Distinguishing the contribution of tau and TDP-43 on medial temporal lobe atrophy

Yasmine Salman (1), **Julia Goloubeva** (1), **Sandra Tomé** (2), **Bernard J Hanseeuw** (1)

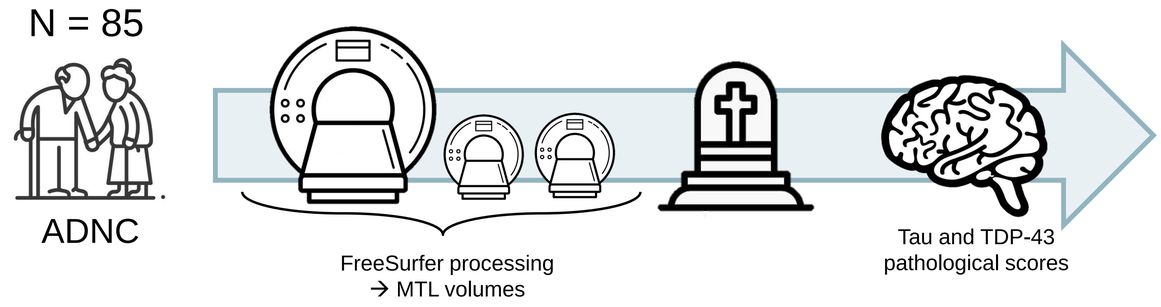
1.Louvain Aging Brain Lab, Institute of Neuroscience, UCLouvain, Brussels, Belgium

2. Laboratory of Neuropathology - Department of Imaging and Pathology and Leuven Brain Institute, KU Leuven, Leuven, Belgium

Background

- Alzheimer's disease (AD) is characterized by aggregation of amyloid-β and neurofibrillary tangles (NFTs)[1].
- Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) is identified by TDP-43 pathology in the limbic areas
- Up to 74% of AD cases also present with TDP-43 inclusions at autopsy, suggesting a comorbid LATE in AD cases[3–6].
- Both pathologies originate in the medial temporal lobe (MTL):
- AD and LATE also share similar clinical manifestations[2].
- LATE can only be diagnosed post-mortem as there is currently no available TDP-43 biomarker.
- **In this study, we aimed to identify MRI biomarkers that could differentiate between AD and LATE or AD from AD + LATE.**

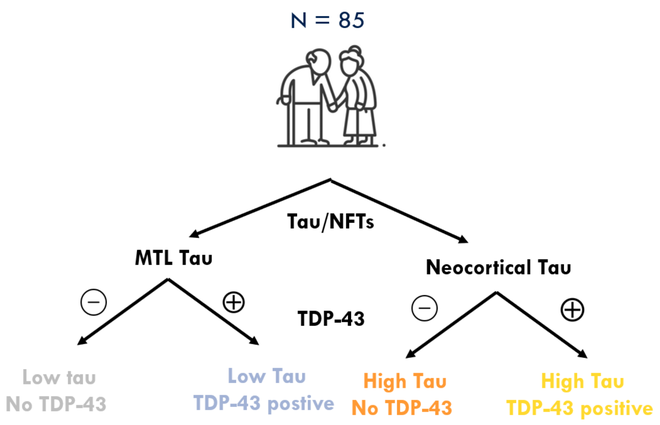
Methods



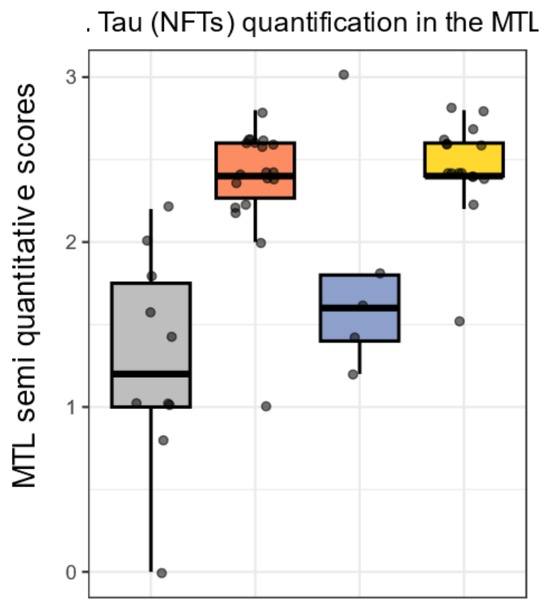
We selected 85 ADNC patients with at least one MRI aquired during life and postmortem neuropathological data. Volumes extracted from the MRI were then compared between groups based on neuropatholgical diagnosis.

Results

A. Group formation and validation : Tau pathology continues to accumulate in the MTL after Braak stage III.



	Low tau No TDP-43	High tau No TDP-43	Low tau TDP-43 MTL	High tau TDP-43 MTL
N	13	29	9	34
Age at death (years)	83.6 ± 6.8	79.6 ± 6.1	85.0 ± 3.4	80.5 ± 7.9
Sex, F (%)	1 (7.69%)	9 (31.03%)	2 (22.22%)	12 (35.29%)
Cognitive status at last MRI		*		***
CN	5 (38.46%)	4 (13.79%)	3 (33.33%)	3 (8.82%)
MCI	8 (61.54%)	16 (55.17%)	5 (55.56%)	12 (35.29%)
Dementia	0	9 (31.03%)	1 (11.11%)	19 (55.88%)
Braak NFT stage	1.92 ± 0.86	5.21 ± 0.56****	1.56 ± 0.76	5.14 ± 0.70****
Thal Aβ Phase	2.46 ± 1.90	4.69 ± 0.54****	2.67 ± 1	4.59 ± 0.78****
LATE-NC stage	0 ± 0	0 ± 0	2.33 ± 0.5****	1.94 ± 0.78****
Other neuropathologies				
LBD (%)	4 (30.8%)	15 (51.7%)	5 (55.6%)	19 (55.9%)
ARTAG (%)	0	3 (10.3%)	1 (11.1%)	7 (20.6%)
AGD (%)	5 (38.5%)	3 (10.3%)	5 (55.6%)	12 (35.3%)
Last MRI – death interval (years)	1.53 ± 1.53	2.25 ± 2.44	2.85 ± 3.46	4.51 ± 3.10 **

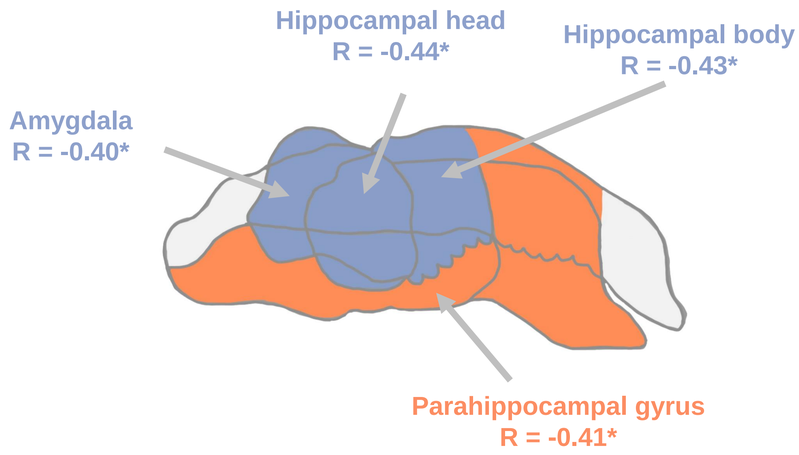


ADNC patients were grouped based on the levels of postmortem levels of tau (low tau [Braak I-III] ; high tau [Braak IV-VI]) and TDP-43 (negative/positive)

By comparing levels of NFTs between groups, we showed that 'high tau' groups continue to accumulate NFTs, justifying the group selection.

B. Neuropath and MTL sub-volumes associations:

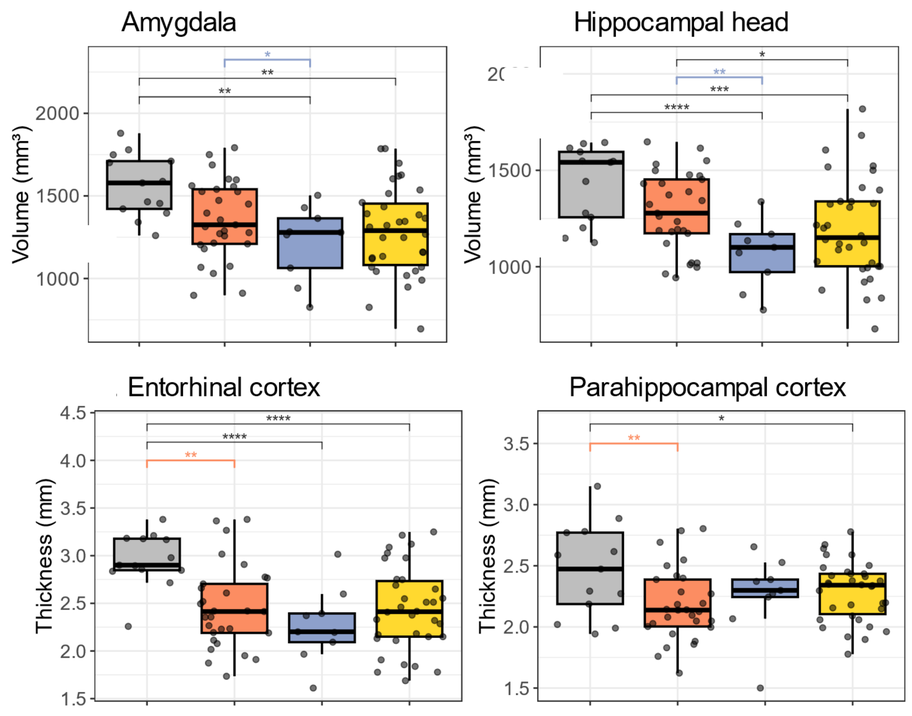
→ **NFTs: Hippocampal body & parahippocampal gyrus**
→ **TDP-43: mostly with hippocampal head**



Partial Spearman corrlelations were computed between MTL substructures volumes and semi quantitative scores of NFTs or TDP-43 in the MTL, adjusting for NFTs or TDP-43, controlling for age, sex and intracranial volume and interval between last MRI and death.

The hippocampal body and parahippocampal gyrus were the only structures whose volume or thickness was associated with NFTs, whereas TDP-43 was primarily linked to the volume of the hippocampal head, as well as the volume of the amygdala and hippocampal body.

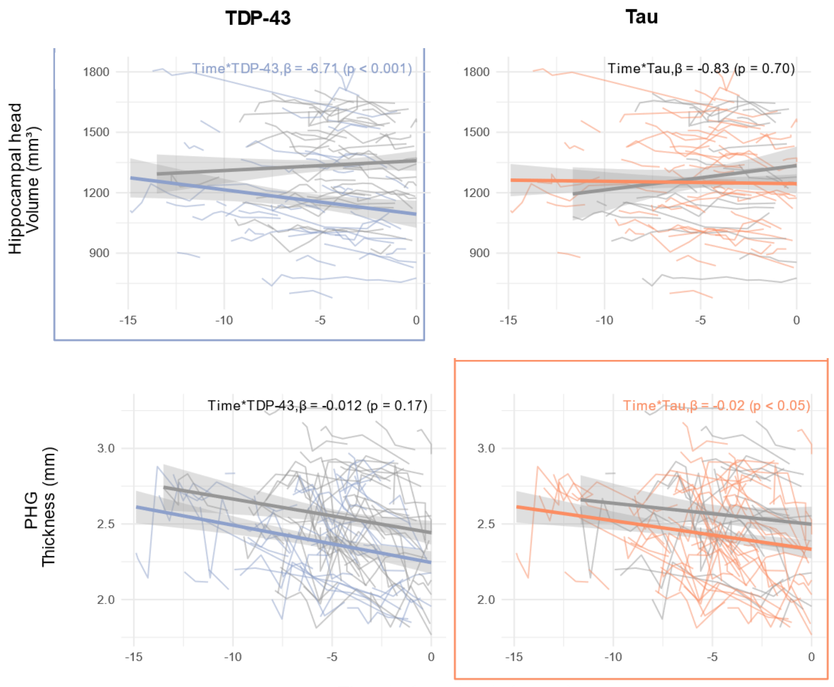
C. Hippocampal head atrophies with TDP-43, parahippocampal cortex with Tau.



Volumes differences were computed between groups using contrast analysis, adjusting for controlling for age, sex and intracranial volume and interval between last MRI and death.

The hippocampal head was the only structure where volume reduction was specifically associated with TDP-43 pathology, while the parahippocampal cortex was the only structure uniquely linked to tau pathology.

D. Hippocampal head atrophies with TDP-43, parahippocampal cortex with Tau – longitudinal analysis.

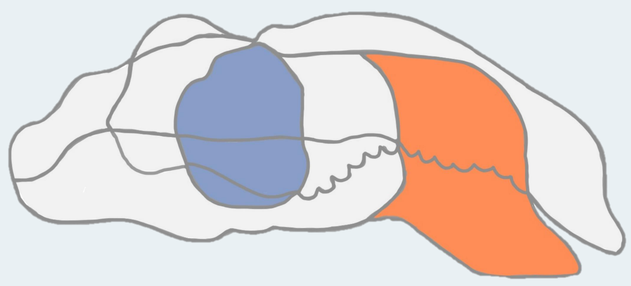


Linear mixed models were computed to investigate longitudinal ante-mortem medial temporal lobe volumes difference based on the levels of tau pathology or TDP-43 presence controlling for age, sex and intracranial volume. .

The hippocampal head was the only structure where volume reduction over time was specifically associated with TDP-43 pathology, while the parahippocampal cortex was the only structure uniquely linked to tau pathology.

Conclusion

Hippocampal head atrophy is specific to TDP-43 pathology while parahippocampal cortex atrophy is specific to neocortical tau pathology.



Hippocampal head atrophy could help distinguishing between AD and AD+LATE patients

Yasmine Salman
yasmine.salman@uclouvain.be