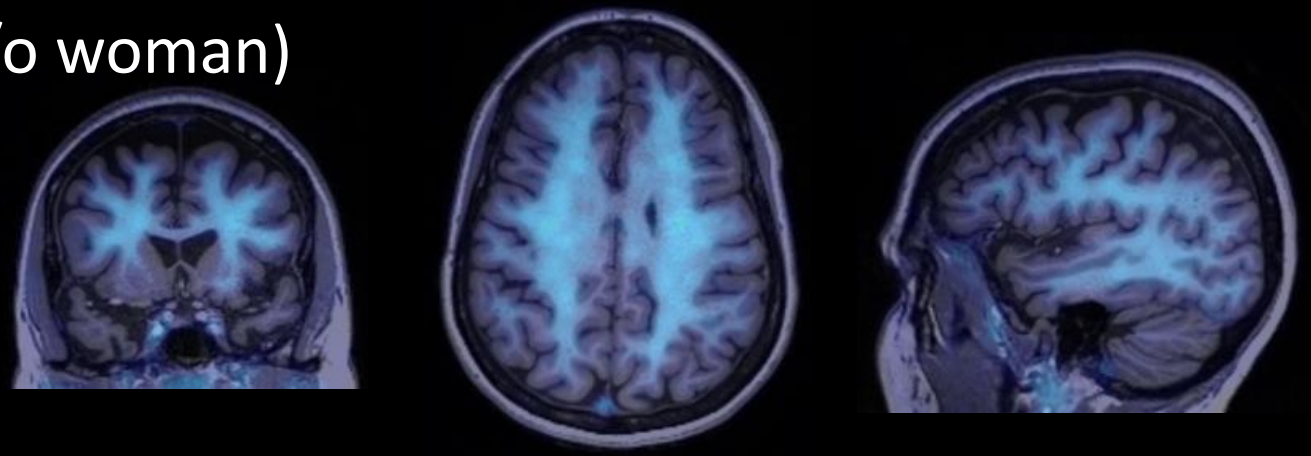
HOUSTON Methodist
LEADING MEDICINE

TSPO PET in FTD

- PET uptake highly focal, mostly in gray matter
  - Can be diagnostically useful in difficult cases
- Corresponds well to the clinical phenotype
  - Behavioral variant FTD
  - Non-fluent primary progressive aphasia (nfvPPA)
  - Semantic variant primary progressive aphasia (svPPA)
    - Inflammation greater in the periphery than in the core of damage

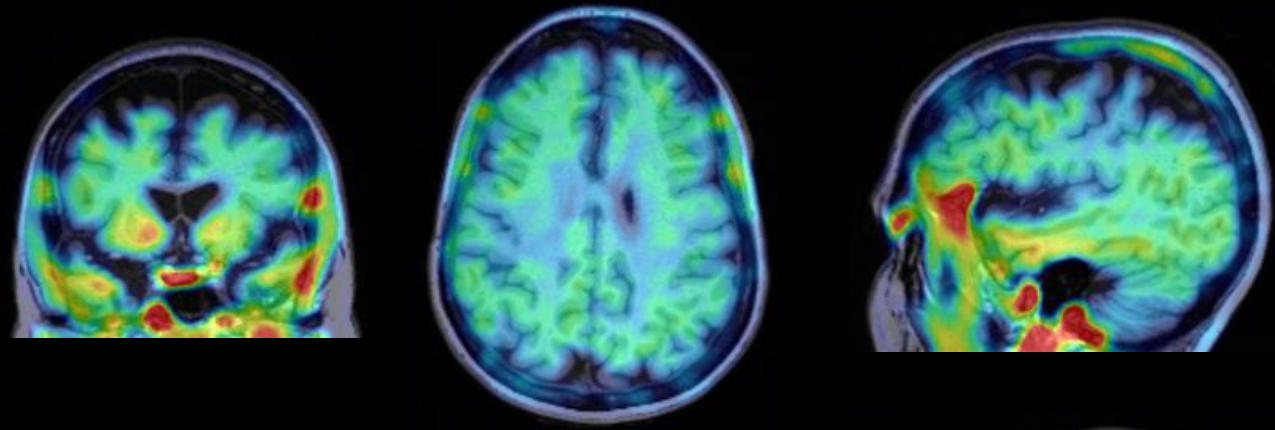
Behavioral variant FTD (50 y/o woman)

Amyloid
^{11}C PIB PET SUV



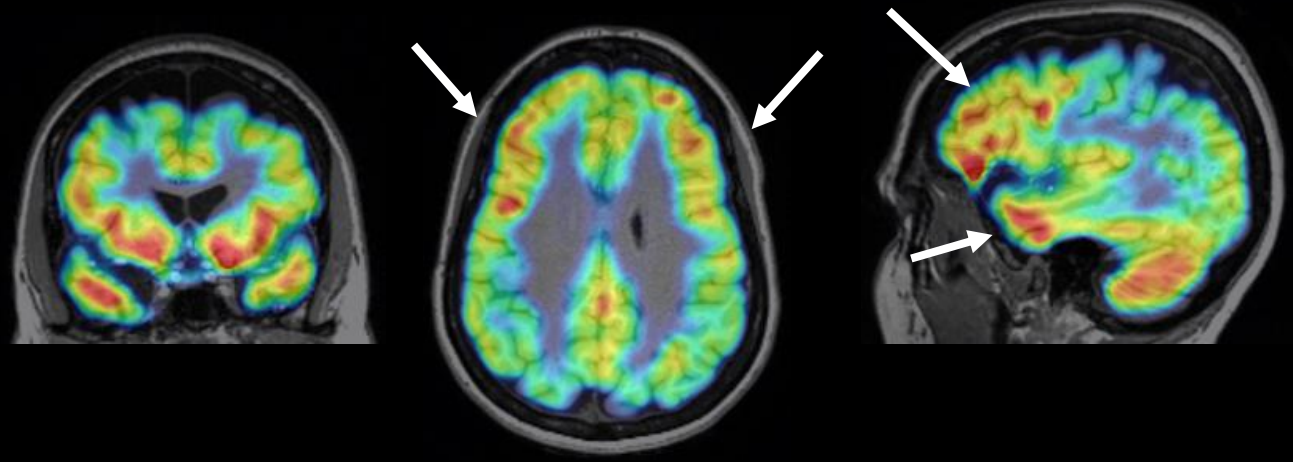
Negative

Tau
^{18}F Flortaucipir PET SUVR



Negative

Inflammation
^{11}C PBR28 PET V_T

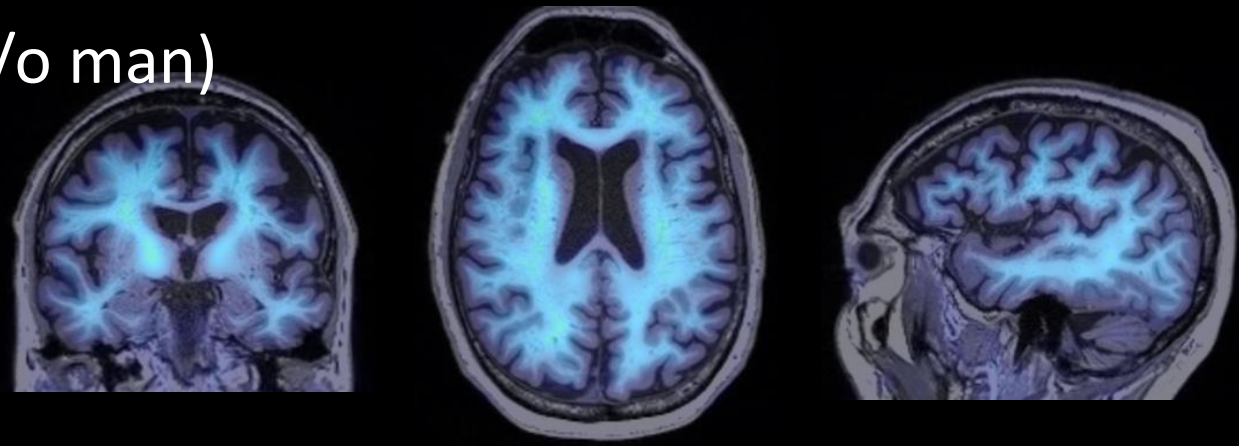


Positive

Non-fluent variant PPA (71 y/o man)

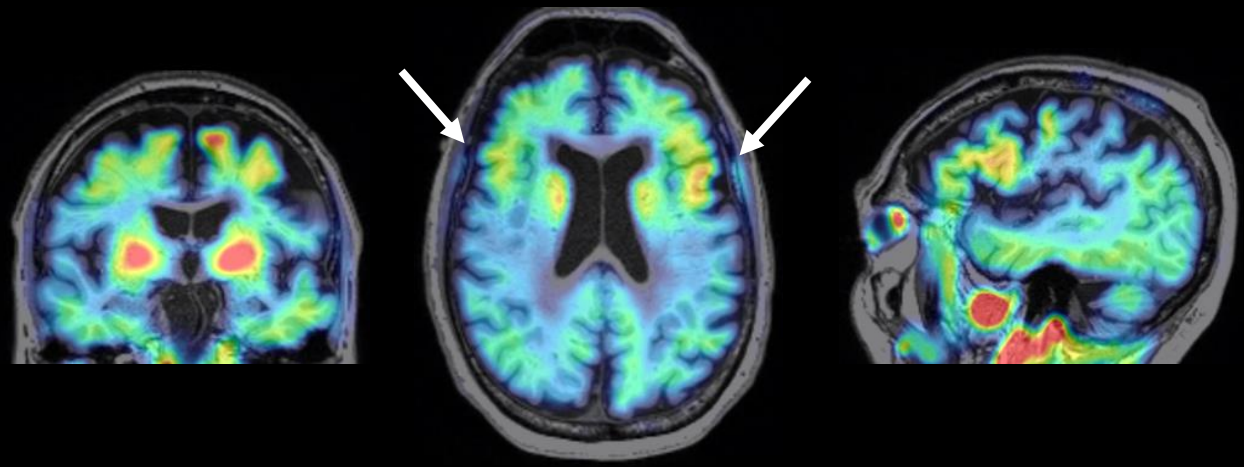
Amyloid

^{11}C PIB PET SUV



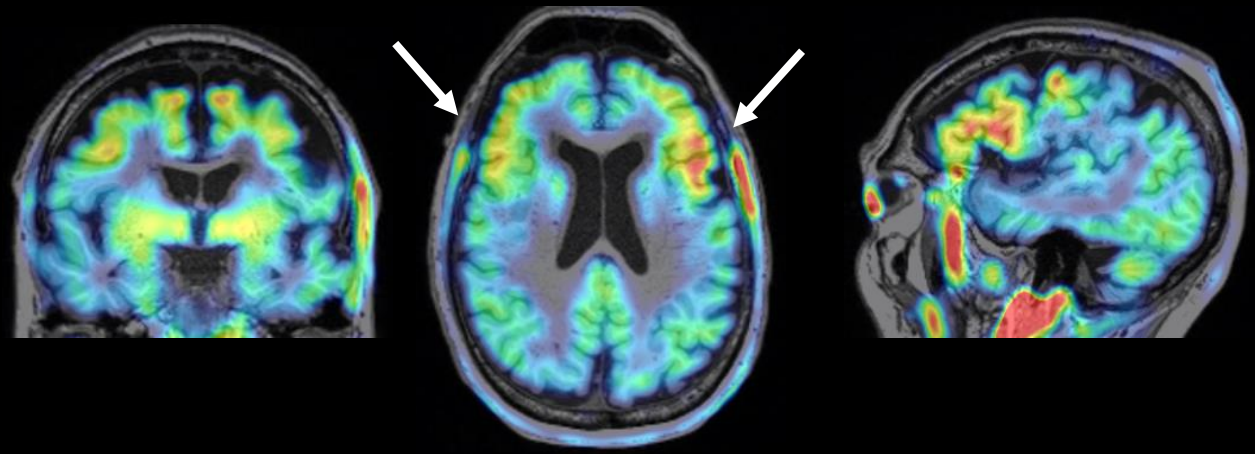
Tau

^{18}F Flortaucipir PET SUVR



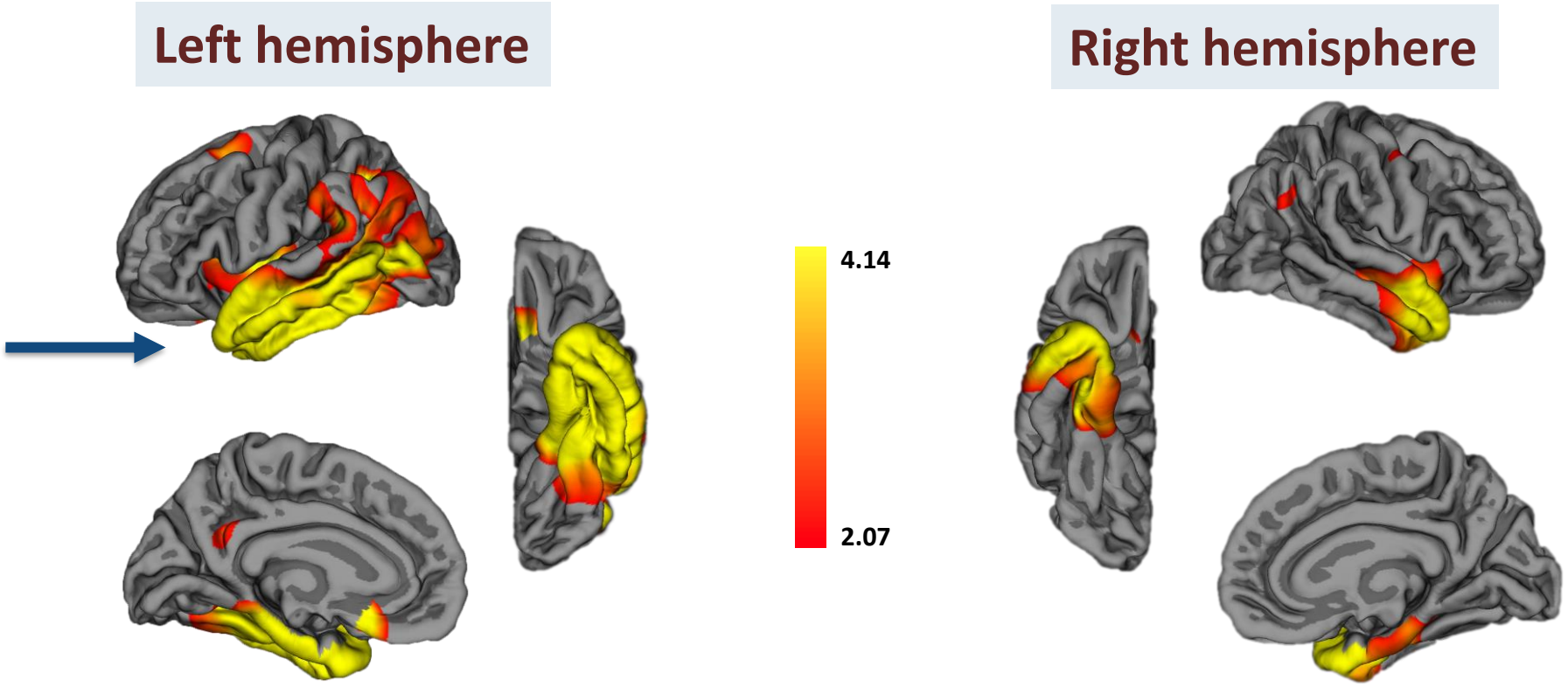
Inflammation

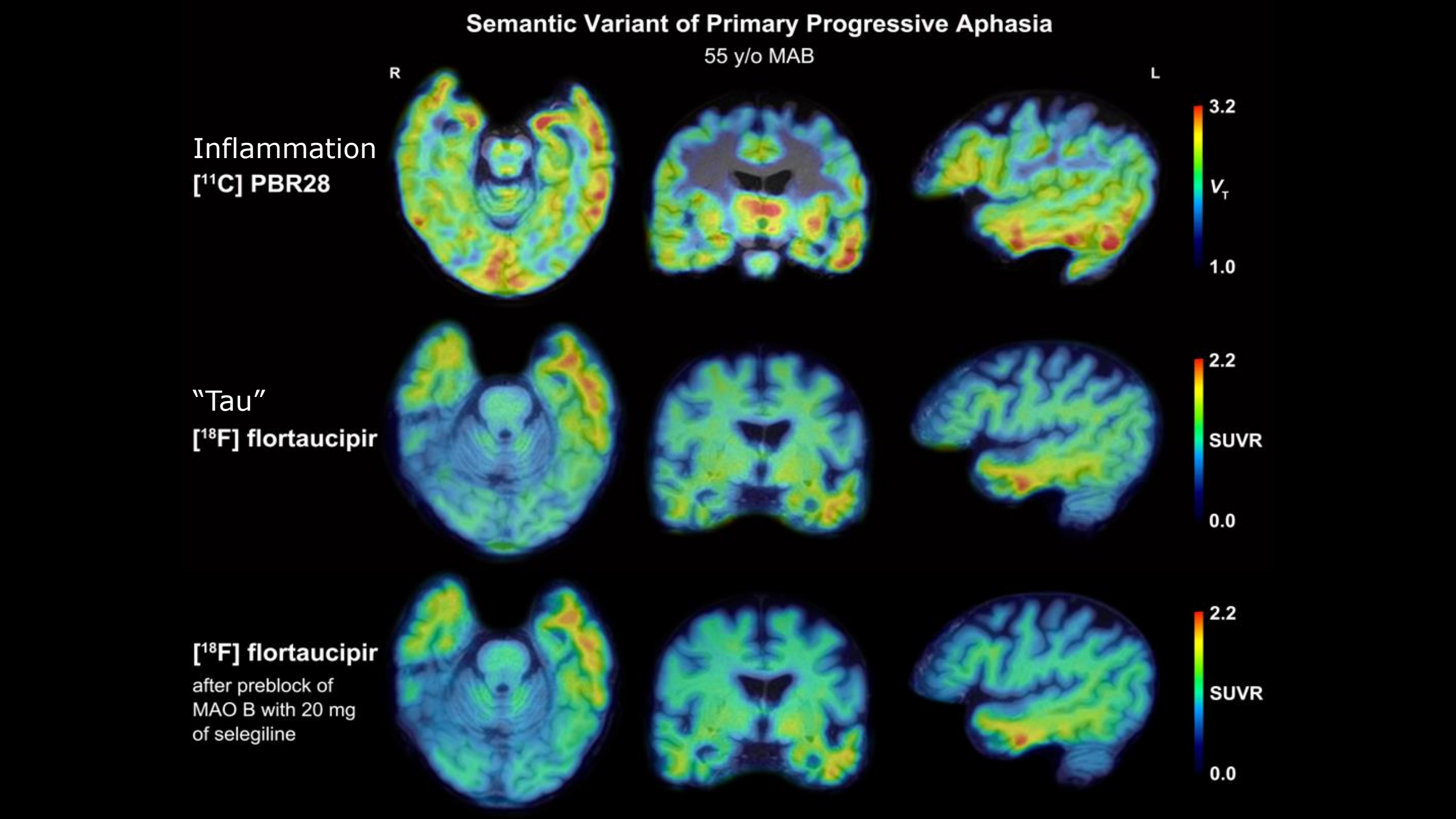
^{11}C PBR28 PET V_T



Cortical Thickness in SvPPA

- Atrophy is earliest and greatest at the left temporal tip



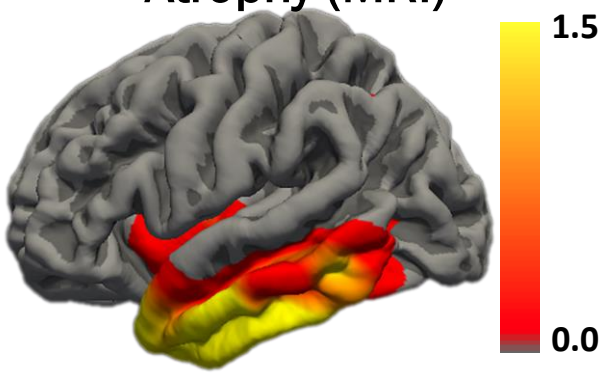

Semantic Variant of Primary Progressive Aphasia
55 y/o MAB
R
L
Inflammation
[11C] PBR28
3.2
VT
1.0
"Tau"
[18F] flortaucipir
2.2
SUVR
0.0
[18F] flortaucipir
after preblock of MAO B with 20 mg of selegiline
2.2
SUVR
0.0

doi:10.1093/brain/awab057 BRAIN 2021: 144; 1565–1575 | 1565

BRAIN
ORIGINAL ARTICLE

Patients > Controls
FWE-corrected p<0.05

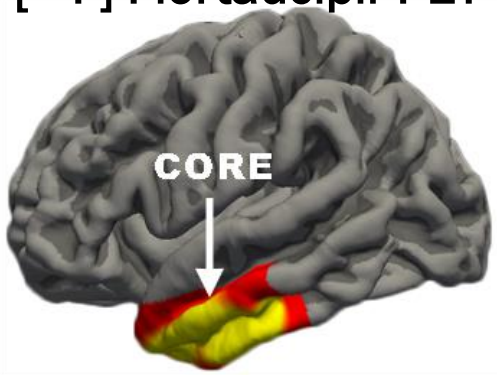
Atrophy (MRI)



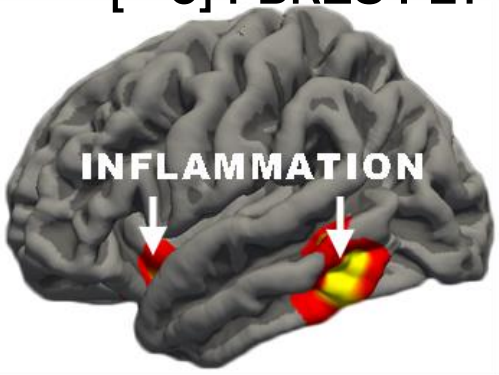
Neuroinflammation is highest in areas of disease progression in semantic dementia

Belen Pascual,[1] Quentin Funk,[1] Paolo Zanotti-Fregonara,[1] Matthew D. Cykowski,[2,3] Mattia Veronese,[4] Elijah Rockers,[1] Kathleen Bradbury,[1] Meixiang Yu,[5] Mohammad O. Nakawah,[1] Gustavo C. Román,[1] Paul E. Schulz,[6] Anithachristy S. Arumanayagam,[2] David Beers,[3] Alireza Faridar,[1] Masahiro Fujita,[1] Stanley H. Appel[3] and Joseph C. Masdeu[1]

[^{18}F] Flortaucipir PET



[^{11}C] PBR28 PET

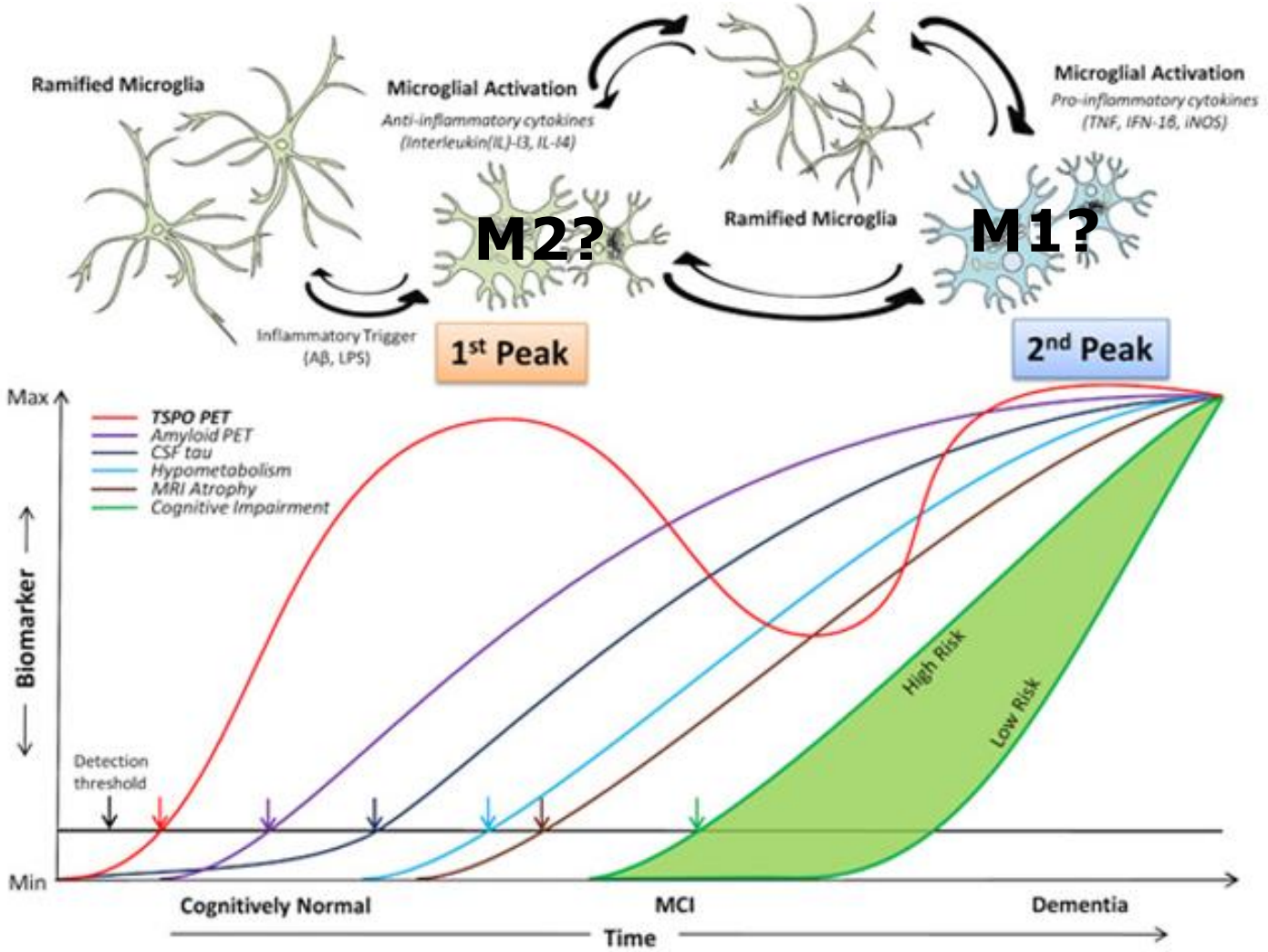


Inflammation Imaging in Dementia: Targets Beyond TSPO

Courtesy of Dr. Masahiro Fujita,
Director, PET Core

HOUSTON Methodist
LEADING MEDICINE

Purine Receptor Imaging



Fan, Z. et al. *Brain* 2017;140:792

- TSPO present in microglia, both
  - M2 (protective)
  - M1 (toxic)
- Purine receptors
  - P2Y12: M2
  - P2X7: M1
    - Van Weehaeghe, D. et al. *J Nucl Med 2020;61:604.*

^{18}F-SMBT-1 PET to Image Astrogliosis in AD

HOUSTON Methodist LEADING MEDICINE

- In collaboration with Prof. N. Okamura and Dr. R. Harada
  - Tohoku University School of Medicine, Sendai, Japan
- SMBT-1 has high and specific binding affinity to MAO-B (Kd = 3.7 nM), expressed by astrocytes
- ^{18}F-SMBT-1 binding was elevated in AD vs controls
  - Consistent with regional brain density of MAO-B in humans
  - Displaceable by selegiline

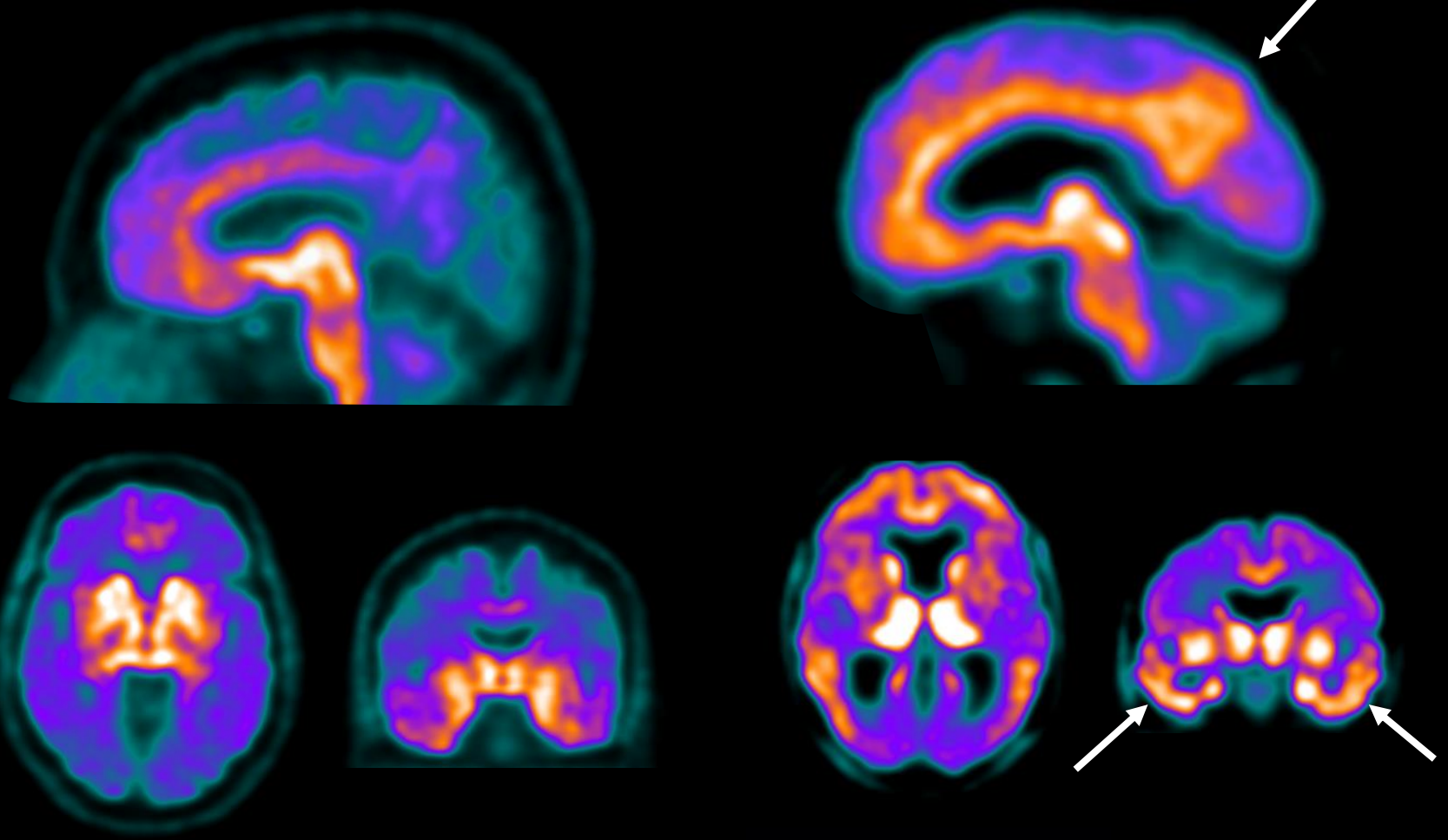
^{18}F-SMBT-1 PET images in healthy control and AD patient

(60-90 min post injection)

75 yo F, MMSE 21

Healthy control

AD



Courtesy of

- N. Okamura
- R. Harada
- C. Rowe
- V. Villemagne

PET Inflammation Imaging

- Inflammation imaging is beginning to show patterns in the progress of dementia, but more work is needed
- Although limited by both cell and state specificity, TSPO imaging is helpful in depicting areas of brain inflammation in dementia
  - And in damage propagation/neuroprotection
- Additional imaging targets, with greater state and cell specificity are being developed

Imaging Dementia: Conclusions

HOUSTON Methodist LEADING MEDICINE

- The anatomical pattern of PET changes separates:
  - Alzheimer's disease (R3-R4 tau)
  - Diffuse Lewy-body disease (alpha synuclein)
  - Frontotemporal dementia (R4 tau, TDP-43)
- PET over time defines the type of therapy
  - Amyloid
  - Tau
- Active research on immunomodulation thanks to PET

The Nantz National Alzheimer Center: A Team Effort

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Obadah Nakawah

Rejani Nair

Kathleen Bradbury

Rebecca Axline

Belen Pascual

Quentin Funk

Nilene Crisci

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Max Yu – Director, Cyclotron Core

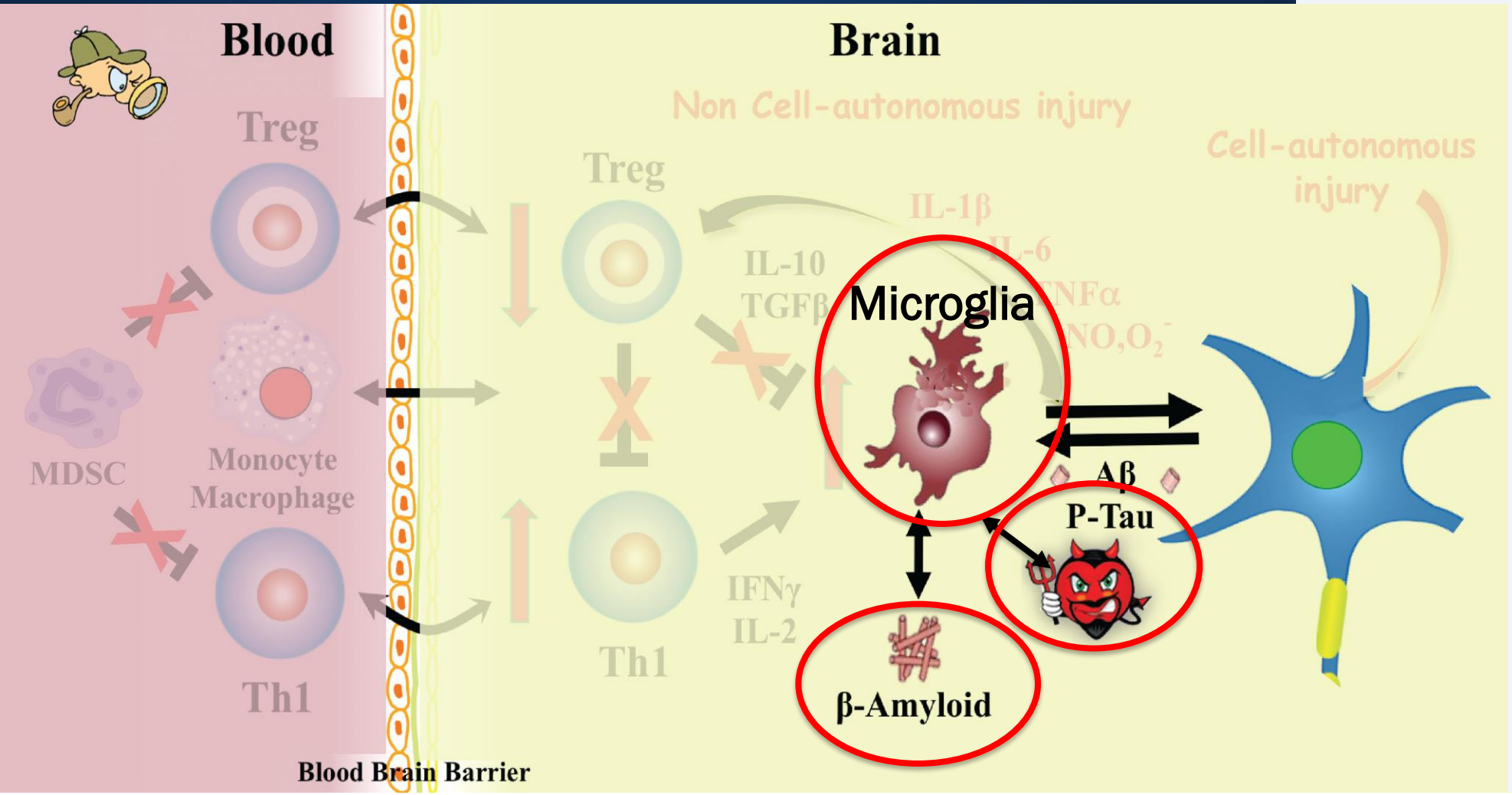
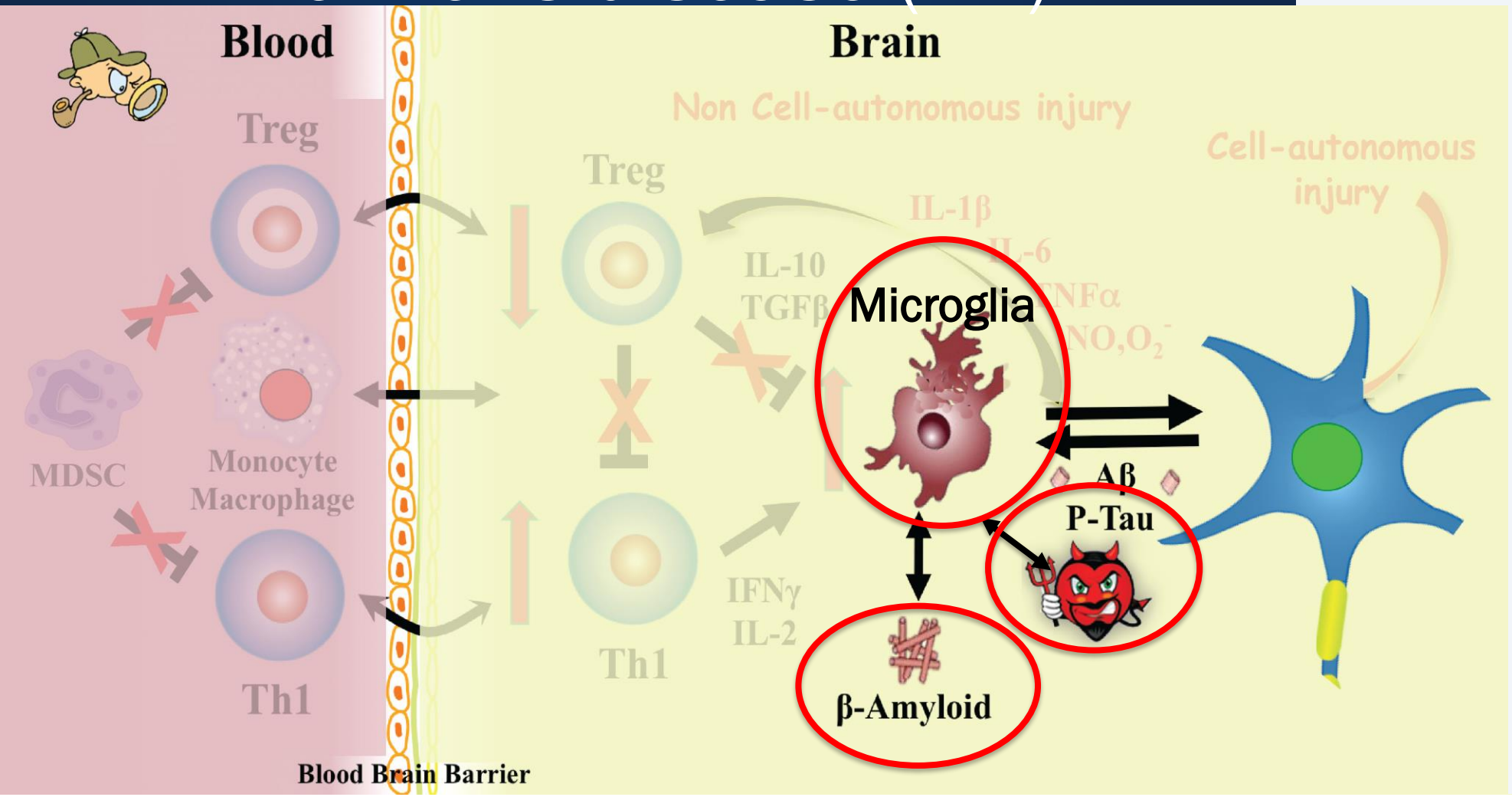
Mattia Veronese

Paolo Zanotti-Fregonara

Acknowledgements

- Eli Lilly for ^{18}F-AV1451 precursor
- ADNI for the healthy older controls' MRIs used for the functional connectivity analysis
- The Nantz, Chao, Dearing, Harrison, Moody and Mary Naylor Methodist Foundation Funds for financial support

Inflammation in AD



Inflammation plays a major role in Alzheimer's disease (AD)