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# IMPACT OF SEX AND APOE- $\epsilon$ 4 GENOTYPE ON REGIONAL BRAIN METABOLISM IN ALZHEIMER'S DISEASE

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## ABSTRACT

Age, sex and APOE- $\epsilon$ 4 genotype have been identified as the strongest predictors of the risk of developing Alzheimer's Disease (AD). This work models the pathological progression of regional brain hypometabolism, using mixed-effect models with latent time variable and longitudinal FDG-PET data. Statistical comparisons then disentangle the effects of sex and APOE- $\epsilon$ 4 genotype on the onset age and pace of progression of hypometabolism in each brain region, while correcting for education level. They provide a brain map of the regions with earlier and/or faster alterations of the metabolism. We show that females are associated with faster hypometabolism in the caudate nuclei, the thalamus and right temporal and medial-occipital lobes, while APOE- $\epsilon$ 4 is associated with earlier hypometabolism in the limbic system (hippocampus, parahippocampus and amygdala) and temporal lobe.

**Index Terms**— Longitudinal studies, Alzheimer's Disease, Brain hypometabolism, Sexual dimorphism

## 1. INTRODUCTION

### 1.1. Motivation

Alzheimer's Disease (AD) is a neurodegenerative pathology that accounts for more than 60% of the 55 millions dementia cases worldwide. A silent prodromal phase shows accumulation of alterations in the brain without specific symptoms, eventually leading to a progressive cognitive decline that translates into a loss of autonomy for daily tasks. Age, female sex and APOE genotype are the strongest three risk factors for AD [1]. Firstly, AD incidence approximately doubles every five years after the age of 60, reaching a prevalence of almost 50% over 85 years old [2]. Secondly, nearly two thirds of patients are female and it is documented that women's cognitive decline and neurodegeneration happen faster compared to men in AD, while being comparatively better preserved in healthy populations [3]. Lastly, The  $\epsilon$ 4-allele of APOE increases AD risk by approximately 4-fold when inherited in one copy and by greater than 10-fold for two doses of the allele [4]. Exhibiting different disease progression patterns across subgroups of patients, such as men vs. women or APOE mutations carriers vs non-carriers, can pave the way for precision medicine and differentiated diagnosis and care.

Neuroimaging data allow the monitoring of the early stages of neurodegeneration before the onset of the symptoms and clinical diagnosis. Structural modalities such as MRI measure the regional loss of grey/white matter while functional modalities such as  $^{18}$ F-DG-Positron Emission Tomography (PET) or functional MRI assess changes in brain activity, unveiling distinct facets of the disease occurring before the clinical phase. Specifically, patients with AD have abnormally low PET measurements of the cerebral metabolic rate for glucose in the brain, and the patterns of hypometabolism are specific to AD [5, 6].

Since AD is a progressive disease, the collection of repeated measurements for each patient allows to leverage information about the dynamics of the alterations, otherwise impossible to notice in cross-sectional studies. Longitudinal models have been applied to the study of cognitive decline [7, 8] and atrophy in regions of interest [8, 9]. Given a disease progression model, one can study the impact of risk factors on the dynamics of the observed alterations. However, longitudinal models have scarcely been applied to the progression of functional imaging data, and the influence of risk factors on alterations patterns has not been precisely described.

In this context, studying the influence of covariates such as sex, APOE genotype and education level on the longitudinal patterns of progression of regional brain hypometabolism could elucidate another aspect of the heterogeneity of AD. Mixed-effects models offer a suitable framework for the study of progression patterns since they describe each patient's trajectory with few interpretable parameters that can be compared for different groups of patients.

### 1.2. Related work

The impact of covariates such as sex and APOE status on cognitive decline and atrophy have been well studied [10, 11, 12], highlighting steeper cognitive decline and neurodegeneration for women and different associations with previous conditions and modifiable risk factors such as BMI. Multiple cross-sectional studies have also established that men and women display different age-related metabolic decrease in healthy ageing and pathological progression [13, 14]. The menopausal transition seems to induce hypometabolism in

the same regions as AD [15], potentially acting as a substrate for a neurological condition. It is also known that APOE- $\epsilon 4$  carriers show steeper decrease of energy metabolism in the regions affected by AD [16]. In [17], authors show that the impact of APOE mutations is stronger for women than for men regarding hypometabolism and atrophy.

To the best of our knowledge no study has yet modeled the joint effects of sex and APOE genotype on the loss of energy metabolism in the brain for AD patients through the use of longitudinal FDG-PET databases. To summarize our contribution, we model the decrease in regional PET measurements using univariate mixed-effects models with an interpretable formulation that describes the onset and pace of decline. We assess the disentangled impact of each covariate on the onset and pace of decline for all anatomical regions of the AAL2 brain atlas. For reference, we compare our results to the previously reported associations between the mentioned risk factors on atrophic patterns across AD progression.

## 2. MATERIALS AND METHODS

### 2.1. Datasets and data processing

We used data from the Alzheimer Disease Neuroimaging Initiative (ADNI). We selected patients with a confirmed AD diagnosis and only kept patients with at least two visits with a FDG-PET scan. Regional measurements are obtained using the "pet-volume" pipeline of Clinica [18]. This pipeline first performs intra-subject registration of the PET image into the space of the subject's t1-weighted MR image using SPM12. The PET image is corrected for partial volume effects using the PETPVC toolbox, and then spatially normalized into MNI space using the DARTEL deformation model of SPM, and intensity normalized using the average PET uptake in the pons. Finally, the average PET uptake is computed for a set of regions obtained from the AAL2 atlas in MNI space.

	Men	Women
Patients	152	108
Visits	581	413
Follow-up (y)	$2.8 \pm 1.9$	$3.1 \pm 2.0$
Age at baseline	$75.2 \pm 6.7$	$73.8 \pm 7.3$
Education (y)	$16.0 \pm 2.9$	$15.2 \pm 2.7$
APOE (0/1/2)	53/74/25	32/56/20
MMSE	$24.4 \pm 3.9$	$23.5 \pm 4.7$
ADASCog13	$25.7 \pm 9.5$	$28.6 \pm 12.0$

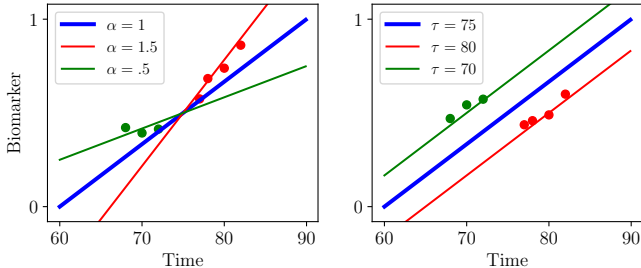
**Table 1.** Cohort demographics. Numerical fields are in the form *mean*  $\pm$  *std.* (0/1/2) represents the number of copies of the  $\epsilon 4$  allele. Cognitive measurements are for all visits.

### 2.2. Longitudinal modeling

Mixed-effects models describe each patient's progression over time as a variation – the random effects – around the average population trajectory – the fixed effects. This study focuses on univariate models, calibrated on the repeated measurements for one brain region at a time. Linear mixed-effects models are widely used for longitudinal modeling and assume that features evolve according to straight lines over time. Inter-patients variability is characterised by individual slopes and intercepts. The slope is the pace of decline of a patient for the given feature, but the intercept is less meaningful. In that setting, we parameterise the inter-subjects variability as the combined effects of an individual onset age, and a pace of decline as suggested in [19]. The onset age is an horizontal intercept and describes the age at which a patient crosses a chosen threshold, and the pace of decline as the slope. Both these temporal parameters allow to align all patients on a common progression timeline. Namely, given a family of feature observations  $\{y_{i,j}\}$  at times  $\{t_{i,j}\}$  where  $1 \leq i \leq N$  indexes the  $N$  patients and  $1 \leq j \leq N_i$  indexes the  $N_i$  visits of patient  $i$ , we resort to the mixed-effect generative model

$$y_{i,j} = p_0 + v_0 \left( \alpha_i * (t_{i,j} - \tau_i) + t_0 \right) + \varepsilon_{i,j}$$

where  $\alpha_i$  and  $\tau_i$ , the *progression pace* and *onset age* of patient  $i$ , are called the individual parameters. Gaussian priors are chosen for the noise  $\varepsilon_{i,j} \sim \mathcal{N}(0, \sigma_\varepsilon^2)$  and random effects  $\tau_i \sim \mathcal{N}(t_0, \sigma_\tau^2)$  and the log-acceleration  $\xi_i = \log(\alpha_i) \sim \mathcal{N}(0, \sigma_\xi^2)$  so that progression paces are distributed around 1. It should be noted that the product of  $\alpha_i$  and  $\tau_i$  makes the time warp non-linear although the trajectories are straight lines.



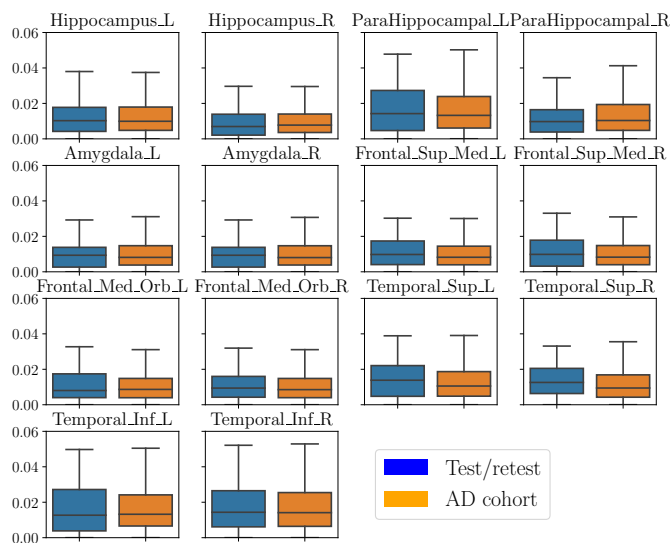
**Fig. 1.** Illustration of the mixed-effect model with time-warp. Blue curve is the average trajectory (parameterised by  $t_0$ ,  $p_0$  and  $v_0$ ) and red and green curves illustrate the effect of progression pace ( $\alpha = e^\xi$ ) and onset age ( $\tau$ ) to match individual measurements (isolated dots) to a continuous trajectory.

### 2.3. Estimation and validation

These longitudinal statistical models are part of a family of geometric models [20, 21]. Estimation can be performed

using Maximum a Posteriori estimation of both random and fixed effects with the MCMC-SAEM procedure in which the estimation step of an EM algorithm is replaced by a stochastic approximation. See [22] for details on the likelihood and proof of convergence and stability. The model and its estimation procedure are implemented in the open-source Leaspy software.

This family of models allows the use of logistic or exponential functions instead of straight-lines modeling in order to allow non-linearities [21]. However, the estimated noise was not improved compared to linear functions. Parametric regression methods that learn the exact shape of the progression [23, 24] also exist but add a computational burden without improving the estimated noise of the fit. To further validate the quality of the fit, we use the baseline and follow-up scans of stable cognitively normal and amyloid-negative subjects in ADNI below the age of 75, as a proxy to test/retest data for measurement uncertainty (116 subjects, 232 visits with an average follow-up time of 16 months). Fig. 2 displays the distributions of this estimated test/retest and of the reconstruction errors of the longitudinal model. Distributions largely overlap, and reconstruction errors fall close to the measurements uncertainty, which hints that our models could not be improved without overfitting.



**Fig. 2.** Distribution of reconstruction errors for the longitudinal model with measurements uncertainty for reference. For readability, only a subset of the 120 regions is displayed.

#### 2.4. Statistical analysis

Once the univariate models are calibrated, we have a family of patient-wise onset ages and progression paces for each

feature. We proceed to statistical testing of the differences between subgroups. We perform covariance analysis using ordinary least squares to regress the individual parameters with respect to sex, number of APOE- $\epsilon$ 4 alleles and educational level of each patient. This evaluates the association of each covariate after correcting for the other ones, and also the significance of the corresponding association. We use False Discovery Rate to correct the  $p$ -values for multiple comparisons.

### 3. RESULTS AND DISCUSSION

APOE- $\epsilon$ 4 mutation carriers display significantly earlier hypometabolism in the limbic system (hippocampus, parahippocampus, amygdala) and caudate nuclei. Female patient display faster progression of hypometabolism in the caudate nuclei, thalamus, right temporal lobe and right medial-occipital lobe. No significant association is recovered in any other parts of the brain. Table 2 reports the regression coefficients and significance for all regions with corrected  $p$ -value below the .05 threshold. The impact of sex seems to be lateralized with a stronger association on the cortex of the right hemisphere, while associations with APOE genotype are symmetric.

Higher education significantly correlates with earlier hypometabolism in parts of the frontal lobe, the entire temporal lobe as well as in the hippocampus, parahippocampus, amygdalas, pallidum and thalamus. In these regions, patients with highest education show average onset ages 8 to 12 years smaller than patients with the least education. Although counter-intuitive, these results are documented [25, 14] and can be explained by the cognitive reserve hypothesis. This hypothesis stipulates that higher education and intellectual attainment allow patients to have better cognitive results for similar brain alterations. Since our cohort only keeps cognitively impaired patients with a confirmed AD diagnosis, it only features educated patients with a higher degree of functional alterations than their less-educated counterparts.

In [26], the same analysis is applied to t1-MRI scans in order to evaluate the effects of sex and APOE genotype on the dynamics of regional atrophy. Comparing both works reveals that brain hypometabolism in the pathological brain showcases more homogeneous progression profiles across the sub-groups than the atrophic patterns, especially regarding the impact of sex which proved to be the most important risk factor for brain atrophy. While higher education shows no significant correlation with atrophic patterns, it does display strong correlations with brain hypometabolism. It is known that regional glucose metabolic abnormalities are not solely the result of atrophy in Alzheimer’s disease [27] and different associations with risk factors are not surprising. The congruent findings between both studies are that the temporal lobe shows faster alterations for women and APOE- $\epsilon$ 4 has a strong

## Associations between female sex and pace of decline

	coeff	$p_{val}$
Caudate_L	.18	2.9e-4
Caudate_R	.21	1.0e-4
Thalamus_L	.010	5.0e-2
Thalamus_R	.023	3.9e-2
Temporal_sup_R	.021	2.6e-3
Temporal_mid_R	.012	3.7e-3
Temporal_inf_R	.025	1.6e-2
SupraMarginal_R	.0084	1.9e-2
Occipital_mid_R	.079	2.8e-2
Fusiform_R	.012	7.6e-3
Lingual_R	.029	4.1e-2

	coeff	$p_{val}$
Hippocampus_L	-3.2	9.1e-5
Hippocampus_R	-2.8	5.4e-5
ParaHippocampus_L	-3.1	5.1e-4
ParaHippocampus_R	-3.3	4.6e-8
Amygdala_L	-4.1	6.7e-5
Amygdala_R	-4.3	7.3e-5
Caudate_L	-1.6	5.8e-3
Temporal_Pole_Sup_L	-1.3	2.5e-2
Temporal_Pole_Sup_R	-1.7	1.3e-2
Temporal_Pole_Mid_L	-2.1	7.8e-4
Temporal_Pole_Mid_R	-2.5	3.0e-3
Temporal_Inf_L	-2.8	1.1e-2
Temporal_Inf_R	-2.5	3.2e-2

**Table 2.** Both tables report the coefficient of association as well as the corrected  $p$ -value for each region showing significant impact of the risk factor. First table reads for instance: "women show a steeper decrease in metabolism in the right thalamus by 2.3%" and second table reads for instance: "for each copy of  $\epsilon$ 4 allele, the right hippocampus is expected to start to decline 2.8 years earlier". Female sex correlates with faster decline and  $\epsilon$ 4 count correlates with earlier decline for all the reported associations. No significant association between sex and onset or APOE status and pace is reported.

influence on the alterations in the limbic system.

A few methodological limitations need to be acknowledged. First, changing the brain atlas and spatial granularity might yield different results. One anatomical region that is positively associated with a covariate can span many ROIs or on the other hand be split between ROIs and prevent the detection of the true underlying association. Secondly, there is no such thing as test-retest for PET measurements and the proxy we used slightly overestimates the measurement error since even healthy patients show a decrease of glucose metabolism over time, which can explain why longitudinal errors are actually lower than the "measurements uncertainty" for most features. Lastly, no open-access cohort provides enough repeated FDG-PET scans to replicate the findings.

#### 4. CONCLUSION

Building on the observation that risk factors such as sex, APOE genotype and education level influence the progression of AD pathology over time, we quantified their impact on brain hypometabolism regarding onset age and pace of decline.  $\epsilon$ 4 alleles correlate with earlier hypometabolism in the limbic system and temporal lobes while female sex correlates with faster hypometabolism in the caudate nuclei, thalamus and right temporal and medial-occipital lobes. The sexual dimorphism of hypometabolism is weaker than that of atrophic patterns. These results provide insights into the not well-understood heterogeneity of AD and emphasize the need to provide care and analyse clinical trials results in a

way that accounts for sex and APOE genotype.

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#### 5. COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval was not required as confirmed by the license attached with the open access data.

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