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

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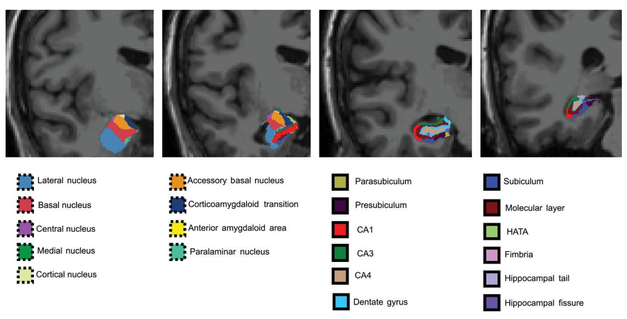
Background

Alzheimer's disease (AD) is characterized by abnormal aggregation of amyloid-β (Aβ) and hyperphosphorylated tau protein into neurofibrillary tangles (NFTs)[1]. On the other hand, Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) is identified by TAR DNA-binding protein 43 (TDP-43) pathology in the limbic areas in individuals without amyotrophic lateral sclerosis or fronto-temporal lobe degeneration due to TDP-43 and can found in patients above 80 years old[2]. Up to 74% of AD cases also present with TDP-43 inclusions at autopsy, suggesting a comorbid LATE neuropathological changes (LATE-NC) in Alzheimer's disease neuropathological changes (ADNC) cases[3–6]. Both pathologies originate in the medial temporal lobe (MTL): while NFTs start accumulating in the transentorhinal and entorhinal cortices before spreading to the hippocampus and amygdala and further to the neocortex[1,7], TDP-43 inclusions start in the amygdala, then progress to the hippocampus and can, in some cases, expend to the middle frontal gyrus [2,8]. Due to their similar progression patterns, AD and LATE also share similar clinical manifestations including progressive cognitive decline starting with memory loss and eventually leading to dementia[2]. Unfortunately, LATE can only be diagnosed post-mortem as there is currently no available TDP-43 biomarker. Distinguishing pure AD from LATE or AD + LATE has therefore crucial implications for treatment development. **In this study, we aimed to identify MRI biomarkers that could differentiate between AD and LATE or AD from AD + LATE.**

Methods

85 ANC patients with antemortem MRI and neuropathological data (ADNI)



Association between volume and neuropathological semi-quantitive scores (Tau and TDP-43 in MTL)

Volumes differences according to tau and TDP-43 levels

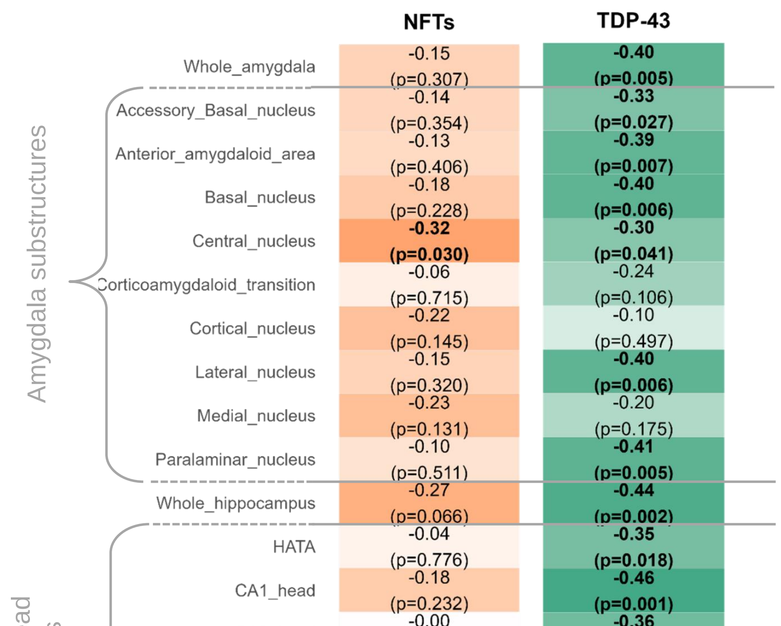
	Low Tau No TDP	High Tau No TDP	Low Tau TDP MTL	High Tau TDP MTL
N	13	29	9	34
Age at death	85.01 ± 6.86	81.86 ± 6.14	87.78 ± 5.09	85.00 ± 7.84
Sex (F/H)	1 / 12	9 / 20	2 / 7	12 / 22
Clinical diagnosis at last MRI CN/MCI/Dem	5 / 8 / 0	4 / 16 / 9 *	3 / 5 / 1	3 / 12 / 19 ****
Braak stage	1.92 ± 0.86	5.21 ± 0.56****	1.56 ± 0.76	5.14 ± 0.70****
TDP43 in neocortex	0	0	3 (33.3 %) *	9 (26.5%) ***
MRI – death interval	1.53 ± 1.53	2.25 ± 2.44	2.85 ± 3.46 **	4.51 ± 3.10

All models were adjusted for age, sex, intracranial volume and interval between MRI and death

Results

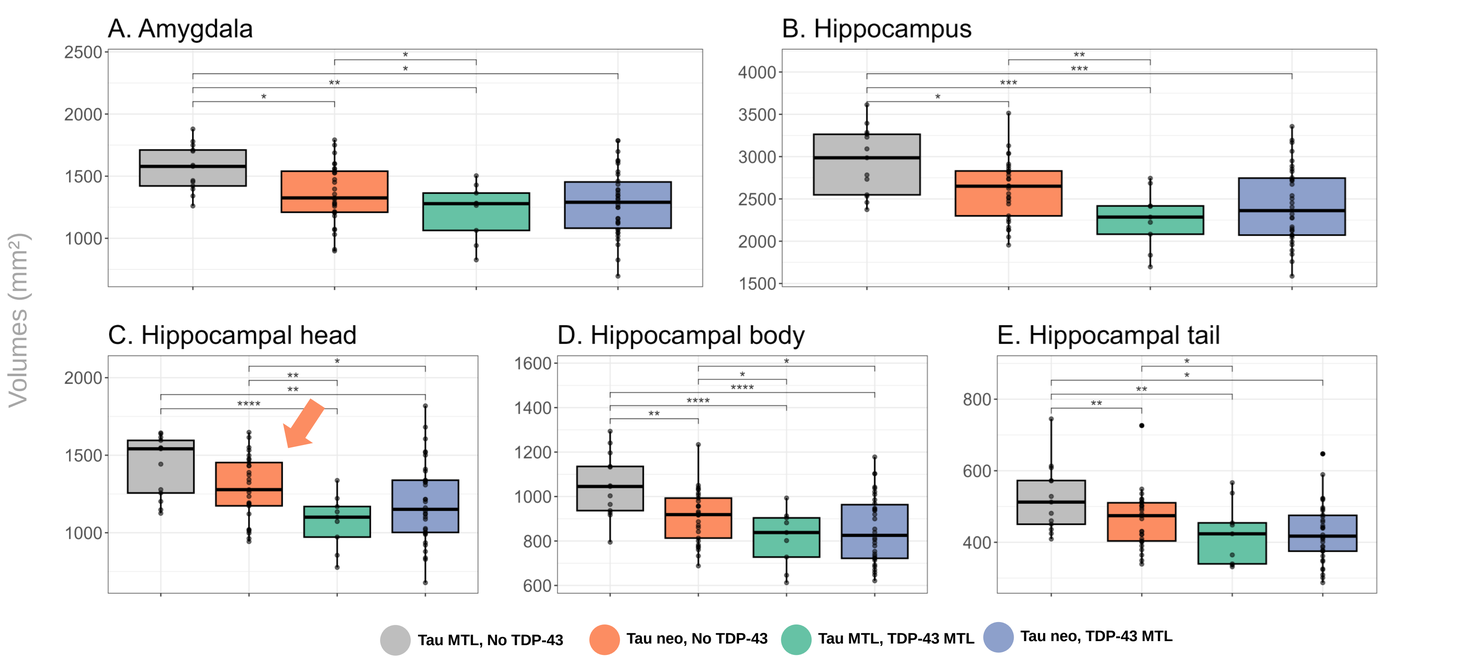
A. Associations with MTL sub-volumes:

→ **NFTs: only with hippocampal body**
→ **TDP-43: mostly with hippocampal head**



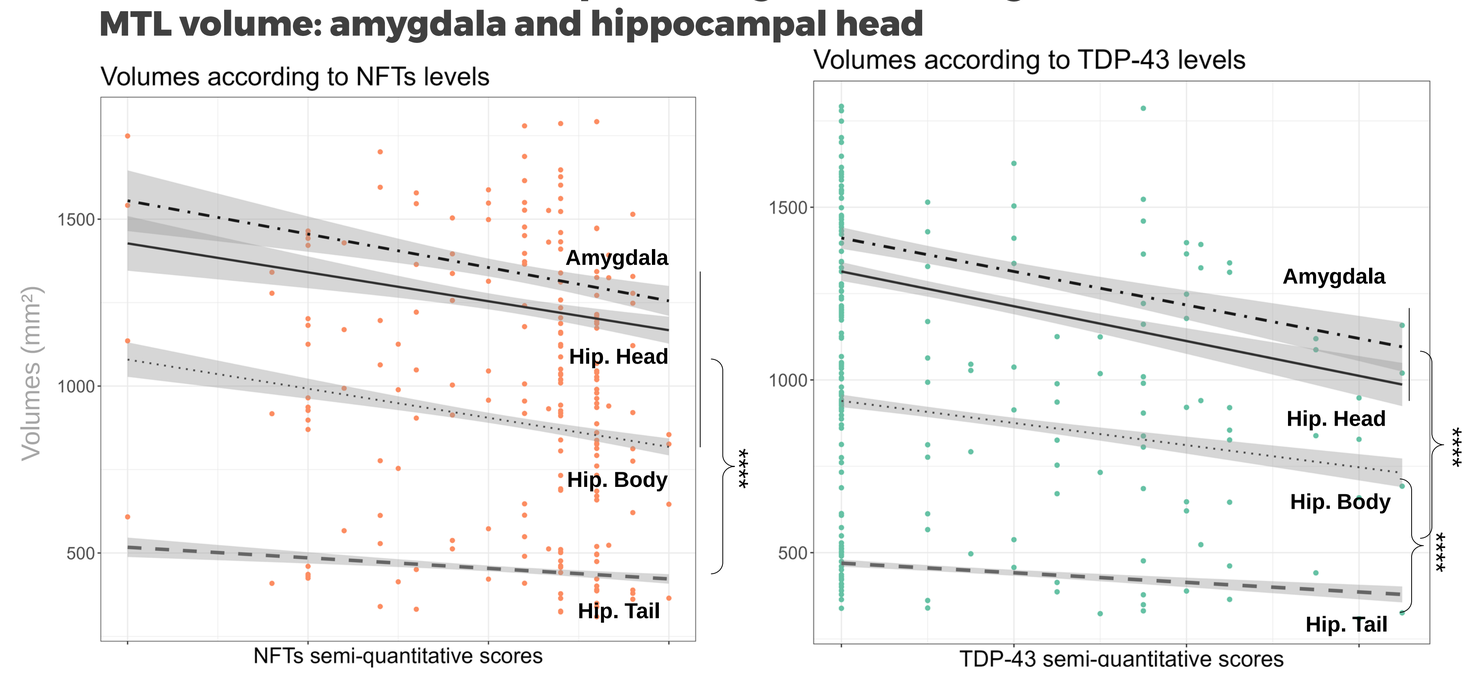
Partial Spearman corrlelation were computed between MTL substructures volumes and semi quantitative scores of NFTs or TDP-43 in the MTL, adjusting f NFTs or TDP-43.

B. In the absence of TDP-43, hippocampal body atrophies with tau, not the head



Patients were grouped according to their tau and TDP-43 levels (Braak 0-3 = Tau MTL ; Braak 4-6 = Tau neo ; presence of TDP-43 within the MTL = TDP-43 MTL).

C. TDP-43 shows an anterioposterior gradient with greater effect on anterior MTL volume: amygdala and hippocampal head



Linear mixed models were permormed to evaluate differences in NFTs and TDP-43 effect on the different MTL subregions volumes.

Conclusion

- ✓ Tau and TDP-43 differently affect the MTL : TDP-43 has a stronger effect than tau on MTL atrophy.
- ✓ TDP-43 affect all MTL volumes with a stronger effect on anterior MTL substructures as the amygdala and hippocampal head.
- ✓ Tau mainly affect the posterior part of the MTL, with stronger effect on the hippocampal body.
- ✓ **Hippocampal head atrophy in ADNC patient is associated with the presence of comorboid LATE-NC**

References

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