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Specific atrophy patterns distinguish tau and TDP-43 pathology: a longitudinal MRI ante-mortem study

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1. Abstract

TDP-43 pathology frequently co-occurs with Alzheimer's disease (AD), indicative of Limbic-predominant Age-related TDP-43 Encephalopathy neuropathologic changes (LATE-NC), which is associated with more severe medial temporal lobe (MTL) atrophy and cognitive decline compared to 'pure' AD. As both tau and TDP-43 target overlapping MTL structures and are associated with similar clinical manifestations, disentangling their respective contributions to neurodegeneration is essential yet challenging. In this study, we investigated the differential impact of tau and TDP-43 pathologies on MTL subregions, with a focus on the anterior-to-posterior and superior--to-inferior gradients, and amygdala subnuclei. We analyzed structural MRI data from 85 ADNI participants with autopsy-confirmed

neuropathology. Participants were stratified by Braak stage (Low tau: 0–III; High tau: IV–VI) and presence of TDP-43 pathology in the MTL. The presence of TDP-43 pathology was significantly associated with hippocampal head volume ($R = -0.47$, $P < 0.01$) and all amygdala subnuclei, while tau pathology was associated with parahippocampal gyrus thickness ($R = -0.41$, $P < 0.01$) and the central nucleus of the amygdala ($R = -0.32$, $P < 0.05$). In individuals with low tau burden, TDP-43 positivity was linked to widespread MTL atrophy, excluding the parahippocampal cortex (PHC), whereas in TDP-43-negative individuals, high tau pathology was associated with atrophy in the PHC and specific amygdala nuclei. Longitudinally, TDP-43 predicted faster hippocampal head volume loss ($\beta = -6.71 \text{ mm}^3/\text{year}$, $P < 0.001$), while tau pathology was associated with greater PHC thinning ($\beta = -0.02 \text{ mm}/\text{year}$, $P < 0.05$). These results highlight an association between TDP-43 and the volume/thickness of anterior MTL regions while tau pathology was more associated with the volume/thickness of posterior MTL. However, it also suggests a superior-to-inferior gradient, TDP-43 predominantly affecting superior regions and tau affecting inferior MTL. Taken together, these findings suggest that the hippocampal head (anterior-superior) atrophy may differentiate AD patients with or without comorbid LATE-NC.

2. Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia in the elderly [18, 33] and is characterized by abnormal aggregation of amyloid- β ($A\beta$) and hyperphosphorylated tau protein into neurofibrillary tangles

(NFTs) [6]. About half of AD cases also present with TDP-43 inclusions at autopsy, known as Limbic-predominant Age-related TDP-43 Encephalopathy neuropathologic changes (LATE-NC) [1, 2, 26, 32, 35, 37]. Both tau and LATE pathologies originate in the medial temporal lobe (MTL). Due to their overlap in distribution patterns, they also underlie similar clinical manifestations including progressive cognitive decline starting with memory loss, eventually leading to dementia [37]. Besides the impact of LATE-NC on cognition in the otherwise healthy population, comorbid LATE-NC in AD has been shown to significantly impact clinical features associated with AD [25, 39]. Indeed, AD + LATE patients show higher Braak NFT stages and increased burden of tau NFTs at death [24, 27, 50], develop more severe dementia, greater hippocampal atrophy, and more pronounced memory decline over time compared to ‘pure’ AD patients [23, 24, 37].

A better understanding of how tau and TDP-43 pathologies contribute to MTL atrophy is critical, not only to better understand AD and LATE pathophysiology but also to support the development of biomarkers to distinguishing these entities *in vivo*. To date, TDP-43 pathology remains without validated in-vivo biomarkers, making LATE-NC diagnosable only at autopsy. This limitation complicates the ability to distinguish LATE from “pure” AD during life, a distinction that is becoming increasingly important in the context of emerging disease-modifying therapies. Given that therapeutic strategies may need to be adjusted to specific underlying pathologies : AD neuropathologic change (ADNC), LATE-NC, or both,

identifying differential atrophy signatures associated with tau and TDP-43 could guide both clinical management and research trials [39, 36].

Although PET tracers targeting TDP-43 are under development, their clinical implementation remains distant, and fluid biomarker discovery is complicated by the intranuclear localization of TDP-43 [37]. In contrast, high-resolution magnetic resonance imaging (MRI) provides a non-invasive approach to detect region-specific structural changes *in vivo* and has shown promise for identifying distinct atrophy patterns associated with tau and TDP-43 pathology. However, the current literature presents inconsistent findings: some studies have reported greater associations between tau and anterior MTL structures [43, 44, 57], others with posterior regions [11]. Similarly, the impact of TDP-43 pathology has been linked to anterior MTL [11, 17, 44] or whole MTL [43, 12, 54]. This variability reflects a lack of clarity regarding how each pathology affects the MTL. So far, only one longitudinal antemortem study investigated global hippocampal atrophy over time in LATE-NC [22] but did not examine anterior-posterior axis of the MTL. Furthermore, despite the early involvement of the amygdala in both AD and LATE, very few studies investigated the relative contributions of tau and TDP-43 to amygdala subnuclei atrophy [31, 53].

The goal of this study was therefore to identify *in vivo* MRI atrophy patterns associated with post-mortem tau and TDP-43 pathology. First, we examined atrophy along the anterior-posterior axis of the MTL. Second, we focused on the amygdala and its subnuclei. We analyzed data from

participants with neuropsychological and longitudinal MRI data acquired during life and neuropathologic assessment obtained after death in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study.

3. Materials and methods

3.1 Data acquisition

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see www.adni-info.org.

Data was downloaded on April 1, 2024, and encompass data collected from September 2005 through December 2023.

3.2 Participants

Participants with available pathology data and at least one structural T1-weighted (T1w) MRI were selected from the ADNI database (N = 101). Ten participants were excluded due to a diagnosis of non-AD neurodegenerative disease (i.e. progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), frontotemporal dementia (FTLD) and six were excluded due to poor image or segmentation quality, leaving 85 participants for the analysis. These included 15 cognitively normal (CN),

41 MCI and 29 individuals with a clinical diagnosis of dementia at last MRI before death.

3.3 Neuropsychological data

Neuropsychological evaluations were conducted at participating ADNI sites on average 2.28 ± 2.79 years before death. Composite neuropsychological factor scores were computed based on the last neuropsychological evaluation before death and obtained from the ADNI database and included memory, executive function, language, and visuospatial functions.

The memory factor score included performance on the Rey Auditory Verbal Learning Test (RAVLT), the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog), the Mini-Mental State Examination (MMSE), and the Logical Memory tests [14].

The executive function factor score included measures from the WAIS-R Digit Symbol Substitution test, Digit Span Backwards, Trail Making Tests A and B, Category Fluency, and the Clock Drawing Test [15].

The language factor score was derived from the Boston Naming Test, animal fluency, and selected items from the MMSE (object naming, sentence repetition, sentence reading and writing, and following a three-step command), the ADAS-Cog (following commands, object naming, ideational praxis), and the Montreal Cognitive Assessment (MoCA; phonemic fluency and sentence repetition) [9].

The visuospatial factor score included the Clock Drawing Test, and selected items from the MMSE (copying interlocking pentagons), and the ADAS-Cog (constructional praxis item) [9].

3.4 MRI acquisition

3D T1w MRI scans in ADNI were acquired at respective sites from September 2005 to January 2020 using imaging protocols detailed in prior publications [21]. The resolution of the scans ranged from $0.94 \times 0.94 \times 1.2$ to $1.25 \times 1.25 \times 1.2$ mm³.

3.5 MRI processing

For each participant, all 3D T1w raw MRI data available from the ADNI database were downloaded from the ADNI archive website and processed locally.

For cross-sectional analysis, subcortical segmentation and cortical parcellation of structural MRI data was performed using FreeSurfer v7.2. Entorhinal cortex (ERC) and parahippocampal cortex (PHC) thickness measures were extracted from the Desikan-Kiliany atlas, and grouped together for some analyses under the term parahippocampal gyrus (PHG) [13]. Detailed segmentation was then performed for the hippocampal subfields and the amygdala subnuclei. The hippocampal formation was divided into hippocampal head, body and tail [19] while the amygdala was divided into nine subnuclei [47].

For longitudinal analysis, volumetric segmentation and parcellation was performed using a developmental toolbox for longitudinal analysis features

(<http://surfer.nmr.mgh.harvard.edu/>) [19]. The FreeSurfer hippocampal subfield longitudinal processing stream was used to extract reliable longitudinal volumes estimates for both the amygdala and the hippocampus substructures [20].

All regions were averaged over the left and right hemispheres.

3.6 Neuropathology

All autopsies were performed at the respective site from April 2008 to December 2023. Most brains were fixed with formalin, except three that were fixed with paraformaldehyde. The tissues from the left hemispheres were then embedded in paraffin blocks and sectioned into 6 μ m slices for immunohistochemistry. Hyperphosphorylated tau was stained with PHF-1 primary antibody (except one for which a non-phospho-specific tau antibody was used). Phospho-specific antibodies were used to stain TDP-43, except in one case where a non-phospho-specific antibody was used. However, no further antibody information was available. ADNC was established according to the criteria of Montine *et al.* [34]. The presence of Lewy body pathology (LBD), aging-related tau astroglialopathy (ARTAG), argyrophilic grain disease (AGD), small vessel disease, and microinfarcts was classified using pre-established criteria, respectively [7, 28, 4, 3].

A subset of participants benefited from detailed neuropathologic semi-quantification per anatomical regions (N = 51, autopsies performed before June 2018, scoring system for NFTs and TDP-43 inclusions is shown in Supplementary Table 1), whereas other participants (N = 30, autopsies after June 2018) had more summarized information including Braak stage,

Thal phase, CERAD score, as well as dichotomous data on the presence or absence of TDP-43 lesions in the spinal cord, amygdala, hippocampus, entorhinal cortex, and frontal cortex according to the Neuropathology NACC Form Version 11.

For the subset of participants with semi-quantitative data, an MTL composite score was calculated by averaging the scores of CA1, DG, ERC, PHC and amygdala for NFTs or TDP-43 inclusions including cytoplasmic inclusions, intranuclear inclusions, dystrophic neurites and glial inclusions.

LATE-NC diagnosis and stages were not formally assessed by the ADNI neuropathology core. We therefore classified individuals as TDP-43 positive if they exhibited at least one TDP-43 inclusion in the MTL (amygdala, ERC, hippocampus) or in the neocortex [37], while those without were classified as TDP-43-negative. Diagnoses of FTLD or amyotrophic lateral sclerosis (ALS) were excluded. LATE-NC staging system was retrospectively assessed with available data and was based on *Nelson et al.* [37, 38]: stage 1 was defined as TDP-43 inclusions in the amygdala region or hippocampus, stage 2 as TDP-43 inclusions in the amygdala and hippocampus, and stage 3 in the aforementioned regions and the frontal cortex.

Participants were grouped based on Braak NFT stages and the presence of TDP-43 inclusions in the MTL at autopsy: participants with Braak stage $\leq$ III were classified as Low tau, while Braak stages $\geq$ IV were considered as High tau. We did not have enough participants with Braak 0 (n=2) to

include a group without tau pathology. We therefore obtained 4 study groups: (1) Low tau, TDP-43-negative, (2) High tau, TDP-43-negative, (3) Low tau, TDP-43-positive, (4) High tau, TDP-43-positive.

3.7 Statistics

3.7.1 Demographics and postmortem data

Demographic data was compared between groups using ANOVA for parametric data, Mann-Whitney tests for non-parametric continuous data and Fisher tests for dichotomous data. Semi quantitative scores for NFTs and TDP-43 inclusions were compared between groups using multiple linear regression models and post-hoc contrast analysis controlling for age and sex.

3.7.2 Neuropsychology factor scores

We compared the last neuropsychology factor score for each domain (memory, executive functions, language and visuospatial functioning) acquired before death between groups based on tau (low/high) and TDP-43 (negative/positive) using linear regression and post-hoc contrast analyses (N = 85), with 'Low tau, TDP-43-negative' as the reference group and controlling for age, sex, interval between neuropsychological evaluation and death and years of education.

3.7.3 Cross sectional imaging analyses

Cross sectional analyses were performed on the last MRI acquired before death (3 ± 2.95 years before death). We first investigated the association between MTL substructures volume or thickness and TDP-43 and NFTs

semi-quantitative scores in the MTL using partial Spearman correlation (subset data, N=51). To assess independent contribution of these proteinopathies to volume/thickness loss, we controlled for NFTs levels when assessing TDP-43 and for TDP-43 when assessing NFTs. We used one-tailed test, anticipating negative associations. Second, we compared volume/thickness of MTL substructures between groups based on tau (low/high) and TDP-43 (negative/positive) using linear regression and post-hoc contrast analyses (N=85), with 'Low tau, TDP-43-negative' as the reference group. Results were then repeated with the first MRI available (6.5 ± 3.5 years before death).

All analyses were FDR corrected and adjusted for age at death, sex, intracranial volume, and the interval between MRI and death.

3.7.4 Longitudinal imaging analyses

Longitudinal analyses were performed on all subjects who had at least two MRI scans acquired before death (number of participants = 82, total number of MRI scans = 452 over an average 4.81 ± 3.24 years of follow-up). We used linear mixed models (LMM) to examine the longitudinal effects of TDP-43 or tau pathologies on MTL volumes or thicknesses. We predicted the volume of the hippocampal head and the thickness of the PHC based on the interaction between TDP-43 (negative/positive) or tau (low/high) groups and time before death, adjusting for the other pathology. LMM included a random intercept for each patient to account for individual variability. We controlled for potential confounders, including age at death, sex, and estimated total intracranial volume. Interaction

between time and age was also included to capture the influence on the longitudinal trajectories.

All analyses were FDR corrected for multiple comparisons and computed in R version 4.2.2 (packages *ppcor*, *emmeans* and *lme4*).

4. Results

4.1 Participant Characteristics and Neuropathologic Outcomes

At the time of the last MRI, participants ($N = 85$) were on average 81.2 years old ($SD = 6.9$), and 28.2% were female, with no significant demographic differences between groups (Table 1). At death, 74.1 % of the participants showed neocortical tauopathy (Braak IV-VI, 'High Tau'), while 50.6 % had TDP-43 inclusions in the MTL ('TDP-43-positive'). Both 'High Tau' groups included significantly more cognitively impaired individuals than the 'Low Tau' groups (Table 1, Fig. 1A). The presence of TDP-43 did not affect the proportion of clinically impaired individuals.

'High tau' groups showed higher Braak NFT stages but also higher Thal A β Phase and CDR than the 'Low tau' groups, suggesting a higher AD likelihood. Of note, no difference in the proportion of comorbid neuropathologies, including LBD, AGD, and ARTAG, was observed between groups.

Although a weak association was observed between NFTs and TDP-43 burdens ($R = 0.07$, $P = 0.03$), the prevalence of both neuropathologies was

independent from each other, i.e., participants with low Braak stages were as likely to have TDP-43 pathology as participants with high Braak stages (Fig. 1B). The semi-quantitative analyses revealed that individuals with high Braak stages had more NFTs deposits in the MTL than individuals with low Braak NFT stages (Fig. 1D, $P < 0.001$), indicating that Braak stage could serve as a proxy for MTL tau pathology in individuals with no semi-quantitative assessment. As expected based on our group selection, the 'TDP-43-positive' groups also had significantly more TDP-43 inclusions in the MTL compared to the 'TDP-43-negative' groups (Fig. 1E, $P < 0.0001$). The 'High Tau, TDP-43-positive' group had more TDP-43 inclusions in the MTL than the 'Low Tau, TDP-43-positive' group ($P < 0.05$). Interestingly, the 'low tau, TDP-43-positive' group did not contain any LATE-NC-stage 1 individuals (Fig. 1C).

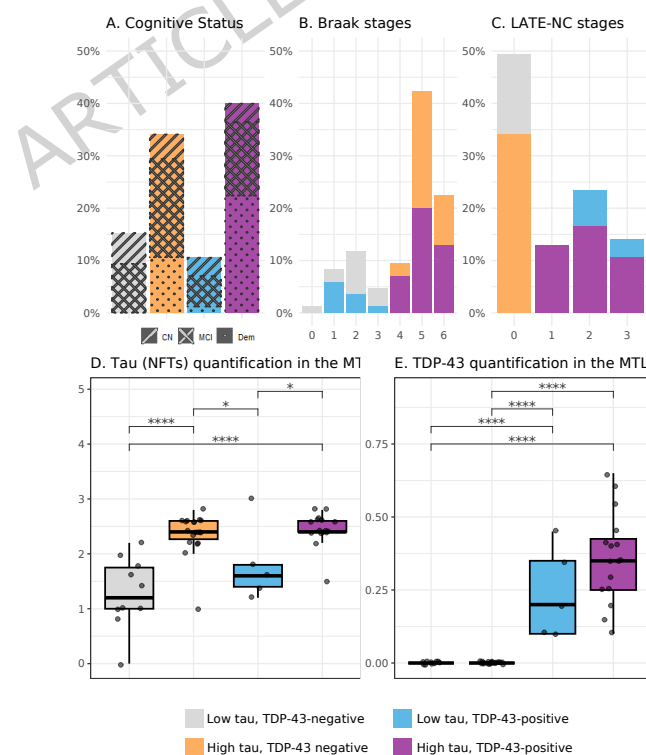


Figure 1: Cognitive and neuropathologic characteristics of the studied population.

A-C : Bar plots illustrate the prevalence of **(A)** cognitive status (CN/MCI/Dementia), **(B)** Braak NFT stages, and **(C)** LATE-NC stages split by groups based on levels of tau pathology and TDP-43 presence. **D-E** : Boxplots represent the distribution of **(D)** neurofibrillary tangles or **(E)** TDP-43 inclusions within the MTL per group. This analysis includes 85 participants for panel A-C (including 13 Low tau, TDP-43 negative individuals (grey), 29 High Tau, TDP-43 negative individuals (orange), 9 Low tau, TDP-positive individuals (blue) and 34 High Tau, TDP-43 positive individuals (purple)) and 51 participants for panel D,E (including 10 Low tau, TDP-43 negative individuals (grey), 19 High Tau, TDP-43 negative individuals (orange), 5 Low tau, TDP-positive individuals (blue) and 16 High Tau, TDP-43 positive individuals (purple)). Reported p values are p values adjusted for age at death and sex: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Abbreviations: CN: Cognitively Normal; MCI: Mild cognitive impairment; NFTs: Neurofibrillary tangles; LATE: Limbic predominant age-related TDP-43 encephalopathy; MTL: Medial temporal lobe

	Low tau No TDP-43	High tau No TDP-43	Low tau TDP-43 MTL	High tau TDP-43 MTL	p-Value	Post-Hoc
Group	1	2	3	4		
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	0.11	/
Sex, F (%)	1 (7.69%)	9 (31.03%)	2 (22.22%)	12 (35.29%)	0.28	/
Cognitive status at last MRI					0.004	
CN	5 (38.46%)	4 (13.79%)	3 (33.33%)	3 (8.82%)		Group 1 ≈ 2 ≈ 3 ≈ 4
MCI	8 (61.54%)	16 (55.17%)	5 (55.56%)	12 (35.29%)		Group 1 ≈ 3 < 2 ≈ 4
Dementia	0	9 (31.03%)	1 (11.11%)	19 (55.88%)		Group 1 ≈ 3 < 2 ≈ 4
<i>APOE</i> ε4 carriers (%)	3 (23.1%)	22 (75.9%)	1 (11.1%)	23 (67.6%)	< 0.001	Group 1 ≈ 3 < 2 ≈ 4
Braak NFT stage	1.92 ± 0.86	5.21 ± 0.56	1.56 ± 0.76	5.14 ± 0.70	< 0.001	Group 1 ≈ 3 < 2 ≈ 4
0	1 (7.69%)	0	0	0		
I	2 (15.38%)	0	5 (55.56%)	0		
II	7 (53.85%)	0	3 (33.33%)	0		
III	3 (23.08%)	0	1 (11.11%)	0		
IV	0	2 (6.89%)	0	6 (17.65%)		
V	0	19 (65.52%)	0	17 (50%)		
VI	0	8 (27.59%)	0	11 (32.35%)		

Thal A β Phase	2.46 $\pm$ 1.90	4.69 $\pm$ 0.54	2.67 $\pm$ 1	4.59 $\pm$ 0.78	< 0.001	Group 1 $\approx$ 3 < 2 $\approx$ 4
0	3 (23.08%)	0	0	0		
1	2 (15.38%)	0	2 (22.22%)	1 (2.94%)		
2	1 (7.69%)	0	0	0		
3	2 (15.38%)	1 (3.45%)	6 (66.67%)	0		
4	3 (23.08%)	7 (24.14%)	1 (11.11%)	10 (29.41%)		
5	2 (15.38%)	21 (72.41%)	0	23 (67.65%)		
CERAD	0.15 $\pm$ 0.38	2.72 $\pm$ 0.70	0.67 $\pm$ 0.50	2.64 $\pm$ 0.77	< 0.001	Group 1 $\approx$ 3 < 2 $\approx$ 4
0	11 (84.62%)	1 (3.44%)	3 (33.33%)	1 (2.94%)		
1	2 (15.38%)	1 (3.44%)	6 (66.67%)	3 (8.82%)		
2	0	3 (10.34%)	0	3 (8.82%)		
3	0	24 (82.76)	0	27 (79.41%)		
LATE-NC stage	0 $\pm$ 0	0 $\pm$ 0	2.33 $\pm$ 0.5	1.94 $\pm$ 0.78	< 0.001	Group 1 $\approx$ 2 < 3 $\approx$ 4
Other neuropathologies						
LBD (%)	4 (30.8%)	15 (51.7%)	5 (55.6%)	19 (55.9%)	0.47	/
ARTAG (%)	0	3 (10.3%)	1 (11.1%)	7 (20.6%)	0.27	/
AGD (%)	5 (38.5%)	3 (10.3%)	5 (55.6%)	12 (35.3%)	0.027	Group 1 $\approx$ 2 < 3 $\approx$ 4
Last MRI - death interval (years)	1.53 $\pm$ 1.53	2.25 $\pm$ 2.44	2.85 $\pm$ 3.46	4.51 $\pm$ 3.10	0.002	Group 1 $\approx$ 2 $\approx$ 3 < 4

341

342 **Table 1: Demographic and neuropathologic profiles of the participants.**

343 Differences between groups were assessed with the Mann-Whitney or Fisher tests. Braak NFT stages, Thal A β Phase, CERAD and LATE-
344 NC stages were evaluated based on previous work respectively (Braak & Braak 1991, 1995; Thal et al. 2002, Montine et al. 2012, Nelson
345 et al. 2019, 2023). LBD, ARTAG and ADG diagnosis were based on established criteria respectively (Braak & Braak 1998; Kovacs et al.
346 2016; Attems et al. 2021).

347 Symbol meanings: “ $\approx$ ” indicates no statistically significant difference ($p > 0.05$); “ $<$ ” indicates a statistically significant difference ($p <$
348 0.05), with the group on the left having lower values than the group on the right; “ $>$ ” indicates a statistically significant difference ($p <$
349 0.05), with the group on the left having higher values than the group on the right.

350 Abbreviations: CN: Cognitively Normal; MCI: Mild cognitive impairment; NFTs: Neurofibrillary tangles; A β : Amyloid-beta; CERAD:
351 Consortium to Establish a Registry for Alzheimer’s disease; LATE-NC: Limbic predominant age-related TDP-43 encephalopathy
352 neuropathologic changes; LBD: Lewy Body disease; ARTAG = Aging-related tau astroglial pathology; AGD: Argyrophilic grain disease.

4.2 Neuropsychological factor scores

We first evaluated the contribution of tau and TDP-43 pathologies to impairment in different cognitive domains (N = 85). Individuals with higher levels of tau pathology showed impaired memory (Fig. 2A: $\beta < -2.13$, $P < 0.0001$), executive functions (Fig. 2B : $\beta < -0.93$, $P < 0.0001$), and language (Fig. 2C: $\beta < -1.75$, $P < 0.0001$) compared to the 'Low tau, TDP-43-negative' group. In contrast, TDP-43-positive individuals with low tau levels ('Low tau, TDP-43-positive') only had memory impairment (Fig. 2A: $\beta = -1.16$, $P < 0.001$) but performed similarly to the 'Low tau, TDP-43-negative' group in language and executive functions (Fig. 2B-C).

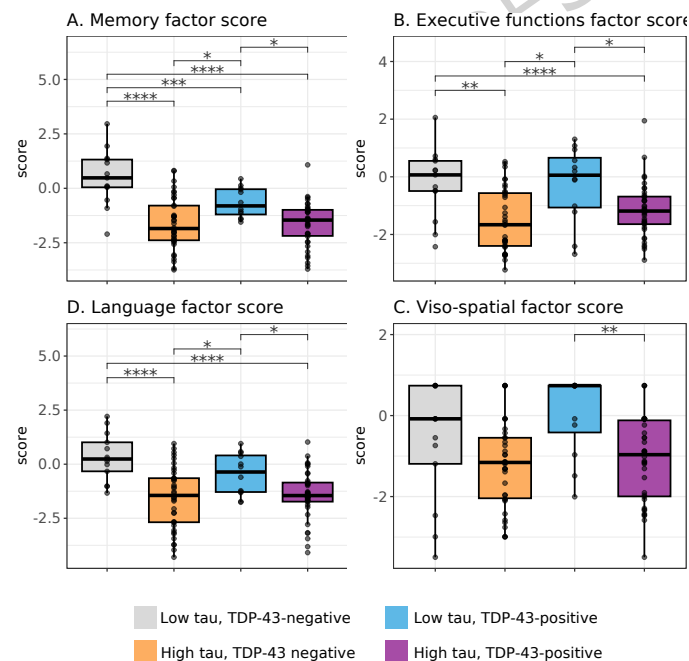


Figure 2 : Ante-mortem factor cognitive scores across groups based on postmortem diagnosis.

Boxplots represents (A) memory, (B) executive functions, (C) language and (D) visuo-spatial factor scores per group based on the levels of tau pathology and TDP-43 presence.

This analysis includes 85 participants including 13 Low tau, TDP-43 negative individuals (grey), 29 High Tau, TDP-43 negative individuals (orange), 9 Low tau, TDP-positive individuals (blue) and 34 High Tau, TDP-43 positive individuals (purple). Reported p values are p values adjusted for age, sex, and years of education: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

4.3 Associations of TDP-43 and NFT Levels with MTL Substructure volumes

We then performed partial Spearman correlations between substructures volume (i.e. hippocampal head-body-tail, amygdala subnuclei) or thickness (ERC, PHC) and NFTs and TDP-43 semi-quantitative ratings within the MTL ($N = 51$). When adjusting for NFTs levels, TDP-43 pathology was associated with almost all amygdala subnuclei volumes as well as the volume of the whole amygdala (Fig. 3; $R = -0.40$, $P < 0.05$), hippocampal head ($R = -0.47$, $P < 0.05$), and hippocampal body ($R = -0.43$, $P < 0.05$). After adjusting for TDP-43 levels, NFTs were associated with the volume of central nucleus ($R = -0.32$, $P < 0.05$) but not with the whole amygdala volume ($R = -0.15$, $P = 0.20$). NFTs were also significantly associated with hippocampal body volume ($R = -0.34$, $P < 0.05$) and the ERC thickness ($R = -0.36$, $P < 0.05$) and showed a trend toward association with PHC thickness ($R = -0.28$, $P = 0.07$). The volume of the hippocampal tail was weakly associated with both neuropathologies (Fig. 3, $P < 0.10$).

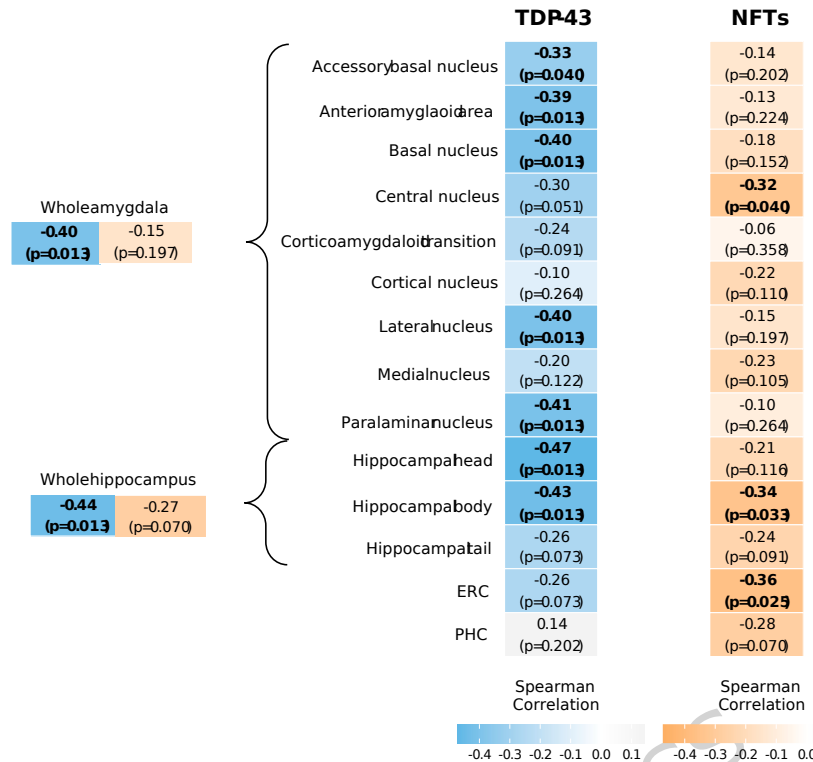


Figure 3 : Relationship between post-mortem pathology measures and ante-mortem MTL measures.

Spearman partial correlations were computed between postmortem semi-quantitative scores of NFT and TDP-43 inclusions that were measured within the medial temporal lobe and ante-mortem medial temporal lobe volumes (N=51). Medial temporal lobe volumes were first divided into amygdala subnuclei and hippocampal head, body and tail, then regrouped into amygdala and hippocampus. Reported *p* values are *p* values adjusted for age, sex, interval between the last MRI and death and either levels of NFTs or TDP-43. Measurements that survived FDR correction are highlighted in bold font.

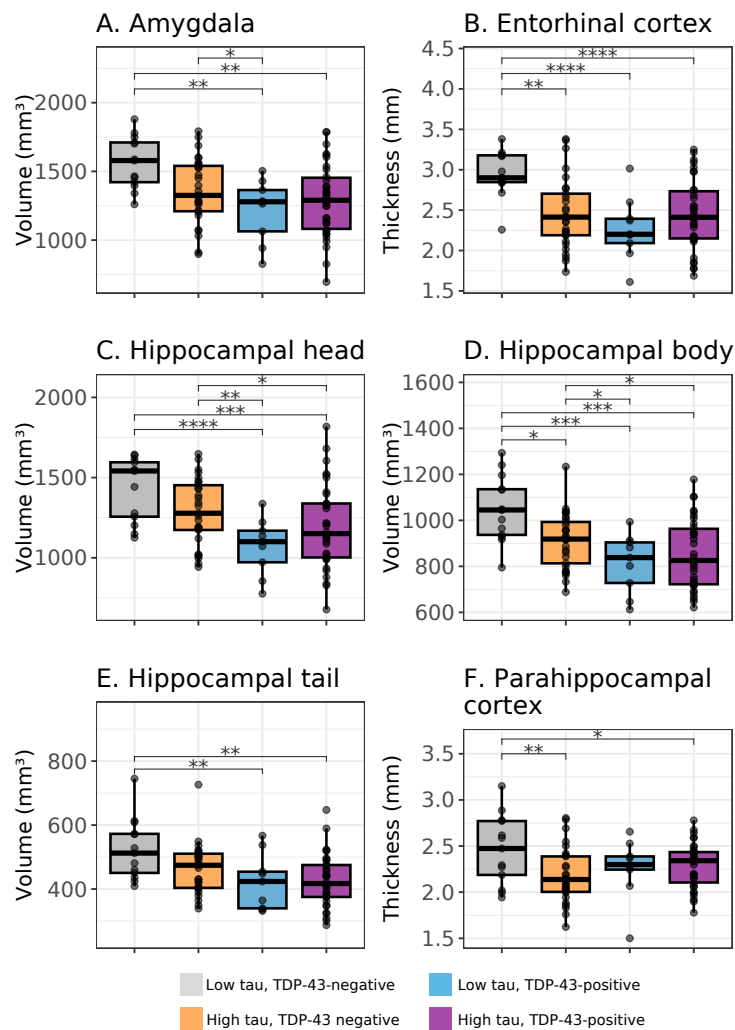
Abbreviations: NFTs: Neurofibrillary tangles; HATA: Hippocampo-amygdala transition; DG: Dentate Gyrus; ERC: Entorhinal Cortex; PHC: Parahippocampal Cortex; PHG: Parahippocampal gyrus; Hip: Hippocampus

Thus, partial correlations suggested a different anatomical effect of both neuropathologies with TDP-43 affecting the anterior MTL (amygdala and hippocampal head) and tau affecting the posterior MTL (hippocampal body and PHG). We also observed that TDP-43 affected the whole volume of the amygdala, whereas NFTs only affected the central nuclei.

4.4 Volumetric Differences by Tau and TDP-43 groups

To confirm our results on the contributions of both neuropathologies on MTL volume loss, we investigated differences in volume/thickness based on the levels of tau (Low vs. High) and TDP-43 (Negative vs. Positive ; N = 85). We first focused on volume loss along the anterior-posterior axis (Fig. 4). Consistent with the correlational analyses, individuals from the 'Low tau, TDP-43-positive' group had atrophy in the amygdala (Fig. 4A: $\beta = -346 \text{ mm}^3$, $P < 0.01$), the hippocampal head (Fig. 4B: $\beta = -358 \text{ mm}^3$, $P < 0.001$), and the hippocampal body (Fig. 4C: $\beta = -236 \text{ mm}^3$, $P < 0.001$), but no atrophy in the PHC ($P = 0.16$) compared to the 'Low tau, TDP-43-negative' group. They also had atrophy in the ERC ($\beta = -76 \text{ mm}^3$, $P < 0.001$) and the hippocampal tail ($\beta = -109.25 \text{ mm}^3$, $P < 0.01$) compared to the TDP-43-negative individuals with low tau, but not when compared to individuals with TDP-43-negative and high tau levels ($P_{ERC} = 0.26$; $P_{Hippocampal Tail} = 0.14$), indicating that these structures were less vulnerable for TDP-43 related atrophy. In contrast, individuals with high tau, but TDP-43-negative had atrophy in the hippocampal body ($\beta = -137 \text{ mm}^3$, $P < 0.05$), the ERC ($\beta = -0.49 \text{ mm}$, $P < 0.01$), and the PHC ($\beta = -0.28 \text{ mm}$, $P < 0.01$),

427 compared to low tau, TDP-43-negative individuals. Finally, when looking
 428 at data per Braak and LATE-NC stages, we noted that volumetric
 429 differences were observed from Braak NFT stage V (Sup. Fig. 1) and LATE-
 430 NC stage 2 (Sup. Fig. 2), i.e., with neocortical tau and hippocampal TDP-
 431 43 deposits, respectively.



432

433 **Figure 4 : Cross sectional ante-mortem MTL volumes difference across groups**
 434 **based on postmortem diagnosis.**

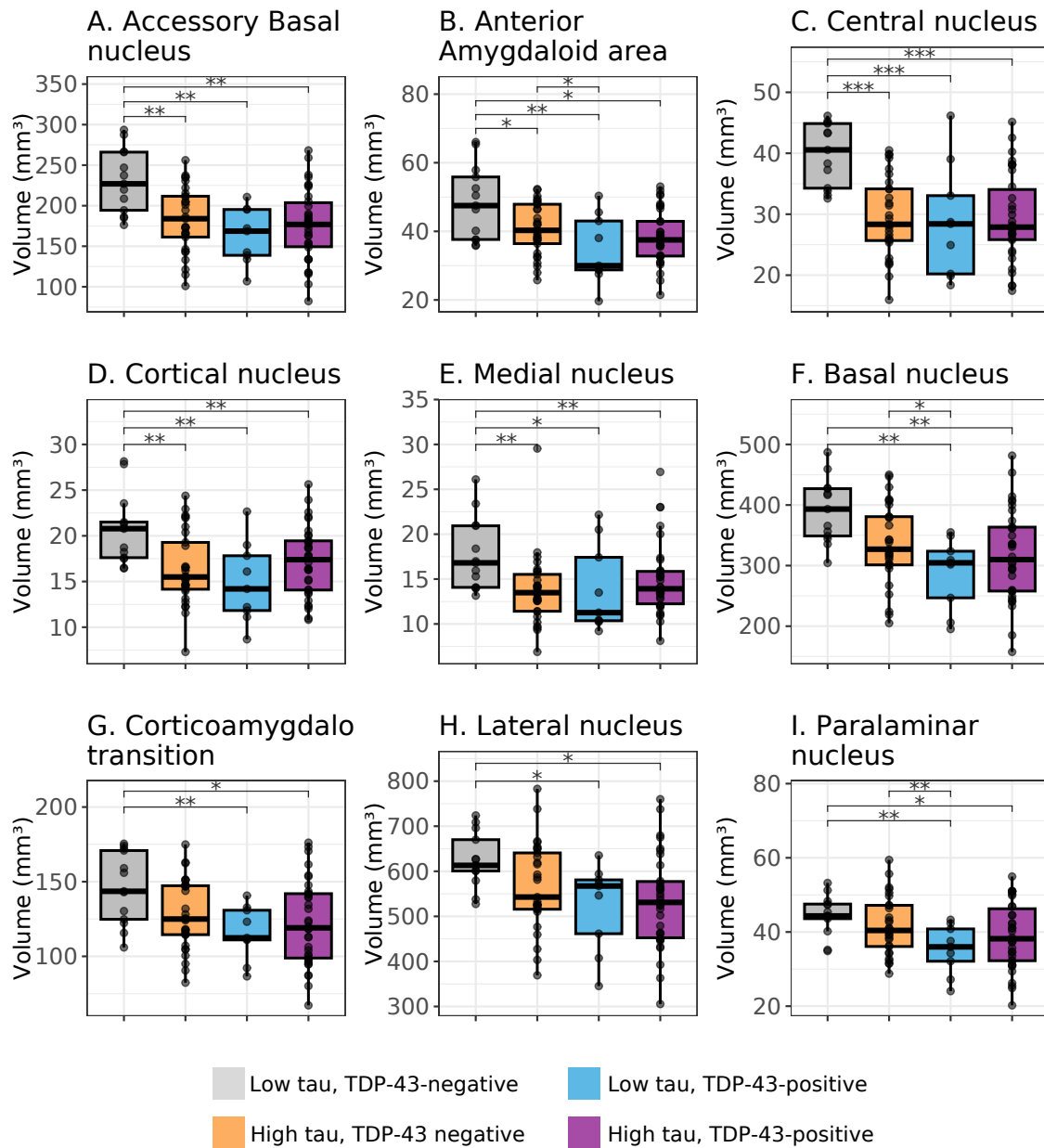
435 Boxplots represent (A) amygdala, (B) hippocampal head, (C) hippocampal body, (D) and
 436 hippocampal tail volumes as well as (E) entorhinal and (F) parahippocampal cortices

thickness per group based on the levels of tau pathology and TDP-43 presence. This analysis includes 85 participants including 13 Low tau, TDP-43 negative individuals (grey), 29 High Tau, TDP-43 negative individuals (orange), 9 Low tau, TDP-positive individuals (blue) and 34 High Tau, TDP-43 positive individuals (purple). Reported p values are p values adjusted for age, sex, intracranial volume and interval between the last MRI and death : * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

We then focused on the amygdala subnuclei atrophy (Fig. 5). Individuals from the 'Low tau, TDP-43-positive' group had atrophy in all amygdala subnuclei compared to the 'Low tau, TDP-43-negative' group. They also had atrophy in the anterior amygdaloid area ($\beta = -7.40 \text{ mm}^3$, $P < 0.05$), basal nucleus ($\beta = -67.25 \text{ mm}^3$, $P < 0.05$) and paralamina nucleus ($\beta = -9.01 \text{ mm}^3$, $P < 0.01$) compared to the TDP-43-negative individuals with higher levels of tau. In contrast, individuals with high tau, but TDP-43-negative only had atrophy in the anterior amygdaloid area ($\beta = -6.68 \text{ mm}^3$, $P < 0.05$), central ($\beta = -9.41 \text{ mm}^3$, $P < 0.001$), cortical ($\beta = -4.01 \text{ mm}^3$, $P < 0.01$) and accessory basal nuclei ($\beta = -41.85 \text{ mm}^3$, $P < 0.01$) compared to low tau, TDP-43-negative individuals.

To confirm that amygdala atrophy was non-uniform in individuals with high levels of tau pathology, we replicated the analyses while accounting for the global volume of the amygdala. We found that the volumes of the accessory basal nucleus ($\beta = -14.02 \text{ mm}^3$, $P < 0.05$), and the central nucleus ($\beta = -6.01 \text{ mm}^3$, $P < 0.05$), were further reduced compared to the whole amygdala in the presence of elevated NFTs levels. We reproduced the analysis using the first MRI available (6.5 ± 3.5 years before death).

Observations were similar to those obtained using the last MRI before death.



463

464 **Figure 5 : Cross sectional ante-mortem amygdala volumes difference across**
 465 **groups based on postmortem diagnosis.**

Boxplots represent amygdala subnuclei volume per group based on the levels of tau pathology and TDP-43 presence. This analysis includes 85 participants including 13 Low tau, TDP-43 negative individuals (grey), 29 High Tau, TDP-43 negative individuals (orange), 9 Low tau, TDP-positive individuals (blue) and 34 High Tau, TDP-43 positive

individuals (purple). Reported p values are p values adjusted for age, sex, intracranial volume and interval between the last MRI and death : * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Cross sectional results (partial correlations and volume differences among the groups) were slightly less significant but similar when adjusting for years of education, MRI scanner strength, or other neuropathologic disease including Thal phases, LBD, ARTAG, AGD and vascular pathology (including small vessel disease and microinfarcts; Sup. Tables 2-3). Analyses separating right and left volumes and thickness measures were also conducted and showed similar results across both hemispheres (Sup. Tables 4-5).

4.5 Longitudinal Atrophy Patterns in Relation to Pathology

We then conducted a longitudinal analysis to assess how atrophy progressed before death, based on pathology determined after death (N = 82). Consistent with the cross-sectional analyses, both TDP-43 and tau pathology affected longitudinal atrophy of the amygdala (TDP-43 : $\beta = -9.99 \text{ mm}^3/\text{year}$, $P < 0.001$; Tau : $\beta = -12.06 \text{ mm}^3/\text{year}$, $P < 0.001$, Fig. 6A-B) and ERC (TDP-43 : $\beta = -0.03 \text{ mm}^3/\text{year}$, $P < 0.05$; Tau : $\beta = -0.03 \text{ mm}^3/\text{year}$, $P < 0.05$, Fig. 6C-D) while only TDP-43 affected longitudinal atrophy in the hippocampal head ($\beta = -8.14 \text{ mm}^3/\text{year}$, $P < 0.001$, Fig. 6E) and tau pathology affected atrophy in the PHC ($\beta = -0.02 \text{ mm}^3/\text{year}$, $P < 0.001$, Fig. 6J). Interestingly, the hippocampal body volume was reduced

494 at baseline in both TDP-43 positive and Tau-positive groups compared to
495 the TDP-43 negative or tau negative groups, but longitudinal rate of
496 atrophy did not differ between the negative and positive groups.

497 Although the longitudinal plots suggested a potential increase in volume
498 for the Low tau / TDP-43-negative group, statistical analyses confirmed
499 that none of the trajectories were significantly different from zero.

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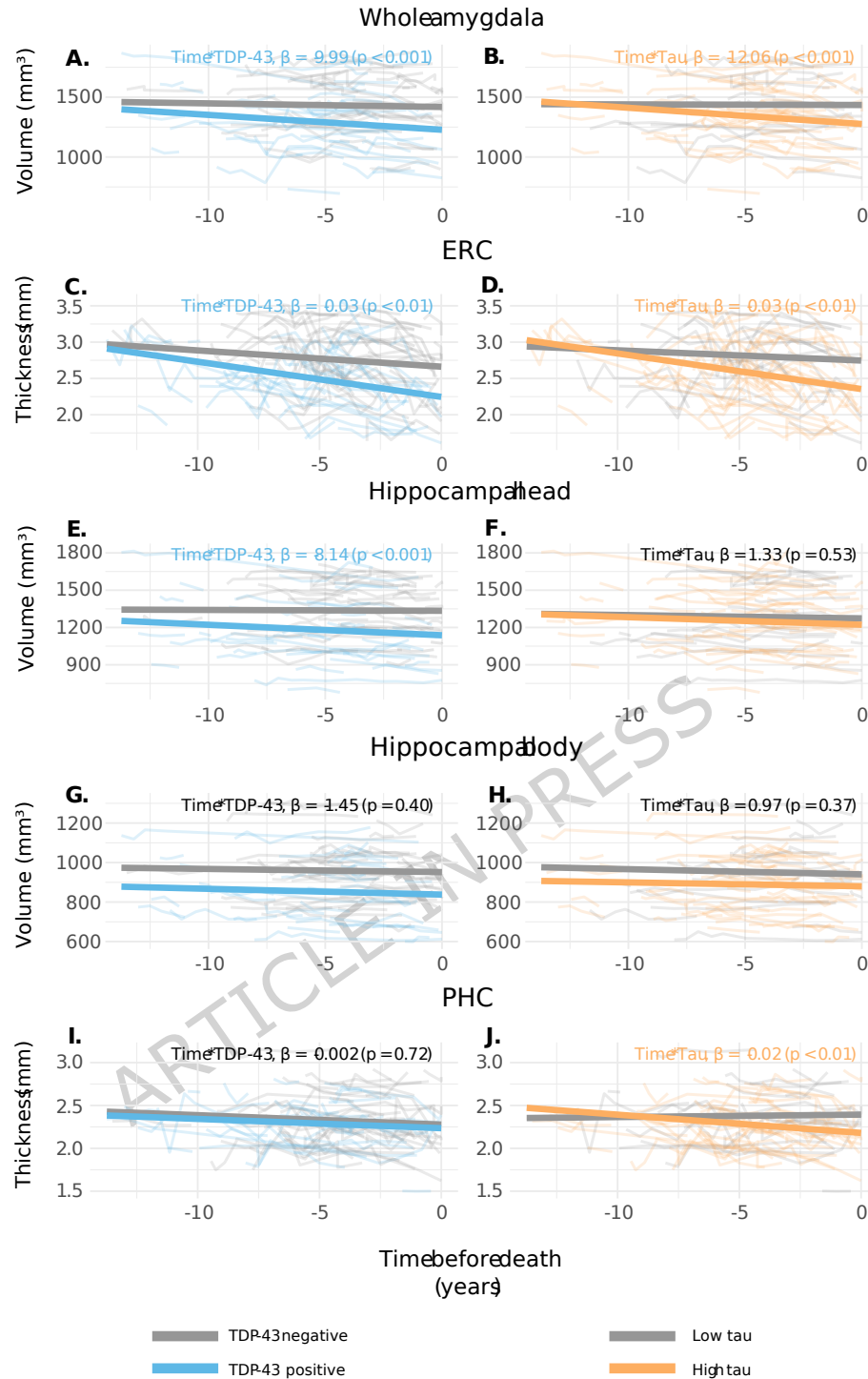


Figure 6 : Longitudinal antemortem MTL volumes difference based on the levels of tau pathology or TDP-43 presence.

Changes in the volume/thickness of the sub-structures of the medial temporal lobe over time before death (with 0 representing the time of death), categorized either by the presence of TDP-43 (left) or by levels of tauopathy (right). Structures with significantly

faster volume reduction in TDP-43-positive compared to TDP-43-negative groups are highlighted in blue, while those with significantly faster volume reduction in high-tau compared to low-tau groups are highlighted in orange. Number of participants included in the analysis = 82, total number of MRI scans = 452 over an average 4.81 ± 3.24 years of follow-up. Reported p values are p values adjusted for age at death, sex, and intracranial volume: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Abbreviations: ERC : entorhinal cortex; PHC : Parahippocampal cortex

We also accounted for the presence of other proteinopathies including LBD, AGD and ARTAG. Although ARTAG pathology significantly affected the volume loss of hippocampal head over time ($\beta = -4.88 \text{ mm}^3/\text{year}$, $P < 0.05$), TDP-43 was still the main driver of hippocampal head atrophy over time ($\beta = -6.02 \text{ mm}^3/\text{year}$, $P < 0.01$). Similarly, AGD affected the thickness loss of the PHC over time ($\beta = -0.002 \text{ mm}/\text{year}$, $P < 0.01$), just as tau pathology ($\beta = -0.002 \text{ mm}/\text{year}$, $P < 0.01$).

When excluding LATE-NC stage 1 cases (as mild TDP-43 pathology is not usually associated with dementia [10]), the results remained similar.

5. Discussion

Using antemortem MRI and neuropathologic data of the ADNI cohort, we highlight an association between TDP-43 and the volume/thickness of anterior-superior MTL regions (i.e. hippocampal head) while tau pathology was more associated with the volume/thickness of posterior-inferior MTL (i.e. PHC). In addition, we showed that the amygdala is homogeneously affected by TDP-43 while tau has a more pronounced effect on the medial amygdala.

Participants were classified based on tau distribution (Low/High) and the presence of TDP-43 (positive/negative) groups did not perfectly align with the diagnoses of AD, LATE, AD+LATE and controls, they served as proxies for these pathologies. Indeed, the 'High tau' groups exhibited higher Braak NFT stages, increased Thal A β phases, higher CDR scores, and a greater proportion of individuals with dementia compared to 'Low tau' groups, reflecting more severe AD pathology. Additionally, these groups showed higher NFT burdens in the MTL, supporting the validity of Braak staging as a proxy for MTL tau pathology.

5.1 Similar neuropsychological profiles

TDP-43 was primarily associated with memory impairment, while tau pathology was linked to multi-domain cognitive decline [37, 39]. These results align with the expected brain-behavior relationships: when only the MTL is affected, as in LATE, cognitive impairment is largely restricted to memory functions, whereas involvement of more widespread brain regions by pathology (e.g., tau) is associated with multi-domain cognitive deficits [41].

5.2 Atrophy patterns in the MTL

Our results do not fully align with previous similar studies showing an anterior-to-posterior gradient [11, 17] (see *Wisse et al. 2025* [55] for review). Instead, they suggest an overlap between the previously described anterior-to-posterior gradient - where TDP-43 more predominantly affects anterior MTL structures (including the amygdala,

ERC, and hippocampal head) and tau more predominantly affects posterior structures (including the hippocampal body and ERC) - and a newly observed superior-to-inferior gradient that has not been reported in the literature (Fig. 7). In this pattern, TDP-43 more predominantly affects superior MTL regions (including the amygdala and hippocampus, Fig. 7A), whereas tau more predominantly affects inferior MTL regions (including the ERC and PHC, Fig. 7B). This dual-gradient framework explains why anterior but inferior structures such as the ERC are also affected by tau, while posterior but superior structures such as the hippocampal body are also affected by TDP-43. Notably, hippocampal head volume (anterior-superior) emerged as the only structure consistently affected by TDP-43, while posterior-inferior structures as the PHC was uniquely affected by tau.

Although such a superior-to-inferior gradient has not yet been explicitly described in the literature, our findings align with previous studies. *De Flores and colleagues (2020)* reported that tau was best associated with the PHC (posterior-inferior) and TDP-43 with the anterior hippocampus (anterior-superior) [11]. Similarly, *Denning and colleagues* observed TDP-43 effects on hippocampal volumes in regions comparable to those identified in our study (anterior and posterior hippocampus as well as the ERC; they did not investigate the amygdala), all of which are anterior or superior structures [12]. In addition, postmortem MRI studies have shown stronger associations between tau and the lateral ERC [30, 43]. These observations suggest that the anterior-to-posterior model may be

incomplete and that a potential superior-to-inferior gradient in the distribution of tau and TDP-43 pathology warrants further investigation.

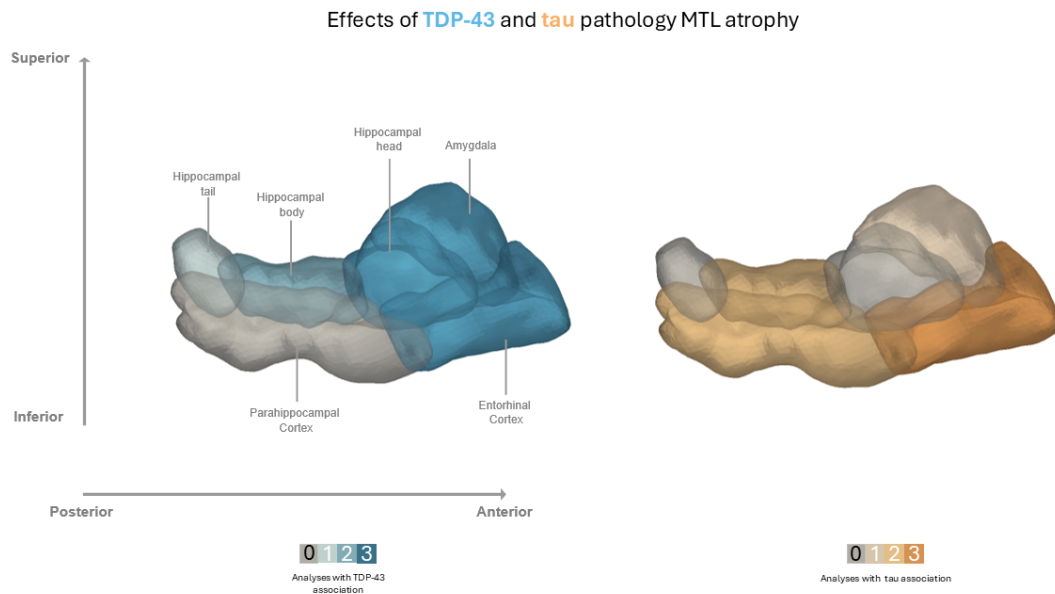


Figure 7 : Illustration of the effect of TDP-43 and tau pathology on medial temporal atrophy. Structures shown in blue are specifically atrophied in the presence of TDP-43. Structures shown in orange are specifically atrophied in the presence of tau. The intensity of the coloring reflects how consistently each structure was identified as affected across up to three analyses performed in this study: partial correlations (Figure 3), group-wise volume differences (Figure 4), and longitudinal volume changes (Figure 6). Structures colored more intensely were identified in all three analyses, whereas lighter shades indicate involvement in only one or two analyses.

Using longitudinal analyses, we found progressive hippocampal head atrophy in patients with TDP-43 pathology, and progressive PHC atrophy in those with tau pathology. To date, only one prior longitudinal study had observed faster global hippocampal atrophy in AD patients with TDP-43 than in those without [22]. Our results refine this observation by

demonstrating that the atrophy is primarily localized to the hippocampal head.

Taken together, these results suggest that hippocampal head atrophy in AD patients may reflect the presence of comorbid LATE-NC. Our results support the recent use of the hippocampal head volume/PHC thickness ratio as an MRI-based proxy of TDP-43 pathology [29].

These findings may also guide future neuropsychological research. Specifically, one may assume that tests targeting anterior hippocampal functions could highlight differences between patients with AD and those with AD + LATE. The anterior hippocampus is known to support pattern completion [45] (i.e., the ability to recall associated items), emotional processing [40], and social cognition due to its connections with the amygdala and anterior temporal lobe [16]. Similarly, semantic deficits have been observed in LATE and are associated with the anterior temporal pole [56]. Future studies should examine whether tasks assessing these aspects can reveal distinct profiles while minimizing the influence of other cognitive domains.

Interestingly, we did not observe a synergistic effect of tau and TDP-43 pathologies, i.e., no greater atrophy or increased memory deficits in individuals presenting with both pathologies compared to those with only one. This finding contrasts with previous literature suggesting that the combination of tau and TDP-43 pathologies worsens cognitive decline, neuronal loss, and medial temporal lobe atrophy [24, 25, 50]. This discrepancy may be explained by methodological differences. Specifically,

the High Tau, TDP-43 positive group included fewer individuals with advanced LATE stages, whereas the Low Tau, TDP-43 positive group included some participants with more advanced LATE-NC stages. This disparity in pathology severity could influence the differences in atrophy observed between groups. Moreover, the Low Tau, TDP-43 positive group included only 9 participants, which likely limited our statistical power to detect significant differences between groups.

5.3 Differential effect of TDP-43 and tau on amygdala atrophy

Beyond the anterior-superior to posterior-inferior gradient in the MTL, our results emphasize a differential impact of TDP-43 and tau on amygdala atrophy. Specifically, TDP-43 appears to affect the whole amygdala volume, whereas tau pathology is associated with selective atrophy of specific subnuclei, including the central, medial, cortical, and accessory basal nuclei, as well as the anterior amygdaloid area, corresponding to the medial section of the amygdala (Fig. 8).

Effect of TDP-43 and tau pathology on amygdala subnuclei atrophy

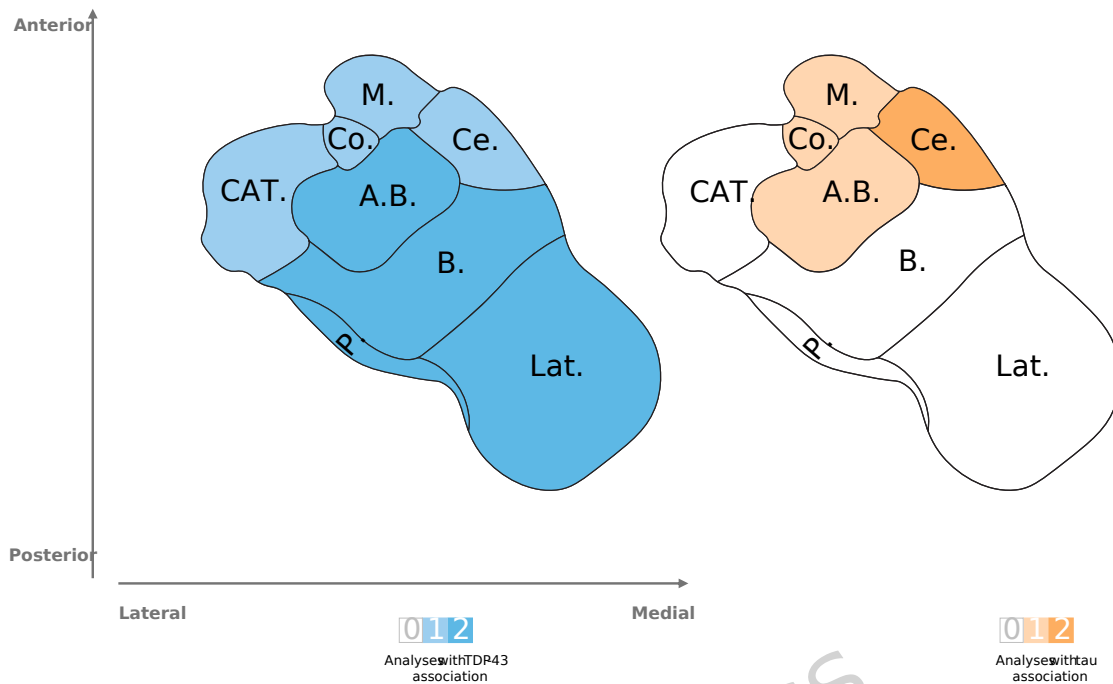


Figure 8 : Illustration of the effect of TDP-43 and tau pathology on amygdala subnuclei atrophy. Structures shown in blue are specifically atrophied in the presence of TDP-43. Structures shown in orange are specifically atrophied in the presence of tau. The intensity of the coloring reflects how consistently each structure was identified as affected across up to two analyses performed in this study: partial correlations (Figure 3) and group-wise volume differences (Figure 5). Structures colored more intensely were identified in both analyses, whereas lighter shades indicate involvement in only one analysis.

Abbreviations: AB : Accessory Basal nucleus; B : Basal nucleus; CAT : Cortico-amygdaloid transition; Ce : Central nucleus; Co : Cortical nucleus; M : Medial nucleus; Lat : Lateral nucleus; P : Paralaminar nucleus.

Little is known about the distribution of TDP-43 burden within the amygdala. However, our findings align with recent evidence showing a relatively uniform distribution of TDP-43 inclusions across the amygdala

in LATE-NC. They are also partially consistent with earlier work [31, 53] suggesting that TDP-43 affects lateral and medio-central amygdala regions. Another study investigating subnuclear amygdala atrophy across FTLD subtypes found that, except for FTLD-TDP type B, most TDP-43 subtypes were associated with global amygdala involvement. Divergences across studies may reflect differences in postmortem diagnostic classification. Further research is needed to confirm the effects of TDP-43 on amygdala subnuclei [5].

In contrast, the effect of tau on amygdala subnuclei is well documented. Our findings are consistent with previous neuropathologic [8, 51, 52], postmortem imaging [48, 57] and in vivo MRI studies [46] demonstrating selective vulnerability of certain nuclei to tau pathology. Specifically, the volumes of the central, cortical, medial, and accessory basal nuclei are consistently associated with tau burden, whether measured via tau-PET or postmortem analysis [46]. These findings support the hypothesis that distinct amygdala subregions exhibit variable susceptibility to tau pathology, possibly due to differences in their structural and functional connectivity. Indeed, the identified nuclei structural connections the locus coeruleus [6], olfactory bulbs [49], CA1 and ERC [42] who all show early tau deposition in the context of AD [6].

Given the distinct patterns of amygdala involvement by tau and TDP-43, future studies should investigate their clinical implications. For instance, it would be of interest to assess whether these different atrophy patterns

translate into distinct memory, olfaction or anxiety profiles between AD and LATE.

5.4 Limitations

First, most patients were diagnosed with ADNC, limiting the ability to study pure LATE-NC cases. This reflects that these processes often overlap and interact, making it challenging to study their effects as fully independent. Our group-based comparisons should therefore be interpreted as reflecting relative contributions of each pathology rather than demonstrating true independence. To overcome this limitation, the analyses were controlled for the opposing pathology.

Regarding our selection criteria, we grouped patients based on TDP-43 presence and Braak NFT stages but small sample sizes in the 'low tau' groups reduced statistical power. Moreover, neuropathologic data was semi-quantitative, and for only a subset of participants (N=51), further reducing statistical power. Finally, formal LATE-NC diagnosis was not assessed and was therefore inferred based on the presence or absence of TDP-43 inclusions in the MTL, without clear information about the level of pathology.

Additionally, the groups investigated in this study were based on Braak NFT and LATE-NC staging, which reflect the distribution, rather than the actual burden of tau and TDP-43 lesions. Therefore, one cannot exclude that slightly additional atrophy patterns could be observed when considering quantitative neuropathologic data. Nevertheless, data shows that the high tau groups (i.e. high Braak NFT stages) show higher burdens

of tau in the MTL, compared to the low tau groups. Consistently, a recent study suggested a strong correlation between Braak NFT stages and tau and pathological burden in the MTL, respectively [12].

Second, antemortem MRI data was acquired up to ten years before death. While we accounted for this delay, neuropathologic changes during this interval could have influenced our findings. Nevertheless, antemortem MRI allows longitudinal analyses, and is easier to generalize to *in vivo* biomarkers than postmortem MRI.

Finally, automatic amygdala segmentation using FreeSurfer is relatively recent and has not yet been extensively validated. The lack of clear anatomical landmarks makes it difficult for the human eye to reliably correct automatic segmentations in the absence of post-mortem validation. Nevertheless, our conclusions do not relate to a specific nucleus, but rather to a broader region of the amygdala, in this case, the medial amygdala. Even if one nucleus were ultimately misclassified or omitted from our cluster, the general conclusion that the medial portion of the amygdala is more affected by tau pathology would remain valid. Despite these limitations, our study has strengths. Postmortem neuropathologic data were used to classify patients, instead of relying on the probable presence of TDP-43 and to exclude cases with FTLD, ALS, or non-AD tauopathies, ensuring our results are specific to tau and TDP-43 in the context of AD and LATE. More importantly, we leveraged longitudinal data covering up to 15 years of imaging history, enabling a comprehensive longitudinal study.

6. Conclusion

By combining antemortem MRI and neuropathologic data, we confirmed the already described anterior to posterior gradient of TDP-43 and tau with TDP-43 mostly affecting anterior MTL and tau predominantly affecting posterior MTL. We also denoted a superior-to-inferior gradient with TDP-43 preferentially affecting superior MTL and tau affecting posterior MTL. This pattern highlights hippocampal head atrophy (anterior-superior) as a potential imaging marker to identify patients with comorbid ADNC LATE-NC.

7. List of abbreviations

Abbreviation	Signification
Aβ	Amyloid- β
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive subscale
ADNC	Alzheimer's disease neuropathologic change
ADNI	Alzheimer's Disease Neuroimaging Initiative study
AGD	Argyrophilic grain disease
ALS	Amyotrophic lateral sclerosis
ARTAG	Aging-related tau astrogliopathy
CBD	Corticobasal degeneration

CERAD	Consortium to Establish a Registry for Alzheimer's disease
CN	Cognitively normal
DG	Dentate Gyrus
ERC	Entorhinal cortex
FTLD	Frontotemporal dementia
HATA	Hippocampo-amygdala transition area
Hip	Hippocampus
LATE	Limbic-predominant Age-related TDP-43 Encephalopathy
LATE-NC	Limbic-predominant Age-related TDP-43 Encephalopathy neuropathologic change
LBD	Lewy body disease
LMM	Linear mixed models
MCI	Mild cognitive impairment
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NFTs	Neurofibrillary tangles
PHC	Parahippocampal cortex

PHG	Parahippocampal gyrus
PSP	Progressive supranuclear palsy
RAVLT	Rey Auditory Verbal Learning Test
T1w	T1-weighted

731

732 **8. Declarations**

733 **8.1 Ethics**

734 The ADNI study was conducted according to Good Clinical Practice
735 guidelines, the Declaration of Helsinki, US 21CFR Part 50 – Protection of
736 Human Subjects, and Part 56 – Institutional Review Boards, and pursuant
737 to state and federal HIPAA regulations. Written informed consent for the
738 study was obtained from all subjects and/or authorized representative.
739 More information can be found in the ADNI documentation.

740 **8.2 Data availability**

741 The ADNI dataset supporting the conclusions of this article is available
742 through the LONI Image and Data Archive (IDA), a secure research data
743 repository.

744 **8.3 Consent to Publish declaration**

745 Not applicable.

8.4 Conflicts of Interest

S.O.T. received consultant honorary from Muna Therapeutics (Belgium).

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8.6 Authors contributions

Y.S., J.G., S.O.T., and B.H. contributed to the study conception and design. Y.S. and J.G. performed the data analyses. Y.S. drafted the first version of the manuscript. L.H. and L.Q. contributed to the discussion section. All authors critically revised the manuscript, provided feedback on previous versions, and approved the final version.

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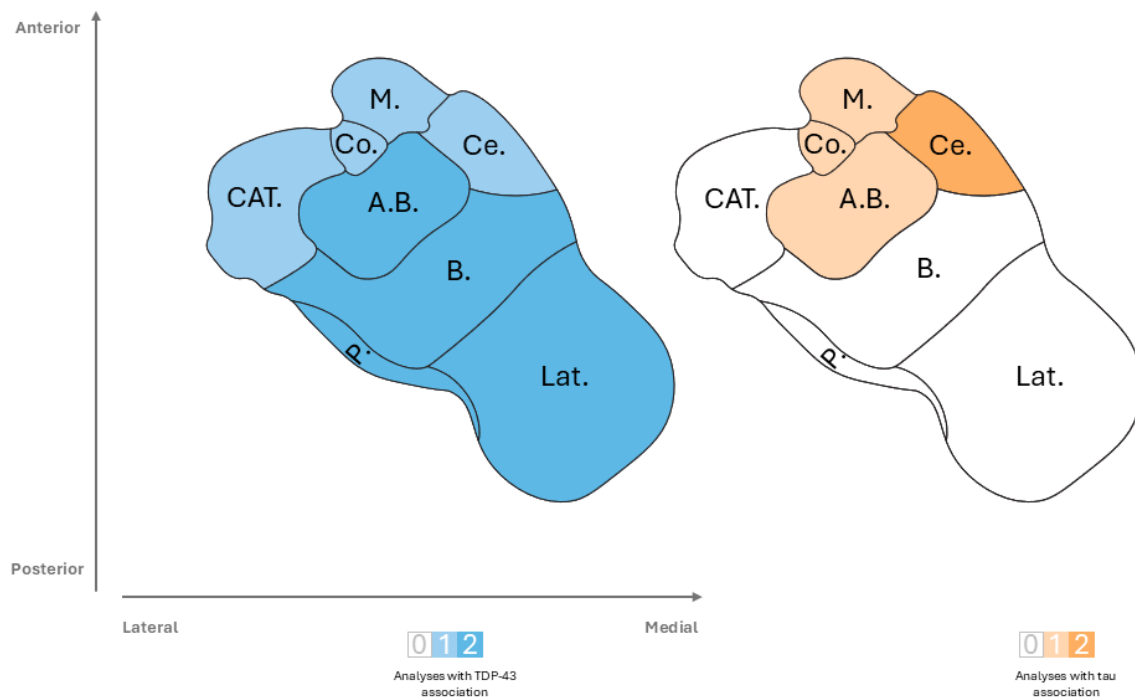
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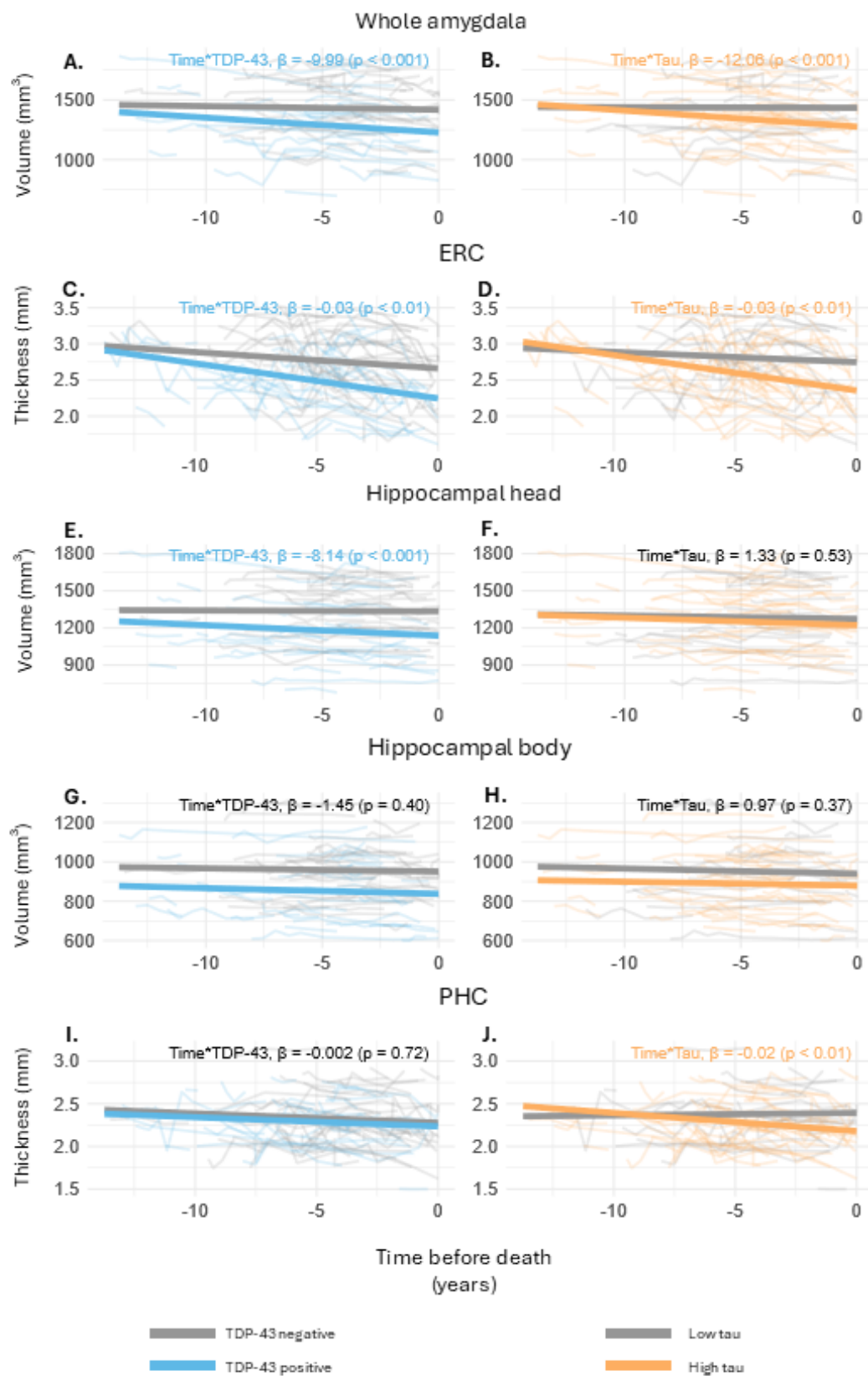
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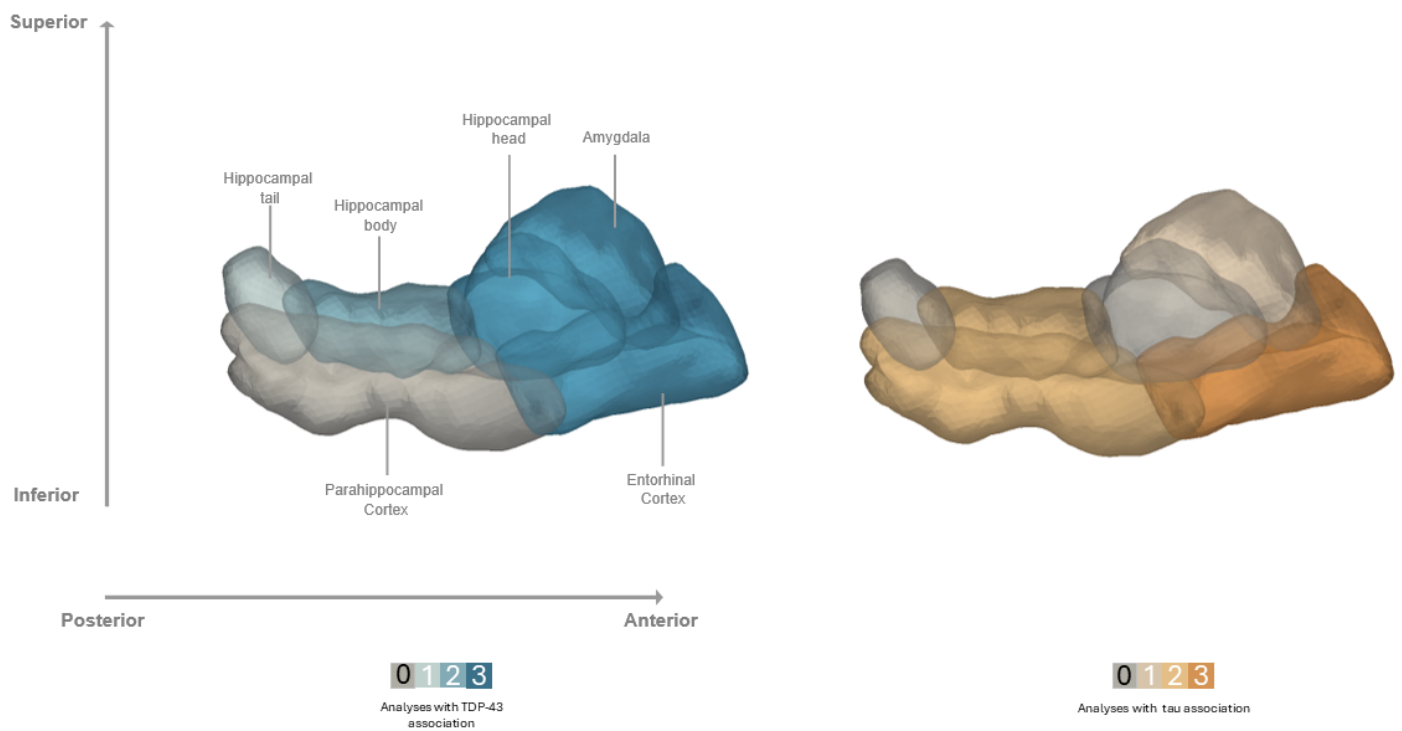
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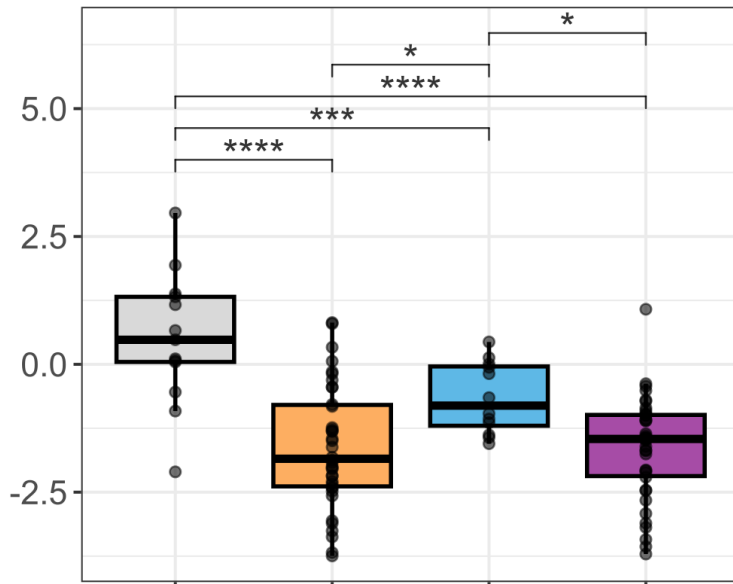
Effects of **TDP-43** and **tau** pathology on amygdala subnuclei atrophy



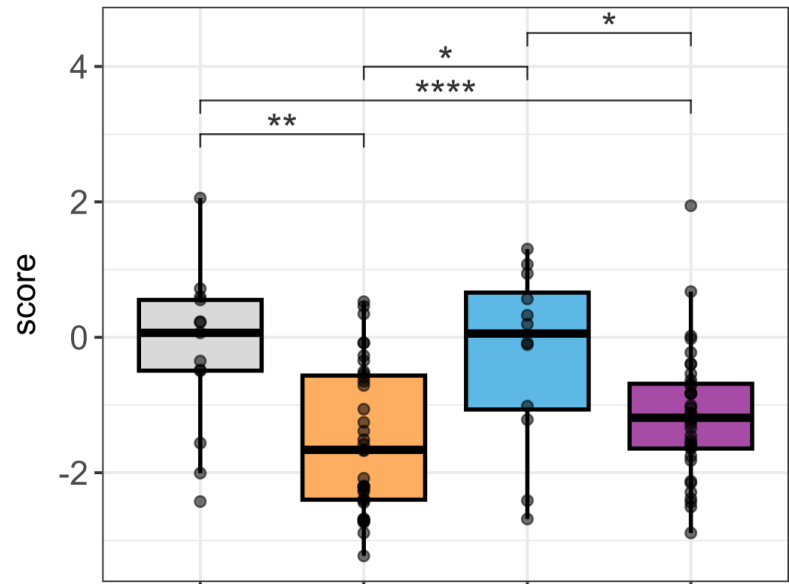
Effects of TDP-43 and tau pathology MTL atrophy



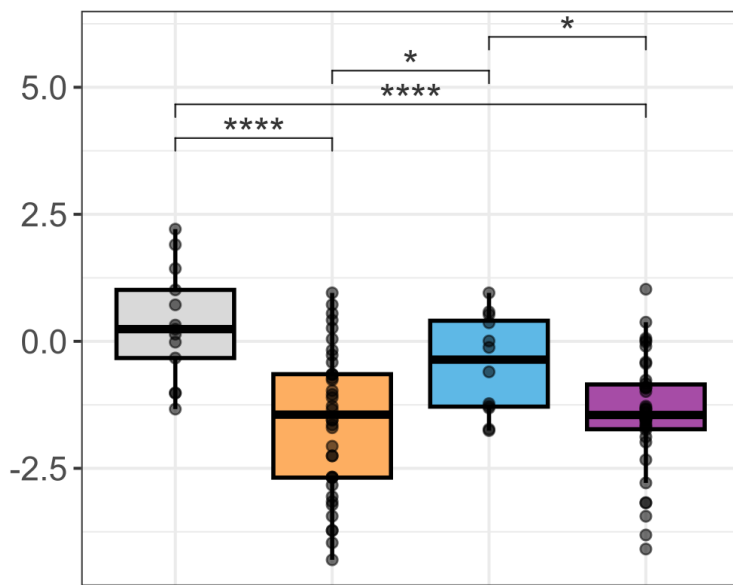
A. Memory factor score



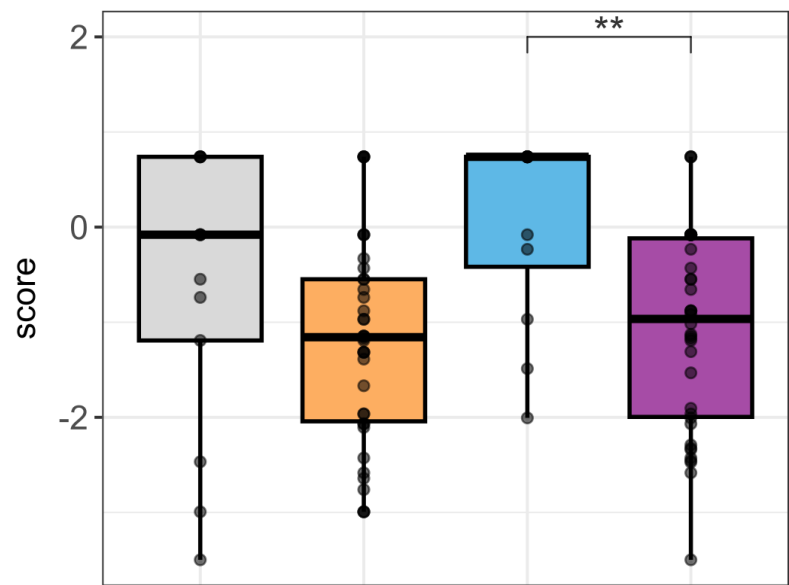
B. Executive functions factor score



D. Language factor score



C. Viso-spatial factor score

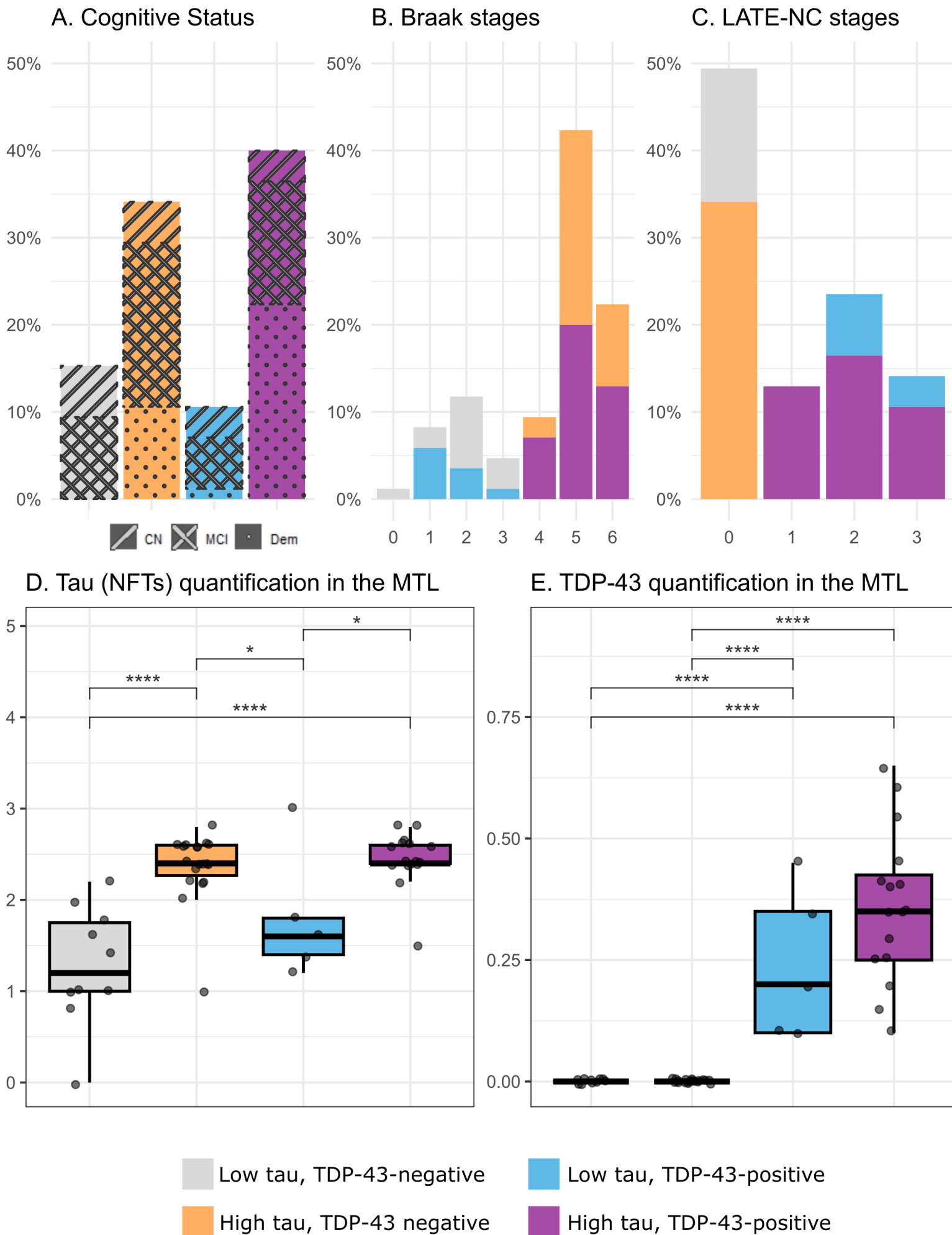


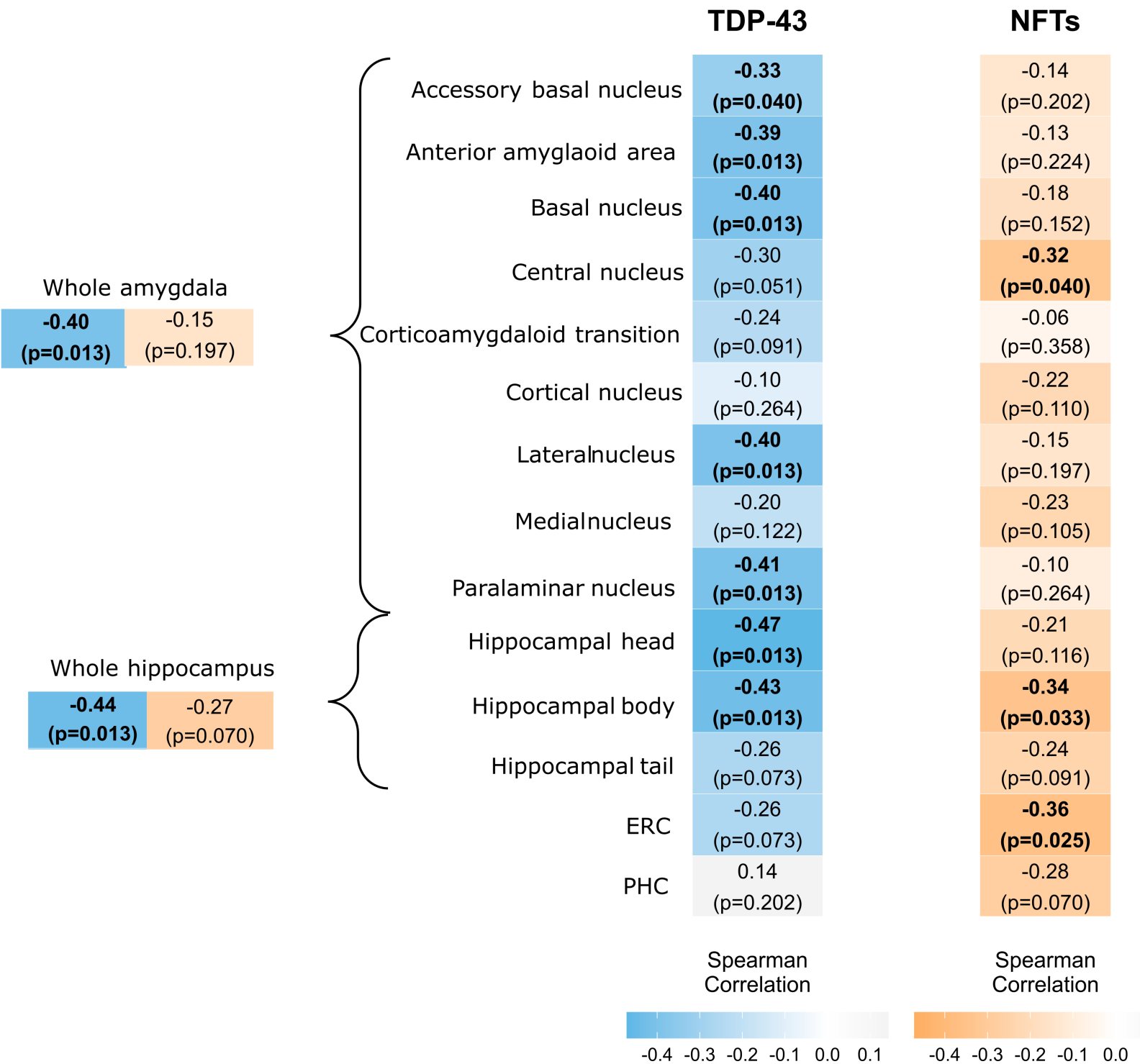
Low tau, TDP-43-negative

High tau, TDP-43 negative

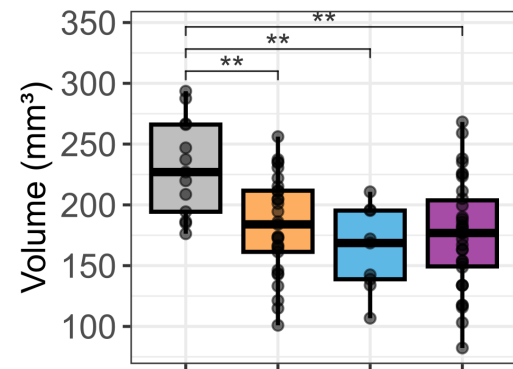
Low tau, TDP-43-positive

High tau, TDP-43-positive

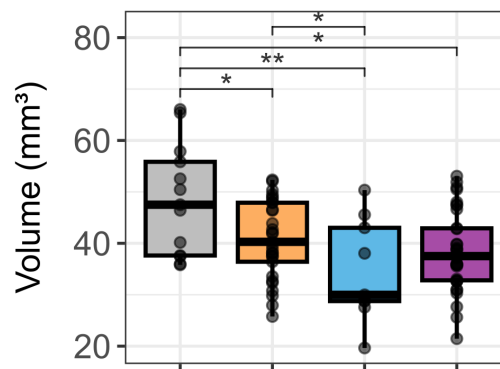




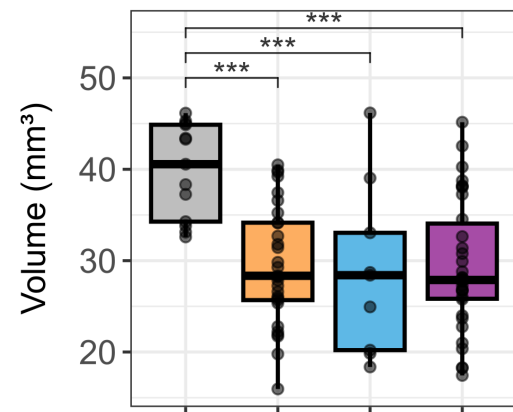
A. Accessory Basal nucleus



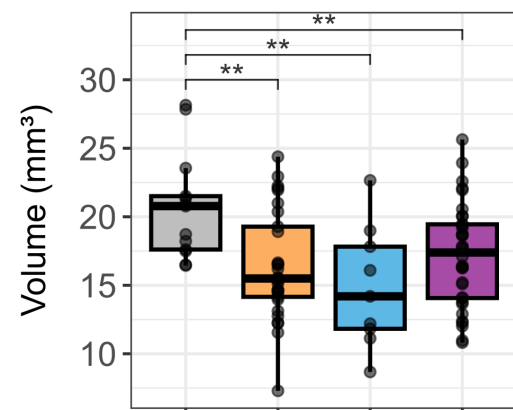
B. Anterior Amygdaloid area



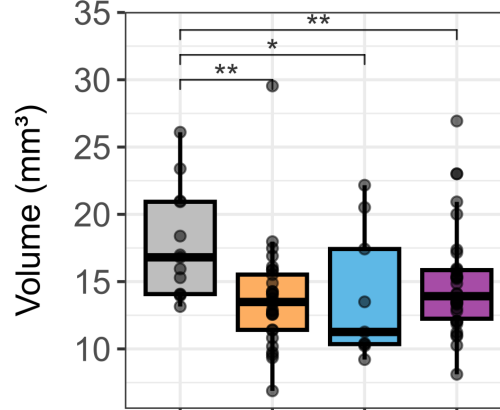
C. Central nucleus



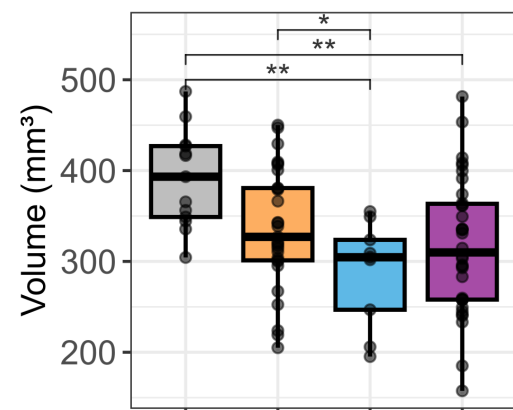
D. Cortical nucleus



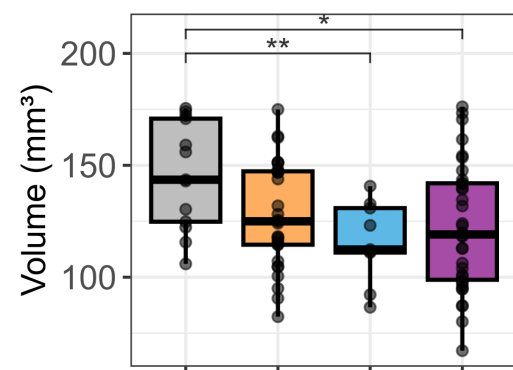
E. Medial nucleus



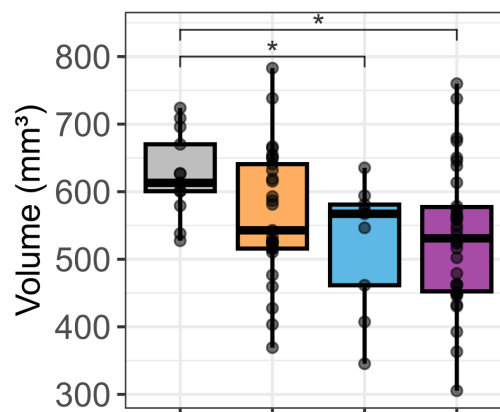
F. Basal nucleus



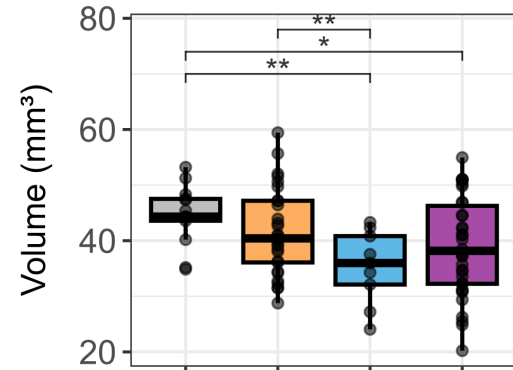
G. Corticoamygdaloid transition



H. Lateral nucleus



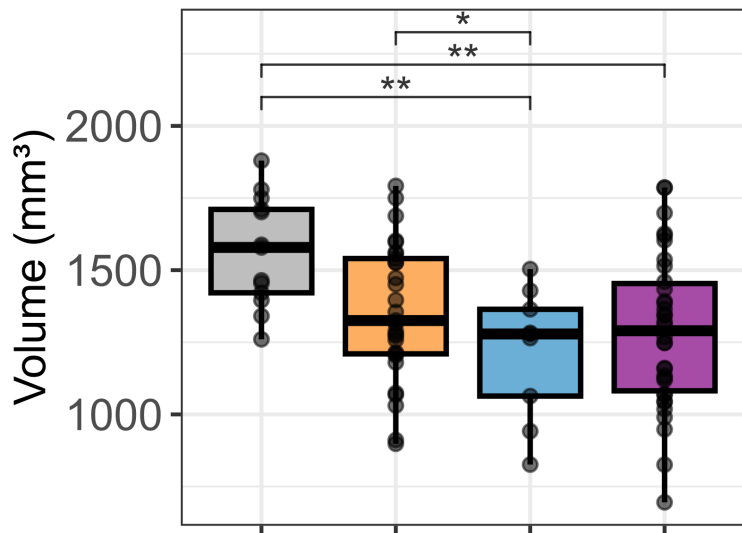
I. Paralaminar nucleus



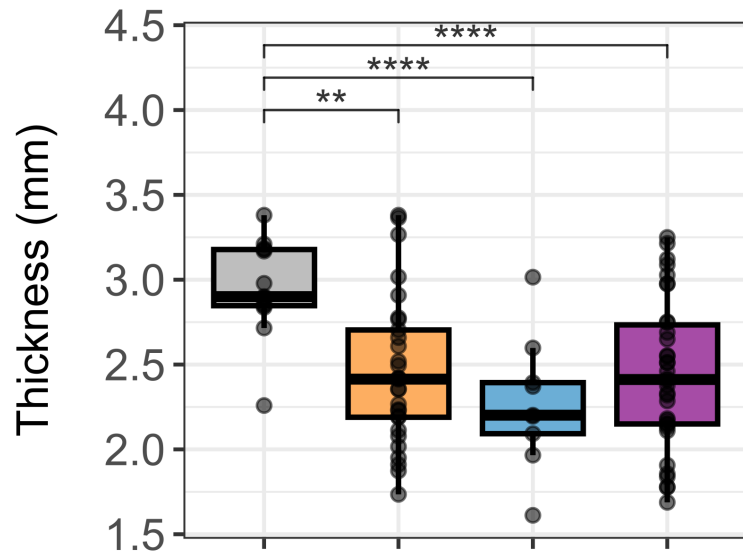
Low tau, TDP-43-negative
 Low tau, TDP-43-positive

High tau, TDP-43 negative
 High tau, TDP-43-positive

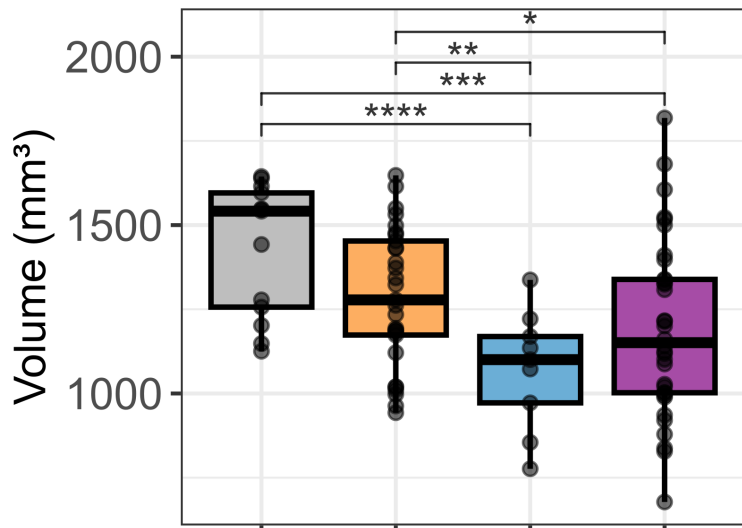
A. Amygdala



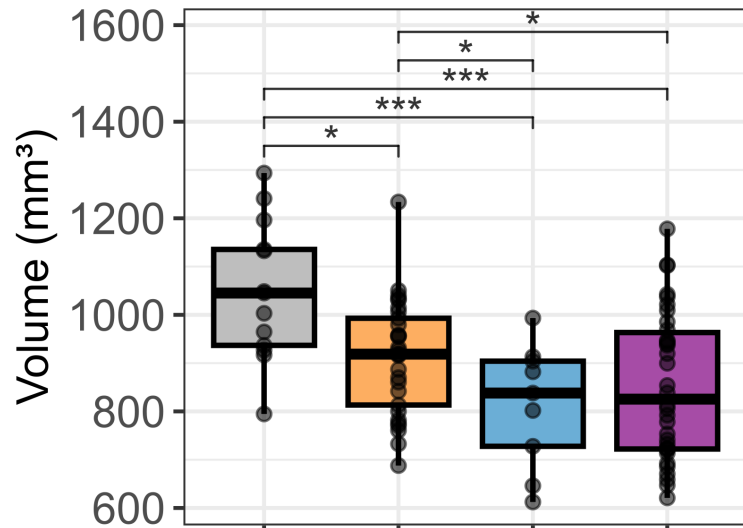
B. Entorhinal cortex



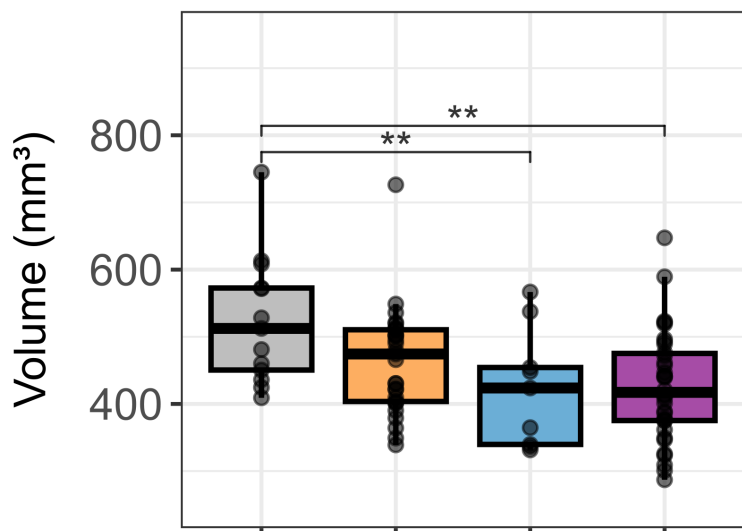
C. Hippocampal head



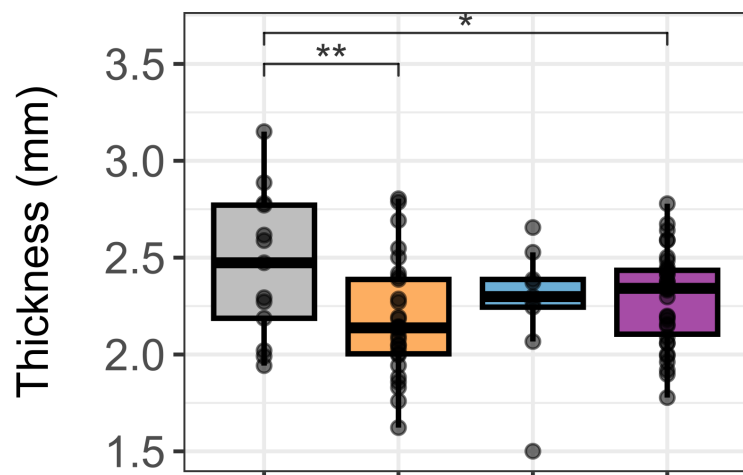
D. Hippocampal body



E. Hippocampal tail



F. Parahippocampal cortex



Low tau, TDP-43-negative

High tau, TDP-43 negative

Low tau, TDP-43-positive

High tau, TDP-43-positive

	Low tau No TDP-43	High tau No TDP-43	Low tau TDP-43 MTL	High tau TDP-43 MTL	p-Value	Post-Hoc
Group	1	2	3	4		
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	0.11	/
Sex, F (%)	1 (7.69%)	9 (31.03%)	2 (22.22%)	12 (35.29%)	0.28	/
Cognitive status at last MRI					0.004	
CN	5 (38.46%)	4 (13.79%)	3 (33.33%)	3 (8.82%)		Group 1 ≈ 2 ≈ 3 ≈ 4
MCI	8 (61.54%)	16 (55.17%)	5 (55.56%)	12 (35.29%)		Group 1 ≈ 3 < 2 ≈ 4
Dementia	0	9 (31.03%)	1 (11.11%)	19 (55.88%)		Group 1 ≈ 3 < 2 ≈ 4
<i>APOE</i> ε4 carriers (%)	3 (23.1%)	22 (75.9%)	1 (11.1%)	23 (67.6%)	< 0.001	Group 1 ≈ 3 < 2 ≈ 4
Braak NFT stage	1.92 ± 0.86	5.21 ± 0.56	1.56 ± 0.76	5.14 ± 0.70	< 0.001	Group 1 ≈ 3 < 2 ≈ 4
0	1 (7.69%)	0	0	0		
I	2 (15.38%)	0	5 (55.56%)	0		
II	7 (53.85%)	0	3 (33.33%)	0		
III	3 (23.08%)	0	1 (11.11%)	0		
IV	0	2 (6.89%)	0	6 (17.65%)		
V	0	19 (65.52%)	0	17 (50%)		
VI	0	8 (27.59%)	0	11 (32.35%)		

Thal A β Phase	2.46 $\pm$ 1.90	4.69 $\pm$ 0.54	2.67 $\pm$ 1	4.59 $\pm$ 0.78	< 0.001	Group 1 $\approx$ 3 < 2 $\approx$ 4
0	3 (23.08%)	0	0	0		
1	2 (15.38%)	0	2 (22.22%)	1 (2.94%)		
2	1 (7.69%)	0	0	0		
3	2 (15.38%)	1 (3.45%)	6 (66.67%)	0		
4	3 (23.08%)	7 (24.14%)	1 (11.11%)	10 (29.41%)		
5	2 (15.38%)	21 (72.41%)	0	23 (67.65%)		
CERAD	0.15 $\pm$ 0.38	2.72 $\pm$ 0.70	0.67 $\pm$ 0.50	2.64 $\pm$ 0.77	< 0.001	Group 1 $\approx$ 3 < 2 $\approx$ 4
0	11 (84.62%)	1 (3.44%)	3 (33.33%)	1 (2.94%)		
1	2 (15.38%)	1 (3.44%)	6 (66.67%)	3 (8.82%)		
2	0	3 (10.34%)	0	3 (8.82%)		
3	0	24 (82.76)	0	27 (79.41%)		
LATE-NC stage	0 $\pm$ 0	0 $\pm$ 0	2.33 $\pm$ 0.5	1.94 $\pm$ 0.78	< 0.001	Group 1 $\approx$ 2 < 3 $\approx$ 4
Other neuropathologies						
LBD (%)	4 (30.8%)	15 (51.7%)	5 (55.6%)	19 (55.9%)	0.47	/
ARTAG (%)	0	3 (10.3%)	1 (11.1%)	7 (20.6%)	0.27	/
AGD (%)	5 (38.5%)	3 (10.3%)	5 (55.6%)	12 (35.3%)	0.027	Group 1 $\approx$ 2 < 3 $\approx$ 4
Last MRI - death interval (years)	1.53 $\pm$ 1.53	2.25 $\pm$ 2.44	2.85 $\pm$ 3.46	4.51 $\pm$ 3.10	0.002	Group 1 $\approx$ 2 $\approx$ 3 < 4

Table 1: Demographical and neuropathological characteristic of the participants.

Differences between groups were assessed with the Mann-Whitney or Fisher tests. Braak NFT stages, Thal A β Phase, CERAD and LATE-NC stages were evaluated based on previous work respectively (Braak & Braak 1991, 1995; Thal et al. 2002, Montine et al. 2012, Nelson et al. 2019, 2023). LBD, ARTAG and ADG diagnosis were based on established criteria respectively (Braak & Braak 1998; Kovacs et al. 2016; Attems et al. 2021).

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