Tauopathy in autosomal dominant and late-onset Alzheimer disease

Charles D. Chen, Timothy R. Holden, Brian A. Gordon, Erin E. Franklin, Richard J. Perrin, John C. Morris, Randall J. Bateman, Tammie L.S. Benzinger, Nigel J. Cairns

Washington University in St. Louis

Disclosures

I have nothing to disclose

alzheimer's association

AAIC 20

POLICIES

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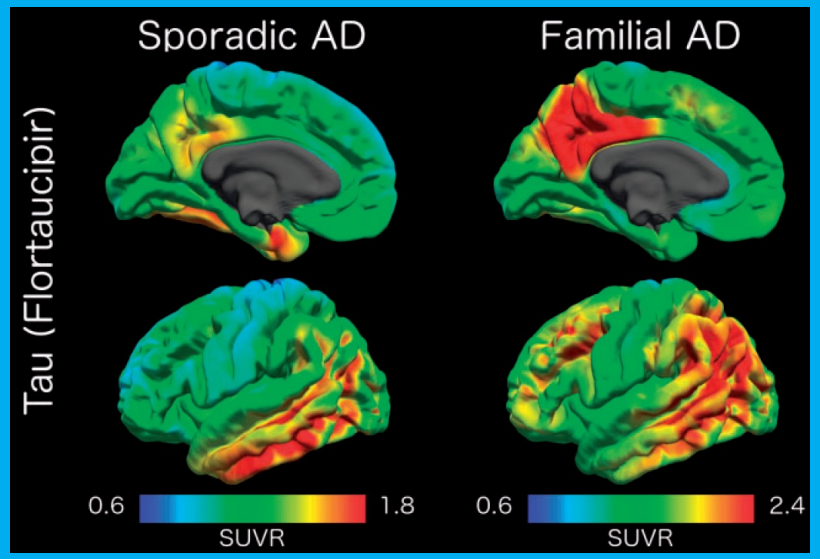
LOAD ADAD



Gordon et al., 2019

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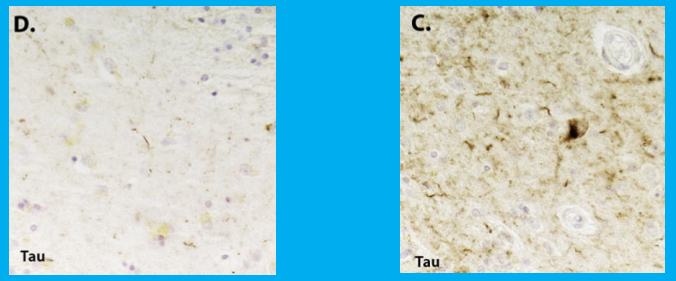

Ringman et al., 2011

Antemortem tau PET imaging suggests elevated tau pathology in autosomal dominant (ADAD) versus late-onset Alzheimer disease (LOAD) at equivalent clinical stage

Compared to LOAD, ADAD showed elevated tau tracer uptake in prefrontal, premotor, inferior parietal (Schöll et al., 2017), precuneus, lateral parietal (Gordon et al., 2019)

The ADAD versus LOAD comparison in tau PET needs to be evaluated with stereology due to concerns of off-target binding, but so far there is an ADAD case report (Smith et al., 2019) and a semi-quantitative comparison (Ringman et al., 2016)

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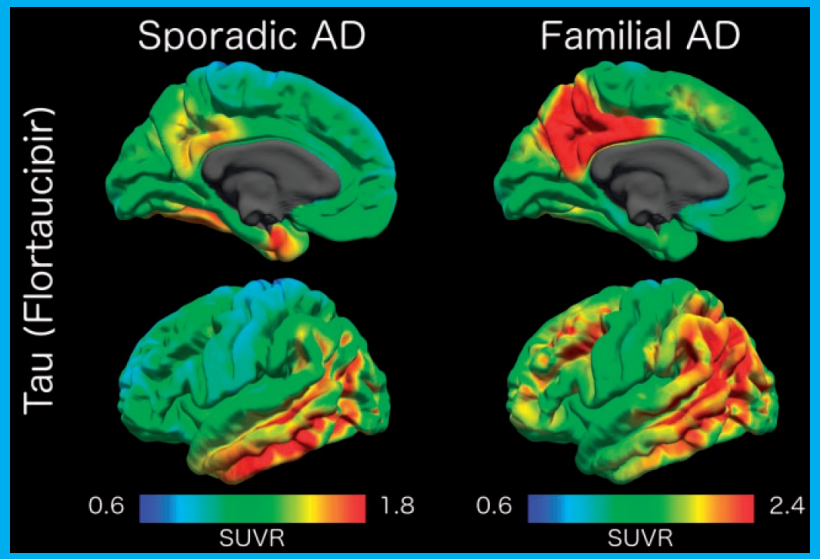

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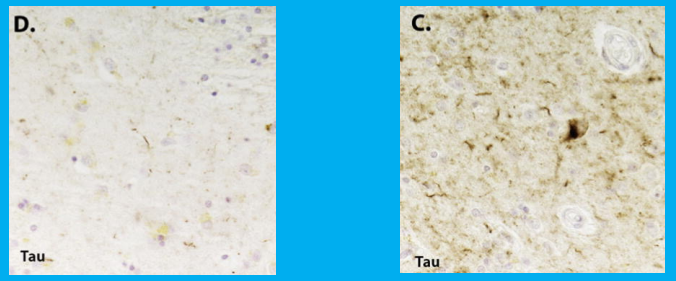

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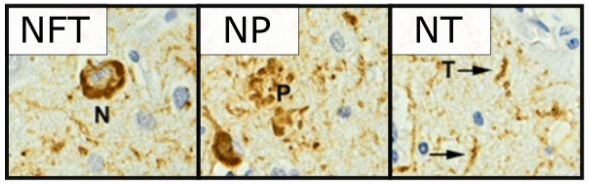
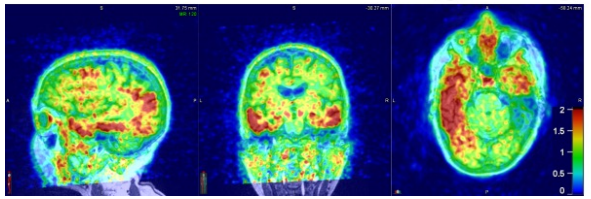
Our approach quantifies ante- and postmortem tau burden across multiple individuals, regions, and pathologies

stereology



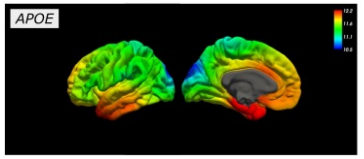
PHF-1 immunostaining

imaging



^{18}F-flortaucipir PET

LOAD



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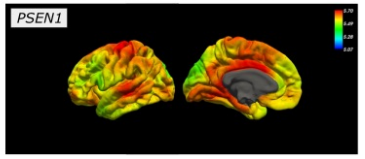


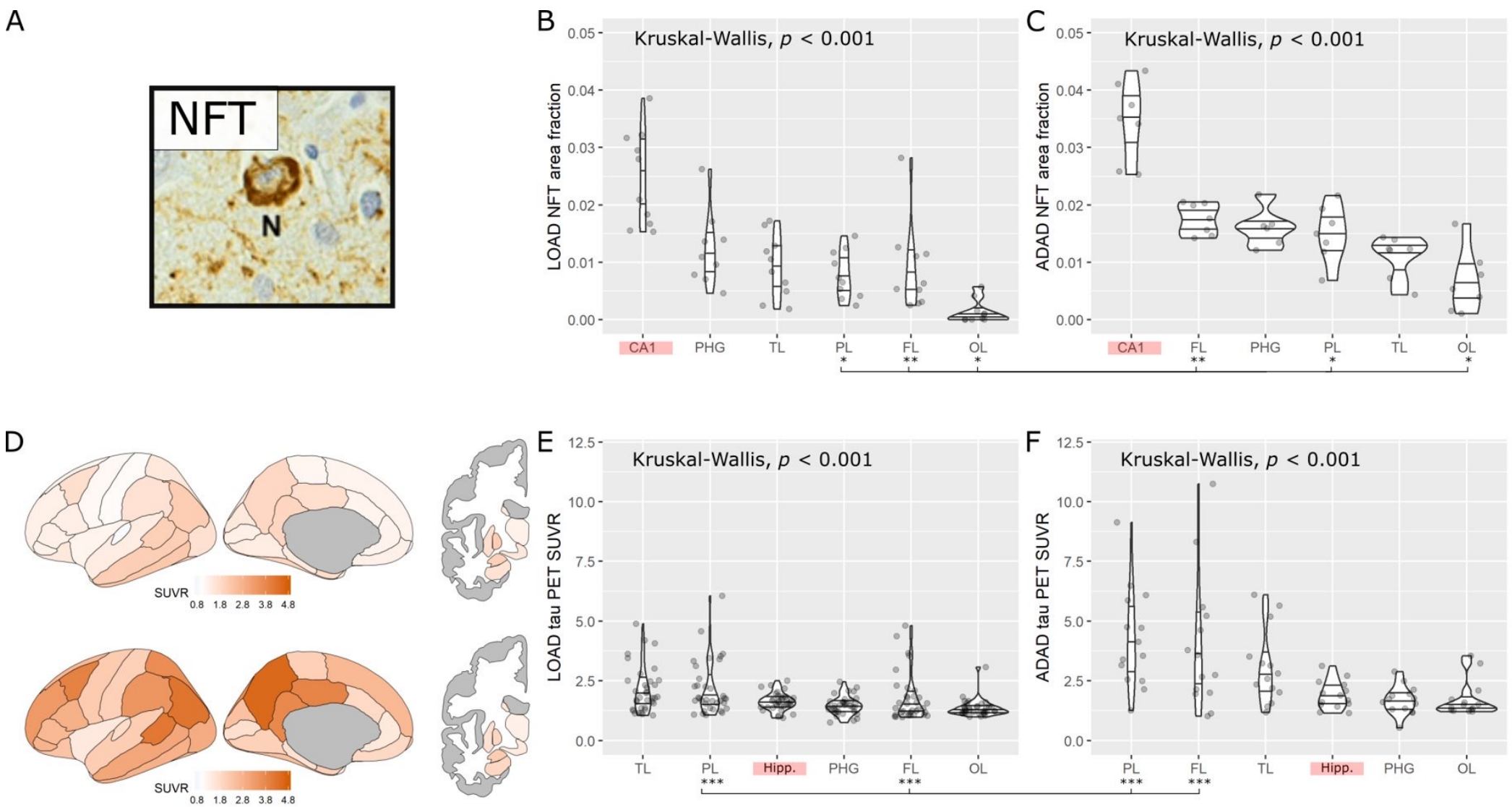
n=10	*n*=7
n=35	*n*=14

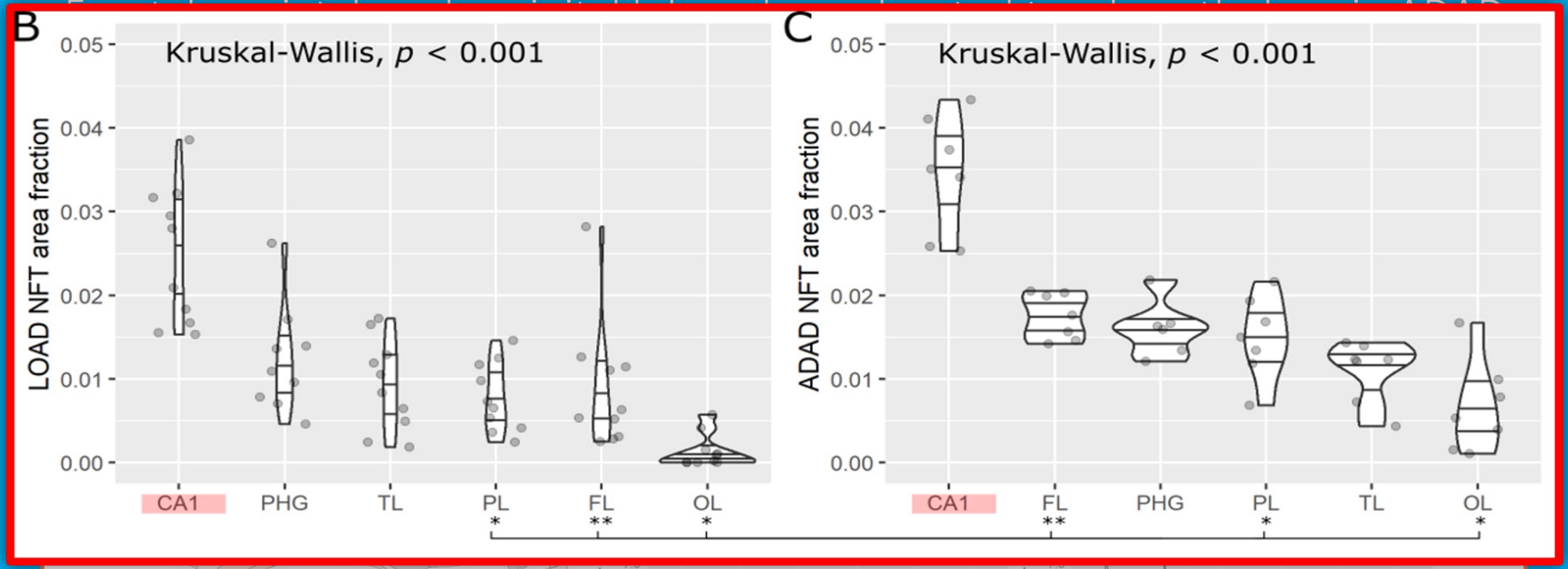
APOE and PSEN1 images from meduniwien.ac.at/neuroimaging/mRNA.html

Cohort demographics

	Neuropathology cohort		Imaging cohort	
	LOAD	ADAD	LOAD	ADAD
Number	10	7	35	14
Age at visit, years (SD)			74.9 (6.75)	50 (12.5)
EYO, years (SD)				1.71 (3.47)
Age at death, years (SD)	73.4 (8.29)	44.9 (7.47)		
Female (%)	6 (60%)	4 (57.1%)	19 (54.3%)	8 (57.1%)
MMSE at visit, score (SD)			25.3 (3.88)	21.9 (6.40)
CDR at visit, score (0/0.5/1/2/3)			0.657 (0/26/8/1/0)	0.714 (0/12/1/0/1)
CDR at death, score (0/0.5/1/2/3)	2.75 (0/0/1/0/7)	3 (0/0/0/0/6)		
APOE ε4 (%)	7/9 (77.8%)	1/7 (14.3%)	22/34 (64.7%)	4/14 (28.6%)
Family Mutation APP/PSEN1/PSEN2		0/7/0		1/12/1
Aβ plaque score (A0/1/2/3)	3 (0/0/0/10)	3 (0/0/0/7)		
NFT stage (B0/1/2/3)	3 (0/0/0/10)	3 (0/0/0/7)		
Neuritic plaque score (C0/1/2/3)	2.9 (0/0/1/9)	3 (0/0/0/7)		

Frontal, parietal, and occipital lobes show elevated tangle pathology in ADAD




B
Kruskal-Wallis, p < 0.001
LOAD NFT area fraction
0.05
0.04
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CA1
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TL
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C
Kruskal-Wallis, p < 0.001
ADAD NFT area fraction
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0.04
0.03
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CA1
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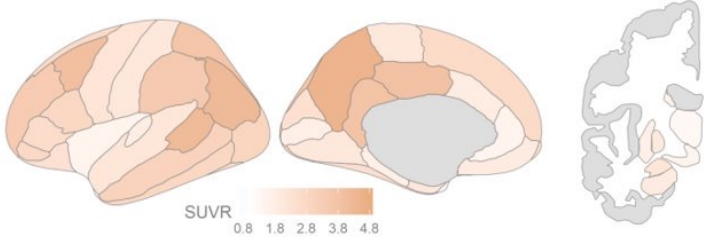
SUVR
0.8 1.8 2.8 3.8 4.8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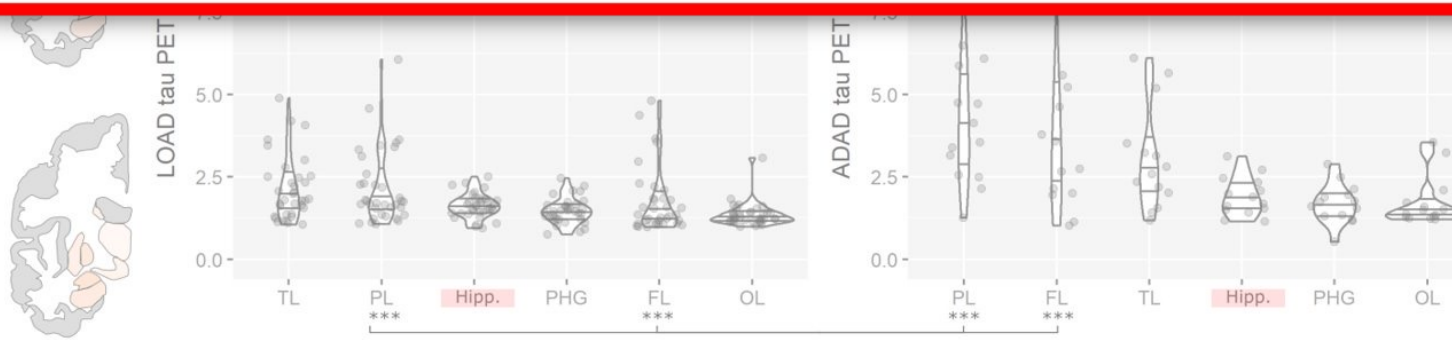
LOAD tau PET
5.0
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ADAD tau PET
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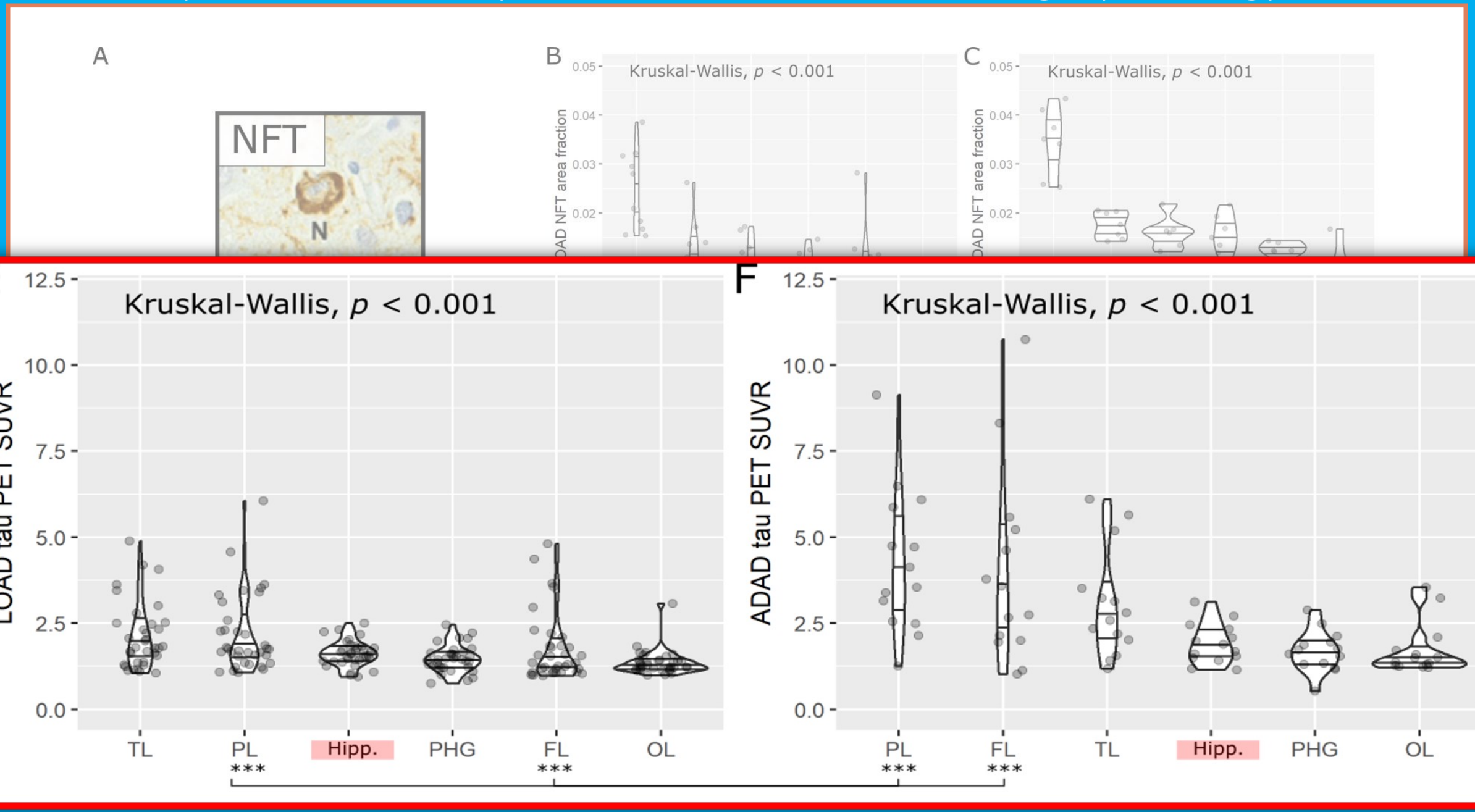
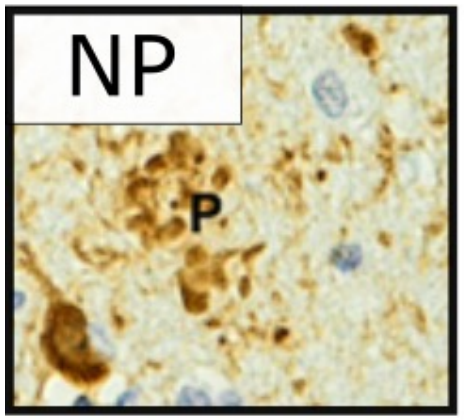
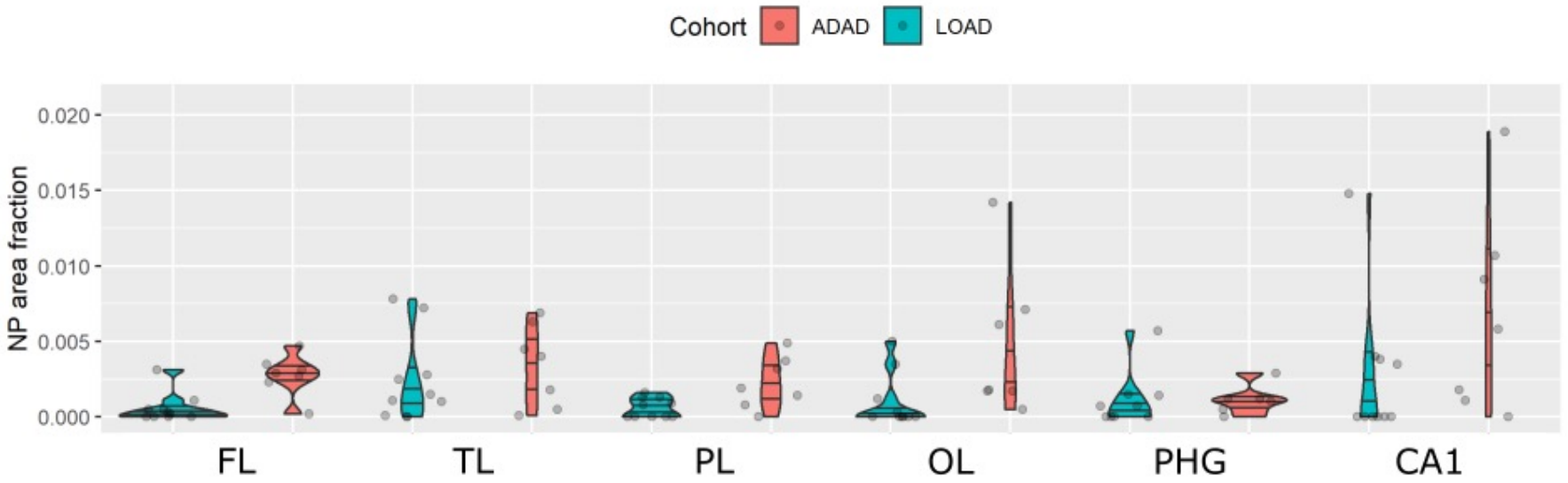
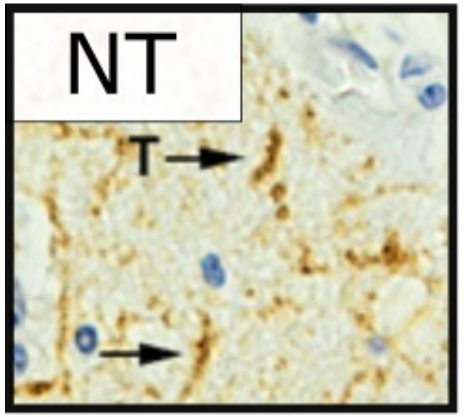
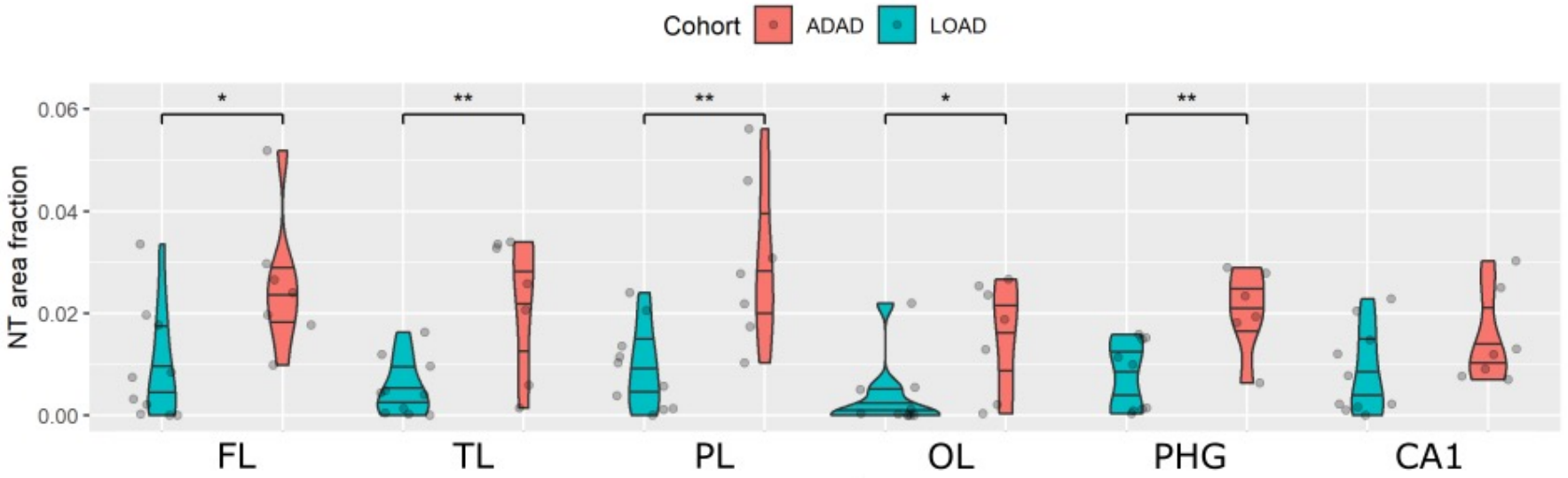


Plaque pathology not elevated; thread pathology elevated in all except CA1

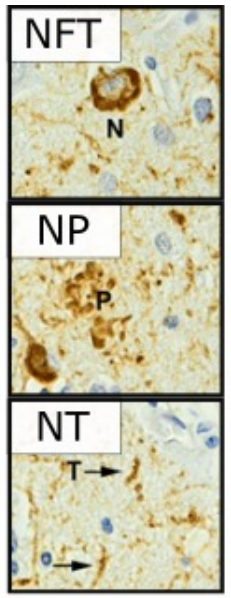


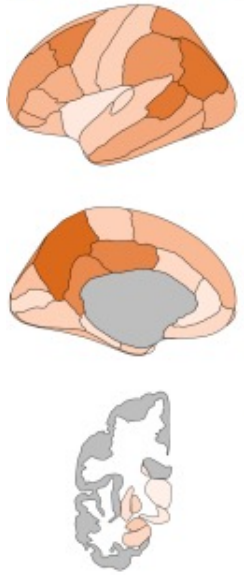






Total tau resembles tau tracer uptake; greatest discordance in OL, PHG, CA1





Summary and future directions

Side notes: Regional patterns do not agree in areas that might have modest tau burden in early symptomatic stages of AD; or are small and difficult to quantify in imaging versus stereology

Tangles and threads may be pathophysiologically more closely linked than plaques, with tangles appearing first, and threads reflecting severe saturation of neuronal processes by abnormal tau

We found that the regional pattern of elevated tau PET radioligand binding is largely concordant with the regional pattern of elevated postmortem total tau burden in ADAD versus LOAD; additionally, we found tangle and thread, but not plaque, burden is elevated in ADAD versus LOAD

Concordance: Smith et al. found regional SUVRs correlated best with regional total tau burden in an ADAD case study; but we did not find a study comparing ADAD and LOAD for tangles, threads, and plaques

Discordance: Smith et al. found threads outnumbered tangles in every region in ADAD; we found no statistical dominance of thread over tangle burden in ADAD or LOAD; Ringman et al. found elevated plaque burden in a larger cohort (ADAD n=60, LOAD n=120) but using a global semi-quantitative score

Limitations: no individuals with postmortem neuropathological assessment had antemortem tau PET imaging; a limited number of regions assessed in neuropathology; individuals with neuropathological assessment were at the end stage of disease

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Neuropathology Core
Yan Li
Dean W. Coble
Hongbo Luo
Beau M. Ances

DIAN:
Neuropathology Core
Carlos Cruchaga
Anne Fagan
Alison Goate
Jason Hassenstab
Celeste Karch
Eric McDade
Chengjie Xiong

DIAN-TU:
James J. Lah
Sarah B. Berman
Jared R. Brosch
Ghulam Surti
Christopher H. van Dyck
Serge Gauthier
Mario Masellis

Knight ADRC (P50AG005681, P01AG026276, P01AG03991)
Neuroimaging Informatics and Analysis Center (P30NS098577)
DIAN (U19AG032438, R01AG052550-01A1)
DIAN-TU (Alzheimer's Association, GHR Foundation, an anonymous organization, DIAN-TU Pharma Consortium)
DIAN-TU-001 Trial (Alzheimer's Association, Eli Lilly and Company, Roche, U01AG042791, U01AG042791-S1, R01AG046179, R01AG53267-S1, Avid Radiopharmaceuticals, GHR Foundation, an anonymous organization, CogState, Bracket)
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Mallinckrodt Institute of Radiology
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DIAN Dominantly Inherited Alzheimer Network
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Summary and future directions

Side notes: Regional patterns do not agree in areas that might have modest tau burden in early symptomatic stages of AD; or are small and difficult to quantify in imaging versus stereology

Tangles and threads may be pathophysiologically more closely linked than plaques, with tangles appearing first, and threads reflecting severe saturation of neuronal processes by abnormal tau

We found that the regional pattern of elevated tau PET radioligand binding is largely concordant with the regional pattern of elevated postmortem total tau burden in ADAD versus LOAD; additionally, we found tangle and thread, but not plaque, burden is elevated in ADAD versus LOAD

Concordance: Smith et al. found regional SUVRs correlated best with regional total tau burden in an ADAD case study; but we did not find a study comparing ADAD and LOAD for tangles, threads, and plaques

Discordance: Smith et al. found threads outnumbered tangles in every region in ADAD; we found no statistical dominance of thread over tangle burden in ADAD or LOAD; Ringman et al. found elevated plaque burden in a larger cohort (ADAD n=60, LOAD n=120) but using a global semi-quantitative score

Limitations: no individuals with postmortem neuropathological assessment had antemortem tau PET imaging; a limited number of regions assessed in neuropathology; Individuals with neuropathological assessment were at the end stage of disease