



HAL
open science

Respective influence of beta-amyloid and APOE ϵ 4 genotype on medial temporal lobe subregions in cognitively unimpaired older adults

Robin de Flores, Solène Demeilliez-Servouin, Elizabeth Kuhn, Léa Chauveau, Brigitte Landeau, Nicolas Delcroix, Julie Gonneaud, Denis Vivien, Gaël Chételat

► To cite this version:

Robin de Flores, Solène Demeilliez-Servouin, Elizabeth Kuhn, Léa Chauveau, Brigitte Landeau, et al.. Respective influence of beta-amyloid and APOE ϵ 4 genotype on medial temporal lobe subregions in cognitively unimpaired older adults. *Neurobiology of Disease*, 2023, 181, pp.106127. 10.1016/j.nbd.2023.106127 . hal-04087221

HAL Id: hal-04087221

<https://hal.science/hal-04087221>

Submitted on 3 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Respective influence of beta-amyloid and APOE ϵ 4 genotype on medial temporal lobe subregions in cognitively unimpaired older adults

Robin de Flores^{a,*}, Solène Demeilliez-Servouin^a, Elizabeth Kuhn^a, Léa Chauveau^a, Brigitte Landeau^a, Nicolas Delcroix^b, Julie Gonneaud^a, Denis Vivien^a, Gaël Chételat^a, on behalf of the Medit-Ageing research group

^a INSERM UMR-S U1237, PhIND “Physiopathology and Imaging of Neurological Disorders”, Institut Blood and Brain @ Caen-Normandie, Caen-Normandie University, GIP Cyceron, France

^b CNRS UMS 3408, GIP Cyceron, France

ARTICLE INFO

Keywords:

Medial temporal lobe
Hippocampal subfields
Amyloid
APOE
Alzheimer's disease
Age

ABSTRACT

Medial temporal lobe (MTL) subregions are differentially affected in Alzheimer's disease (AD), with a specific involvement of the entorhinal cortex (ERC), perirhinal cortex and hippocampal cornu ammonis (CA)1. While amyloid ($A\beta$) and APOE ϵ 4 are respectively the first molecular change and the main genetic risk factor in AD, their links with MTL atrophy remain relatively unclear.

Our aim was to uncover these effects using baseline data from 130 participants included in the Age-Well study, for whom ultra-high-resolution structural MRI, amyloid-PET and APOE ϵ 4 genotype were available.

No volume differences were observed between $A\beta+$ ($n = 24$) and $A\beta-$ ($n = 103$), nor between APOE4+ ($n = 35$) and APOE4- ($n = 95$) participants. However, our analyses showed that both $A\beta$ and APOE ϵ 4 status interacted with age on CA1, which is known to be specifically atrophied in early AD. In addition, APOE ϵ 4 status moderated the effects of age on other subregions (subiculum, ERC), suggesting a more important contribution of APOE ϵ 4 than $A\beta$ to MTL atrophy in cognitively unimpaired population.

These results are crucial to develop MRI-based biomarkers to detect early AD.

1. Introduction

The medial temporal lobe (MTL) is among the most studied brain region because of its involvement in a myriad of cognitive processes and its sensitivity to ageing, neurological and psychiatric diseases, including Alzheimer's disease (AD) (Moscovitch et al., 2006; Small et al., 2011). In the context of AD, histological studies have reported that the MTL is the first region to be targeted by neurofibrillary tangles (NFT), although MTL subregions are not affected homogeneously (Braak and Braak, 1991). NFTs first target the perirhinal and entorhinal cortices (PRC and ERC, respectively) before propagating to the hippocampal subfield CA1, then the subiculum (SUB), CA2, CA3 and the dentate gyrus (DG) (Braak and Braak, 1991). Importantly, the pattern of atrophy reported in magnetic resonance imaging (MRI) studies are consistent with these histopathological observations, with an involvement of ERC, PRC and CA1 in early AD stages (ie in patients with mild cognitive impairment [MCI]) while all MTL subregions appeared to be atrophied at the AD-

dementia stage (Adler et al., 2018; de Flores et al., 2015a; Gertje et al., 2016; Hata et al., 2019; Pini et al., 2016; Wolk et al., 2017; Xie et al., 2019). Thus, MTL atrophy is commonly used as a biomarker to monitor AD-related neurodegeneration in-vivo, and provides important pathologic staging information (Jack et al., 2018). However, results are sparse and less consistent in preclinical AD (i.e. $A\beta$ -positive ($A\beta+$) cognitively unimpaired [CU] individuals), with studies reporting atrophy in SUB/preSUB (Hsu et al., 2015; Parker et al., 2019), Brodmann area 35 (BA35 - a subregion of PRC) (Wolk et al., 2017) or no atrophy (Xie et al., 2019) in comparison to $A\beta-$ CU. The same conclusion applies to the effects of APOE ϵ 4, the main genetic risk factor for sporadic AD, with limited and inconsistent findings (Vilor-Tejedor et al., 2021). For example, studies reported no effects of APOE ϵ 4 on hippocampal subfield volumes (Voineskos et al., 2015) while others reported atrophy of CA3/DG (Mueller et al., 2008) or CA1 stratum radiatum lacunosum moleculare (SRLM) (Kerchner et al., 2014). All these discrepancies in the literature most likely reflect the variability in the anatomical definition

* Corresponding author at: Inserm U1237-PhIND, GIP Cyceron, Bd Henri Becquerel, BP 5229, 14074, Caen cedex 5, France.

E-mail address: deflores@cyceron.fr (R. de Flores).

<https://doi.org/10.1016/j.nbd.2023.106127>

Received 23 January 2023; Received in revised form 11 April 2023; Accepted 12 April 2023

Available online 13 April 2023

0969-9961/© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

of hippocampal subfields across laboratories as well as the use of different segmentation protocols (e.g. manual vs automatic approaches). Notably, several groups applied FreeSurfer to MRI scans with approximately $1 \times 1 \times 1$ mm³ resolution, which raised serious concerns given that this resolution is generally insufficient for visualizing the internal structure of the hippocampus (de Flores et al., 2015b; Wisse et al., 2021).

Since MTL subregional volumetry could be useful in the early diagnosis and monitoring of AD, it is particularly important to better characterize the deleterious effects of A β and APOE genotype on these structures. Our aim was to uncover these effects, for the first time in the same cohort, to further our understanding of the mechanisms underlying MTL atrophy in the context of AD. To that end, dedicated ultra-high-resolution T2-weighted scans acquired in cognitively unimpaired elderly were used together with a tailored automatic segmentation algorithm.

2. Methods

2.1. Participants

Participants from the baseline visit of the Age-Well randomized clinical trial of the Medit-Ageing European Project were included in the present study (Poinsnel et al., 2018). Participants were recruited from the general population from November 2016 until March 2018, older than 65 years, native French speakers, retired for at least 1 year, educated for at least 7 years, and performed within the normal range on standardized cognitive tests. They did not show evidence of a major neurological or psychiatric disorder (including alcohol or drug abuse), history of cerebrovascular disease, presence of a chronic disease or acute unstable illness, and current or recent medication usage that may interfere with cognitive functioning. Only participants with available dedicated ultra-high-resolution structural MRI, ¹⁸F florbetapir PET and APOE genotype were included. A global SUVR measure extracted from the ¹⁸F florbetapir PET was used to dichotomize the population into A β positive (A β +) and negative (A β -) based on a threshold corresponding to the 99.9th percentile of the neocortical standard uptake value ratio distribution among 45 healthy young individuals younger than 40 years (André et al., 2020). In addition, the cohort was dichotomized into APOE ϵ 4 carriers (at least one ϵ 4 allele; ϵ 4+) and non-carriers (no ϵ 4 allele; ϵ 4-). Baseline data were collected from November 2016 until April 2018. The Age-Well randomized clinical trial was approved by the local ethics committee (Comité de Protection des Personnes Nord-Ouest III, Caen, France; trial registration number: EudraCT: 2016-002,441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819) and all participants gave written informed consent prior to the examinations.

2.2. MRI data acquisition and handling

Each subject underwent an MR scan at the CYCERON center (Caen, France) using a 3 T Philips (Eindhoven, The Netherlands) scanner. First, T1-weighted structural images were acquired (Repetition Time (TR) = 6.8 ms; Echo Time (TE) = 3.1 ms; flip angle = 6°; 180 slices; slice thickness = 1 mm; Field of View (FoV) = 256 \times 256 mm²; matrix = 256 \times 256; in-plane resolution = 1 \times 1 mm²; acquisition time = 5 min16). In addition, two ultra-high-resolution T2-weighted structural images (TR = 5310 ms; TE = 110 ms; flip angle = 90°; 23 slices; slice thickness = 2.5 mm; FOV = 140 \times 111 mm²; matrix = 352 \times 352; in-plane resolution = 0.398 \times 0.398 mm², acquisition time = 3 min43) were acquired perpendicularly to the long axis of the hippocampus, and both images were then coregistered and averaged using SPM12.

Hippocampal subfields (CA1, CA2, CA3, DG, SUB) and extra-hippocampal regions (ERC, BA35, BA36, and parahippocampal cortex [PHC]) volumes were estimated automatically for each participant from their averaged ultra-high-resolution T2-weighted image using the Automated Segmentation for Hippocampal Subfields (ASHS) software

(Yushkevich et al., 2015). For an example of ASHS segmentation, see Fig. 1. Note that a customized atlas was first created for this purpose. This was motivated by recent observations based on ex vivo MRI and histology data showing that the dark band, a hypointense line appearing within the gray matter of the hippocampus on T2 images frequently used in segmentation protocols as the boundary between DG and SUB/CA, is exclusively composed of SRLM (de Flores et al., 2020a). Thus, dark band voxels should be labeled as SUB/CA only, but were split evenly between SUB/CA and DG in the original atlas provided with ASHS (ashs_atlas_upennpmc20170810) (Yushkevich et al., 2015). Therefore, we manually edited the segmentations from the original atlas (29 subjects) to label all dark band voxels as SUB/CA and generated a new atlas. Leave-one-out cross-validation analyses showed similar accuracy as compared to the original atlas (Dice coefficients: CA1 = 0.82, CA2 = 0.56, CA3 = 0.53, DG = 0.80, SUB = 0.76, ERC = 0.79, BA35 = 0.72, BA36 = 0.78, PHC = 0.78). The volume of the whole hippocampus was estimated as the sum of the five hippocampal subfields. All ASHS segmentations were visually inspected and manually edited when feasible (see the QC procedure in supplementary material). All volumetric measures were normalized to the total intracranial volume (TIV, calculated using SPM12 by summing the volumes of the gray matter,

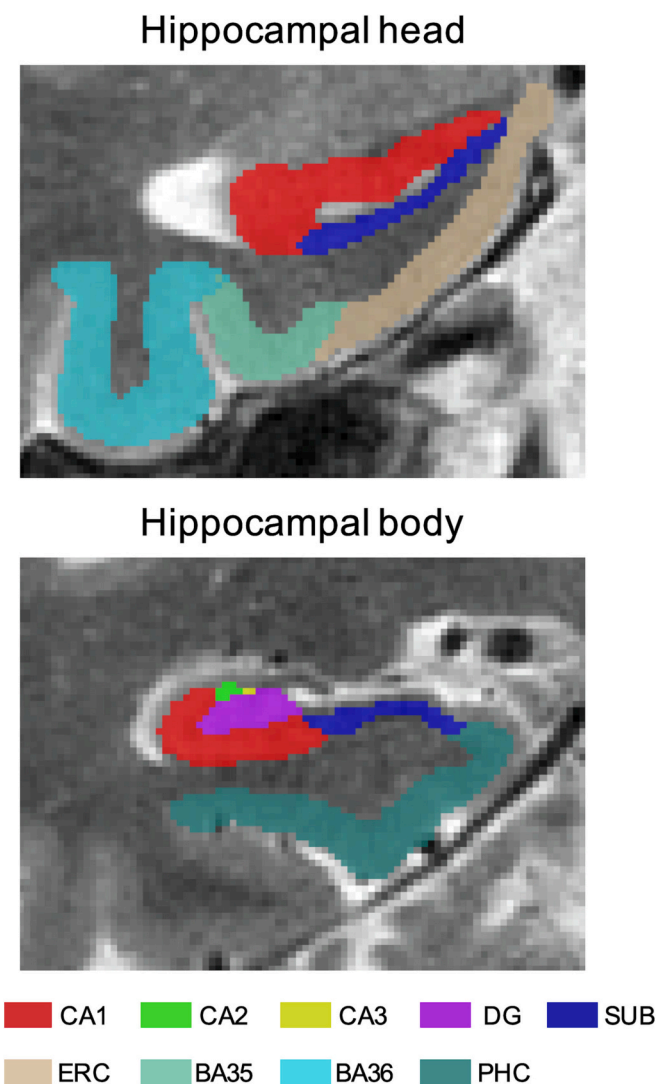


Fig. 1. : Example of an ASHS segmentation in the hippocampal head and hippocampal body. Abbreviation: BA: Brodmann area; CA: cornu ammonis; DG: dentate gyrus; ERC: entorhinal cortex; PHC: parahippocampal cortex; SUB: subiculum.

white matter and cerebrospinal fluid) to compensate for interindividual variability in head size. Note that raw volumes are reported in Supplementary Table 1.

2.3. Statistical analyses

For each MTL subregion, group comparisons were performed (Aβ + vs Aβ- participants and ε4+ vs ε4- participants) using ANCOVAs, including age, sex and education as covariates. Interactions with age (i. e., Aβ status*age and APOE ε4 status*age) were also investigated for each subregion. In case of significant interaction ($p < 0.05$), post-hoc correlation analyses (Pearson) were performed to investigate the associations between age and MTL volumes within specific groups (Aβ + vs Aβ- individuals and ε4+ vs ε4- individuals). Lastly, both the Aβ and APOE status were entered in the same model (including age, sex and education as covariates) and all analyses were repeated. This allowed us to assess whether specific effects of Aβ or APOE existed while controlling for the other one. Finally, we further evaluated the associations between amyloid pathology and MTL atrophy by performing Pearson's correlations between global florbetapir SUVr and MTL volumes.

3. Results

One hundred and thirty cognitively unimpaired older adults were included. Demographics of the cohort are reported in Table 1. Twenty-seven subjects were classified as Aβ + while 103 were Aβ-. In addition, 35 subjects were ε4+ and 95 were ε4-. No significant differences were found in terms of age, education or female/male ratio between Aβ + and Aβ- subjects nor between ε4+ and ε4- subjects. However, the proportion of ε4+ subjects was higher in the Aβ + group (52%) than in the Aβ- group (20%) ($X^2 = 10.8, p = 0.001$).

No significant group differences were found between Aβ + vs Aβ-

Table 1
Demographics of the population.

| | Full cohort | Aβ- | Aβ+ | p | ε4- | ε4+ | p |
|------------------------------|-------------|-------------|-------------|--------------|-------------|-------------|------|
| N | 130 | 103 | 27 | - | 95 | 35 | - |
| Age (years, mean ± SD) | 68.9 ± 3.8 | 68.5 ± 3.4 | 70.2 ± 4.7 | 0.07 | 69.0 ± 3.7 | 68.4 ± 4.0 | 0.38 |
| Gender (F/M) | 80/50 | 63/40 | 17/10 | 0.86 | 63/32 | 17/18 | 0.06 |
| Education (years, mean ± SD) | 13.2 ± 3.1 | 13.3 ± 3.0 | 12.8 ± 3.4 | 0.48 | 13.2 ± 3.0 | 13.3 ± 3.3 | 0.89 |
| APOE Genotype (ε4-/ε4+) | 95/35 | 82/21 | 13/14 | 0.001 | - | - | - |
| E2/3 | 11 | 11 | 0 | - | 11 | 0 | - |
| E3/3 | 84 | 71 | 13 | - | 84 | 0 | - |
| E2/4 | 2 | 0 | 2 | - | 0 | 2 | - |
| E3/4 | 29 | 18 | 11 | - | 0 | 29 | - |
| E4/4 | 4 | 3 | 1 | - | 0 | 4 | - |
| Global cognition (mean ± SD) | 141.0 ± 2.7 | 141.0 ± 2.7 | 141.0 ± 2.6 | 0.86 | 141.2 ± 2.4 | 140.4 ± 3.1 | 0.21 |
| Episodic memory (mean ± SD) | 57.5 ± 8.2 | 58.1 ± 7.7 | 55.4 ± 9.6 | 0.18 | 57.1 ± 8.0 | 58.7 ± 8.8 | 0.37 |

SD: standard deviation, F: female, M: male, Aβ: amyloid-β. Global cognition was assessed using the Mattis DRS. Episodic memory was assessed using the California Verbal Learning Test sum of trials 1-5. Continuous variables were compared using 2-sample t-tests while categorical variables were compared using chi-square tests. Significant results ($p < 0.05$) are highlighted in bold font.

individuals nor between ε4+ vs ε4- individuals for any MTL subregions (Table 2). In the full cohort, no significant associations were found between global florbetapir SUVr and MTL volumes (see Supplementary Table 1). However, a significant interaction was found between age and Aβ status on CA1 ($F = 4.47, p = 0.04$). More precisely, CA1 was negatively associated with age in Aβ + individuals ($r = -0.48, p = 0.01$) but not in Aβ- individuals ($r = -0.05, p = 0.58$) (Fig. 2).

In addition, significant interactions were found between age and APOE status on CA1 ($F = 4.31, p = 0.04$), SUB ($F = 5.21, p = 0.02$), ERC ($F = 4.56, p = 0.03$), and the whole hippocampus ($F = 4.97, p = 0.03$). Post-hoc analyses showed that the volumes of CA1, SUB and the whole hippocampus were significantly associated with age in ε4+ subjects ($r = -0.43, p = 0.01$; $r = -0.41, p = 0.01$; $r = -0.41, p = 0.01$, respectively), while a trend was found for ERC ($r = -0.31, p = 0.07$). In contrast, none

Table 2
Effects of Aβ and APOE4 status and their interaction with age on MTL subregions.

| | a) Aβ Status | | Group comparison (Aβ- vs Aβ+) | | Interaction (Aβ status*age) | |
|-------------------|-----------------------------------|--------------|-------------------------------|-------------|-------------------------------|-------------|
| | TIV-normalized volume (mean ± SD) | | F | P | F | P |
| | Aβ- | Aβ+ | | | | |
| CA1 | 0.96 ± 0.10 | 0.93 ± 0.14 | 0.59 | 0.44 | 4.47 | 0.04 |
| CA2 | 0.02 ± 0.003 | 0.02 ± 0.004 | 1.70 | 0.19 | 0.58 | 0.45 |
| CA3 | 0.05 ± 0.01 | 0.06 ± 0.01 | 4.10 | 0.05 | 0.05 | 0.82 |
| DG | 0.42 ± 0.05 | 0.40 ± 0.07 | 0.54 | 0.46 | 1.95 | 0.17 |
| SUB | 0.32 ± 0.04 | 0.32 ± 0.04 | 0.55 | 0.46 | 1.20 | 0.28 |
| ERC | 0.41 ± 0.04 | 0.40 ± 0.07 | 0.63 | 0.43 | 3.56 | 0.06 |
| BA35 | 0.36 ± 0.06 | 0.35 ± 0.04 | 1.22 | 0.27 | 2.03 | 0.16 |
| BA36 | 1.24 ± 0.18 | 1.25 ± 0.19 | 0.39 | 0.53 | 1.47 | 0.23 |
| PHC | 0.67 ± 0.09 | 0.66 ± 0.09 | 0.05 | 0.82 | 3.68 | 0.06 |
| Whole hippocampus | 1.77 ± 0.18 | 1.73 ± 0.24 | 0.47 | 0.49 | 3.54 | 0.06 |
| | b) APOE Status | | Group comparison (ε4- vs ε4+) | | Interaction (APOE status*age) | |
| | TIV-normalized volume (mean ± SD) | | F | P | F | P |
| | ε4- | ε4+ | | | | |
| CA1 | 0.96 ± 0.10 | 0.93 ± 0.13 | 1.06 | 0.30 | 4.31 | 0.04 |
| CA2 | 0.02 ± 0.003 | 0.02 ± 0.004 | 0.39 | 0.53 | 0.01 | 0.92 |
| CA3 | 0.05 ± 0.01 | 0.05 ± 0.01 | 0.91 | 0.34 | 0.47 | 0.50 |
| DG | 0.41 ± 0.05 | 0.41 ± 0.07 | 0.18 | 0.68 | 3.78 | 0.05 |
| SUB | 0.32 ± 0.04 | 0.32 ± 0.04 | 0.14 | 0.71 | 5.21 | 0.02 |
| ERC | 0.41 ± 0.04 | 0.40 ± 0.06 | 0.09 | 0.76 | 4.56 | 0.03 |
| BA35 | 0.37 ± 0.06 | 0.34 ± 0.06 | 3.82 | 0.05 | 0.46 | 0.50 |
| BA36 | 1.24 ± 0.16 | 1.26 ± 0.22 | 0.03 | 0.87 | 2.61 | 0.11 |
| PHC | 0.67 ± 0.08 | 0.66 ± 0.10 | 0.06 | 0.81 | 2.66 | 0.11 |
| Whole hippocampus | 1.77 ± 0.17 | 1.73 ± 0.24 | 0.76 | 0.39 | 4.97 | 0.03 |

All volumes were normalized by the total intracranial volume. CA: cornu ammonis; DG: dentate gyrus; SUB: subiculum; ERC: entorhinal cortex; BA: Brodmann area; PHC: parahippocampal cortex.

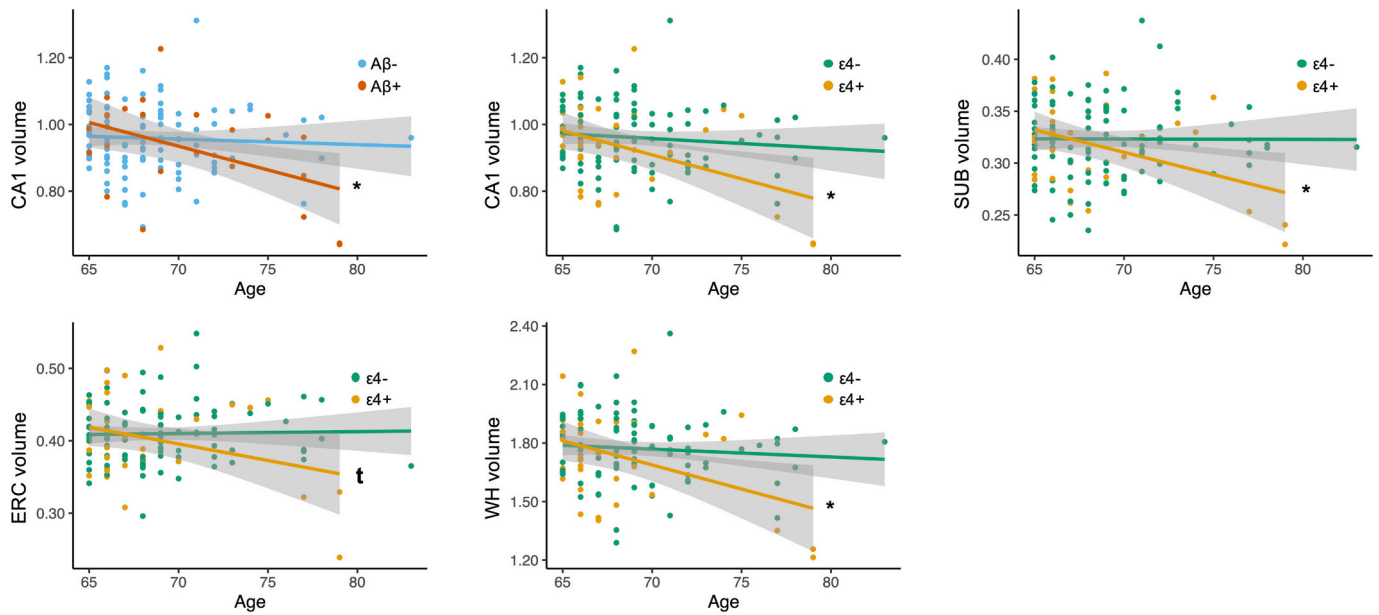


Fig. 2. : Significant interactions between A β status and age as well as between $\epsilon 4$ status and age on medial temporal lobe structures. All medial temporal lobe volumes obtained using ASHS were normalized by the total intracranial volume. CA: cornu ammonis; SUB: subiculum; ERC: entorhinal cortex; WH: whole hippocampus.

Interactions were investigated using ANCOVAs, including age, sex and education as covariates. In case of significant interaction ($p < 0.05$), post-hoc correlation analyses (Pearson) were performed to investigate the associations between age and MTL volumes within specific groups. t, trend; * $p < 0.05$.

of these subregions were associated with age in $\epsilon 4-$ individuals ($r = -0.11, p = 0.31$; $r = -0.01, p = 0.97$; $r = -0.09, p = 0.40$; $r = 0.02, p = 0.82$, respectively) (Fig. 2).

Results remained overall unchanged when both the A β and APOE status were entered in the same model, with i) no significant group differences between A $\beta +$ subjects vs A $\beta-$ subjects nor between $\epsilon 4+$ subjects vs $\epsilon 4-$ subjects and ii) a significant interaction between age and A β status on CA1 ($F = 4.16, p = 0.04$) as well as significant interactions between age and APOE status on CA1 ($F = 4.07, p = 0.04$), SUB ($F = 4.81, p = 0.03$), ERC ($F = 4.13, p = 0.03$) and the whole hippocampus ($F = 4.75, p = 0.03$) (Supplementary Table 3).

4. Discussion

In the present study, we used dedicated ultra-high-resolution T2-weighted images together with a tailored automatic segmentation algorithm using a customized atlas to investigate the effects of A β and APOE $\epsilon 4$ status on MTL structures in cognitively unimpaired elderly. We did not find significant differences in volume between A $\beta +$ and A $\beta-$ individuals nor between $\epsilon 4+$ and $\epsilon 4-$ individuals. In contrast, our analyses revealed significant interactions between A β status and age on CA1 as well as between APOE $\epsilon 4$ status and age on CA1, SUB and ERC, suggesting accelerated age-related volume decrease in A $\beta +$ and/or $\epsilon 4+$ individuals in these subregions.

Characterizing the contribution of A β to atrophy in cognitively unimpaired population is particularly important to identify biomarkers that are sensitive and specific to early (preclinical) AD, especially since the disease tends to be defined biologically (Jack et al., 2018). Results from the literature are very heterogeneous, with cross-sectional studies reporting atrophy of the hippocampus (Nosheny et al., 2019; Whitwell et al., 2013) or BA35 (Wolk et al., 2017) in A $\beta +$ subjects as compared to their A $\beta-$ counterparts, while other groups failed to report such differences (Chauveau et al., 2021; Mattsson et al., 2014; Yushkevich et al., 2015). Regarding hippocampal subfields, two studies reported atrophy in SUB/preSUB (Hsu et al., 2015; Parker et al., 2019). However, the method used in these papers, which consisted in applying FreeSurfer to MRI scans with approximately $1 \times 1 \times 1 \text{ mm}^3$ resolution, raised serious

concerns given that this resolution is generally insufficient for visualizing the internal structure of the hippocampus (de Flores et al., 2015b; Wisse et al., 2021). Interestingly, Mueller et al. (2018) tested several image types and algorithms to detect A β associated subfield atrophy in cognitively normal subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Using high resolution T2 hippocampal images, the authors found volume reduction in PHC and ERC with ASHS, and in SUB with FreeSurfer 6. Using T1 images, they did not find atrophy with FreeSurfer 5.1 but showed atrophy in CA1 using shape analyses. These inconsistencies may only reflect the variability in the anatomical definition of MTL subregions across techniques but might also suggest the inexistence of a reliable neuroanatomical signature of preclinical AD, as expressed by Whitwell et al. (2013).

Although we did not find direct group differences between A $\beta +$ and A $\beta-$ individuals, our analysis showed a significant interaction between A β status and age on CA1, with this region being negatively associated with age in A $\beta +$ subjects but not in A $\beta-$ subjects. Interestingly, this region has been extensively described as atrophied in early AD (de Flores et al., 2015a). To our knowledge, no other study has investigated the interactions between age and A β on hippocampal subfields. The mechanisms that link amyloid- β to brain atrophy are poorly understood and still debated (Jagust, 2016; Jeong, 2017; La Joie et al., 2020). On one hand, an important number of studies support that soluble A β oligomers contribute to neurodegeneration in AD through several mechanisms; for example by acting on multiple synaptic receptors including NMDA-type glutamate and $\alpha 7$ -nicotinic acetylcholine ($\alpha 7$ -nACh) receptors (Palop and Mucke, 2016; Spire-Jones and Hyman, 2014) or via A β -related mitochondrial dysfunction (Cho et al., 2009). However, it is important to keep in mind that PET targets aggregated forms of amyloid- β which might explain why we do not observed direct associations between amyloid SUVR and MTL volumes. On the other hand, autopsy data have consistently shown a quantitative and topographical dissociation between amyloid plaques and neurodegeneration (Falke et al., 2003; Gómez-Isla et al., 1997). In addition, several studies showed that tau pathology was more tightly associated with atrophy than amyloid (de Flores et al., 2020b; La Joie et al., 2020), which is in line with autopsy studies showing that A β -associated neurodegeneration is rare in the

absence of tau (Price and Morris, 1999) or other pathologies (Wilson et al., 2013). Thus, it is possible that the effects we observed are mediated by tau pathology. Indeed, Wisse et al. (2022) recently showed that CSF p-tau levels partially mediated age effects on hippocampal atrophy rates. In addition, several studies using tau PET tracers showed higher MTL uptake in A β + subjects as compared to A β - (Jagust, 2018; Maass et al., 2017). Thus, the association between age and the volume of CA1 in A β + participants could reflect the presence of tau pathology, especially since CA1 is the first hippocampal region to be targeted by tau in AD (Braak and Braak, 1991). However, this hypothesis is purely speculative and cannot be tested given that we do not have any measures regarding tau pathology in this population.

In addition to the effect of A β , we also aimed at assessing the effects of APOE genotype on MTL structures. We did not find any significant differences between APOE ϵ 4 carriers and non-carriers individuals. APOE ϵ 4 is the largest genetic risk factor for sporadic AD and its effect on brain atrophy has been largely studied, with discrepant findings (Fouquet et al., 2014; Tzioras et al., 2019). Thus, studies found significant differences in hippocampal volume between ϵ 4 carriers and non-carriers (Cacciaglia et al., 2018; Honea et al., 2009; Veldsman et al., 2021; Wishart et al., 2006) while others did not (Dong et al., 2019; Khan et al., 2017; Van Etten et al., 2021). Results are also inconsistent when specifically investigating hippocampal subfield atrophy. Indeed, studies reported volume reductions of CA3/DG (Mueller et al., 2008), CA1-SRLM (Kerchner et al., 2014), the molecular layer (Dounavi et al., 2020), SUB (Donix et al., 2010) in APOE ϵ 4 carriers whereas others failed to report such differences (Burggren et al., 2008; Reiter et al., 2017).

While we did not find significant differences between APOE ϵ 4 carriers and non-carriers, our analysis showed significant interactions between APOE ϵ 4 status and age on CA1, SUB, ERC and the whole hippocampus, with these structures being negatively associated with age in carriers only. Note that previous studies using standard T1 isotropic 1 mm³ images reported inconstant results, with no effects (Chauveau et al., 2021), effects on CA1 (Martí-Juan et al., 2021) or in all FreeSurfer 6 subfield ROIs (Veldsman et al., 2021). Recently, several studies showed higher MTL tau-PET uptake in APOE ϵ 4 carriers in comparison to non-carriers (La Joie et al., 2021; Salvadó et al., 2021; Therriault et al., 2020). Similarly to the effects we described for A β , the interactions we observed for APOE might also reflect the accumulation of tau pathology with advancing age in APOE ϵ 4 carriers. Interestingly, Van Etten et al. (2021) recently showed a negative association between age and hippocampal volume which was modulated by white matter hyperintensities (WMH) in APOE ϵ 4 carriers but not in non-carriers. These results provide an alternative explanation to our results, where vascular vulnerabilities would be the main driver (or an additional contributor) of age-related atrophy in APOE ϵ 4 carriers.

It is well known that APOE ϵ 4 increases the risk of AD in part by driving earlier and more abundant A β pathology through several mechanisms, including a deficit of clearance and an increased production and formation of fibrils (Yamazaki et al., 2019). Thus, the interaction we found between age and A β status on CA1 could be driven by APOE. To test this hypothesis, we repeated our analyses by entering both the amyloid and APOE status in the same model. Results were similar, suggesting independent effects of amyloid and APOE on MTL atrophy.

The present study has strengths and limitations. First, a major strength is the use of a tailored method to estimate MTL structures volume, consisting of dedicated ultra-high-resolution T2-weighted images together with the ASHS algorithm and a custom atlas taking into account recent observations based on ex vivo MRI and histology data. In addition, this work is the first, to our knowledge, to investigate both the effects of A β and APOE on MTL subregions in the same sample using ultra-high-resolution hippocampal images. However, the interactions we found between A β status and age as well as between APOE ϵ 4 status and age on several MTL subregions were not strong and did not survive correction for multiple comparisons. This might be explained by a lack

of statistical power given the relatively small sample size. Thus, these analyses need to be replicated in a larger cohort, potentially enriched in A β + and APOE ϵ 4 carriers individuals. Nevertheless, it is important to keep in mind that the effects of A β and APOE on atrophy are certainly subtle, potentially explaining the discrepancies in the literature.

Altogether, our results provide new insight regarding age-related atrophy in these populations at-risk for AD. These results are important in the perspective of developing MRI-based biomarkers to detect early AD and further our understanding of MTL atrophy in normal and pathological ageing.

Funding

The Age-Well randomized clinical trial is part of the Medit-Ageing project and is supported by the European Union's Horizon 2020 Research and Innovation Program (grant 667696), Region Normandie (Label d'Excellence), and Fondation d'Entreprise MMA des Entrepreneurs du Futur. Institut National de la Santé et de la Recherche Médicale (INSERM) is the sponsor.

Contributions

Robin de Flores: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data.

Solène Demeilliez-Servouin: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data.

Elizabeth Kuhn: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data.

Léa Chauveau: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data.

Brigitte Landeau: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data.

Nicolas Delcroix: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data.

Julie Gonneau: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data.

Denis Vivien: Drafting/revision of the manuscript for content, including medical writing for content.

Gaël Chételat: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

CRediT authorship contribution statement

Robin de Flores: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Solène Demeilliez-Servouin:** Methodology, Resources, Writing – review & editing. **Elizabeth Kuhn:** Methodology, Resources, Writing – review & editing. **Léa Chauveau:** Methodology, Resources, Writing – review & editing. **Brigitte Landeau:** Methodology, Resources, Writing – review & editing. **Nicolas Delcroix:** Methodology, Writing – review & editing. **Julie Gonneau:** Methodology, Resources, Writing – review & editing. **Denis Vivien:** Methodology, Resources, Writing – review & editing. **Gaël Chételat:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Data availability

Data is available on request following a formal data sharing agreement and approval by the consortium and executive committee. The

data sharing request form can be downloaded at <https://silversantestudy.eu/2020/09/25/data-sharing/>

Acknowledgments

The authors thank Marine Faure, Jeanne Lepetit, Marie Saville, and the Cyceron MRI-PET staff members for help with recruitment and neuroimaging data acquisition; INSERM administrative, financial, and legal departments; INSERM Transfert (Delphine Smaghe); Aurélie Cognet and Valérie Lefranc for administrative support; the sponsor (Pole de Recherche Clinique at INSERM, Dr. Hélène Espérou); the Euclid Team (Dr Eric Frison) for data management; and the participants of the study and their families.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nbd.2023.106127>.

References

- Adler, D.H., Wisse, L.E.M., Ittyerah, R., Pluta, J.B., Ding, S.-L., Xie, L., Wang, J., Kadivar, S., Robinson, J.L., Schuck, T., Trojanowski, J.Q., Grossman, M., Detre, J.A., Elliott, M.A., Toledo, J.B., Liu, W., Pickup, S., Miller, M.L., Das, S.R., Wolk, D.A., Yushkevich, P.A., 2018. Characterizing the human hippocampus in aging and Alzheimer's disease using a computational atlas derived from ex vivo MRI and histology. *Proc. Natl. Acad. Sci. U. S. A.* 115, 4252–4257. <https://doi.org/10.1073/pnas.1801093115>.
- André, C., Rehel, S., Kuhn, E., Landeau, B., Moulinet, I., Tournon, E., Ourry, V., Le Du, G., Mézence, F., Tomadesso, C., de Flores, R., Bejanin, A., Sherif, S., Delcroix, N., Manrique, A., Abbas, A., Marchant, N.L., Lutz, A., Klimecki, O.M., Collette, F., Arenaza-Urquijo, E.M., Poinsnel, G., Vivien, D., Bertran, F., de la Sayette, V., Chételat, G., Rauchs, G., for the Medit-Ageing Research Group, 2020. Association of sleep-disordered breathing with Alzheimer disease biomarkers in community-dwelling older adults: a secondary analysis of a randomized clinical trial. *JAMA Neurol.* 77, 716. <https://doi.org/10.1001/jamaneurol.2020.0311>.
- Braak, H., Braak, E., 1991. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 82, 239–259.
- Burggren, A.C., Zeineh, M.M., Ekstrom, A.D., Braskie, M.N., Thompson, P.M., Small, G. W., Bookheimer, S.Y., 2008. Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E 4 carriers. *NeuroImage* 41, 1177–1183. <https://doi.org/10.1016/j.neuroimage.2008.03.039>.
- Cacciaglia, R., Molinuevo, J.L., Falcón, C., Brugulat-Serrat, A., Sánchez-Benavides, G., Gramunt, N., Esteller, M., Morán, S., Mingullón, C., Fauria, K., Gispert, J.D., for the ALFA study, 2018. Effects of APOE-ε4 allele load on brain morphology in a cohort of middle-aged healthy individuals with enriched genetic risk for Alzheimer's disease. *Alzheimers Dement.* 14, 902–912. <https://doi.org/10.1016/j.jalz.2018.01.016>.
- Chauveau, L., Kuhn, E., Palix, C., Felisatti, F., Ourry, V., de La Sayette, V., Chételat, G., de Flores, R., 2021. Medial temporal lobe subregional atrophy in aging and Alzheimer's disease: a longitudinal study. *Front. Aging Neurosci.* 13, 750154. <https://doi.org/10.3389/fnagi.2021.750154>.
- Cho, D.-H., Nakamura, T., Fang, J., Cieplak, P., Godzik, A., Gu, Z., Lipton, S.A., 2009. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. *Science* 324, 102–105. <https://doi.org/10.1126/science.1171091>.
- de Flores, R., La Joie, R., Chételat, G., 2015a. Structural imaging of hippocampal subfields in healthy aging and Alzheimer's disease. *Neuroscience* 309, 29–50. <https://doi.org/10.1016/j.neuroscience.2015.08.033>.
- de Flores, R., La Joie, R., Landeau, B., Perrotin, A., Mézence, F., de La Sayette, V., Eustache, F., Desgranges, B., Chételat, G., 2015b. Effects of age and Alzheimer's disease on hippocampal subfields: comparison between manual and FreeSurfer volumetry. *Hum. Brain Mapp.* 36, 463–474. <https://doi.org/10.1002/hbm.22640>.
- de Flores, R., Berron, D., Ding, S.-L., Ittyerah, R., Pluta, J.B., Xie, L., Adler, D.H., Robinson, J.L., Schuck, T., Trojanowski, J.Q., Grossman, M., Liu, W., Pickup, S., Das, S.R., Wolk, D.A., Yushkevich, P.A., Wisse, L.E.M., 2020a. Characterization of hippocampal subfields using ex vivo MRI and histology data: lessons for in vivo segmentation. *Hippocampus* 30, 545–564. <https://doi.org/10.1002/hipo.23172>.
- de Flores, R., Wisse, L.E.M., Das, S.R., Xie, L., McMillan, C.T., Trojanowski, J.Q., Robinson, J.L., Grossman, M., Lee, E., Irwin, D.J., Yushkevich, P.A., Wolk, D.A., 2020b. Contribution of mixed pathology to medial temporal lobe atrophy in Alzheimer's disease. *Alzheimers Dement.* 3–5. <https://doi.org/10.1002/alz.12079>.
- Dong, Q., Zhang, W., Wu, J., Li, B., Schron, E.H., McMahon, T., Shi, J., Gutman, B.A., Chen, K., Baxter, L.C., Thompson, P.M., Reiman, E.M., Caselli, R.J., Wang, Y., 2019. Applying surface-based hippocampal morphometry to study APOE-ε4 allele dose effects in cognitively unimpaired subjects. *NeuroImage: Clin.* 22, 101744. <https://doi.org/10.1016/j.nicl.2019.101744>.
- Donix, M., Burggren, A.C., Suthana, N.A., Siddarth, P., Ekstrom, A.D., Krupa, A.K., Jones, M., Martin-Harris, L., Ercoli, L.M., Miller, K.J., Small, G.W., Bookheimer, S.Y., 2010. Family history of Alzheimer's disease and hippocampal structure in healthy people. *Am. J. Psychiatry* 167, 1399–1406. <https://doi.org/10.1176/appi.ajp.2010.09111575>.
- Dounavi, M.-E., Mak, E., Wells, K., Ritchie, K., Ritchie, C.W., Su, L., O'Brien, J.T., 2020. Volumetric alterations in the hippocampal subfields of subjects at increased risk of dementia. *Neurobiol. Aging* 91, 36–44. <https://doi.org/10.1016/j.neurobiolaging.2020.03.006>.
- Falke, E., Nissano, J., Mitchell, T.W., Bennett, D.A., Trojanowski, J.Q., Arnold, S.E., 2003. Subicular dendritic arborization in Alzheimer's disease correlates with neurofibrillary tangle density. *Am. J. Pathol.* 163, 1615–1621. [https://doi.org/10.1016/S0002-9440\(10\)63518-3](https://doi.org/10.1016/S0002-9440(10)63518-3).
- Fouquet, M., Besson, F.L., Gonneaud, J., La Joie, R., Chételat, G., 2014. Imaging brain effects of APOE4 in cognitively normal individuals across the lifespan. *Neuropsychol. Rev.* 24, 290–299. <https://doi.org/10.1007/s11065-014-9263-8>.
- Gertje, E.C., Pluta, J., Das, S., Mancuso, L., Kliot, D., Yushkevich, P., Wolk, D., 2016. Clinical application of automatic segmentation of medial temporal lobe subregions in prodromal and dementia-level Alzheimer's disease. *J. Alzheimers Dis.: JAD* 1–11. <https://doi.org/10.3233/JAD-160014>.
- Gómez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J.H., Petersen, R.C., Parisi, J.E., Hyman, B.T., 1997. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann. Neurol.* 41, 17–24. <https://doi.org/10.1002/ana.410410106>.
- Hata, K., Nakamoto, K., Nunomura, A., Sone, D., Maikusa, N., Ogawa, M., Sato, N., Matsuda, H., 2019. Automated Volumetry of medial temporal lobe subregions in mild cognitive impairment and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 33, 206–211. <https://doi.org/10.1097/WAD.0000000000000318>.
- Honea, R.A., Vidoni, E., Harsha, A., Burns, J.M., 2009. Impact of APOE on the healthy aging brain: a voxel-based MRI and DTI study. *J. Alzheimers Dis.* 18, 553–564. <https://doi.org/10.3233/JAD-2009-1163>.
- Hsu, P.-J., Shou, H., Benzinger, T., Marcus, D., Durbin, T., Morris, J.C., Sheline, Y.I., 2015. Amyloid burden in cognitively normal elderly is associated with preferential hippocampal subfield volume loss. *J. Alzheimers Dis.: JAD* 45, 27–33. <https://doi.org/10.3233/JAD-141743>.
- Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., Elliott, C., Masliah, E., Ryan, L., Silverberg, N., 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 14, 535–562. <https://doi.org/10.1016/j.jalz.2018.02.018>.
- Jagust, W., 2016. Is amyloid-β harmful to the brain? Insights from human imaging studies. *Brain* 139, 23–30. <https://doi.org/10.1093/brain/awv326>.
- Jagust, W., 2018. Imaging the evolution and pathophysiology of Alzheimer disease. *Nat. Rev. Neurosci.* 19, 687–700. <https://doi.org/10.1038/s41583-018-0067-3>.
- Jeong, S., 2017. Molecular and cellular basis of neurodegeneration in Alzheimer's disease. *Mol. Cell* 40, 613–620. <https://doi.org/10.1016/j.molcel.2017.0096>.
- Kerchner, G.A., Berdnik, D., Shen, J.C., Bernstein, J.D., Fenesy, M.C., Deutsch, G.K., Wyss-Coray, T., Rutt, B.K., 2014. APOE ε4 worsens hippocampal CA1 apical neuropil atrophy and episodic memory. *Neurology* 82, 691–697. <https://doi.org/10.1212/WNL.0000000000000154>.
- Khan, V., Giampietro, V., Banaschewski, T., Barker, G.J., Bokke, A.L.W., Büchel, C., Conrod, P., Flor, H., Frouin, V., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Lemaitre, H., Nees, F., Paus, T., Pausova, Z., Rietschel, M., Smolka, M.N., Ströhle, A., Gallinat, J., Vellas, B., Soininen, H., Kloszewska, I., Tsohaki, M., Beckmann, P., Spenger, C., Villemagne, V.L., Masters, C.L., Muehlboeck, J.-S., Bäckman, L., Fratiglioni, L., Kalpouzos, G., Wahlund, L.-O., Schumann, G., Lovestone, S., Williams, S.C.R., Westman, E., Simmons, A., Alzheimer's Disease Neuroimaging Initiative, AddNeuroMed Consortium, Australian, Imaging, Biomarkers, and Lifestyle Study Research Group, IMAGEN consortium, 2017. A multi-cohort study of ApoE ε4 and amyloid-β effects on the Hippocampus in Alzheimer's disease. *J. Alzheimers Dis.* 56, 1159–1174. <https://doi.org/10.3233/JAD-161097>.
- La Joie, R., Visani, A.V., Baker, S.L., Brown, J.A., Bourakova, V., Cha, J., Chaudhary, K., Edwards, L., Iaccarino, L., Janabi, M., Lesman-Segev, O.H., Miller, Z.A., Perry, D.C., O'Neil, J.P., Pham, J., Rojas, J.C., Rosen, H.J., Seeley, W.W., Tsai, R.M., Miller, B.L., Jagust, W.J., Rabinovici, G.D., 2020. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci. Transl. Med.* 12, 1–13. <https://doi.org/10.1126/scitranslmed.aau5732>.
- La Joie, R., Visani, A.V., Lesman-Segev, O.H., Baker, S.L., Edwards, L., Iaccarino, L., Soleimani-Meigooni, D.N., Mellinger, T., Janabi, M., Miller, Z.A., Perry, D.C., Pham, J., Strom, A., Gorno-Tempini, M.L., Rosen, H.J., Miller, B.L., Jagust, W.J., Rabinovici, G.D., 2021. Association of APOE4 and clinical variability in Alzheimer disease with the pattern of tau- and amyloid-PET. *Neurology* 96, e650–e661. <https://doi.org/10.1212/WNL.00000000000011270>.
- Maass, A., Landau, S., Baker, S.L., Horng, A., Lockhart, S.N., La Joie, R., Rabinovici, G.D., Jagust, W.J., 2017. Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. *NeuroImage* 157, 448–463. <https://doi.org/10.1016/j.neuroimage.2017.05.058>.
- Martí-Juan, G., Sanroma-Guell, G., Cacciaglia, R., Falcon, C., Operto, G., Molinuevo, J.L., González Ballester, M.A., Gispert, J.D., Piella, G., Initiative, T.A.D.N., Study, T.A., 2021. Nonlinear interaction between APOE ε4 allele load and age in the hippocampal surface of cognitively intact individuals. *Hum. Brain Mapp.* 42, 47–64. <https://doi.org/10.1002/hbm.25202>.
- Mattsson, N., Insel, P.S., Nosheny, R., Tosun, D., Trojanowski, J.Q., Shaw, L.M., Jack, C. R., Donohue, M.C., Weiner, M.W., 2014. Emerging β-amyloid pathology and accelerated cortical atrophy. *JAMA Neurol.* 71, 725. <https://doi.org/10.1001/jamaneurol.2014.446>.
- Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A., Rosenbaum, R.S., 2006. The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr. Opin. Neurobiol.* 16, 179–190. <https://doi.org/10.1016/j.conb.2006.03.013>.

- Mueller, S.G., Schuff, N., Raptentsetsang, S., Elman, J., Weiner, M.W., 2008. Selective effect of Apo e4 on CA3 and dentate in normal aging and Alzheimer's disease using high resolution MRI at 4 T. *NeuroImage* 42, 42–48. <https://doi.org/10.1016/j.neuroimage.2008.04.174>.
- Mueller, S.G., Yushkevich, P.A., Das, S., Wang, L., Van Leemput, K., Iglesias, J.E., Alpert, K., Mezher, A., Ng, P., Paz, K., Weiner, M.W., 2018. Systematic comparison of different techniques to measure hippocampal subfield volumes in ADNI2. *NeuroImage: Clin.* 17, 1006–1018. <https://doi.org/10.1016/j.nicl.2017.12.036>.
- Nosheny, R.L., Insel, P.S., Mattsson, N., Tosun, D., Buckley, S., Truran, D., Schuff, N., Aisen, P.S., Weiner, M.W., 2019. Associations among amyloid status, age, and longitudinal regional brain atrophy in cognitively unimpaired older adults. *Neurobiol. Aging* 82, 110–119. <https://doi.org/10.1016/j.neurobiolaging.2019.07.005>.
- Palop, J.J., Mucke, L., 2016. Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nat. Rev. Neurosci.* 17, 777–792. <https://doi.org/10.1038/nrn.2016.141>.
- Parker, T.D., Cash, D.M., Lane, C.A.S., Lu, K., Malone, I.B., Nicholas, J.M., James, S.-N., Keshavan, A., Murray-Smith, H., Wong, A., Buchanan, S.M., Keuss, S.E., Sudre, C.H., Modat, M., Thomas, D.L., Crutch, S.J., Richards, M., Fox, N.C., Schott, J.M., 2019. Hippocampal subfield volumes and pre-clinical Alzheimer's disease in 408 cognitively normal adults born in 1946. *PLoS One* 14, e0224030. <https://doi.org/10.1371/journal.pone.0224030>.
- Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., Galluzzi, S., Marizzoni, M., Frisoni, G.B., 2016. Brain atrophy in Alzheimer's disease and aging. *Ageing Res. Rev.* 30, 1–24. <https://doi.org/10.1016/j.arr.2016.01.002>.
- Poisnel, G., Arenaza-Urquijo, E., Collette, F., Klimecki, O.M., Marchant, N.L., Wirth, M., de La Sayette, V., Rauchs, G., Salmon, E., Vuilleumier, P., Frison, E., Maillard, A., Vivien, D., Lutz, A., Chételat, G., 2018. The age-well randomized controlled trial of the Medit-ageing European project: effect of meditation or foreign language training on brain and mental health in older adults. *Alzheimers Dement.: Transl. Res. Clin. Interv.* 4, 714–723. <https://doi.org/10.1016/j.trci.2018.10.011>.
- Price, J.L., Morris, J.C., 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann. Neurol.* 45, 358–368. [https://doi.org/10.1002/1531-8249\(199903\)45:3<358::aid-ana12>3.0.co;2-x](https://doi.org/10.1002/1531-8249(199903)45:3<358::aid-ana12>3.0.co;2-x).
- Reiter, K., Nielson, K.A., Durgerian, S., Woodard, J.L., Smith, J.C., Seidenberg, M., Kelly, D.A., Rao, S.M., 2017. Five-year longitudinal brain volume change in healthy elders at genetic risk for Alzheimer's disease. *J. Alzheimers Dis.* 55, 1363–1377. <https://doi.org/10.3233/JAD-160504>.
- Salvadó, G., Grothe, M.J., Groot, C., Moscoso, A., Schöll, M., Gispert, J.D., Ossenkoppele, R., for the Alzheimer's Disease Neuroimaging Initiative, 2021. Differential associations of APOE-ε2 and APOE-ε4 alleles with PET-measured amyloid-β and tau deposition in older individuals without dementia. *Eur. J. Nucl. Med. Mol. Imaging* 48, 2212–2224. <https://doi.org/10.1007/s00259-021-05192-8>.
- Small, S.A., Schobel, S.A., Buxton, R.B., Witter, M.P., Barnes, C.A., 2011. A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nat. Rev. Neurosci.* 12, 585–601. <https://doi.org/10.1038/nrn3085>.
- Spires-Jones, T.L., Hyman, B.T., 2014. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron* 82, 756–771. <https://doi.org/10.1016/j.neuron.2014.05.004>.
- Therriault, J., Benedet, A.L., Pascoal, T.A., Mathotaarachchi, S., Chamoun, M., Savard, M., Thomas, E., Kang, M.S., Lussier, F., Tissot, C., Parsons, M., Qureshi, M.N.I., Vitali, P., Massarweh, G., Soucy, J.-P., Rej, S., Saha-Chaudhuri, P., Gauthier, S., Rosa-Neto, P., 2020. Association of Apolipoprotein E ε4 with medial temporal tau independent of amyloid-β. *JAMA Neurol.* 77, 470. <https://doi.org/10.1001/jamaneurol.2019.4421>.
- Tzioras, M., Davies, C., Newman, A., Jackson, R., Spires-Jones, T., 2019. Invited review: APOE at the interface of inflammation, neurodegeneration and pathological protein spread in Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* 45, 327–346. <https://doi.org/10.1111/nan.12529>.
- Van Etten, E.J., Bharadwaj, P.K., Hishaw, G.A., Huentelman, M.J., Trouard, T.P., Grilli, M.D., Alexander, G.E., 2021. Influence of regional white matter hyperintensity volume and apolipoprotein E ε4 status on hippocampal volume in healthy older adults. *Hippocampus* 31, 469–480. <https://doi.org/10.1002/hipo.23308>.
- Veldsman, M., Nobis, L., Alfaro-Almagro, F., Manohar, S., Husain, M., 2021. The human hippocampus and its subfield volumes across age, sex and APOE ε4 status. *Brain Communications* 3, fcaa219. <https://doi.org/10.1093/braincomms/fcaa219>.
- Vilor-Tejedor, N., Evans, T.E., Adams, H.H., González-de-Echavarrri, J.M., Molinuevo, J.L., Guigo, R., Gispert, J.D., Operto, G., 2021. Genetic influences on hippocampal subfields: an emerging area of neuroscience research. *Neurol. Genet.* 7, e591 <https://doi.org/10.1212/NXG.0000000000000591>.
- Voineskos, A.N., Winterburn, J.L., Felsky, D., Pipitone, J., Rajji, T.K., Mulsant, B.H., Chakravarty, M.M., 2015. Hippocampal (subfield) volume and shape in relation to cognitive performance across the adult lifespan. *Hum. Brain Mapp.* 36, 3020–3037. <https://doi.org/10.1002/hbm.22825>.
- Whitwell, J.L., Tosakulwong, N., Weigand, S.D., Senjem, M.L., Lowe, V.J., Gunter, J.L., Boeve, B.F., Knopman, D.S., Dickerson, B.C., Petersen, R.C., Jack, C.R., 2013. Does amyloid deposition produce a specific atrophic signature in cognitively normal subjects? *NeuroImage: Clin.* 2, 249–257. <https://doi.org/10.1016/j.nicl.2013.01.006>.
- Wilson, R.S., Yu, L., Trojanowski, J.Q., Chen, E.-Y., Boyle, P.A., Bennett, D.A., Schneider, J.A., 2013. TDP-43 pathology, cognitive decline, and dementia in old age. *JAMA Neurol.* 70, 1418–1424. <https://doi.org/10.1001/jamaneurol.2013.3961>.
- Wishart, H.A., Saykin, A.J., McAllister, T.W., Rabin, L.A., McDonald, B.C., Flashman, L.A., Roth, R.M., Mamourian, A.C., Tsongalis, G.J., Rhodes, C.H., 2006. Regional brain atrophy in cognitively intact adults with a single APOE 4 allele. *Neurology* 67, 1221–1224. <https://doi.org/10.1212/01.wnl.0000238079.00472.3a>.
- Wisse, L.E.M., Chételat, G., Daugherty, A.M., Flores, R., Joie, R., Mueller, S.G., Stark, C.E.L., Wang, L., Yushkevich, P.A., Berron, D., Raz, N., Bakker, A., Olsen, R.K., Carr, V.A., 2021. Hippocampal subfield volumetry from structural isotropic 1 mm3 MRI scans: a note of caution. *Hum. Brain Mapp.* 42, 539–550. <https://doi.org/10.1002/hbm.25234>.
- Wisse, L.E., Xie, L., Das, S.R., de Flores, R., Hansson, O., Habes, M., Doshi, J., Davatzikos, C., Yushkevich, P.A., Wolk, D.A., 2022. Tau pathology mediates age effects on medial temporal lobe structure. *Neurobiol. Aging* 109, 135–144. <https://doi.org/10.1016/j.neurobiolaging.2021.09.017>.
- Wolk, D.A., Das, S.R., Mueller, S.G., Weiner, M.W., Yushkevich, P.A., 2017. Medial temporal lobe subregional morphometry using high resolution MRI in Alzheimer's disease. *Neurobiol. Aging* 49, 204–213. <https://doi.org/10.1016/j.neurobiolaging.2016.09.011>.
- Xie, L., Wisse, L.E.M., Pluta, J., de Flores, R., Piskin, V., Manjón, J.V., Wang, H., Das, S.R., Ding, S.-L., Wolk, D.A., Yushkevich, P.A., 2019. Automated segmentation of medial temporal lobe subregions on in vivo T1-weighted MRI in early stages of Alzheimer's disease. *Hum. Brain Mapp.* 40, 3431–3451. <https://doi.org/10.1002/hbm.24607>.
- Yamazaki, Y., Zhao, N., Caulfield, T.R., Liu, C.-C., Bu, G., 2019. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nat. Rev. Neurosci.* 15, 501–518. <https://doi.org/10.1038/s41582-019-0228-7>.
- Yushkevich, P.A., Pluta, J.B., Wang, H., Xie, L., Ding, S.-L., Gertje, E.C., Mancuso, L., Kliot, D., Das, S.R., Wolk, D.A., 2015. Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. *Hum. Brain Mapp.* 36, 258–287. <https://doi.org/10.1002/hbm.22627>.