LATEST ADVANCES IN NEUROIMAGING: Interactive Case Sessions

Paul E. Schulz MD

Joseph Masdeu MD

ASN 42ND ANNUAL MEETING
JANUARY 24-26, 2019
PUERTO RICO

DISCLOSURES

- **FOUNDATION SCIENTIFIC BOARDS**: Weston Brain Institute, FTLD Association
- **FOUNDATION GRANTS**: Halle Discount Tire, Kleberg Foundation
- **NIH Grants**
- **ADVISOR**: Eli Lilly
- **SPEAKER**: Acadia

ASN 42ND ANNUAL MEETING
JANUARY 24-26, 2019
PUERTO RICO

OBJECTIVES

- Review case Hxs to demonstrate how neuroimaging has significantly helped with
  - Neurologic **diagnoses**
  - Being a biomarker to get the **correct patients enrolled** in Rx trails
  - As a biomarker for **Rx success**, and
  - Understanding the **pathophysiology** underlying NDDs

OBJECTIVES

- Review case Hxs to demonstrate how neuroimaging has significantly helped with
  - Neurologic **diagnoses**
  - Being a biomarker to get the **correct patients enrolled** in Rx trails
  - As a biomarker for **Rx success**, and
  - Understanding the **pathophysiology** underlying NDDs

PATIENT 1:
WORD FINDING ISSUES

HPI

- 76 yo RH WM whom we saw b/o being mute
- 2012: family noticed mild cognitive changes, i.e. forgetting people‘s names
- 2013: very confused post CABG
- 2015: told he had a stroke based on an MRI
- Often “forgets who his wife is.”

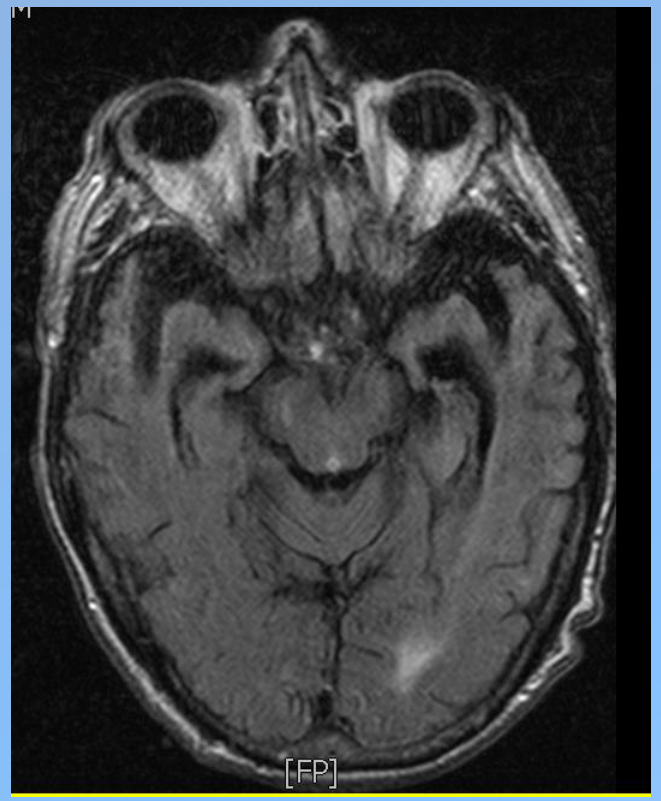
HPI

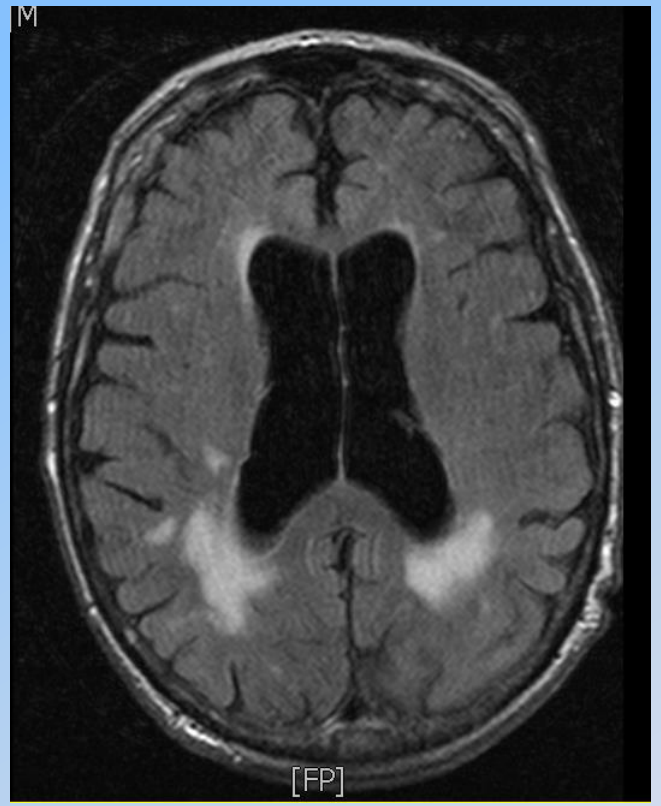
- 2018
  - Stopped driving 6 months prior
  - Recently unable to locate items when asked to, e.g. a sink or cabinet
  - Unable to follow questions
  - **Mute** during our interview

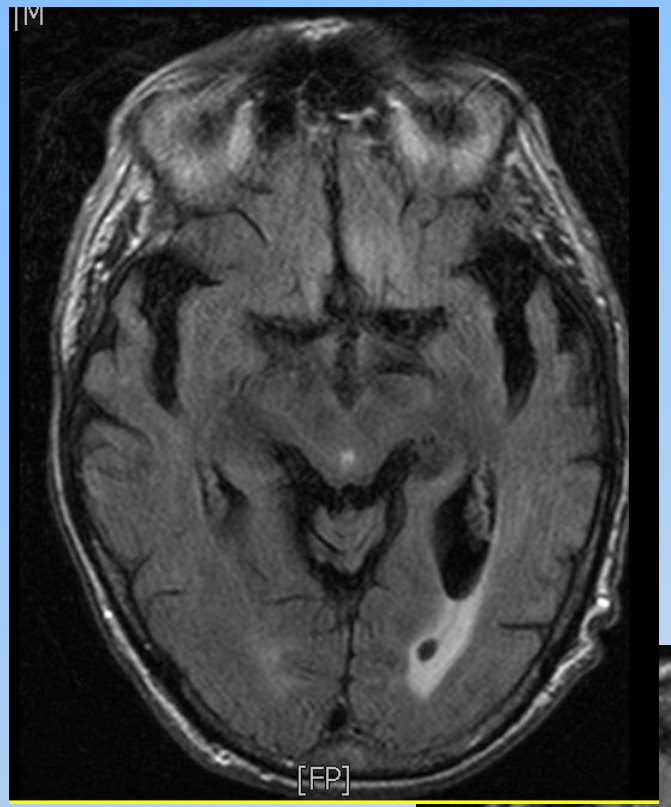
- 20% AD, 80% FTD: in the past, could not tell which applied

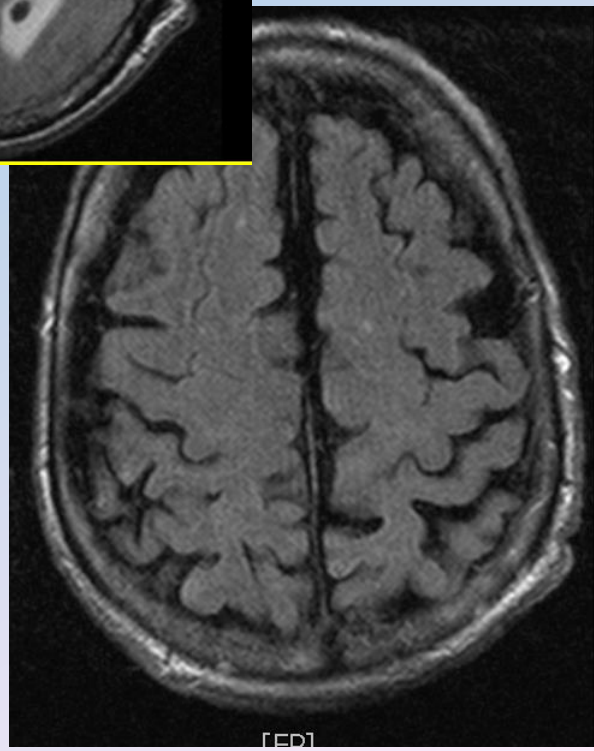
- MRI

MRI BRAIN



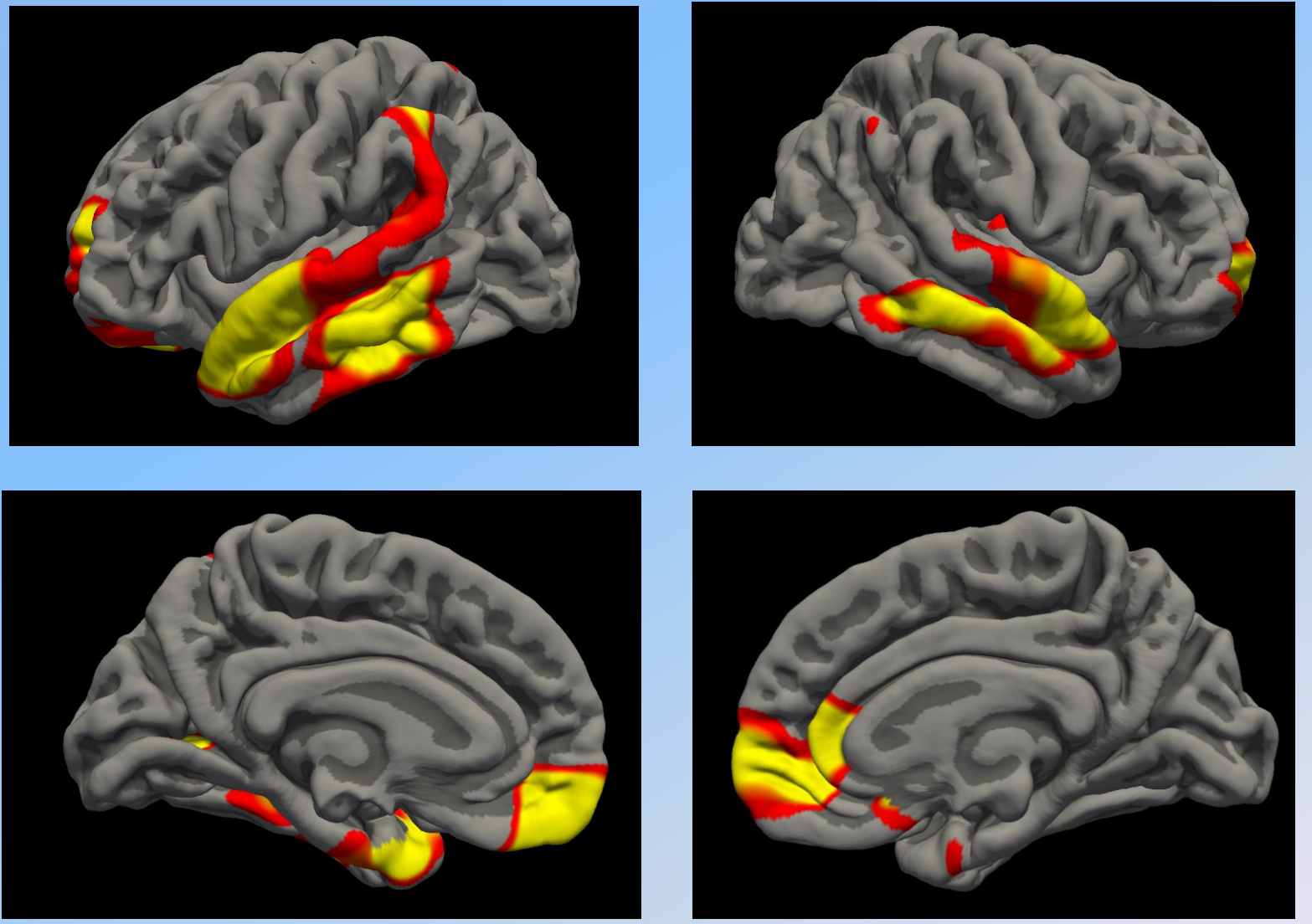






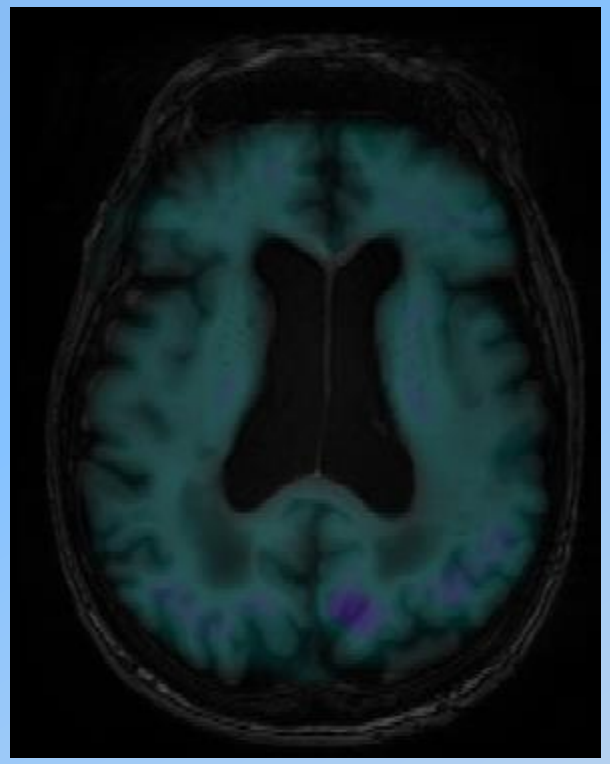
MRI: Cortical Thickness

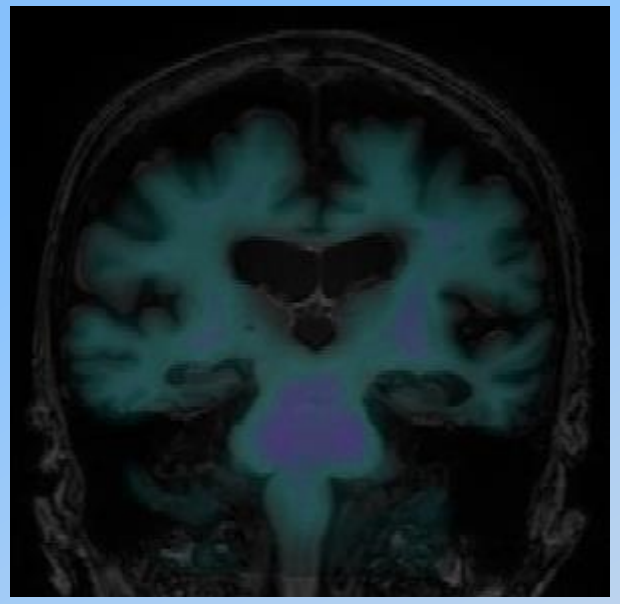
L

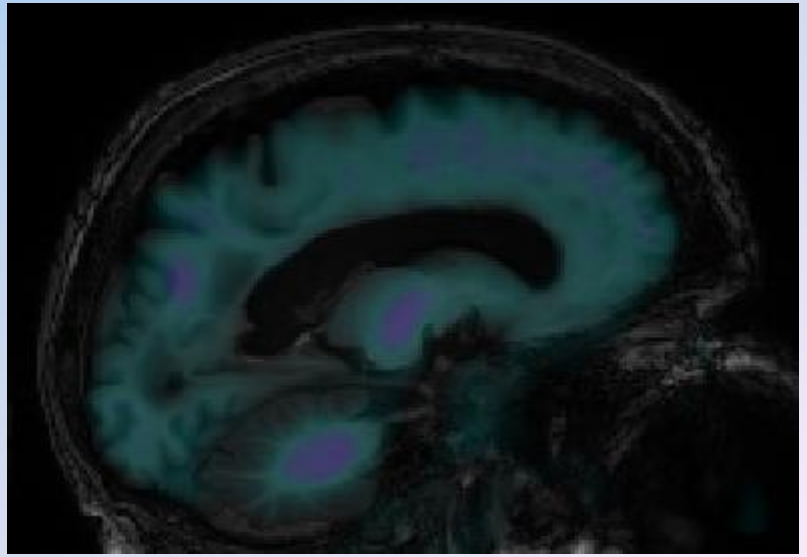


R

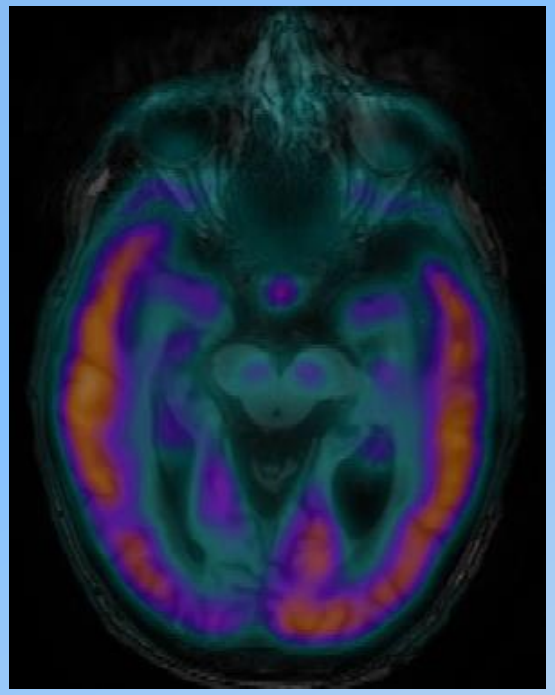
11C PIB

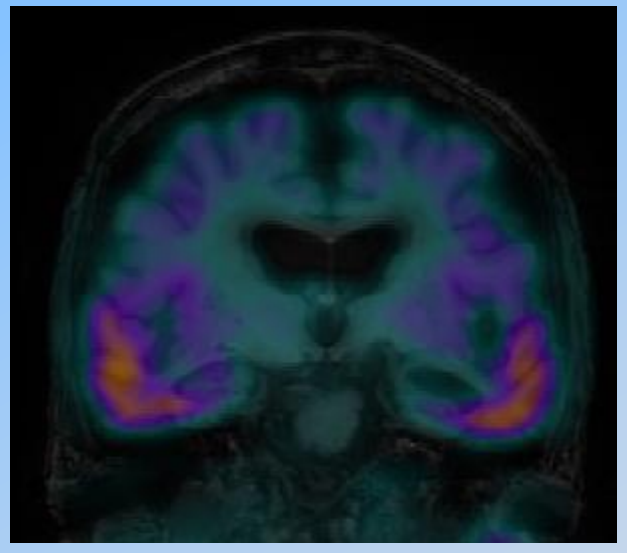


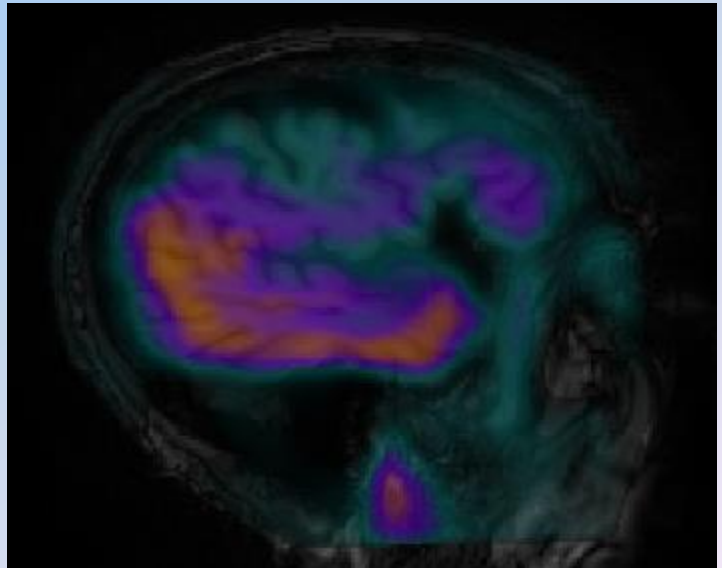




[18]F-AV1451







SYNTHESIS

- **Dx**
  - Language onset (SD) FTD and now mute 2/2 tauopathy

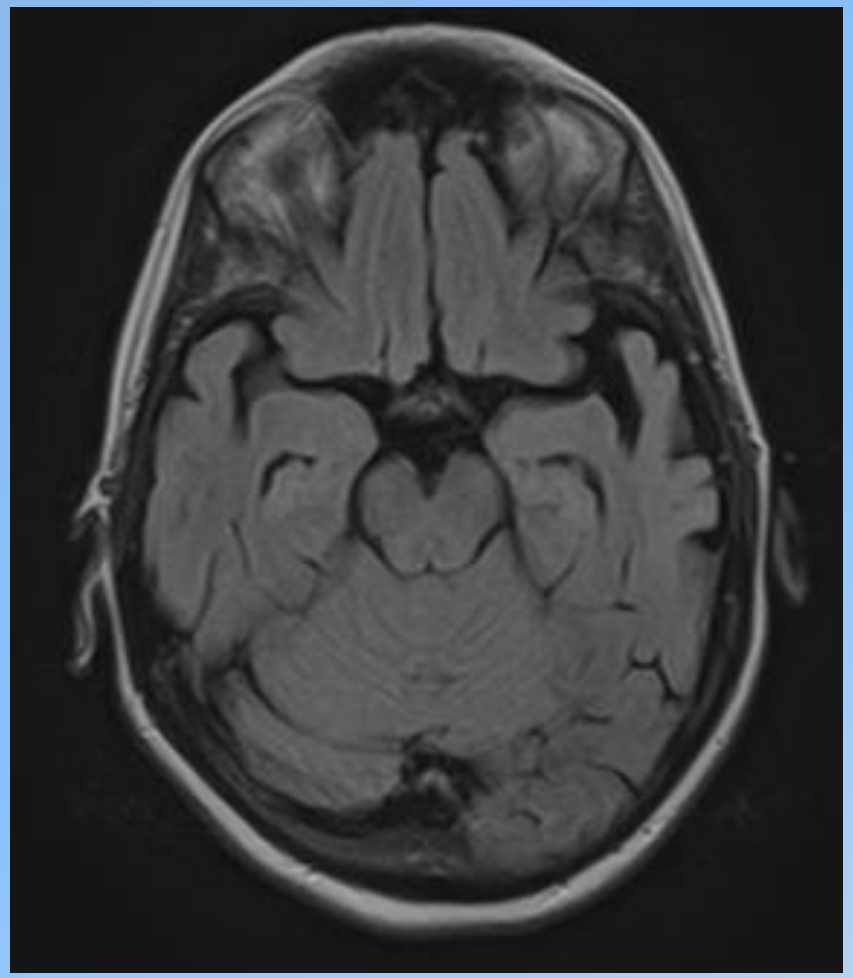
- Note
  - While experimental, we can now diagnose **tauopathies**
  - Very **focal** onset: L>R temporal lobes alone
  - **Hippocampal** and anterior temporal atrophy: might have guessed AD

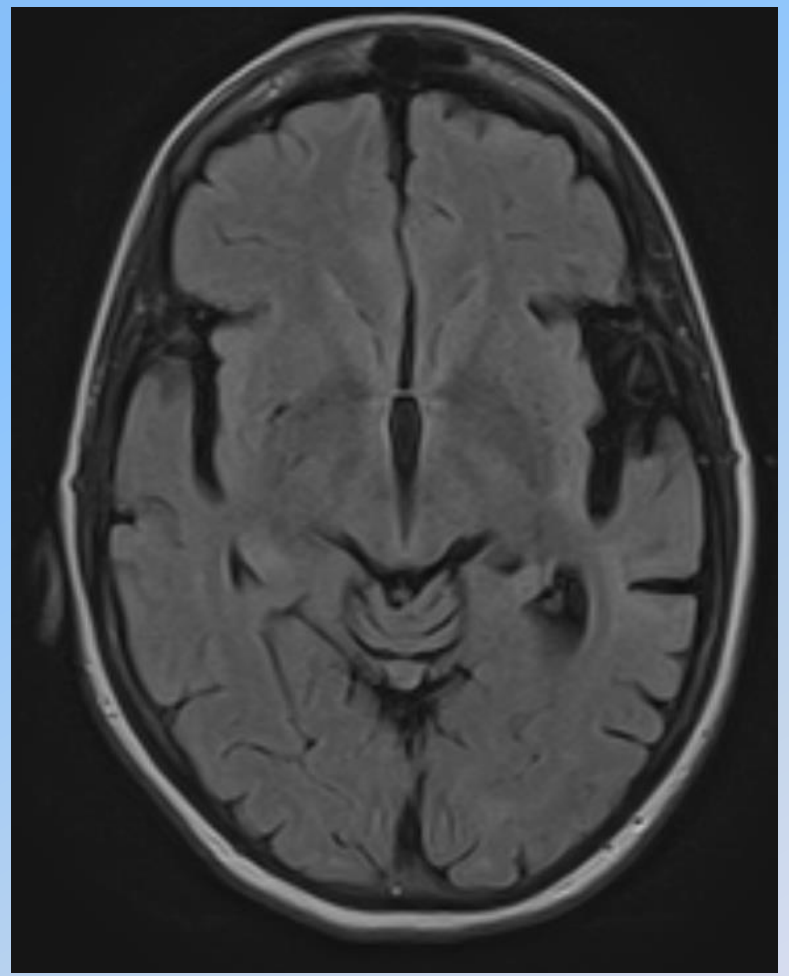
PATIENT 2:
WORD FINDING ISSUES

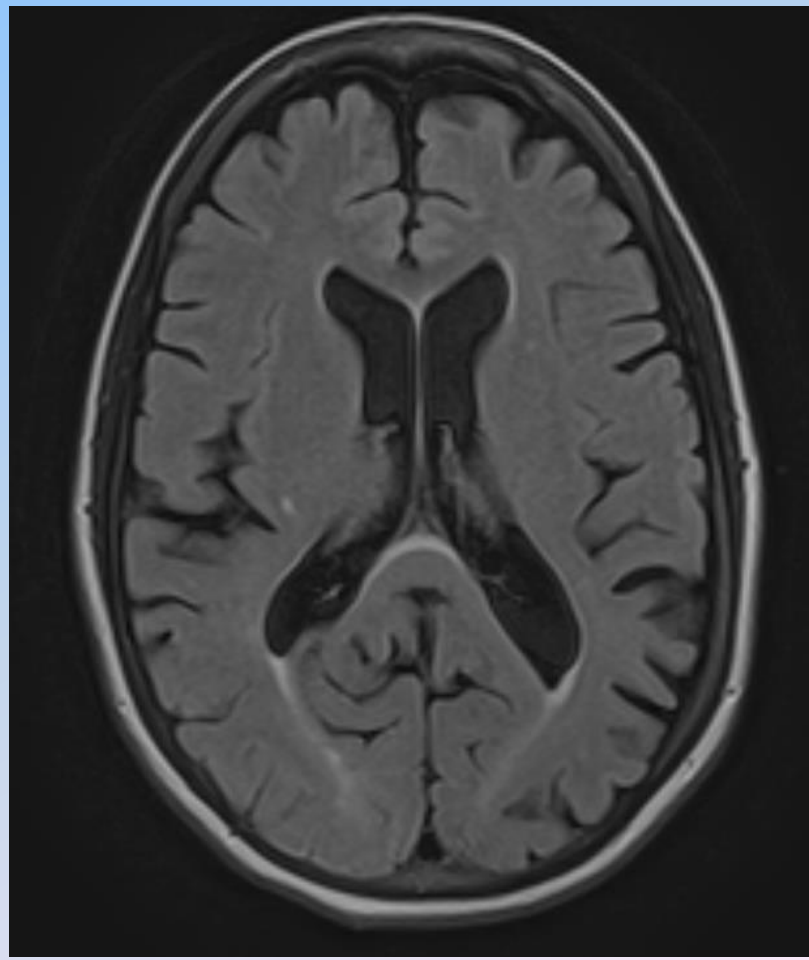
HISTORY

- 60 yo RH WF presenting w/classic language onset disorder
- Nouns and verbs predominantly
- Same semantic dementia phenotype as previous pt

MRI BRAIN

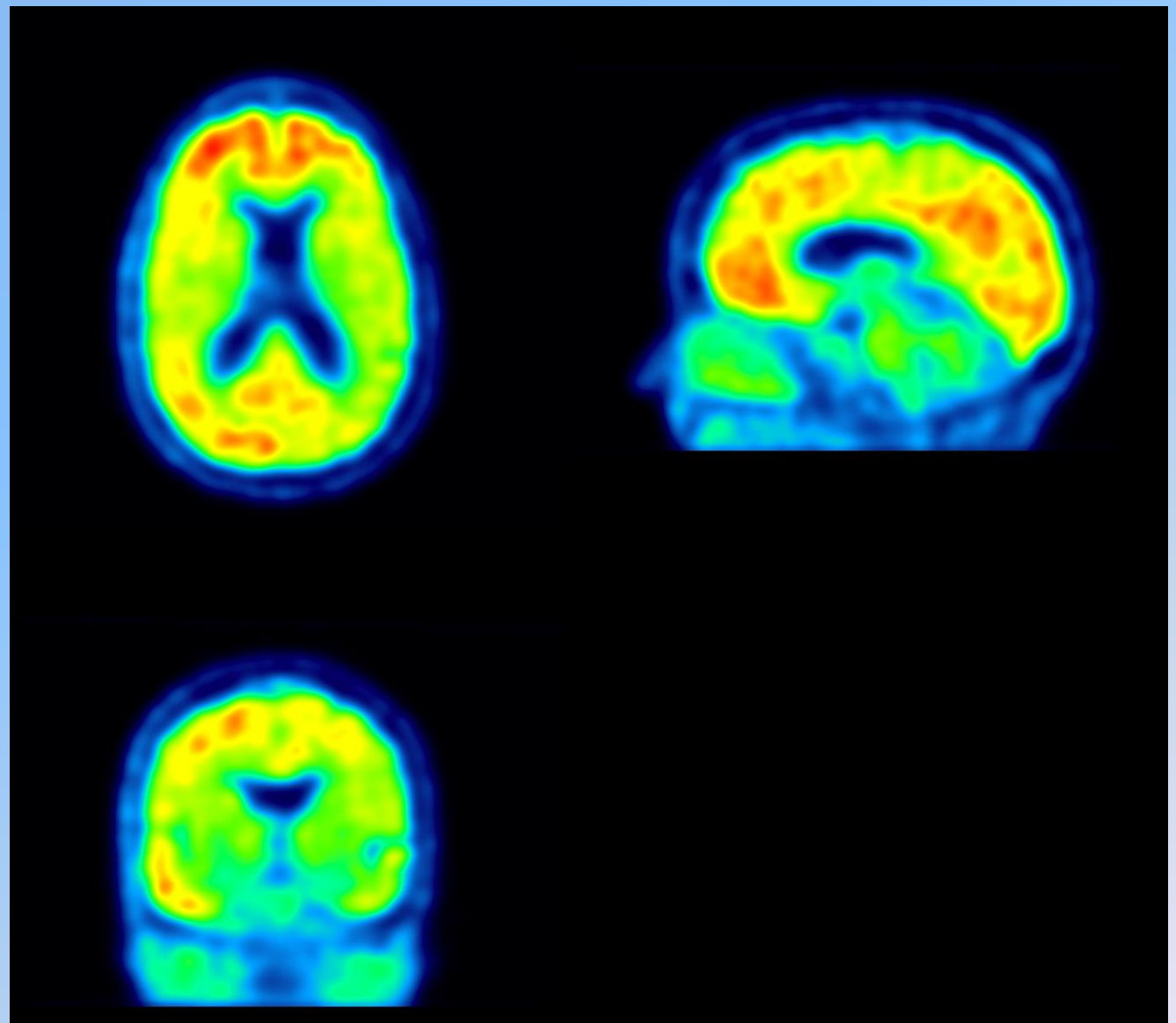






Amy Pet

AMYLOID PET IMAGING: (+)



SYNTHESIS

- **Language onset SD** can be due to
  - **FTD**, such as Tau deposition ~80%
  - **AD** 2/2 amyloid ~20%

- NOTE
  - Tau may localize where **symptoms** arise
  - Amyloid deposition is typically **unrelated** to sx location

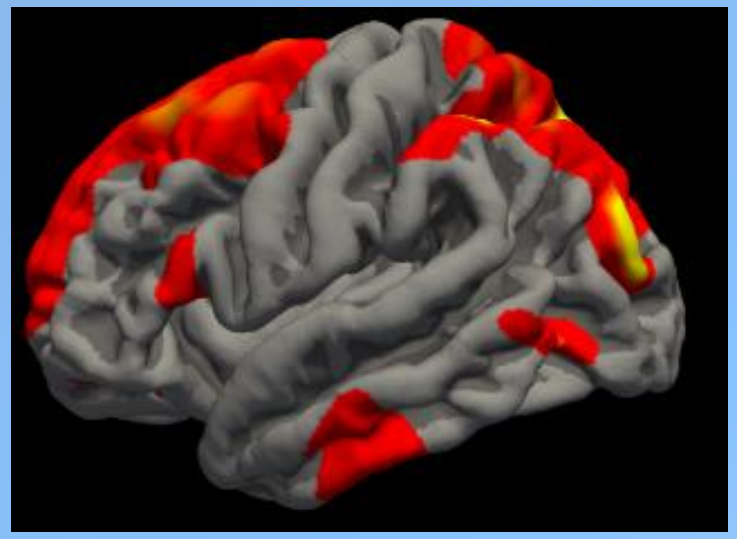
PATIENT 3:
NOT RECOGNIZING OBJECTS

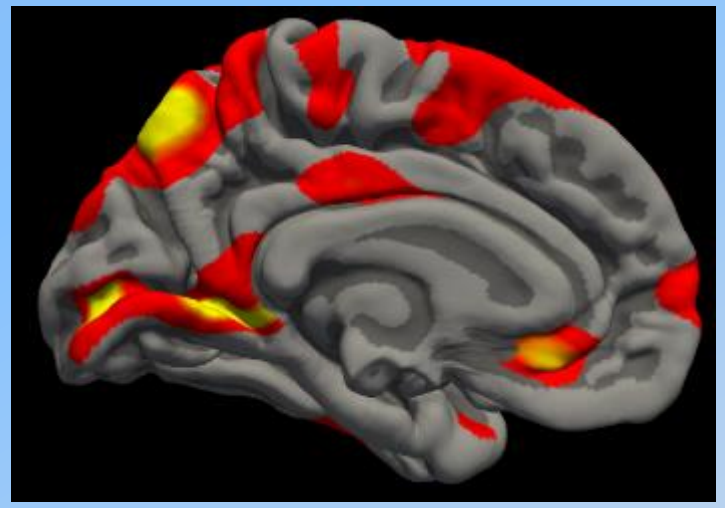
HPI

- 57 yo RH CF presenting with a c/o difficulties recognizing objects
- Milder word finding issues

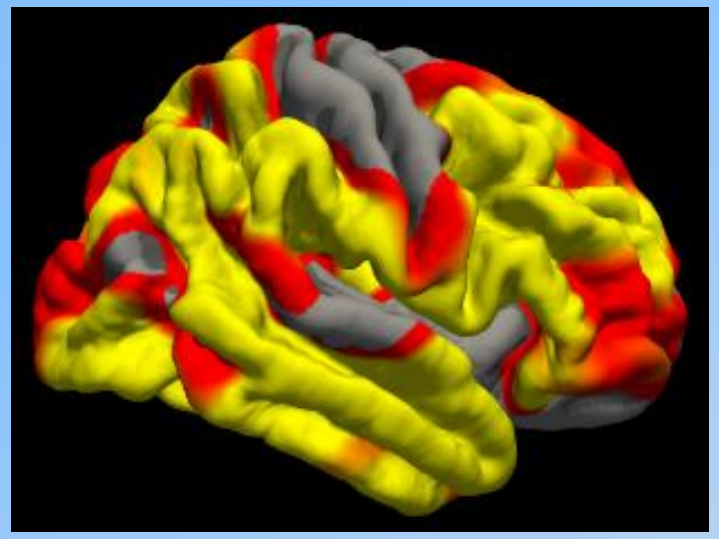
Cortical Thickness

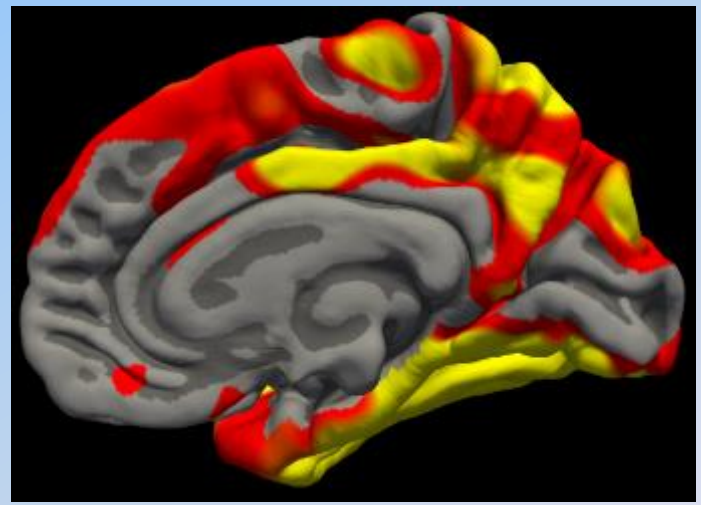
L





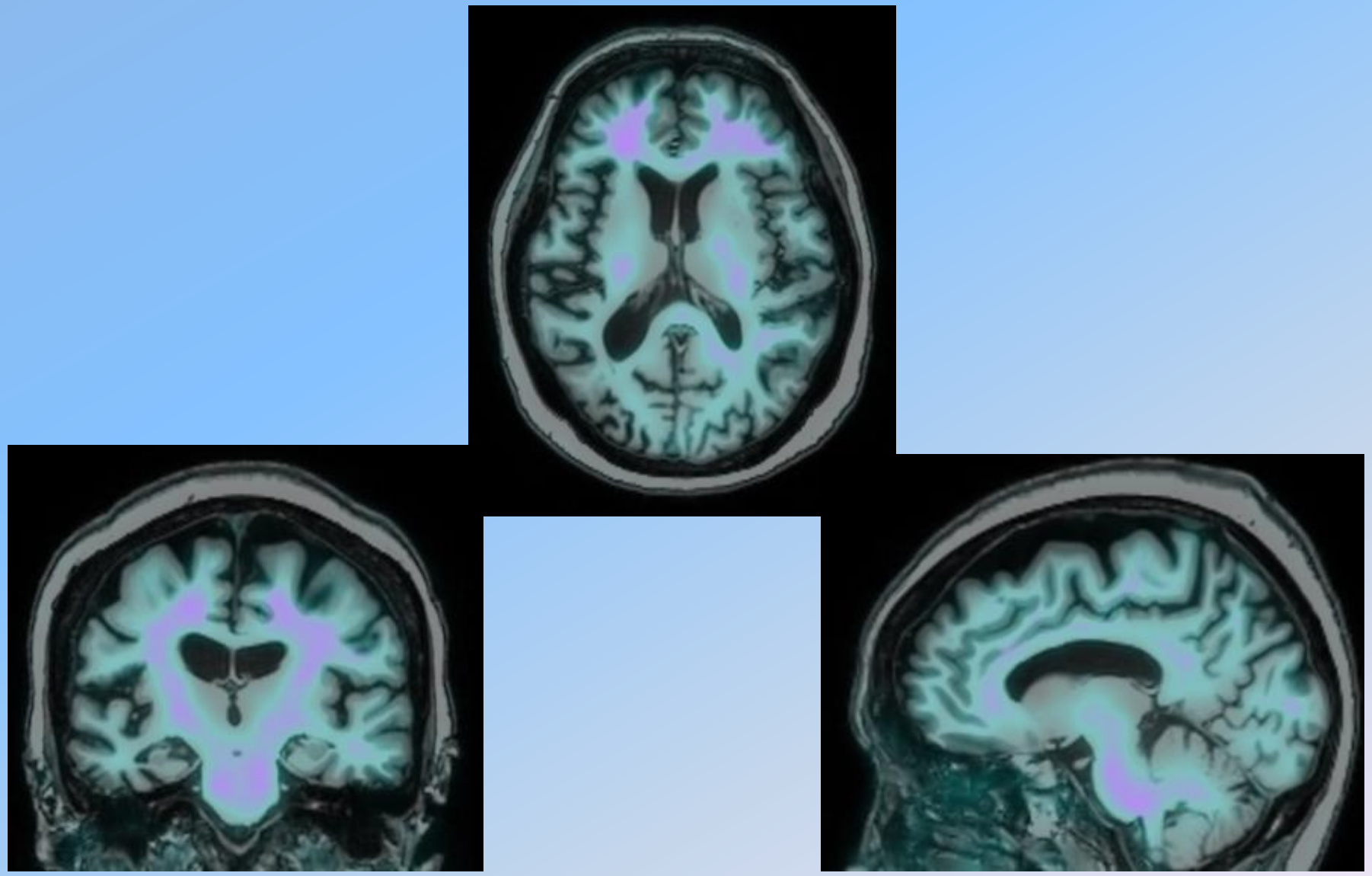
R



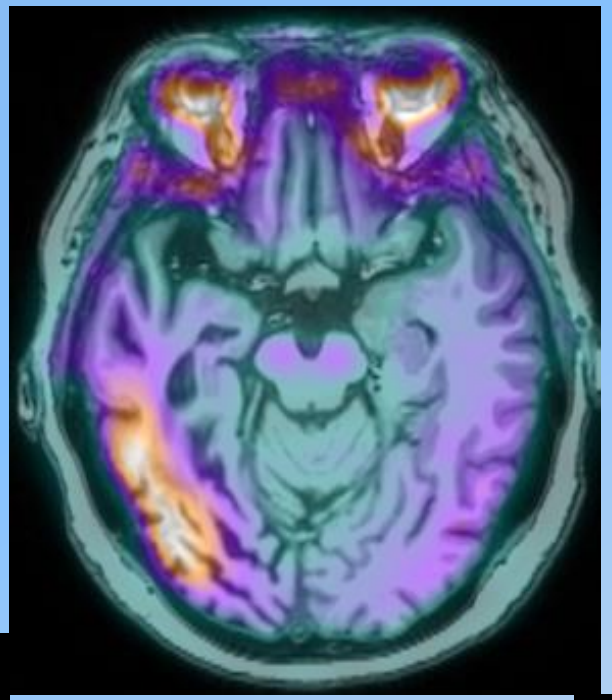


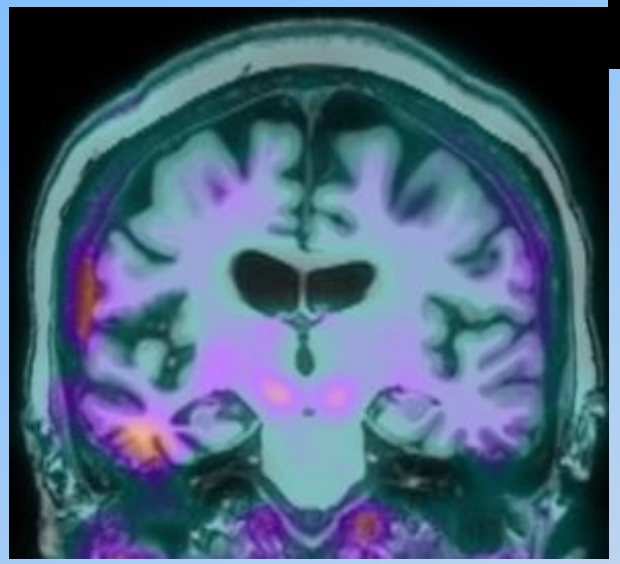
- Great asymmetry
- R>L loss
- F, P, & T

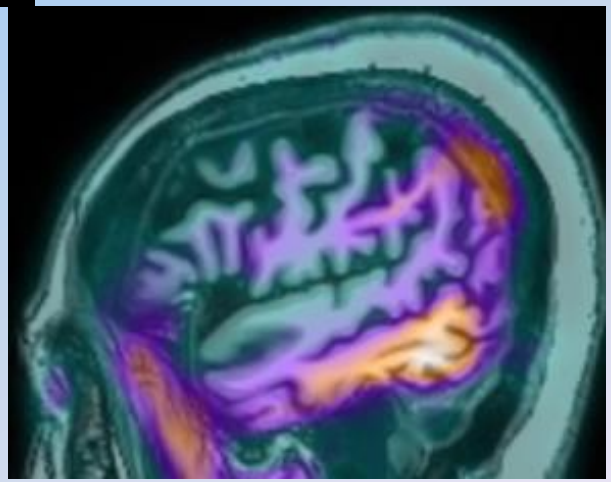
[11]C-PIB



[18]F-AV1451







Note: Tau positivity is not as extensive as the cortical thinning in this case

Contrasts w/amyloid

SUMMARY OF PATIENT

- **Dx**
  - Right temporal lobe onset tauopathy
  - RIGHT→ lack of recognizing **objects**
  - LEFT in previous cases → deficit in **naming** objects

NOTE

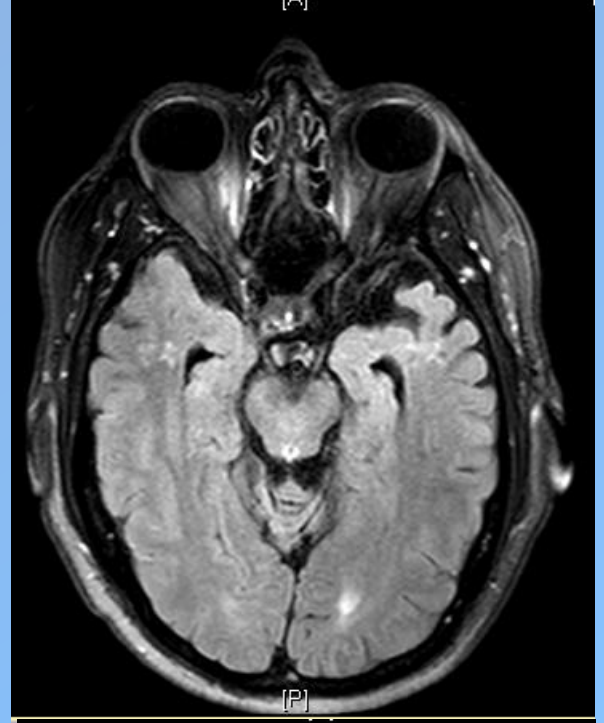
- This “FTD” includes **parietal** atrophy

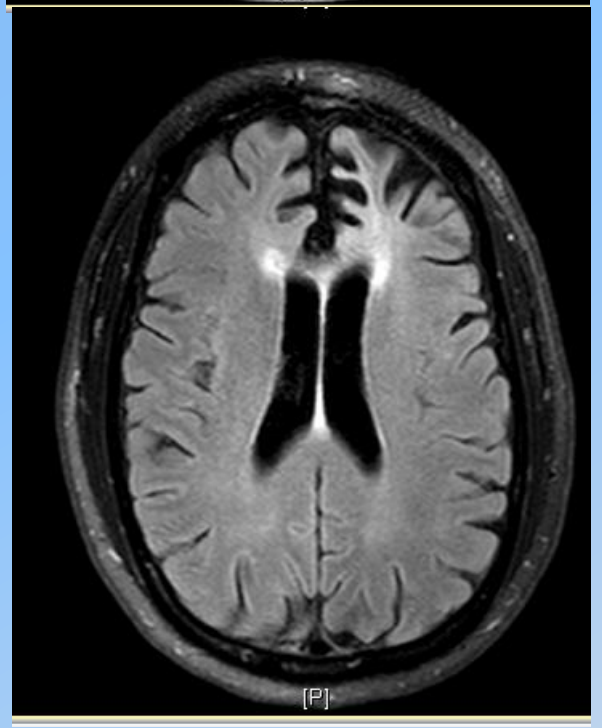
PATIENT 4:
STRAIGHT SHOOTER

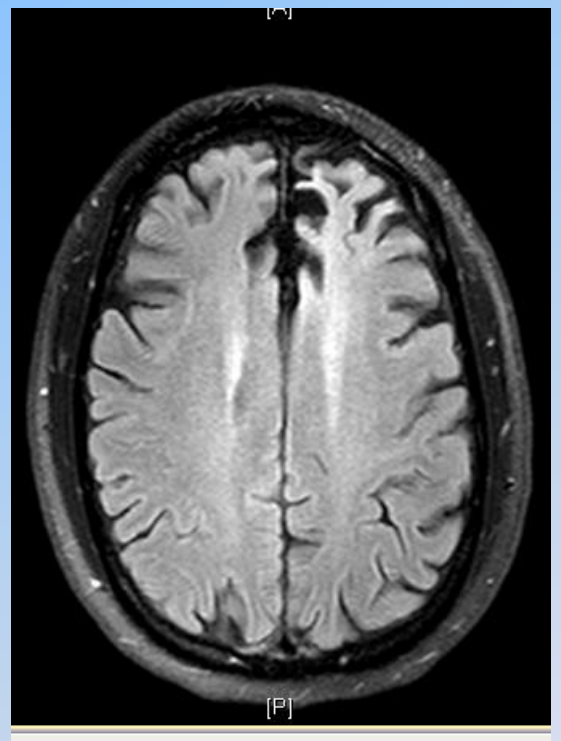
HPI

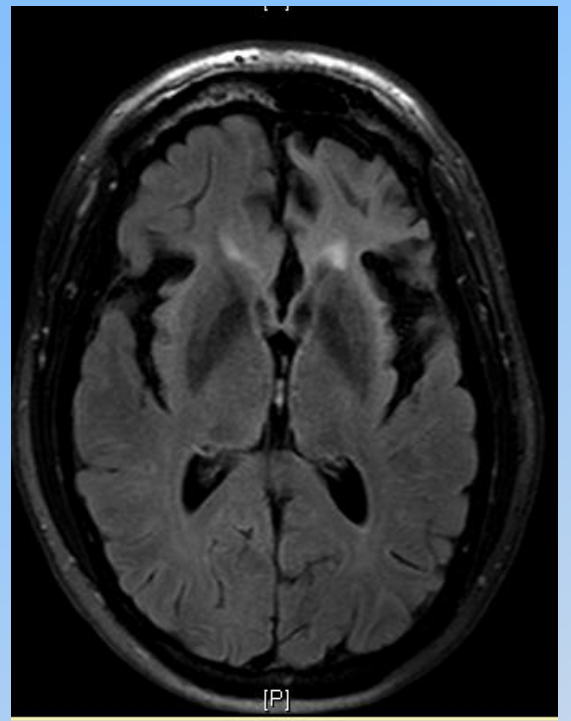
- **59 yo ophthalmologist** from another state
- Very engaging and normal seeming in conversations
- **Surgical techniques** are very good
  - Brags about doing the most surgeries of anyone in his group
- Partners asked him to be examined, and then leave his group
  - "They say I'm **too straight forward** with my patients." "I don't really see it."
  - Wife: they say he can't "**empathize** with them."
  - He's a bright guy who gives that history based on what his partners have said, but is upset since his still technically very good.

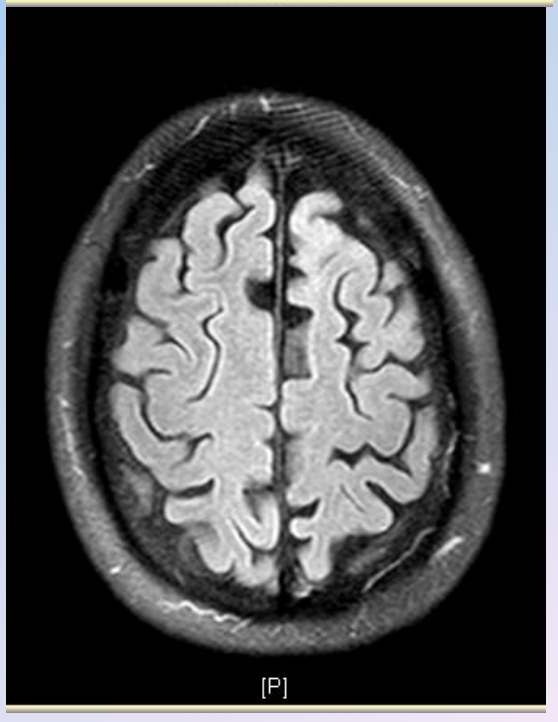
MRI BRAIN





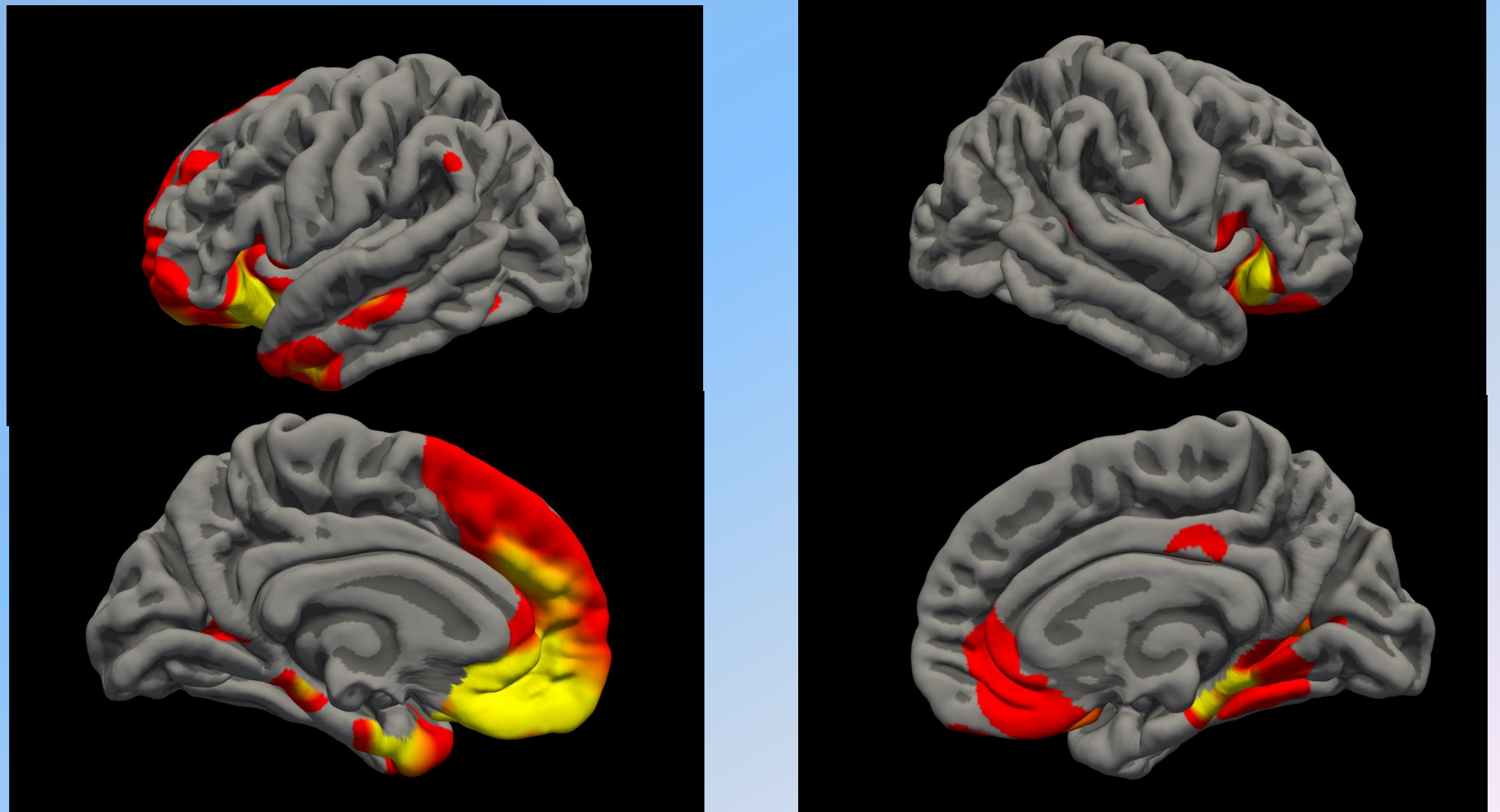






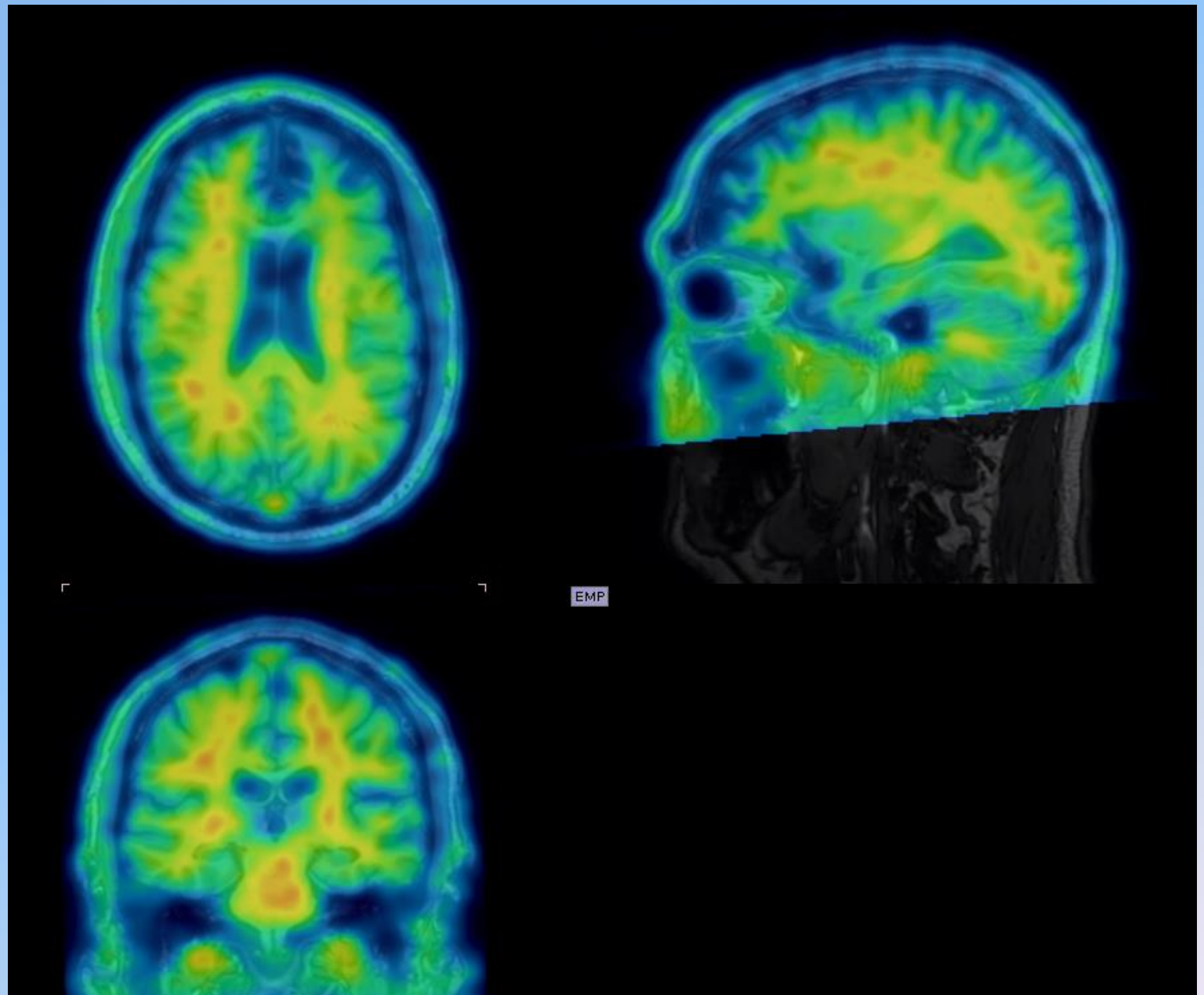
CORTICAL THICKNESS

L

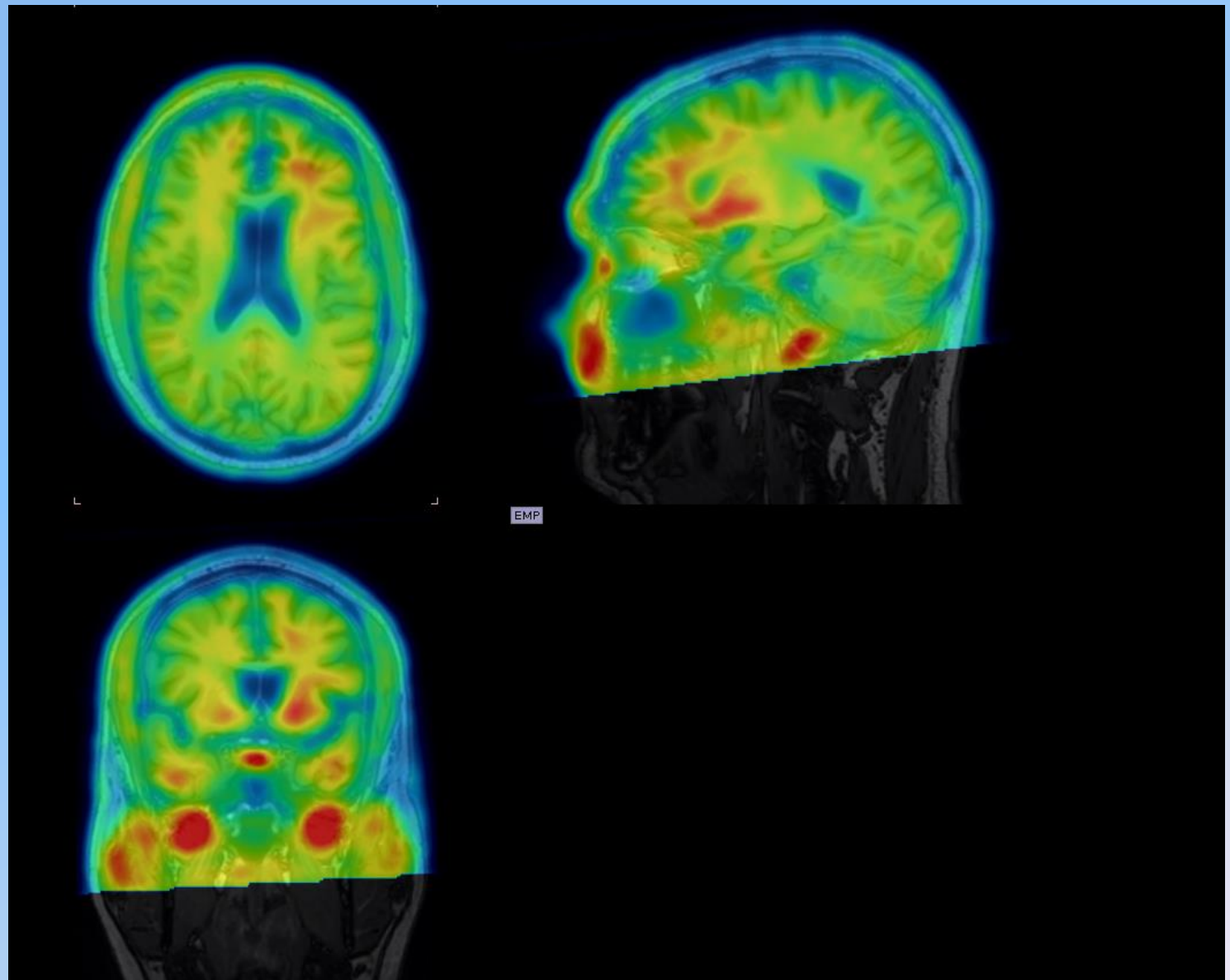


R

[11]C-PIB



[18]F-AV1451



SYNTHESIS

- **Dx**
  - Left frontal onset **bvFTD**
- Don’t usually see left frontal onset bvFTD phenotypes
  - Usually right frontal
- Asked him about his handedness when going over the films
  - Left handed

PATIENT 5:
CHANGES MEMORY, WORD FINDING, & IN DEXTERITY

HPI

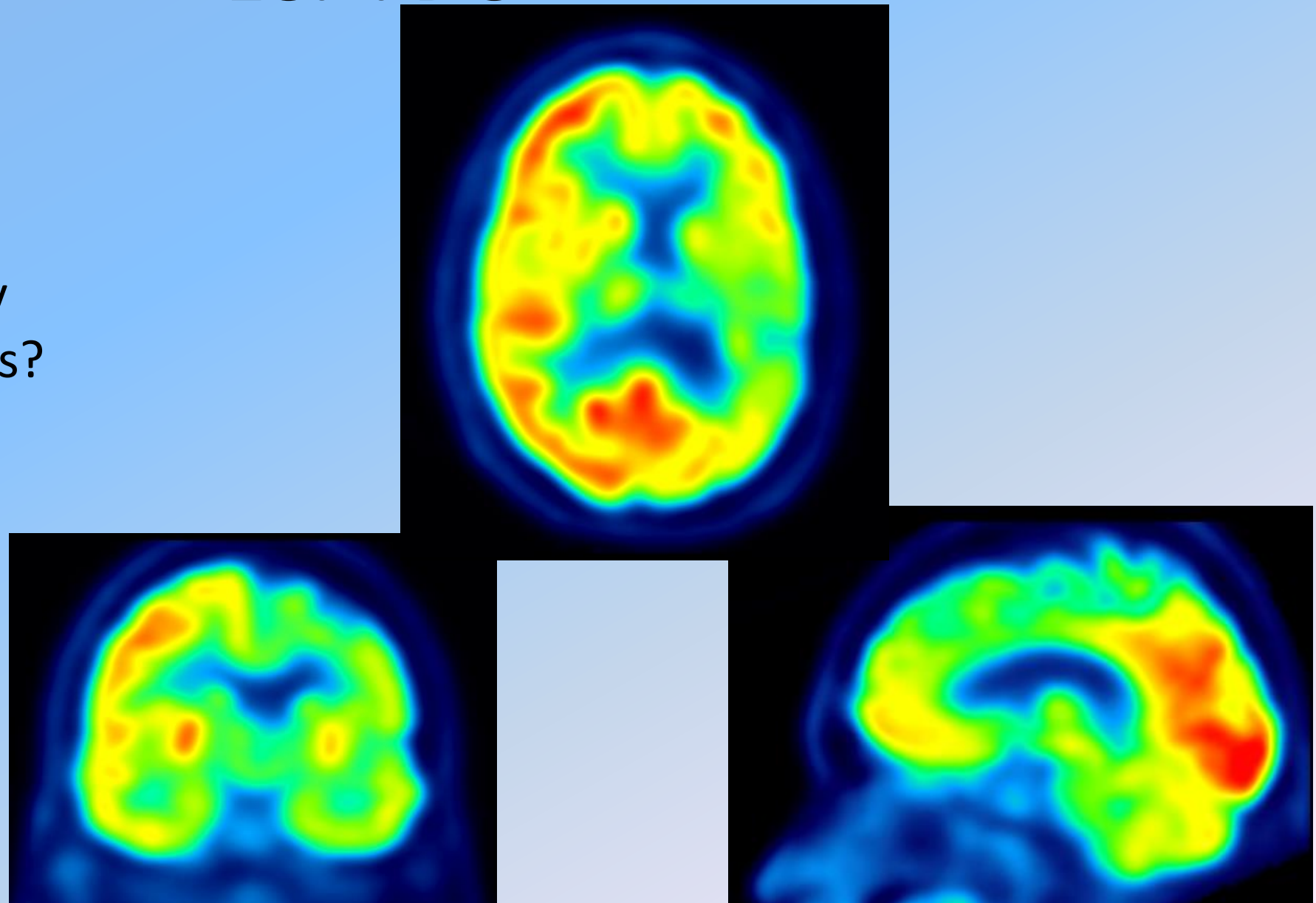
- 56 yo RH WM anesthesiologist from another state
- Changes in **memory** and **word finding** starting 2 yrs ago
- **Gait changes**: trouble w/balance & weakness in his RLE x 2 yrs
- Friends noticed he **leans** to the side
- **Dexterity** issues w/tying back of mask or buttoning up shirt
- **Signature** has changed; R hand displays the most dexterity change

HPI

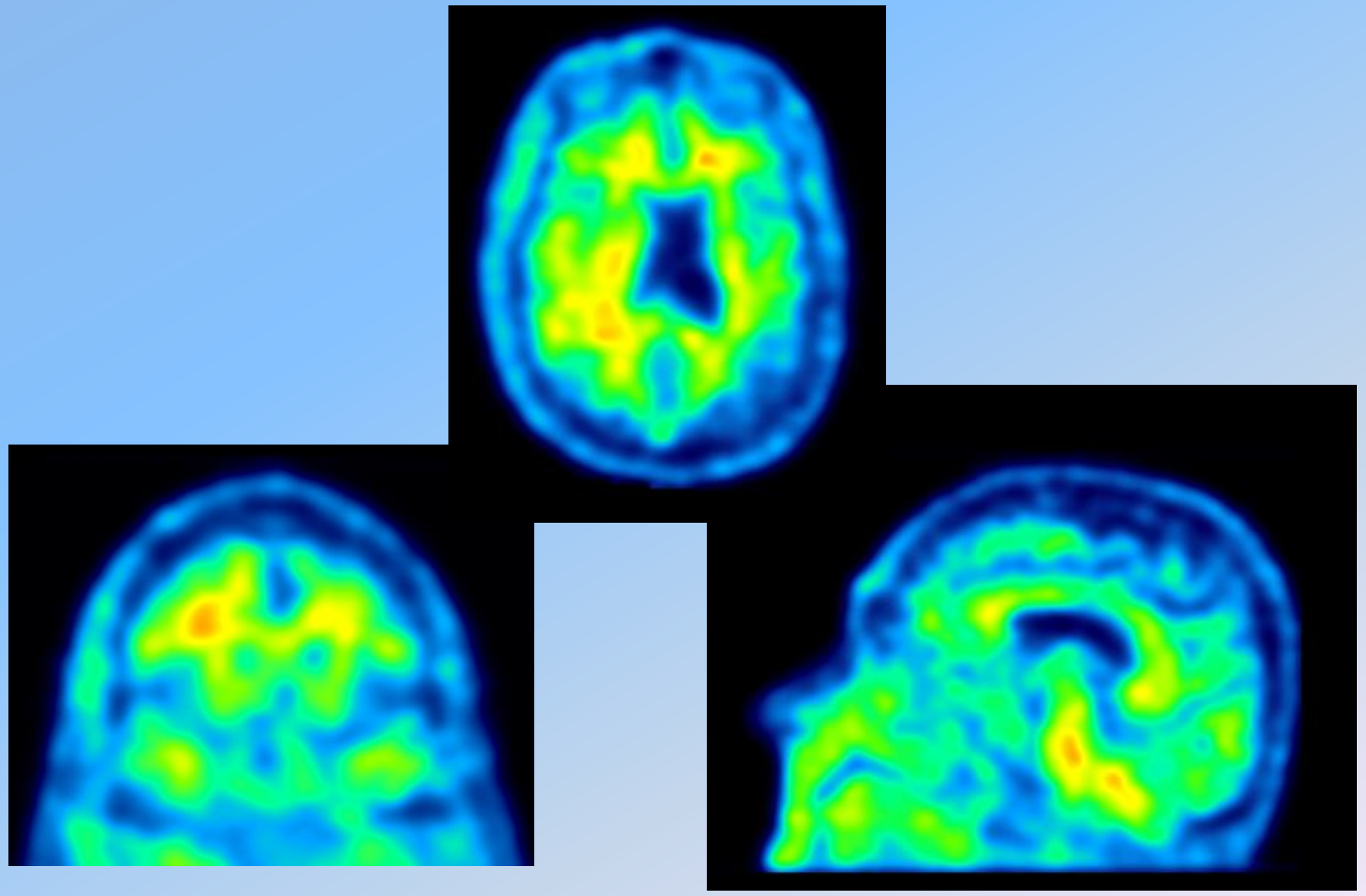
- May mispronounce words; e.g., "fatoug" instead of fatigue
- Switches words and number; e.g., he may say 68 as 86
- Takes pauses before starting a sentence
- Wife noted slowed speech
- Mood: wife mentioned some recent changes, but not significantly

18F FDG

- Profound asymmetry
  - What pathology accounts for this?

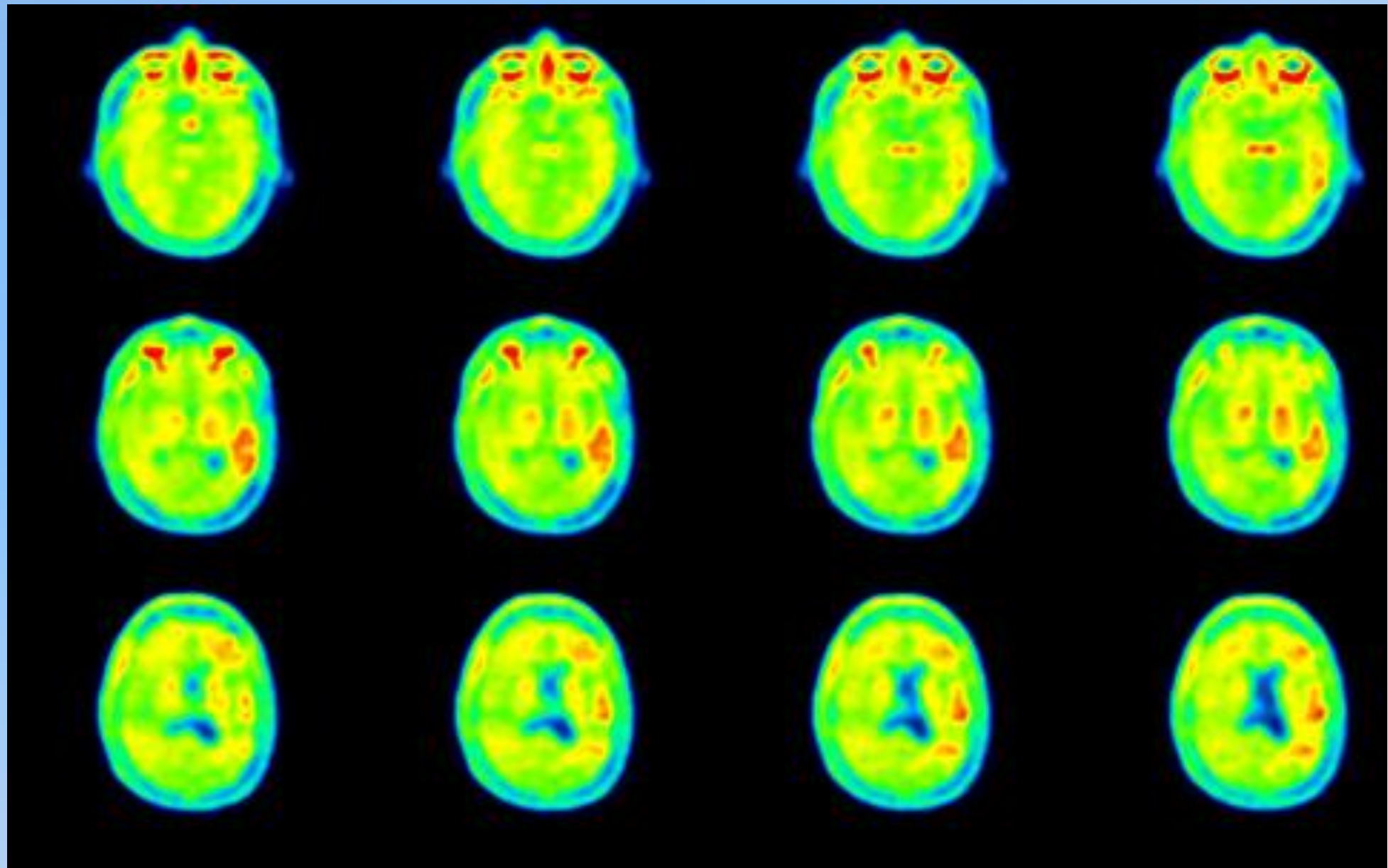


[11]C-PIB (-)



[18]F-AV1451

- Left temporal > frontal tau positivity



CSF

- A-beta 42: **960** pg/ml
- T-Tau: **392.45** pg/ml
- P-Tau: 62.3 pg/ml
- ATI: **1.37** (Abeta over tau levels times 1.7 plus a constant).
- Not cw AD
  - Our interpretation: cw FTD in having markedly elevated tau levels. The amyloid levels are also high, but that does not have disease implications and is normal

CONCLUSIONS FROM THIS PATIENT

- 56 yo w/changes in **memory** and **word finding x** 2 yrs
- **Gait & balance changes**
- **R hand dexterity** issues
- Imaging and CSF point to **tau** based disorder
- **NOTE**
  - F, P, T involvement
    - **What tauopathy includes P lobes** with F & T?
  - **Early dexterity & motor changes w/Tau pathology**

PATIENT 6:
CHANGES IN PRAXIS, WORD FINDING, & GAIT

cbd

HPI

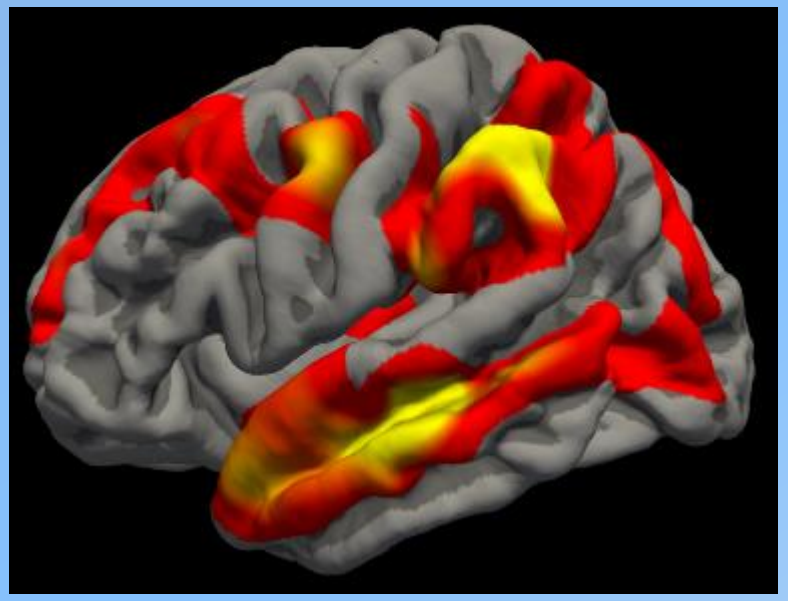
- 64 yo RH WF c/o not performing her job as an accountant
  - Retired 2013
- 2014: Stopped driving b/o condition, but always had problems w/directions
- 2017: new difficulty with word finding
- Frustration at being unable to complete tasks
- Husband cooking more often x 2 yrs
  - Trouble following recipes and reading in general. She states she is unable to read like before

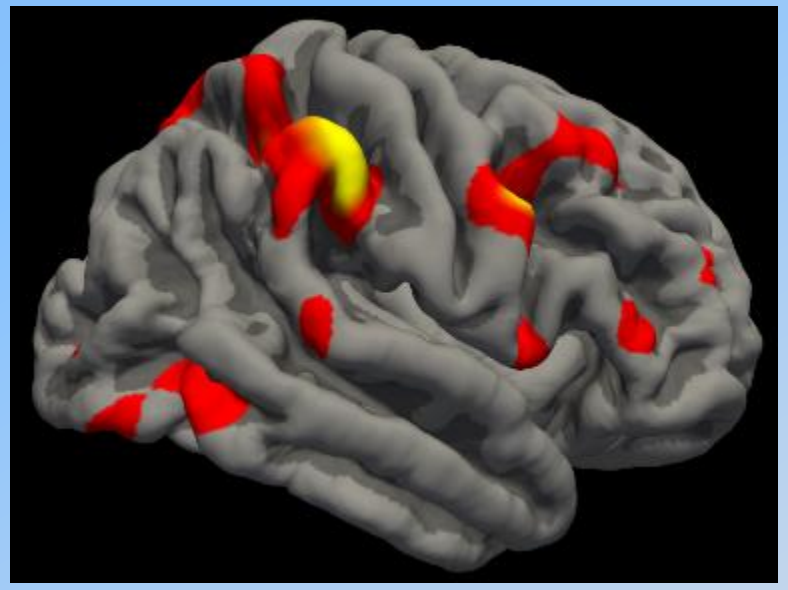
HPI

- Gait **speed** has decreased, **shuffling**
- Hand-shake: trouble **finding** my hand
  - Praxis issues?
  - Right sided neglect?
- Husband: unable to complete a **sequence of steps**, she will be able to start the sequence but needs reminders to complete them

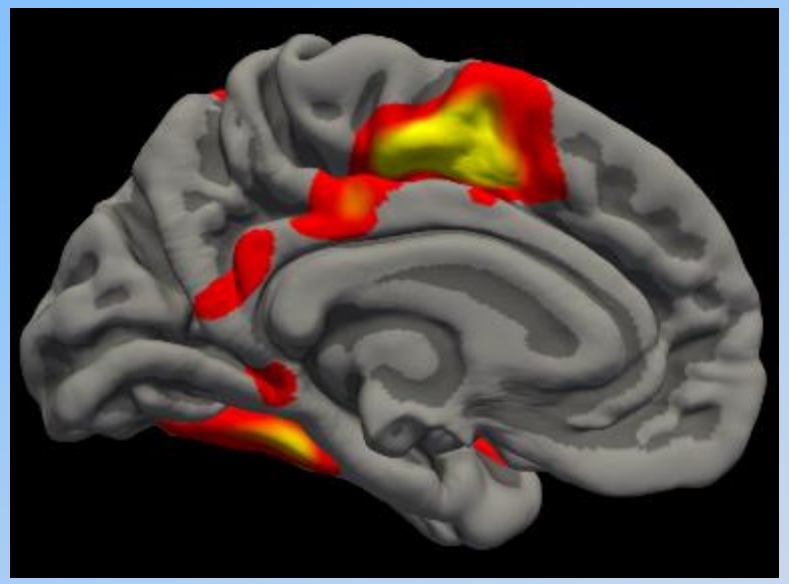
Cortical Thickness

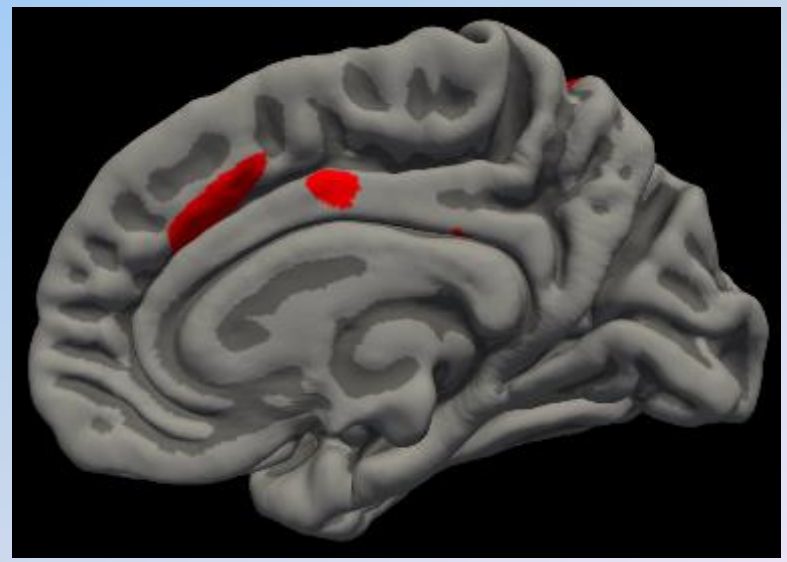
L





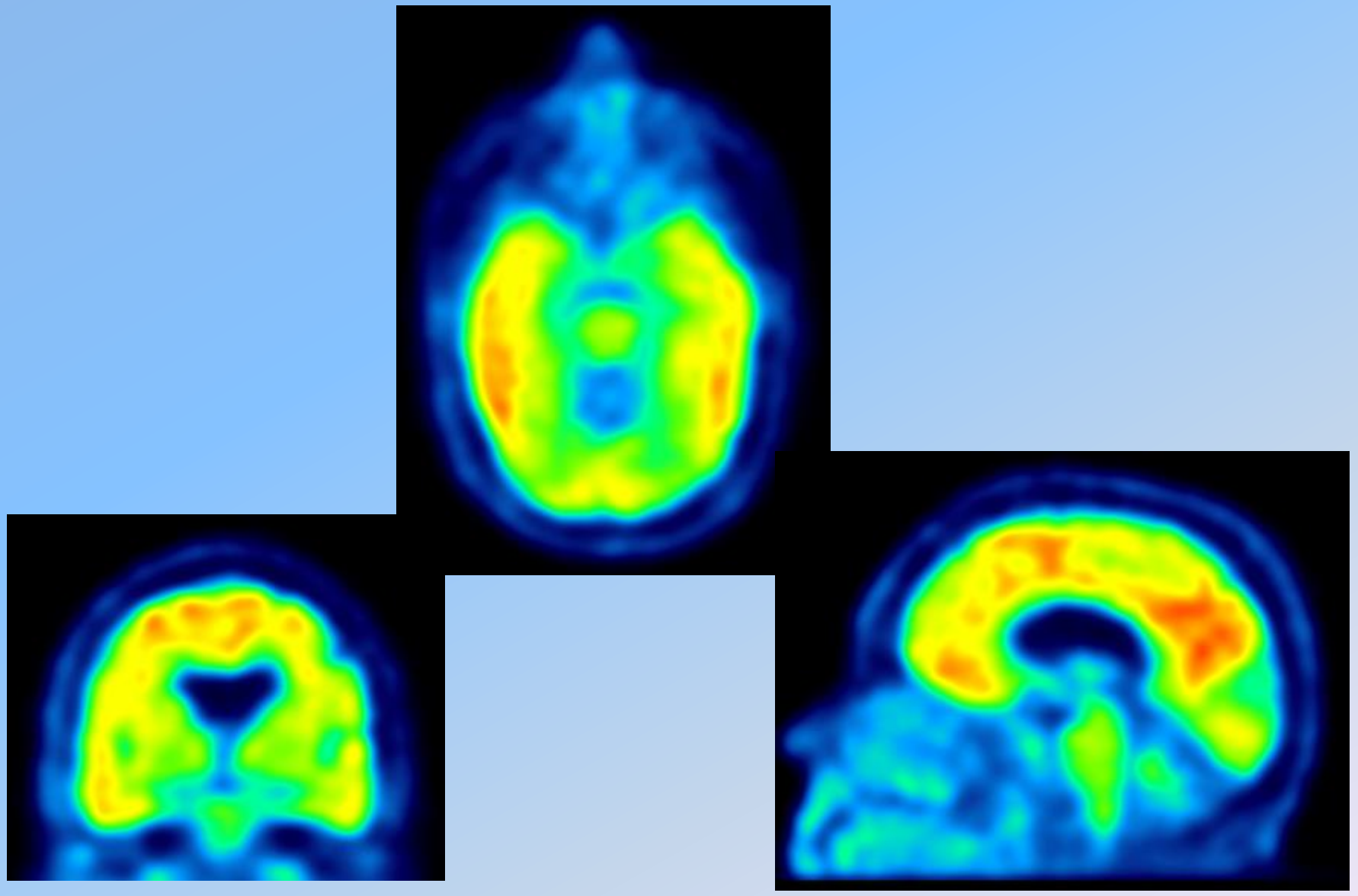
R





FTD Appearance

[11]C-PIB (+)



SYNTHESIS

- SYMPTOMS
  - Apraxia, R neglect?, Word finding challenges; PCA-like
  - Reduced gait speed
- FINDINGS
  - Very asymmetric atrophy
  - Amyloid (+)
- UNUSUAL for AD
  - So asymmetric, affecting gait so early, and affecting F, P, & T lobes

PATIENT 7:
PROBLEMS RECOGNIZING FACES

HPI

- 69 yo RH WM c/o onset 2015
- **PROSOPAGNOSIA**
  - c/o lack of **recognition of faces**
  - Rx'd w/cataract removal but no chg vision
  - Difficulties tying his shoe/tie
  - **L VF change** OU
  - ANATOMY: temporal (faces) & right parietal (left neglect)

HPI

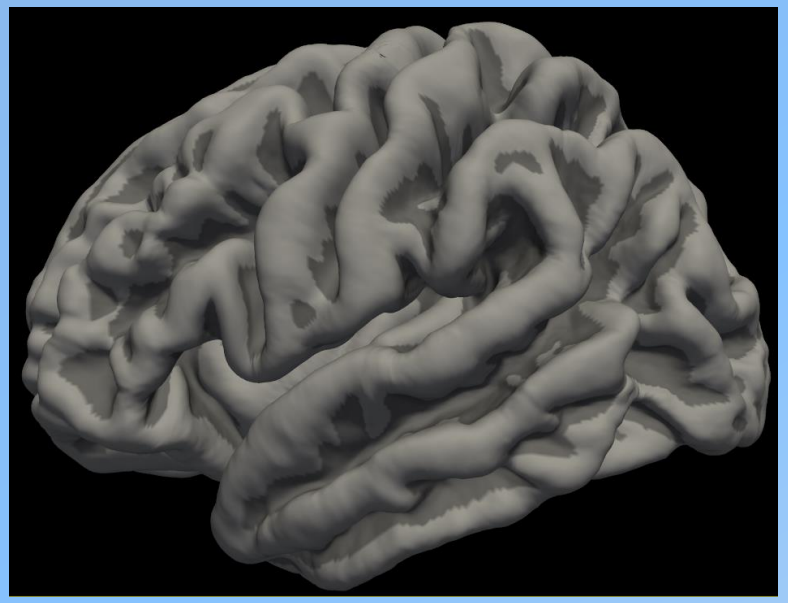
- **LANGUAGE**
  - **Substitutes words**
  - Was eating eggs for breakfast → “crepe”
  - Difficulty finding desired words
  - Understands others
  - Difficulty writing
  - Difficulty reading
  - ANATOMY: left temporal

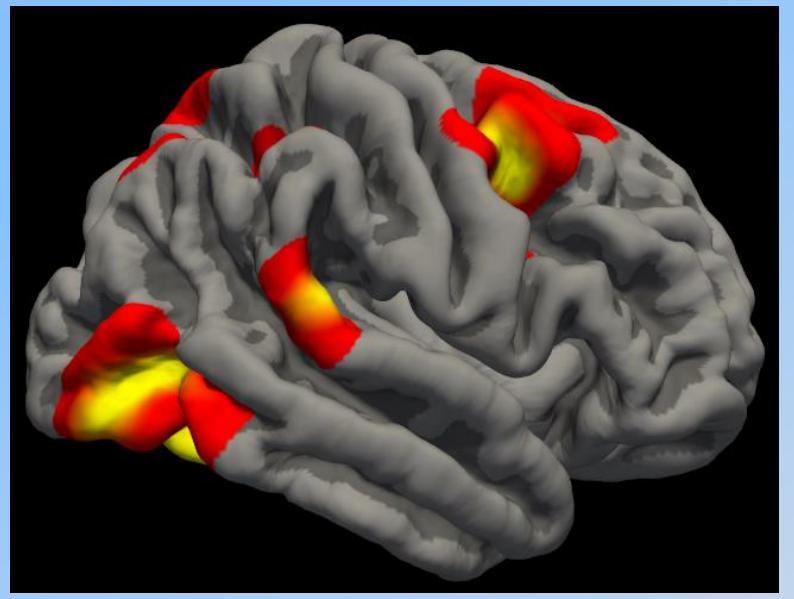
HPI

- **MOOD**
  - Less engaged
  - More timid; less confident
- **ADLs**
  - Not driving b/o visual loss

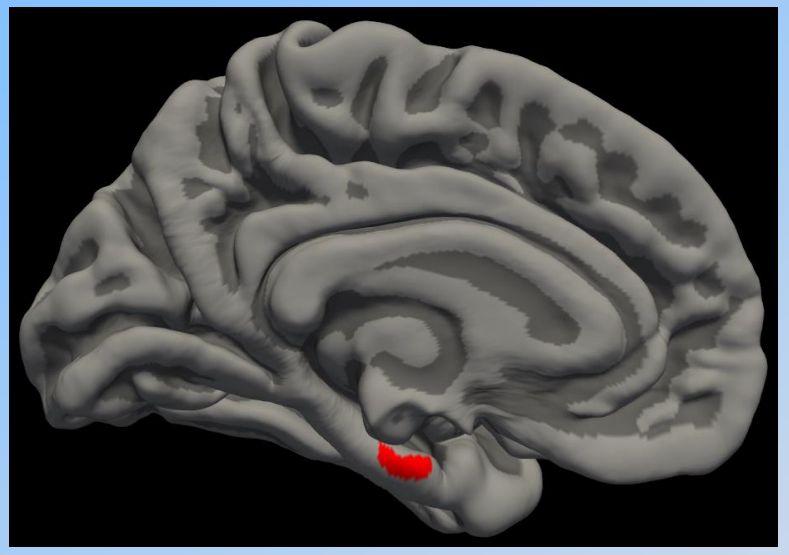
Cortical Thickness

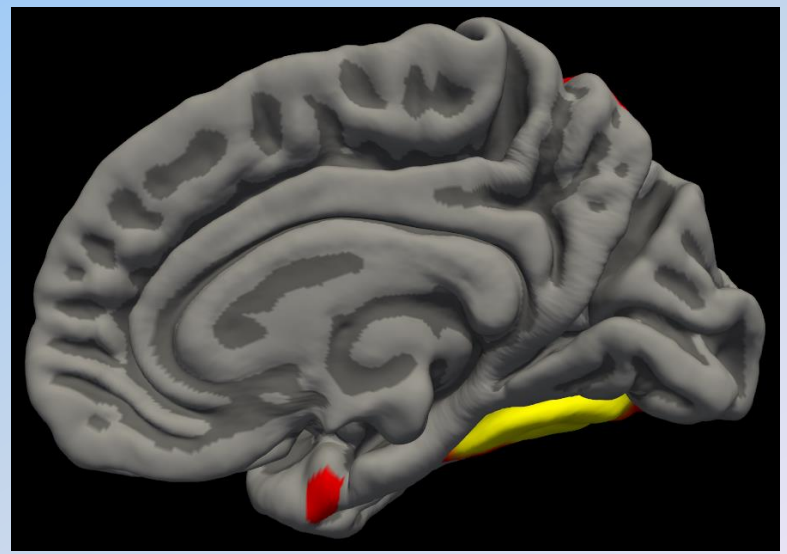
L



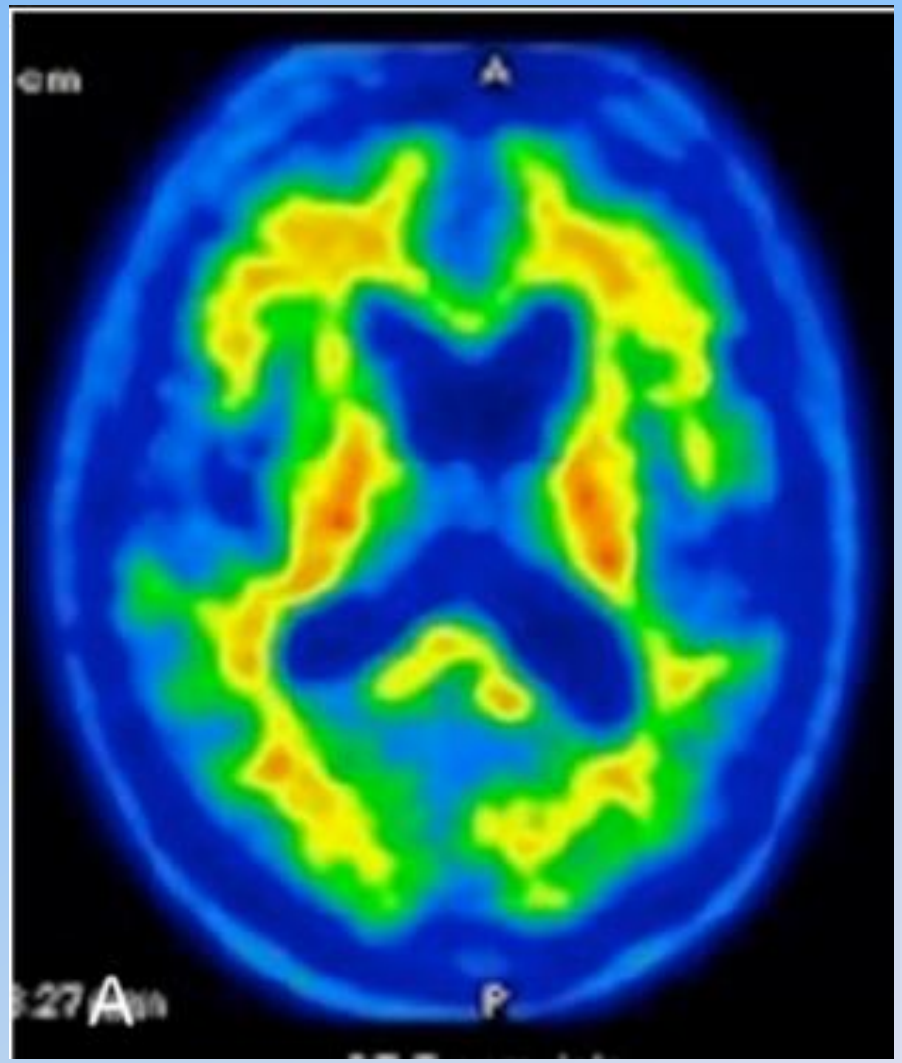


R

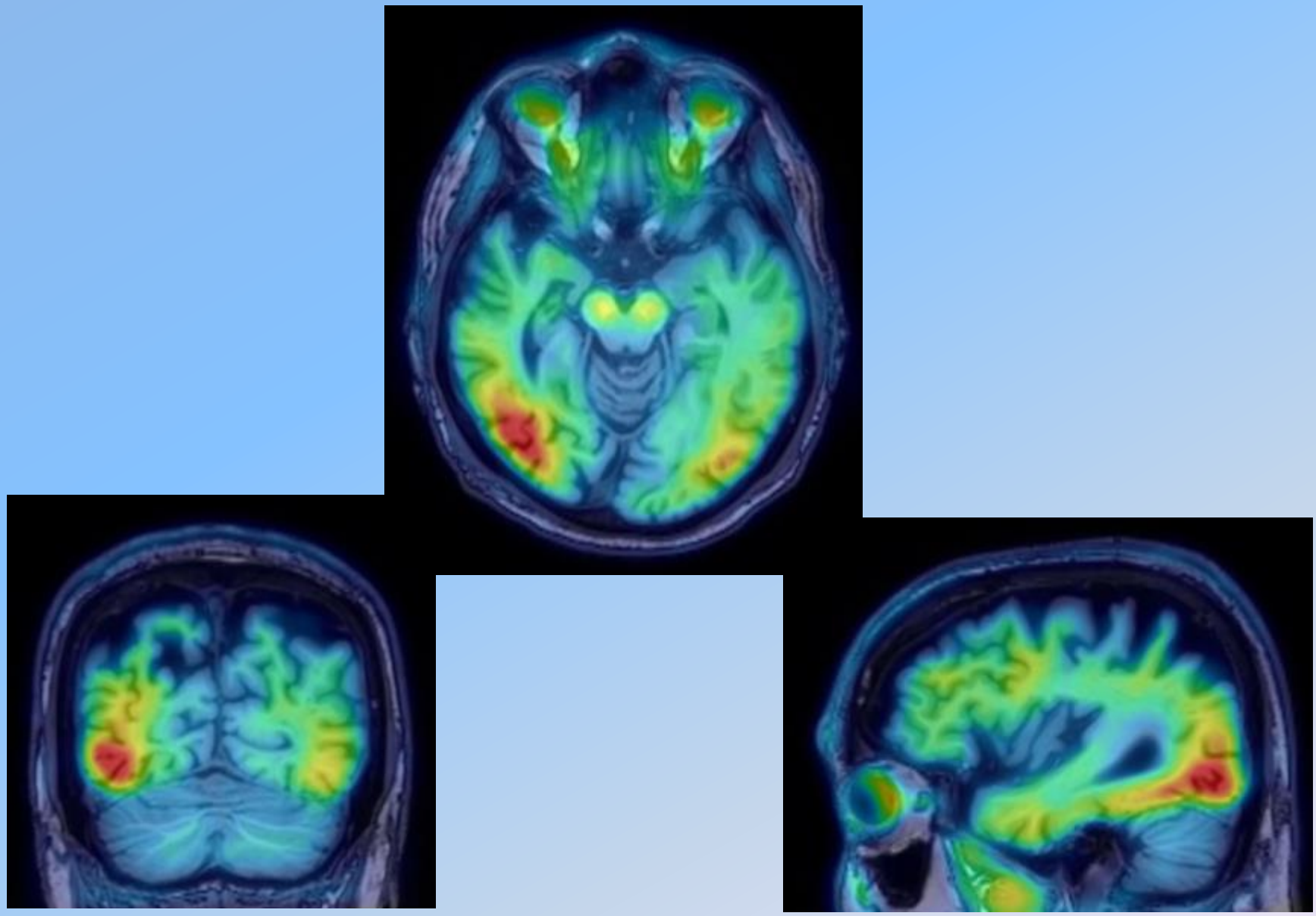




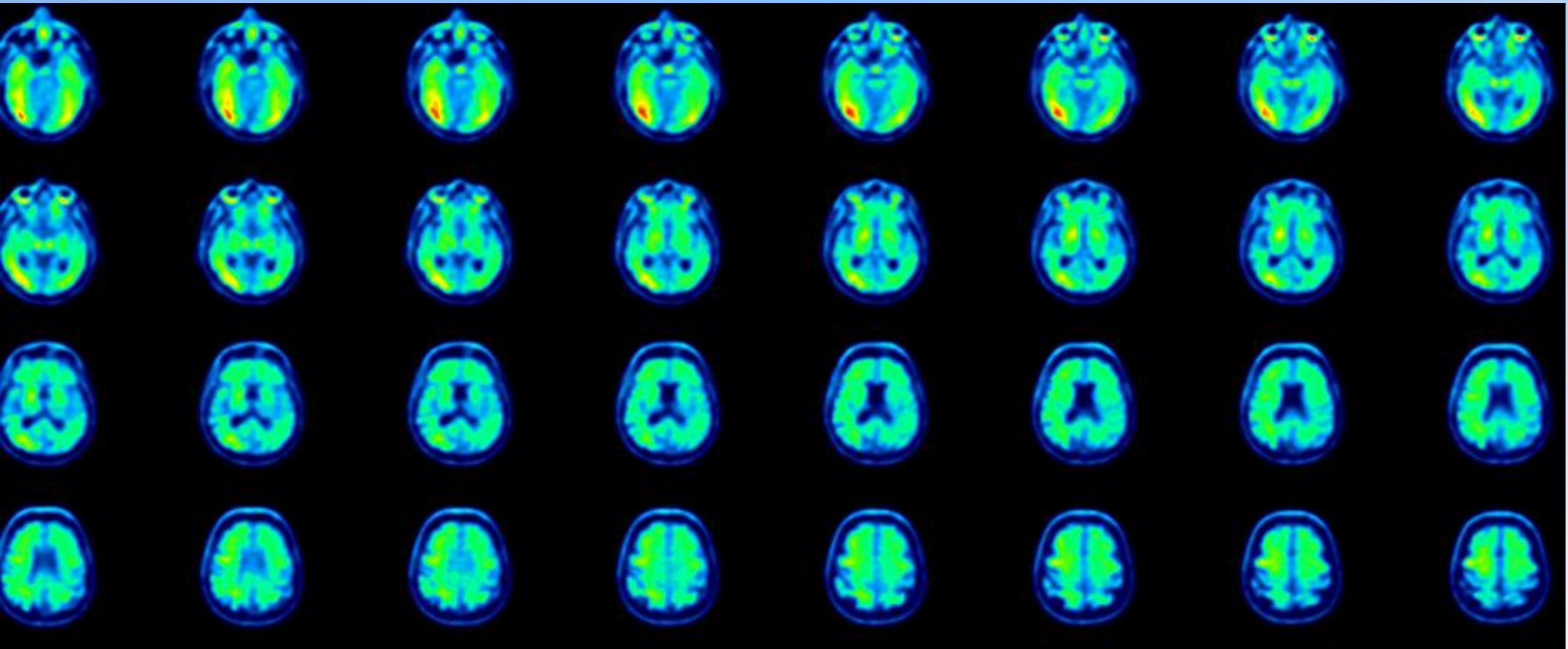
AMYLOID PET IMAGING



18F AV1451: FLORTAUCIPIR



R T-O & maybe R P



DX

- **Prosopagnosia** due to a **tauopathy**

- **Not PCA** variant of AD: Amyloid PET (-)
- **Not CBD**: not R P, and no neglect or alien hand
- **No such flavor** as prosopagnosia 2/2 tau
  - Also, **P & F changes clinically** do **not correlate** w/Tau deposition
  - Discovering new patterns of tau deposition as we image more!!
  - Would not have guessed tauopathy if it weren't for new imaging

TAUOPATHY STUDY

MASDEU, SCHULZ, et al

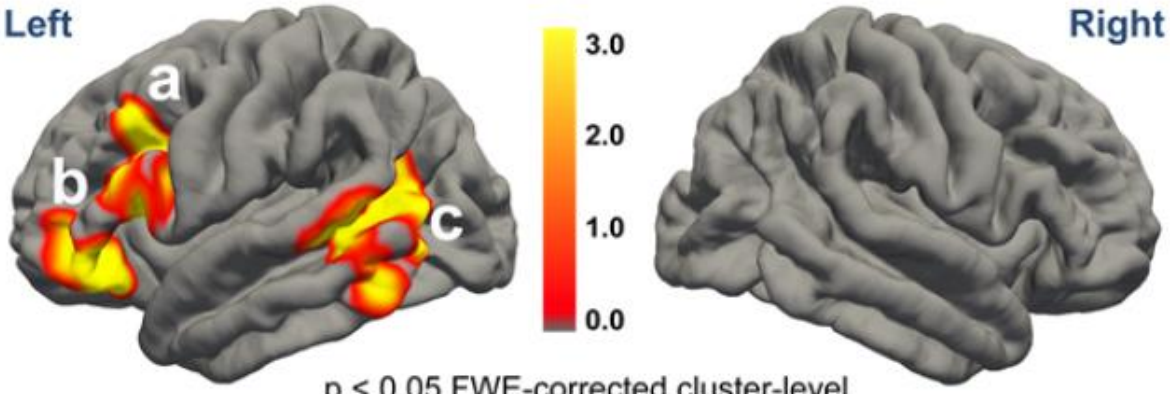
nfPPA PATIENTS

C

[^{18}F]AV-1451 uptake in nfvPPA

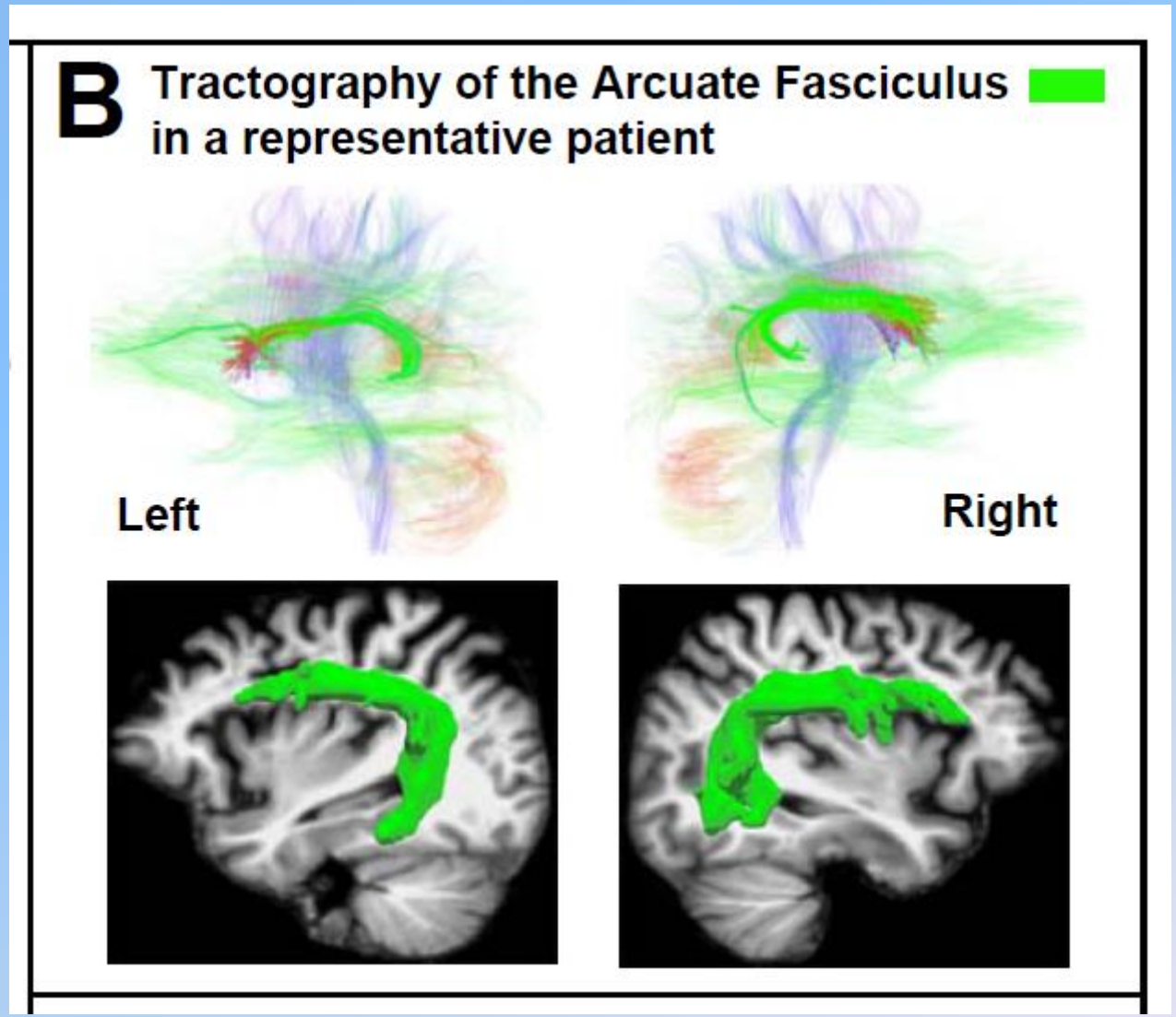
Tau PET on fsaverage surface

nfvPPA < Healthy Controls



p < 0.05 FWE-corrected cluster-level

	cluster-level			MNI coordinates		
	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E			
(a)	0.003	0.007	456	- 48	16	12
(b)	0.047	0.070	245	- 48	32	- 8
(c)	0.000	0.001	690	- 56	- 44	12


B
Tractography of the Arcuate Fasciculus
in a representative patient
Left
Right

SUMMARY OF CASES THUS FAR

- LEFT TEMPORAL
  - Pt 1. SD 2/2 tauopathy
  - Pt 2. SD 2/2 AD
- RIGHT TEMPORAL
  - Pt 3. Not recognizing objects: right temporal tauopathy
- LEFT FRONTAL
  - Pt 4. Straight shooter; bvFTD 2/2 tauopathy
- LEFT TEMPORAL> FRONTAL
  - Pt 5. Changes in memory, word finding, and right sided dexterity; 2/2 tauopathy
- LEFT PARIETAL> FRONTAL AND TEMPORAL
  - Pt 6: apraxia, word finding, gait 2/2 AD
- RIGHT TEMPORO-OCCIPITAL
  - Pt 7. Prosopagnosia, L VF, word substitution 2/2 Right temporo-occipital and small left frontal tauopathy

PATIENT 8:
FALLS

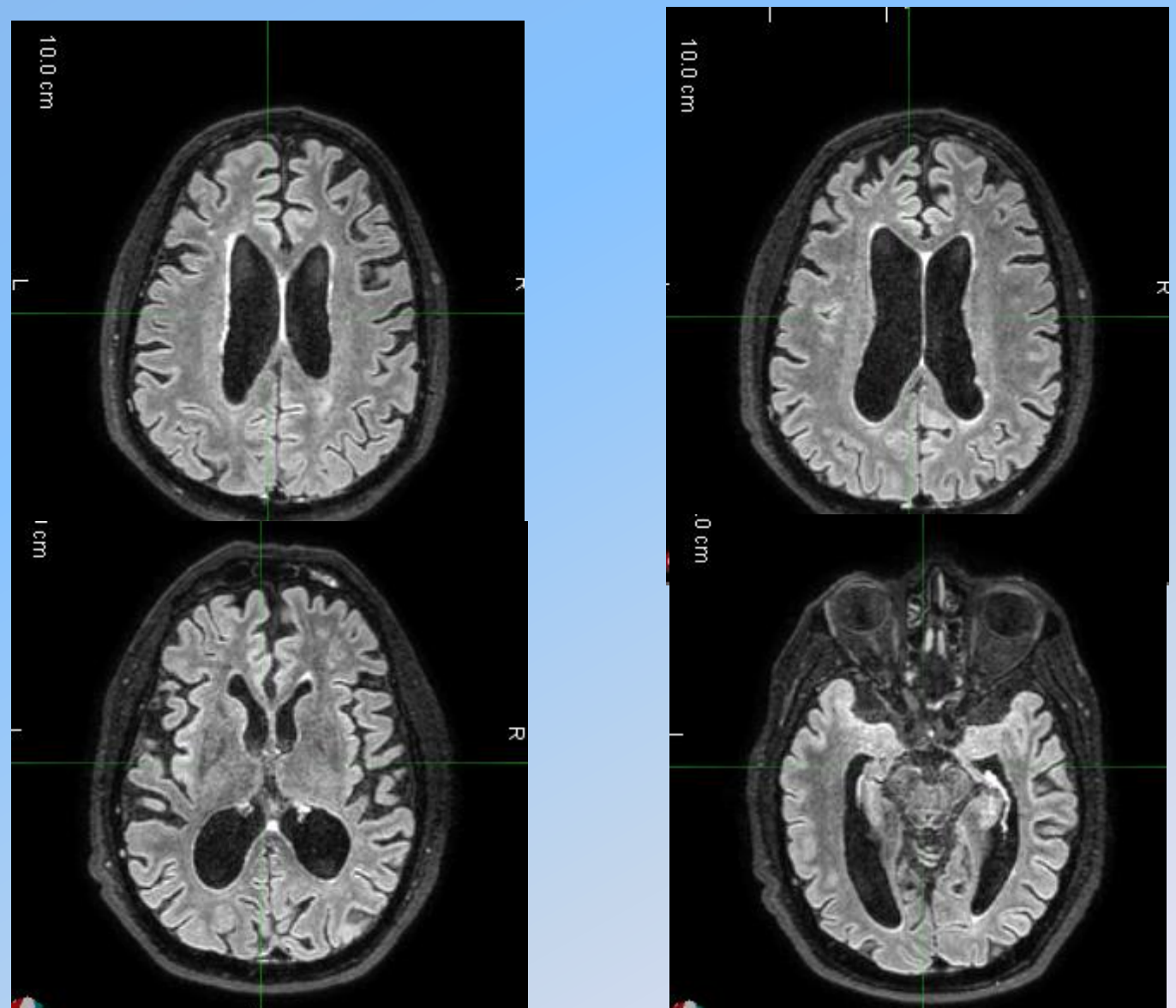
HPI

- Reported that he was Dx'd w/MDD & anxiety disorder
- Wanted to see us b/o falling more often lately
  - 30-40 times in past mo
  - Tripping and bumping into walls
  - Recently went to the museum and he felt that he could not stop himself from walking
- Coworker noticed that his STM has been bad lately
  - Lost an art piece for the first time in 25 years
- Attention also declining: "cant seem to be able to focus."
  - When he is talking, he forgets what he is talking about, and has to go back to think about what he needed to say
- Has also been having urinary incontinence

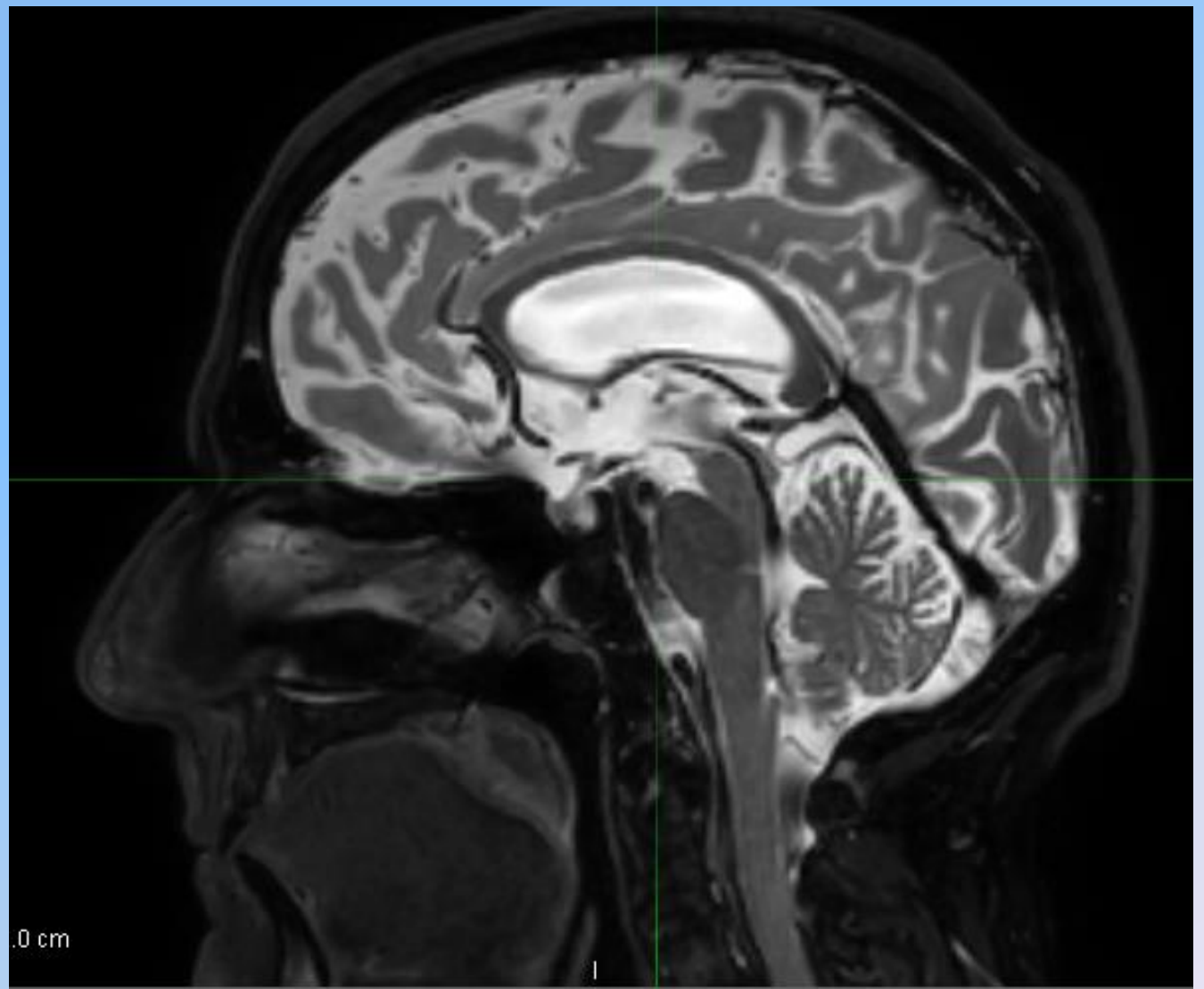
NPT

- Declines in
  - Attention/processing speed
  - Executive function
  - Memory domains
  - Preserved functional abilities

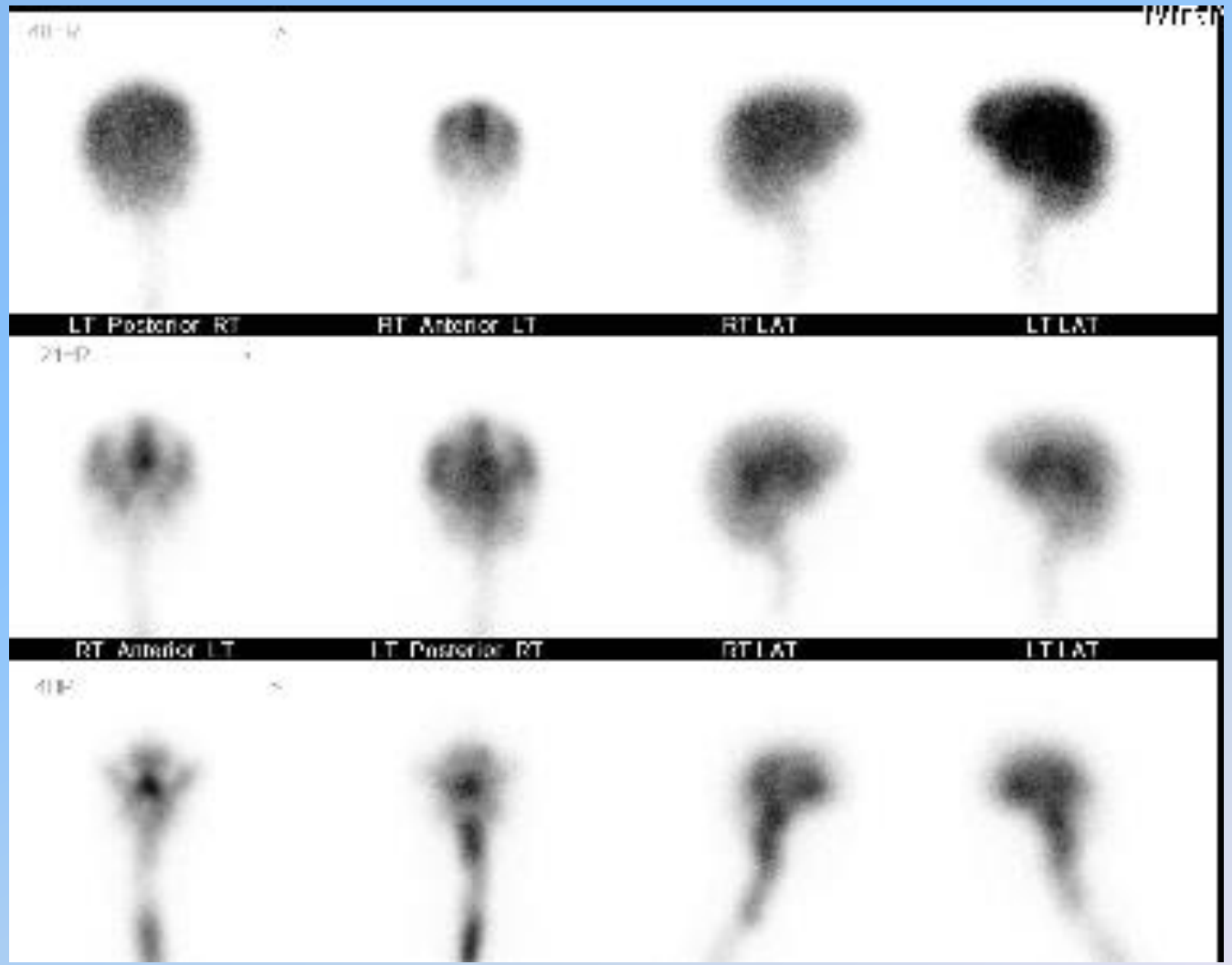
3T MRI w/DTI



SAGITTAL: CSF FLOW RATE



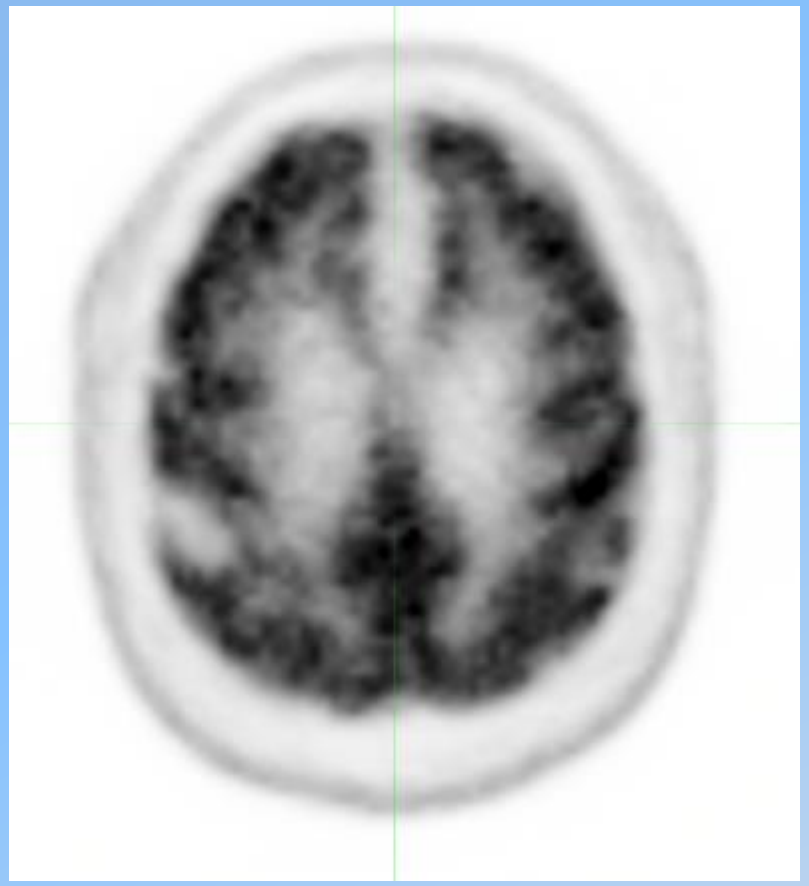
CISTERNOGRAM

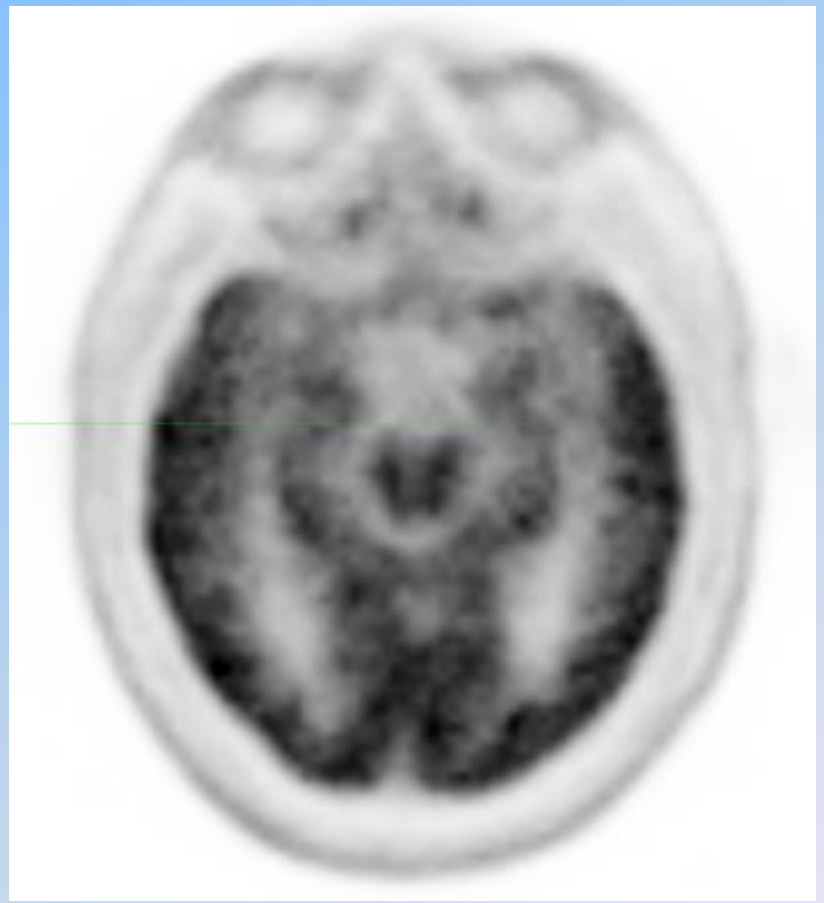


CSF Abeta & Tau

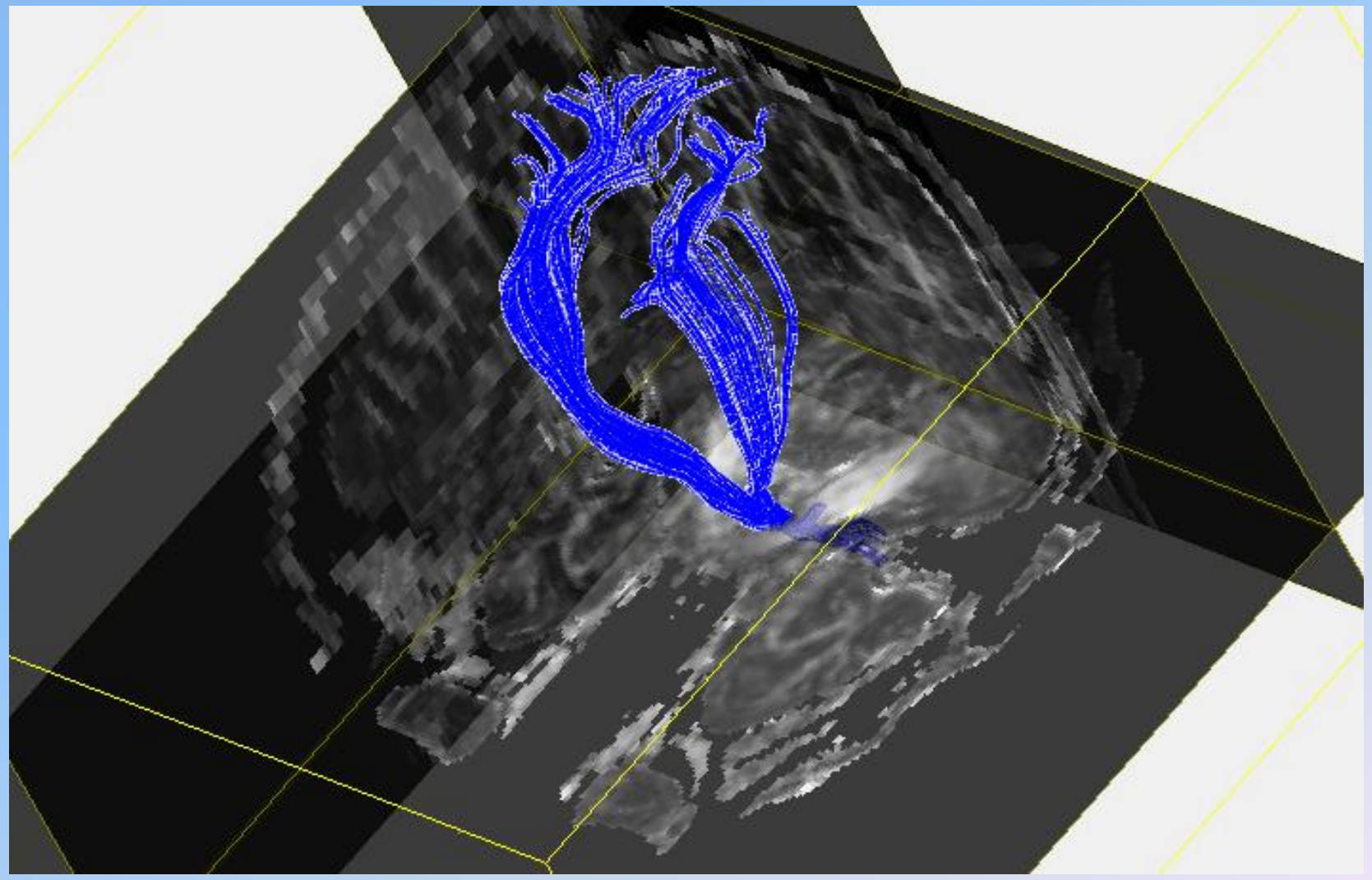
- IMPRESSION: This analysis detected CSF levels of A-beta 42 peptide, total tau, and phospho-tau proteins, which provide **conflicting information** with respect to a diagnosis of AD.
- P-TAU: 51.35 pg/ml (not cw AD: P-TAU <64 pg/ml)
- A-beta: 388.5 pg/ml
- ATI 0.76 (<0.80)

FDG PET

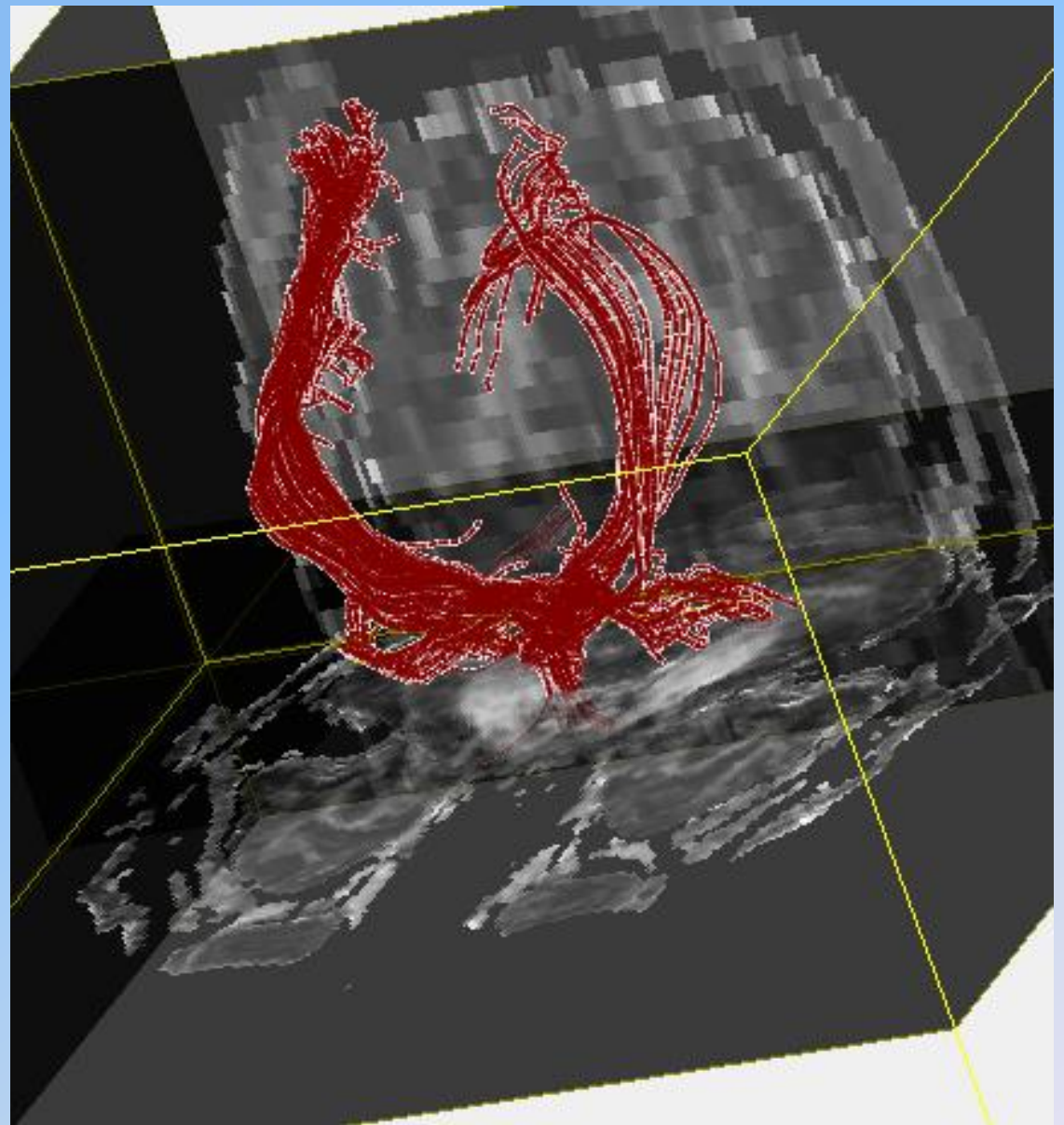




NPH_19_CORTICOSPINAL TRACT



NPH_19_DENTATORUBRO THALAMIC TRACT



J NEUROIMAGING, 2018

- Compressed CST (diffusivity changes)
- Ventricular-to-Sulcal CSF ratios differentiate AD from NPH

Diffusion Tensor Imaging of the Superior Thalamic Radiation and Cerebrospinal Fluid Distribution in Idiopathic Normal Pressure Hydrocephalus

Kyan Younes, Khader M. Hasan, Arash Kamali, Christine E. McGough, Zafer Keser, Omar Hasan, Tomas Melicher, Larry A. Kramer, Paul E. Schulz, the Alzheimer's Disease Neuroimaging Initiative Researchers

From the Department of Neurology, McGovern Medical School, University of Texas Health Science Center (UTHSC), Houston, TX (KY, CEM, ZK, OH, PES); Department of Diagnostic and Interventional Imaging, McGovern Medical School, University of Texas Health Science Center (UTHSC), Houston, TX (KMH, AK, LAK); and Department of Psychiatry, McGovern Medical School, University of Texas Health Science Center (UTHSC), Houston, TX (TM).

ABSTRACT

BACKGROUND AND PURPOSE: Ventricular enlargement in elderly raises a challenging differential diagnosis to physicians. While Alzheimer's disease is the most common form of dementia, idiopathic normal pressure hydrocephalus (iNPH) constitutes a potentially reversible syndrome. iNPH has a unique pathophysiology pertaining to cerebrospinal fluid (CSF) dynamics and periventricular white matter. We aimed to determine the effects of iNPH on periventricular white matter bundles and to further characterize its ventricular and sulcal CSF distribution by using diffusion tensor tractography (DTT) and CSF volumetrics on high resolution T1-weighted magnetic resonance imaging data.

METHODS: Deterministic DTT and validated volumetric parcellation were performed on 20 healthy elderly, 13 Alzheimer's disease (AD), and 9 iNPH patients. The superior thalamic radiation, corticospinal tract, and dentatorubrothalamic tract were traced and quantified using DTI studio software. Cloud-based volumetric parcellation was also performed on 138 healthy subjects across the lifespan, 13 AD, and 9 iNPH-patients. Ventricular and sulcal CSF volumes in the three groups were compared.

RESULTS: Combining increased mean diffusivity of the superior thalamic radiation with ventricular volume resulted in clear separation of iNPH from the AD and age-matched healthy subject groups. Additionally, ventricular to sulcal CSF ratio, utilizing fully automated methods, was significantly greater in the iNPH patients compared to AD and healthy age-matched controls.

CONCLUSIONS: Combined microstructural (DTT) and macrostructural (ventricular volume) changes is a promising radiological approach in studying ventriculomegaly. Automated estimation of the disproportionate ventricular and sulcal CSF ratio in patients presenting with ventriculomegaly may be important as radiologic markers in differentiating iNPH from other causes of ventriculomegaly.

Keywords: dentatorubrothalamic tract, diffusion tensor tractography, normal pressure hydrocephalus, superior thalamic radiation, ventricular volume.

Acceptance: Received May 31, 2018, and in revised form October 25, 2018. Accepted for publication October 26, 2018.

Correspondence: Address correspondence to Khader M. Hasan, Department of Diagnostic and Interventional Radiology, McGovern Medical School, University of Texas, 6431 Fannin St. Houston, TX 77030. E-mail: Khader.M.Hasan@uth.tmc.edu.

Acknowledgements: This study was funded in part by DUNN research foundation to KMH. We wish to thank Vipul Kumar Patel for helping in data acquisition. The Alzheimer's disease Neuroimaging Initiative Data used in preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Conflicts of Interest: The authors have no potential conflict of interest to disclose.

J Neuroimaging 2018;00:1-10.
DOI: 10.1111/jon.12581

OBJECTIVES

- Review case Hxs to demonstrate how neuroimaging has significantly helped with
  - Neurologic **diagnoses**
  - Being a biomarker to get the **correct patients enrolled** in Rx trails; and,
  - As a biomarker for **Rx success**
  - Understanding the **pathophysiology** underlying NDDs

ADACANUMAB: AMYLOID PLAQUE CHANGES AT 1 YR

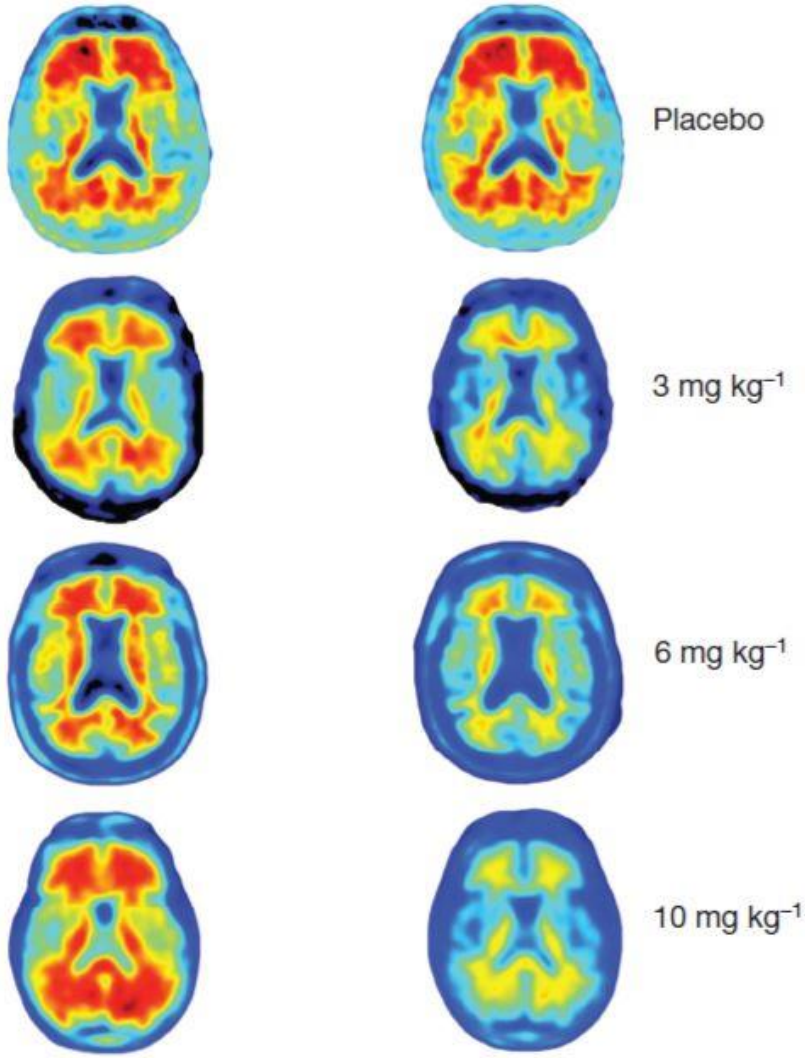
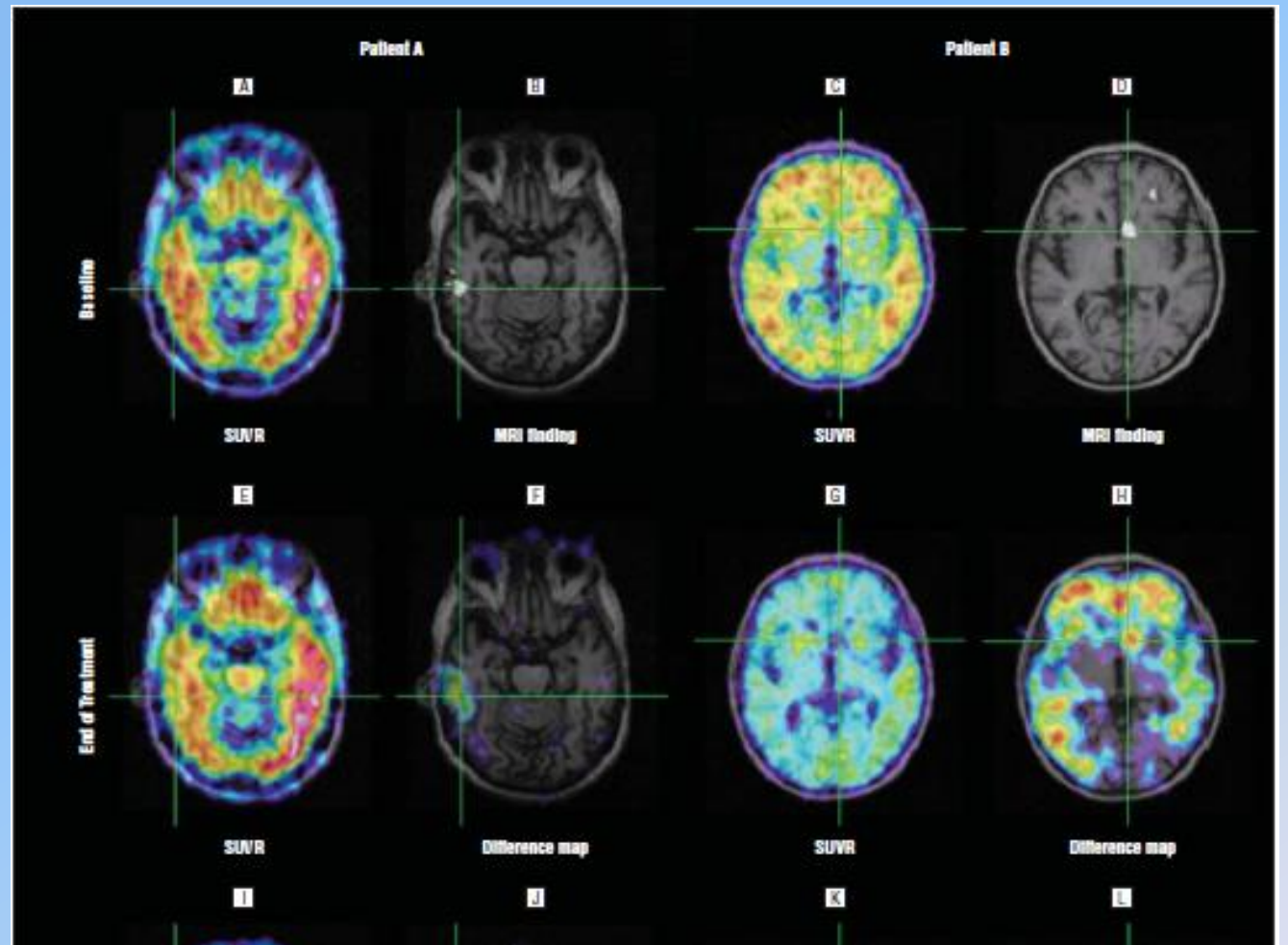


Figure 1 | Amyloid plaque reduction with aducanumab: example amyloid PET images at baseline and week 54. Individuals were chosen based on visual impression and SUVR change relative to average one-year response for each treatment group ($n = 40$, 32, 30 and 32, respectively). Axial slice shows anatomical regions in posterior brain putatively related to AD pathology. SUVR, standard uptake value ratio.

GANTENERUMAB: CHANGE IN AMYLOID PLAQUES

CONTROL TREATED

Ostrowitzki et al, 2012



BASELINE PET (A,C) & MRI (B,D)

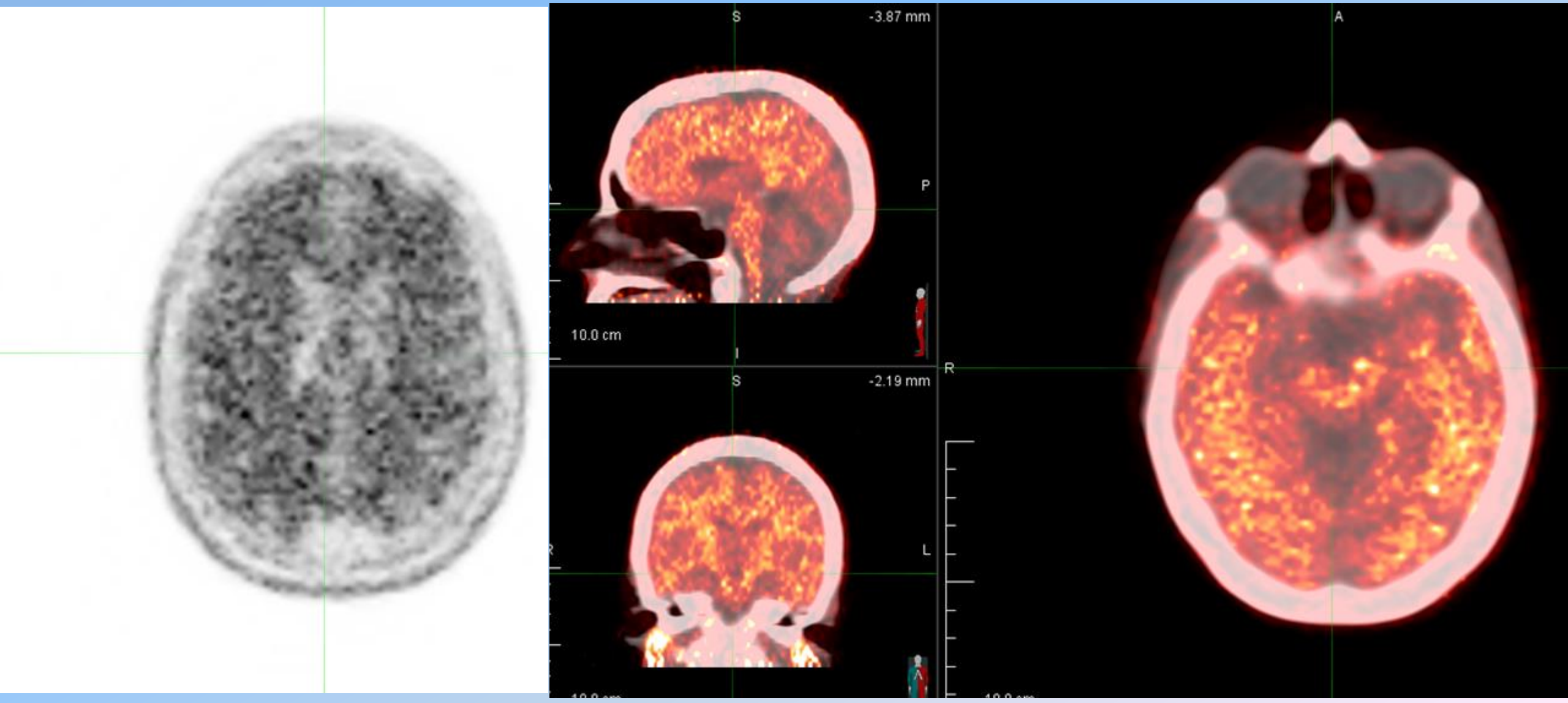
END OF TRIAL-AMY PET (F, G) & DIFFERENCE (F, H)

OBJECTIVES

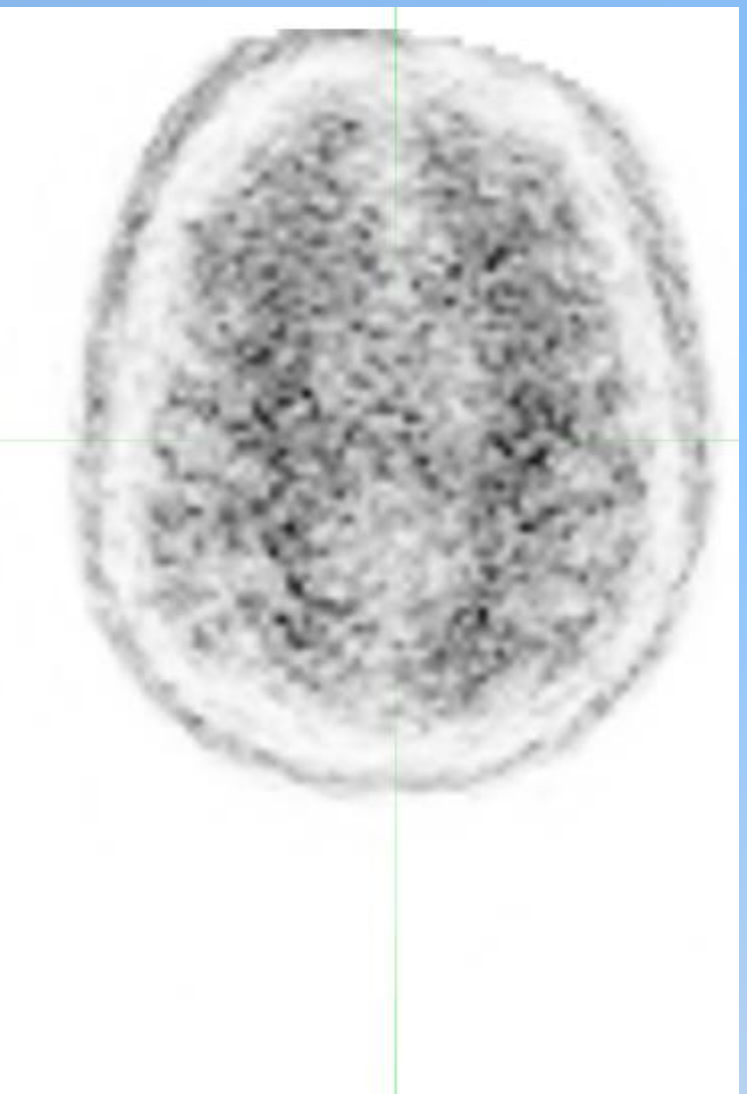
- Review case Hxs to demonstrate how neuroimaging has significantly helped with
  - Neurologic **diagnoses**
  - Being a biomarker to get the **correct patients enrolled** in Rx trails; and,
  - As a biomarker for **Rx success**
  - Understanding the **pathophysiology** underlying NDDs

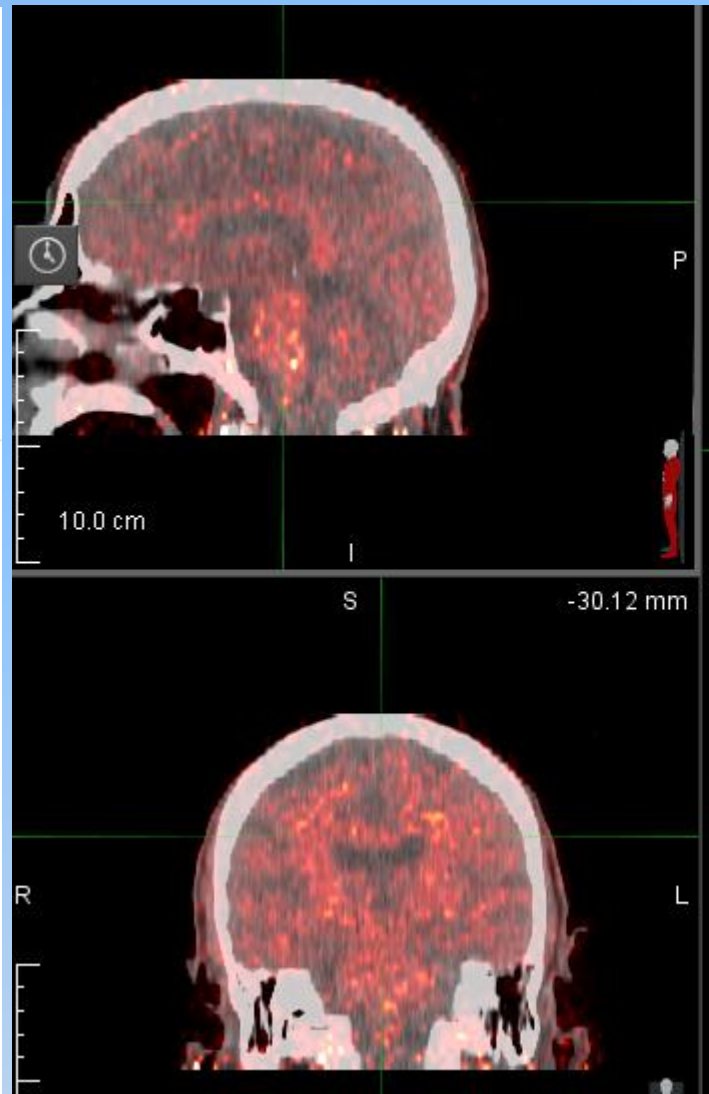
IDENTIFYING AD, PRESYMPTOMATICALY

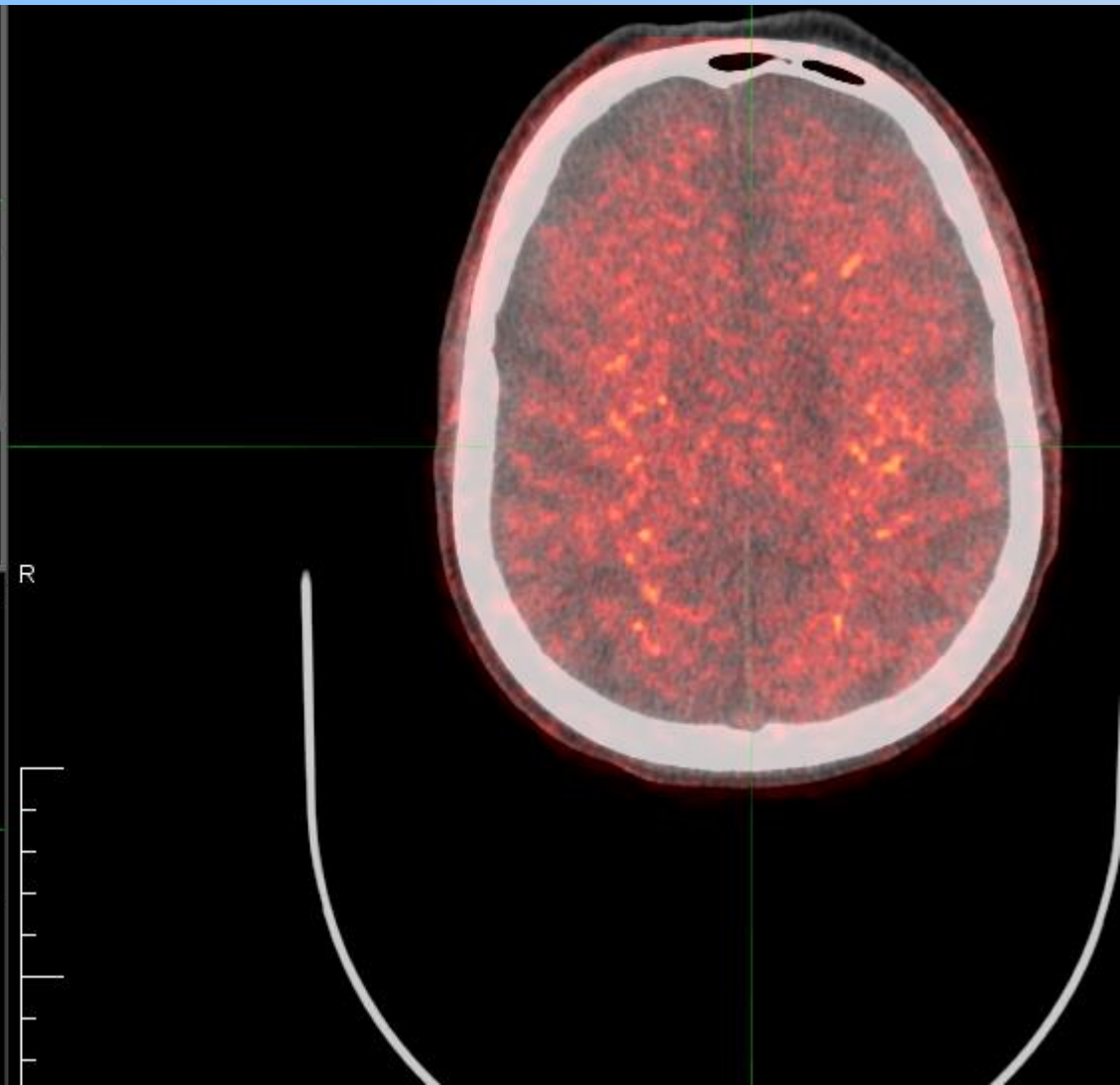
(+) AMYLOID PET IMAGING YEARS PRIOR TO SYMPTOMS: UNIQUE STUDY POPULATION



(-) AMYLOID PET IMAGING: UNIQUE STUDY POPULATION







SUMMARY

- Neuroimaging is often **driven** by **desire for better Dx**
  - E.g., amyloid PET →↑ **Dx accuracy**
  - And better Dx= **better advice** to patients: you have VaD or EtOH dementia, not AD, so the course will differ
  - Now, **Tau PET** is opening a whole new area of (+) Dx
- Turns out to be VERY USEFUL for **Rx trials**
  - 12-30% of patients in AD trials prior to **amyloid PET imaging were (-)**

SUMMARY

- Giving INSIGHTS into **underlying processes**
  - Amyloid deposition visible on PET **20 years prior** to the 1st symptom
    - **CSF** may change prior to that
  - Abn proteins may spread along pathways, not cell to cell
    - Transmitted like an **infection**
    - Ideas for **designing new treatments:** can we ↓spread
- **EXCITING NEW PET TECHNIQUES, e.g. TAU PET**
  - ↑ **Dx accuracy** of tau based disorders
    - Can be challenging to diagnose clinically
    - But, variation in tau PET **between agents,** which need to be understood (maybe b/o 3 repeat vs 4 repeat disorders, location, and concentration

THANK YOU!

Paul Schulz MD

Rick McCord Professor of Neurology

Director, Memory Disorders and Dementia Clinic,

McGovern Medical School of UTHealth Houston