White matter integrity is **affected** in **cognitively normal APOE-ε4 carriers**, especially **homozygotes**, as shown using DWI and T1w/T2w ratio maps, suggesting an **age-accelerating impaired myelination**.

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Age and APOE Genotype Interaction on White Matter Myelin in Cognitively Normal Middle-Aged Participants

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INTRODUCTION

- **Age** and **APOE ε4 allele** (major genetic risk for sporadic AD) have a strong impact on **white matter microstructure** in **cognitively normal subjects** [1].
- Such alterations are often regarded as potential **thinning of the myelin sheath** rather than axonal degeneration.
- Aim: we studied differences in myelin maps obtained using **T1w/T2w-ratio maps** [2], across cognitively normal subjects with at genetic risk for Alzheimer's Disease (AD).

METHODS

- **N=515 cognitively normal subjects** aged from 45 to 74 from the **ALFA study**, a large cohort for imaging biomarkers of preclinical AD in the general population [3]

	Total sample (N=515)	Non-carriers (N=250)	ε4-heterozygous (N=197)	ε4-homozygous (N=68)	Inferential statistics
Age (in years) (SD)	58.00 (7.41)	58.40 (7.55)	58.57 (7.35)	54.94 (6.18)	F=6.88 p=0.008
Education (in years) (SD)	13.64 (3.57)	13.62 (3.61)	13.752 (3.53)	13.38 (3.46)	F=0.27 p=0.76
MMSE (SD)	29.04 (1.08)	29.00 (1.12)	29.02 (1.10)	29.26 (0.77)	F=1.54 p=0.22
TFR (SD)	16.47 (5.16)	16.23 (5.15)	16.37 (5.12)	17.73 (5.12)	F=2.24 p=0.11
TPR (SD)	24.11 (4.50)	23.72 (4.84)	24.24 (4.23)	25.19 (3.68)	F=2.84 p=0.06
WM lesion load [Q1,Q3]	3.18 [1.09, 3.65]	3.22 [1.13, 3.41]	3.03 [1.08, 3.70]	3.47 [1.13, 3.82]	H=0.60 p=0.65
Fazekas scales	**0**: 247 **1**: 211 **2**: 39 **3**: 2	**0**: 113 **1**: 115 **2**: 17 **3**: 2	**0**: 101 **1**: 80 **2**: 14	**0**: 33 **1**: 26 **2**: 8	χ^2=3.82 p=0.43
Males / females	201 / 314	88 / 162	88 / 109	25 / 43	χ^2=4.32 p=0.12

- Using **TBSS** [4] we assessed the **impact of age** and **APOE genotype** - and their interaction - on T1w/T2w maps used as an **indirect descriptor of myelin content**.
- Age was modeled as a quadratic term in accordance with the expected course of myelination.
- We repeated this analysis using the same workflow and model on **diffusion-weighted imaging** (DWI) parametric maps from the exact same participants.

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RESULTS

- **Extensive decrease** of T1w/T2w with **age** (**Figure 1**) and in **APOE-ε4 carriers** in a **dose-dependent** manner (**Figures 2, 4**).
- **Replicated in DWI** with increased MD, RD and AxD in **ε4 carriers** in the **recessive** and **additive** contrasts (**Figure 3**).
- Also found to **interact with age** in T1w/T2w, suggesting an **earlier decline in myelin content** in individuals with **more ε4 alleles** (**Figure 5**). Such interaction was found not significant when applying the same models on DWI metrics.

(*) Contrasts: **recessive** (ε4-homozygotes vs others), **dominance** (ε4 carriers vs others), **additive** (the more ε4 alleles the stronger)

CONCLUSIONS

- **Confirmed higher vulnerability** of WM tracts in healthy APOE-ε4 carriers using **both DWI** and **T1w/T2w**.
- This burden **worsens with the number of copies carried**, which could be observed thanks to the high number of homozygotes in this dataset.
- Early alterations of myelination may result from **impaired capacity of the ε4 isoform of the ApoE protein** to transport cholesterol, potentially leading to the vulnerability of APOE-ε4 carriers to AD pathology.

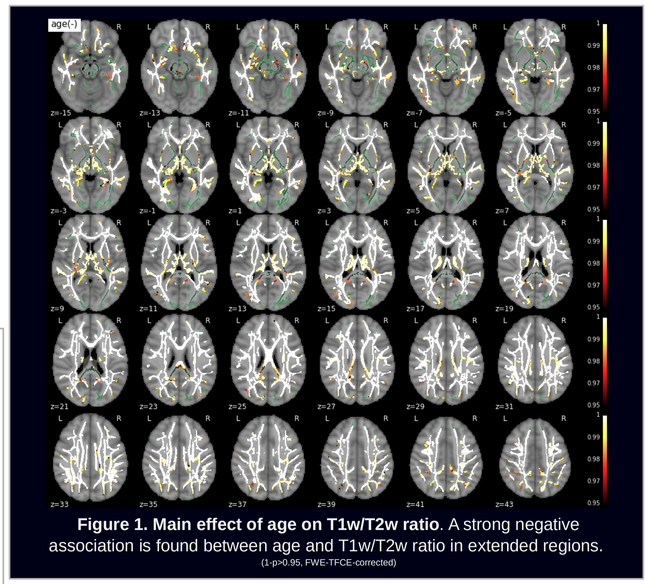

Figure 1. Main effect of age on T1w/T2w ratio. A strong negative association is found between age and T1w/T2w ratio in extended regions. (1-p=0.99, FWE-TFCE-corrected)

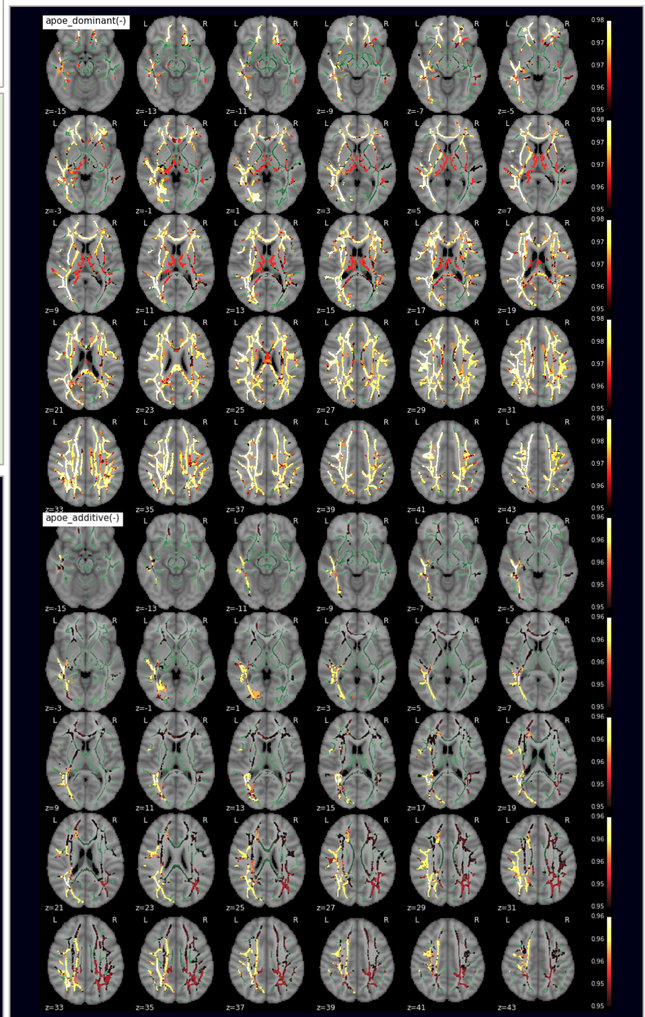

Figure 2. Effect of APOE on T1w/T2w (from top to bottom - dominant and additive components) - no recessive component was observed - **ε4 carriers showed lower T1w/T2w values in extensive regions** (1-p=0.95, FWE-TFCE-corrected)

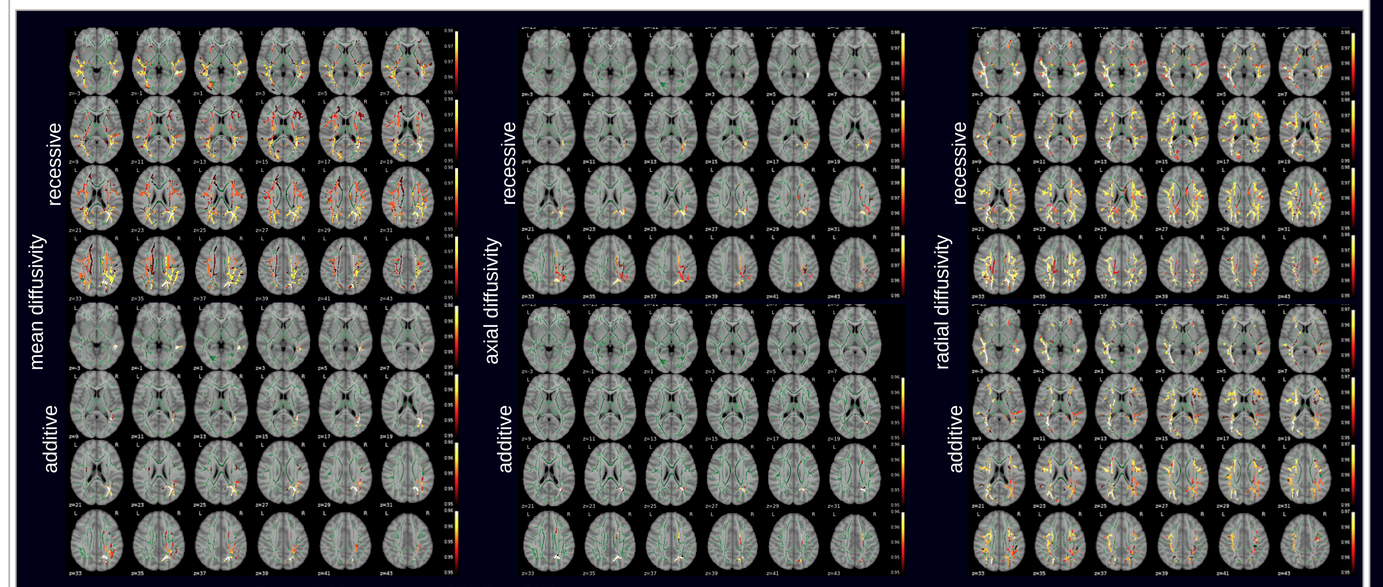

Figure 3. Main effect of APOE on DWI parametric maps (from top to bottom - recessive and additive components) - no dominant component was observed - **larger increases in RD as compared to AxD** are suggestive of **altered myelination**. (1-p=0.95, FWE-TFCE-corrected)

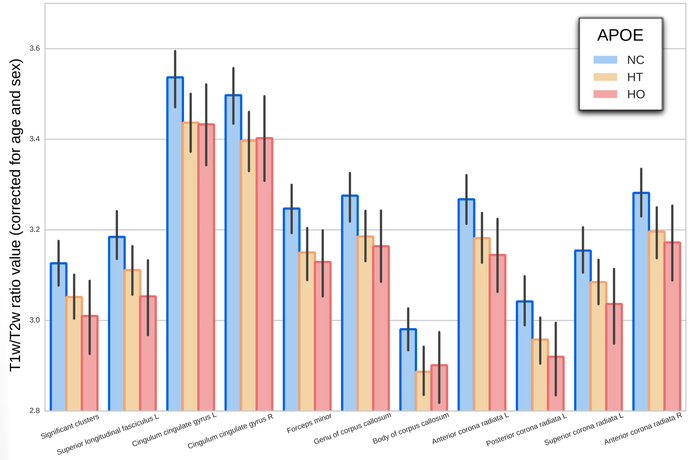

Figure 4. Main effect of APOE status on T1w/T2w ratio across fiber tracts. Each bar represents the mean value extracted from the corresponding significant tract ROI (from JHU WM atlas) along with standard error (CI: 95%) (p=0.05 FWE corrected)

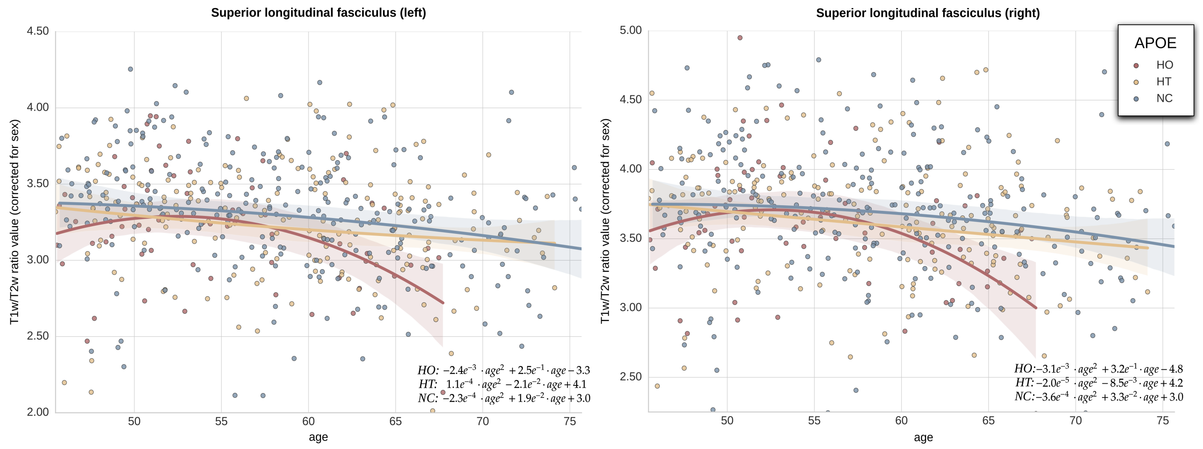

Figure 5. Effect of aging and APOE genotype on T1w/T2w ratios (unitless) in the SLF area. Each dot represents a subject (red: ε4 homozygotes [HO], green: ε4 heterozygotes [HT], blue: non-carriers [NC]). Quadratic regression (by age correcting for sex) is displayed (solid curves) for each APOE group.

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