HOUSTON Methodist NEUROLOGICAL INSTITUTE

Functional Imaging in Cognitive Disorders: A Research Case

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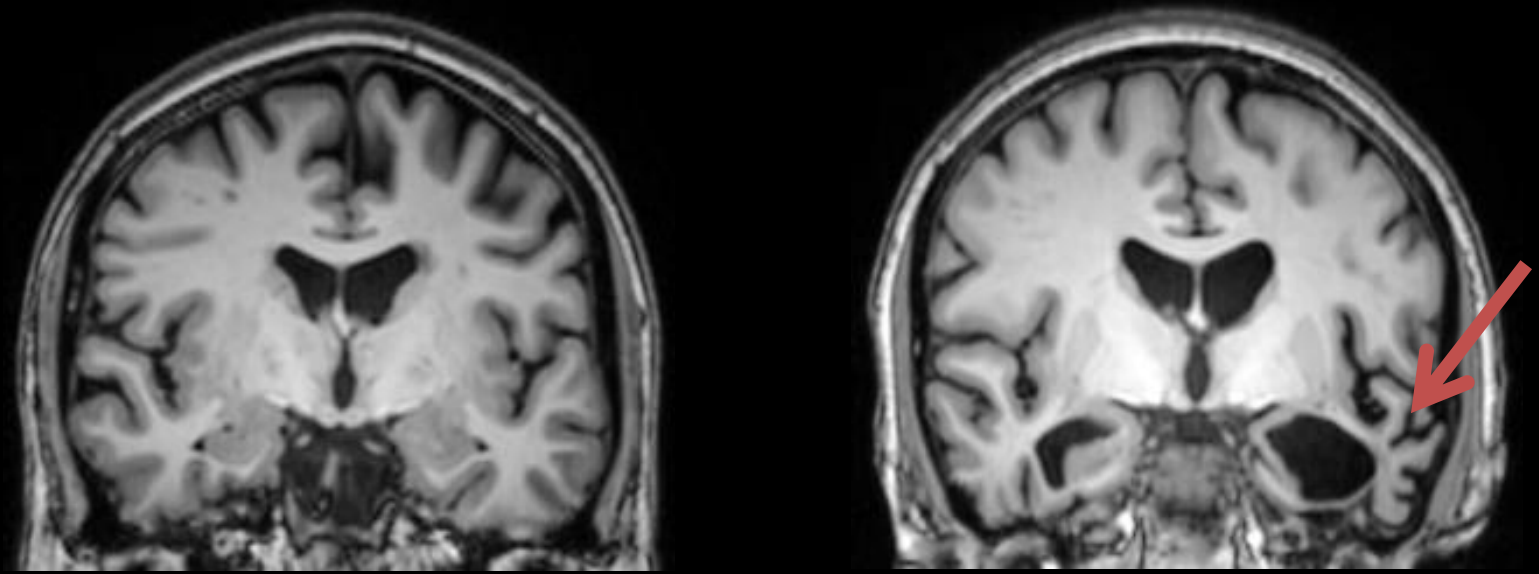
Semantic Dementia

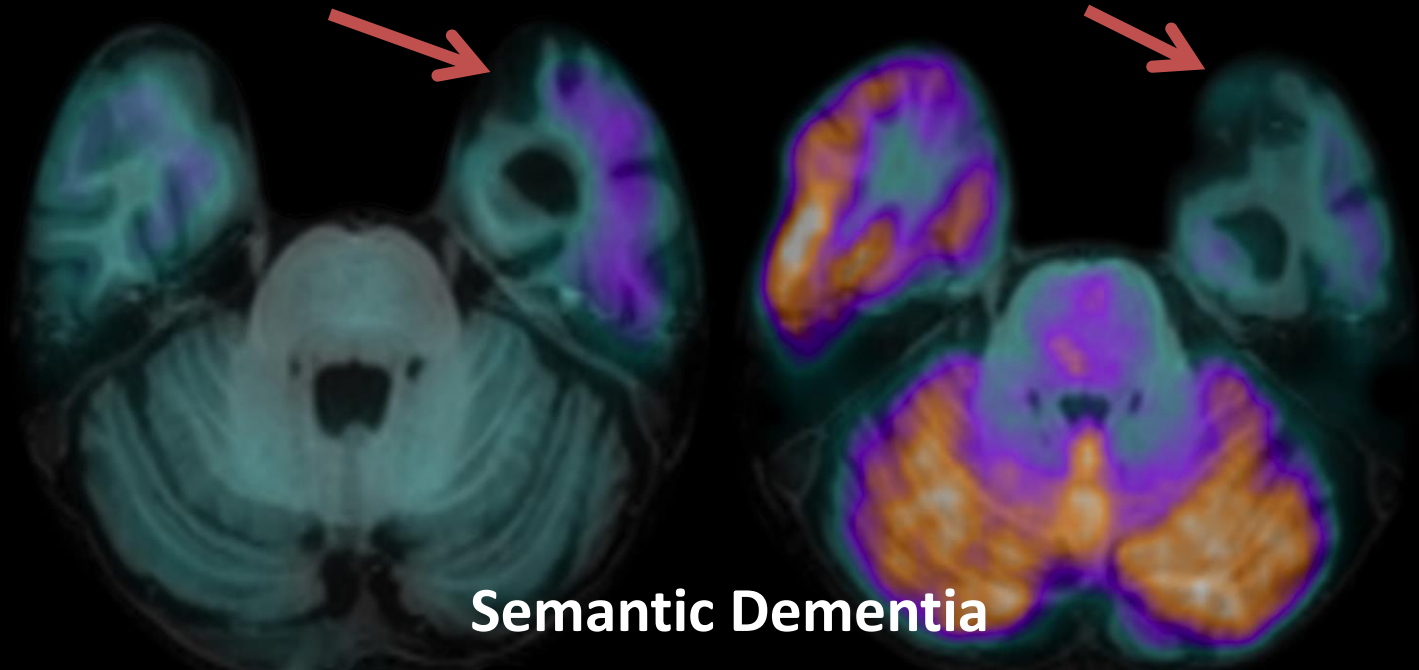
- Semantic variant primary progressive aphasia
- Progressive naming and comprehension impairment
- Asymmetric atrophy of the temporal poles, L>R



Inverse Correlation of [^{18}F]AV-1451 with Metabolism

Increased [^{18}F]AV-1451 (flortaucipir)

Decreased metabolism



Semantic Dementia

Tau PET

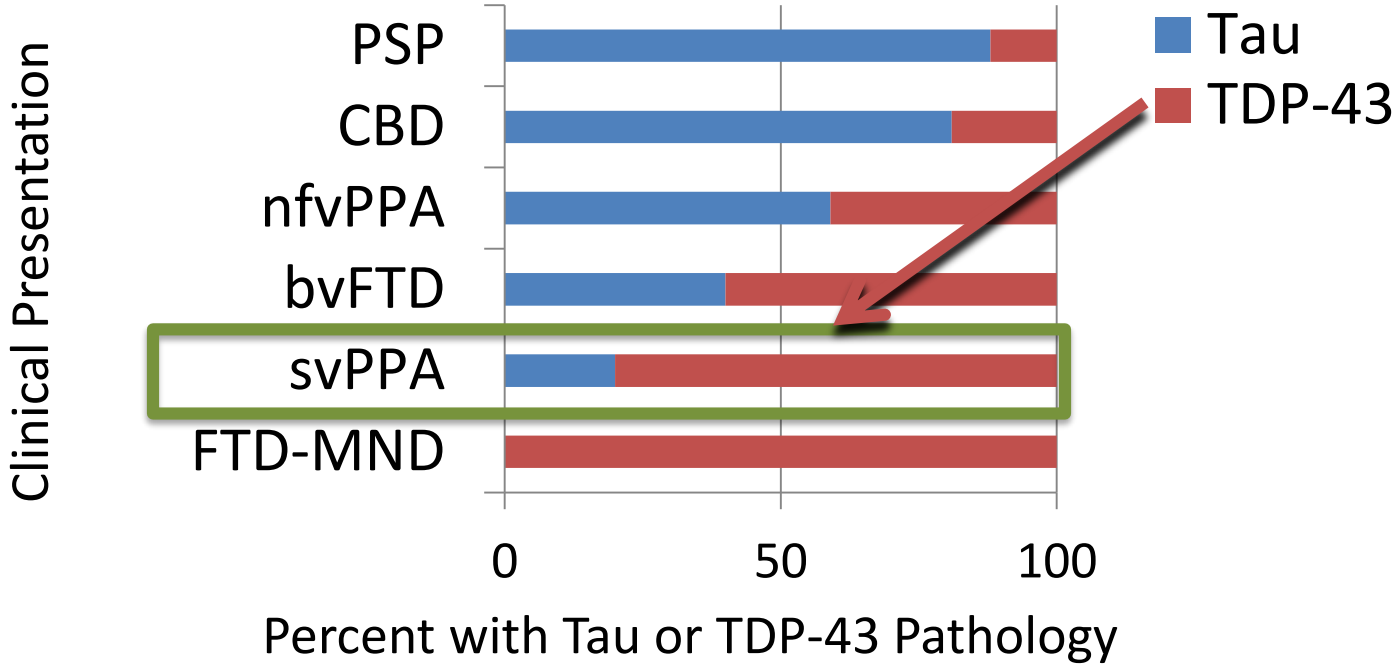
[^{18}F]AV-1451

FDG PET

Metabolism

Only About 20% of Semantic Dementia Cases Have Tau

Most Have TDP-43 Pathology



Josephs KA et al. 2011; Acta Neuropathol 122:137

The Flortaucipir Semantic Dementia Paradox

- Even though the majority of semantic dementia cases are not associated with tau deposition
  - But with TDP-43 aggregates
- Flortaucipir consistently shows increased uptake, particularly in temporal poles
- But flortaucipir is supposed to bind to tau, not to TDP-43

» Lin YG et al. HAI 2015

Could Regional Inflammation Explain This Paradox?

- Semantic dementia is associated with inflammation
  - Semantic dementia patients are more likely to have autoimmune diseases and have increased levels of TNF-alpha in blood
    - » Miller ZA et al. J Neurol Neurosurg Psychiatry 2013;84:956
  - Immune-related risk genes are enriched in SD
    - » Broce I et al. PLoS Med 2018, doi: 10.1371/journal.pmed.1002487
- Regional brain inflammation is associated with increased MAO B
    - » Meulendyke KA et al. J Infect Dis 2014:210:904
  - Possibly causing non-specific flortaucipir binding

Objective:

To determine whether in semantic dementia (SD) there is an association between

- ^{18}F AV-1451 uptake and
- inflammation, measured with the TSPO tracer ^{11}C PBR28
  - TSPO is overexpressed in activated microglia

so that inflammation could explain the ^{18}F AV-1451 uptake in SD

Hypothesis:

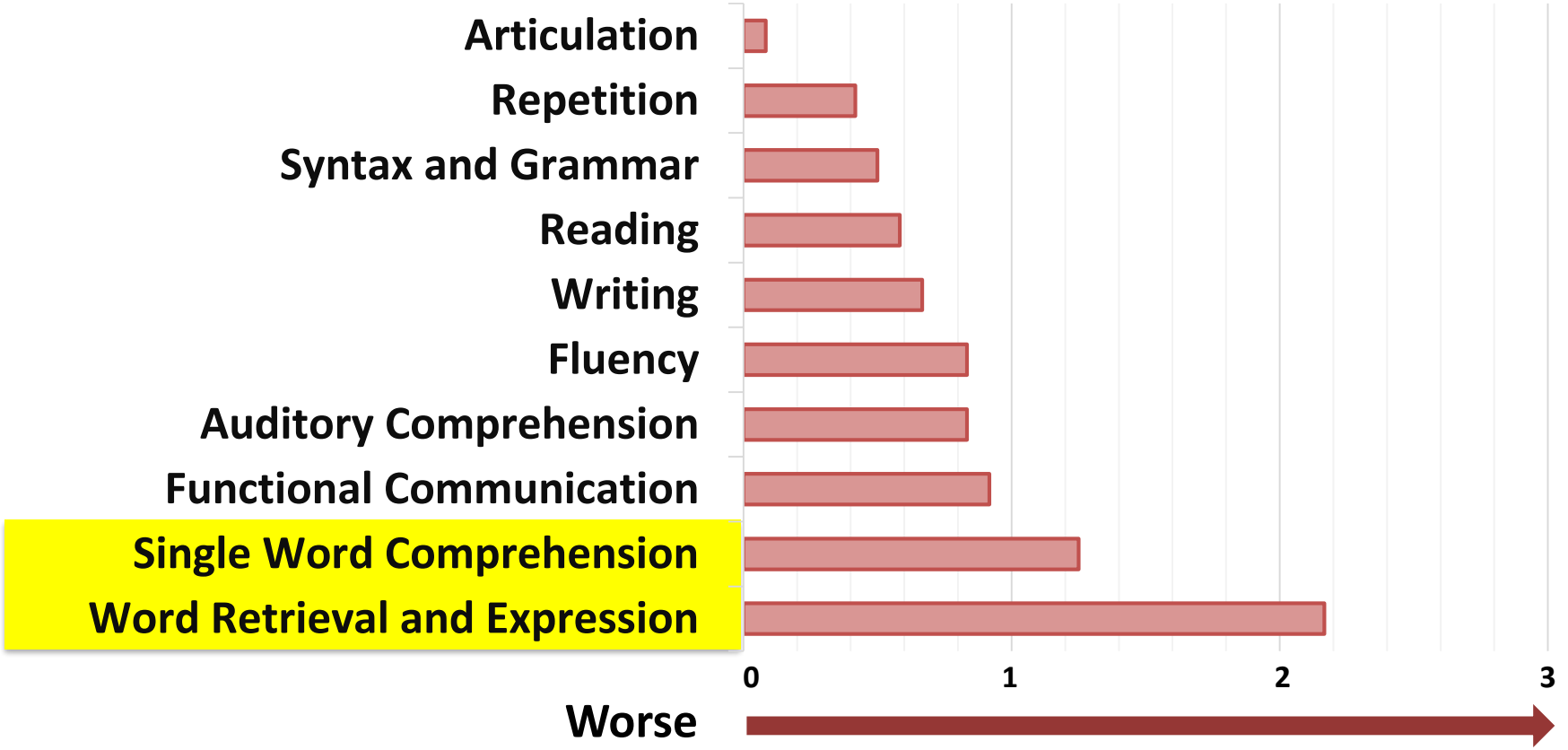
The flortaucipir (^{18}F AV-1451) signal in semantic dementia reflects regional inflammation, rather than tau levels

We performed ^{18}F AV-1451 tau PET and ^{11}C PBR28 PET in patients with Semantic Dementia (SD) and healthy controls (HC)

	SD	HC for ^{18}F AV-1451	HC for ^{11}C PBR28
N	6	8	10
Women / Men	4 / 2	4 / 4	6 / 4
Age	69 ± 8.5	69 ± 7.4	68.2 ± 4.9
MMSE	21.2 ± 8.5	29.5 ± 1.1	29.5 ± 0.8
^{11}C PIB / ^{18}F Florbetapir	Negative	N/A	N/A
TSPO High-Affinity binders*	6/6	N/A	4/10
TSPO Mixed-Affinity Binders*	0/6	N/A	6/10

*Determined by TSPO Ala147Thr (rs6971) polymorphism genotyping

Naming and single word comprehension were most affected in Semantic Dementia, suggesting maximal involvement of the anterior portion of the left temporal lobe



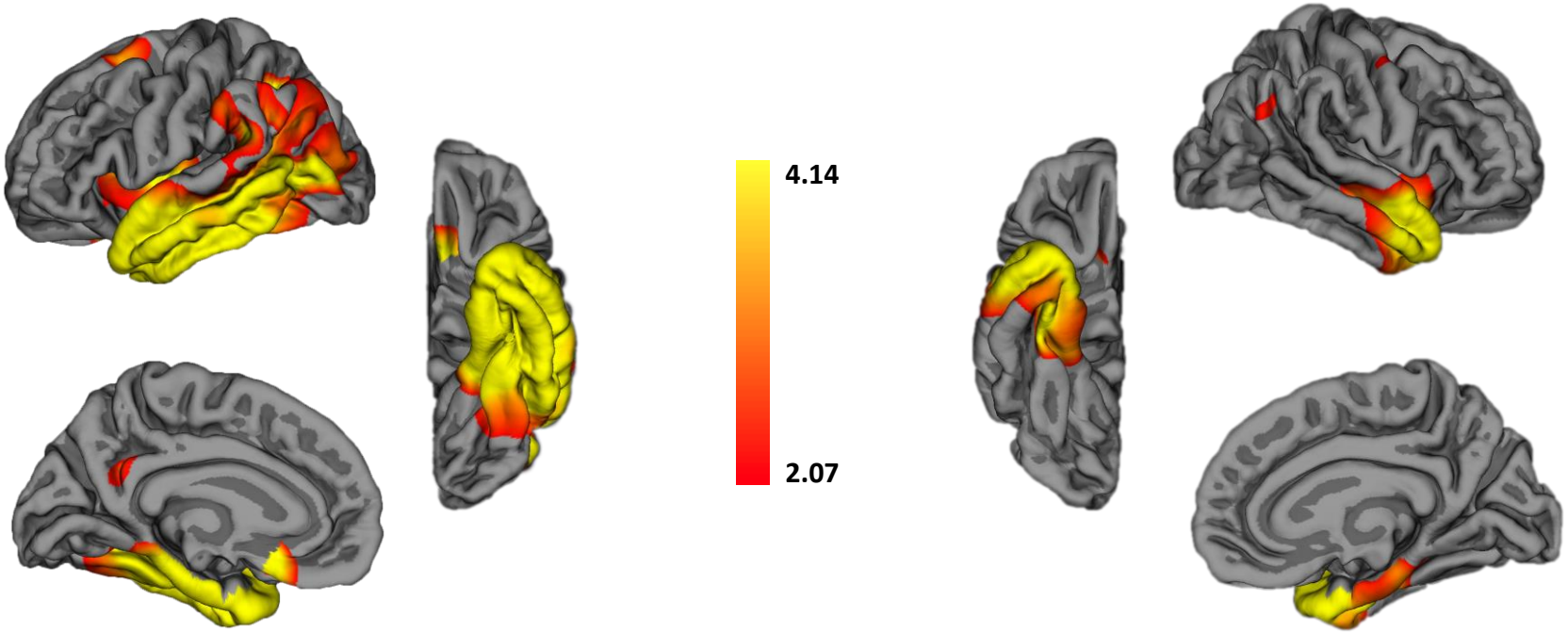
Cortical Thickness on fsaverage surface

6 SD < 18 HC

p < 0.05 FDR-corrected

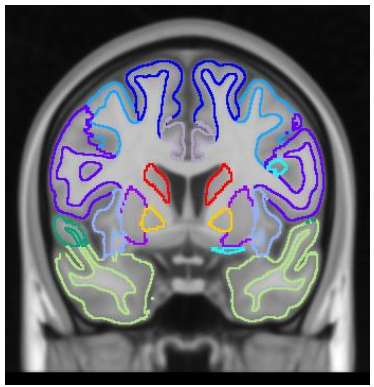
Left hemisphere

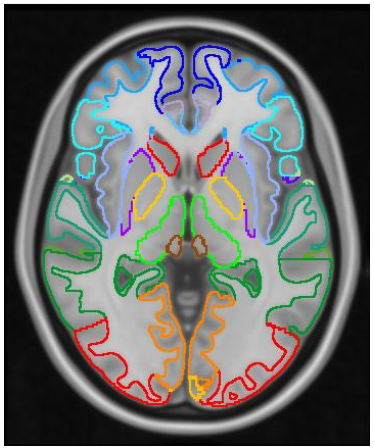
Right hemisphere

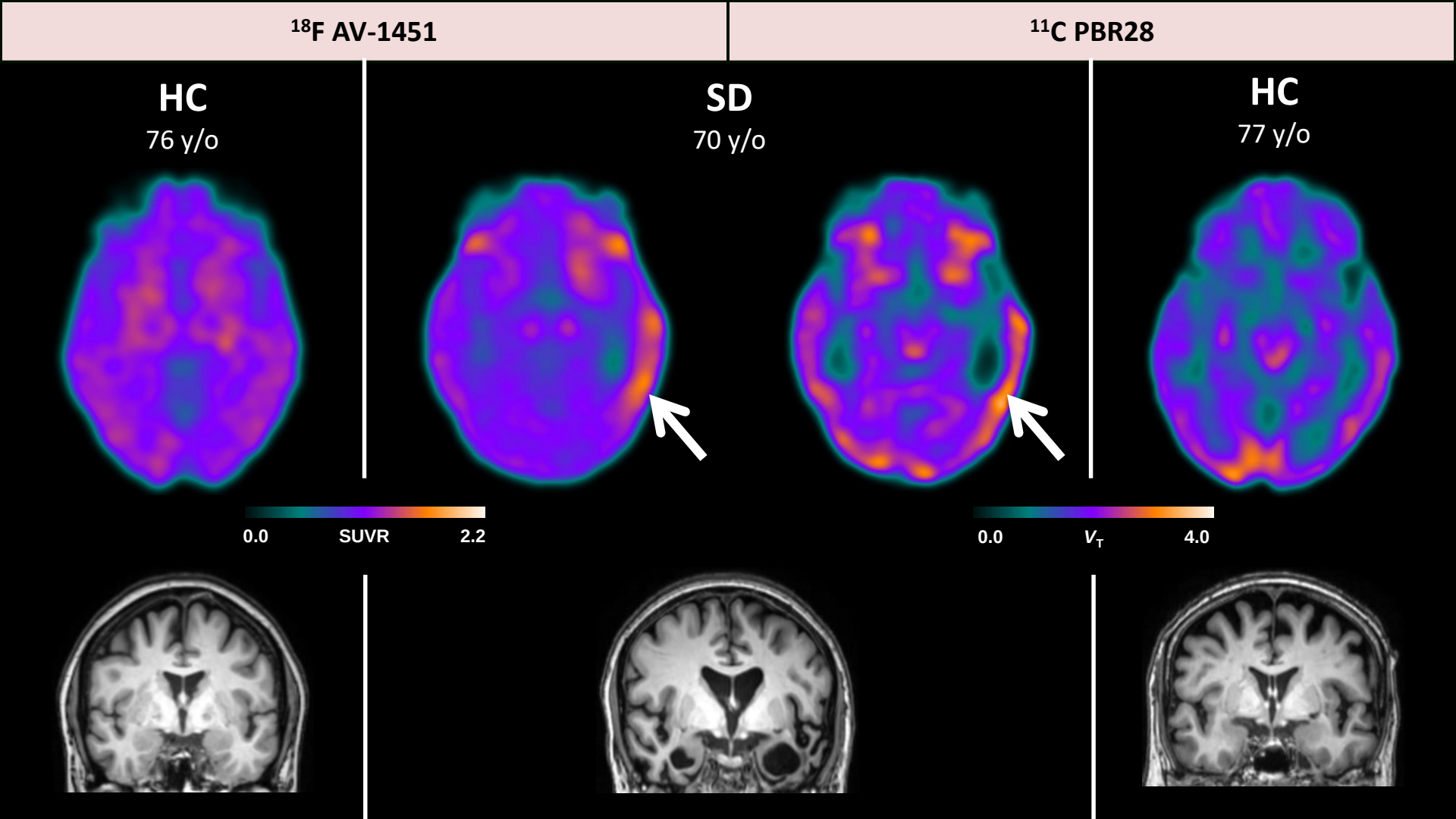


PET Imaging Processing

- **^{18}F-AV1451** scans were quantified with the ratio over the cerebellum (**SUVR** from 80 to 100 minutes).
- **^{11}C-PBR28** scans lasted 90 minutes, and were quantified with the Logan model and a metabolite-corrected arterial input function (V_T) after drawing 24 blood samples per subject from a catheter in the radial artery.
- Scans were analyzed **with and without Partial Volume Correction** with the Geometric Transfer Matrix Algorithm
- **56** Brain regions were defined with the **Hammers' atlas**, 28 for each hemisphere



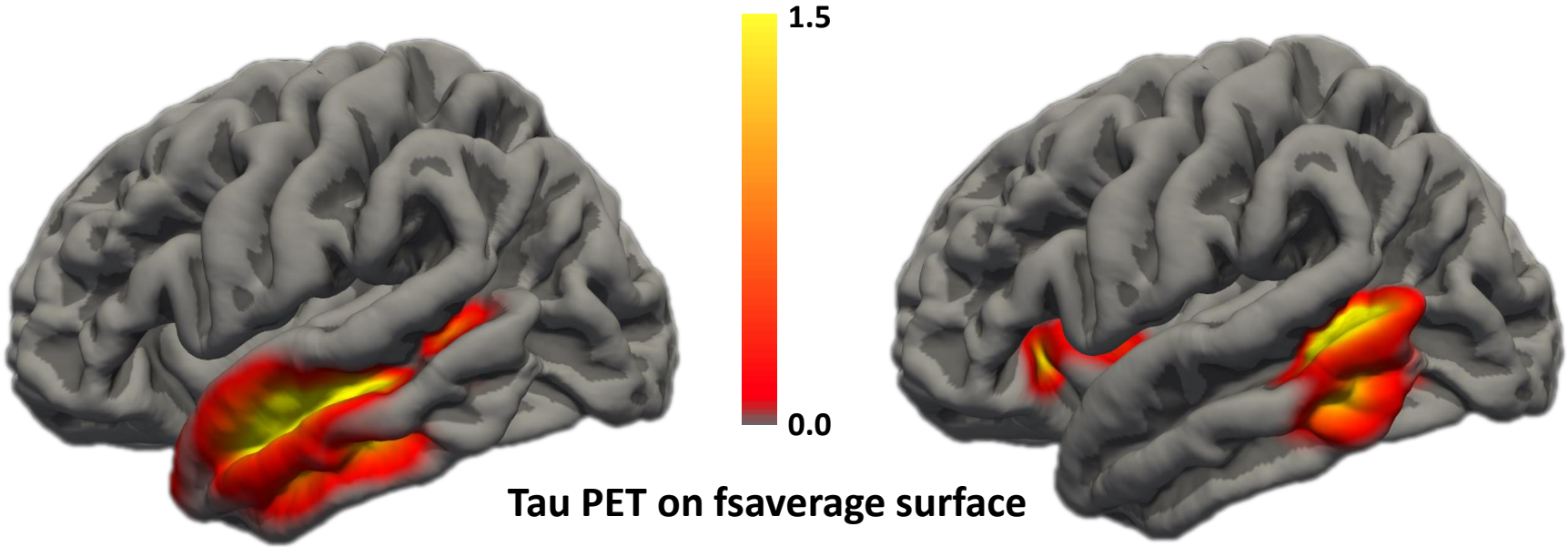



^{18}F AV-1451
^{11}C PBR28
HC
76 y/o
SD
70 y/o
HC
77 y/o
0.0
SUVR
2.2
0.0
V_T
4.0

Group Analysis ^{18}F AV1451 and ^{11}C PBR28 uptake in Semantic Dementia

^{18}F AV1451 Uptake in SD

SD > HC



^{11}C PBR28 Uptake in SD

Tau PET on fsaverage surface

p < .001 uncorrected

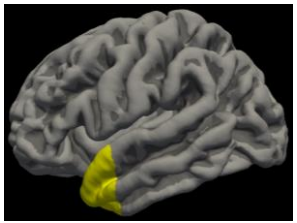
In yellow, FWE corrected

cluster-level			
$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}
0.001	0.001	865	0.000

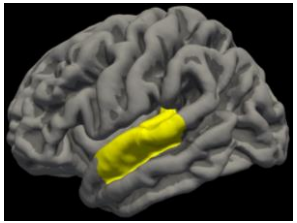
cluster-level			
$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}
0.080	0.478	337	0.016
0.042	0.478	422	0.008

Regions where SD > HC SUVR or V_T – Mann Whitney U

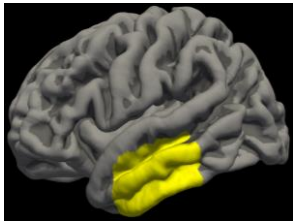
LEFT
Anterior Temporal Lobe



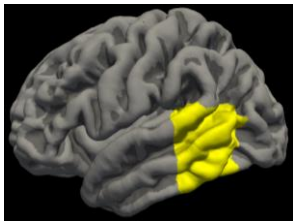
LEFT
Posterior Superior Temporal Gyrus



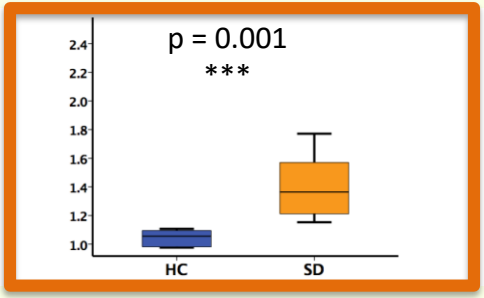
LEFT
Middle and Inferior Temporal Gyrus

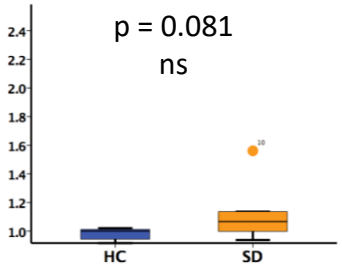


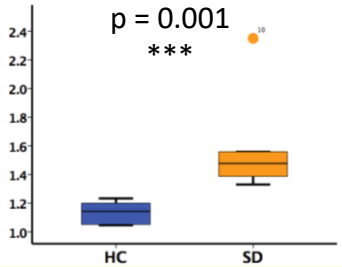
LEFT
Posterior Temporal Lobe

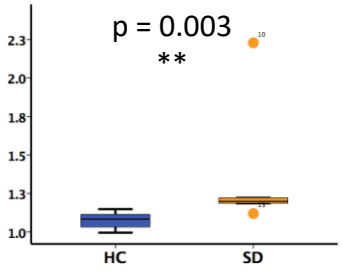


^{18}F AV-1451 SUVR – without partial volume correction (PVC)

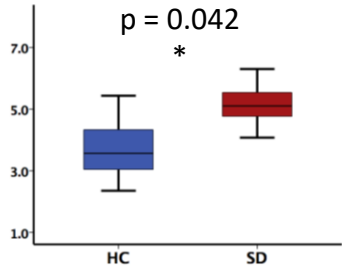


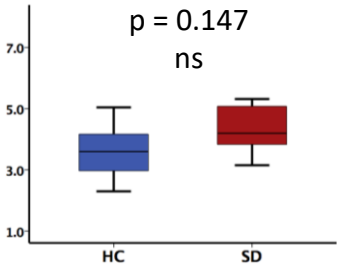


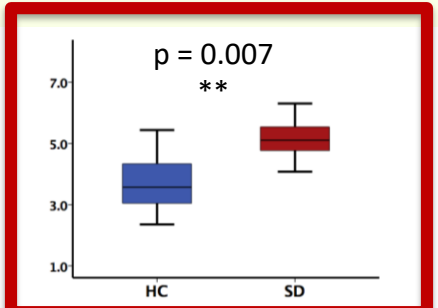


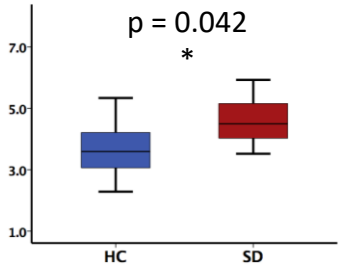


^{11}C PBR28 – without PVC









Regions where SD > HC SUVR or V_T – Mann Whitney U

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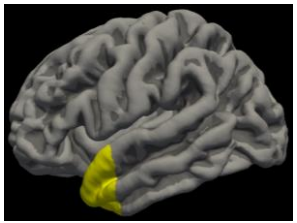

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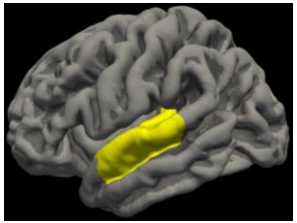
Posterior Superior Temporal Gyrus



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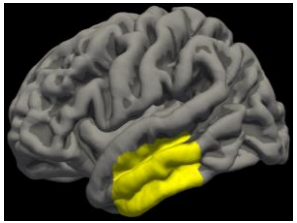
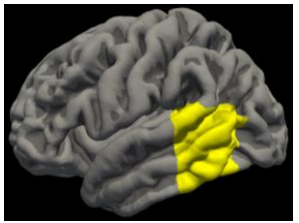
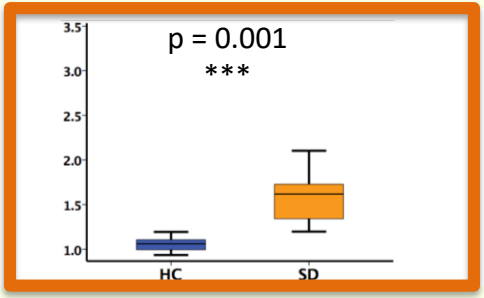
Middle and Inferior Temporal Gyrus

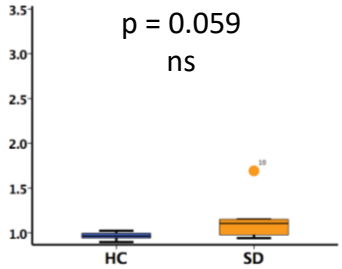


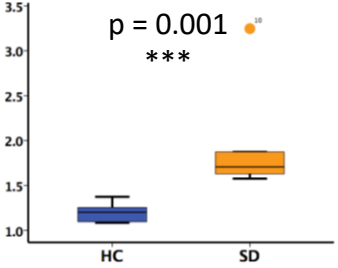
LEFT
Posterior Temporal Lobe

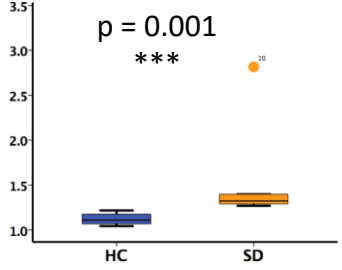


^{18}F AV-1451 SUVR – with partial volume correction (PVC)

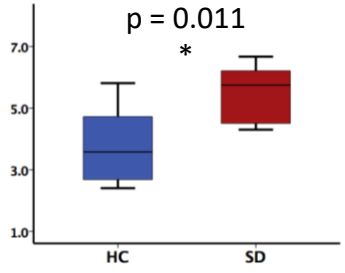


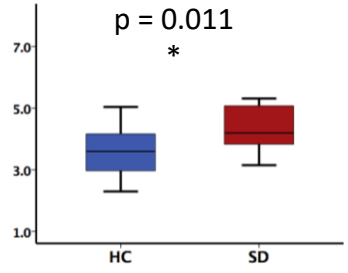


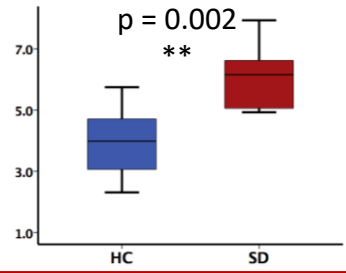


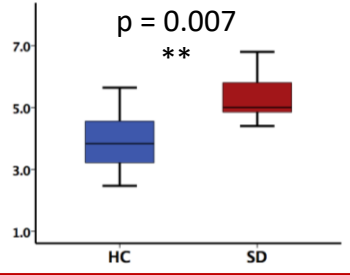


^{11}C PBR28 – PVC





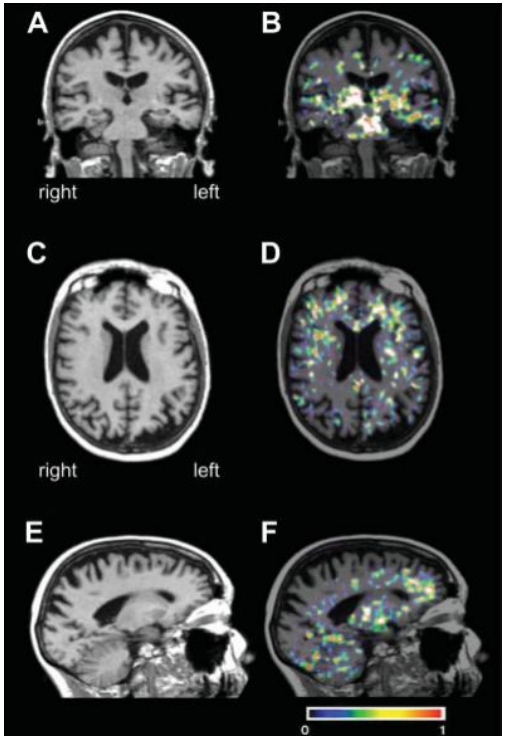




Previous Reports on the Brain Distribution of Inflammation in Semantic Dementia

- None found for semantic dementia
  - Neuropathology
  - Imaging

- To the right, ^{11}C *(R)*-PK11195 PET of a 69-year-old with frontotemporal lobar degeneration



Cagnin A et al. *Ann Neurol 2004;56:894-897*

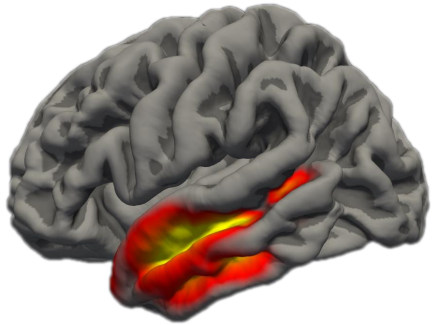
Inflammation Seems Greatest at the Periphery of the Core of Pathologic Damage

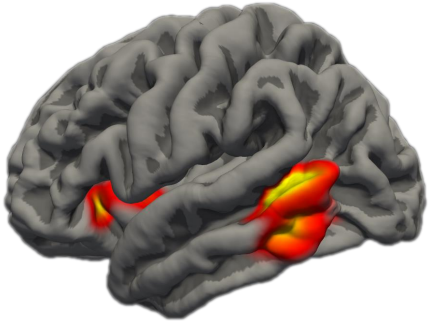
^{18}F AV1451 / Flortaucipir

SD > HC

Inflammation

Semantic Dementia





Schilder's Disease (Tumor-like Demyelination)

Conclusions

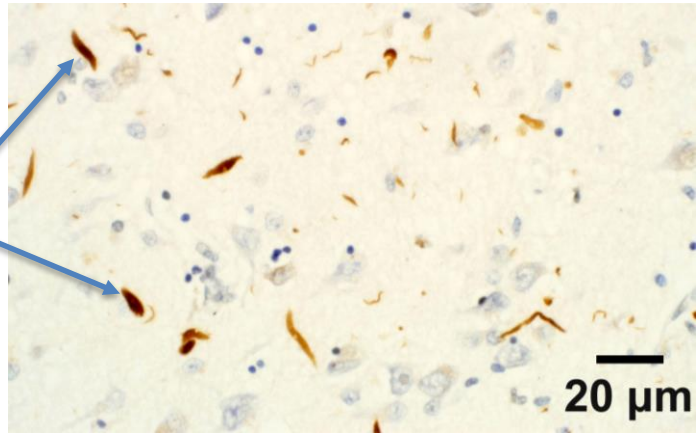
- ^{18}F-AV-1451 and ^{11}C-PBR28 were increased in similar regions,
  - **but their distribution in these regions differed for either tracer**
- Therefore, inflammation **does not** explain the ^{18}F AV-1451 signal
- Our findings leave the door open for neurobiological processes other than inflammation to explain the increased ^{18}F-AV-1451 SUVR values in anterior temporal regions in semantic dementia
  - Likely, binding to some configurations of TDP-43 aggregates, as already suggested
    - » Makaretz SJ, et al. *J Neurol Neurosurg Psychiatry* 2018 Oct;89:1024-1031
    - » Bevan-Jones WR, et al. *J Neurol Neurosurg Psychiatry* 2018 Oct;89:1032-1037

Semantic Dementia: TDP-43 Type C

TDP-43 aggregates in thickened neurites

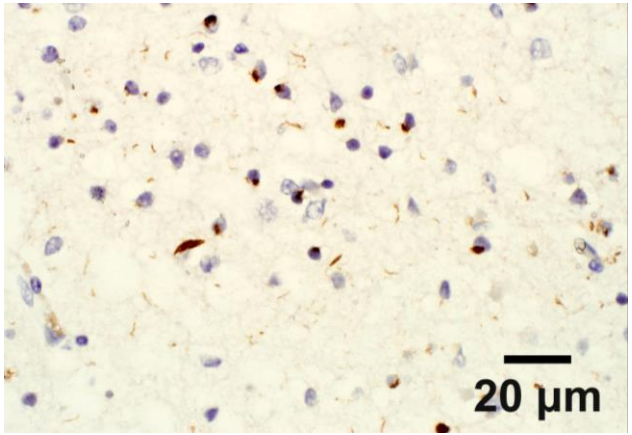
TDP-43 Type C in SD

- Temporal cortex



TDP-43 Type A in FTD with ALS

- Frontal cortex



The more dense and numerous TDP-43 aggregates in semantic dementia may explain flortaucipir binding in semantic dementia

The Nantz National Alzheimer Center: A Team Effort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Paolo Zanotti-Fregonara – Director, PET Core

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HMNI-HMRI Neuroimaging Lab