Both **age** and the **APOE ε4** allele have a **negative differential impact** on **hippocampal subfields** in cognitively normal subjects.

ε4-homozygotes show **heavier burden** than heterozygotes and non-carriers.

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Effect of Age and APOE on Hippocampal Subfields in Cognitively Normal Subjects (N=1168, single site)

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INTRODUCTION

- **Hippocampal atrophy** is associated with memory deficits and is used to monitor disease progression such as **Alzheimer's Disease** (AD) [1].
- **Age** and **APOE ε4 allele** (major genetic risk for sporadic AD) have a strong impact on hippocampal volume in cognitively normal subjects [2].
- Aim: in this study, we estimated **hippocampal subfield volumes** in **cognitively normal participants** and looked for associations with age, sex, education and APOE.

METHODS

- **N=1168** cognitively healthy participants aged between 45 and 74 years were selected from the ALFA study, which is a large cohort program for neuroimaging biomarkers of preclinical AD in the general population [3]. Acquired data covers **multimodal MRI**, **DNA extraction**, **CSF** and **blood sampling**, full cognitive and lifestyle habits evaluation.

	Total sample (N=1168)	Non-carriers (N=678)	ε4-heterozygous (N=417)	ε4-homozygous (N=73)	Inferential statistics
Age (in years) (SD)	59.41 (6.82)	59.23 (7.00)	60.06 (6.55)	57.57 (5.98)	F=4.84 p=0.008
Education (in years) (SD)	13.43 (3.49)	13.33 (3.47)	13.62 (3.51)	13.19 (3.44)	F=1.02 p=0.36
Males / Females	412 / 756	240 / 438	149 / 268	23 / 50	χ^2=0.5 p=0.78

- **Single MR scanner**: Philips Ingenia CX 3T (3DT1, 0.75-mm isotropic voxels, TR=9.9ms, TE=4.6ms, TI=600ms, Flip Angle=8°, sagittal plane, FOV 320×320 mm, imaging matrix 240×240×180).
- Segmentation of subfields was achieved using **FreeSurfer 6.0** [4].
- **Statistical analysis**: we performed a group ROI-based analysis and assessed the effect of APOE on each subfield and its interaction with age by fitting a general linear model. Age was modeled as a quadratic term centered at age 55. We partitioned genetic variance using 3 dummy regressors coding for the number of ε4 alleles carried. Sex, education and total intracranial volume were included as confounding variables. Results shown at p<.05 corrected for multiple comparisons.
- Both raw and processed data are stored on an **XNAT platform**. Processing workflows were implemented and run on that platform. Statistical analysis was performed using Python (*statsmodels* 0.9).

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RESULTS

- **APOE ε4 carriers** showed **reduced volumes** as compared to non-carriers (**Figure 1**).
- Bilateral effect of APOE found in CA3, CA4, dentate gyrus and hippocampal tail and whole hippocampus. Effects found in both recessive and additive contrasts(*).
- Only fimbria showed **larger volumes** in ε4 carriers, also in both recessive and additive contrasts(*).
- Left hippocampal fissure is found **larger** in **ε4 carriers** in the dominant contrast(*).
- All subfields **decrease in volume with age**, except right hippocampal fissure (p=0.8).
- **Strongest effect** of age was found, in decreasing order of magnitude, in whole hippocampus, hippocampal tail, molecular layer, CA1, presubiculum, subiculum, dentate gyrus, CA4, fimbria, CA3, HATA, left hippocampal fissure and parasubiculum (**Figure 2**).

Pairwise comparisons revealed **stronger age-related atrophy** in:

- hippocampal tail > CA1, CA3, CA4, fimbria, parasubiculum, hippocampal fissure, HATA and subiculum
- molecular layer > CA3, fimbria, parasubiculum, hippocampal fissure and HATA
- presubiculum and CA1 > parasubiculum

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

CONCLUSIONS

- Highlights the impact of both **age** and **APOE ε4** status on **hippocampal subfields** in **cognitively normal participants**. Both factors show a differential effect across subfields.
- With a uniquely **high number of homozygotes**, this study shows that carrying **two copies of the ε4 allele** is also associated with a significantly higher impact.

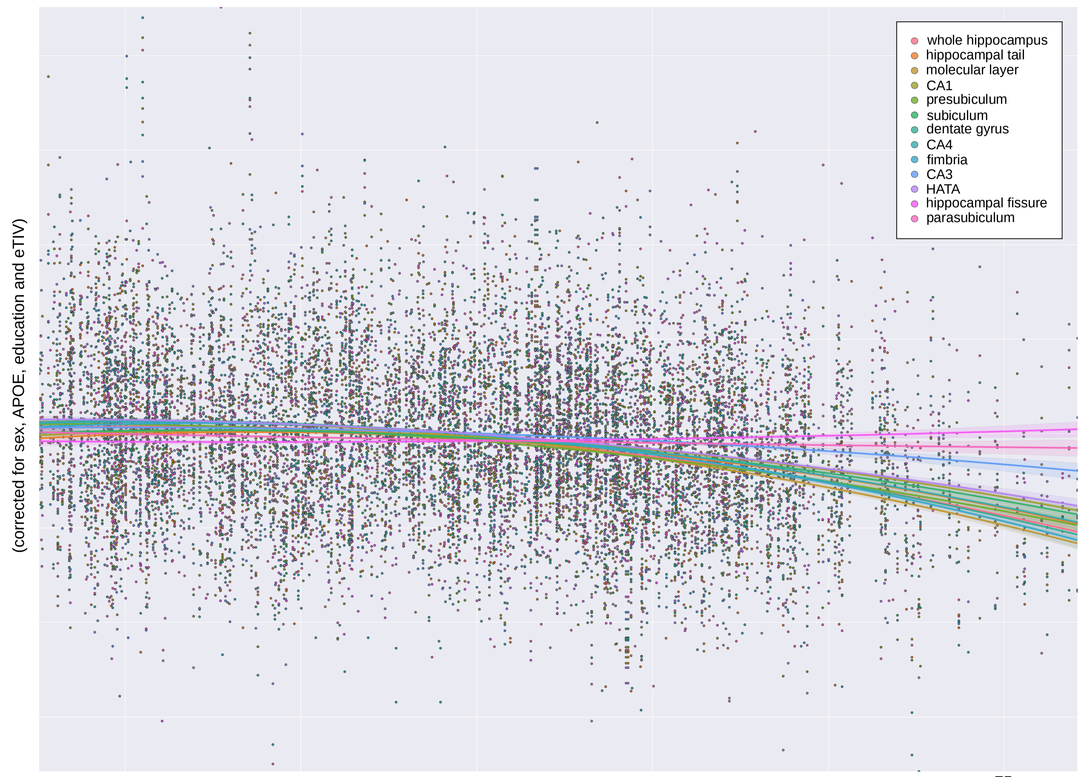

Figure 2. Differential main effect of age on hippocampal subfield volumes (in z-scores). Quadratic regression is displayed (in solid curves) for each subfield. Each dot represents one subfield in one individual subject.

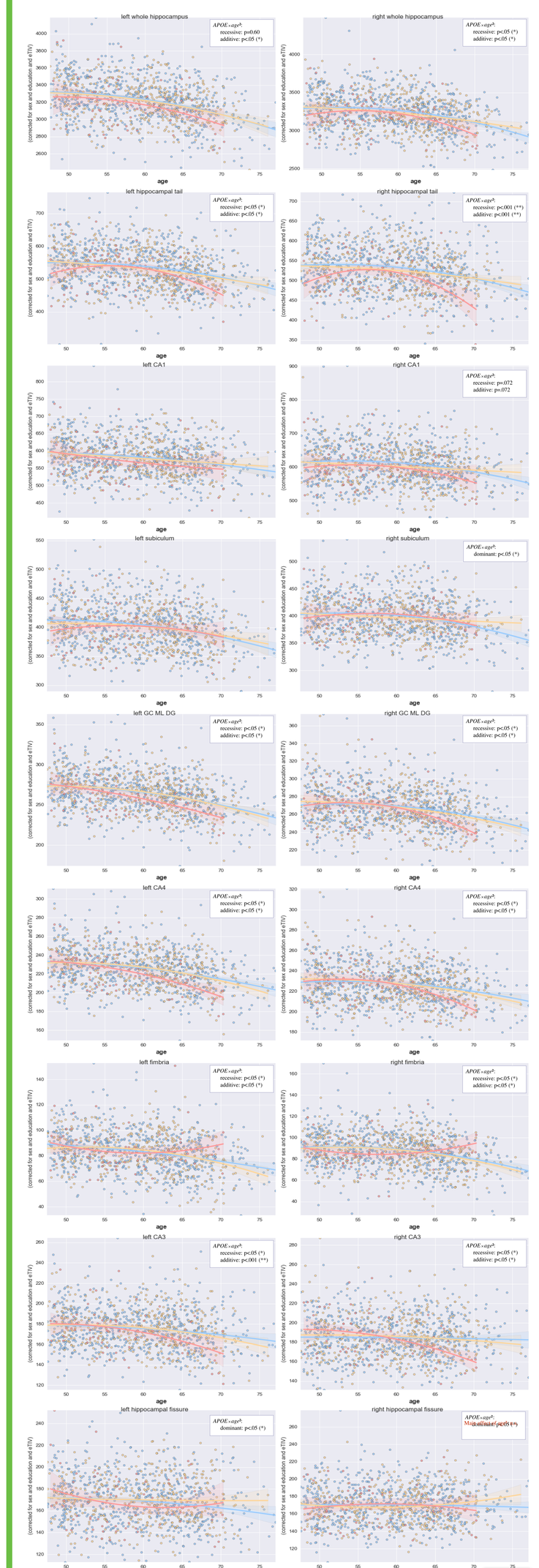

Figure 1. Effect of aging and APOE on hippocampal subfield volumes (in mm³). CA: Cornu Ammonis - GC ML DG: Dentate Gyrus - eTIV: total intracranial volume

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