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Impact of sex and APOE- ϵ 4 genotype on patterns of regional brain atrophy in Alzheimer's Disease and healthy ageing.

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Abstract

Age, sex and APOE- ϵ 4 genotype have been identified as the strongest predictors of the risk of developing Alzheimer's Disease (AD). It is well documented that women's cognitive decline and neurodegeneration happen faster compared to men in AD, while being comparatively better preserved in healthy populations. This work analyses regional cortical thinning and brain atrophy over time using non-linear mixed-effect models, and assesses the association of both sex and APOE- ϵ 4 genotype with the onset and pace of atrophy in each region. Statistical comparisons allow to isolate the effect of both those genetic covariates and to provide a brain map of the regions whose atrophic patterns are most affected. This study is provided for both AD progression and healthy ageing. We found that female sex is a stronger risk factor for neurodegeneration than APOE- ϵ 4 genotype in AD, and women experience much faster atrophic rates, but slightly later onset, after correcting for the APOE status. APOE- ϵ 4 genotype lead to earlier and faster atrophy for most regions of the brain for AD patients but not for healthy patients. Healthy patients with higher education experience slightly delayed atrophy but not patients with neurodegeneration. Lastly, for a cohort of patients with mild cognitive impairment, sex shows the same association as for the cognitively normal cohort, while APOE- ϵ 4 genotype shows the same association as in the AD cohort.

Keywords:

Alzheimer's Disease, Longitudinal studies, Brain atrophy, Genetic covariates, Sexual dimorphism, Ageing

1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative pathology that accounts for more than 70% of the about 55 millions dementia cases worldwide (Alzheimer's Association et al., 2016). A silent phase, referred to as prodromal phase, shows accumulation of structural alterations in the brain without specific symptoms, eventually leading to a progressive cognitive decline that translates into a loss of the patient's autonomy for daily tasks, with impaired mnemonic, visuospatial and communicative functions as well as unusual behaviors such as paranoia and aggressiveness. For people under the age of 75, the incidence of AD has been estimated below 1.0%, while it reaches 8.4% (Hebert et al., 1995, 2010) for patients over 85, making older age the most important risk factor of the disease. Other risk factors have been identified with certainty and are briefly presented below.

The second most important risk factor is often said to be the presence of hereditary gene mutations (Tanzi, 2012). More precisely, the inheritance of AD can be of two types. On one hand, rare autosomal dominant mutations in APP, PSEN1, and PSEN2, that encode amyloid precursors and presenilin proteins, leading to early-onset (<60 years old) familial AD, which accounts for 5% of cases (Tanzi, 2012), and are often dismissed from studies on risk factors because of their low prevalence and understood causality. On the other hand, frequent gene polymorphisms, such as the ϵ 4 and ϵ 2 variants of the APOE gene, can influence susceptibility for 50% of the common late-onset AD (Tanzi, 2012). Genome wide association studies also identified a handful of other loci as potential risk factors, but thus far, the only gene variant considered to be an established risk factor for late onset AD is the APOE- ϵ 4 allele (Saunders et al., 1993; Farrer et al., 1997; Alzheimer's Association et al., 2016). The APOE gene provides the blueprint for the apolipoprotein E that transports cholesterol in the bloodstream and helps bind A β to cerebrospinal fluid, effectively clearing the brain of excess A β . The

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20 presence of $\epsilon 4$ allele hinders $A\beta$ clearance and leads to reduced neuronal injury response (Mahley and Huang, 2012), and
21 in turns correlate with higher AD risks.

22 The other genetic factor that is known to impact AD risk rates is the sex of patients. Two thirds of AD patients are
23 women (Alzheimer’s Association et al., 2016) and their cognitive decline is faster than for men (Laws et al., 2016). By
24 contrast, healthy ageing tends to display delayed cognitive decline and structural alterations for women. Beam et al. (2018)
25 review conflicting studies on the topic of incidence rates and reach the conclusion that before the age of 75, no significant
26 difference in incidence rates is detected, while incidence rates get significantly higher for women than for men after that
27 inflexion point. The longer longevity of women has long been thought to be the sole cause for this discrepancy. However,
28 the loss of the protective effects of estrogens during menopause, demonstrated in vitro and in vivo (Czlonkowska et al.,
29 2006; Genazzani et al., 2007), has also been suggested as a cause. Evidence also highlight a faster loss of autonomy but a
30 longer lifespan after diagnosis for women (Sinforiani et al., 2010). These facts raise the question of a sexual dimorphism
31 of AD. A precise understanding of the distinct patterns of structural and functional brain alterations over time is still
32 lacking. Accurate descriptions of those patterns could help to implement better practices to care for both men and women.
33 Besides, women are still underrepresented in clinical trials (Martinkova et al., 2021) and only 15% of trials report results
34 stratified by sex (Schwartz and Weintraub, 2021), although this proportion increases in more recent studies.

35 Another often-mentioned risk factor is the education level. According to the cognitive reserve hypothesis, having
36 more years of education increases the connections between neurons and enables the brain to compensate for the early
37 changes of Alzheimer’s by using alternate routes of neuron-to-neuron communication to complete a cognitive task (Roe
38 et al., 2007; Stern, 2012). Women are believed to benefit even more from higher education than men, albeit receiving less
39 education (Subramaniapillai et al., 2021). Mungas et al. (2018) confirm that education is an indicator of cognitive reserve,
40 but that the protective effects on cognition are depleted as neurodegeneration progresses.

41
42 Building on the observation that the influence of sex on the progression of AD is not well understood, and that
43 APOE- $\epsilon 4$ status is the strongest known genetic variant associated with AD, this work aims to describe the disentangled
44 contributions of both those genetic factors on patterns of structural brain alterations, while accounting for biases due to
45 varying education level. Such alterations, that are visible through MRI scans, reveal neurodegeneration occurring before
46 the onset of the cognitive symptoms, and is thus crucial to understanding the early stages of the disease and for the
47 design of drug trials. Leveraging the information from repeated measurements of cortical thicknesses and the volumes
48 of subcortical regions allows to describe each patient’s atrophic dynamics and compare across populations. Our goal is
49 thus to provide a map of the brain regions that show significant correlation between sex or APOE- $\epsilon 4$ status and onset
50 age and pace of regional atrophy. We provide this analysis for AD diagnosed and cognitively normal patients in order to
51 emphasize the specificities of Alzheimer’s progression.

52 *1.1. Related work*

53 *Cross-sectional studies.* Over the course of AD progression, the link between cognitive decline and various covariates
54 such as BMI (Subramaniapillai et al., 2021), cardiac pathologies, APOE- $\epsilon 4$ genotype (Altmann et al., 2014; Sampedro
55 et al., 2015; Neu et al., 2017; Buckley et al., 2018) and sex have been explored, highlighting a higher impact of comor-
56 boidities and APOE- $\epsilon 4$ genotype for women on the severity of the disease symptoms. Ferretti et al. (2018) and Laws et al.
57 (2018) review the state of knowledge about the differences across sexes in AD clinical manifestations, biomarkers patterns
58 and risk factors.

59 On the other hand, healthy ageing displays comparatively more spared alteration profiles for women compared to men,
60 for both brain atrophy and cognitive decline. Seminal works dating back to the beginning of in-vivo imaging modalities
61 report higher size decreases in men for average brain (Coffey et al., 1998) and frontal and temporal lobes (Cowell et al.,
62 1994). Many studies have since provided more insights into the differences between sexes for cognitive decline and link
63 with comorbidities (McCarrey et al., 2016; Armstrong et al., 2019), exhibiting opposite correlation than in Alzheimer’s
64 studies. Jack et al. (2015) exhibit associations between male sex, worse memory and higher hippocampal atrophy.

65 *Longitudinal studies.* The collection of repeated measurements of neuroimaging data and clinical assessment allows a
66 finer understanding of pathological pathways. Notorious modeling approaches include event-based models (Fonteijn

67 et al., 2012; Young et al., 2014), Gaussian-Process models (Lorenzi et al., 2019; Abi Nader et al., 2020), Deep Learning
68 methods (Couronné et al., 2019; Sauty and Durrleman, 2022a) and mixed-effects models. Application of such longitu-
69 dinal models are frequent for the assessment of cognitive decline (Ito et al., 2011; Samtani et al., 2012; Bilgel et al.,
70 2014; Jedynak et al., 2012; Fonteijn et al., 2012; Schiratti et al., 2015a; Koval et al., 2017a; Raket, 2020) but less used
71 for imaging features. Bernal-Rusiel et al. (2013a) advocate the use of linear mixed-effects models (LME) for progression
72 models of neuroimaging data and apply LME to a mesh of control points of cortical thickness in a mass-univariate setting
73 in Bernal-Rusiel et al. (2013b). Sabuncu et al. (2014) correlate these progression models with diagnosis in order to exhibit
74 regions of the cortex that are most representative of the cognitive state of patients. Other studies also apply progression
75 models to a few ROIs of the brain (Risacher et al., 2010; Tustison et al., 2019; Li et al., 2020) in order to display the
76 regions that correlate most with diagnosis. Applying this kind of modeling to a study of sex differences, Hua et al. (2010)
77 confirm that atrophy rates are higher for female than male patients and they decrease with age, while Sangha et al. (2021)
78 explain that brain volumes and cortical thicknesses are consistently smaller for cognitively normal males after accounting
79 for age, and that the differences get smaller as cohorts are chosen at a more advanced state of cognitive decline, until
80 they get indistinguishable for confirmed AD patients. Many studies report the impact of APOE polymorphisms on brain
81 atrophy for AD progression and link $\epsilon 4$ with faster cortical thinning (Gutiérrez-Galve et al., 2009; Abushakra et al., 2020)
82 and hippocampal atrophy (Liu et al., 2015; Li et al., 2016), with increasing effects as patients get older (Kim et al., 2018).

84 1.2. Contributions

85 Overall, many studies explored the differences between men and women regarding AD progression and healthy brain
86 ageing, as well as the influence of APOE polymorphisms. However, many of them rely on cross-sectional data that
87 miss important information about the progression of the disease. Longitudinal tools have been proposed to leverage such
88 information, and have been successfully applied to biomarkers for disease progression models. However, these studies
89 have either focused on the patterns of cognitive decline, or on a chosen set of ROIs to assess structural alterations, thus
90 not providing a detailed map of the differences across the brain. Some longitudinal studies have proposed analysis of
91 cortical thinning or brain atrophy with a high spatial resolution, however the focus has always been put on finding re-
92 gions that correlate best with diagnosis in order to obtain valuable information about the brain alterations most specific
93 to AD. To the best of our knowledge, no study has yet provided a quantitative comparison between male and female
94 patterns of structural alterations over time, while accounting for APOE- $\epsilon 4$ genotype, in order to provide a map of the
95 brain regions that showcase distinct age-related alterations profiles. Besides, former works usually focus on the impact
96 of one single factor, while only a joint analysis of both the genetic factors allows to isolate the contributions from each one.

97
98 In this context, it seems relevant to further explore the differences between men and women regarding the onset
99 and pace of alterations of the brain in both normal and AD progression, with a high degree of spatial resolution, while
100 accounting for APOE- $\epsilon 4$ genotype and education level. Longitudinal studies allow to leverage information about the
101 progression over time, while mixed-effect models allow for an interpretable modeling of each feature's trajectory across
102 time. To sum up our contributions :

- 103 • We model regional cortical thinning and brain atrophy using non-linear mixed-effect models, and propose a formu-
104 lation that disentangles the onset age and the pace of atrophy,
- 105 • for each region, we proceed to a multivariate regression for the individual parameters with regard to female sex,
106 APOE- $\epsilon 4$ allele count and education level, in order to isolate the effect of each factor,
- 107 • we obtain a brain map of p -values that assess how significantly each factor influences the patterns of atrophy over
108 time, when corrected for the other covariates,
- 109 • we display the regions that differ the most regarding onset age and pace of structural atrophy for the chosen covari-
110 ate, for both healthy and AD progression.

111 This statistical pipeline addresses the lack of understanding of the influence of sex and APOE on structural brain
112 alterations, and disentangles the joint effects of the multiple risk factors.

113 2. Material and Methods

114 *Data sets.* We performed the analysis on publicly available data from all waves (GO,1,2,3) of the Alzheimer’s Disease
 115 Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), as it provides repeated MRI scans for both cognitively
 116 normal elderly and AD patients. The ADNI was launched in 2003 as a public-private partnership and its primary goal
 117 has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological
 118 markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive
 119 impairment (MCI) and early Alzheimer’s disease (AD). We selected all patients with at least 2 visits with a MRI scan and
 120 split the patients in three cohorts : an AD cohort with patients with at least one confirmed AD diagnosis, an healthy cohort
 121 with patients who are diagnosed cognitively normal at every visit and an intermediate cohort of patients with at least one
 122 MCI diagnosis but no AD conversion. Table 1 reports the demographics for ADNI patients that present at least 2 visits
 123 with a MRI scan.

	AD cohort		MCI cohort		Healthy cohort	
	Male	Female	Male	Female	Male	Female
Patients	427	318	399	277	210	264
Visits	1,918	1,382	1,901	1,304	1,063	1,169
Follow-up (y)	3.7 ± 2.9	3.6 ± 3.0	4.5 ± 3.4	4.6 ± 3.3	4.6 ± 3.3	4.1 ± 3.0
Age at baseline	75.0 ± 7.1	73.6 ± 7.5	75.4 ± 7.5	71.5 ± 7.8	74.0 ± 6.1	72.7 ± 6.0
Education (y)	16.1 ± 2.8	14.9 ± 2.6	16.4 ± 2.8	15.5 ± 2.7	17.2 ± 2.4	16.1 ± 2.8
APOE-ε4 (2/1/0)	76/201/150	50/158/110	32/127/240	24/89/164	5/51/154	7/75/182
MMSE	24.4 ± 4.0	23.8 ± 4.6	28.0 ± 2.0	28.2 ± 2.1	29.0 ± 1.2	29.2 ± 1.1
ADAS13	26.2 ± 10.6	27.7 ± 12.0	14.5 ± 6.7	12.6 ± 6.7	10.0 ± 4.6	8.3 ± 4.3

Table 1: Demographics for cohorts selected from ADNI. Numeric fields are in the form mean ± standard deviation. (y) is years. (2/1/0) refers to the amount of APOE-ε4 alleles. Cognitive scores are for all visits (not just baseline).

124 *Data processing.* These results have been obtained using the t1-freesurfer pipeline of Clinica (Routier et al., 2021). This
 125 pipeline is a wrapper of different tools of the FreeSurfer (v6.0) software (<http://surfer.nmr.mgh.harvard.edu/>)
 126 (Fischl, 2012). This processing includes segmentation of subcortical structures (corpus callosum, ventral Diencephalon,
 127 choroid plexus, acumbens area, amygdalas, hippocampi, caudate nuclei, putamen, pallidum and thalamus), extraction of
 128 cortical surfaces, spatial normalization onto the FreeSurfer surface template (FsAverage) and cortical thickness estimation
 129 with respect to the 148 gyral and sulcal structures defined by the Destrieux atlas (Destrieux et al., 2010). The subcortical
 130 volumes are normalized by intracranial volumes to account for the size of the head.

131 In order to validate our findings on another modality, we extract gray matter density maps from the same t1-MRI data
 132 from ADNI. Theses features are been obtained using the t1-volume pipeline of Clinica (Routier et al., 2021). This pipeline
 133 is a wrapper of the Segmentation, Run Dartel and Normalise to MNI Space routines implemented in the SPM12 software
 134 and yields a map of the average gray matter densities in each anatomical region defined in the AAL2 atlas (Tzourio-
 135 Mazoyer et al., 2002), which splits the brain into 80 gyri and sulci for the cortex and 14 subcortical regions. It displays
 136 a similar granularity to the Destrieux atlas and allows comparison. Gray matter density is fundamentally different from
 137 cortical thicknesses and regional volumes, and could potentially exhibit different progression patterns, especially since it
 138 is well documented that women have on average more gray matter and less white matter than men after correcting for
 139 brain size, in most of the brain (Luders et al., 2006; Chen et al., 2007; Lotze et al., 2019).

140 *Longitudinal modeling.* Mixed-effects models describe each patient’s progression over time as a small variation – the
 141 random effects of the model – around the average population trajectory – the fixed effects of the model. This study
 142 focuses on univariate models, that are calibrated on the repeated measurements for one region of the cortex or subcortical
 143 structure at a time. Linear mixed-effects models are widely used for longitudinal modeling and assume that features
 144 evolve according to straight lines over time. Each patient is thus characterised by a slope and an intercept. The slope can

145 be interpreted as the pace of decline of a patient for the given feature, but the intercept is less meaningful. In that setting,
 146 we choose to parametrize the inter-subjects variability as the combined effects of an individual onset age, and a pace of
 147 decline as suggested in Schiratti et al. (2015a). The onset age can be understood as a horizontal intercept and describes
 148 the age at which a patient crosses a chosen threshold, and the pace of decline as the slope. Both these temporal parameters
 149 allow to align all patients on a common progression timeline. Namely, given a family of feature observations $\{y_{i,j}\}$ at times
 150 $\{t_{i,j}\}$ for $1 \leq i \leq N$ 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
 151 generative model

$$y_{i,j} = f\left(e^{\xi_i}(t_{i,j} - \tau_i) + t_0\right) + \varepsilon_{i,j}$$

152 where e^{ξ_i} and τ_i , respectively the *progression pace* and *onset age* of patient i are called the individual parameters that
 153 provide an affine time warp to account for the variability in pace and onset of decline between patients. These individual
 154 parameters form the random effects of the model. We choose the Gaussian priors for the noise $\varepsilon_{i,j} \sim \mathcal{N}(0, \sigma_\varepsilon^2)$ and random
 155 effects $\tau_i \sim \mathcal{N}(t_0, \sigma_\tau^2)$ and $\xi_i \sim \mathcal{N}(0, \sigma_\xi^2)$. In a linear mixed-effects framework, f is an affine function $t \mapsto p_0 + v_0 * (t - t_0)$,
 156 while for non-linear mixed-effects it is usually chosen to be the logistic function $t \mapsto \left(1 + \left(\frac{1}{p_0}\right) \exp\left(\frac{-v_0 t}{p_0(1-p_0)}\right)\right)^{-1}$. The
 157 parameters p_0 , v_0 and t_0 are respectively a reference *position*, *velocity* and *time* and describe the average trajectory.
 158 Together with the variances $\sigma_\varepsilon, \sigma_\tau, \sigma_\xi$, they form the fixed-effects of the model.

159 In practice, logistic regression is one of the most popular shape of trajectory, so we add a min-max normalization to
 160 put all features in the range $[0, 1]$, and since cortical thicknesses and brain volumes decrease over time, we flip data around
 161 $.5$, using the rotation $x \mapsto 1 - x$, in order to ensure increasingness, which is required for logistic modeling.

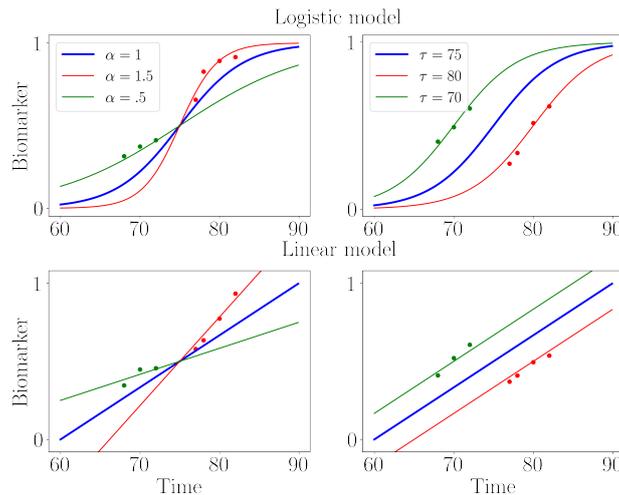


Figure 1: Illustration of logistic (first row) and linear (second row) mixed effects models. Blue curve is the average trajectory (parametrized by t_0 , p_0 and v_0) and red and green curves illustrate the effect of progression pace ($\alpha = e^{\xi}$) and onset age (τ), which allow to match individual measurements (isolated dots) to a continuous trajectory.

162 *Calibration of the model.* These longitudinal statistical models are part of a family of geometric models that have been
 163 studied in Schiratti et al. (2015b) and Koval et al. (2017b). We can proceed to a Maximum a Posteriori estimation of both
 164 random and fixed effects with the MCMC-SAEM procedure in which the estimation step of an EM algorithm is replaced
 165 by a stochastic approximation. See Kuhn and Lavielle (2004) and Allasonnière et al. (2010) for details on the complete
 166 likelihood and proof of convergence and stability. One model is calibrated on each of the three cohorts. All analysis is
 167 done using the Leaspy software. When provided with longitudinal data, the model provides a set of individual parameters
 168 that describe all patients' trajectories.

169 *Logistic versus linear regression.* As mentioned above, the choice of f in the mixed-effect formulation should reflect
 170 the average progression of the feature. A few methods exist to learn the exact shape of the progression profile (Gruffaz
 171 et al., 2021; Sauty and Durrleman, 2022b) but add a strong computational burden. We compared the two most widespread

172 available shapes, namely linear and logistic curves, in order to assess the stability of convergence as well as the estimated
173 noise of the longitudinal fit. The logistic curve marginally surpassed the linear curve for both these criteria.

174 *Goodness of fit.* In order to ensure that the longitudinal models accurately describe the atrophy of each feature, we
175 compare the distributions of reconstruction errors (the differences between the predicted values of the models at the time
176 of each visit and the actual measurements) for the three cohorts to the distribution of measurements noise. Imaging data are
177 indeed subject to variations in the experimental conditions and in the processing pipeline. In order to evaluate this noise,
178 some visits are acquired twice within a few hours. For ADNI, we dispose of 1604 duplicate images from 285 different
179 patients. We provide boxplots that display the empirical distributions of test/re-test errors and of the reconstruction errors
180 for the three cohorts in supplementary materials. Distributions largely overlap, and reconstruction errors fall close to the
181 measurements uncertainty, which hints that our models could not be improved without overfitting.

182 For all features, reconstruction errors gets slightly higher as the selected cohort gets more cognitively altered. That could
183 be attributed to the considered brain regions being smaller due to a higher level of neurodegeneration, and thus yield a
184 higher error in parcellation. That could also explain why for some features the reconstruction errors of the CN cohort are
185 marginally lower than the re-test errors that are computed with patients at all stages of brain atrophy.

186 *Statistical analysis.* Once the univariate models are calibrated, we have a family of patient-wise onset ages and progres-
187 sion paces for each feature. We can thus proceed to statistical testing of the differences between subgroups. To do so,
188 we perform covariance analysis using ordinary least squares to regress the individual parameters with regard to female
189 sex, number of APOE- ϵ 4 alleles and education level of each patient. This evaluates the impact of each covariate after
190 correcting for the other ones, and also the significance of the corresponding association. Since we are in a multiple testing
191 setting, we use False Discovery Rate (FDR) (Benjamini and Yekutieli, 2005) to obtain a map of corrected p -values that
192 assess how certain it is that the chosen covariate influences the onset or pace of atrophy for each region. Given the high
193 number of statistical tests (one for each of the 148 regions of the Destrieux atlas), a more stringent correction method such
194 as Family-Wise Error Rates would be unsuitable as it would discard significant correlations.

195 *Interpretability of the p -values.* For each feature, patients are aligned on a common timeline with the individual onset
196 age and pace of atrophy. One can, for instance, observe that for the inferior temporal gyrus, cortical thinning occurs on
197 average 1.5 years earlier for each copy of the ϵ 4 allele, and on average 23% faster for women, after correcting for the
198 other covariates. However these multiple timelines are learned independently and cannot be compared directly in order to
199 exhibit the regions that are mostly affected by a covariate, as it may not be statistically significant if the variability is big.
200 Resorting to statistical testing, using welsh t-tests, allows to circumvent this issue as it normalizes all the effect sizes by
201 the natural temporal scale associated with the region. Besides, for a fixed sample size, p -values are monotonically related
202 to effect sizes, so lower corrected p -values can be interpreted as indicative of a bigger impact of the covariate, and allow
203 comparison across brain regions and covariates.

204
205 We provide a map of cortical regions and a list of sub-cortical volumes that display significant differences when
206 stratified for sex or APOE- ϵ 4 status, regarding onset age and pace of atrophy, for AD, MCI and healthy ageing. Corrected
207 p -values higher than .05 are **discarded** for readability purposes. For cortical thinning maps, the significant p -values are
208 presented in **logarithmic scale** (base 10), and **the sign** of the corresponding regression coefficient is added to provide
209 both the direction and the strength of the association. Negative values thus mean higher onset or pace for female patients
210 and APOE- ϵ 4 carriers and positive values mean lower onset or pace for female patients and APOE- ϵ 4.

211 3. Results

212 Scales of signed log p -values vary greatly between each plot and should be taken into account to evaluate the strength
213 of the considered risk factor. For visualization purposes, cortical thinning maps are presented by cohort (AD in Fig. 2,
214 control cohort in Fig. 3 and MCI in Fig. 4) while all results for subcortical volumes are compiled in Table. 2.

215 *Impact of sex on cortical thinning for AD progression.* Almost all regions of the cortex display a significantly higher
 216 progression pace for female patients, with the exception of the motor cortex, sensory areas and inferior frontal lobe.
 217 Regions that are most accelerated in females are the entire temporal lobe, the middle and superior frontal lobe, the entire
 218 occipital lobe and the anterior and medial parietal lobe. Onset ages are, on the other hand, more homogeneous across
 219 sexes. The motor cortex, the cingulate gyrus and the medial parietal lobe display an earlier onset for men, while the
 220 inferior temporal lobe and inferior frontal lobe display an earlier onset age for female patients. All other regions do not
 221 allow to reject the null hypothesis.

222 *Impact of APOE- ϵ 4 genotype on cortical thinning for AD progression.* Almost all regions of the cortex also display a
 223 significantly higher progression pace for APOE- ϵ 4 carriers. The most affected regions are located roughly in the same
 224 areas as for the impact of sex, but with different regions of highest intensity, and an overall lower effect. The temporal
 225 lobe, the parietal lobe and the frontal lobe also display an earlier onset for APOE- ϵ 4 carriers. The region that presents the
 226 most advanced onset for mutations carriers is the hippocampal gyrus.

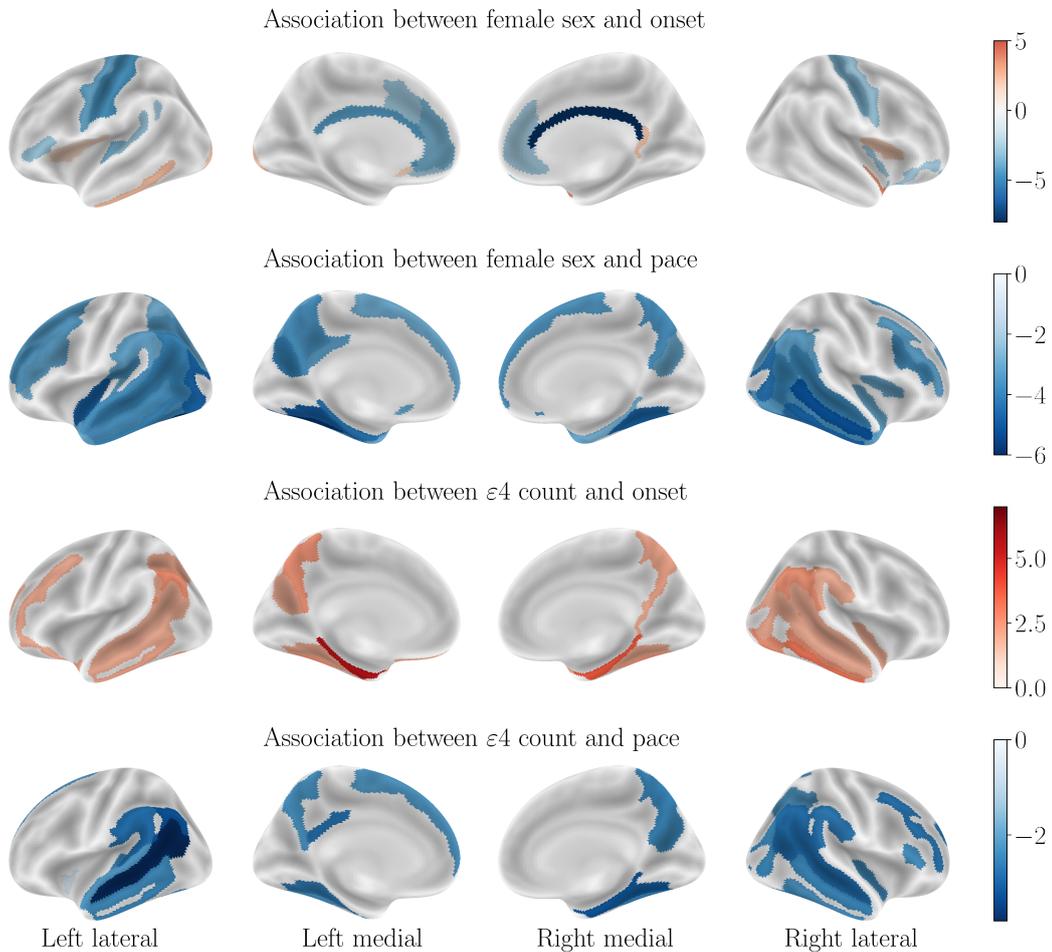


Figure 2: Cortical thinning over the course of AD progression. Legend bars shows signed log p -values. The sign gives the direction of the association and the absolute value gives its strength. It should be noted that blue values indicate that the considered covariate (female sex or APOE- ϵ 4 genotype) is a protective factor for onset age but a risk factor for pace of atrophy, since higher onset age is better but higher progression pace is worse.

227 *Impact of sex on cortical thinning for healthy ageing.* Contrary to what was seen in AD progression, the sexual dimor-
 228 phism for healthy ageing manifests mainly through a significantly earlier onset age for male subjects, especially in the
 229 parietal and frontal lobes. Only the inferior temporal lobe and subcallosal gyrus display a slightly earlier onset for women.
 230 On the other hand, progression paces are similar across sexes except for the cingulate gyrus that is much accelerated in
 231 female patients, while a few regions of the parietal lobe display a higher pace of atrophy for male patients.

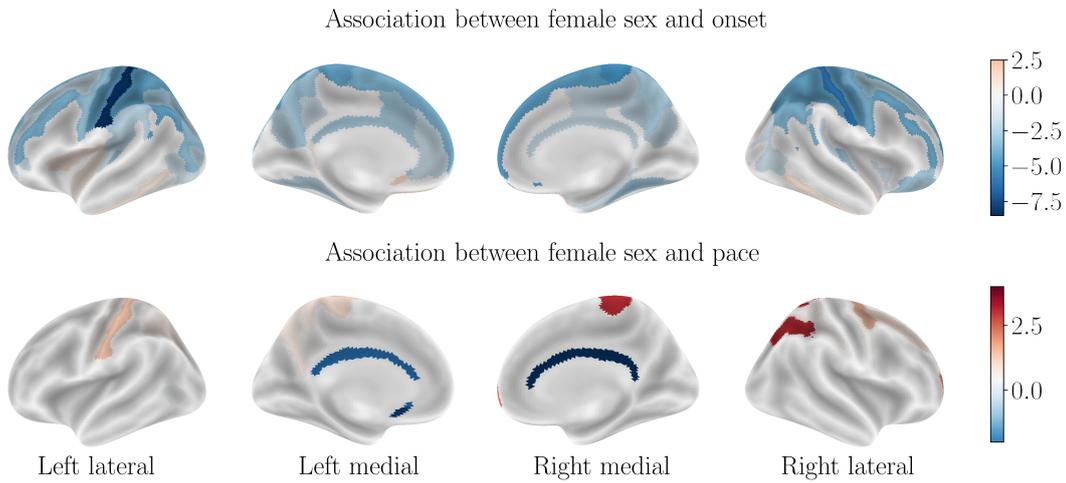


Figure 3: Cortical thinning over the course of cognitively normal ageing. Associations with APOE- ϵ 4 status are not displayed as they are not significant.

232 *Impact of APOE- ϵ 4 genotype on cortical thinning for healthy ageing.* In order to assess the impact of the APOE- ϵ 4 gene
 233 mutation on cognitively normal ageing, we also stratified regarding this factor. Interestingly, the mutation carriers do not
 234 display significantly different patterns for cortical thinning across healthy ageing, which leads to believe that APOE- ϵ 4
 235 by itself does not cause the accelerated atrophy of the brain but only serves as one cog of the unraveling of AD.

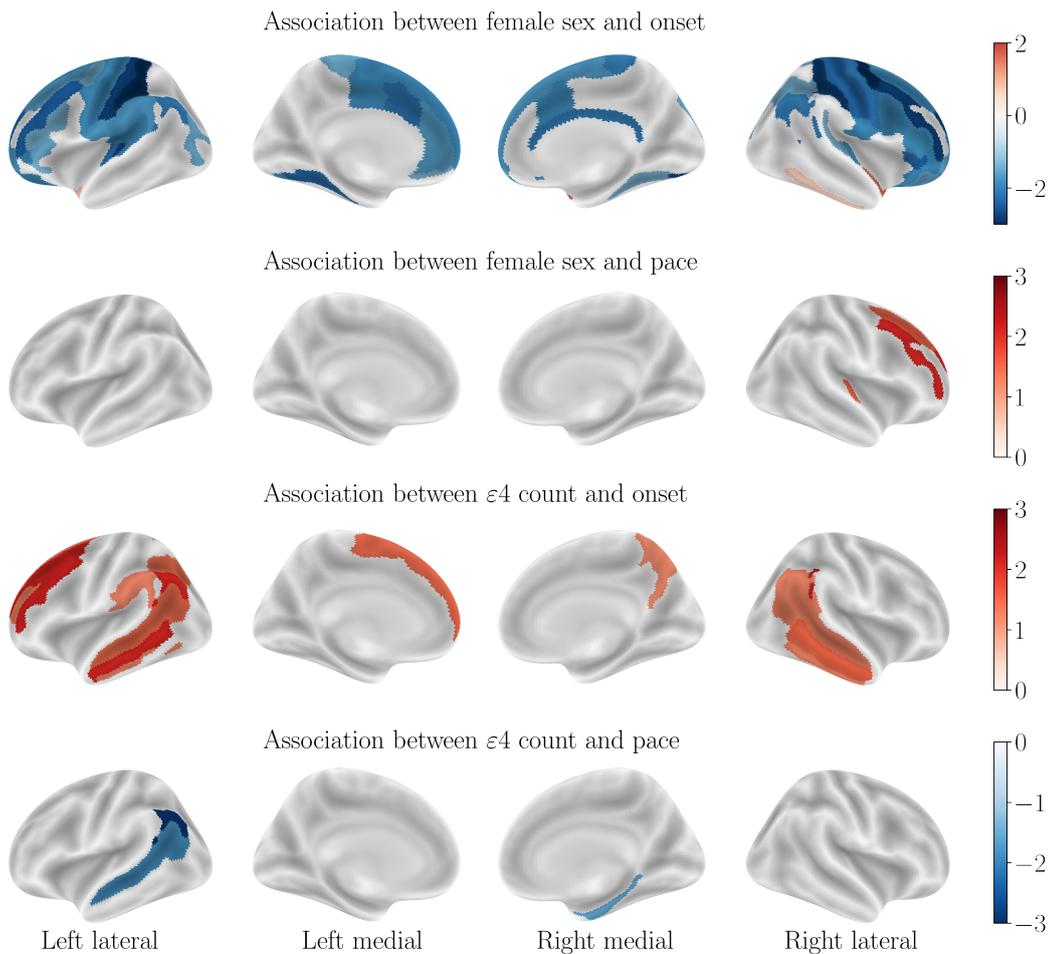


Figure 4: Cortical thinning over the course of MCI patients' ageing.

236 *Influence of both cofactors for patients with MCI.* The progression paces show little significant correlation with both
 237 covariates, however, for onset age the correlations with sex are similar to those displayed for healthy ageing while the
 238 correlations with APOE- ϵ 4 status are similar to those displayed for AD progression, although of a weaker effect.

239 *Correlations with the patterns of atrophy for subcortical structures.* For healthy ageing, male sex correlates with an
 240 earlier onset age for most regions with no significant differences in pace of atrophy, while no significant correlation is
 241 found for APOE- ϵ 4 genotype. For the AD cohort on the other hand, female sex correlates with an earlier onset for most
 242 regions, and higher paces of the hippocampi and bilateral amygdalas while APOE- ϵ 4 genotype correlates with earlier
 243 onset and higher pace for the hippocampi and bilateral amygdalas. We reach the same conclusion regarding the MCI
 244 cohort as for cortical thinning : sex correlates with atrophy in a similar fashion to the healthy cohort, while APOE- ϵ 4
 245 genotype correlates in a similar fashion to the AD cohort. Regions without correlations are not displayed.

		Correlations with sex			Correlations with APOE- ϵ 4		
		p_{val} CN	p_{val} MCI	p_{val} AD	p_{val} CN	p_{val} MCI	p_{val} AD
Amygdala (L)	Onset	-	-	8.1e-03	-	4.9e-03	1.9e-07
	Pace	-	-	1.2e-06	-	2.2e-03	7.0e-06
Amygdala (R)	Onset	-	-	7.4e-05	-	3.2e-02	1.4e-06
	Pace	-	-	2.3e-05	-	2.5e-05	1.9e-02
Caudate (L)	Onset	5.5e-07	6.7e-04	1.7e-04	-	-	-
	Pace	-	-	-	-	-	-
Caudate (R)	Onset	1.2e-04	1.8e-04	8.3e-04	-	-	-
	Pace	-	-	-	-	-	-
Hippocampus (L)	Onset	4.7e-06	1.2e-02	-	-	3.0e-03	1.5e-07
	Pace	-	-	3.9e-05	-	5.7e-04	1.2e-02
Hippocampus (R)	Onset	1.1e-04	1.2e-02	-	-	2.1e-03	1.1e-09
	Pace	-	-	1.2e-04	-	3.9e-04	2.6e-02
Pallidum (L)	Onset	4.6e-04	6.9e-04	4.9e-02	-	-	-
	Pace	-	-	-	-	-	-
Pallidum (R)	Onset	6.5e-03	1.8e-04	3.1e-05	-	-	-
	Pace	-	-	-	-	-	-
Thalamus (L)	Onset	1.3e-06	7.8e-12	1.5e-07	-	-	-
	Pace	-	1.1e-02	-	-	-	-
Thalamus (R)	Onset	4.1e-06	4.6e-09	5.5e-08	-	-	-
	Pace	-	-	-	-	-	-

Table 2: Significant correlations with subcortical atrophy. For all the significant features, APOE- ϵ 4 genotype correlate with lower onset age and higher pace, and female sex correlates with higher onset age and higher pace, although correlations with pace are rare and only present in AD and MCI cohorts.

246 *Differences between left and right hemisphere.* For AD progression, the left hemisphere displays more regions that differ
 247 significantly for both sex and APOE- ϵ 4 stratification. However, the average p -values are 30% smaller for the left regions
 248 for the sex differences, while identical for APOE- ϵ 4 differences. For healthy ageing on the other hand, the same number
 249 of regions display significant association in both hemispheres, and the average p -values are identical for sex stratification.
 250 This confirms that atrophic patterns are asymmetric but not completely lateralized (Derflinger et al., 2011), and hints that
 251 female sex is a stronger risk factor for the right hemisphere while APOE- ϵ 4 is a stronger risk factor for the left hemisphere.

252 *Impact of education level.* Fig. 5 illustrates the impact of education level on cortical thinning patterns, after accounting
 253 for sex and APOE- ϵ 4 mutation status. Correlations are only found in the healthy cohort, and higher education level
 254 correlates with higher onset age for the postcentral gyrus, the medial parietal and medial occipital lobes, as well as the left
 255 superior temporal lobe, and lower pace of atrophy for parts of the frontal and occipital lobes. No significant correlation is
 256 found for the AD cohort, in line with former studies (Koval et al., 2021). For subcortical volumes, only the hippocampal
 257 atrophy is delayed for more educated healthy patients, and no significant correlation is found for AD patients. One
 258 hypothesis is that education level is not, in itself, helping delay the atrophy for healthy controls, but acts as a proxy of

259 lifestyle healthiness, which influences metabolic pathways and brain atrophy. In AD cohort, that small preserving effect
260 is likely to be cancelled by the influence of other covariates that cause massive atrophy.

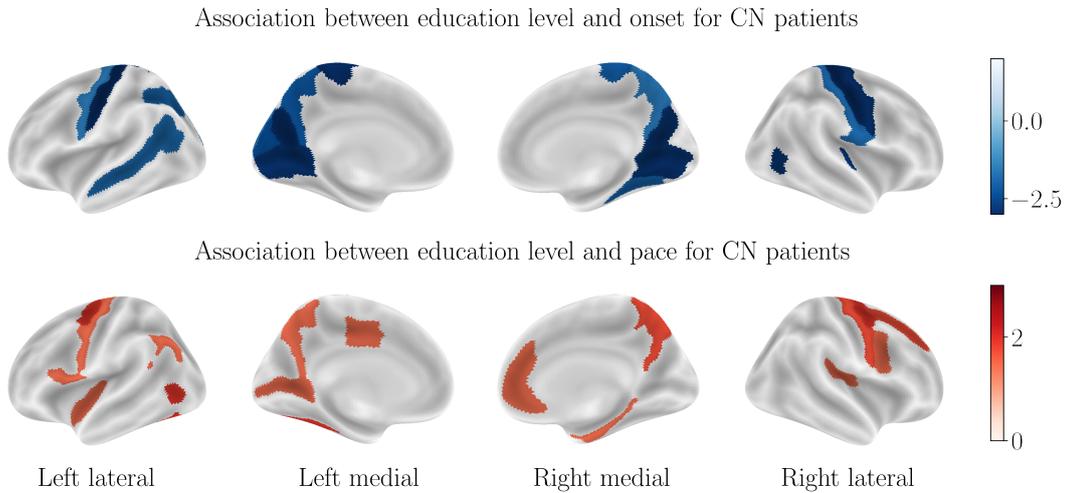


Figure 5: Correlation between education level and cortical thinning dynamics for CN patients. Correlations observed for the AD patients are not significant enough and are thus not displayed.

261 *Validation on other modalities from ADNI.* Despite the strong sexual dimorphism in regional gray/white matter ratios, we
262 recover most results from the main analysis. For AD patients, the same regions display a strong dimorphism : almost all of
263 the temporal lobe, frontal lobe and occipital lobe display a much stronger atrophic pace for women, while the postcentral
264 gyrus displays an earlier onset for men. APOE- $\epsilon 4$ allele also correlates with a faster pace and earlier onset in the medial
265 temporal and parietal lobes, as well as in the temporal lobe and parts of the frontal lobe. For CN patients, we recover the
266 absence of association with APOE genotype, while men display a much earlier onset for almost all regions (with emphasis
267 on the parietal lobe and postcentral gyrus), while a few isolated regions of the frontal and temporal lobe display an faster
268 pace of decline for men. The conclusions regarding the MCI cohort and the impact of education level are also confirmed.
269 The differences with the main analysis are thus only a matter of a few isolated regions and of the order of magnitude of
270 the statistical associations. We provide the association figures for cortical thinning and the tables for subcortical structures
271 in supplementary materials.

272 4. Discussion

273 *Major takeaways.* Our study allows to isolate the contributions from sex, APOE status and education level on both onset
274 age and pace of atrophy for each region of the cortex and brain, while accounting for the other cofactors. We find that :

- 275 • Sex is a more important risk factor than APOE- $\epsilon 4$ genotype for cortical thinning and brain atrophy for AD patients.
276 The significant p -values are indeed on average 50% smaller for sex than for APOE- $\epsilon 4$ stratification.
- 277 • Female AD patients decline much faster than male patients, however, the onset of the atrophy is still earlier for male
278 patients, in line with the healthy ageing patterns. This suggests that the disease strikes female patients with much
279 more intensity, but do not present an earlier onset. This point is revealed by the use of longitudinal studies and has
280 important implications for practitioners for the follow-up of patients.
- 281 • Education level seems to be a protective factor for healthy patients but is not significant in AD progression.
- 282 • For the MCI cohort, the influence of sex is similar to that of the healthy cohort, while the effect of APOE- $\epsilon 4$
283 genotype is similar to that of the AD cohort, although of an overall weaker effect.

284 *Clinical characterization of diagnosis in ADNI.* For the control cohort, we used the CN patients in ADNI, because it
285 allows a fair comparison between AD progression and cognitively normal ageing, without acquisition biases. Since
286 ADNI is not an epidemiological study on healthy ageing, the cognitively normal patients may not represent accurately
287 the general population because of ADNI's inclusion criteria. For the MCI cohort, it is important to note that MCI is a
288 cognitive status defined by subjective memory complaints and does not always lead to AD as other factors can cause
289 patients to have it. The prevalence of MCI symptoms are found to be between 15 and 20% for patients over 60 years old
290 (Gauthier et al., 2006), and roughly 8 to 15% of these convert to AD each year (Petersen, 2016). This facts makes the
291 cohort heterogeneous, and the results found for MCI patients are not to be understood as "pre-AD". However, Petersen
292 et al. (2010) assert that the recruited cohorts for CN, MCI and AD patients successfully describe the associated clinical
293 status.

294 *Validation cohort.* Reproducing this study is tedious because of the lack of publicly available longitudinal database of
295 the same scale as ADNI. Our statistical pipeline requires to split the patients between CN and AD patients, while only
296 keeping patients with more than 2 visits with a t1-MRI scan. For instance, in the Australian Imaging Biomarkers and
297 Lifestyle Study of Ageing (AIBL), often used to validate findings on ADNI, the AD cohort only contains 38 patients
298 with a total 105 visits, and the healthy cohort 128 patients with 431 visits, before the additional stratification by sex or
299 APOE- ϵ 4 genotype. The sample sizes are thus too small to provide enough statistical power to reproduce the regional
300 map of significant correlations.

301 *Impact of the chosen atlas.* It must be taken into account that the choice of different atlas might yield different results. One
302 anatomical region that is positively associated with a covariate can span many ROIs or on the other hand be split between
303 ROIs and prevent the detection of the true underlying association. On the other hand, our mixed effect formulation cannot
304 be fitted directly to vertex-wise thickness measurements because the onset age (or horizontal intercept) will not converge
305 for features that display little progression compared to the feature noise.

306 *Regions normalization.* Since subcortical regions' volumes are correlated with the volumes of the skull and brain, it is
307 standard practice to normalize by the intracranial volume in order to allow a fair comparison between subjects. The impact
308 of such normalization is discussed in former studies : in Whitwell et al. (2001); Westman et al. (2013); Voevodskaya
309 et al. (2014) authors suggest that subcortical volumes should be normalized with total intracranial volume, while cortical
310 thicknesses should not, for diagnosis prediction and progression models. On the other hand, Zhou et al. (2014) find that
311 cortical thicknesses should be normalized with either intracranial volume or average thickness to help predict the cognitive
312 status of a patient. Luders et al. (2006) discuss the effect of normalizing cortical thicknesses to allow a fair comparison
313 between healthy male and female subjects. Allometric scaling is often used to circumvent this issue, but Williams et al.
314 (2021) find that allometric and linear scaling yield similar effect sizes and coefficients when evaluating the effect of sex
315 and age on brain measurements.

316 *Interpretability of the onset age.* As opposed to the straightforward pace of atrophy, the onset age needs to be interpreted
317 with caution. It represents the age at which a patient crosses a chosen threshold (chosen to be the average value for
318 the whole cohort). Brain atrophy does not have a well-defined starting point and the notion of onset age is thus to be
319 understood with regard to a reference point in the average progression.

320 *Clinical implications.* The discrepancies in alteration patterns of the brain between sexes and APOE genotypes reinforce
321 the idea that the disease manifests differently between subpopulation and care should be provided accordingly. Besides,
322 clinical trials that monitor the effect of a drug on neurodegeneration should put an emphasis on both having more repre-
323 sentative demographics after enrolment, and evaluating the impact of drugs in a stratified manner as patients are likely to
324 react differently to the drug depending on both the explored genetic risk factors.

325 *Perspectives.* This statistical pipeline can be applied to other modalities of neuroimaging data. For instance, considering
326 FDG-PET scans instead of structural MRI could display a sexual dimorphism of AD regarding brain hypo-metabolisms,
327 which would complement the study of brain atrophy in order to assess the patterns of brain alterations. Other imaging
328 modalities specific to AD, such as amyloid-PET or tau-PET, are also under investigation within this pipeline. A strong

329 sexual dimorphism for the spreading patterns of pathological protein tangles in the brain would prompt the latest clinical
330 trials, that choose amyloid load as a primary disease outcome, to put great care in evaluating the differentiated results
331 between male and female patients.

332 **5. Conclusion**

333 Structural alterations of the brain happen before the onset of cognitive decline and the collection of MRI-derived
334 features reveals varying patterns of atrophy between subgroups of patients. Female sex, APOE- ϵ 4 genotype and low
335 education level have been identified as the biggest risk factors for cognitive decline, but their impact on early-stage
336 structural alterations is not yet well understood. In this work we described the disentangled effects of these 3 covariates
337 on the onset and pace of regional atrophy and cortical thinning. This reveals that female sex is actually a stronger risk factor
338 for neurodegeneration than APOE- ϵ 4 genotype, and women experience much faster atrophic rates after correcting for
339 the APOE genotype. APOE- ϵ 4 genotype leads to earlier and faster atrophy for most regions of the brain for AD patients
340 but not for healthy patients. Healthy patients with higher education experience slightly delayed atrophy but not patients
341 with neurodegeneration. This work calls for further exploration of the sexual dimorphism of AD regarding structural
342 alterations.

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348
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