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

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Abstract

Alzheimer's Disease (AD) is a heterogeneous disease that disproportionately affects women and people with the APOE- ϵ 4 susceptibility gene. We aim to describe the not-well-understood influence of both risk factors on the dynamics of brain atrophy in AD and healthy aging. Regional cortical thinning and brain atrophy were modeled over time using non-linear mixed-effect models and the FreeSurfer software. Covariance analysis was used to disentangle the effect of sex and APOE genotype on the regional onset age and pace of atrophy, while correcting for educational level. A map of the regions most affected by neurodegeneration is provided. Results were confirmed on gray matter density data from the SPM software. Women experience faster atrophic rates in the temporal, frontal, parietal lobes and limbic system and earlier onset in the amygdalas, but slightly later onset in the postcentral and cingulate gyri as well as all regions of the basal ganglia and thalamus. APOE- ϵ 4 genotypes leads to earlier and faster atrophy in the temporal, frontal, parietal lobes and limbic system in AD patients, but not in healthy patients. Higher education was found to slightly delay atrophy in healthy patients, but not for AD patients. A cohort of amyloid positive patients with MCI showed a similar impact of sex as in the healthy cohort, while APOE- ϵ 4 showed similar associations as in the AD cohort. Female sex is as strong a risk factor for AD as APOE- ϵ 4 genotype regarding neurodegeneration. Women experience a sharper atrophy in the later stages of the disease although not a significantly earlier onset. These findings may have important implications for the development of targeted intervention.

Keywords:

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

1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative pathology that accounts for about 70% of the more than 55 millions dementia cases worldwide [1]. 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% [2, 3] 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 [4]. 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 roughly 5% of cases [4], 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 roughly 50% of the common late-onset AD [4]. 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 [5, 6, 1]. 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

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excess $A\beta$. The presence of $\epsilon 4$ allele hinders $A\beta$ clearance and leads to reduced neuronal injury response [7], and in turns correlate with higher AD risks.

The other genetic factor that is known to impact AD risk rates is the sex of patients. Two thirds of AD patients are women [1] and their cognitive decline is faster than for men [8]. By contrast, healthy aging tends to display delayed cognitive decline and structural alterations for women. [9] review conflicting studies on the topic of incidence rates and reach the conclusion that before the age of 75, no significant difference in incidence rates is detected, while incidence rates get significantly higher for women than for men after that inflexion point. The longer longevity of women has long been thought to be the sole cause for this discrepancy. However, the loss of the protective effects of estrogens during menopause, demonstrated in vitro and in vivo [10, 11], has also been suggested as a cause. Evidence also highlight a faster loss of autonomy but a longer lifespan after diagnosis for women [12]. These facts raise the question of a sexual dimorphism of AD. A precise understanding of the distinct patterns of structural and functional brain alterations over time is still lacking. Accurate descriptions of those patterns could help to implement better practices to care for both men and women. Besides, women are still underrepresented in clinical trials [13] and only 15% of trials report results stratified by sex [14], although this proportion increases in more recent studies. As suggested in [15], several gendered factors other than sex can also mediate the observed associations, although data is rarely available in large scales datasets.

Another often-mentioned risk factor is the education level. According to the cognitive reserve hypothesis, having more years of education increases the connections between neurons and enables the brain to compensate for the early changes of Alzheimer’s by using alternate routes of neuron-to-neuron communication to complete a cognitive task [16, 17]. Women are believed to benefit even more from higher education than men, albeit receiving less education [18]. [19] confirm that education is an indicator of cognitive reserve, but that the protective effects on cognition are depleted as neurodegeneration progresses.

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

1.1. Related work

Cross-sectional studies. Over the course of AD progression, the link between cognitive decline and various covariates such as BMI [18], cardiac pathologies, APOE- $\epsilon 4$ genotype [20, 21, 22, 23] and sex have been explored, highlighting a higher impact of comorbidities and APOE- $\epsilon 4$ genotype for women on the severity of the disease symptoms. [24] and [25] review the state of knowledge about the differences across sexes in AD clinical manifestations, biomarkers patterns and risk factors.

On the other hand, healthy aging displays comparatively more spared alteration profiles for women compared to men, for both brain atrophy and cognitive decline. Seminal works dating back to the beginning of in-vivo imaging modalities report higher size decreases in men for average brain [26] and frontal and temporal lobes [27]. Many studies have since provided more insights into the differences between sexes for cognitive decline and link with comorbidities [28, 29], exhibiting opposite correlation than in Alzheimer’s studies. [30] exhibit associations between male sex, worse memory and higher hippocampal atrophy.

Longitudinal studies. The collection of repeated measurements of neuroimaging data and clinical assessment allows a finer understanding of pathological pathways. Notorious modeling approaches include event-based models [31, 32],

Gaussian-Process models [33, 34], Deep Learning methods [35, 36] and mixed-effects models. Application of such longitudinal models are frequent for the assessment of cognitive decline [37, 38, 39, 40, 31, 41, 42, 43] but less used for imaging features. [44] advocate the use of linear mixed-effects models (LME) for progression models of neuroimaging data and apply LME to a mesh of control points of cortical thickness in a mass-univariate setting in [45]. [46] correlate these progression models with diagnosis in order to exhibit regions of the cortex that are most representative of the cognitive state of patients. Other studies also apply progression models to a few ROIs of the brain [47, 48, 49] in order to display the regions that correlate most with diagnosis. Applying this kind of modeling to a study of sex differences, [50] confirm that atrophy rates are higher for female than male patients and they decrease with age, while [51, 52] explain that brain volumes and cortical thicknesses are consistently smaller for cognitively normal males after accounting for age, and that the differences get smaller as cohorts are chosen at a more advanced state of cognitive decline, until they get indistinguishable for confirmed AD patients, with a sharper decline for women. Those study do not take into account important covariates such as APOE status and educational level, and do not disentangle the age of onset and the pace of atrophy. Many studies report the impact of APOE polymorphisms on brain atrophy for AD progression and link $\epsilon 4$ with faster cortical thinning [53, 54] and hippocampal atrophy [55, 56], with increasing effects as patients get older [57].

1.2. Contributions

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

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

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

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

2. Material and Methods

Data sets. We performed the analysis on publicly available data from all waves (GO,1,2,3) of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), as it provides repeated MRI scans for both cognitively normal elderlies and AD patients. The ADNI was launched in 2003 as a public-private partnership and its primary goal has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer’s disease (AD). All scans are quality-checked by trained anatomists. We selected all patients with at least 2 visits with a MRI scan and selected three cohorts : an AD cohort with patients with at least one confirmed AD diagnosis, an healthy cohort with patients who are diagnosed cognitively normal at every visit and an intermediate cohort of amyloid positive patients (see [58] for the chosen cutoffs) with at least one MCI diagnosis but no AD conversion. Patients with inconsistent AD diagnosis that revert to CN or MCI (107 patients) and amyloid negative patients (50 patients) are removed from the pathological cohort. Table 1 reports the demographics for the selected ADNI patients. The AD cohort is composed mostly of late-onset AD (566 patients) but also features a few early-onset cases (24 patients).

	AD cohort		A β + MCI cohort		Healthy cohort	
	Male	Female	Male	Female	Male	Female
Patients (N)	329	261	262	176	210	264
Visits (N_{scan})	1,447	1,092	1,164	794	1,063	1,169
Total follow-up (y)	3.7 ± 2.9	3.4 ± 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 ± 7.7	75.4 ± 7.5	71.5 ± 7.8	74.0 ± 6.1	72.7 ± 6.0
Education (y)	16.1 ± 2.8	14.7 ± 2.6	16.4 ± 2.8	15.5 ± 2.7	17.2 ± 2.4	16.1 ± 2.8
APOE- ϵ 4 (2/1/0)	69/163/97	44/133/84	32/99/121	24/71/81	5/51/154	7/75/182
MMSE	24.0 ± 4.0	23.2 ± 4.6	27.7 ± 2.0	28.2 ± 2.1	29.0 ± 1.2	29.2 ± 1.1
ADAS-Cog13	26.5 ± 10.6	29.2 ± 11.8	15.3 ± 6.9	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 \pm standard deviation. (y) is years. (2/1/0) refers to the amount of APOE- ϵ 4 alleles. Cognitive scores are for all visits (not just baseline).

Data processing. These results have been obtained using the t1-freesurfer pipeline of Clinica [59]. This pipeline is a wrapper of different tools of the FreeSurfer (v6.0) software (<http://surfer.nmr.mgh.harvard.edu/>) [60]. This processing includes segmentation of subcortical structures (corpus callosum, ventral Diencephalon, choroid plexus, acum-bens area, amygdalas, hippocampi, caudate nuclei, putamen, pallidum and thalamus), extraction of cortical surfaces using the ”recon-all” pipeline, spatial normalization onto the FreeSurfer surface template (FsAverage) and cortical thickness estimation with respect to the 148 gyral and sulcal structures defined by the Destrieux atlas [61]. The subcortical volumes are normalized by intracranial volumes to account for the size of the head. Late releases of FreeSurfer have been demonstrated to yield similar atrophic rates to those obtained by manual segmentation for AD patients [62, 63].

In order to validate our findings on another modality, we extract gray matter density maps from the same t1-MRI data from ADNI. These features are obtained using the t1-volume pipeline of Clinica [59]. This pipeline is a wrapper of the Segmentation, Run Dartel (using a ADNI-based template) and Normalise to MNI Space routines implemented in the SPM12 software and yields a map of the average gray matter densities in each anatomical region defined in the AAL2 atlas [64], which splits the brain into 80 gyri and sulci for the cortex and 14 subcortical regions. It displays a similar granularity to the Destrieux atlas and allows comparison. Gray matter density is fundamentally different from cortical thicknesses and regional volumes, and could potentially exhibit different progression patterns, especially since it is well documented that women have on average more gray matter and less white matter than men after correcting for brain size, in most of the brain [65, 66, 67].

MRI images from ADNI are acquired with either 1.5T (3440 samples) or 3T (3289 samples) scanners. As noted in [68], Freesurfer outputs on 3T images are significantly thicker than for 1.5T images, which can hurt longitudinal

141 modeling and bias population-level comparisons. As is common in longitudinal studies, we proceed to bias correction
 142 through histogram matching within each diagnosis group for each extracted feature.

143 *Longitudinal modeling.* Mixed-effects models describe each patient’s progression over time as a small variation – the
 144 random effects of the model – around the average population trajectory – the fixed effects of the model. This study
 145 focuses on univariate models, that are calibrated on the repeated measurements for one region of the cortex or subcortical
 146 structure at a time. Linear mixed-effects models are widely used for longitudinal modeling and assume that features
 147 evolve according to straight lines over time. Each patient is thus characterised by a slope and an intercept. The slope
 148 can be interpreted as the pace of decline of a patient for the given feature, but the intercept is less meaningful. In that
 149 setting, we choose to parametrize the inter-subjects variability as the combined effects of an individual onset age, and a
 150 pace of decline as suggested in [41]. The onset age can be understood as a horizontal intercept and describes the age at
 151 which a patient crosses the population-average-value threshold, and the pace of decline as the slope. Both these temporal
 152 parameters allow to align all patients on a common progression timeline. Namely, given a family of feature observations
 153 $\{y_{i,j}\}$ at times $\{t_{i,j}\}$ 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
 154 mixed-effect generative model

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

155 where e^{ξ_i} and τ_i , respectively the *progression pace* and *onset age* of patient i are called the individual parameters that
 156 provide an affine time warp to account for the variability in pace and onset of decline between patients. These individual
 157 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
 158 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 $t \mapsto p_0 + v_0 * (t - t_0)$,
 159 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
 160 parameters p_0 , v_0 and t_0 are respectively a reference *position*, *velocity* and *time* and describe the average trajectory.
 161 Together with the variances $\sigma_\varepsilon, \sigma_\tau, \sigma_\xi$, they form the fixed-effects of the model.

162 In practice, logistic regression is one of the most popular shape of trajectory, so all features should be normalized to
 163 the range $[0, 1]$. We thus discard outliers using the so-called three sigma rule and add a min-max normalization within
 164 each cohort, providing realistic asymptotes. Since cortical thicknesses and brain volumes decrease over time, we flip data
 165 around .5, using the rotation $x \mapsto 1 - x$, in order to ensure increasingness, which is required for logistic modeling.

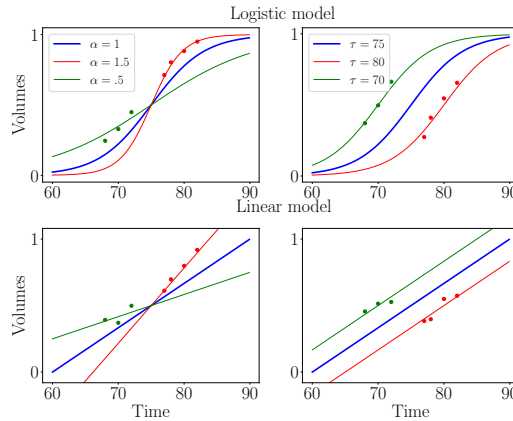


Figure 1: Illustration of logistic (first row) and linear (second row) mixed-effects models. Blue curve is the average trajectory (parametrized by t_0 , p_0 and v_0) and red and green curves illustrate the effect of progression pace ($\alpha = e^{\xi}$) and onset age (τ), which allow to match individual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

166 *Calibration of the model.* These longitudinal statistical models are part of a family of geometric models that have been
 167 studied in [69] and [70]. We can proceed to a Maximum a Posteriori estimation of both random and fixed effects with
 168 the MCMC-SAEM procedure in which the estimation step of an Expectation-Maximization algorithm is replaced by a
 169 stochastic approximation. See [71] and [72] for details on this procedure, description of the complete likelihood and proof
 170 of convergence and stability. One model is calibrated on each of the three cohorts. All analysis is done using the Leaspy
 171 software.

172 *Logistic versus linear regression.* As mentioned above, the choice of f in the mixed-effect formulation should reflect the
173 average progression of the feature. A few methods exist to learn the exact shape of the progression profile [73, 74] but
174 add a strong computational burden. We compared the two most widespread available shapes, namely linear and logistic
175 curves, in order to assess the stability of convergence as well as the estimated noise of the longitudinal fit. The logistic
176 curve marginally surpassed the linear curve for both these criteria.

177 *Goodness of fit.* In order to ensure that the longitudinal models accurately describe the atrophy of each feature, we
178 compare the distributions of reconstruction errors (the differences between the predicted values of the models at the time
179 of each visit and the actual measurements) for the three cohorts to the distribution of measurements noise. Imaging data are
180 indeed subject to variations in the experimental conditions and in the processing pipeline. In order to evaluate this noise,
181 some visits are acquired twice within a few hours. For ADNI, we dispose of 1604 duplicate images from 285 different
182 patients. We provide boxplots that display the empirical distributions of test/re-test errors and of the reconstruction errors
183 for the three cohorts in supplementary materials. Distributions largely overlap, and reconstruction errors fall close to the
184 measurements uncertainty, which hints that our models could not be improved without overfitting. Additionally, it is
185 important to note that the reconstruction errors are not biased regarding sex, APOE status, education level, ADNI phases
186 nor field strength.

187 *Statistical analysis.* Once the univariate models are calibrated, we have a family of patient-wise onset ages and progres-
188 sion paces for each feature. We can thus proceed to statistical testing of the differences between subgroups. To do so,
189 we perform covariance analysis using ordinary least squares to regress the individual parameters with regard to female
190 sex, number of APOE- $\epsilon 4$ alleles and education level of each patient. This evaluates the impact of each covariate after
191 correcting for the other ones, and also the significance of the corresponding association. Since we are in a multiple testing
192 setting, we use False Discovery Rate (FDR) [75] to obtain a map of corrected p -values that assess how certain it is that
193 the chosen covariate influences the onset or pace of atrophy for each region. Given the high number of statistical tests
194 (one for each of the 148 regions of the Destrieux atlas), a more stringent correction method such as Family-Wise Error
195 Rates would be unsuitable as it would discard significant correlations. Absolute pairwise-correlations between covariates
196 are .02 for APOE/sex, .05 for APOE/education and .18 for sex/education, which means that regressing with regards to the
197 education level might mitigate the strength of the observed sexual dimorphism, but interactions between covariates are
198 less likely for the other pairs.

199 *Interpretability of the p -values.* For each feature, patients are aligned on a common timeline with the individual onset
200 age and pace of atrophy. One can, for instance, observe that for the inferior temporal gyrus, cortical thinning occurs on
201 average 1.5 years earlier for each copy of the $\epsilon 4$ allele, and on average 23% faster for women, after correcting for the
202 other covariates. However these multiple timelines are learned independently and cannot be compared directly in order to
203 exhibit the regions that are mostly affected by a covariate, as it may not be statistically significant. Resorting to statistical
204 testing, using t-tests under the null hypothesis that the regression coefficient is 0, allows to circumvent this issue as it
205 normalizes all the effect sizes by the natural temporal scale associated with the region. Besides, for a fixed sample size,
206 p -values are monotonically related to effect sizes, so lower corrected p -values can be interpreted as indicative of a bigger
207 impact of the covariate, and allow comparison across brain regions and covariates.

208

209 We provide a map of cortical regions and a list of sub-cortical volumes that display significant differences when
210 stratified for sex or APOE- $\epsilon 4$ status, regarding onset age and pace of atrophy, for AD, amyloid positive MCI and healthy
211 aging. Corrected p -values higher than .05 are discarded and the remaining p -values are presented in logarithmic scale
212 (base 10) for cortical thinning maps.

213 3. Results

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

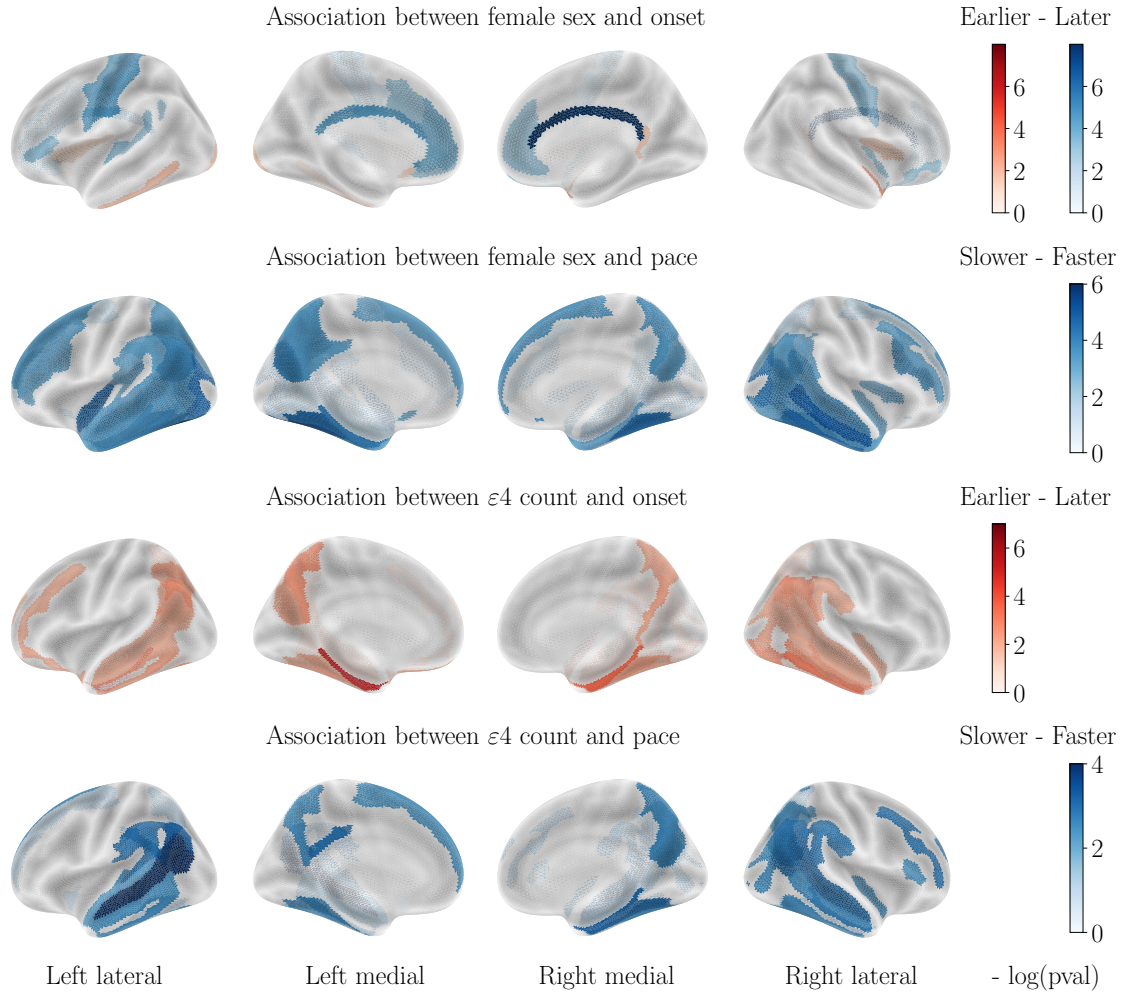


Figure 2: Cortical thinning over the course of AD progression. Legend bars shows negative log p -values. It should be noted that blue values indicate that the considered covariate (female sex or APOE- $\epsilon 4$ genotype) is a protective factor for onset age but a risk factor for pace of atrophy, since higher onset age is better but higher progression pace is worse.

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

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

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

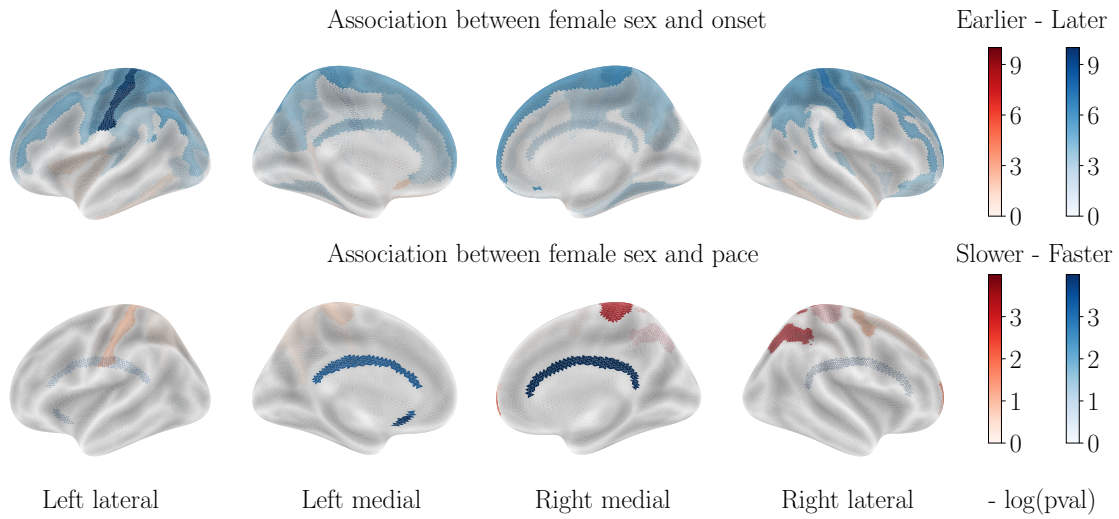


Figure 3: Cortical thinning over the course of cognitively normal aging. Associations with APOE- $\epsilon 4$ status are not displayed as they are not significant.

234 *Impact of APOE- $\epsilon 4$ genotype on cortical thinning for healthy aging.* In order to assess the impact of the APOE- $\epsilon 4$
 235 genotype on cognitively normal aging, we also stratified regarding this factor. Interestingly, the $\epsilon 4$ allele carriers do not
 236 display significantly different patterns for cortical thinning across healthy aging, which leads to believe that APOE- $\epsilon 4$ by
 237 itself does not cause the accelerated atrophy of the brain but only serves as one cog of the unraveling of AD. It should be
 238 noted however that the small amount of $\epsilon 4$ carriers in the healthy cohort can bias this result.

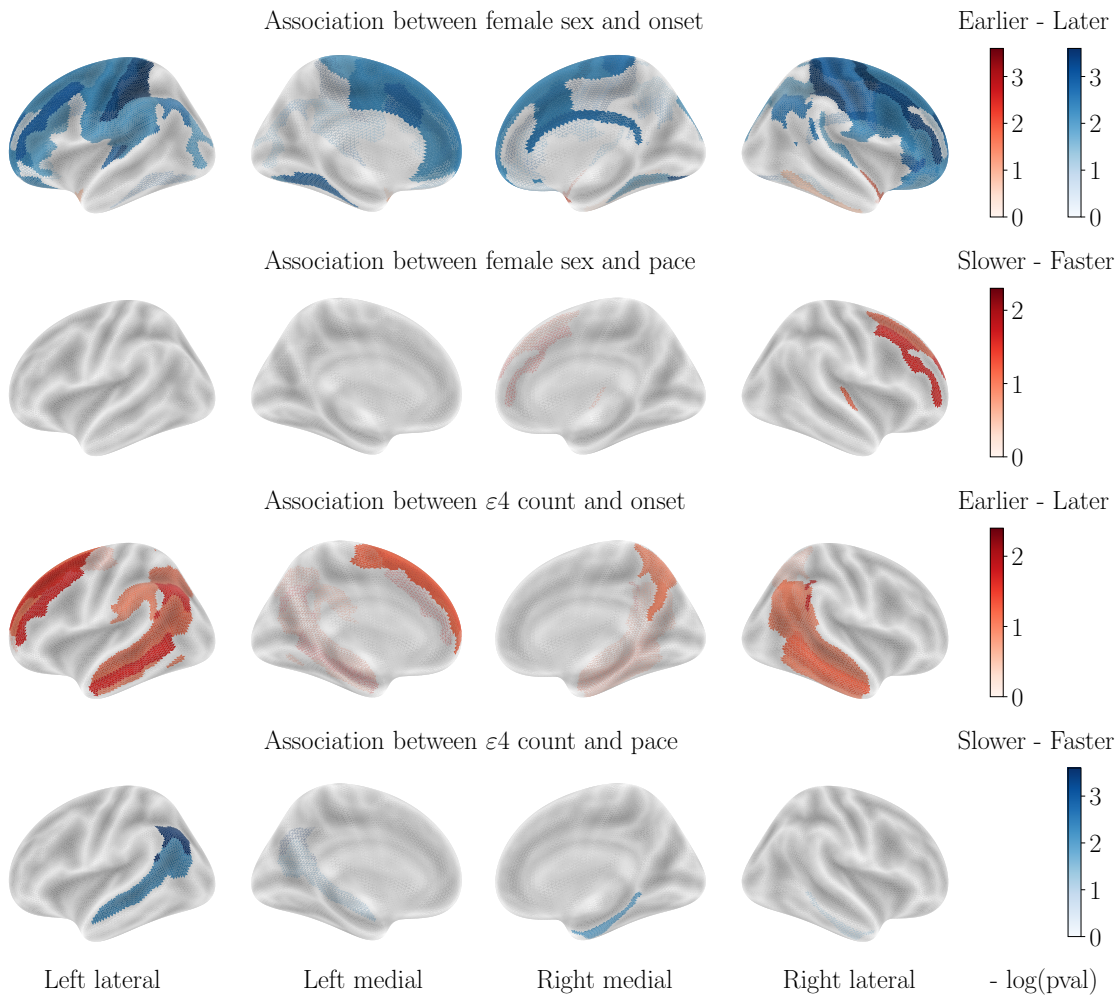


Figure 4: Cortical thinning over the course of MCI patients' aging.

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

242 *Correlations with the patterns of atrophy for subcortical structures.* For healthy aging, male sex correlates with an earlier
243 onset age for most regions with no significant differences in pace of atrophy, while no significant correlation is found for
244 APOE- ϵ 4 genotype. For the AD cohort on the other hand, female sex correlates with an earlier onset for most regions, and
245 higher paces of the hippocampi and bilateral amygdalas while APOE- ϵ 4 genotype correlates with earlier onset and higher
246 pace for the hippocampi and bilateral amygdalas. We reach the same conclusion regarding the MCI cohort as for cortical
247 thinning : sex correlates with atrophy in a similar fashion to the healthy cohort, while APOE- ϵ 4 genotype correlates in a
248 similar fashion to the AD cohort. Regions without significant 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.

249 *Differences between left and right hemisphere.* For AD progression, the left hemisphere displays more regions that dif-
250 fer significantly for both sex and APOE- ϵ 4 stratification, but the associated t-values do not significantly differ between
251 hemispheres. This confirms that atrophic patterns are asymmetric but not completely lateralized [76].

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 status. Correlations are only found in the healthy cohort, and higher education level correlates
254 with higher onset age for the postcentral gyrus, the medial parietal and medial occipital lobes, as well as the left superior
255 temporal lobe, and lower pace of atrophy for parts of the frontal and occipital lobes. No significant correlation is found
256 for the AD cohort, in line with former studies [77]. For subcortical volumes, only the hippocampal atrophy is delayed for
257 more educated healthy patients, and no significant correlation is found for AD patients. One hypothesis is that education
258 level is not, in itself, helping delay the atrophy for healthy controls, but acts as a proxy of lifestyle healthiness, which
259 influences metabolic pathways and brain atrophy. In AD cohort, that small preserving effect is likely to be cancelled by
260 the influence of other covariates that cause massive atrophy.

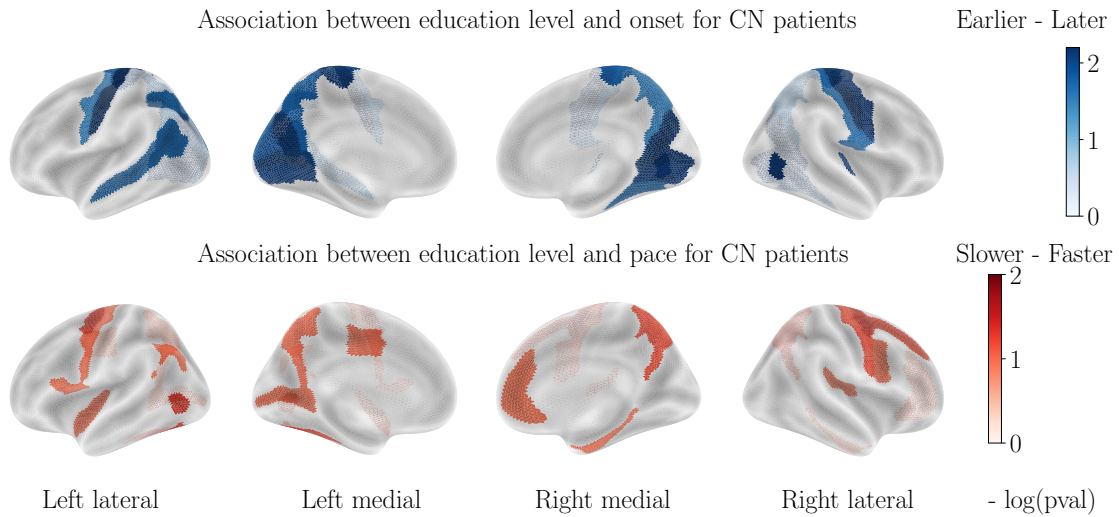


Figure 5: Correlation between education level and cortical thinning dynamics for CN patients. Correlations observed for the AD patients are not significant and thus not displayed.

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

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

- Sex is as important a risk factor as APOE- $\epsilon 4$ genotype for cortical thinning and brain atrophy for AD patients, as both stratifications yield effect sizes that are not significantly different.
- Female AD patients decline much faster than male patients, however, the onset of the atrophy is still earlier for male patients, in line with the healthy aging patterns. This suggests that the disease strikes female patients with much more intensity, but do not present an earlier onset. This point is revealed by the use of longitudinal studies and has important implications for practitioners for the follow-up of patients.
- Education level seems to be a protective factor for healthy patients but is not significant in AD progression.
- For the MCI cohort, the influence of sex is similar to that of the healthy cohort, while the effect of APOE- $\epsilon 4$ genotype is similar to that of the AD cohort, although of an overall weaker effect.

4. Discussion

Several limitations and design choices need to be acknowledged in order to put results in perspective.

Clinical characterization of diagnosis in ADNI. For the control cohort, we used the CN patients in ADNI, because it allows a fair comparison between AD progression and cognitively normal aging, without acquisition biases. Since ADNI is not an epidemiological study on healthy aging, the cognitively normal patients may not represent accurately the general

population because of ADNI's inclusion criteria. For the MCI cohort, it is important to note that MCI is a cognitive status defined by subjective memory complaints and does not always lead to AD as other factors can cause patients to have it. The prevalence of MCI symptoms are found to be between 15 and 20% for patients over 60 years old [78], and roughly 8 to 15% of these convert to AD each year [79]. In order to make the cohort less heterogeneous, we decided to only keep amyloid positive patients in order to interpret this cohort as describing AD pathogenesis. [80] assert that the recruited cohorts for CN, MCI and AD patients successfully describe the associated clinical status.

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

Impact of the chosen atlas. It must be taken into account that the choice of different atlas 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. On the other hand, our mixed-effect formulation cannot be fitted directly to vertex-wise thickness measurements because the onset age (or horizontal intercept) will not converge for features that display little progression compared to the feature noise.

Regions normalization. Since subcortical regions' volumes are correlated with the volumes of the skull and brain, it is standard practice to normalize by the intracranial volume in order to allow a fair comparison between subjects. The impact of such normalization is discussed in former studies : in [81, 82, 83] authors suggest that subcortical volumes should be normalized with total intracranial volume, while cortical thicknesses should not, for diagnosis prediction and progression models. On the other hand, [84] find that cortical thicknesses should be normalized with either intracranial volume or average thickness to help predict the cognitive status of a patient. [65] discuss the effect of normalizing cortical thicknesses to allow a fair comparison between healthy male and female subjects. Allometric scaling is often used to circumvent this issue, but [85] find that allometric and linear scaling yield similar effect sizes and coefficients when evaluating the effect of sex and age on brain measurements.

Interpretability of the onset age. As opposed to the straightforward pace of atrophy, the onset age needs to be interpreted with caution. It represents the age at which a patient crosses a chosen threshold (chosen to be the average value for the whole cohort). Brain atrophy does not have a well-defined starting point and the notion of onset age is thus to be understood with regard to a reference point in the average progression. For instance, the earlier onset ages for men in the CN cohort can be understood as describing the fact that cortical thicknesses are significantly thinner than for women. Since the difference in onset gets way smaller for the AD cohort, it agrees with former findings that the gap between men and women closes as neurodegeneration progresses, with a greater pace of decline for women in the late stages of the disease [51, 52].

Clinical implications. The discrepancies in alteration patterns of the brain between sexes and APOE genotypes reinforce the idea that the disease manifests differently between subpopulation and care should be provided accordingly. Besides, clinical trials that monitor the effect of a drug on neurodegeneration should put an emphasis on both having more representative demographics after enrolment, and evaluating the impact of drugs in a stratified manner as patients are likely to react differently to the drug depending on both the explored genetic risk factors. It is also interesting to note that most regions significantly affected by the considered risk factors are known to be associated with AD (e.g. medial temporal lobe, limbic system, frontal lobe, etc). This work could be interpreted jointly with studies that describe the sexual differences in associations between cortical thickness and cognition such as [52] in order to provide a complete description of the sexual dimorphism of neurodegeneration and its link with AD cognitive symptoms.

333 *Perspectives.* This statistical pipeline can be applied to other modalities of neuroimaging data. For instance, [86] applies
334 the same statistical pipeline to FDG-PET scans instead of structural MRI in order to assess the sexual dimorphism of AD
335 and influence of APOE genotype regarding brain hypometabolism, which complements the study of brain atrophy. Other
336 imaging modalities specific to AD, such as amyloid-PET or tau-PET, are also under investigation within this pipeline. A
337 strong sexual dimorphism for the spreading patterns of pathological protein tangles in the brain would prompt the latest
338 clinical trials, that choose amyloid load as a primary disease outcome, to put great care in evaluating the differentiated
339 results between male and female patients.

340 5. Conclusion

341 Structural alterations of the brain happen before the onset of cognitive decline and the collection of MRI-derived
342 features reveals varying patterns of atrophy between subgroups of patients. Female sex, APOE- ϵ 4 genotype and low
343 education level have been identified as the biggest risk factors for cognitive decline, but their impact on early-stage
344 structural alterations is not yet well understood. In this work we described the disentangled effects of these 3 covariates
345 on the onset and pace of regional atrophy and cortical thinning. This reveals that female sex is actually as strong a risk
346 factor for neurodegeneration as APOE- ϵ 4 genotype, and women experience much faster atrophic rates after correcting for
347 the APOE genotype. APOE- ϵ 4 genotype leads to earlier and faster atrophy for most regions of the brain for AD patients
348 but not for healthy patients. Healthy patients with higher education experience slightly delayed atrophy but not patients
349 with neurodegeneration. The results were validated with congruent findings from the same study applied to the regional
350 loss of gray matter density. This work calls for further exploration of the sexual dimorphism of AD regarding structural
351 alterations.

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358
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362 adni.loni.usc.edu. (This article does not contain any studies with human participants performed by any of the authors).

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