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Review Article

Sex differences in functional and molecular neuroimaging biomarkers of Alzheimer's disease in a monocenter cohort of 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 nonamyloid markers.

Results: Men compared with women showed higher anterior cingulate 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.

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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.

Keywords: Alzheimer's disease; Sex; Amyloid; Cortical thickness; FDG-PET; Hippocampus; Basal forebrain; Metabolism; APOE; Aging; Cognitively intact older individuals

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 frontal lobe [11–13]. Studies using 2-deoxy-2-[fluorine-18]fluoro-D-glucose–positron emission tomography (FDG-PET), a functional surrogate marker of synaptic and 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 ε4* 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 to investigate in vivo sex differences on the following: (1) PET 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. 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 $\geq$27, Clinical Dementia Rating score 0, and Free and Cued Selective Reminding Test total recall score $\geq$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 ($\pm$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 precuneus (Pcu), posterior