

Special Topic Section: Sex and Gender in Alzheimer's Disease

Sex differences in functional and molecular neuroimaging biomarkers of Alzheimer's disease in cognitively normal older adults with subjective memory complaints

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Abstract

Introduction: Observational multimodal neuroimaging studies indicate sex differences in Alzheimer's disease pathophysiological markers.

Methods: Positron emission tomography brain amyloid load, neurodegeneration (hippocampus and basal forebrain volumes adjusted to total intracranial volume, cortical thickness, and 2-deoxy-2-[fluorine-18]fluoro-D-glucose-positron emission tomography metabolism), and brain resting-state functional connectivity were analyzed in 318 cognitively intact older adults from the INSIGHT-preAD cohort (female n = 201, male n = 117). A linear mixed-effects model was performed to investigate sex effects and sex*apolipoprotein E genotype interaction on each marker as well as sex*amyloid group interaction for non-amyloid markers.

Results: Men compared with women showed higher anterior cingulate cortex amyloid load ($P = .009$), glucose hypometabolism in the precuneus ($P = .027$), posterior cingulate ($P < .001$) and inferior parietal ($P = .043$) cortices, and lower resting-state functional connectivity in the default mode network ($P = .024$). No brain volumetric markers showed differences between men and women. Sex*apolipoprotein E genotype and sex*amyloid status interactions were not significant.

[†]The full list of members of the INSIGHT-preAD study group is reported in the Acknowledgment section.

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Discussion: Our findings suggest that cognitively intact older men compared with women have higher resilience to pathophysiological processes of Alzheimer's disease.

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1. Introduction

Epidemiological studies have shown that women have a higher lifetime risk for developing Alzheimer's disease (AD) than men [1–4]. Women in their 60s show significantly faster age-related decline and greater deterioration of cognition than men [5–7]. Reasons for the higher frequency and age-specific prevalence of AD in women at older ages are not well understood.

Sex differences have been described by neuroimaging and postmortem human studies on AD dementia patients showing contrasting results [8]. In postmortem investigations, women showed more extensive senile plaques deposition throughout the brain than men at each early neurofibrillary tangle stage. At later neurofibrillary tangle stages (IV, V, and VI), both men and women had similarly extensive senile plaque deposits [8]. In vivo studies examined brain atrophy, a surrogate marker of neurodegeneration topographically correlated with neurofibrillary tangle. Although contrasting results were reported [9,10], findings showed brain atrophy differences in AD dementia patients stratified by sex in the hippocampus (HP) and in the frontal lobe [11–13]. Studies using 2-deoxy-2-[fluorine-18] fluoro-D-glucose–positron emission tomography (FDG-PET), a functional surrogate marker of neurodegeneration, reported significant decrease in brain glucose metabolism in men compared with women [14–16], whereas others did not find sex differences or increased glucose metabolism in cognitively older adults [17]. These inconsistent findings might be due to methodological aspects such as sample size features, statistical analysis, and the different approaches used to control for head size in volumetric magnetic resonance imaging (MRI) studies [18].

Sex differences were also reported in resting-state brain functional connectivity (rsFC) in the default mode network (DMN) regions [19,20], usually altered in clinical and prodromal stages of AD [21,22].

Apolipoprotein E (*APOE*) genotype is the best-characterized risk gene for sporadic AD [23]. However, results for the sex-dependent role of *APOE* $\epsilon 4$ allele in increasing the risk of developing AD in cognitively intact older women are contrasting [24,25].

Although sex differences have been reported in the incidence, prevalence, and biomarker profiles of AD [24,26,27], the reasons underlying these differences are still under debate. In particular, little evidence is available regarding the differential expression of imaging markers of AD between women and men in both aging and preclinical

stages of AD, as well as the effect of sex**APOE* genotype and sex*amyloid status interactions on such markers.

In the present multimodal imaging study, we aimed at investigating in vivo sex differences on the following markers: (1) brain amyloid load; (2) neurodegeneration (cortical thickness, HP volume, basal forebrain (BF) volumes, and FDG-PET metabolism); and (3) brain rsFC in a cohort of cognitively intact older adults with subjective memory complaints, a clinical risk factor for AD. Moreover, we investigated how sex**APOE* genotype and sex*amyloid status interactions affect these neuroimaging markers to provide insights for AD prevention and to take a step forward into the development of personalized, sex-specific precision medicine in the field of AD.

2. Methods

2.1. Participants from the INSIGHT-preAD study

Participants were recruited in the Investigation of Alzheimer's Predictors in Subjective Memory Complainers (INSIGHT-preAD) study, a monocentric French cohort at the Pitié-Salpêtrière University Hospital in Paris, with the goal of investigating the earliest preclinical stages of AD and its development, including influencing factors and markers of progression [28]. The INSIGHT-preAD study includes 318 cognitively normal Caucasian individuals from the Paris area, between 70 and 85 years of age, with subjective memory complaints and intact cognition and memory performances (Mini-Mental State Examination score ≥ 27 , Clinical Dementia Rating score 0, and Free and Cued Selective Reminding Test total recall score ≥ 41).

A comprehensive neuropsychological battery was administered to all INSIGHT-preAD cohort participants. A complete description of the cohort and its clinical and neuropsychological features was previously published [28]. Details on the cohort description are reported in the [Supplementary Materials Paragraph 2.1](#).

2.2. PET scan acquisitions and processing

Florbetapir-PET scans were acquired in a single session on a Philips Gemini GXL CT-PET scanner 50 (± 5) minutes after injection of approximately 370 MBq (333–407 MBq) of Florbetapir. The amyloid uptake was detected in certain regions of interest (ROIs), namely the precuneus (Pcu), the posterior and anterior cingulate, the parietal, temporal, and the orbitofrontal cortices [29].

During a distinct session, brain FDG-PET scans were obtained 30 minutes after injection of 2 MBq/kg of 2-deoxy-2-(^{18}F)fluoro-D-glucose. Brain glucose metabolism was detected in the following ROIs: (1) posterior cingulate cortex (PCC); (2) inferior parietal lobule; (3) Pcu; and (4) inferior temporal gyrus. Details on florbetapir-PET and FDG-PET acquisition protocols and image postprocessing are reported in the [Supplementary Materials, Paragraph 2.2](#).

2.3. MRI acquisitions and processing

Brain MRI acquisitions were conducted using a 3 Tesla MRI scanner (Siemens Magnetom Verio, Siemens Medical Solutions, Erlangen, Germany). Details regarding the 3D-T1 and resting state functional magnetic resonance imaging protocols of acquisition are reported in the [Supplementary Materials, Paragraph 2.3](#).

2.3.1. Cortical signature of prodromal AD

Cortical reconstruction was performed on the 3D-T1 MRIs using the FreeSurfer image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>), by the CATI—Multi-center Neuroimaging Platform, in France (<http://cati-neuroimaging.com>). The technical details of these procedures are described in the [Supplementary Materials, Paragraph 2.3.1](#). For statistical analysis, we exclusively considered 7 ROIs affected by AD: (1) medial temporal cortex; (2) inferior temporal gyrus; (3) temporal pole; (4) superior frontal gyrus; (5) superior parietal lobule; (6) supramarginal gyrus; and (7) Pcu [30,31]. For each region, we calculated the mean cortical thickness from the cortical thickness measurements obtained for each hemisphere (right and left).

2.3.2. HP and BF volumes

For the automated calculation of individual HP and BF volumes, the 3D-T1 MRI data were processed using [statistical parametric mapping](#) (SPM8, Wellcome Trust Center for Neuroimaging) and the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm>). The technical details of these procedures are described in the [Supplementary Materials, Paragraph 2.3.2](#). The delineation of the HP follows the consensual standard space harmonized protocol labels as described in detail by Wolf and colleagues [32]. Modulated white matter voxel values were included in the HP volume calculation because the harmonized protocol explicitly specifies to include small white matter regions (alveus and fimbria) in HP segmentation [33]. The delineation and localization of the cholinergic BF followed the Mesulam's nomenclature based on the histological serial coronal sections and postmortem MRI scan of a brain from a 56-year-old man, as previously described [34]. HP and BF volumes were corrected to the total intracranial volume (TIV) using the residuals method. First, a linear regression of the volume of a neuroanatomical structure on the TIV was fitted

to the entire dataset. From the fitted model, the residuals, which are differences between actual volume and fitted volume based on a subject's TIV, were calculated [35]. The TIV-corrected measurements were expressed as $Vol_{adj_i} = Vol_i - b (TIV_i - meanTIV)$ [36,37]. Vol_{adj_i} is the TIV-adjusted volume of the subject i , Vol_i is the original uncorrected volume of the subject i , b is the slope from the linear regression of Vol on TIV , TIV_i is the TIV for the subject i , and $meanTIV$ is the mean TIV across all subjects.

2.4. Resting-state functional MRI preprocessing and seed-based functional connectivity analysis

Resting state functional magnetic resonance imaging data were preprocessed using Data Processing Assistant for Resting-State fMRI advanced edition V4.3 [38] implemented in Data Processing & Analysis for Brain Imaging Version V3.0 (<http://rfmri.org/dpabi>), based on SPM8. The technical details of these procedures are described in the [Supplementary Materials, Paragraph 2.4](#).

A seed-to-seed rsFC analysis was conducted to explore sex-related differences in crucial nodes within the DMN. The ROIs used in the seed-to-seed analyses were anterior medial prefrontal cortex—PCC, left and right Pcu—HP, and left and right PCC—HP.

The Data Processing Assistant for Resting-State fMRI advanced edition toolbox was used to extract individual subject seed-to-seed connectivity values including several steps. First, the mean time series of each seed region was extracted and correlated (Pearson's correlation) with that of the second seed region. Then, the Fisher's r -to- z transform was applied to standardize the resulting correlation values [39]. Fisher's z values were extracted for each pairwise functional connectivity for each individual.

2.5. APOE genotype

DNA was extracted from frozen blood samples of participants applying the 5Prime ArchivePure DNA purification system. The *APOE* genotypes were determined using the Sanger method. Technical details on *APOE* genotyping are reported in the [Supplementary Materials, Paragraph 2.5](#).

2.6. Statistical analysis

Demographic, clinical, and global cognitive features were compared between males and females. Chi-square test was performed on categorical variables, and one-way analysis of variance two-tailed test was used for continuous variables.

Differences in imaging markers between men and women and the sex interaction with *APOE* genotype or amyloid status were assessed using linear models for the HP and the BF volumes. For imaging markers of brain amyloid load, cortical thickness, glucose metabolism, and functional brain connectivity, we used linear mixed-effects models because for these markers, values from several ROIs were extracted for each subject. The effect of *APOE* genotype and amyloid

status on imaging markers was investigated performing two independent models for each imaging marker. The following variables were included in each model as covariates: age; educational level; alcohol consumption; smoking; hypertension; obstructive sleep apnea; and mood disorders. Fixed effects of our linear mixed models were ROIs, sex, *APOE* genotype/amyloid status, their interactions, and the potential confounding covariates mentioned earlier; each subject was included in the model as random effect. Using the linear mixed-effects models, we have handled the multiple-testing problem in each neuroimaging metric. Glycemia levels were exclusively considered in the model investigating brain glucose metabolism. Individuals with genotype $\epsilon 2/\epsilon 4$ were not included in the statistical analysis investigating the effect of *APOE* with sex. Post hoc tests were performed to compare sex differences when the interaction with ROIs was significant. Because the randomized effects of standardized uptake value ratio (SUVR) of amyloid PET were not normally distributed, we ranked the SUVR in each ROI before fitting the model. The statistical models used were verified for normal distribution of residuals, random effects, and homoscedasticity of residuals. Statistical analyses were performed using SPSS v.22.00 and R 3.3.2.

3. Results

3.1. Clinical risk factors, demographic and neuropsychological features

Table 1 describes demographic features of the INSIGHT-preAD population. Women had lower level of education than men ($P = .014$). Lifestyle, cardiovascular risk factors, and clinical comorbidities revealed that men significantly differed from women in terms of alcohol consumption ($P < .001$) and cigarette smoking ($P < .001$). Men more frequently had hypertension ($P = .013$) and obstructive sleep apnea ($P = .049$) than women. Compared with men, women suffered more from mood disorders ($P < .001$). Women and men did not differ in glycemia concentrations (women, 95.56 mg/dL [12.60]; men, 98.26 mg/dL [13.54]; $P = .075$). No differences in the frequencies of *APOE* alleles were detected between women and men. Women and men significantly differed in terms of TIV (Table 1). Women showed higher memory performances and lower visuospatial abilities than men (Table 2).

3.2. Sex and sex*APOE genotype group effects on in vivo regional brain amyloid PET uptake

No differences in the frequencies of amyloid positive individuals were detected between women and men (Table 1). Table 3 summarizes the main effects investigated for brain amyloid load. We found a significant global effect of sex in modulating brain amyloid load (sex differences [men-women] in rank SUVR: mean, 24.02; standard error, 10.62; $P = .025$; Table 3 Model 1). The significant sex*ROIs interaction ($P = .010$) indicated that this effect was not the same

Table 1
Sociodemographic features, clinical comorbidities, and genetic risk factors in the INSIGHT-preAD cohort stratified by sex

	Women, N = 201	Men, N = 117	P value
Age	76.02 (3.24)	76.05 (3.85)	.938
Education			
High	126 (62.69%)	89 (76.07%)	.014
Low	75 (37.31%)	28 (23.93%)	
Risk factors			
Memory complaints (McNair)	12.85 (6.21)	13.02 (6.09)	.818
Alcohol consumption (weekly cups)*	5.27 (6.46)	10.41 (9.44)	<.001
Smoking			
Never	137 (68.16%)	43 (36.75%)	<.001
Previously	51 (25.537%)	65 (55.156%)	
Currently	13 (6.47%)	9 (7.69%)	
BMI	25.08 (3.85)	25.44 (2.94)	.383
Hypertension	71 (35.32%)	58 (49.57%)	.013
Atrial fibrillation	16 (7.96%)	12 (10.26%)	.486
Heart disease	17 (8.46%)	18 (15.38%)	.057
Dyslipidemia	80 (39.80%)	53 (45.30%)	.338
Diabetes	9 (4.48%)	6 (5.13%)	.792
Obstructive sleep apnea	8 (3.98%)	11 (9.40%)	.049
Head trauma	20 (9.95%)	6 (5.13%)	.130
Mood disorders	71 (35.32%)	14 (11.97%)	<.001
B12 deficiency	3 (1.49%)	1 (0.85 %)	.623
Posttraumatic stress disorder	0 (0.00%)	1 (0.85%)	.189
TIV	1289.55 (88.52)	1465.61 (104.37)	<.001
Amyloid status			
Positive	56 (27.86%)	32 (27.35%)	.992
Negative	145 (72.14%)	85 (72.65%)	
<i>APOE</i> genotype			
E2/E2	1 (0.50%)	0 (0.00%)	.309
E2/E3	24 (11.97%)	17 (14.53%)	
E2/E4	4 (1.99%)	0 (0.00%)	
E3/E3	135 (67.16%)	79 (67.52%)	
E3/E4	35 (17.41%)	17 (14.53%)	
E4/E4	2 (1.00%)	4 (3.42%)	

Abbreviation: *APOE*, apolipoprotein E; BMI, body mass index; TIV, total intracranial volume.

NOTE. Numbers denote mean (standard deviation) and frequency (percentage). P value indicates significant sex differences using the Chi-square Test and the Analysis of Variance for categorical and continuous variables, respectively. P values $<.05$ are reported in bold.

*Alcohol consumption (female N = 197, male M = 116): low education, scores ≤ 5 at the 8-point scale; high education, scores ≥ 5 at the 8-point scale (high school graduate).

among the different ROIs. In particular, the anterior cingulate cortex showed higher amyloid uptake in men than in women ($P = .009$; Fig. 1) at the post hoc comparison. The interaction among sex*ROIs*APOE genotype did not show a significant impact on in vivo amyloid load ($P = .438$).

3.3. Sex, sex*APOE genotype, and sex*amyloid status group effects on markers of neurodegeneration

3.3.1. Cortical AD signature

No significant results were found for the global effect of sex ($P = .277$; Table 3 Model 1) or its interaction with brain

Table 2
Neuropsychological performances, stratified by sex, of 318 cognitively intact older adults with subjective cognitive complaints from the INSIGHT-preAD cohort

	Women, N = 201	Men, N = 117	P value*	P value corrected [†]
MMSE	28.69 (0.95)	28.62 (0.96)	.501	.644
FCSRT total score	46.48 (1.83)	45.42 (2.06)	<.001	<.001
Rey figure copy	33.06 (3.58)	34.01 (1.93)	<.001	<.001
Rey figure recall (30 min)	15.71 (6.31)	19.26 (6.21)	<.001	<.001
Frontal assessment battery	16.32 (1.72)	16.54 (1.61)	.606	.682
Trail making test (B-A)	52.97 (38.01)	41.51 (30.54)	.054	.121
Lexical fluency	22.61 (5.56)	22.11 (6.46)	.141	.254
Semantic fluency	31.48 (7.16)	31.06 (7.01)	.254	.381

Abbreviations: FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; TIV, total intracranial volume.

NOTE. Means and standard deviation are shown for the two groups, as well as *P* values, to indicate statistically significant group differences. *P* values <.05 are reported in bold.

**P* values adjusted for age, education level, hypertension, alcohol consumption, mood disorders, obstructive sleep apnea, smoking, and TIV.

[†]*P* values corrected for multiple testing using Benjamini-Hochberg correction.

areas belonging to the AD cortical thickness signature ($P = .622$; Table 3 Model 1). No significant effect was found in the sex**APOE* genotype and in the sex*ROIs**APOE* genotype interactions ($P = .635$ and $P = .382$, respectively; Table 3 Model 1). The interaction between sex and amyloid status on the brain areas examined for the AD cortical thickness signature was not significant as described in Table 3.

3.3.2. HP and BF volumes

No effect of sex was found on both HP and BF volumes (Table 3). In addition, no differences among women and

men with different *APOE* genotype or different amyloid status were found both in HP ($P = .8484$ and $P = .5438$, respectively; Table 3) and BF ($P = .1523$ and $P = .5438$, respectively; Table 3).

3.3.3. Brain glucose hypometabolism

Table 3 summarizes the main effects investigated for FDG-PET. A global effect of sex on glucose metabolism was found (sex differences [men-women]: mean, -0.079 ; standard error, 0.030 ; $P = .009$; Table 3 Model 1) and also the interaction between sex and ROIs resulted significant ($P < .001$; Table 3 Model 1). In particular, post hoc comparisons revealed lower glucose metabolism in men than in women in the posterior cingulate, inferior parietal cortices and Pcu (Fig. 2). No significant effect of *APOE**sex*ROIs and amyloid status*sex*ROIs interactions was found ($P = .744$ and $P = .770$, respectively; Table 3).

3.4. Sex, sex**APOE* genotype, and sex*amyloid status group effects on brain functional connectivity at rest

Table 3 summarizes the main effects investigated for rsFC. A significant global effect of sex on rsFC was found. In particular, a significant reduction of rsFC was found in men compared with women (sex differences [men-women]: mean, -0.034 ; standard error, 0.015 ; Fig. 3). However, this difference was not significantly different among the ROIs considered ($P = .498$; Table 3 Model 1). No significant effect of *APOE**sex*ROIs and amyloid status*sex*ROIs interactions was reported ($P = .634$ and $P = .909$, respectively; Table 3).

4. Discussion

Our results suggest sex differences in AD biomarkers of amyloidosis, neurodegeneration, and rsFC in cognitively

Table 3
Summary of global effect of sex on imaging markers of AD and its interaction with brain regions, *APOE* genotype, or amyloid status in cognitively intact older adults

Models	AMY-PET F value; <i>P</i> value	Cortical thickness F value; <i>P</i> value	HP F value; <i>P</i> value	BF F value; <i>P</i> value	FDG-PET F value; <i>P</i> value	rsFC F value; <i>P</i> value
Model 1						
Sex	5.101; .025	1.2; .277	0.5482; .4597	0.0454; .8315	6.77; .009	4.57; .033
Sex*ROIs	3.022; .010	0.7; .622	—	—	11.30; <.001	0.84; .498
Sex* <i>APOE</i>	0.328; .694	0.5; .635	0.1645; .8484	1.8952; .1523	0.15; .859	2.10; .124
Sex*ROIs* <i>APOE</i>	1.003; .438	1.1; .382	—	—	0.58; .744	0.76; .634
Model 2						
Sex	—	1.3; .260	0.4106; .5222	0.4106; .5222	6.25; .012	4.78; .029
Sex*ROIs	—	0.8; .569	—	—	11.15; <.001	0.88; .476
Sex* <i>Amyloid</i>	—	2.8; .097	0.3694; .5438	0.3694; .5438	0.05; .817	1.87; .172
Sex*ROIs* <i>Amyloid</i>	—	1.0; .393	—	—	0.38; .770	0.25; .909

Abbreviations: AMY-PET, amyloid PET; *APOE*, apolipoprotein E; BF, basal forebrain; FDG-PET, 2-deoxy-2-[fluorine-18]fluoro-D-glucose-PET; HP, hippocampus; ROIs, regions of interest; rsFC, resting-state functional connectivity.

NOTE. Reported are the main effect of sex and the interaction effects of sex*ROIs/*APOE*/amyloid status, sex*ROIs**APOE*/amyloid status. Main effects of *APOE*/amyloid status and of ROIs were also included in the model together with the covariates described in the statistical section but are not shown here for brevity. Data are given as F values and *P* values. *P* values <.05 are reported in bold.

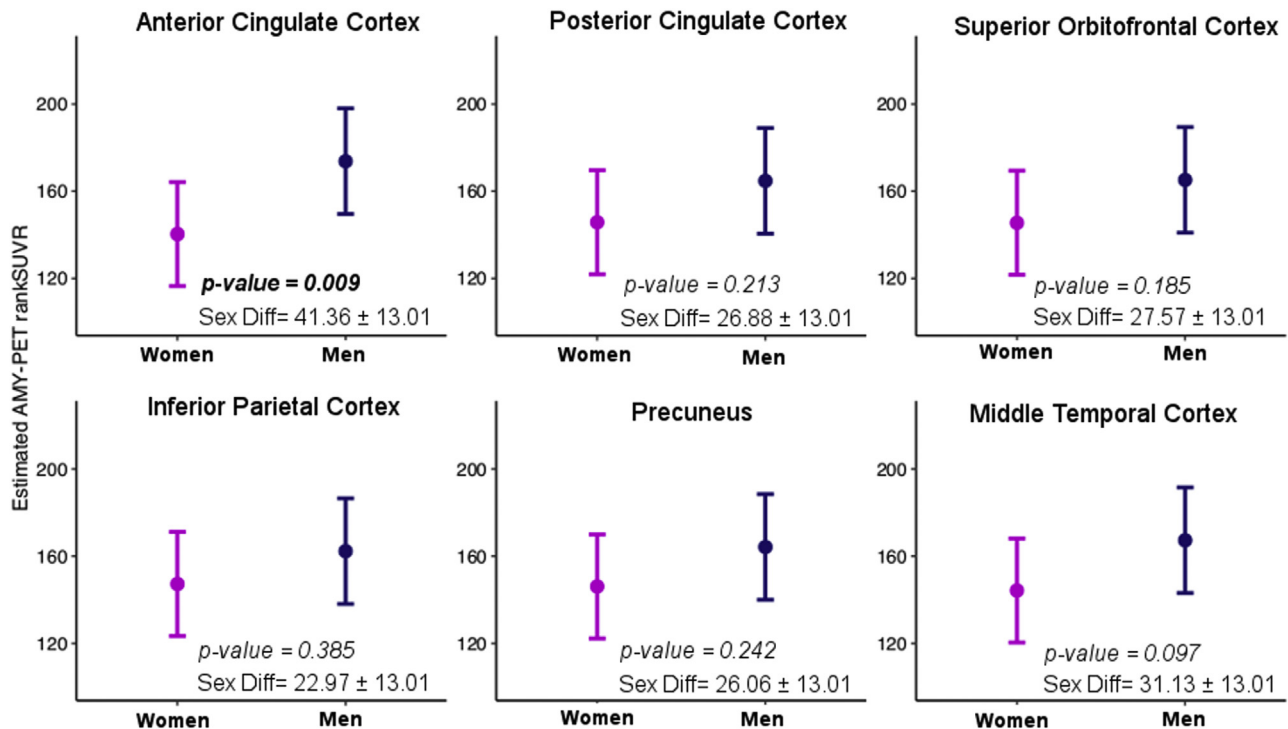


Fig. 1. Estimated mean of rank amyloid-PET standardized uptake value ratio (SUVR) according to sex and regions of interest (ROIs). Significantly reduced brain amyloid load in the anterior cingulate cortex was found in women compared with men. Geometric points denote mean effects, whereas error bars denote lower and upper confidence intervals. Sex Diff, Sex differences between men and women.

intact individuals older than 70 years. In particular, male compared with female sex was associated with higher amyloid load in the anterior cingulate cortex and lower glucose metabolism in the PCC, inferior parietal lobule, and Pcu. In addition, lower DMN rsFC was found in men than in women. These effects were independent from the *APOE* genotype and the amyloid status. These results revealed that cognitively intact older men compared with women are able to accumulate more AD-related pathology suggesting that men may be more resilient to AD pathophysiological processes.

In terms of clinical comorbidities, we found a higher prevalence of hypertension and obstructive sleep apnea in men than in women, which is consistent with the literature [40,41]. On the other hand, women compared with men showed higher prevalence in the history of mood disorders, as previously described in patients with AD dementia and older cognitively intact individuals [42–44].

Sex differences in neuropsychological performances are in line with previous evidence showing, in cognitively intact individuals, better verbal memory performances in women than in men [45–48] and higher visuospatial abilities in men than in women [46,49].

No differences in the prevalence of *APOE* $\epsilon 4$ allele were present between women and men in our cohort, matching previous findings from population-based studies [50,51].

We found significantly higher accumulation of *in vivo* brain amyloid load in the anterior cingulate cortex in men than in women. Recently, independent cohorts reported re-

sults similar to ours [48,51–53], indicating that a greater amyloid load is necessary before men manifest the disease [54]. In addition, previous evidence from the INSIGHT-preAD study group showed no impact of amyloid load in cognitive performances [28] as previously determined in independent preclinical AD cohort [55].

We did not find any significant effect of sex on AD regional cortical thickness, whereas two previous studies using the same methodology in cognitively intact older individuals showed reduced cortical thickness in men compared with that in women [56,57]. Different to our study, none of them included comorbidities and cardiovascular risk factors as covariates, which have been shown to be associated with reduced cortical thickness [56,58,59].

Results of sex effects on other imaging markers of neurodegeneration, such as the HP, revealed no significant differences between the groups. These results are in line with the recent findings by Perlaki [18] and the results of the meta-analysis conducted by Tan and colleagues on 4000 brains showing no sexual dimorphism in the hippocampal volume [60]. Contrasting evidence showing a reduced HP volume in cognitively intact men compared with women was also reported [48,61]. However, the majority of studies conducted so far did not investigate HP volumes separately in males and females [62].

No effect of sex was found on the BF volume, and to the best of our knowledge, this is the first study investigating the influence of sex on BF volume. The findings reported so far

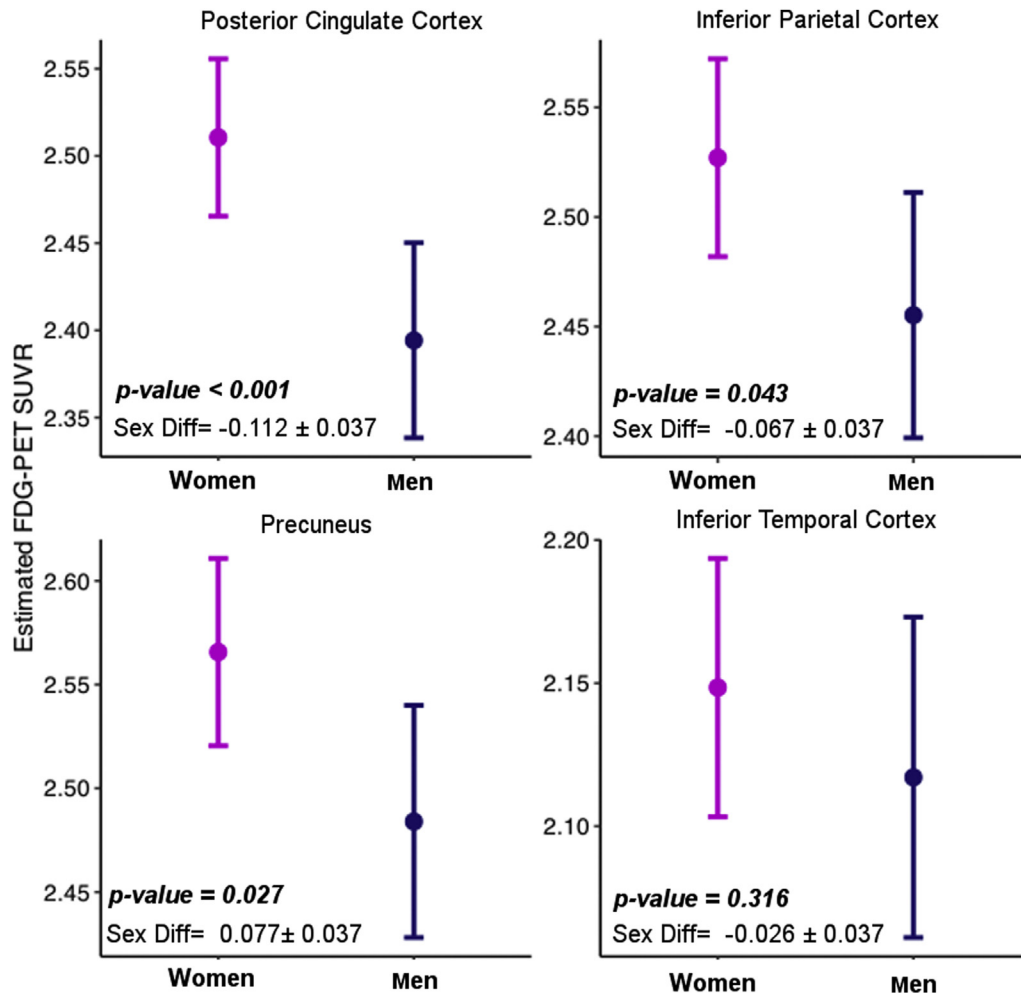


Fig. 2. Estimated mean of FDG-PET standardized uptake value ratio (SUVR) according to sex and ROIs. Significantly reduced glucose metabolism in the posterior cingulate cortex, inferior parietal, and precuneus was found in men compared with women. Geometric points denote mean effects, whereas error bars denote lower and upper confidence intervals. Abbreviations: FDG-PET, 2-deoxy-2-[fluorine-18]fluoro-D-glucose/positron emission tomography; ROIs, regions of interest; Sex Diff, Sex differences between men and women.

in cognitively intact individuals, prodromal patients, and AD dementia patients accounted for sex as a covariate in the statistical analysis, thus preventing the opportunity to investigate sex effects on BF volume. The mean BF volumes described in our population are similar to the ones reported in other cohorts of cognitively intact older individuals [63,64].

We found lower glucose metabolism in the PCC, inferior parietal lobule, and Pcu in men than in women, which is in line with previous findings that described similar results in frontal areas [15,17]. In a cohort of young adults (mean age of 28 years), men compared with women showed higher glucose metabolism in temporal-limbic regions and cerebellum [17]. The difference between our findings and the ones described by Gur and colleagues might suggest the presence of interacting mechanisms between sex and age. In other words, aging compensatory mechanisms might be different between men and women. In line with this hypothesis, no difference between men and women was found, considering a broader population in terms of age range be-

tween 20 and 90 years [14,65]. The lack of sex differences in the latter studies might be due to the presence of increased (in young) and decreased (in elderly) glucose metabolism in men compared with women, which has consequently flattened the results. However, the majority of previous studies adjusted their results by sex [66,67] or compared specific populations within sex (premenopause, perimenopause, and menopause women) [68] preventing the possibility to investigate the interaction of age and sex on the brain glucose metabolism. Further longitudinal studies investigating age trajectories separately for men and women will help clarify this hypothesis.

In addition, men and women from the INSIGHT-preAD study showed different brain functional connectivity at rest in the main nodes of the DMN. Sexual dimorphisms in the expression of the human genome [69] are known to influence physiological variables that can affect brain functional connectivity [17,70]. In line with our results, previous studies reported sex differences in DMN rsFC displaying adult and older women with greater rsFC than men [20,71,72].

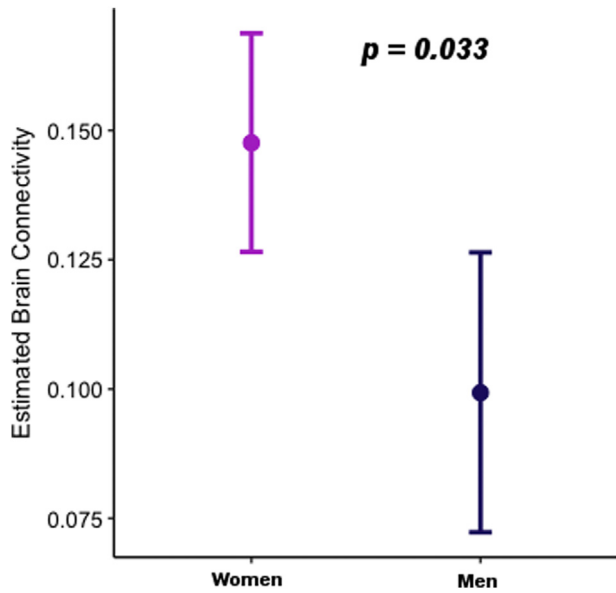


Fig. 3. Estimated mean resting-state functional connectivity (rsFC). Significantly reduced rsFC was found in men compared with women. Geometric points denote mean effects, whereas error bars denote lower and upper confidence intervals. Measures of rsFC were obtained from the Fisher's *r*-to-*z* transform values.

However, other studies have failed to observe any sex differences in rsFC in adult brains [19]. To our knowledge, no similar results have been reported in aging so far. The reduced rsFC found in men is in line with the effect observed for glucose metabolism, suggesting that cognitively intact older men might have higher brain reserve capacity than cognitively intact women. However, future studies should further investigate this hypothesis.

In our study, in spite of equal levels of global intact cognition and after controlling for age, educational level, and clinical comorbidities, men compared with women showed more pronounced amyloid load, neurodegeneration, and reduced functional connectivity in the DMN. These findings suggest that men may have higher brain resilience to pathophysiological processes of AD than women.

No association between sex and *APOE* genotype was displayed in our study (Table 3) as found in independent studies [48,73]. This finding is in contrast to previous evidence showing reduced HP volumes, glucose hypometabolism, and abnormal functional connectivity in cognitively normal female *APOE* $\epsilon 4$ carriers compared with male carriers [8,74–76]. Our results suggest that sex and *APOE* genotype may independently impact neuroimaging markers of AD.

No interaction between sex and amyloid status on markers of neurodegeneration and rsFC was found in our cohort (Table 3). To our knowledge, this is the first study investigating this question. The lack of significant effects suggests that sex does not moderate the effect of amyloid on the volumetric, metabolic, and functional imaging marker of AD, and thus the effect of sex is independent by the amyloid status.

Multiple mechanisms may explain different vulnerabilities to AD between men and women: (1) developmental

[77]; (2) hormonal modulation [78] that may influence epigenetics [79,80]; and (3) sex-biased gene expression [69]. The interaction of sex hormones, genetics, and environmental factors will likely determine whether a woman/man develops a disorder [79]. This is crucial to understand the biological mechanisms by which hormone fluctuation may increase/reduce the risk of developing a specific disease. On the other hand, significant neurodegeneration processes, such as brain glucose hypometabolism, found in our group of men might be associated with adverse lifestyle factors or prevalence of risk factors (such as cardiovascular) [81], although we took into account the impact of cardiovascular risk factors, such as hypertension, in our data analysis. Sex-biased gene expression and the subsequent phenotypic diversity associated with it have implications beyond the evolutionary biology that might affect medical genetics and the precision medicine approach.

Several limitations of the present study should be considered. First of all, our results refer to a specific population of cognitively intact individuals because they all have subjective memory complaints and an age range between 70 and 80 years. Men in our cohort were highly educated compared with women, which suggests a recruitment bias. Accordingly, we controlled for education in our models. Second, our results lack longitudinal evidence that may better explain the evolution of AD neuroimaging markers in association with sex and its interaction with *APOE* genotype and amyloid status. However, future investigations will be conducted in this direction.

Finally, owing to violations of the normality assumption of randomized effects of amyloid load values, we investigated possible additional effects, such as global cognition or glucose metabolism. None of them influenced the distribution of the randomized effects, suggesting that missing information, such as the future conversion of some individuals to cognitive impairment and AD dementia, might have had an effect on the distribution of randomized effects. For this reason, we had to rank the amyloid load values for our statistical analysis.

Despite these limitations, our results highlighted interesting evidence for sex effects on diverse multimodal neuroimaging markers of AD. Based on these findings, sex appears to be a central driver of phenotypic variability in neuroimaging markers of AD among cognitively intact older adults, which may relate to differences in brain reserve capacity between sexes. Therefore, the role of sex should be carefully considered when designing strategies for prevention, detection, and treatment of AD. Analysis of sex effects, alone and in combination with genetic, epigenetic, and phenotypic traits, should be the first step toward a more personalized and patient-centered precision medicine approach to AD [82,83].

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- *In Vitro* Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Patent Number: 8916388
- *In Vitro* Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Patent Number: 8298784
- Neurodegenerative Markers for Psychiatric Conditions Publication Number: 20120196300
- *In Vitro* Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100062463
- *In Vitro* Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100035286
- *In Vitro* Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Publication Number: 20090263822
- *In Vitro* Method for The Diagnosis of Neurodegenerative Diseases Patent Number: 7547553
- CSF Diagnostic in Vitro Method for Diagnosis of Dementias and Neuroinflammatory Diseases Publication Number: 20080206797
- *In Vitro* Method for The Diagnosis of Neurodegenerative Diseases Publication Number: 20080199966
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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2018.05.014>.

RESEARCH CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources. Sex differences have been reported in the incidence, prevalence, and biomarker profiles of Alzheimer's disease (AD). Little evidence is available regarding imaging markers of AD between women and men both in aging and preclinical stages of AD, as well as the interaction effect with Apolipoprotein E (APOE) genotype and amyloid status on such markers. These relevant citations are appropriately cited.
2. Interpretations: We found evidence for sex effects on diverse multimodal neuroimaging markers of AD. Sex appears to be a central driver of phenotypic variability in neuroimaging markers of AD among cognitively intact older adults, which may relate to differences in brain reserve capacity between sexes.
3. Future directions: Sex should be carefully considered when designing strategies for prevention, detection, and treatment for AD. The analysis of sex effects may help in making steps toward a more personalized and patient-centered approach to the disease.

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