Concordance Of PET Tau Visual Reads With PET Tau Quantification and CSF PTau

Charles D. Chen, Jordan A. Lang, Shaney Flores, Suzanne E. Schindler, Anne M. Fagan, John C. Morris, Tammie L.S. Benzinger, Maria Rosana Ponisio

Disclosures

- I have nothing to disclose

Tau status can be determined in different ways

- The Amyloid(Aβ)/Tau/Neurodegeneration (A/T/N) system has been used since 2016 to place individuals along a biomarker-defined Alzheimer disease (AD) continuum
- Aggregated tau and associated pathophysiology, or tau status (T), was first defined by cerebrospinal fluid (CSF); later, by positron emission tomography (PET)

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	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Biomarker profiles and categories (Jack et al. 2018)

Tau status can be determined in different ways

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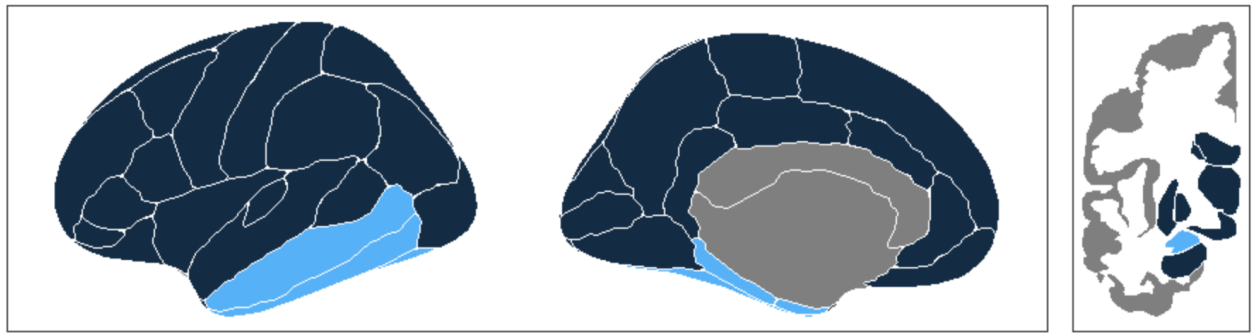
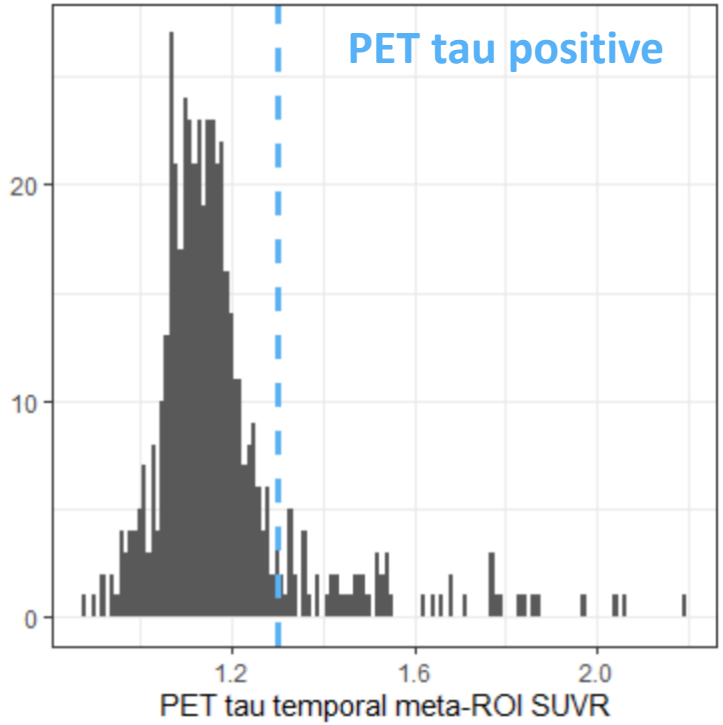
- Aggregated tau and associated pathophysiology, or tau status (T), was first defined by cerebrospinal fluid (CSF); later, by positron emission tomography (PET)
- In many research pipelines, PET tau standardized uptake value ratios (SUVRs) from relevant regions of interest (ROIs) are binarized to determine tau positivity





Tau status can be determined in different ways

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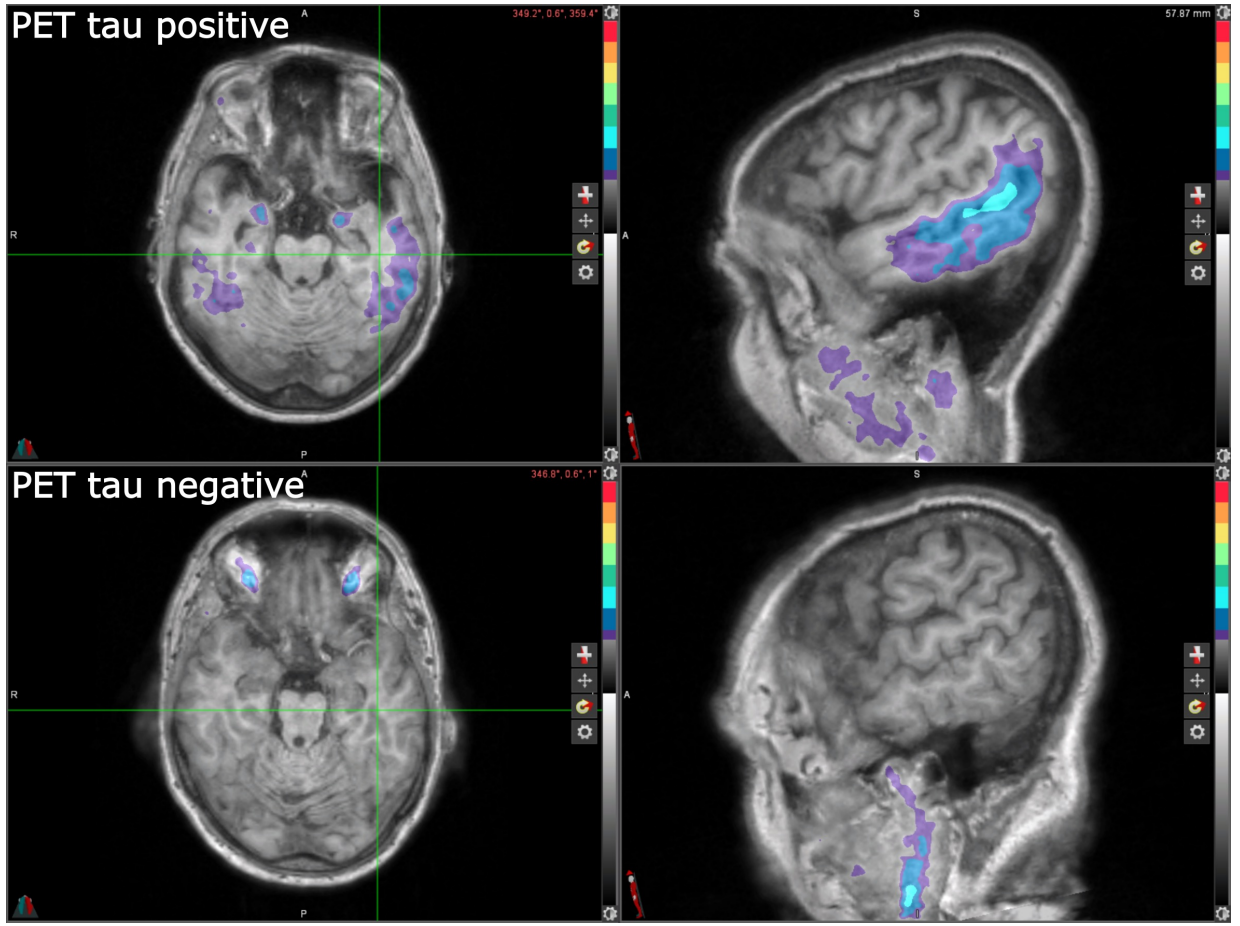
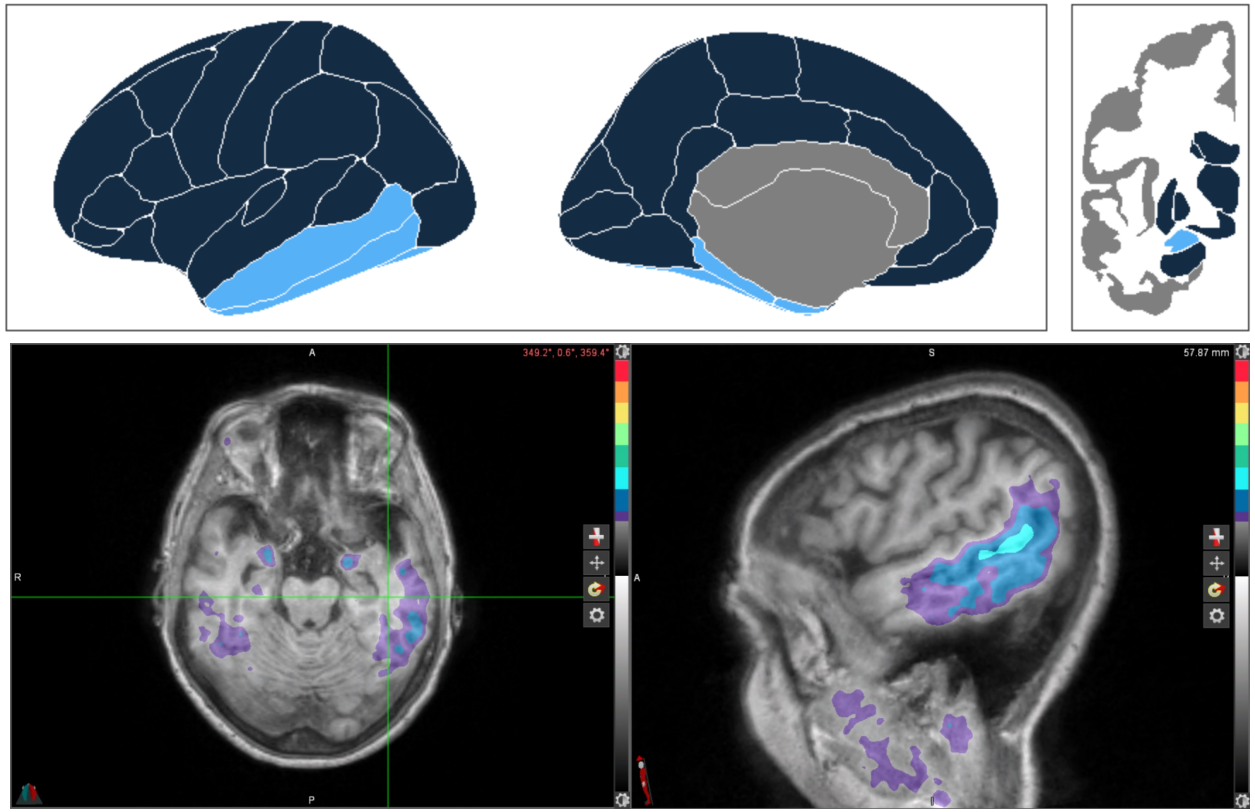
- In many research pipelines, PET tau standardized uptake value ratios (SUVRs) from relevant regions of interest (ROIs) are binarized to determine tau positivity
- In 2020, the U.S. Food and Drug Administration (FDA) approved Tauvid (flortaucipir), along with the manufacturer's guidelines for its visual interpretation



Tau status can be determined in different ways, but do they agree?

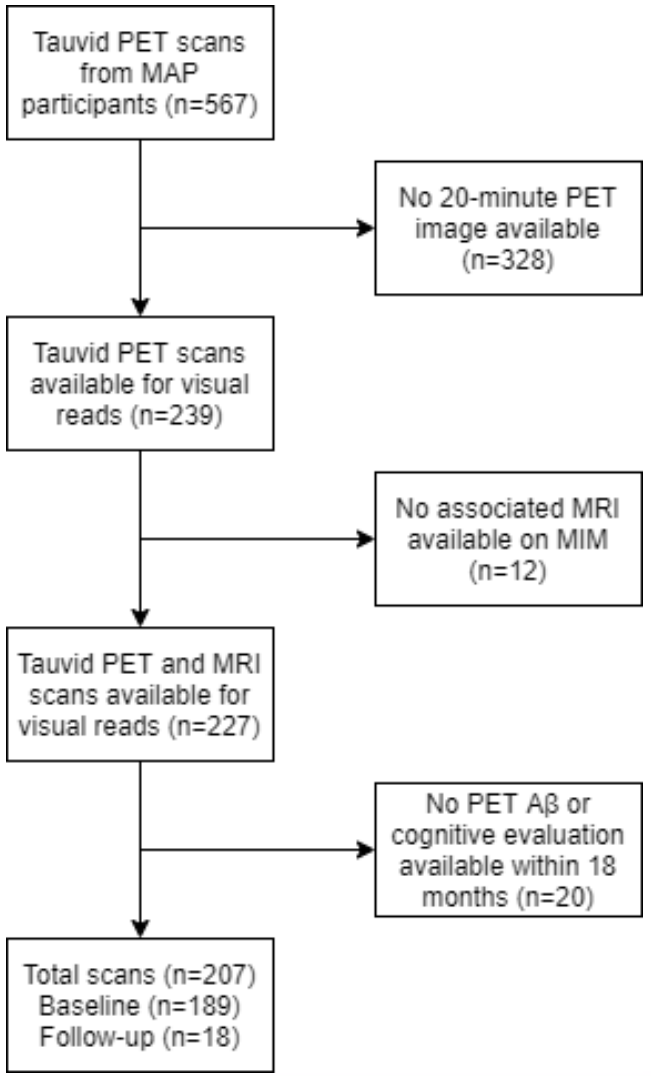
- The Amyloid(Aβ)/Tau/Neurodegeneration (A/T/N) system has been used since 2016 to place individuals along a biomarker-defined Alzheimer disease (AD) continuum
- Aggregated tau and associated pathophysiology, or tau status (T), was first defined by cerebrospinal fluid (CSF); later, by positron emission tomography (PET)
- In many research pipelines, PET tau standardized uptake value ratios (SUVRs) from relevant regions of interest (ROIs) are binarized to determine tau positivity
- In 2020, the U.S. Food and Drug Administration (FDA) approved Tauvid (flortaucipir), along with the manufacturer's guidelines for its visual interpretation
- To what extent do clinical interpretations of PET tau images agree with results from research pipelines for PET tau quantification?



Participants

- Participants were enrolled in studies of the Charles F. and Joanne Knight Alzheimer Disease Research Center (n=189)
- All participants met the inclusion criteria of having a Tauvid PET, PET Aβ (Pittsburgh compound B (PiB) or florbetapir), MRI, and cognitive evaluation within 18 months
- Participants were on average 70 years old with normal cognition and no *APOE4* allele

Inclusion criteria for Tauvid PET scans



Participant demographics

Number		189
Mean age (SD)		69.8 (8.51)
Female (%)		105 (55.6)
Mean MMSE (SD)		28.8 (1.94)
CDR	**0**	166
	0.5	16
	1	6
	2	1
APOE	**22**	1
	23	28
	24	7
	33	91
	34	53
	44	8
	NA	1

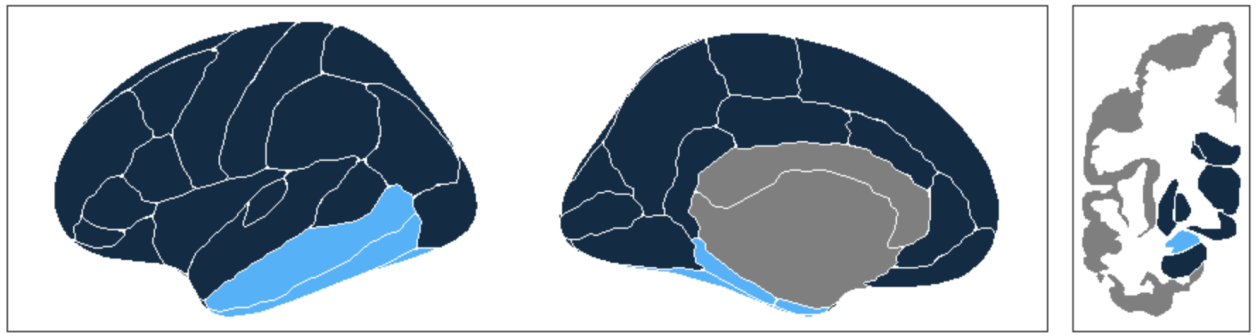
PET tau acquisition

- Participants were scanned on a Siemens Biograph 40 (Siemens Healthineers, Erlangen, Germany)
- Participants received a single intravenous bolus injection of Tauvid (Eli Lilly and Company, Indianapolis, IN, USA)
- Emission data were collected 80-100 minutes post injection
- List-mode data were reconstructed using ordered subset expectation maximization
- Reconstructed PET images were attenuation compensated with CT images

Photo credit: Farzaneh Rahmani

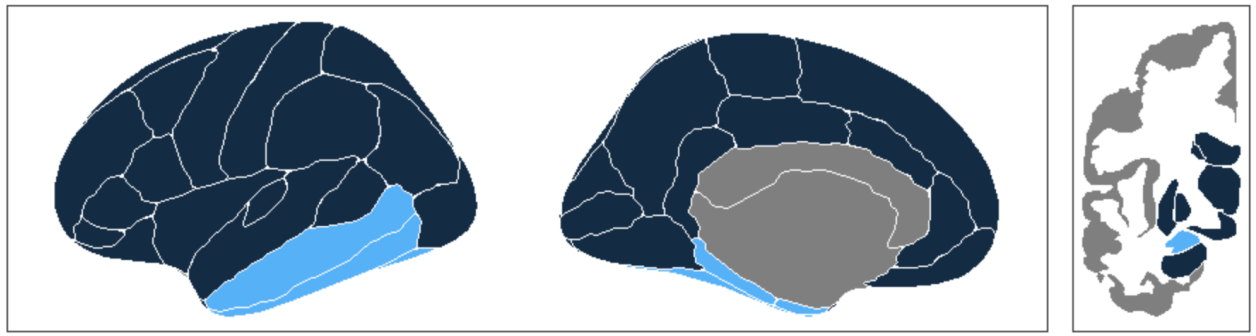
PET tau SUVRs

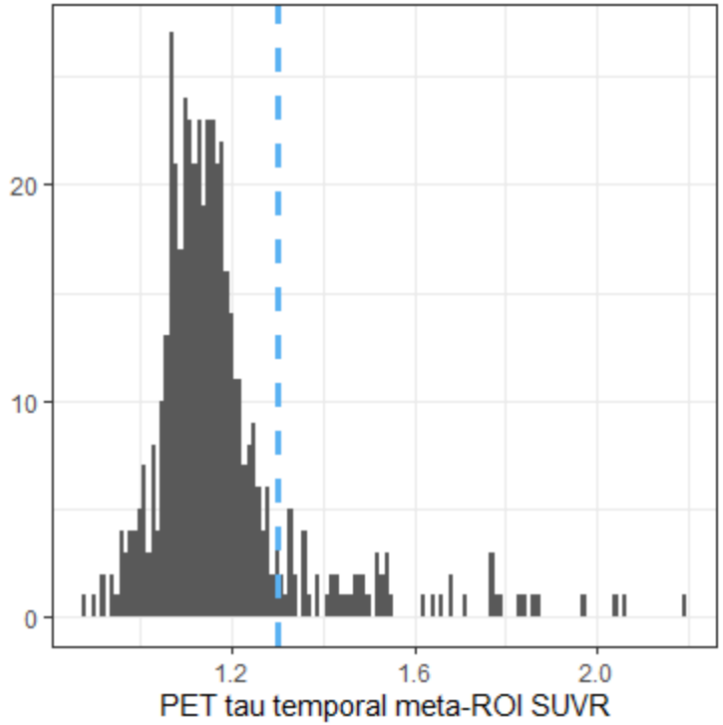
- In many research pipelines, PET tau standardized uptake value ratios (SUVRs) from relevant regions of interest (ROIs) are binarized to determine PET tau positivity
- Reconstructed PET images were further processed (e.g. smoothed with 8 mm Gaussian kernel, registered to MR images) using the PET Unified Pipeline (Su et al. 2013, Su et al. 2015)
- Using MR images segmented into ROIs with FreeSurfer 5.3 (Fischl 2012), regional SUVRs were defined using cerebellar gray as a reference region
- Temporal meta-ROI SUVRs were defined as the sums of the mean bilateral SUVRs of the amygdala, entorhinal, fusiform, parahippocampal, inferior temporal, and middle temporal ROIs (Jack et al. 2016, Schwarz et al. 2021)



PET tau SUVRs

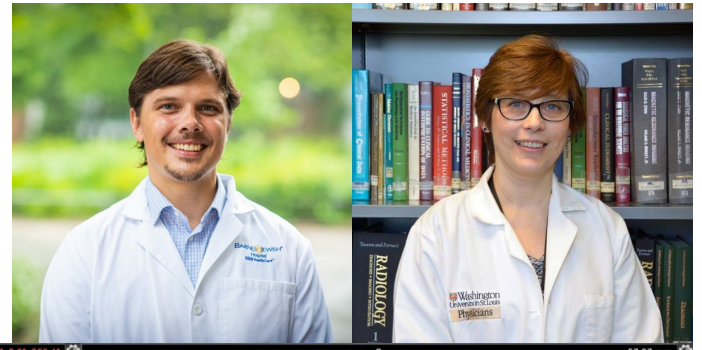
- Reconstructed PET images were smoothed
- Regional SUVRs were defined using FreeSurfer
- Temporal meta-ROI SUVRs were defined
- In R (R Core Team 2021), a tau positivity threshold was defined by fitting a two-component univariate Manly mixture model (Zhu and Melnykov 2018) to the SUVR data and finding its decision boundary (SUVR=1.3)
- Manly mixture models were chosen to compensate for possible severe skewness in the data

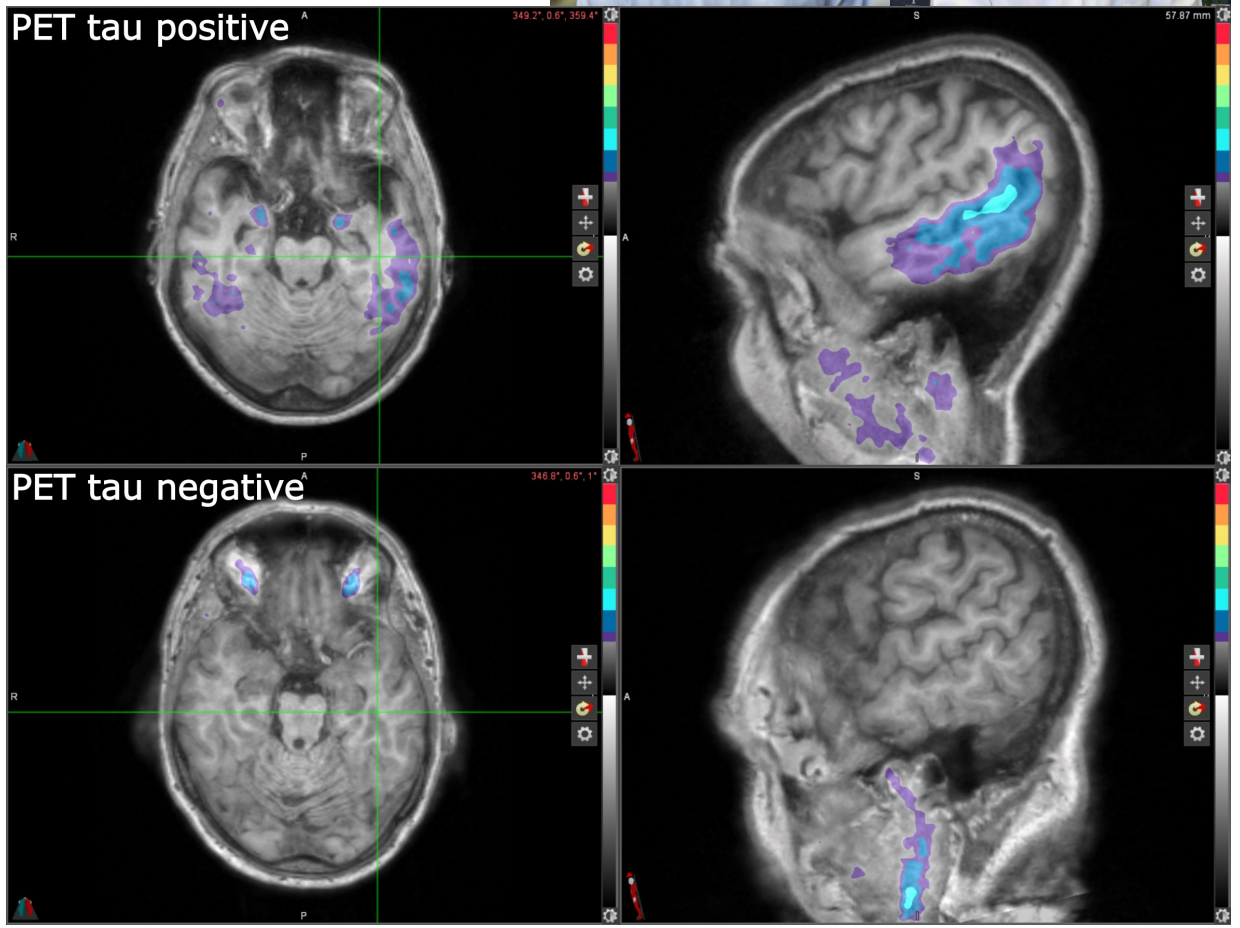




PET tau SUVRs and visual reads

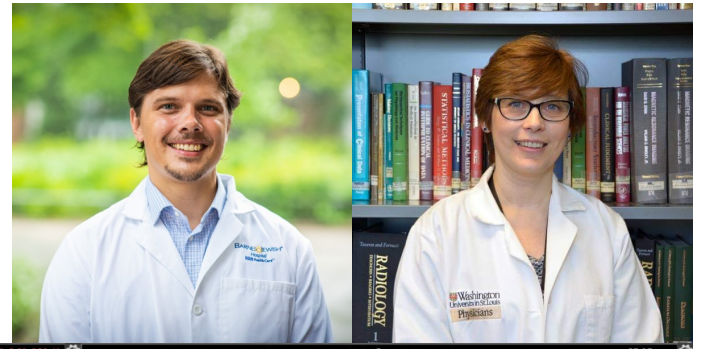
- In 2020, the U.S. Food and Drug Administration (FDA) approved Tauvid (18F-flortaucipir), along with the manufacturer's guidelines for its visual interpretation
- Two radiologists (J.A.L. and M.R.P.) followed manufacturer's guidelines to classify scans as positive or negative
- Tauvid PET images were fused with MR images in MIM (MIM Software Inc., Beachwood, OH)
- A ROI was drawn around the whole cerebellum in the axial plane that maximizes its cross section
- The SUV 2.5 Black color scale was selected, and the transition between grayscale and color was set at 1.65x the mean cerebellar counts

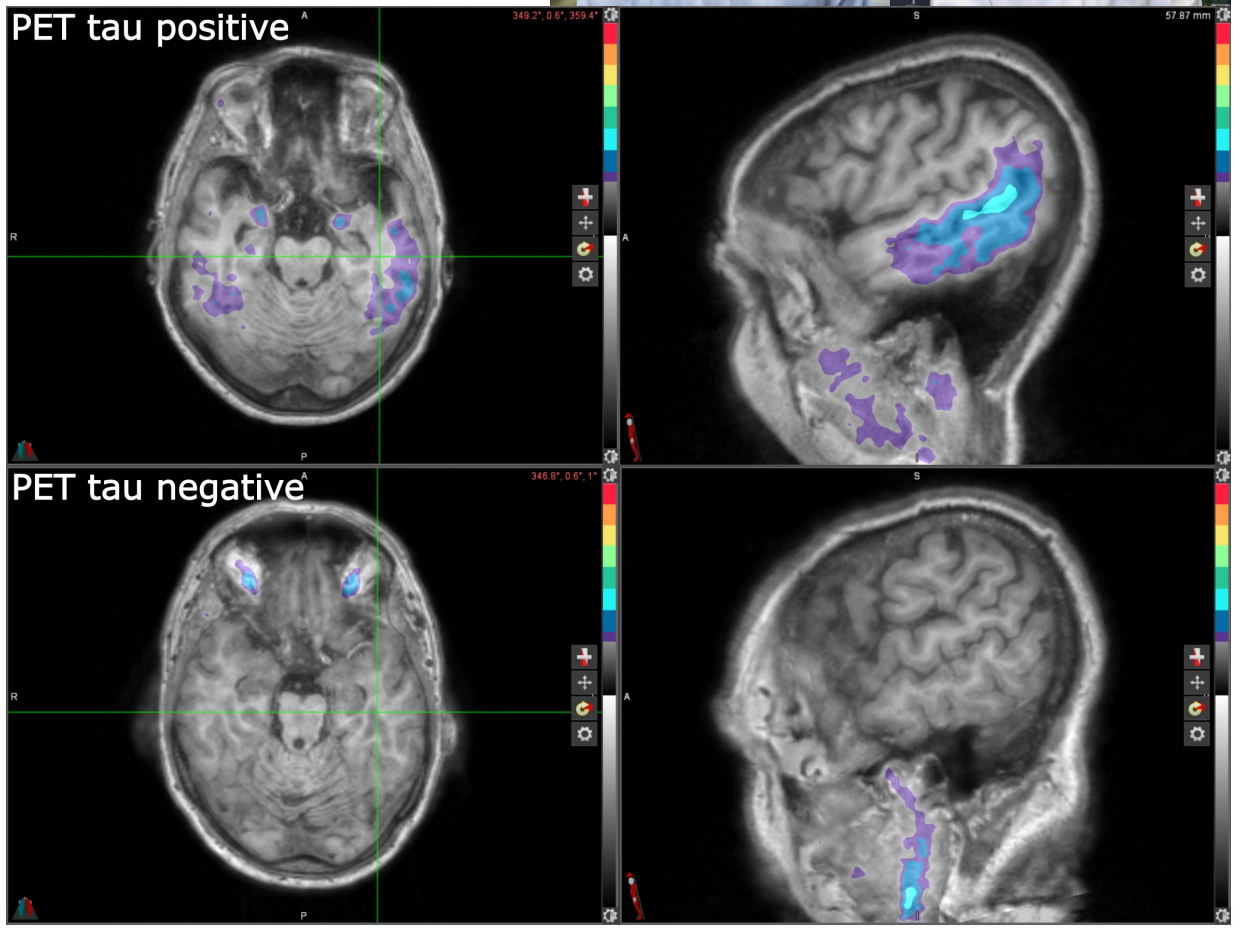




PET tau SUVRs and visual reads

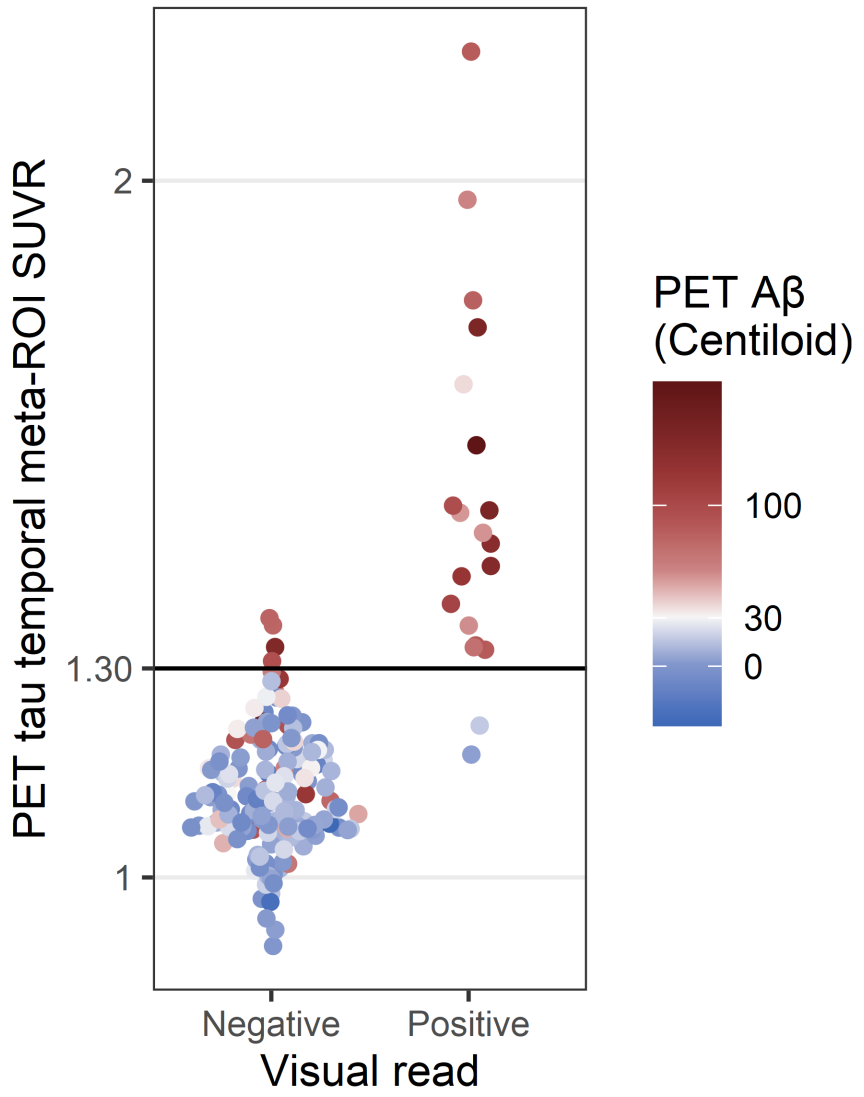
- Tauvid PET images were fused with MR images
- A whole cerebellum ROI was drawn
- A rapid transition between grayscale and color was set at 1.65x the mean cerebellar counts
- The temporal lobe was divided into quadrants by placing the horizontal crosshair posterior to the brainstem nuclei (ventral midbrain nuclei), then scrolling inferiorly and placing the vertical crosshair to bisect the widest portion of the temporal pole
- This obtains the anterolateral, anterior mesial, posterolateral, and posterior mesial temporal quadrants (ALT, AMT, PLT, and PMT)
- An image was classified as positive if it showed confluent activity above threshold (1.65x the mean cerebellar counts) in the cortical gray matter of the PLT, occipital, or parietal/precuneus regions





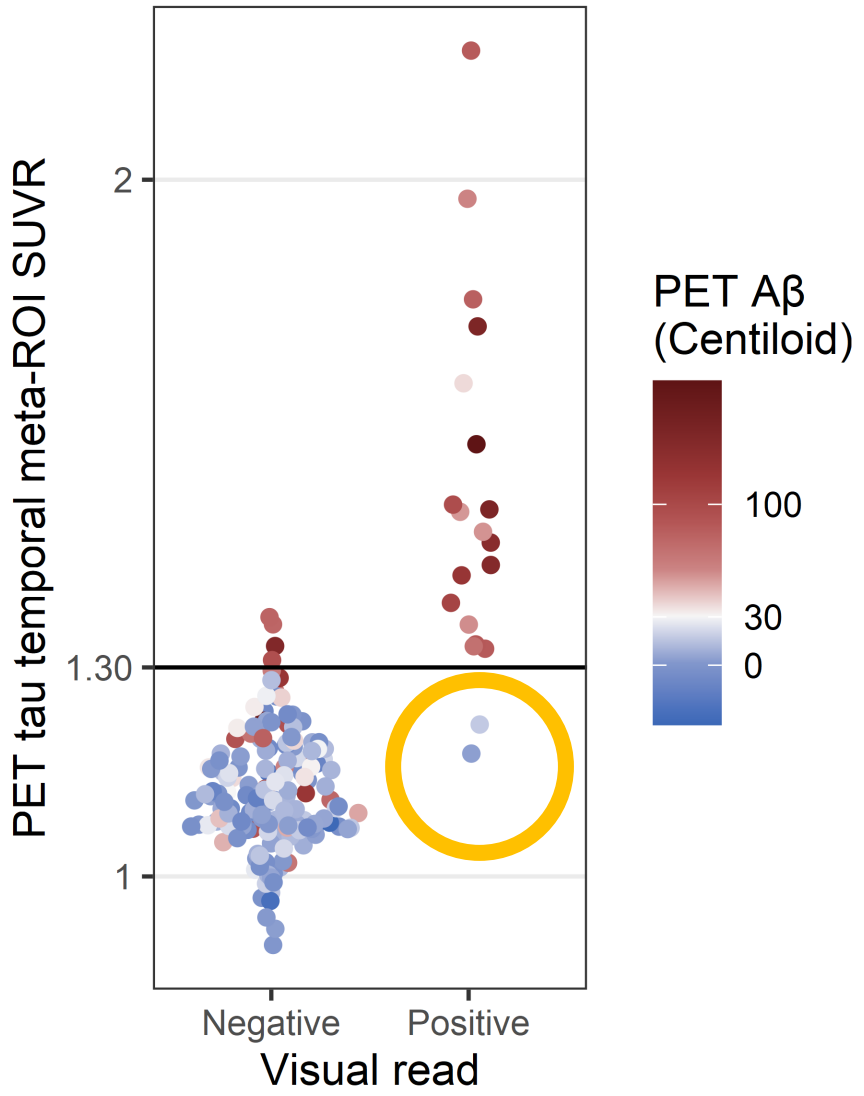
PET tau SUVRs and visual reads are highly concordant

- Across baseline PET tau scans (n=189), agreement between radiologists was perfect (100%, κ=1)
- Agreement between radiologists and the research pipeline was high (96.8%, κ=0.839)



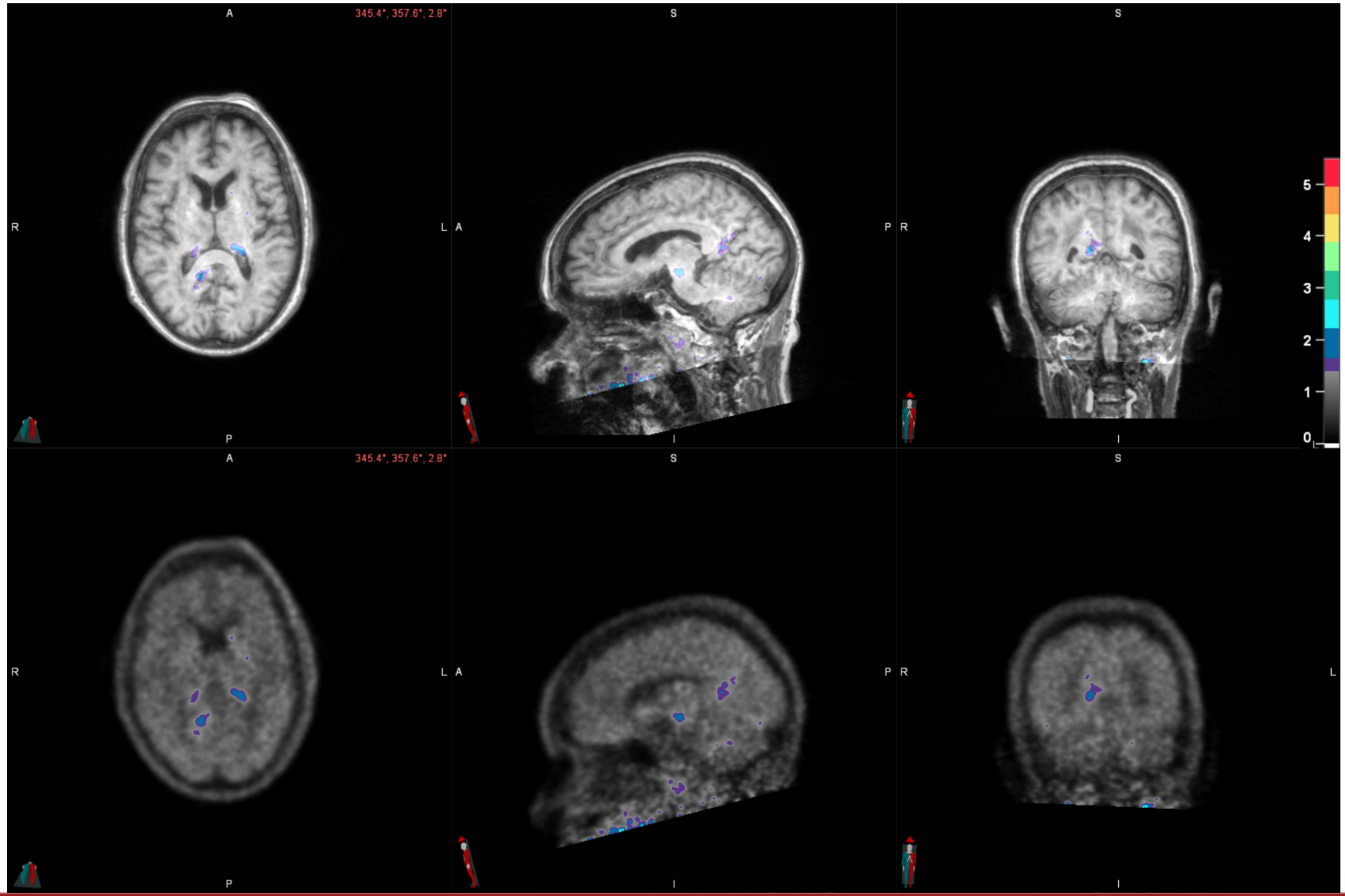
PET tau false negatives

- Across baseline PET tau scans (n=189), agreement between radiologists was perfect (100%, κ=1)
- Agreement between the radiologists and the research pipeline was high (96.8%, κ=0.839)
- Using the radiologists' visual reads as a standard, the two false negatives from the research pipeline had asymmetric parietal/precuneus or occipital uptake



PET tau false negatives due to small bleed

80-year-old man



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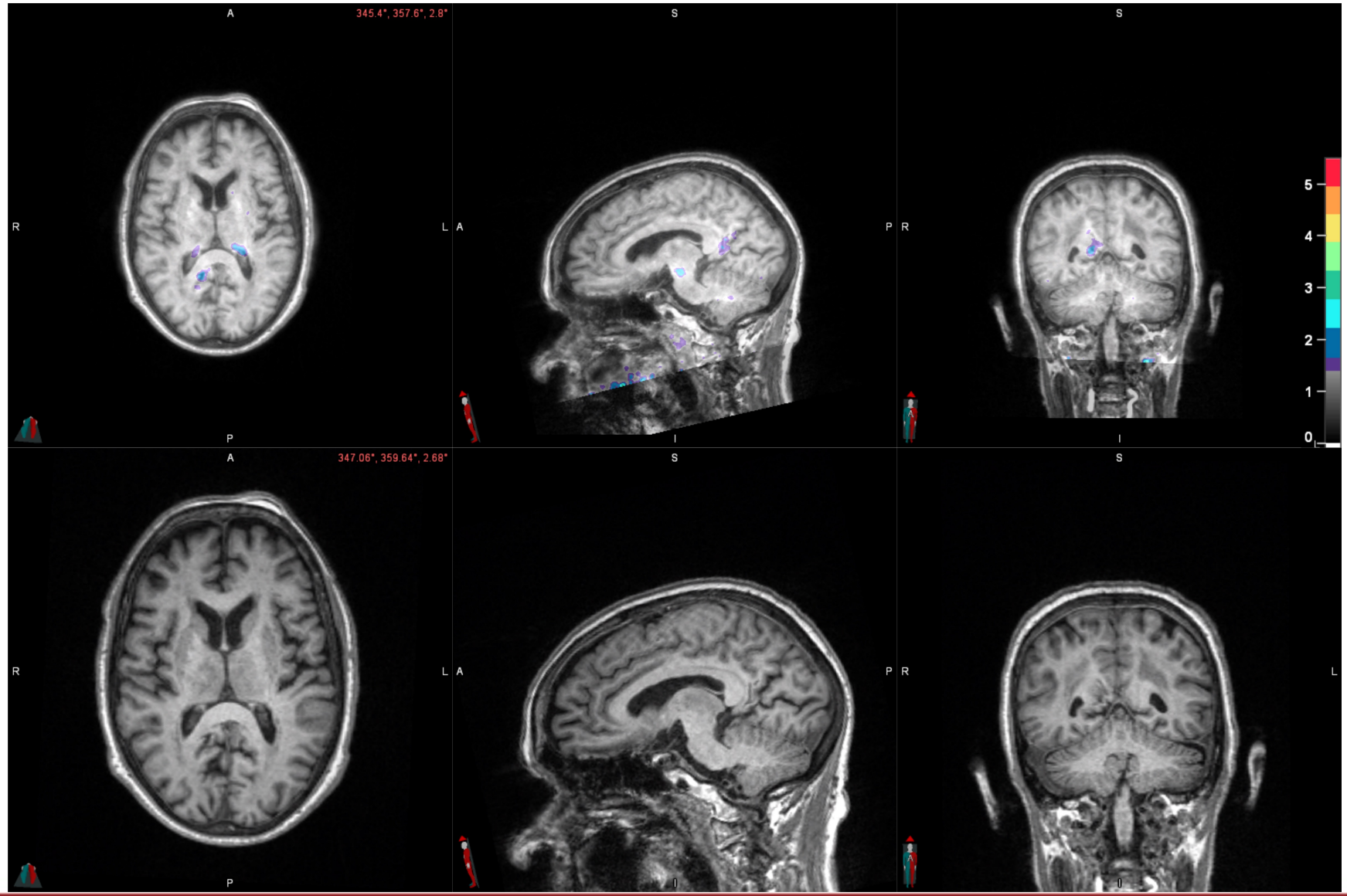

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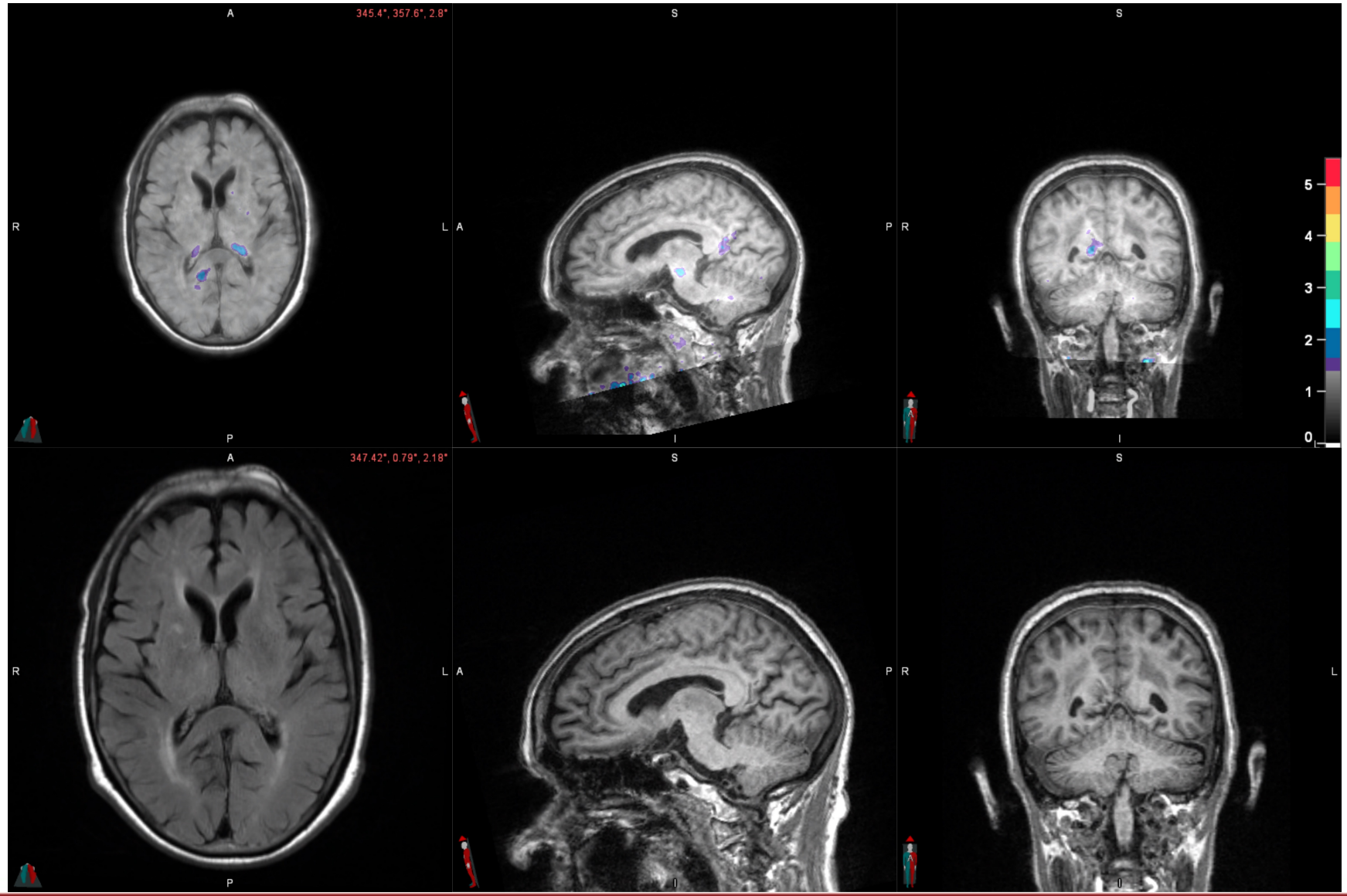
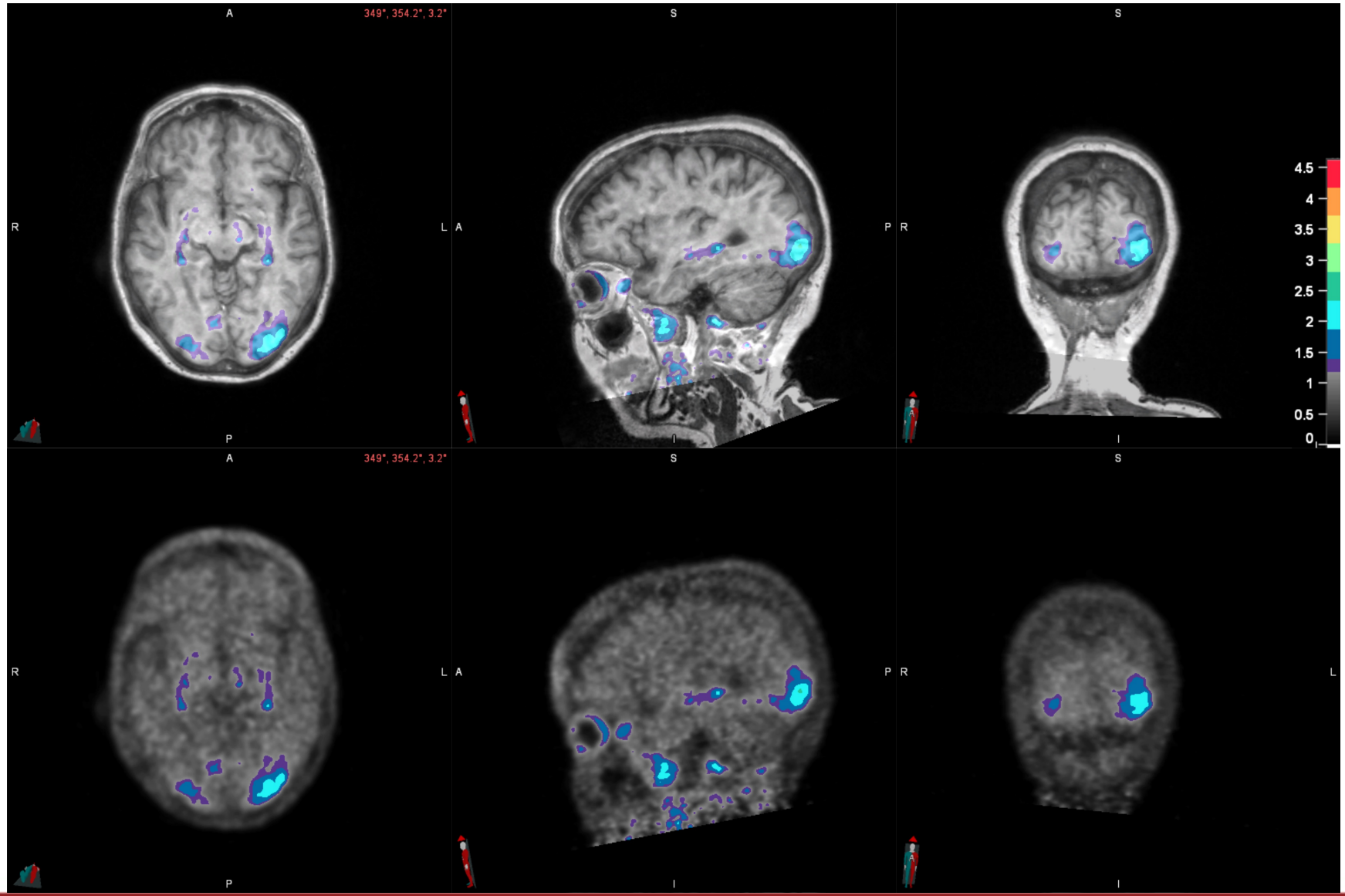


PET tau false negative due to occipital predominant tau subtype

72-year-old woman



PET tau false negatives due to small bleed or occipital subtype

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- PET Aβ and CSF biomarkers suggest the occipital case is on the AD continuum

	Age	**Sex**	***APOE***	**Clinical status (CDR®)**	**PET Aβ (Centiloid)**	**PET tau (SUVR)**	**CSF Aβ42/ Aβ40**	**CSF pTau (pg/ml)**
Parietal/ precuneus	80	M	34	Cognitively normal	3.87	1.18	0.0975	21.6
Occipital	72	F	34	Cognitively normal	17.0 → 50.0	1.22	0.0523	69.2

PET tau false positives

- Across baseline PET tau scans (n=189), agreement between radiologists was perfect (100%, κ=1)
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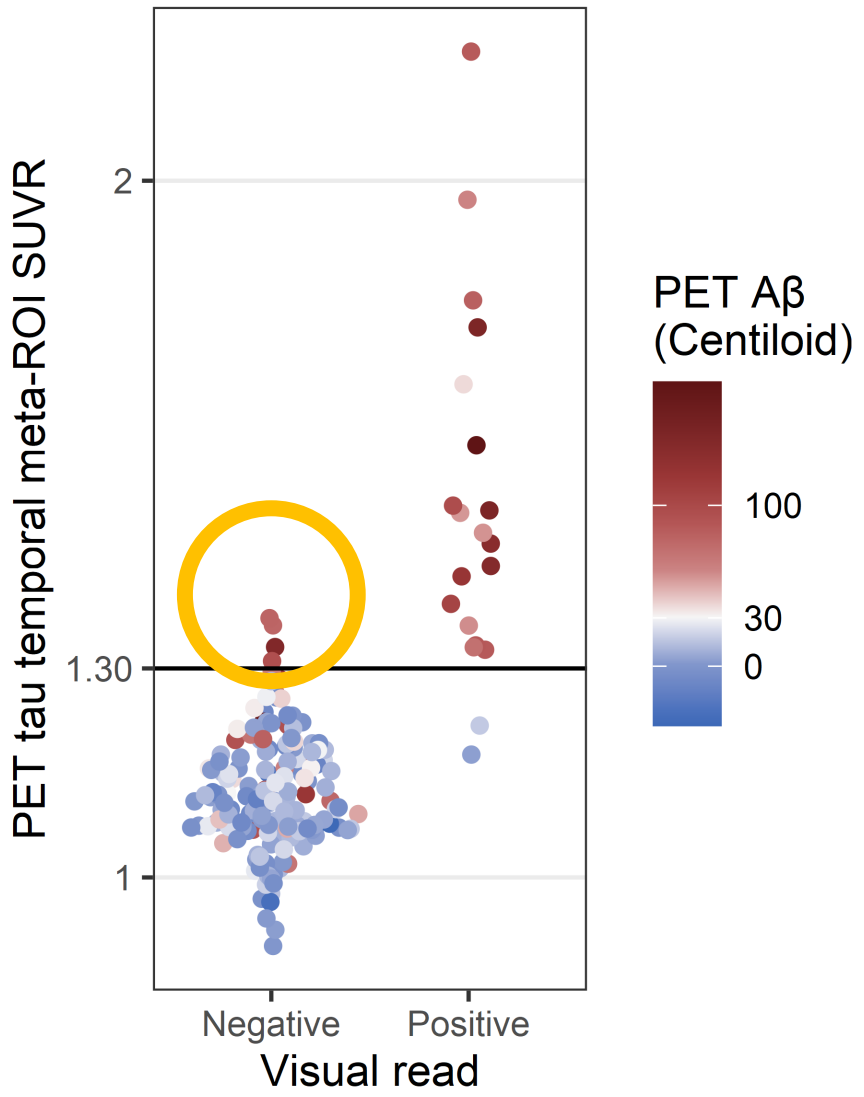
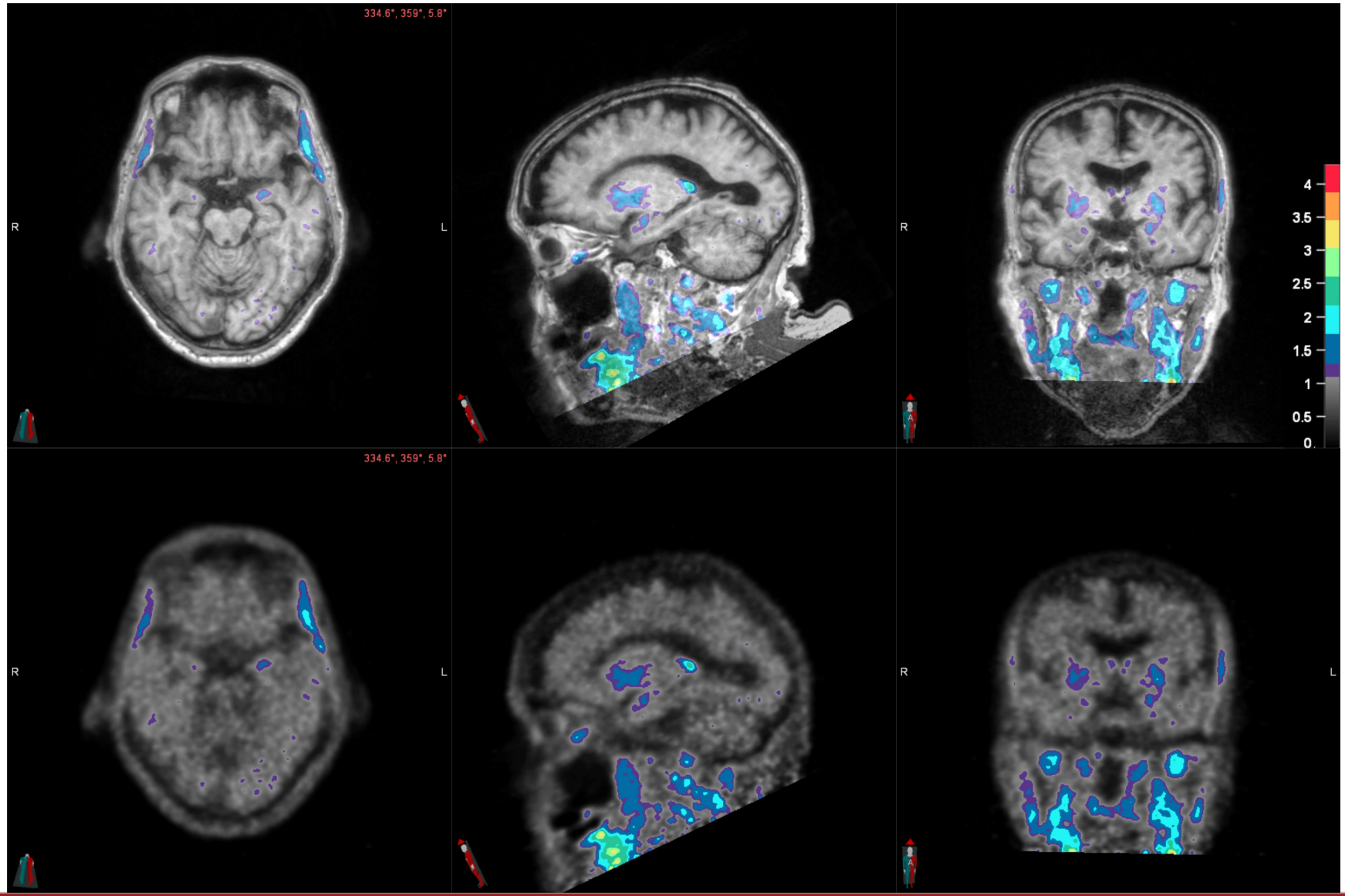
- Using the radiologists' visual reads as a standard, the two false negatives from the research pipeline had asymmetric parietal/precuneus or occipital uptake
- PET Aβ and CSF biomarkers suggest the occipital case is on the AD continuum
- The four false positives had no PLT, occipital, or parietal/precuneus uptake



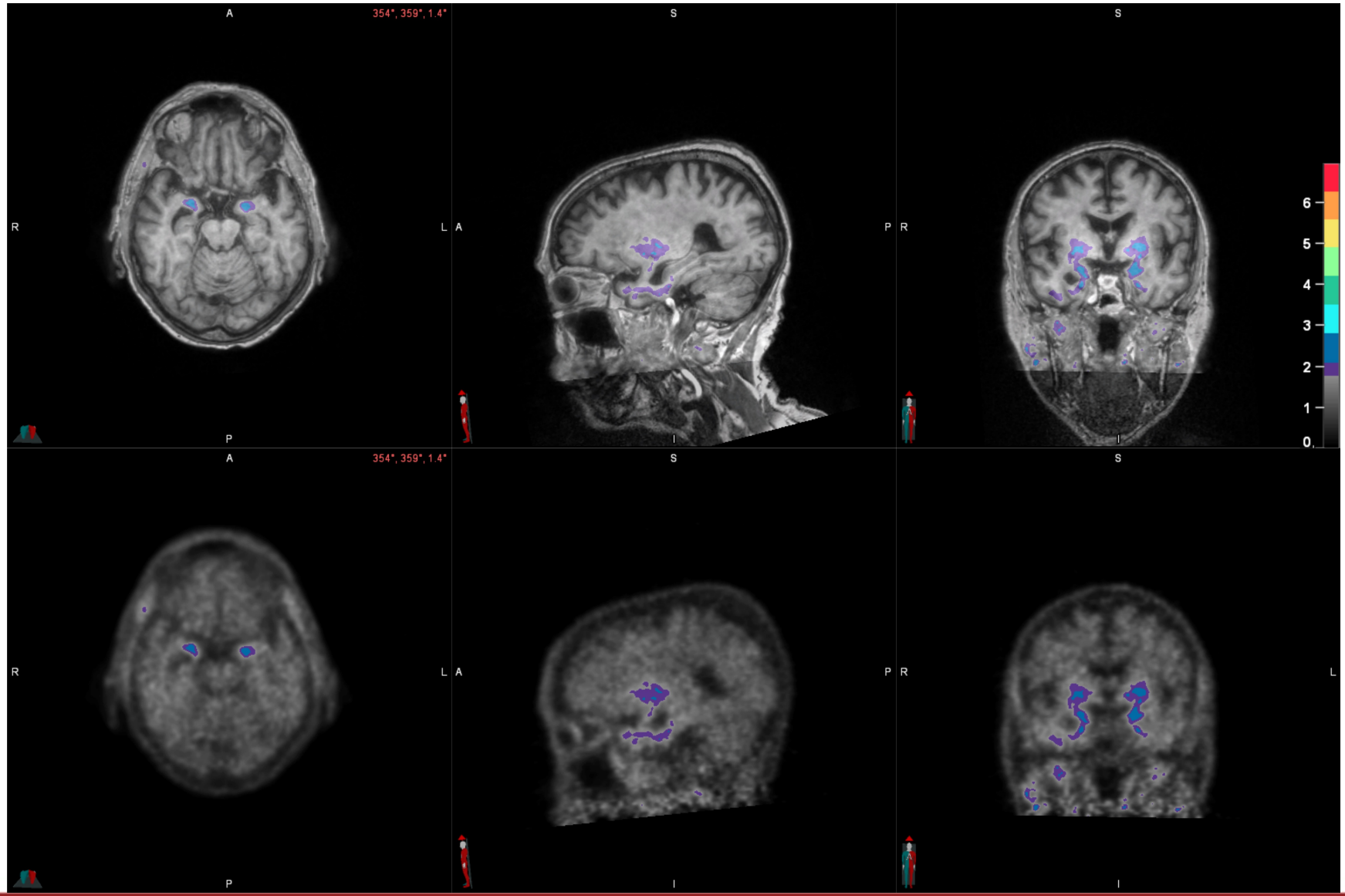
PET tau false positives due to medial temporal lobe (MTL) uptake

81-year-old man



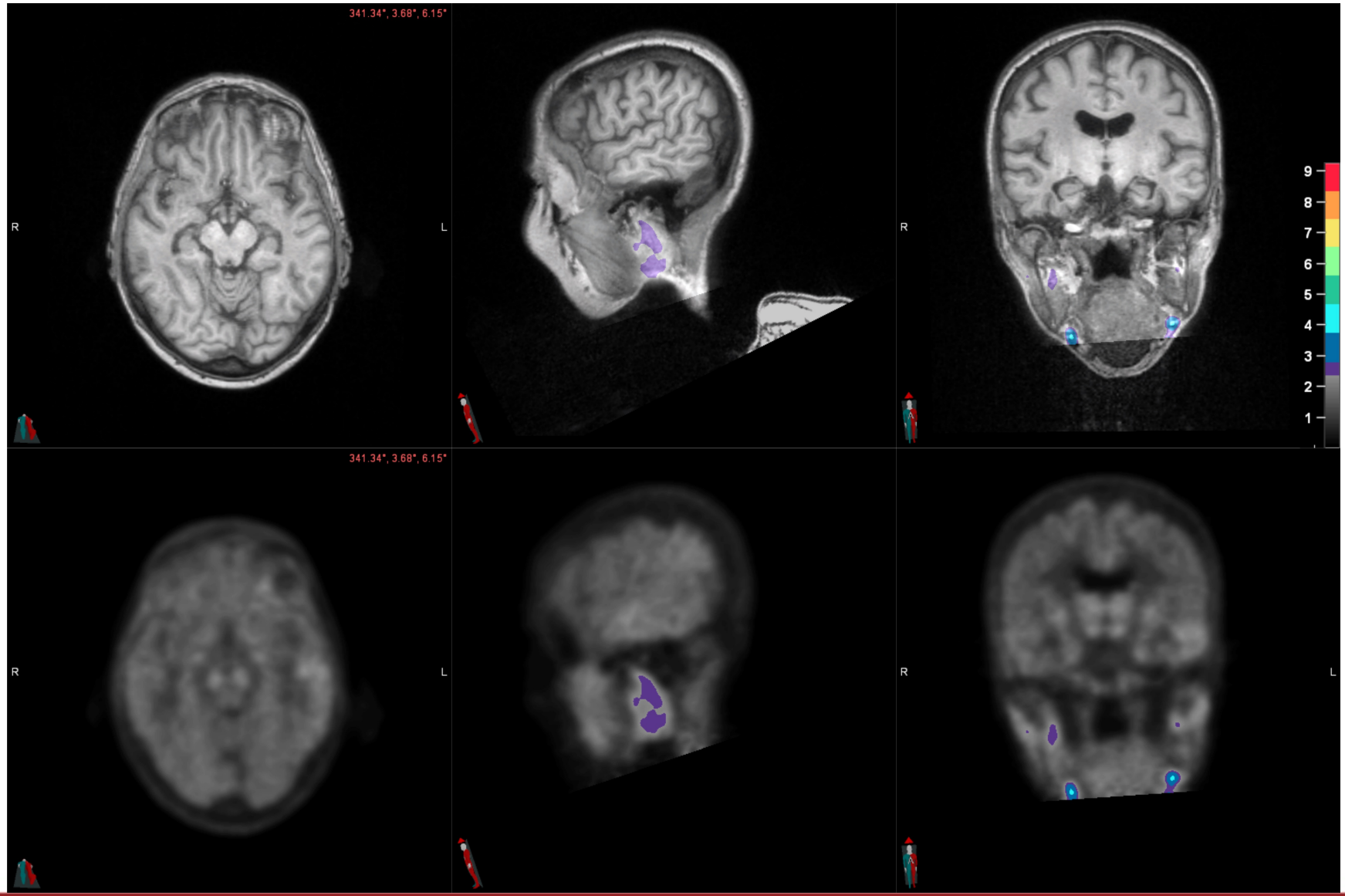
PET tau false positives due to MTL uptake

89-year-old man



PET tau false positives due to MTL or subthreshold uptake

71-year-old woman



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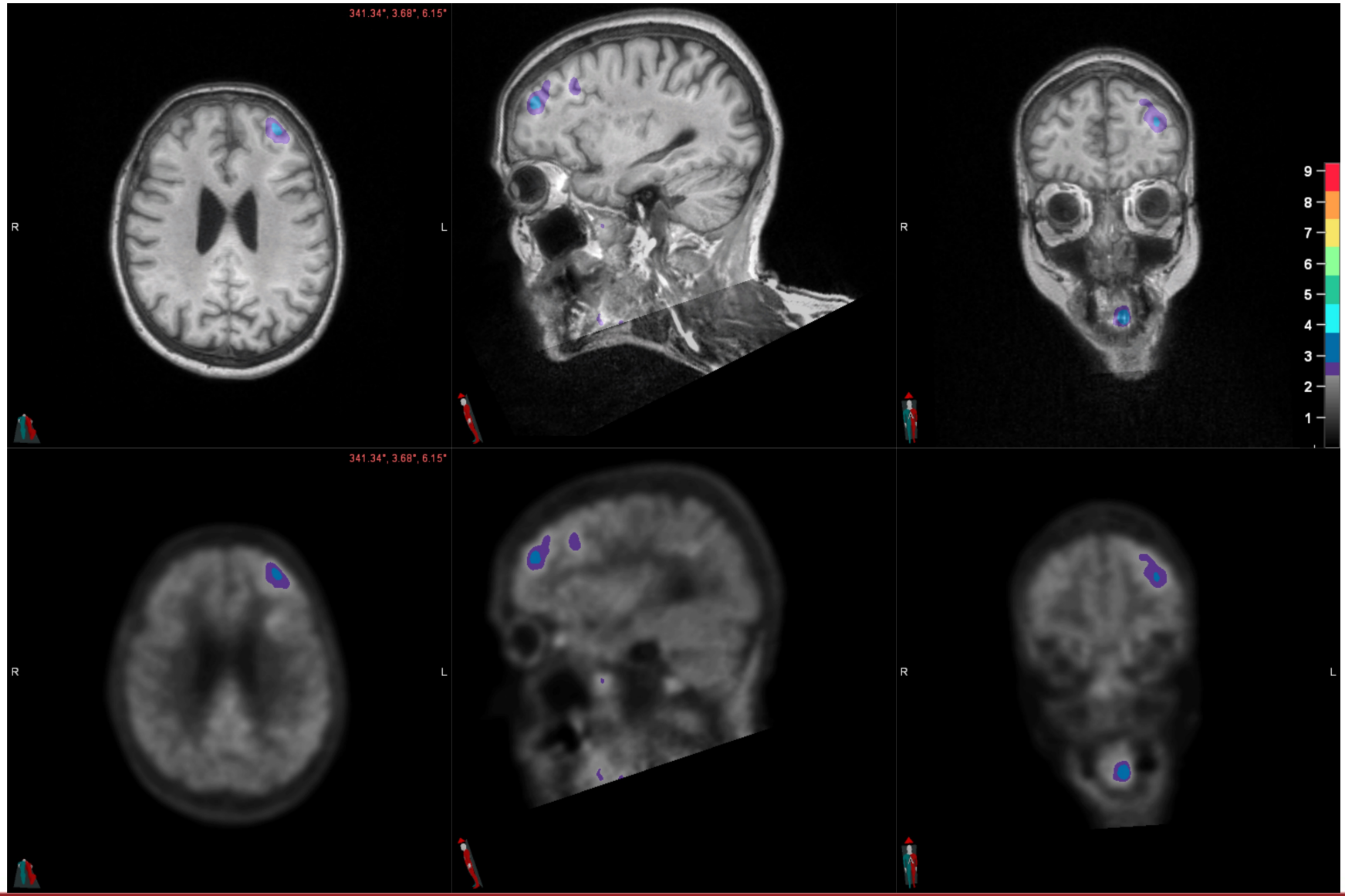
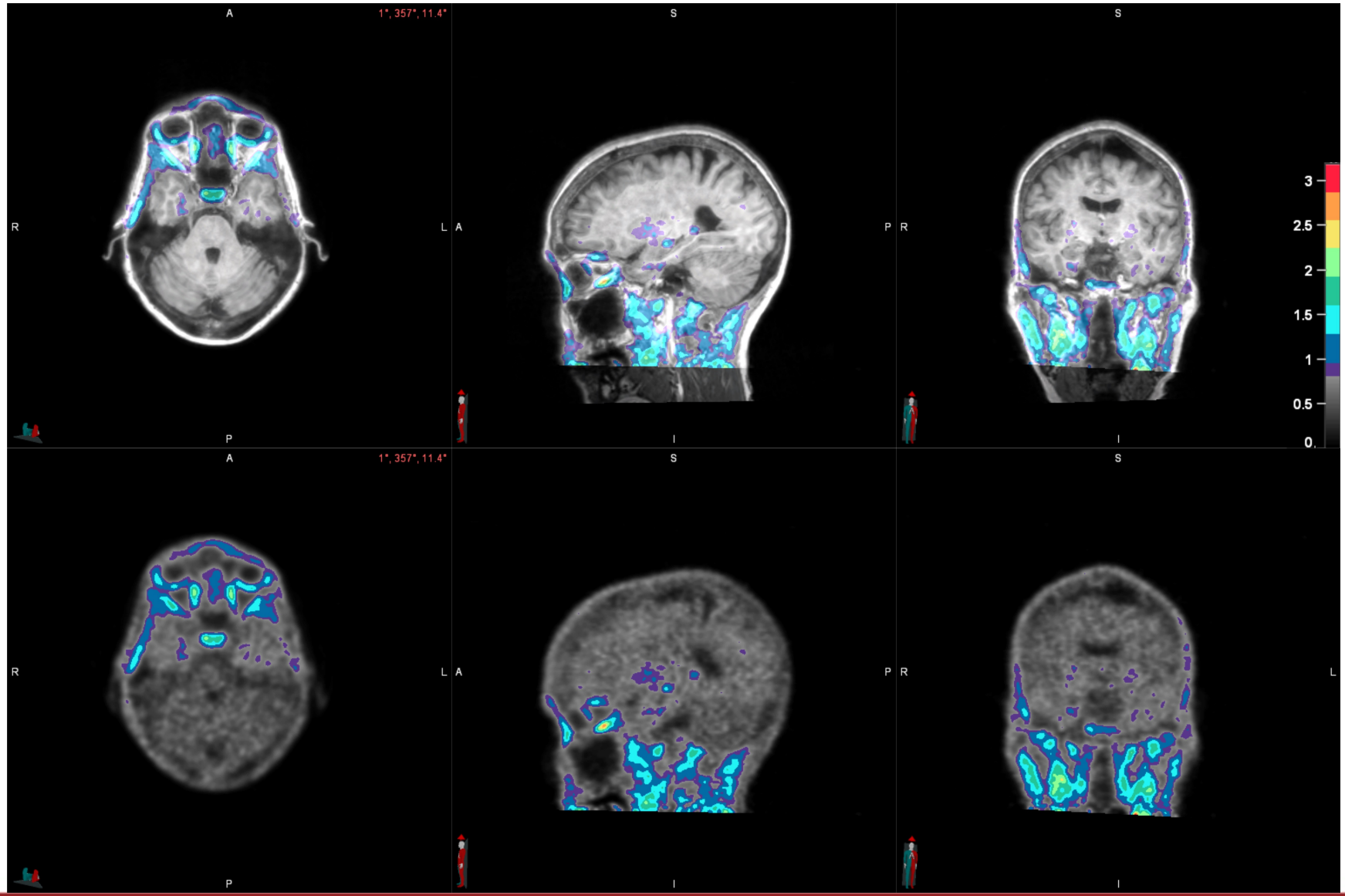


PET tau false positives due to MTL or subthreshold uptake

67-year-old woman



PET tau false positives due to MTL or subthreshold uptake

- Across baseline PET tau scans (n=189), agreement between radiologists was perfect (100%, κ=1)
- Agreement between radiologists and research pipeline was high (96.8%, κ=0.839)
- Using the radiologists' visual reads as a standard, the two false negatives from the research pipeline had asymmetric parietal/precuneus or occipital uptake
- PET Aβ and CSF biomarkers suggest the occipital case is on the AD continuum
- The four false positives had no PLT, occipital, or parietal/precuneus uptake
- PET Aβ and CSF biomarkers suggest all four cases are on the AD continuum
- MTL/subthreshold uptake suggest first three cases demonstrate early tau accumulation

	Age	Sex	*APOE*	Clinical status (CDR®)	PET Aβ (Centiloid)	PET tau (SUVR)	CSF Aβ42/ Aβ40	CSF pTau (pg/ml)
1	81	M	34	Cognitively normal	141	1.33	0.0343	76.0
2	89	M	34	Cognitively normal	78.6	1.36	0.0301	168
3	71	F	44	Uncertain dementia	80.1	1.37	0.0311	103
4	67	F	44	Cognitively normal	95.1	1.31	0.0339	36.4

PET tau false positives due to MTL or subthreshold uptake

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- The fourth case is borderline (1.28, 1.32) when considering a "blurred threshold" with a width of the Coefficient of Variation of our PET tau pipeline (Schwarz et al. 2021)

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2	89	M	34	Cognitively normal	78.6	1.36	0.0301	168
3	71	F	44	Uncertain dementia	80.1	1.37	0.0311	103
4	67	F	44	Cognitively normal	95.1	1.31	0.0339	36.4

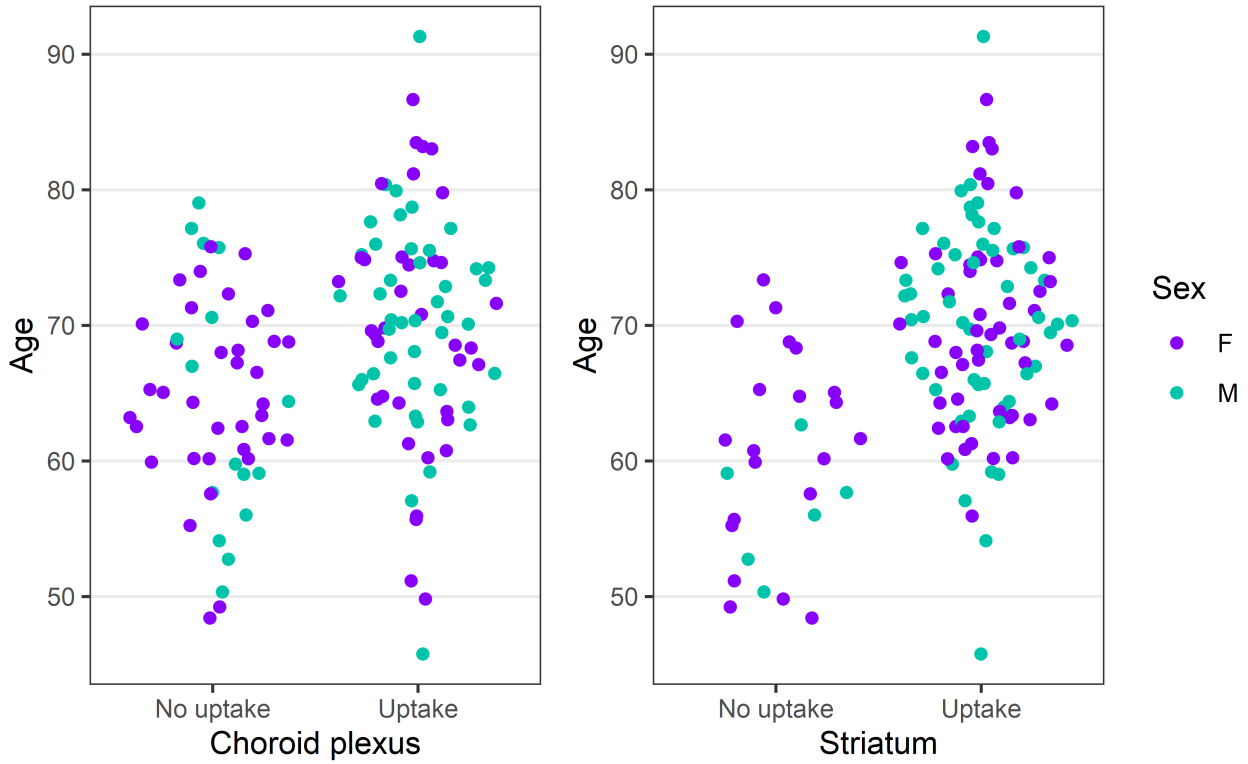
Off-target binding and PART unlikely to contribute to discordance

- Primary Age-Related Tauopathy (PART, Crary et al. 2014) encompasses cases with tau, but not Aβ, pathology, with tau restricted to the MTL
- In our study, no PET Aβ negative case was PET tau positive (max SUVR=1.28)

Off-target binding and PART unlikely to contribute to discordance

- In our study, no PET Aβ negative case was PET tau positive (i.e. no PART cases)

- Off-target binding encompasses PET tracer binding to non-tau deposits, usually in the choroid plexus, striatum, brainstem, and bone/meninges
- In our study, no PET Aβ negative, cognitively normal case was PET tau positive (max SUVR=1.28)
- From this group (n=132), individuals with choroid plexus or striatum off-target binding
  - Did not show increased PET tau SUVRs (t=1.97 or 1.85, p=0.0512 or 0.0729)
  - Tended to be older (t=3.87 or 6.44, p=$1.81*10^{-4}$ or $9.99*10^{-8}$)
- Individuals without choroid plexus or striatum off-target binding
  - Tended to be female (X^2=5.84 or 5.84, p=0.0157 or p=0.0157)



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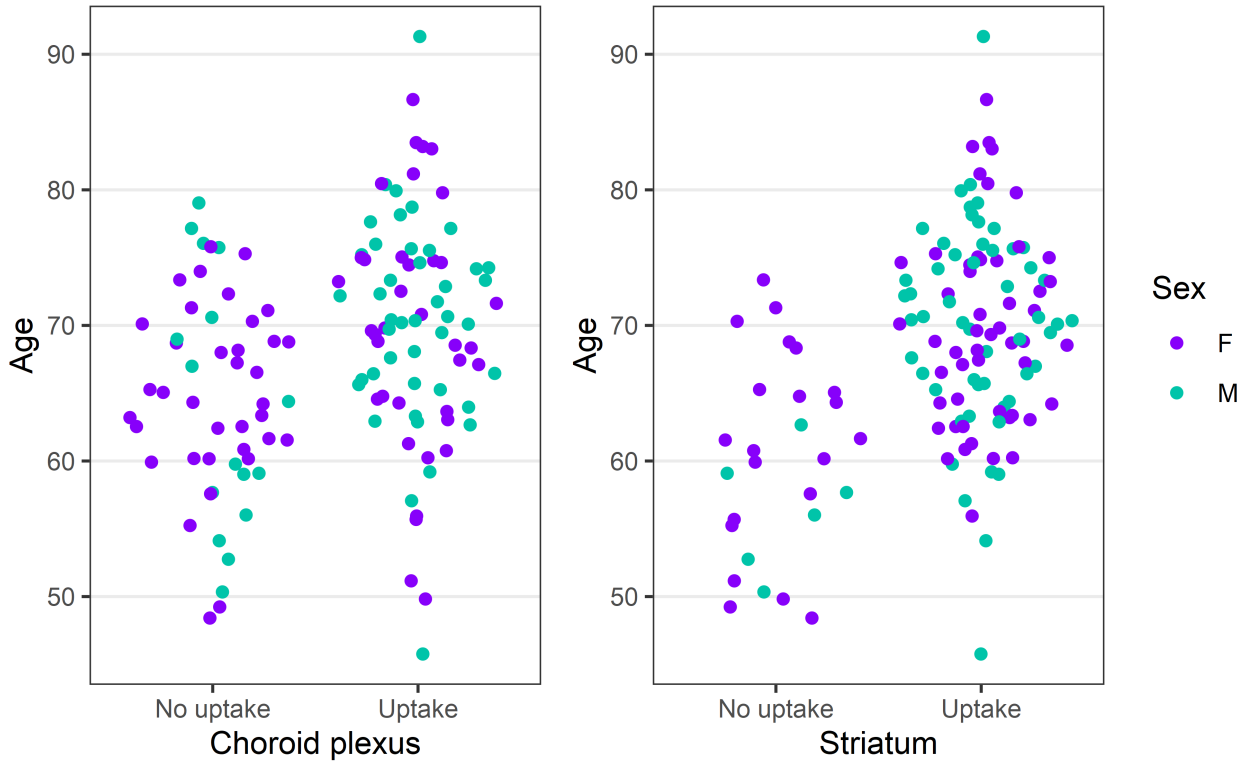
- From this group (n=132), individuals with choroid plexus or striatum off-target binding
  - Did not show increased PET tau SUVRs
  - Tended to be older
- Individuals without choroid plexus or striatum off-target binding
  - Tended to be female
- Nearly all individuals demonstrated brainstem (n=127) or bone/meninges (n=125) off-target binding



Incidental meningiomas demonstrate PET tau uptake

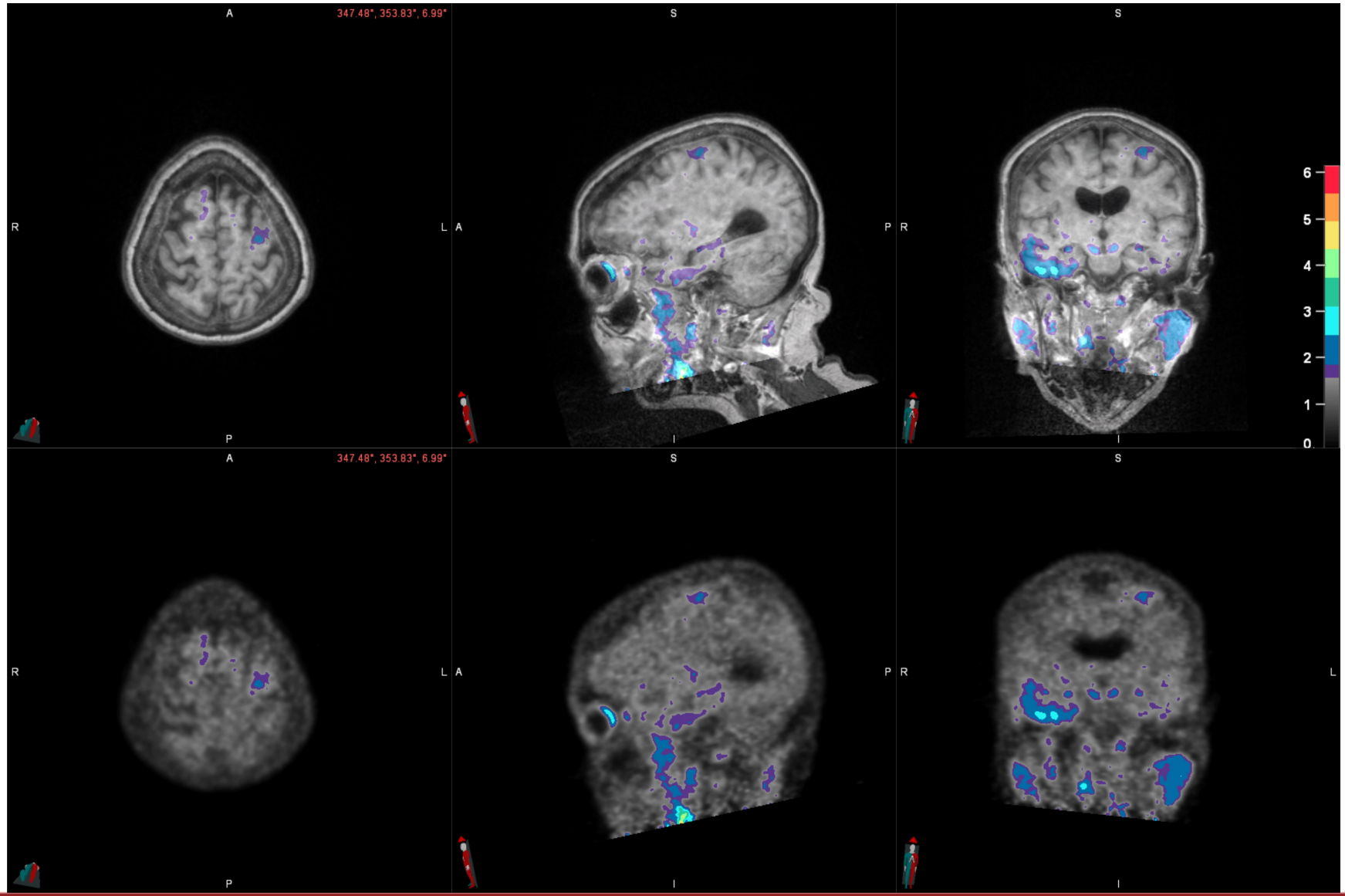
- Two cases had frontal lobe meningioma
- There is likely no influence on AD pathophysiology

	Age	Sex	*APOE*	Clinical status (CDR®)	PET Aβ (Centiloid)	PET tau (SUVR)	CSF Aβ42/ Aβ40	CSF pTau (pg/ml)
Left posterior frontal	75	F	24	Cognitively normal	177	1.62	0.0481*	49.9*
Left frontal	79	M	23	Cognitively normal	8.94	1.13	0.0848*	30.3*

*CSF lumbar punctures were approximately 10 years prior to imaging

Incidental meningiomas demonstrate PET tau uptake

75-year-old woman



Incidental meningiomas demonstrate PET tau uptake

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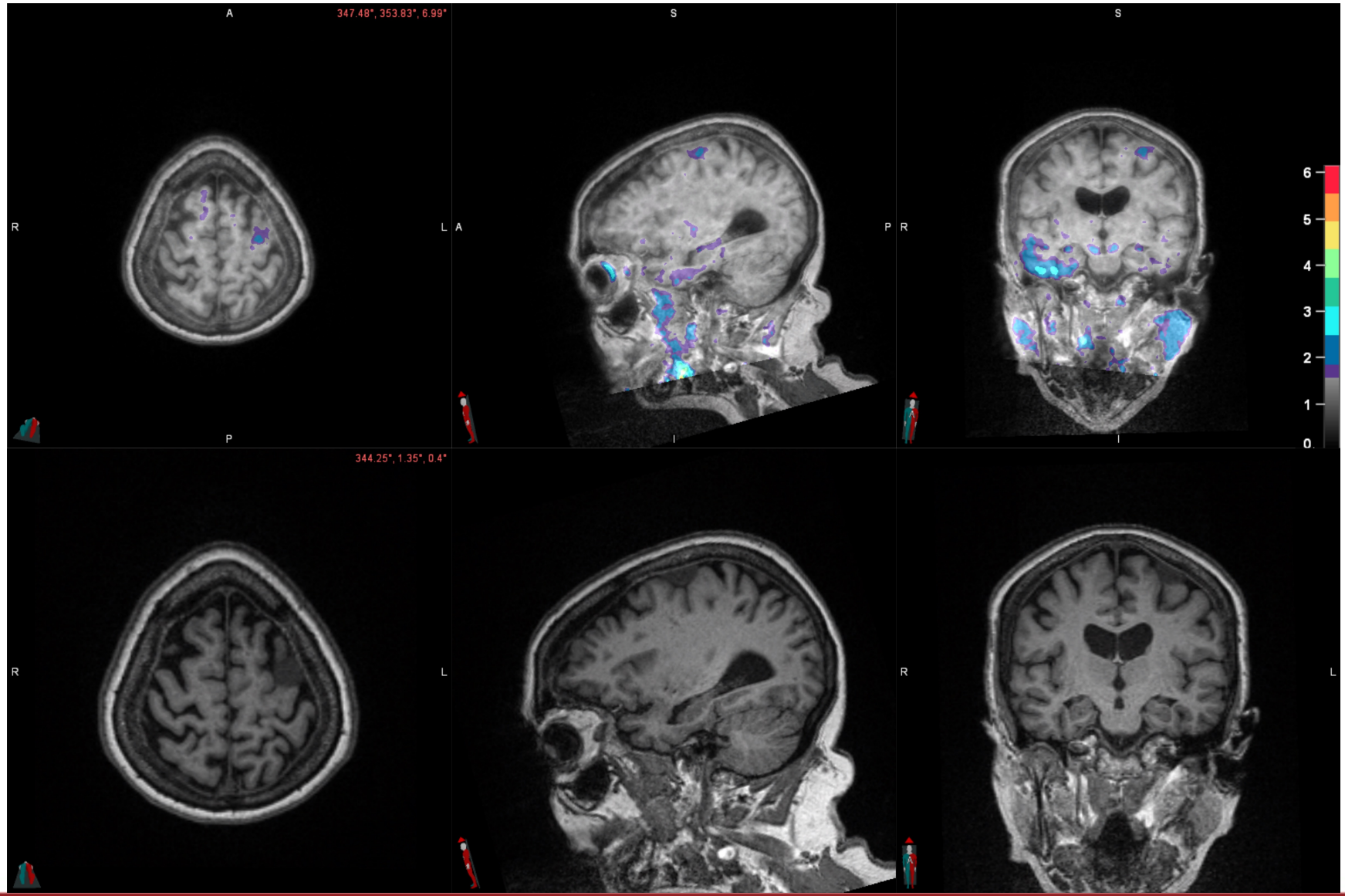
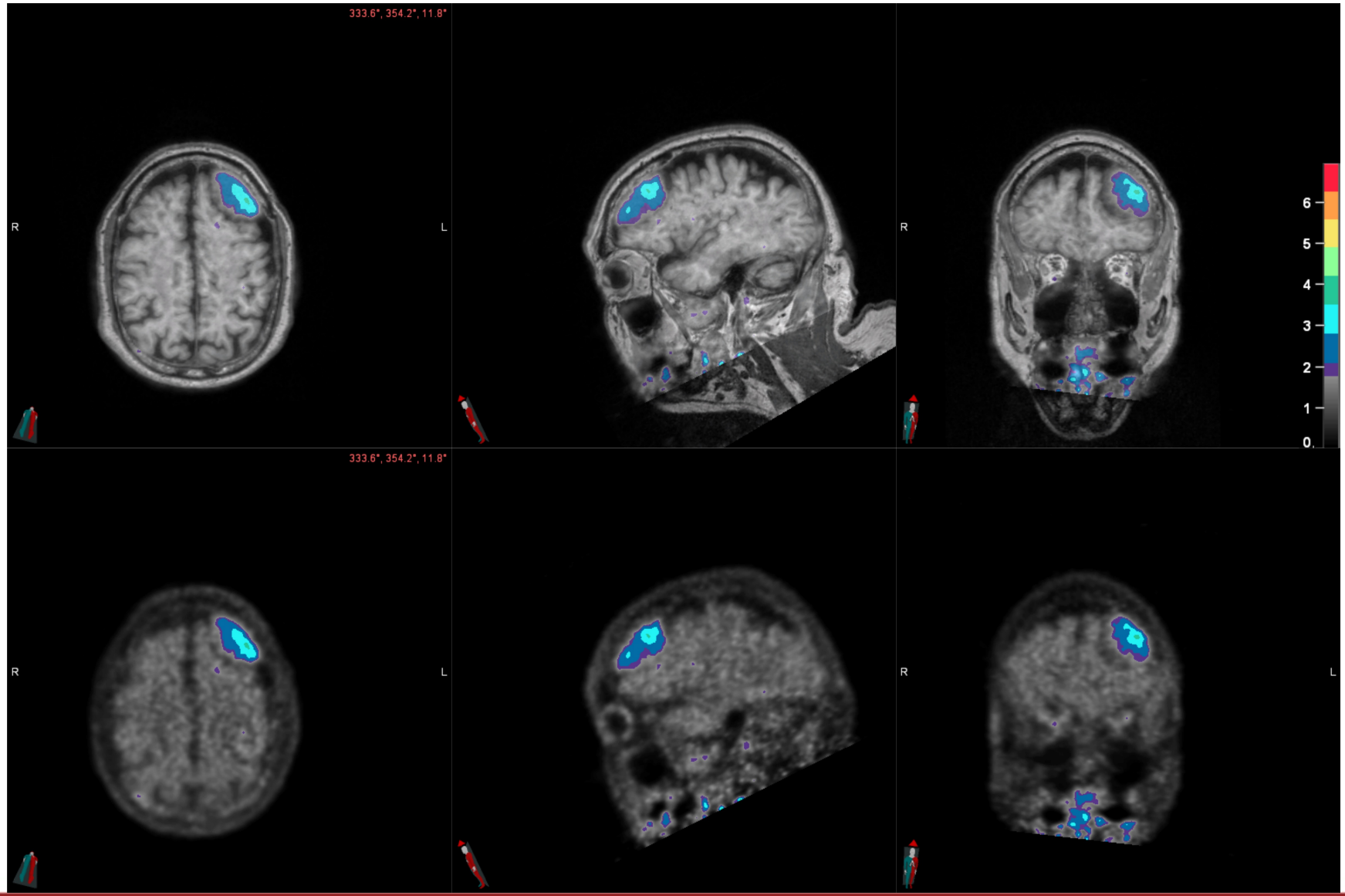


Incidental meningiomas demonstrate PET tau uptake

79-year-old man



Incidental meningiomas demonstrate PET tau uptake

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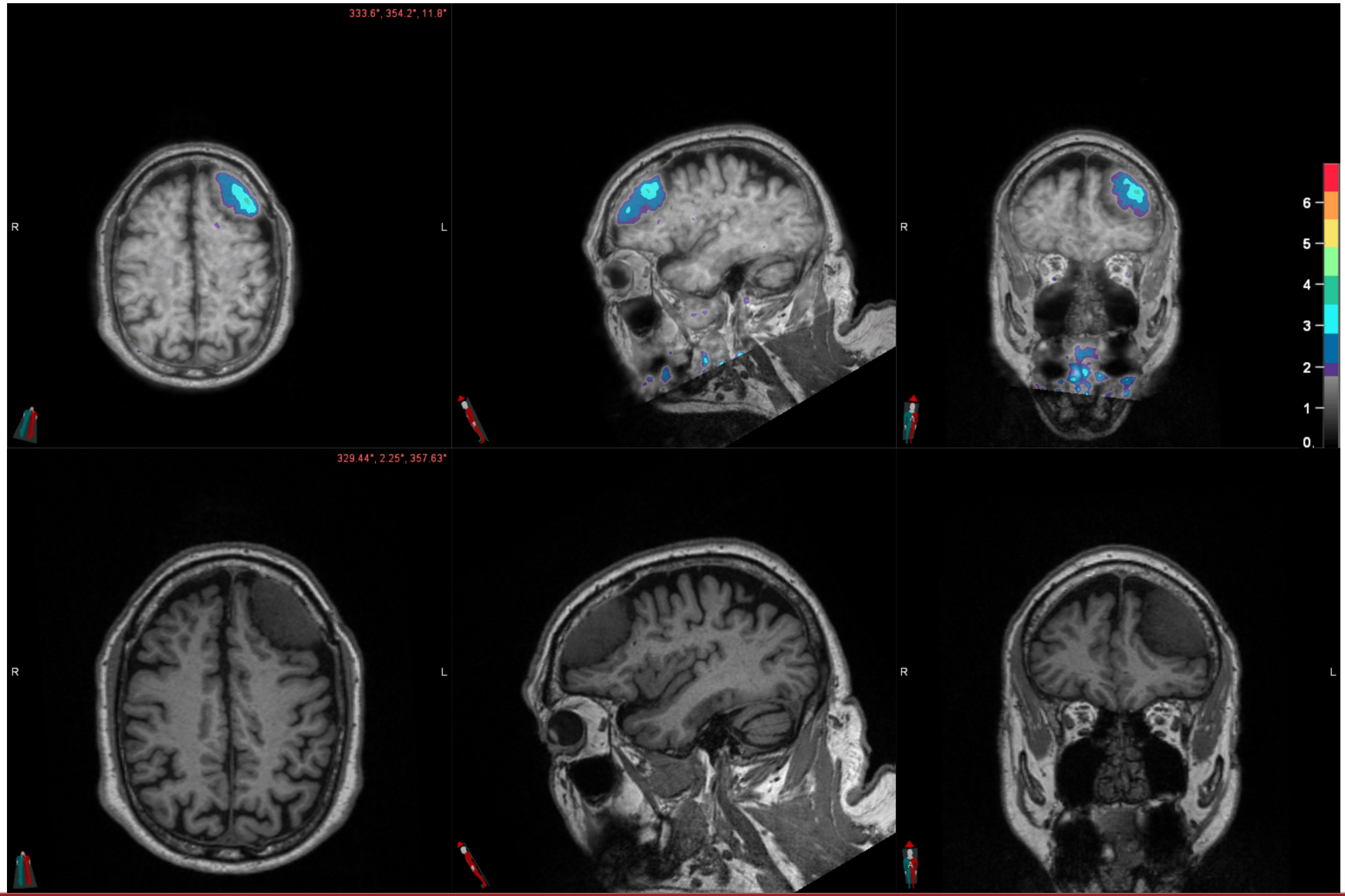


Tau status can also be determined by CSF

- Aggregated tau and associated pathophysiology, or tau status (T), was first defined by cerebrospinal fluid (CSF); later, by positron emission tomography (PET)
- To what extent does PET tau imaging agree with results from CSF pTau quantification?

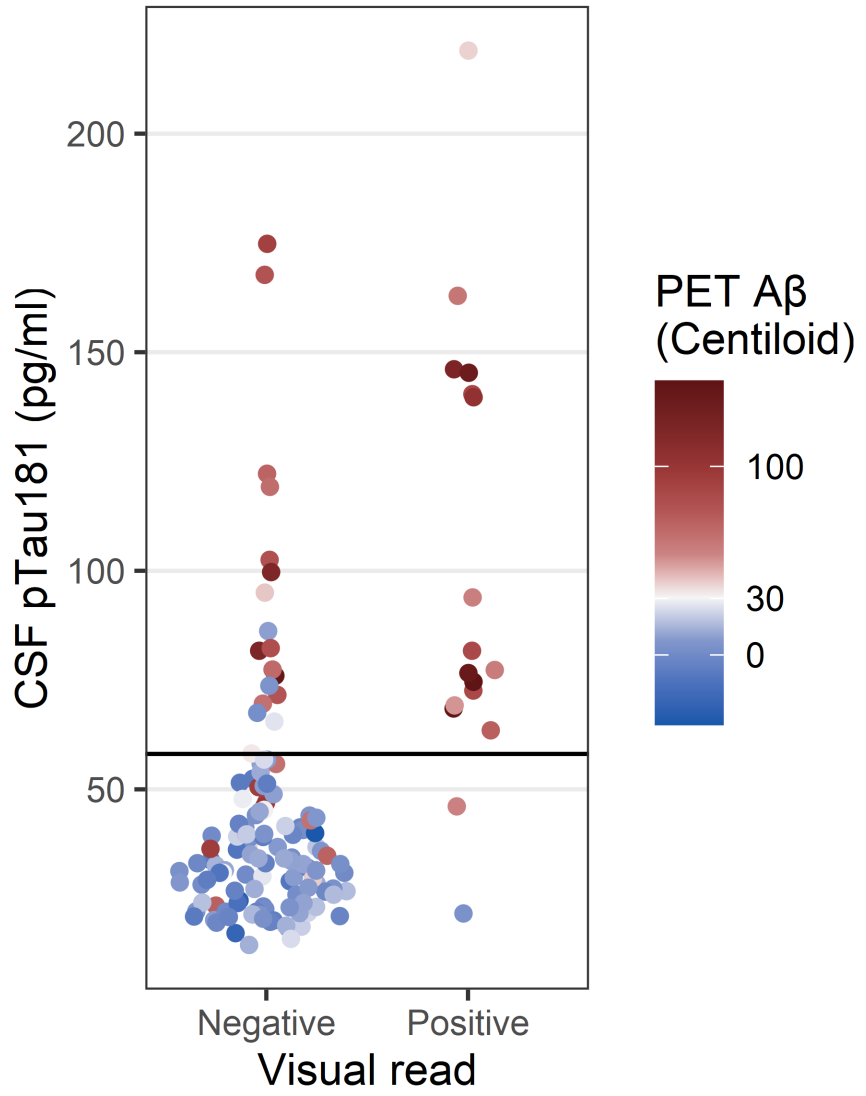
CSF acquisition

- A majority of participants underwent lumbar puncture (n=144 out of 189) within 18 months of a PET tau imaging visit
- Participants underwent lumbar puncture (L4-L5) in the morning following overnight fasting
- 20 to 30 ml of CSF was collected in a 50 ml polypropylene tube via gravity drip using an atraumatic Sprotte 22 gauge spinal needle
- Samples were kept on ice and centrifuged at low speed within two hours of collection, then all volume (but the bottom 0.5 ml) was transferred to another 50 ml tube
- CSF was aliquoted at 500 µl into polypropylene tubes and stored at -80°C
- Concentrations of Aβ40, Aβ42, tTau, and pTau181 were measured by chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE G1200, Fujirebio, Malvern, PA)

Photo credit: Fujirebio

PET tau and CSF pTau are mildly concordant

- Agreement between PET tau visual reads and CSF pTau181 was mild (86.1%, κ=0.526)



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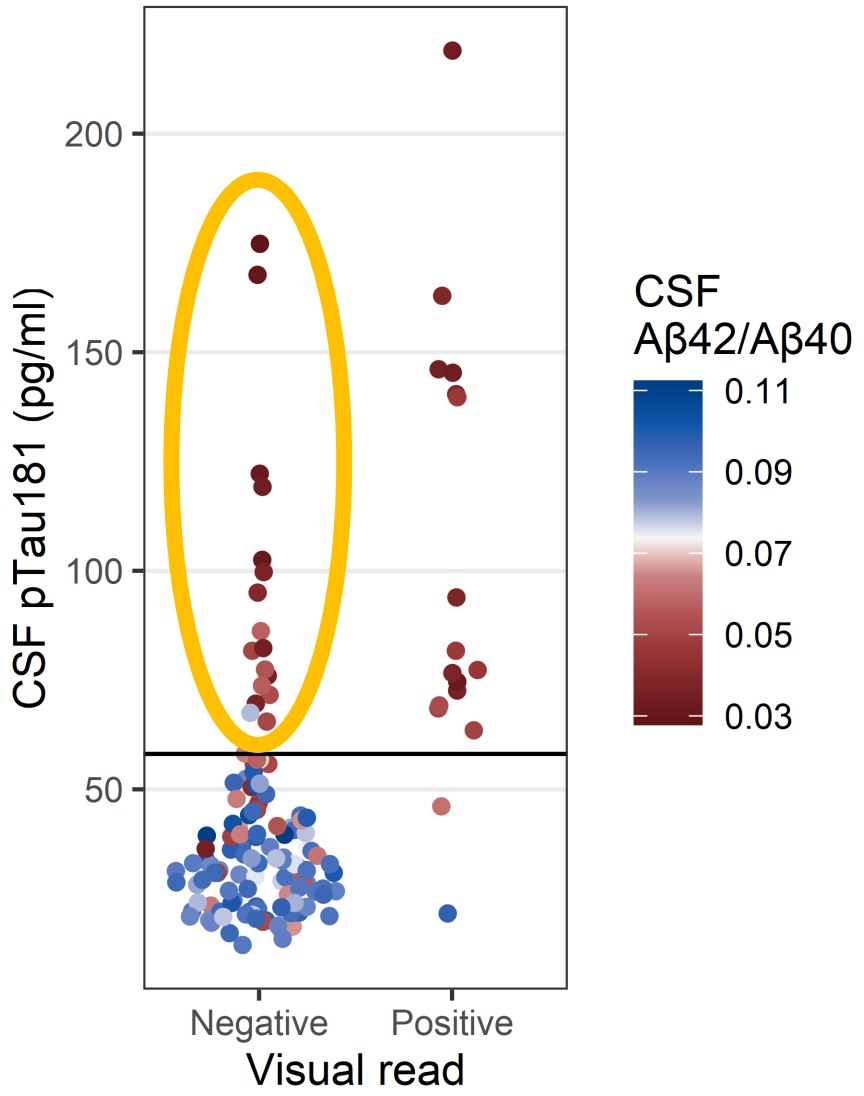
- False positives (n=18) tended to have elevated PET Aβ and/or CSF Aβ42/Aβ40
- This suggests CSF pTau181 becomes abnormal before PET tau in AD pathoprogression



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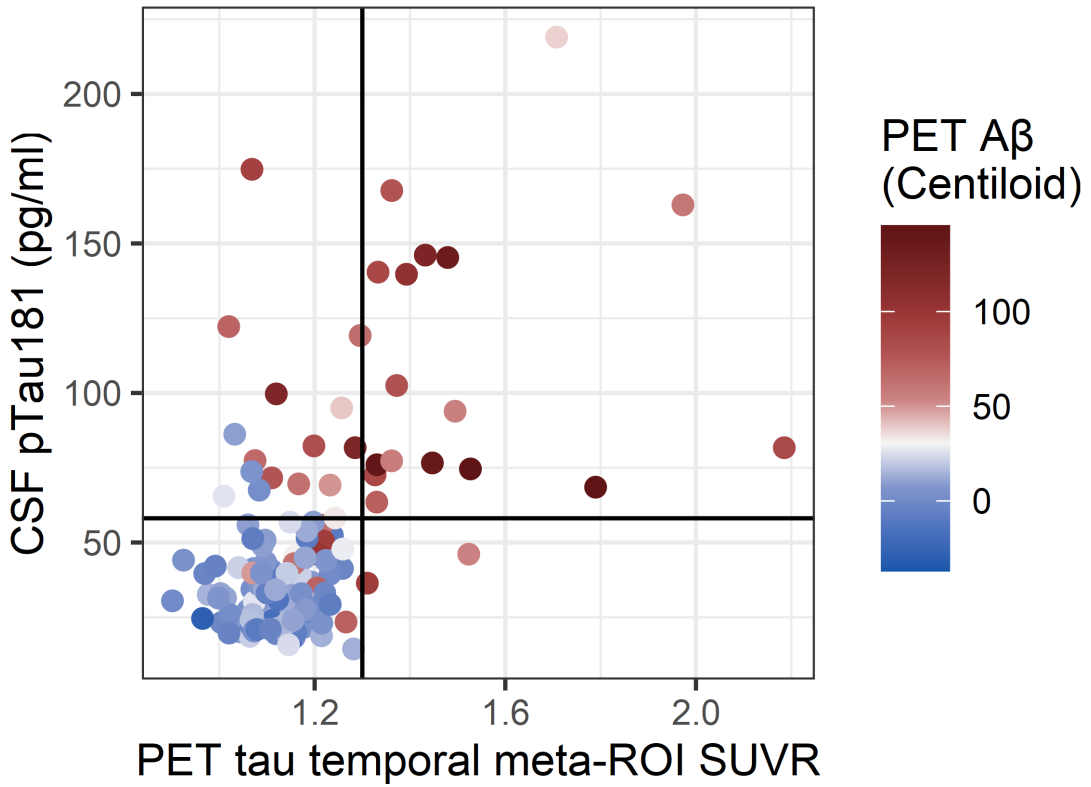

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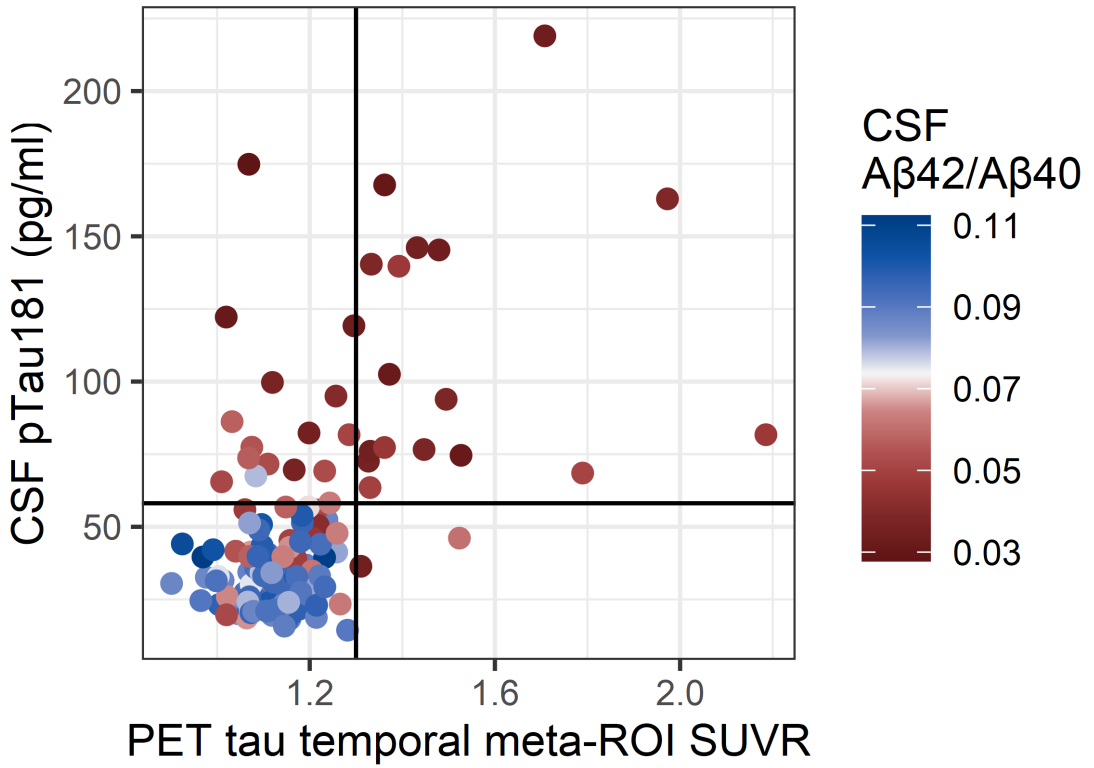
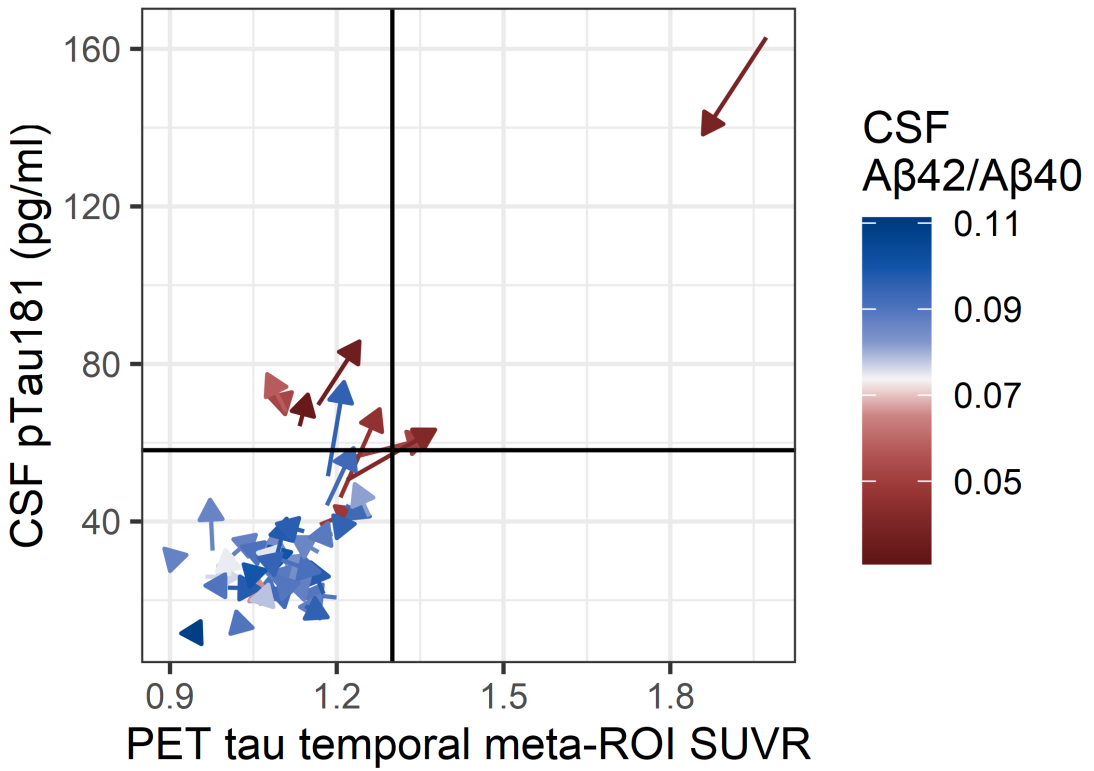


Three-year follow-up suggests discordance is due to disease stage

- 12 participants had longitudinal PET tau visual reads, PET tau quantification, and CSF pTau
- Ignoring visual reads, 378 participants from the Knight ADRC (at the time of DF17) had at least one PET tau imaging visit and lumbar puncture within 18 months
- 47 of these participants had longitudinal PET tau quantification and CSF pTau (average follow-up time=3.1 years)
- 2 participants converted from PET-/CSF- to PET-/CSF+
- 2 participants converted from PET-/CSF- to PET+/CSF+



Key assertions

- PET tau visual reads are perfectly concordant between radiologists (100%, κ=1)
- PET tau visual reads and PET tau quantification are highly concordant (96.8%, κ=0.839)
- Things that can cause discordance
  - Incidental findings (bleeds, meningiomas)
  - Occipital-predominant AD subtype
  - MTL and subthreshold uptake (visual reads are more conservative regarding disease stage)
- PET tau visual reads and CSF pTau quantification are mildly concordant (86.1%, κ=0.526)
- Things that can cause discordance
  - Disease stage (biofluids typically become abnormal before imaging)
- Don’t blindly follow visual read guidelines or research pipelines – look at all available imaging (MRI!) to make a holistic decision

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