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Influence of Gender on Tau Precipitation in Alzheimer's Disease According to ATN Research Framework

Ying Zhang[1] · Jiaying Lu[2] · Min Wang[1] · Chuantao Zuo[2] · Jiehui Jiang[3]

Abstract

Tau proteins accumulation and their spreading pattern were affected by gender in cognitive impairment patients, especially in the progression of Alzheimer's disease (AD). However, it was unclear whether the gender effects for tau deposition influenced by amyloid deposition. The aim of this study was to investigate gender differences for tau depositions in $A\beta$ positive (A^+) subjects. In this study, tau and amyloid positron emission tomography images, structural magnetic resonance imaging images, and demographic information were collected from 179 subjects in Alzheimer's Disease Neuroimaging Initiative (ADNI) database and 63 subjects from Huashan Hospital. Subjects were classified as T^+ or T^- according to the presence or absence of tau (T) biomarkers. We used two-sample t test and one-way analysis of variance test to analyze the effect of gender with adjusting for age, years of education, and Minimum Mental State Examination. In the ADNI cohort, we found differences in Tau deposition in fusiform gyrus, inferior temporal gyrus, middle temporal gyrus and parahippocampal gyrus between the female T^+ (FT^+) and male T^+ (MT^+) groups ($p < 0.05$). Tau deposition did not differ significantly between female T^- (FT^-) and male T^- (MT^-) subjects ($p > 0.05$). In the Huashan Hospital cohort, there was no difference in Tau deposition between FT^+ and MT^+ ($p > 0.05$). The results show that tau depositions significantly increased in females in above brain regions. Our findings suggest that tau deposition is influenced by gender in the A^+ subjects. This result has important clinical implications for the development of gender-guided early interventions for patients with both Tau and Amyloid depositions.

Keywords Alzheimer's disease · Gender · Amyloid positron emission computed tomography · Tau positron emission computed tomography

Introduction

Alzheimer's disease (AD) is one of the major neurodegeneration diseases in the elderly, and it has become an important medical challenge due to its incurability and irreversibility (Jia et al. 2020; Long and Holtzman 2019). According to the 2018 AT N research framework proposed by the National Institute on Aging and Alzheimer's Association, the diagnosis of AD is defined by the presence of amyloid β (Aβ), phosphorylated tau, and neurodegeneration. Among them, Aβ and tau protein deposition in the brain are two most important AD biomarkers (Ossenkoppele et al. 2018). Especially, while Aβ-positive (A^+) subjects are considered to enter the AD continuum, tau pathology, as a major driver of local neurodegeneration (La Joie et al. 2020), has high clinical relevance in AD late stages (Jack et al. 2013).

Gender plays an important role in brain development and aging (Kaczkurkin et al. 2019), as well as the occurrence and development of neurodegeneration (Ferretti

Ying Zhang and Jiaying Lu have contributed equally to this work.

✉ Chuantao Zuo
zuochuantao@fudan.edu.cn

✉ Jiehui Jiang
jiangjiehui@shu.edu.cn

1 School of Communication and Information Engineering, Shanghai University, Shanghai 200444, China

2 PET Center and National Research Center for Aging and Medicine and National Center for Neurological Disorders, Huashan Hospital, Fudan University, Shanghai 201206, China

3 Institute of Biomedical Engineering, School of Life Science, Shanghai University, Shanghai 200444, China

et al. 2018). In AD, gender is believed to be a crucial factor for heterogeneity. While the impact of gender on AD epidemiology is the subject of intense current investigation, the concept of sex-specific clinicopathological AD phenotypes is largely unexplored (Ferretti et al. 2018). In many AD studies, gender is usually considered as a covariable similar to age, without further exploration. Fortunately, gender differences in AD pathological biomarkers have attracted people's attention in recent years (Demetrius et al. 2021; Ferretti et al. 2018), which is of great significance for the development of AD precision medicine. Additionally, the effect of gender on brain tau deposition has also been explored in a few in vitro studies but limited in vivo studies with controversial findings (Barnes et al. 2005; Hu et al. 2021; Jack et al. 2017a; Mattsson et al. 2017; Oveisgharan et al. 2018; Salehi et al. 1998). Hence, to expand the current knowledge of gender effect on brain tau accumulation in the AD continuum, we conducted a two-cohort study including Caucasian and Asian subjects with two different tau positron emission computed tomography (PET) tracers in A^+ populations (Jack et al. 2018). By addressing such phenotypic variation, the current study may have significant implications for the development of precise and effective therapeutics in AD.

Materials and Methods

Subjects

The subjects of this study were drawn from two cohorts, the Alzheimer's Disease Neuroimaging Initiative (ADNI) and Huashan cohorts. The study was also approved by the Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China. All subjects from Huashan Hospital provided written informed consent.

Table 1 shows the characteristics of all 242 participants. The ADNI cohort consisted of 179 subjects and the Huashan cohort consisted of 63 subjects. Notably, all 63 subjects from Huashan cohort are with A^+ and Tau-positive (T^+). Each subject provided detailed clinical information including: gender, age, years of education, Mini-Mental State Examination (MMSE), Clinical Dementia Rating-Sum of Boxes (CDR-SB), the Alzheimer's Disease Assessment Scale-Cognitive 13 (ADAS-Cog 13; ADNI only) and Montreal Cognitive Assessment (MoCA; ADNI only), and imaging data, including ^{18}F-florbetapir (^{18}F-AV-45) PET, ^{18}F-flortaucipir (^{18}F-AV-1451, ADNI only) PET, ^{18}F-florzolotau PET [also known as ^{18}F-APN-1607, or ^{18}F-PM-PBB3 (Lu et al. 2020; Mattsson et al. 2017); Huashan only] and T1-weighted structural MRI.

In the ADNI cohort, the inclusion criteria of normal controls (NC), mild cognitive impairment (MCI) and AD

Table 1 The demographic and clinical information of all subjects

	ADNI				Huashan Hospital	
	Female		Male		Female	Male
n	94		85		35	28
T^-/T^+	63/31		64/21		0/35	0/28
APOE ε4 carriers	50 (53.2%)		27 (31.8%)		22 (62.9%)	19 (67.9%)
Diagnosis						
NC	48 (51.1%)		35 (41.2%)		0	0
CI	46 (48.9%)		50 (58.8%)		35 (100%)	28 (100%)
Age, years ± SD (range)	74.1±8.0 (57–89)	74.3±6.8 (63–89)	77.4±7.1 (66–92)[a]	80.0±8.5 (63–94)[b]	66.0±9.4 (51–80)	66.1±9.9 (44–83)
Education, years ± SD	15.9±2.3	15.6±2.0	16.9±2.4[a]	18.1±2.4[b]	10.3±3.2	10.9±4.1
MMSE, score ± SD	28.1±2.4	24.6±5.2	27.9±2.7	26.4±3.3	21.0±5.4	21.1±5.7
CDR-SB, score ± SD	0.9±1.8	2.5±2.8	1.1±1.7	2.4±2.9	6.5±3.1	6.4±2.7
ADAS13, score ± SD	15.1±8.0	24.2±12.1	17.6±8.2	21.7±6.6	–	–
MoCA, score ± SD	24.9±3.9	20.1±6.5	24.4±3.0	22.4±3.9[b]	–	–

ADAS13 Alzheimer's Disease Assessment Scale-Cognitive 13, *APOE* Apolipoprotein E, *CDR-SB* Clinical Dementia Rating Scale-Sum of Boxes, *CI* cognitive impairment, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *NC* normal controls, *SD* Standard Deviation

[a]$p < 0.05$ compared to FT$^-$

[b]$p < 0.05$ compared to FT$^+$

refer to ADNI_GeneralProceduresManual.pdf (https://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf). The NC group was the subjects with clinical diagnosis of NC in the ADNI cohort. The cognitive impairment (CI) group included MCI and AD subjects. In Huashan cohort, NC was defined as the subjects with normal performance in neuropsychological tests with visual confirmation of amyloid negative on ^{18}F-AV-45 or ^{11}C-PiB PET. The CI group comprised subjects with MCI and AD. The inclusion criteria for MCI were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) criteria (Samuel 1995). Only those who were not diagnosed with dementia were considered for a diagnosis of MCI, which was defined according to Petersen's criteria (Petersen 2004). The inclusion of AD dementia was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al. 1984).

The inclusion criteria of the subjects in the ADNI cohort were as follows: (1) no history of stroke, hypertension, brain disease or mental illness; (2) all subjects were A$^+$ [^{18}F-AV-45 PET standardized uptake value ratio (SUVR) of cerebral relative to cerebellum is higher than 1.18] (Chen et al. 2015). For Huashan cohort, all subjects were with visual confirmation of A$^+$ on ^{18}F-AV-45 or ^{11}C-PiB PET (Lundeen et al. 2018). The other inclusion criteria were same as ADNI cohort. Figure 1 shows the data inclusion and exclusion process for all subjects in the ADNI cohort.

Image Acquisition and Preprocessing

The detailed information of image acquisition for ADNI data was available on the LONI website (https://ida.loni.usc.edu/login.jsp). The details of the image acquisition for Huashan data were described previously (Li et al. 2021; Shi et al. 2020).

The preprocessing steps were as follows. First, the original digital imaging and communications in medicine (DICOM) data were converted to the neuroimaging informatics technology initiative (NIFTI) file format using DCM-2NII (http://people.cas.sc.edu/rorden/mricron/index.html). Second, the gray matter (GM), white matter, and cerebrospinal fluid images were segmented from T1-weighted images by using the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat/). Third, the PET images were co-registered with their corresponding T1-weighted images and corrected for partial volume effects (PVE) based on the Muller-Gartner algorithm (Gonzalez-Escamilla et al. 2017) using the PETPVE12 toolbox (http://www.fil.ion.ucl.ac.uk/spm/ext/#PETPVE12). Fourth, the GM images were normalized to the Montreal Neurological Institute (MNI) standard space, and the PVE-corrected PET images were normalized to the MNI space using the forward transformation parameters determined by the GM image spatial normalization. Finally, these PET images were smoothed with an 8-mm full width at half-maximum (FWHM) Gaussian kernel. We also performed preprocessing without PVE correction (PVC) in parallel. All procedures were implemented using the Statistical Parametric Mapping (SPM8) software (www.fil.ion.ac.uk/spm).

More details on the image acquisition and Muller–Gartner correction method are described in the Supplement material.

Fig. 1 Flowchart of the inclusion and exclusion of subjects in this study (ADNI dataset)
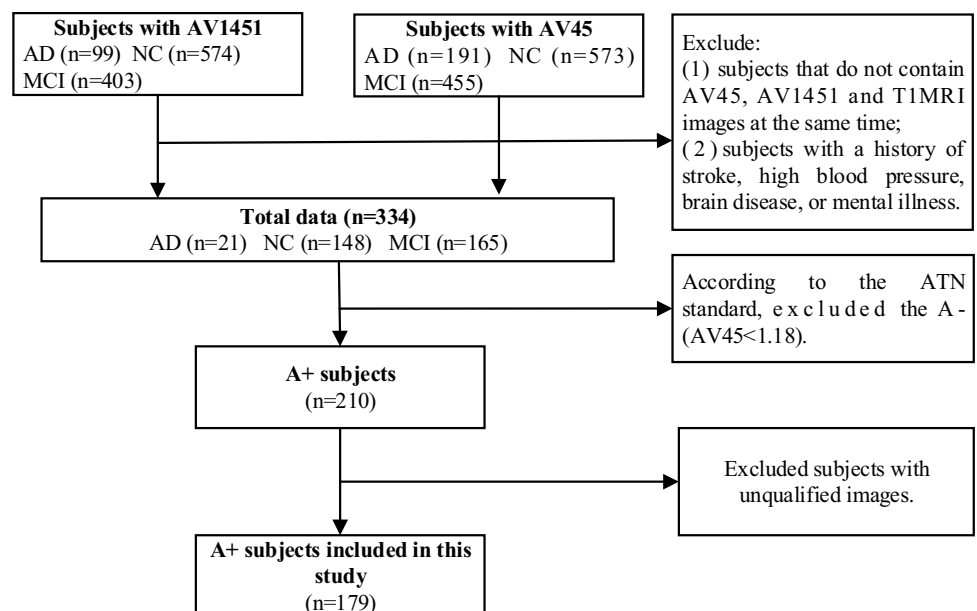
Extraction of Meta-ROI and SUVR Calculation

According to previous studies (Chotipanich et al. 2020), we selected 10 meta-regions of interest (meta-ROI) based on the Anatomical Automatic Labeling (AAL) template, including fusiform gyrus, inferior temporal gyrus, lingual gyrus, middle temporal gyrus, occipital gyrus, parahippocampal, superior parietal gyrus, posterior cingulate gyrus, and precuneus. The tau SUVR of the ROIs was calculated using the cerebellar gray matter as a reference brain region in standard MNI space (Jack et al. 2017b).

Definition of $A^+/A^-/T^+/T^-$

In the ADNI cohort, the definitions of $A^+/A^-/T^+/T^-$ were from previous studies; For ^{18}F-AV45 PET, the whole cerebellum was used as the reference region, and the whole cerebral cortex was used as the ROI to calculate the SUVR; The SUVR of 1.18 was considered as a cut-off point for A^+/A^- (Chen et al. 2015).

For ^{18}F-AV1451 PET, based on previous study, a bilateral weighted SUVR value from a composite temporal meta-ROI (entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal regions) was calculated by a reference region (cerebellar GM); The SUVR of 1.33 was considered as a cut-off point for T^+/T^- (Jack et al. 2017b). We also performed a visual assessment to validate the results. In Huashan cohort, due to the lack of cut-off criterion of T^+/T^- for ^{18}F-florzolotau PET images, and the ununified amyloid tracers for A^+/A^- (^{18}F-AV-45 or ^{11}C-PiB), grouping was done with visual assessment by three experienced neuroradiologists (CTZ: 25 years of experience; HWZ: 15 years of experience; JYL: 5 years of experience), who were blind to the clinical diagnosis. ^{18}F-Florzolotau PET images were displayed with the Mango viewer software (version 4.1; Research Imaging Institute, The University of Texas Health Science Center, San Antonio, TX, USA; http://ric.uthscsa.edu/mango). The maximum intensity was manually adjusted so that the predominant color in the inferior cerebellar cortex would be the midpoint of the spectrum color scale. Images were evaluated in the transverse, sagittal, and coronal views, and the overall pattern of each scan was scored as positive or negative for global cortical binding. In particular, the reader was instructed to evaluate binding in hippocampus, temporal lobe, parietal lobe, occipital lobe, frontal lobe, and cingulate gyrus, and only scans with negativity in all assessed regions would be defined as T^-. The final decision of T^+/T^- was based on the consensus of at least two independent assessors.

Statistical Analysis

Quantitative values of SUVR to be analyzed for all subjects were calculated using MATLAB 2017a, and subjects' clinical information and quantitative results were statistically analyzed by SPSS 25.0 (SPSS Inc., IBM Corporation, Chicago, USA), and Prism software (available from PrismGraphPad) was used to plot and visualize the statistical data of this study. Differences of clinical variables in different groups were analyzed using two-sample t test and one-way Analysis of Variance (ANOVA) test. For tau deposition, in the ADNI cohort, the differences of Tau SUVR in different ROIs were analyzed at the gender level without distinguishing T^+ and T^-, as well as at gender-specific population with homologous tau pathology [female tau positive (FT$^+$) versus male tau positive (MT$^+$), female tau negative (FT$^-$) versus male tau negative (MT$^-$)]. A two-sample t test was used to analyze the effect of gender on the SUVR for the 10 ROIs after adjusting for tau SUVR of the 10 ROIs according to age, years of education, and MMSE. In the Huashan cohort, since only patients with T^+ were included, the comparison between genders was just performed between FT$^+$ and MT$^+$ using the same method as the ADNI cohort analysis. The above experiments were repeated using data without PVC and the results are summarized in the Supplementary material. $p < 0.05$ was considered statistically significant.

Results

Demographic Characteristics

Table 1 lists demographic information and related indicators of AD cognitive ability assessment. In the ADNI cohort, compared to FT$^+$, MT$^+$ was slightly older ($p = 0.005$) and more educated ($p < 0.001$). In addition, the MoCA scale score of group MT$^+$ was slightly higher than that of FT$^+$ ($p = 0.043$). There was no statistical difference in global disease severity as per MMSE ($p = 0.57$), CDR-SB ($p = 0.60$), and ADAS13 ($p = 0.48$) between T^+ groups of different genders. In the T^- cohort, men were older ($p = 0.012$) and more educated ($p = 0.016$) than female, too. Similarly, no significant difference between MT$^-$ and FT$^-$ in MMSE ($p = 0.57$), CDR-SB ($p = 0.27$), ADAS13 ($p = 0.057$), and MoCA ($p = 0.097$) was found. In addition, we also calculated the cortical thickness of 10 ROIs, including entorhinal, fusiform, inferior temporal gyrus, lateral occipital, lingual gyrus, middle temporal gyrus, parahippocampal, superior parietal gyrus, posterior cingulate gyrus and precuneus. There was no significant difference for all regions for Huashan cohort ($p > 0.05$). Right parahippocampal gyrus was slightly thicker in

females than that in males for ADNI cohort ($p = 0.02$). There were no significant differences in other ROIs for ADNI cohort ($p > 0.05$). For details, see Table S2.

In the Huashan cohort, no difference between MT^+ and FT^+ was found (age: $p = 0.98$, years of education: $p = 0.27$, MMSE: $p = 0.86$, CDR-SB: $p = 0.98$). In addition, only cognitively impairment patients with "A^+T^+" were included in Huashan cohort because in the hospital-based cohort the subjects with normal cognition and with cognitive dysfunction but showing "A^+T^-" were very limited. Further validation within the "A^+T^-" subjects will be carried out when we have enough data.

Effects of Gender on Regional Tau SUVR in ADNI Cohort

Female had higher tau SUVR values in the fusiform gyrus ($p = 0.027$), inferior temporal gyrus ($p = 0.046$), lingual gyrus ($p = 0.005$), middle temporal gyrus ($p = 0.046$), occipital lobe ($p = 0.006$), parahippocampal ($p = 0.005$), and superior parietal lobe ($p = 0.027$) regions (Fig. 2). There was no statistical difference in posterior cingulate gyrus ($p = 0.32$) and precuneus ($p = 0.14$) between males and females.

Analysis of the data without PVC found that the lingual gyrus ($p = 0.097$), occipital lobe ($p = 0.005$), parahippocampal gyrus ($p = 0.027$), and superior parietal lobe ($p < 0.001$) preserve the effect of gender on tau SUVR (Supplementary Fig. S1).

## Effects of Gender on Regional Tau SUVR in T^+/T^- Group in the Two Cohorts

The ^{18}F-florzolotau PET mean images with PVC (Huashan cohort) (Fig. 3a) demonstrated increased contrast among FT^+ compared to MT^+. The same result is also consistent in the ADNI cohort (Fig. 3b).

In the Huashan cohort, since only T^+ patients were enrolled, the comparison between genders were only done with homologous tau pathology. In line to the above findings in the ADNI cohort, higher Tau SUVR values in the parahippocampal gyrus ($p = 0.38$) were found in females than that in males (Fig. 4). Table 2 shows the detailed Tau SUVR of each ROI in different groups.

In the data without PVC, tau deposits were found to be higher in females than that in males only in the parahippocampal gyrus ($p = 0.018$). The results are shown in Supplementary Fig. S2.

In the T^+ ADNI cohort, tau SUVR values were higher in the fusiform gyrus ($p = 0.009$), inferior temporal gyrus ($p = 0.009$), middle temporal gyrus ($p = 0.041$), and parahippocampal ($p = 0.041$) in the females than that in males, while no significant difference was found in lingual gyrus, occipital lobe, superior parietal lobe, posterior cingulate gyrus and precuneus ($p > 0.05$). In the T^- subset, all ROIs had similar Tau SUVR values between genders (Fig. 5).

Analysis of data without PVC found that compared with MT^+, FT^+ had higher tau deposition in the fusiform gyrus ($p = 0.078$), inferior temporal gyrus ($p = 0.023$), middle temporal gyrus ($p = 0.023$), occipital gyrus ($p = 0.023$) and superior parietal gyrus ($p = 0.02$). Gender had no effect on tau
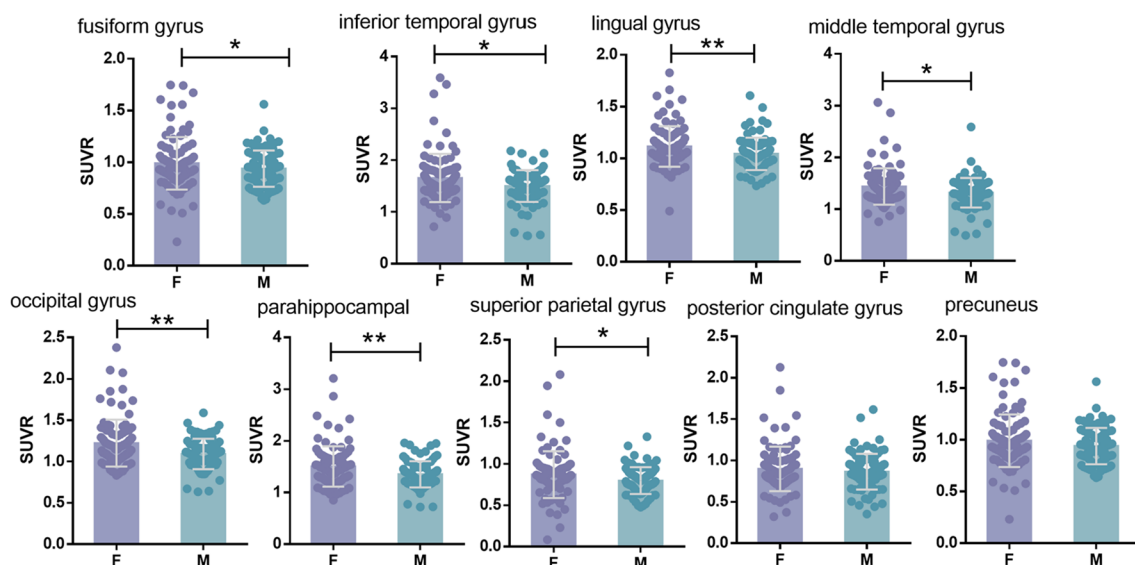
Fig. 2 In the ADNI cohort, grouped by sex, there were regions of interest for differences in AV-1451 SUVR. AV-1451 SUVR for female (purple) and male (blue) are depicted. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Fig. 3 Mean images with PVC. **a** ¹⁸F-florzolotau PET SUVR mean images with PVC in Huashan cohort. **b** ¹⁸F-flortaucipir PET SUVR mean images with PVC in ADNI cohort. The color scale represents the SUVR
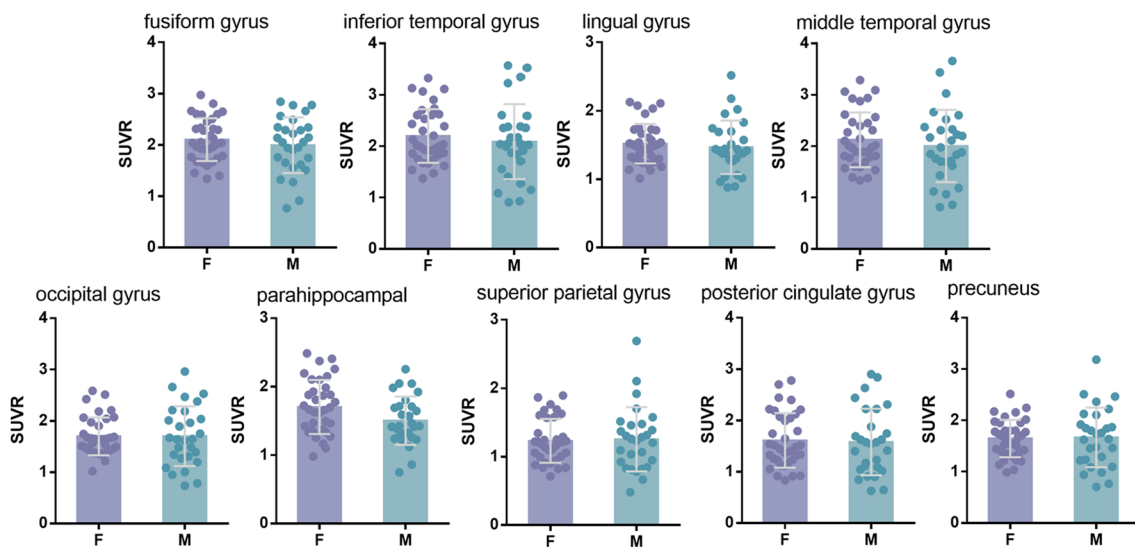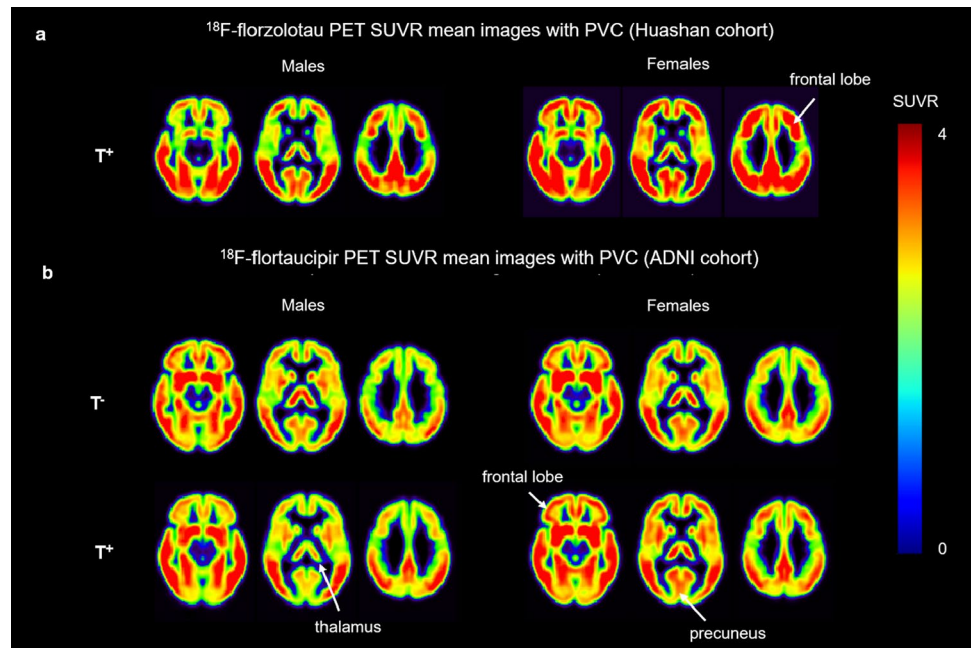
Fig. 4 In the Huashan cohort, grouped by sex, there were regions of interest for differences in florzolotau SUVR. Florzolotau SUVR for female (purple) and male (blue) are depicted. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

deposition in lingual gyrus, parahippocampal, posterior cingulate gyrus and precuneus (Supplementary Fig. S3).

The comparison results without PVC are summarized in the supplementary material (Supplementary Fig. S1–S4 and Table S1).

Discussion

In this study, we explored the gender effect on tau accumulation in A⁺ subjects using two different tau PET tracers

Table 2 The detailed tau SUVR of each ROI in different groups

	ADNI						Huashan Hospital			
	FT[−]	FT[+]	MT[−]	MT[+]	*p value*	p_{adjust}	FT[+]	MT[+]	*p value*	p_{adjust}
Fusiform gyrus	1.5 ± 0.2	2.0 ± 0.4	1.5 ± 0.2	1.7 ± 0.3[b]	0.002	0.009	2.1 ± 0.4	2.0 ± 0.5	0.38	0.97
Inferior temporal gyrus	1.5 ± 0.2	2.0 ± 0.6	1.5 ± 0.3	1.6 ± 0.3[b]	0.001	0.009	2.2 ± 0.5	2.1 ± 0.7	0.49	0.97
Lingual gyrus	1.0 ± 0.1	1.2 ± 0.4	1.0 ± 0.1	1.2 ± 0.1	1.00	1.00	1.5 ± 0.3	1.5 ± 0.4	0.55	0.97
Middle temporal gyrus	1.3 ± 0.2	1.7 ± 0.5	1.3 ± 0.3	1.4 ± 0.2[a]	0.016	0.041	2.1 ± 0.5	2.0 ± 0.7	0.45	0.97
Occipital gyrus	1.1 ± 0.1	1.4 ± 0.6	1.1 ± 0.2	1.2 ± 0.2	0.12	0.18	1.7 ± 0.4	1.7 ± 0.6	0.98	0.98
Parahippocampal	1.4 ± 0.2	1.8 ± 0.5	1.3 ± 0.2	1.5 ± 0.3[a]	0.018	0.041	1.7 ± 0.4	1.5 ± 0.3[a]	0.042	0.38
Superior parietal gyrus	0.8 ± 0.2	1.0 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	0.06	0.11	1.2 ± 0.3	1.3 ± 0.5	0.83	0.97
Posterior cingulate gyrus	0.8 ± 0.2	1.0 ± 0.4	0.8 ± 0.2	1.0 ± 0.2	1.00	1.00	1.6 ± 0.5	1.6 ± 0.6	0.84	0.97
Precuneus	0.9 ± 0.2	1.2 ± 0.3	0.9 ± 0.2	1.0 ± 0.2	0.24	0.31	1.6 ± 0.4	1.7 ± 0.5	0.86	0.97

p_{adjust} *p* value after Benjamini and Hochberg correction

[a] $p < 0.05$ compared to FT[+]

[b] $p < 0.01$ compared to FT[+]
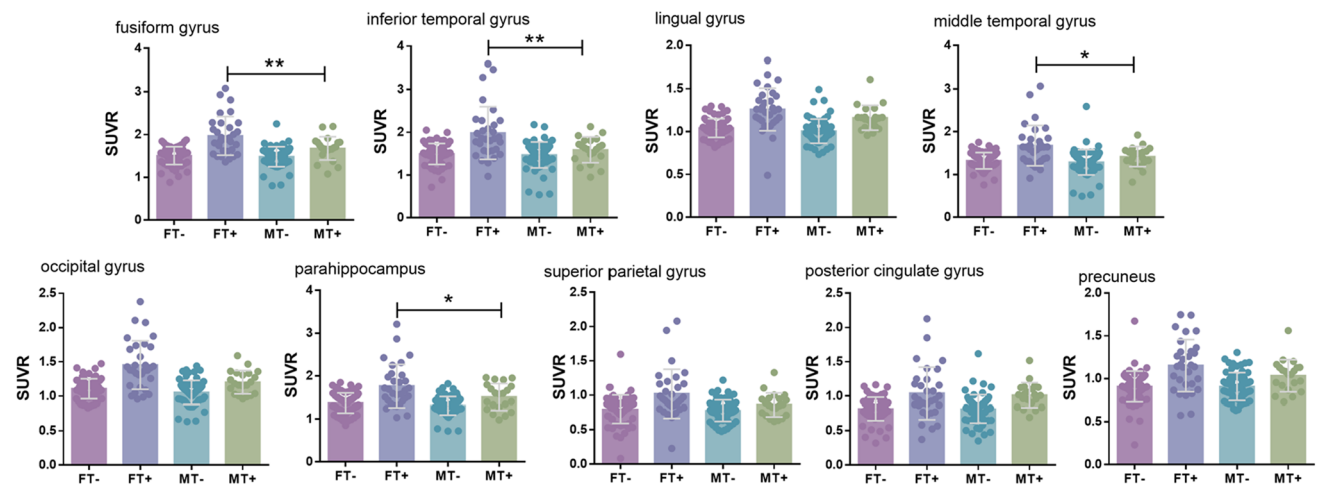
Fig. 5 In the ADNI cohort, grouped by FT[−], FT[+], MT[−], and MT[+], there were regions of interest for differences in tau SUVR. AV-1451 SUVR for female (red and purple) and male (blue and green) are depicted. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$

in two different ethnicities, and we consistently found that in T[+] individuals, females suffered from heavier tau burden than males after controlling other confounding factors including age, education degree, and global cognitive dysfunction.

In the study, we found more tau deposition in women than men among those who entered the AD disease spectrum and were tau-positive. Previous studies have shown that women have a greater tau burden than men, which is consistent with our findings (Yan et al. 2021). In addition, based on ROI analysis, we also found inconsistent regions of interest in the ADNI cohort and the Huashan cohort in which sex caused differences in tau deposition. In the ADNI cohort, we found higher tau SUVR values in the cingulate gyrus, inferior temporal gyrus, middle temporal gyrus, and parahippocampal gyrus FT[+] groups than that in the MT[+] group.

The ROI difference of tau deposition in the two cohorts may be caused by ethnic differences. Ethnic differences in AD biomarkers have been reported (Meeker et al. 2021; Shadlen et al. 1999; Tang et al. 1998; Weuve et al. 2018; Xiong et al. 2022). Most of the subjects in the ADNI cohort were from Europe and the United States, while the subjects included in the Huashan cohort were all from Asia. The differences in brain structure and cognitive reserve between subjects in both cohorts also may be a reason for the different tau deposition in various brain regions of ethnic groups.

Gender has been recognized as a potential risk factor for AD and has drawn a lot of attention in the scientific community over the past few decades. Although the greater prevalence of AD in females is considered an indirect consequence of the greater longevity, other social and biological factors such as education degrees, sex hormones, and genes

are also thought to contribute to the AD-related sex differences (Medeiros and Silva 2019; Zhu et al. 2021). Among these factors, deviations in brain structure and biomarkers are one of the important biological explanations for such sexual dimorphism in AD. For example, in brain development, the average brain volume of female was found to be smaller than male, and hence more sensitive to pathological agents for AD (Mielke et al. 2014). More rapid neurodegeneration (i.e., annual atrophy rate) was also found in female patients of AD than males (Ardekani et al. 2016; Hua et al. 2010). For the two key pathological mechanisms—Aβ and phosphorylated tau accumulation, several studies have been conducted to explore the differences. In AD, no clear sex differences in Aβ burden have been found (Barnes et al. 2005; Holland et al. 2013; Jansen et al. 2015; Mattsson et al. 2017), except one post-mortem study indicated a higher degree of cerebral amyloid angiopathy in men than in women (Shinohara et al. 2016). For tau pathology, most post-mortem pathological studies in patients with AD did not suggest any effect of sex on global burden of tau, while individual reports indicated possible effects in specific brain regions where women had higher numbers of neurofibrillary tangles (Barnes et al. 2005; Salehi et al. 1998). And in cognitively intact elderly individuals, significantly higher Braak stages for tangles in women than men were only seen after 80 years (Hu et al. 2021). Cerebrospinal fluid (CSF) research in vivo reported similar findings, one of which reported no difference between genders in patients with AD (Mattsson et al. 2017), and another reported higher tau concentrations in women than in men with MCI (undefined) (Holland et al. 2013). One Tau PET study in cognitively unimpaired individuals aged 50 years and older found no sex differences in prevalence of tau positive (Jack et al. 2017a),while the possible sex effects on tau accumulation in vivo in specific regions in subjects under biological AD category (A^+T^+) required further investigation. Furthermore, a recent post-mortem study in community-based elders found that women had higher levels on a global measure of AD pathology, especially tau tangle density than men (Oveisgharan et al. 2018), which encouraged the further exploration for the possible sex effect on brain tau accumulation in vivo in those under Alzheimer's continuum.

Herein, we conducted a two-cohort study with two different tau PET tracers, one of which was ^{18}F-AV1451, the same first-generation ligand as reported in the previous study (Jack et al. 2017a), and another was ^{18}F-florzolotau, a second-generation ligand with high affinity for both 3R and 4R tau deposits (Chini et al. 2020) in A^+ subjects. Whereas no gender differences were found in A^+T^- participants with ^{18}F-AV1451 PET scans, and the significantly higher tau burden was observed in FT^+ than that in MT^+ with both tau tracers when eliminating the confounding effects of age, education degree, and global cognitive dysfunction. The

specific regions with elevated tau located in early involved regions in Braak stage system (Braak et al. 2006), including fusiform gyrus, inferior temporal gyrus, middle temporal gyrus, parahippocampal gyrus in the ADNI cohort, as well as parahippocampal gyrus in the Huashan cohort, which were also previously found to harbor significant higher ^{18}F-AV1451 bindings in female APOE ε4 carriers than male APOE ε4 carriers (Yan et al. 2020). The similar tau burden in A^+T^- between genders might result from the relatively young ages, since in vitro study in cognitive unimpaired elders only saw the differences in those older than 80 years (Hu et al. 2021).

It is worth noting that the FT^+ suffered from higher tau deposition than MT^+, but had similar age, education degree, and disease severity (global cognition). It is widely accepted that in vivo Tau SUVR is a sensitive index for disease severity monitoring and progression prediction (Ossenkoppele et al. 2016). One possible explanation for such inconsistent tau level and disease severity in females might be the different vulnerability of the downstream dysfunction of tau—neurodegeneration, given that female brain was found to have 1) a persistently younger metabolic brain age compared with the male brain on ^{18}F-FDG PET images, which relative to the chronological age (Goyal et al. 2019), and 2) greater cortical thickness throughout the lifespan on MRI images (Sowell et al. 2007). Meanwhile, although sex is found to modify APOE ε4 dose effect on brain tau deposition in cognitively impaired individuals (Yan et al. 2021), this study did not combine gender and APOE information for analysis because of some subjects in the ADNI cohort lacked APOE ε4. The conclusion in this study is that FT^+ has a higher Tau burden than MT^+, and whether it is related to APOE ε4 needs further investigation. Another possible reason was sex hormones since a previous hormone-based study found that testosterone has a protective effect on tau protein, which was lower in women (Sundermann et al. 2020).

Many studies have shown that PVC can effectively increase the correspondence of the measured signal with the true regional tracer uptake (Wolters et al. 2018; Zhao et al. 2019), thus has better regulating effect on SUVRs. In our study, PVC was performed for all data. Compared with the results without partial volume adjustment, most results were consistent but little more brain regions were found to differ in the analysis of gender groups, namely the fusiform gyrus, middle temporal gyrus, and inferior temporal gyrus.

There are some limitations to this study. First, the small sample size limits the statistical ability of data. We tried to overcome this problem by including other center subjects, but the requirement to receive both Aβ PET and Tau PET scans in the A^+ group greatly limited the number of potential participants. In addition, the Huashan cohort is an ongoing hospital-based investigation; therefore, the number of subjects with normal cognition and cognitively impaired

patients with "A$^+$T$^-$" is very limited. We expect to supplement this data and carry out more comprehensive research in the future. Second, our study was cross-sectional, and long-term longitudinal follow-up data could further support our hypothesis. Third, this study included the data from the two centers, but did not consider the impact of different imaging devices on the data. Fourthly, we only carried out the experiment of calculating Tau SUVR by using cerebellar gray matter as the reference brain region, and selecting different reference brain regions may affect the results. Fifthly, in the Huashan cohort, tau PET uses a new imaging agent that currently lacks T$^+$/T$^-$ threshold studies. Visual assessment results were affected by subjective factors, and we expect to divide T$^+$/T$^-$ with an objective quantitative threshold to verify our results in the future. Finally, lack of APOE ε4 in some participants restricted further exploration of possible gene effect on such brain tau deposition between genders. Considering the shortcomings of this study, future multi-center cooperation is required to include more participants to verify the robustness of the results.

Conclusion

Despite these limitations, our current data represent a promising step in understanding the sex effect on brain tau accumulation. As a conclusion, gender differences effected tau deposition in A$^+$ subject, which might help the future development of a "precision medicine" approach in AD.

Authors' Contributions All authors significantly contributed to planning, writing, and editing of the manuscript.

Data Availability Data from the ADNI cohort are available on the website (https://adni.loni.usc.edu/). Data from the Huashan cohort were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Huashan Hospital.

Code Availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study was approved by the Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China.

Consent to participate All subjects from Huashan Hospital provided written informed consent.

Consent for publication Not applicable.

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