Nantz National Alzheimer Center

HOUSTON Methodist NEUROLOGICAL INSTITUTE

Molecular Imaging for Differential Dementia Diagnosis 10:07-10:30

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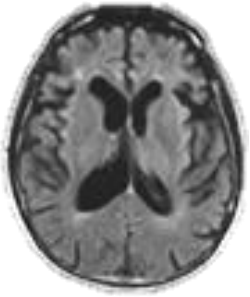
Faculty Disclosure

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research
General Electric Health	X	X	X
Eli Lilly	X		X
Avanir			X
Abbvie			X
ALS Association			X
Biogen			X
NIH (NIA)			X
Novartis			X

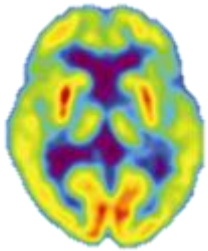
Learning Objectives

- List what imaging modalities are useful for the study of dementia
- Indicate why and how molecular imaging may help detect brain changes in neurodegenerative dementia before MRI does
- Describe the positron emission tomography patterns of the most common neurodegenerative dementias

Imaging Modalities for Neurodegenerative Dementias



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

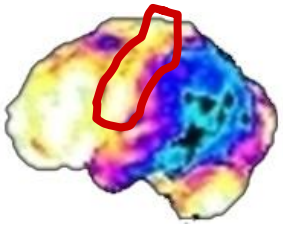


- PET (Positron Emission Tomography)
  - Metabolism
  - β-amyloid load
  - $_{p}$Tau load
  - Inflammation
- SPECT (Perfusion)

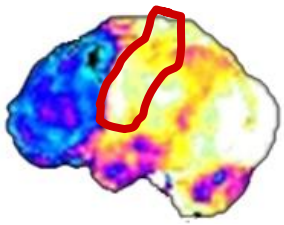
Metabolism (FDG) **PET**

- **Regional pattern** (space)

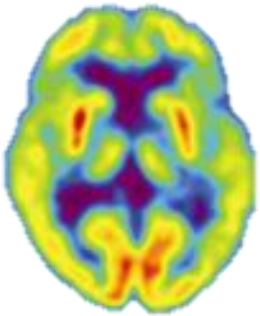
Alzheimer Disease (**AD**)



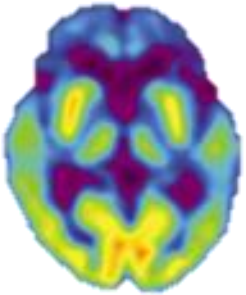
Frontotemporal Dementia (**FTD**)



- **Disease stage** (time)



2 years later



Neuroimaging in the Diagnosis of Degenerative Dementias

	Atrophy (MRI)	**↓ metabolism, perfusion (PET, SPECT)**	**Amyloid**	**Tau**
Alzheimer's	Medial temporal, other limbic	Parieto-temporal association cortex, retrosplenial	Yes	Yes
Semantic dementia	Both temporal tips (L>>R)		Yes (20%) No (80%)	20%
Behavioral type FTD	Frontotemporal poles		No	50%
Progressive non-fluent aphasia	Left perisylvian association cortex		No	80%
CBD	High fronto-parietal association cortex		No	Yes

Josephs KA et al. *Neurology* 2006;66:41-8

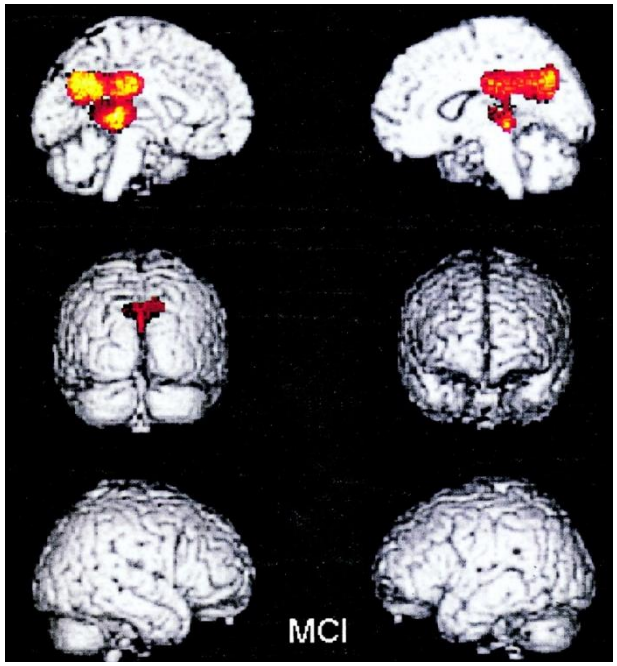
Why PET to Diagnose Neurodegenerative Dementias?

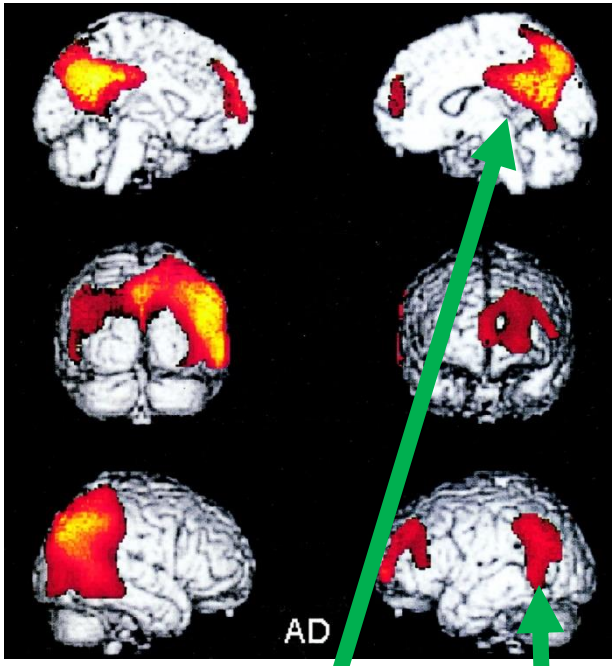
- Patients and families prefer PET to lumbar puncture ("spinal tap" )
  - Orthostatic headache

While some dementias such as Creutzfeldt-Jakob disease have accurate CSF biomarkers, other disease types such as dementia with Lewy bodies, vascular dementia, and frontotemporal dementia lack reliable biomarkers for their specific clinical diagnosis

Llorens F et al. *Prog Neurobiol* 2016:138-140:36-53

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



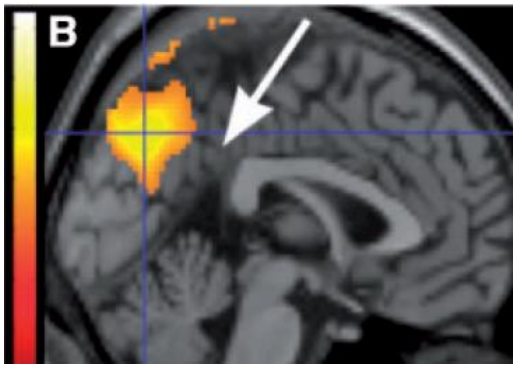


Alzheimer's disease

Affected (in red or yellow above):

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

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



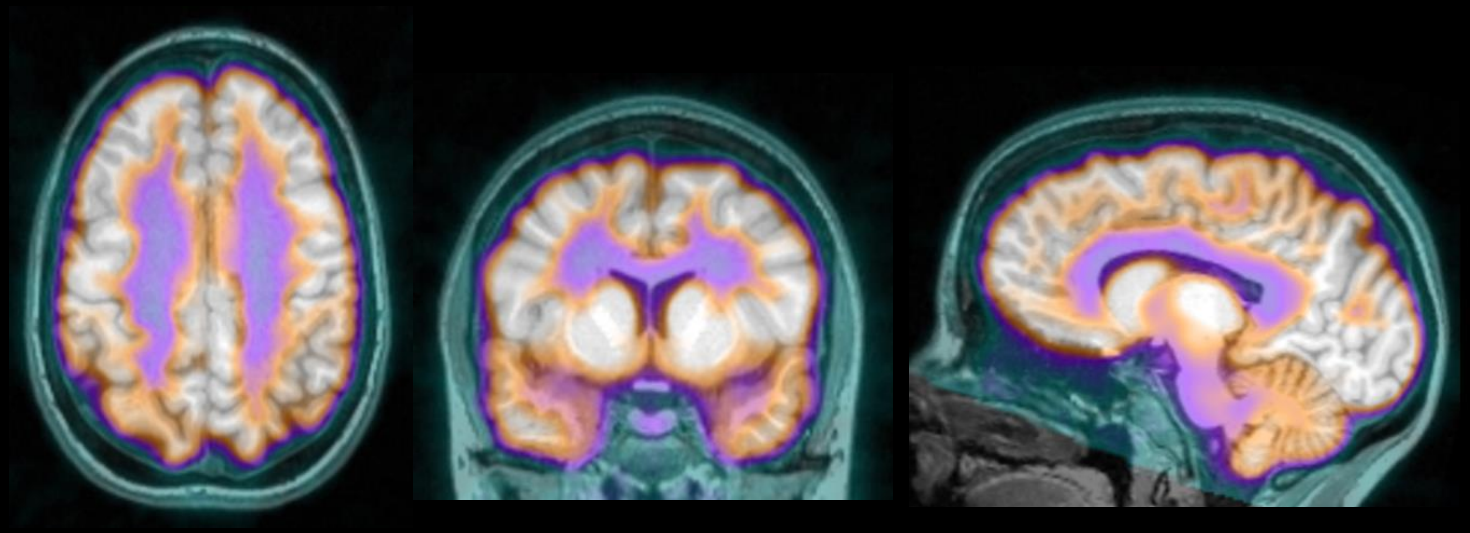
Diffuse Lewy body disease

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

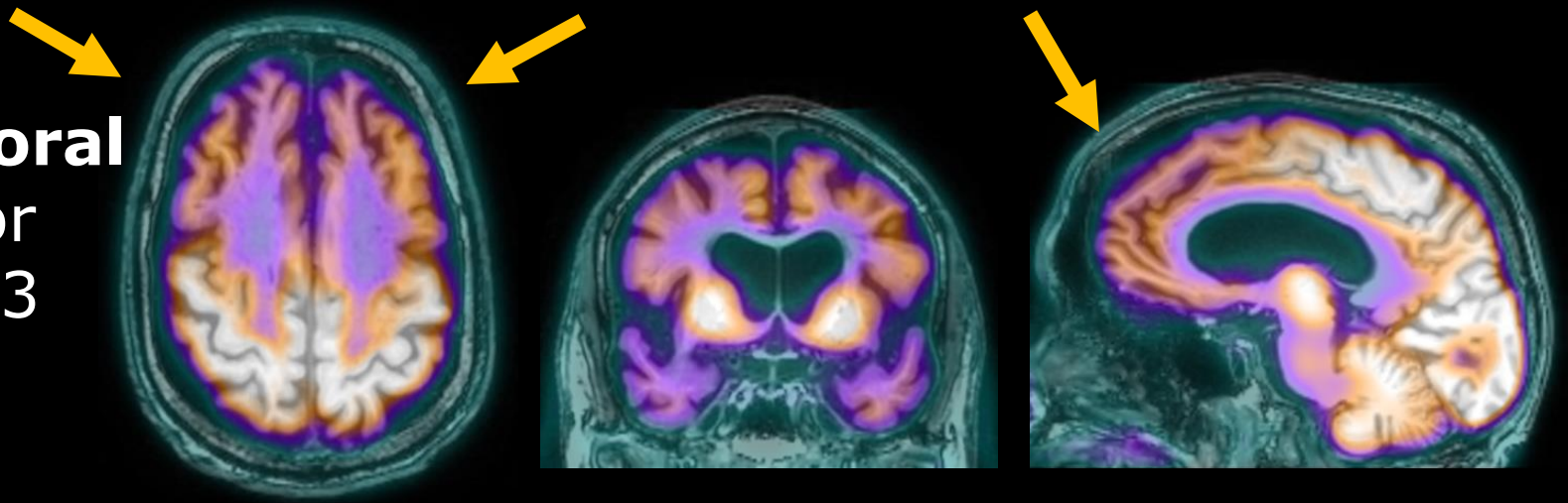
Masdeu JC et al. *Brain* 2012;135:2440

Frontotemporal Dementia Variants
(Amyloid Negative)

Healthy Control

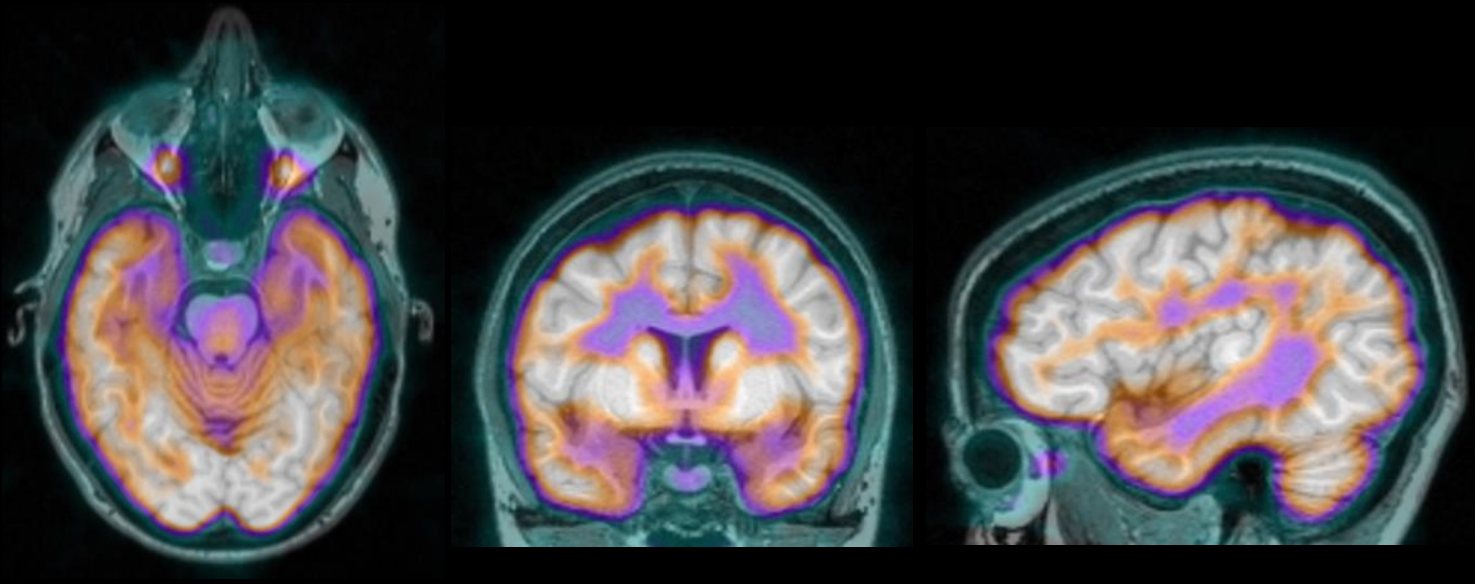


Behavioral
Tau or
TDP43



Frontotemporal Dementia Variants

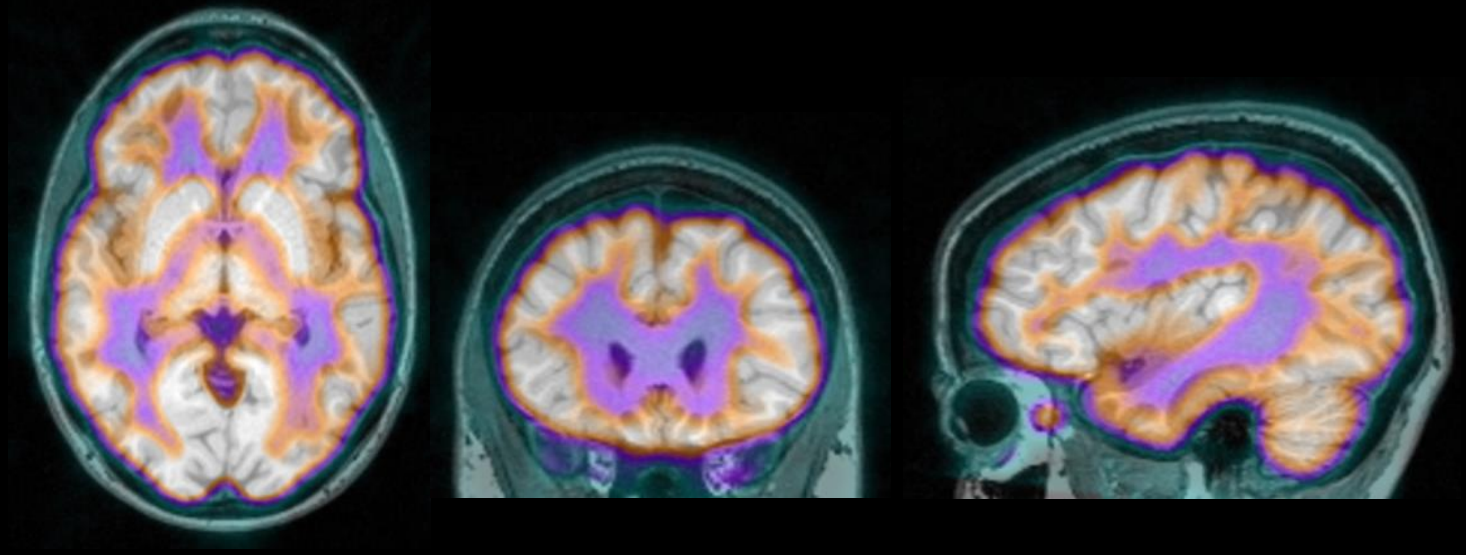
Healthy Control



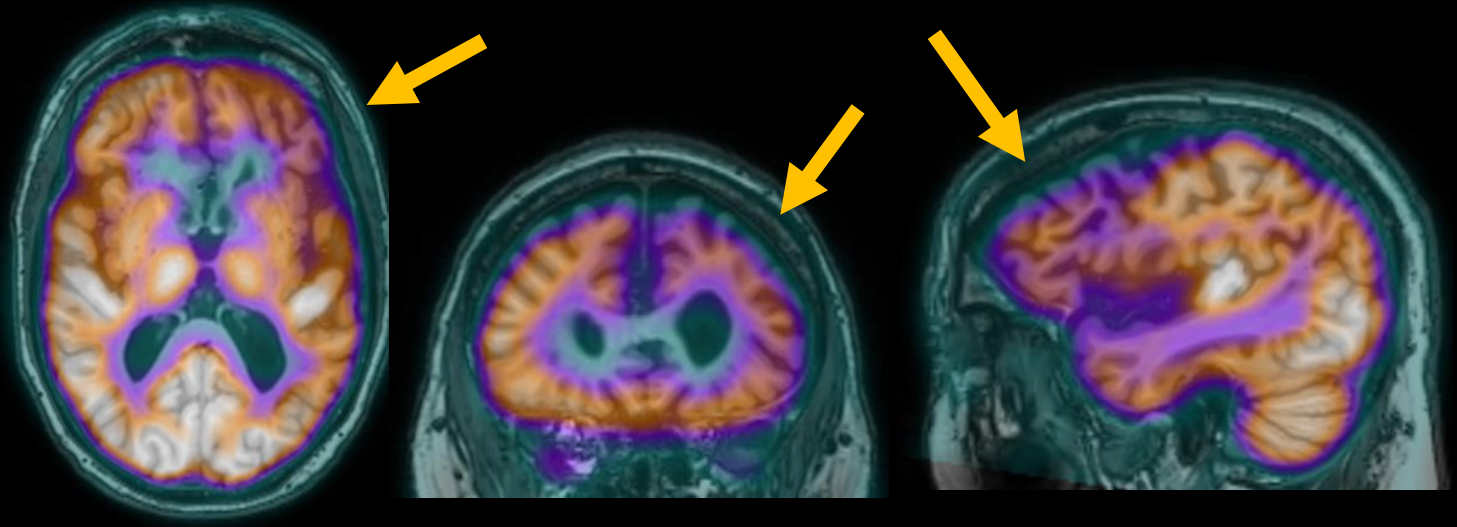
Semantic Dementia
TDP43

Frontotemporal Dementia Variants

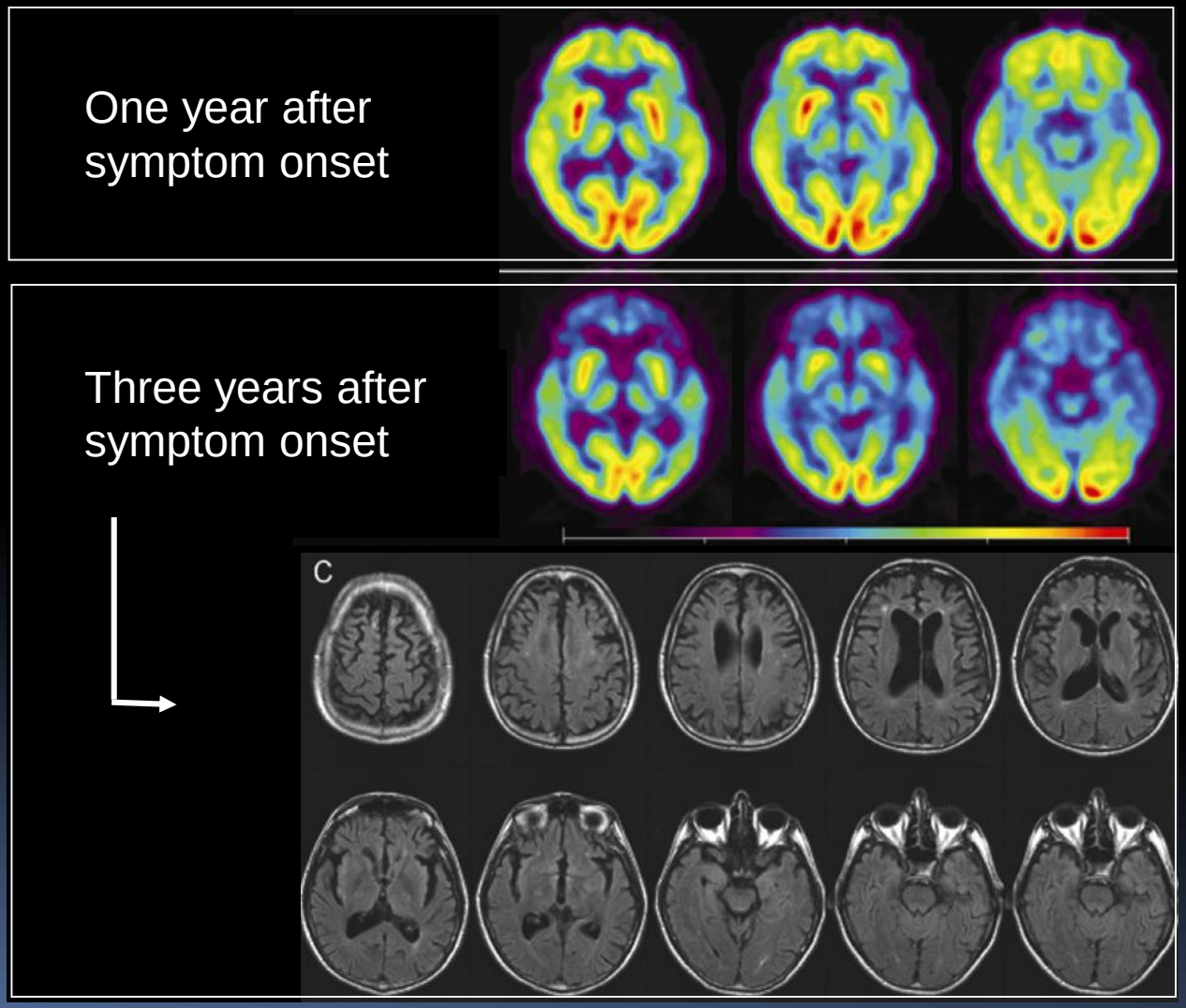
Healthy Control



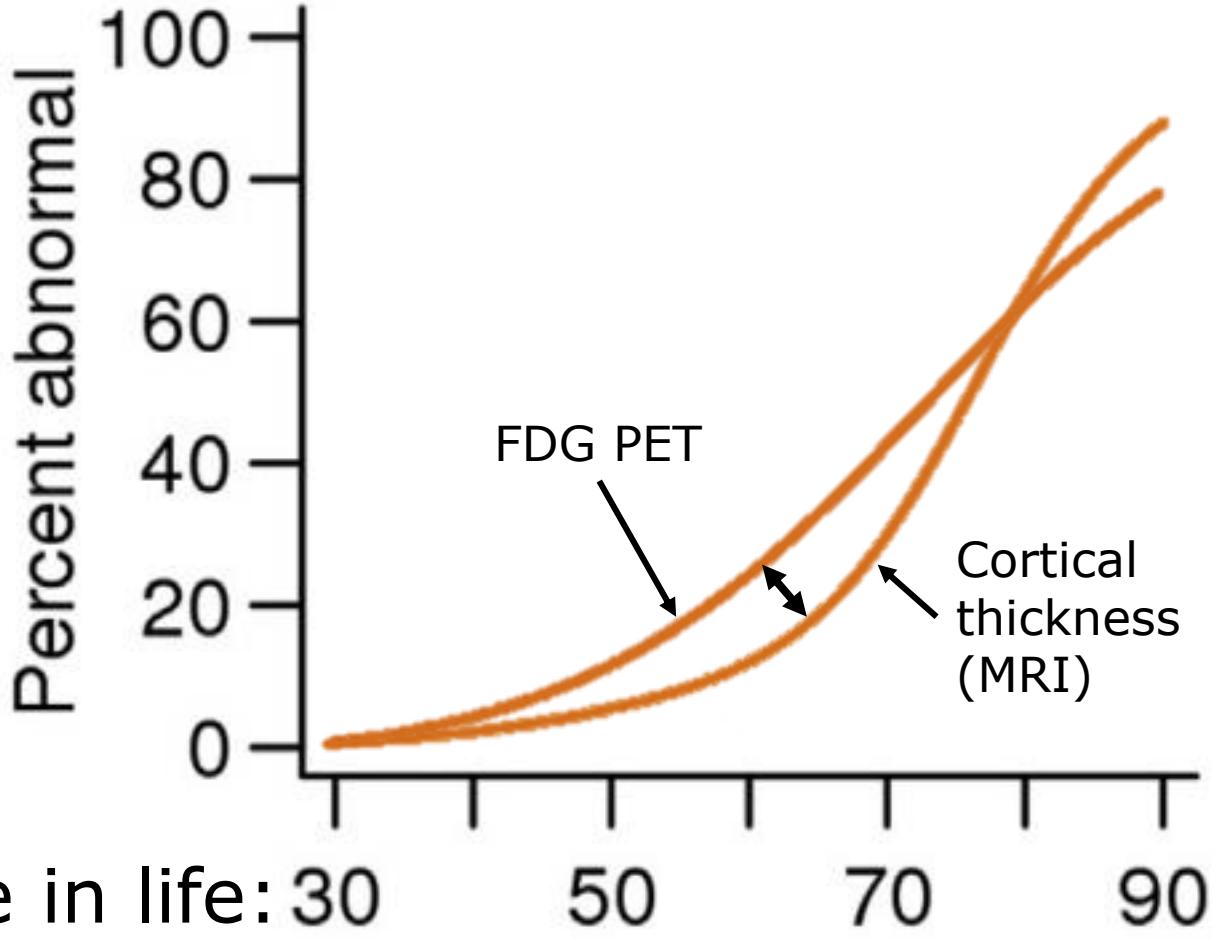
Agrammatic PPA
Tau



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

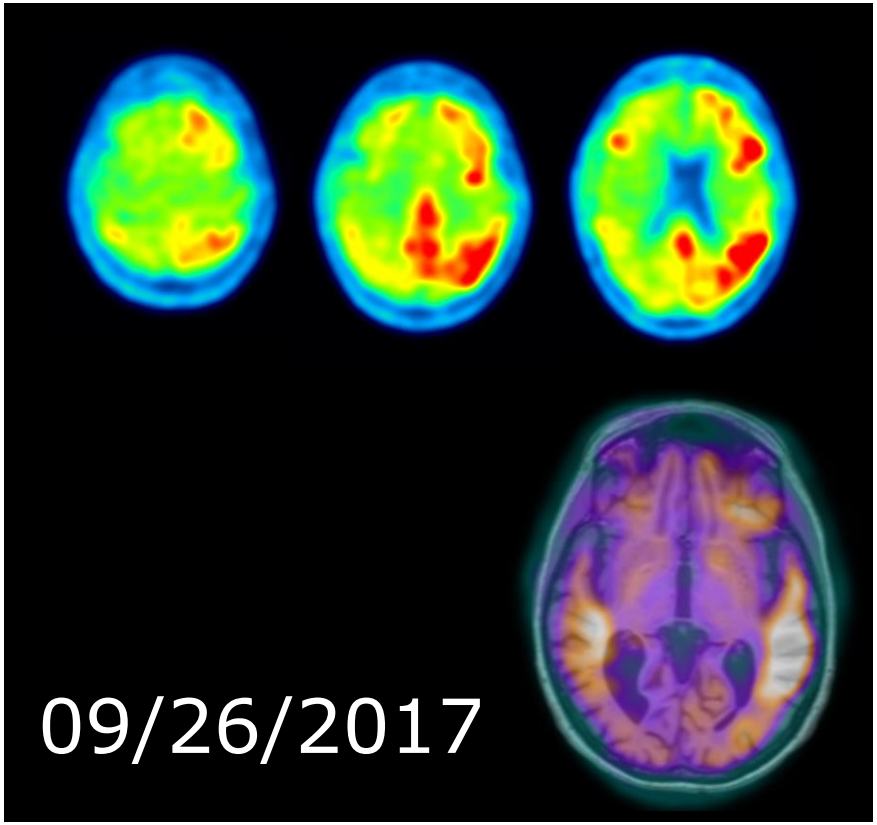
Why FDG PET to Diagnose Neurodegenerative Dementias?

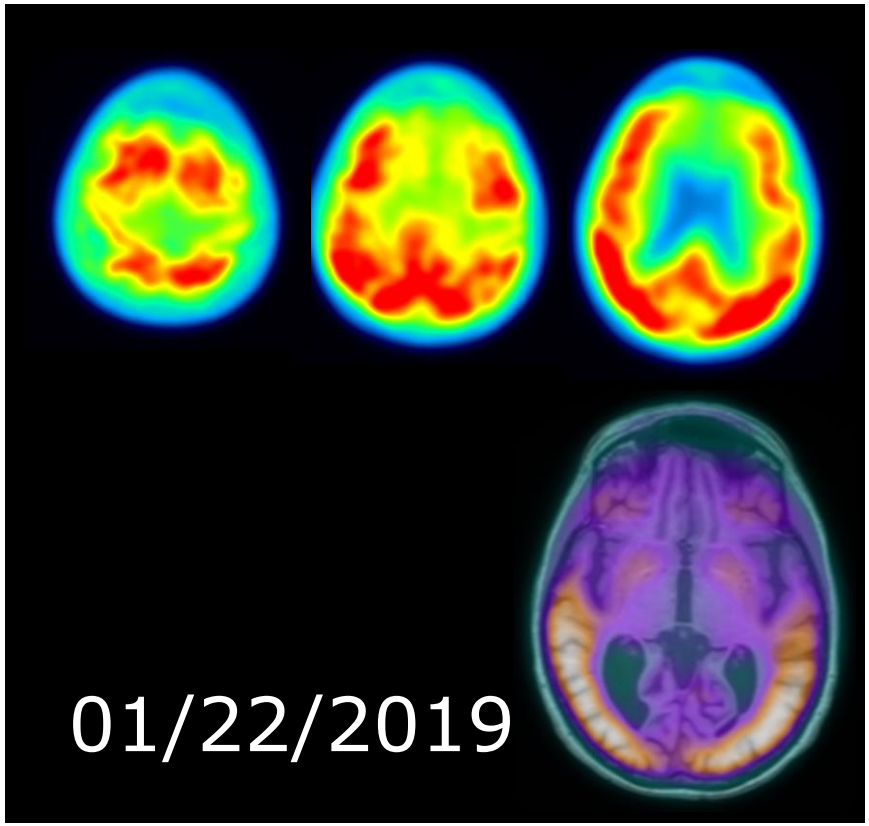
- Patients and families prefer PET to lumbar puncture ("spinal tap" )
  - Orthostatic headache

- More information than CSF for non-AD disorders
  - Frontemporal lobar degeneration
  - Diffuse Lewy body disease

Tau Imaging Outcome

^{18}F-AV1451 PET





Clear-cut, quantifiable worsening in about 15 months

Misfolded tau: Linked to neurodegeneration

Brain Metabolism Versus Brain Tau: Yin-Yang Relationship

Where Tau is High, Metabolism is Depressed

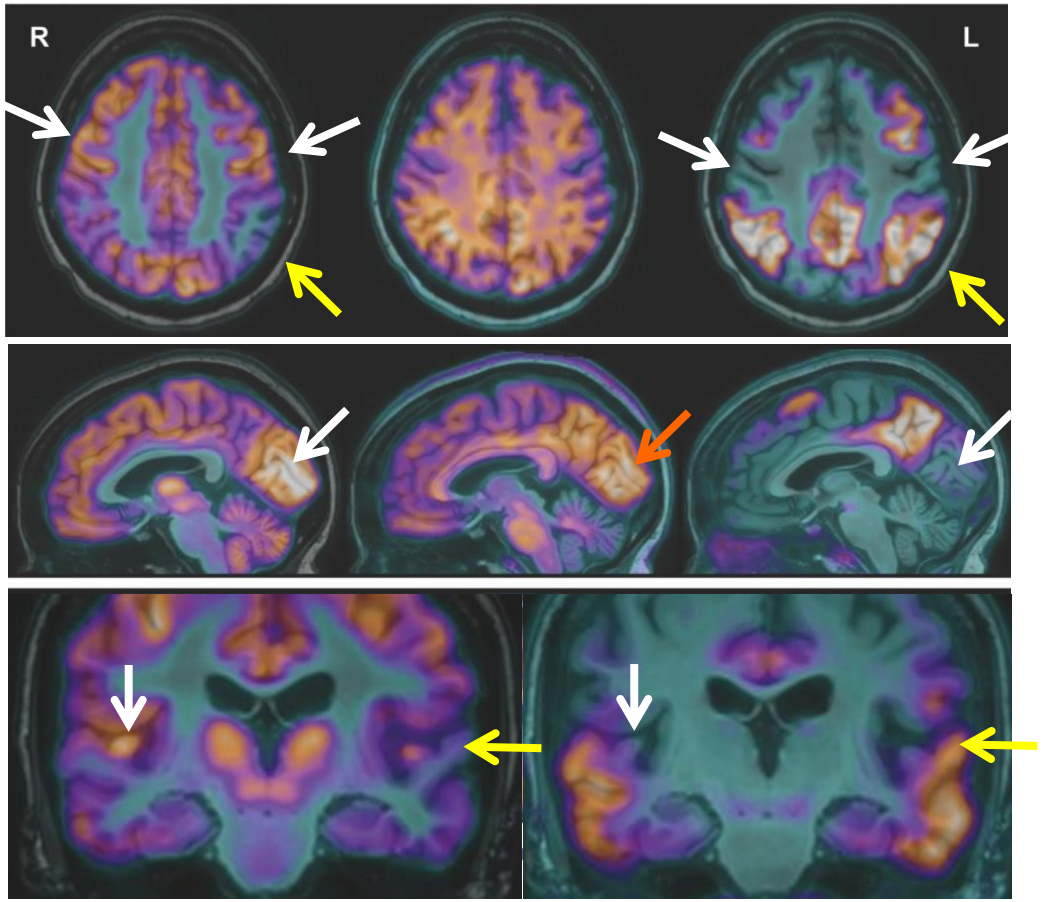
Logopenic Aphasia (Alzheimer disease)

Metabolism	**β-amyloid**	**Tau**
^{18}F-FDG	^{18}F-florbetapir	^{18}F-T807

- **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

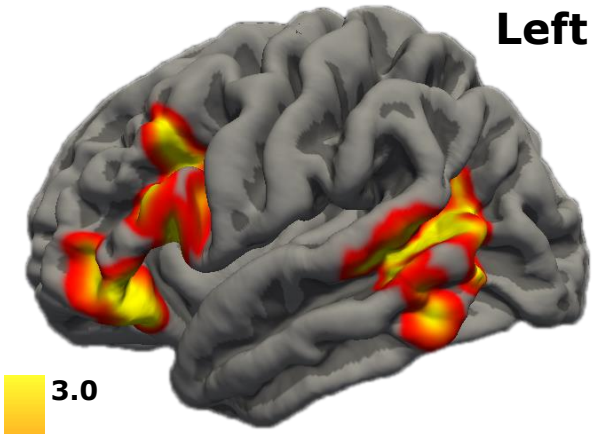
Pascual et al. *Neurology* 2016;85:487

Tau Propagation Along Natural Brain Networks

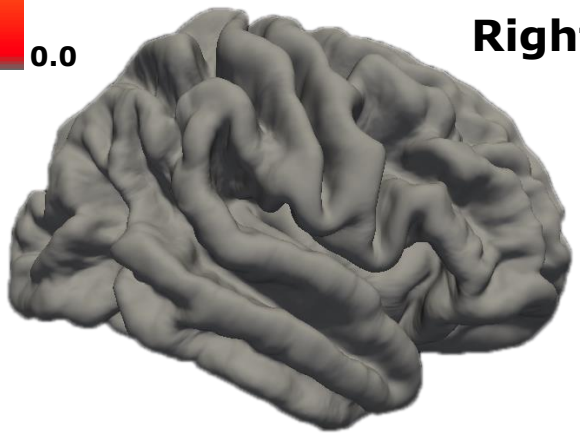
Tau deposits in anterior and posterior neuronal nodes of the syntactic network

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)

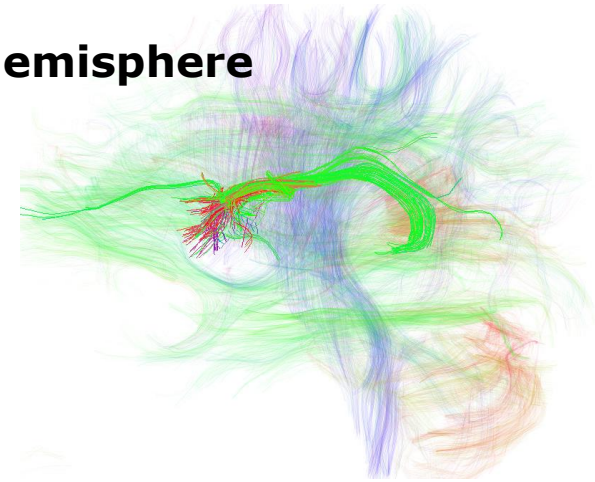


P < 0.05 FWE-corrected cluster-level

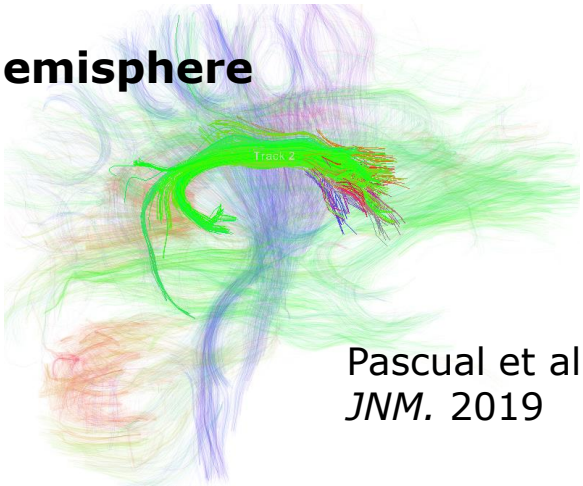


Arcuate Fasciculus Tractography

Left hemisphere

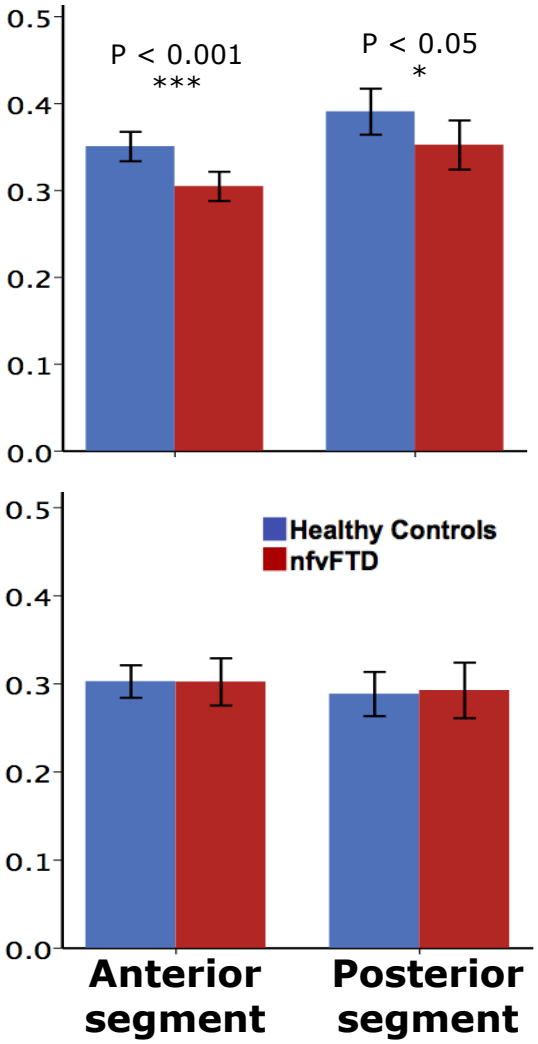


Right hemisphere



Pascual et al. *JNM.* 2019

Fractional Anisotropy of Arcuate Fasciculus



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5. Masdeu JC, Pascual B. Genetic and degenerative disorders primarily causing dementia. *Handb Clin Neurol.* 2016;135:525-564.

6. Pascual B, Prieto E, Arbizu J, et al. Decreased carbon-11-flumazenil binding in early Alzheimer's disease. *Brain*. 2012;135:2817-2825.

7. Goker-Alpan O, Masdeu JC, Kohn PD, et al. The neurobiology of glucocerebrosidase-associated parkinsonism: a positron emission tomography study of dopamine synthesis and regional cerebral blood flow. *Brain*. 2012;135:2440-2448.