Sex Mediates Relationships Between Regional Tau Pathology and Cognitive Decline

Rachel F. Buckley, PhD,[1,2,3†] Matthew R. Scott, BA,[1†] Heidi I. L. Jacobs, PhD,[4,5] Aaron P. Schultz, PhD,[1] Michael J. Properzi, BEng,[1] Rebecca E. Amariglio, PhD,[1,2] Timothy J. Hohman, PhD,[6] Danielle V. Mayblyum, BS,[5] Zoe B. Rubinstein, BA,[5] Lyssa Manning, MA,[1] Bernard J. Hanseeuw, MD, PhD,[1,7] Elizabeth C. Mormino, PhD,[8] Dorene M. Rentz, PhD,[1,2] Keith A. Johnson, MD,[2,5] and Reisa A. Sperling, MD[1,2]

Objective: The goal of this study was to examine sex differences in tau distribution across the brain of older adults, using positron emission tomography (PET), and investigate how these differences might associate with cognitive trajectories.
Methods: Participants were 343 clinically normal individuals (women, 58%; 73.8 [8.5] years) and 55 individuals with mild cognitive impairment (MCI; women, 38%; 76.9 [7.3] years) from the Harvard Aging Brain Study and the Alzheimer's Disease Neuroimaging Initiative. We examined ^{18}F-Flortaucipir (FTP)-positron emission tomography (PET) signal across 41 cortical and subcortical regions of interest (ROIs). Linear regression models estimated the effect of sex on FTP-signal for each ROI after adjusting for age and cohort. We also examined interactions between sex*Aβ-PET positive / negative (+ / −) and sex*apolipoprotein ε4 (APOEε4) status. Linear mixed models estimated the moderating effect of sex on the relationship between a composite of sex-differentiated tau ROIs and cognitive decline.
Results: Women showed significantly higher FTP-signals than men across multiple regions of the cortical mantle ($p < 0.007$). β-amyloid (Aβ)-moderated sex differences in tau signal were localized to medial and inferio-lateral temporal regions ($p < 0.007$); Aβ + women exhibited greater FTP-signal than other groups. APOEε4-moderated sex differences in FTP-signal were only found in the lateral occipital lobe. Women with higher FTP-signals in composite ROI exhibited faster cognitive decline than men ($p = 0.04$).
Interpretation: Tau vulnerability in women is not just limited to the medial temporal lobe and significantly contributed to greater risk of faster cognitive decline. Interactive effects of sex and Aβ were predominantly localized in the temporal lobe, however, sex differences in extra-temporal tau highlights the possibility of accelerated tau proliferation in women with the onset of clinical symptomatology.

ANN NEUROL 2020;88:921–932

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25878

Received Mar 4, 2020, and in revised form Aug 13, 2020. Accepted for publication Aug 13, 2020.

Address correspondence to Reisa A. Sperling, Harvard Aging Brain Study, Department of Neurology, Massachusetts General Hospital, 149 13th Street, Charlestown, MA 02129. E-mail: reisa@bwh.harvard.edu

[†]Both of these authors contributed equally to this work.

A complete listing of the Harvard Aging Brain Study investigators can be found at: http://nmr.mgh.harvard.edu/lab/harvardagingbrain/aboutus.

Some data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

From the [1]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [2]Brigham and Women's Hospital, Department of Neurology, Center for Alzheimer Research and Treatment, Boston, MA, USA; [3]Melbourne School of Psychological Science, University of Melbourne, Melbourne, VIC, Australia; [4]Faculty of Health, Medicine and Life Sciences, School for Mental Health and Neuroscience, Alzheimer Centre Limburg, Maastricht University, Maastricht, The Netherlands; [5]Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA; [6]Department of Neurology, Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA; [7]Department of Neurology, Cliniques Universitaires Saint-Luc, Institute of Neuroscience, Université Catholique de Louvain, Brussels, Belgium; and [8]Department of Neurology, Stanford University, Stanford, CA, USA

Additional supporting information can be found in the online version of this article.

Growing evidence suggests women exhibit higher levels of tau burden than men[1–7]; this is particularly apparent in those with genetic risk for sporadic Alzheimer's disease (eg, apolipoprotein ε4 [APOEε4] carriers)[3] or with elevated levels of β-amyloid (Aβ) burden.[5] Levels of both cerebrospinal fluid (CSF) total tau and phospho-tau (p-tau) are higher in female APOEε4 carriers across the cognitive impairment spectrum,[1] including those who are clinically normal.[3] Postmortem findings also observe a greater amount of tau tangles in women than men,[6,7] as supported by a recent meta-analysis of postmortem samples across multiple cohorts.[3] Although in vivo CSF findings are consistent, this modality does not provide regionally specific information about tau burden.

Relatively few reports of tau-positron emission tomography (PET) findings have focused on topographical sex differences in tau signal.[8] We recently found that clinically normal older women with higher levels of global Aβ exhibit higher levels of entorhinal tau burden than men.[5] Our findings, however, were limited to a priori regions of interest (ROIs), leaving open the question as to whether there existed a broader sex dimorphic topographical distribution of tau-PET across the brain. Other studies have reported sex differences in regional tau-PET, but only within the context of glucose metabolism[9] or APOEε4 status.[10] Taken together, the literature is sparse and has not addressed the question of sex differences in the spatial distribution of tau across the brain. Further, it remains unclear how sex dimorphic tau-PET signal might impact rates of cognitive decline. Understanding these differences, particularly within the context of Aβ levels and APOEε4 genetic risk, has implications for pinpointing underlying biological mechanisms driving susceptibility to tau, and the extent to which they are reflecting an Alzheimer's disease (AD)-related pathway or other (eg, age, inflammation, cardiovascular, hormones, and methodology).

The aim of this study was to examine sex differences in tau-PET signal across the brain, both as a main effect and interaction with global Aβ and APOEε4 carriage. We hypothesized that women would have higher levels of tau across multiple regions, beyond the entorhinal cortex alone, which has been reported in multiple cohorts.[5,9] We hypothesized that additional regions of the temporal lobe would be implicated, particularly as they represent the early stages of disease in clinically normal individuals and those diagnosed with mild cognitive impairment (MCI). We also examined whether a composite of these regions that were sex dimorphic would be associated with sex-moderated rates of cognitive decline.

Methods

Participants

Data from 343 participants (199 women, 58%; 74 [8.5] years, range: 50–94 years) and 55 individuals with MCI (21 women, 38%; 77 [7.3] years, range: 60–92 years) were obtained from the Harvard Aging Brain Study (HABS) and Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu accessed in February 2018). Sex was categorized on the basis of self-report in both studies. Initial inclusion criteria for recruitment for both HABS and ADNI have been published previously.[11,12] In the current study, participants from both studies were diagnosed as clinically normal or having MCI at the time of their first ^{18}F-Flortaucipir (FTP)-PET scan. A total of 251 individuals were included from HABS and 147 individuals from ADNI. For HABS, the time between the first tau-PET scan and the closest Aβ-PET scan was a median (interquartile range) of 43 (7–112) days (max = 3 years). For ADNI, the interval was 7 (2–32) days (max = 4.8 years). Twenty-one participants had a lag of longer than 1 year between scans (HABS: n = 6; ADNI: n = 15). We conducted the procedures for this study under the ethical guidelines stipulated by the Partners Human Research Committee, which is the Institutional Review Board for the Massachusetts General Hospital and Brigham and Women's Hospital. Written consent from all individuals was obtained in each cohort (Table).

APOE Genotyping

A blood sample was collected in each study for direct genotyping of APOE (heterozygotes and homozygotes for the ε4 allele were collapsed into one category, with ε2–ε4 individuals removed).

Magnetic Resonance Imaging

Structural T1-weighted anatomic images closest to each participant's tau-PET scan were utilized in both cohorts. T1-weighted images were then processed with FreeSurfer version 6.0 to identify gray-white as well as pial surfaces and to produce automatic Desikan-Killany cortical and aseg subcortical ROI parcellations,[13] with quality control measures previously described.[11]

Aβ Positron Emission Tomography

Harvard Aging Brain Study (HABS) used ^{11}C Pittsburgh compound-B (PiB), whereas ADNI used ^{18}F-Florbetapir (FBP). The PET acquisition parameters for each study have been published previously.[14–16] Distribution volume ratios (DVRs) were computed using Logan plotting 40 to 60 minutes postinjection, and summary measures were computed from a weighted average within a large

TABLE. Demographic comparisons between HABS and ADNI cohorts

	HABS				ADNI				
	F	M	Test Statistic	*p*	F	M	Test Statistic	*p*	All
N, % subsample	152	99			68	79			398
APOE ε3ε4 haplotype	34 (22)	18 (18)	$\chi^2 = 0.64$	0.42	24 (35)	19 (24)	$\chi^2 = 2.23$	0.14	95 (24)
APOE ε4ε4 haplotype	3 (2)	1 (1)	$\chi^2 = 0.36$	0.55	3 (4)	7 (9)	$\chi^2 = 1.14$	0.29	14 (4)
High Aβ	42 (28)	26 (26)	$\chi^2 = 0.06$	0.81	32 (47)	29 (38)	$\chi^2 = 1.61$	0.20	129
Global CDR 0.5	8 (5)	6 (6)	$\chi^2 = 0.07$	0.79	23 (34)	34 (43)	$\chi^2 = 1.31$	0.25	71 (18)
Median [IQR]									
CDR sum of boxes	0 [0–0]	0 [0–0]	$Z = 0.47$	0.64	0 [0–0.5]	0 [0–1.375]	$Z = -0.66$	0.51	0 [0–0.5]
Mean (SD)									
Age	72.2 (9.5)	74.8 (8.3)	$t(249) = -2.21$	0.02*	74.7 (6.2)	76.7 (7.4)	$t(145) = -1.82$	0.07#	74.2 (8.5)
MMSE	29.3 (1.0)	29.1 (1.1)	$t(249) = 1.30$	0.20	28.7 (1.6)	28.4 (2.0)	$t(144) = 0.96$	0.34	29.0 (1.4)
PACC	0.27 (0.6)	−0.02 (0.6)	$t(200) = -3.59$	<0.001*	0.56 (0.4)	0.39 (0.4)	$t(139) = -2.57$	0.01*	0.26 (0.6)
Years of education	16.0 (2.8)	16.3 (3.1)	$t(249) = -0.85$	0.40	15.8 (2.7)	16.8 (2.6)	$t(145) = -2.34$	0.02*	16.2 (2.8)
Aβ DVR/SUVr	1.2 (0.2)	1.2 (0.2)	$t(247) = 0.59$	0.55	1.2 (0.2)	1.1 (0.2)	$t(145) = 2.66$	0.008*	1.2 (0.2)

Aβ = β-amyloid; ADNI = Alzheimer's Disease Neuroimaging Initiative; APOE = apolipoprotein; CDR = Clinical Dementia Rating; DVR = distribution volume ratio; HABS = Harvard Aging Brain Study; IQR = interquartile range; MMSE = Mini-Mental State Examination; SUVr = standardized uptake value ratio.
* signifies <0.05
# signifies <0.10

aggregate cortical ROI consisting of precuneus, rostral anterior cingulate, medial orbitofrontal, superior frontal, rostral middle frontal, inferior parietal, inferior temporal, and middle temporal (which is termed FLR) regions, and referenced to cerebellum grey.[17] In ADNI, FBP cortical summary standardized uptake value ratios (SUVrs) were downloaded from data previously processed by the University of California Berkeley from the LONI data access point (http://adni.loni.usc.edu/). Briefly, FBP SUVrs were calculated by combining retention values across cortical ROIs from lateral and medial frontal, anterior, and posterior cingulate, lateral parietal, and lateral temporal regions, and was referenced to the whole cerebellum.[14] As each cohort used different tracers and processing pipelines, Aβ-PET signal was expressed dichotomously using a 1.11 SUVr threshold in ADNI[18] and a 1.185 DVR threshold in HABS,[19] although Aβ-focused analyses were also conducted with the continuous measure within each cohort for validation.

Tau Positron Emission Tomography

Both studies use the FTP tracer (formerly AV1451 or T807). FTP-PET acquisition parameters for each study have been described elsewhere[20] (for ADNI see, http://adni.loni.usc.edu/methods/petanalysis-method/pet-analysis/). Processing of FTP-PET imaging data for both HABS and ADNI was completed by in-house processing pipelines.[20] Standardized uptake value ratios (SUVrs) were created by referencing to cerebellar grey.[20,21] All FTP ROI data are partial volume corrected (PVC) using the Geometric Transfer Matrix (GTM) method,[22] although associations involving non-PVC data were also explored. Due to off-target binding with FTP-PET,[23] the choroid plexus, putamen, vermis, and brainstem were excluded from analyses and hippocampal, which resulted in 41 ROIs for analysis. Hippocampal FTP signal was residualized from choroid plexus signal. In addition, we explored vertex wise maps, normalized in FreeSurfer subject space with PVC using the Muller-Gartner Extended method.[24]

Tau Analysis

Analyses were run in R version 3.3.3 (The R Foundation, Vienna, Austria) and MATLAB version R2018b (MathWorks, Natick, MA). Our primary investigation included a series of linear regression models to examine the main effect of sex, and interactions of interest, on FTP SUVrs across 41 cortical and subcortical ROIs. For the sake of parsimony, and due to a lack of a priori assumptions on lateralization, all ROIs were expressed as bihemispheric. All models covaried for age and cohort. To

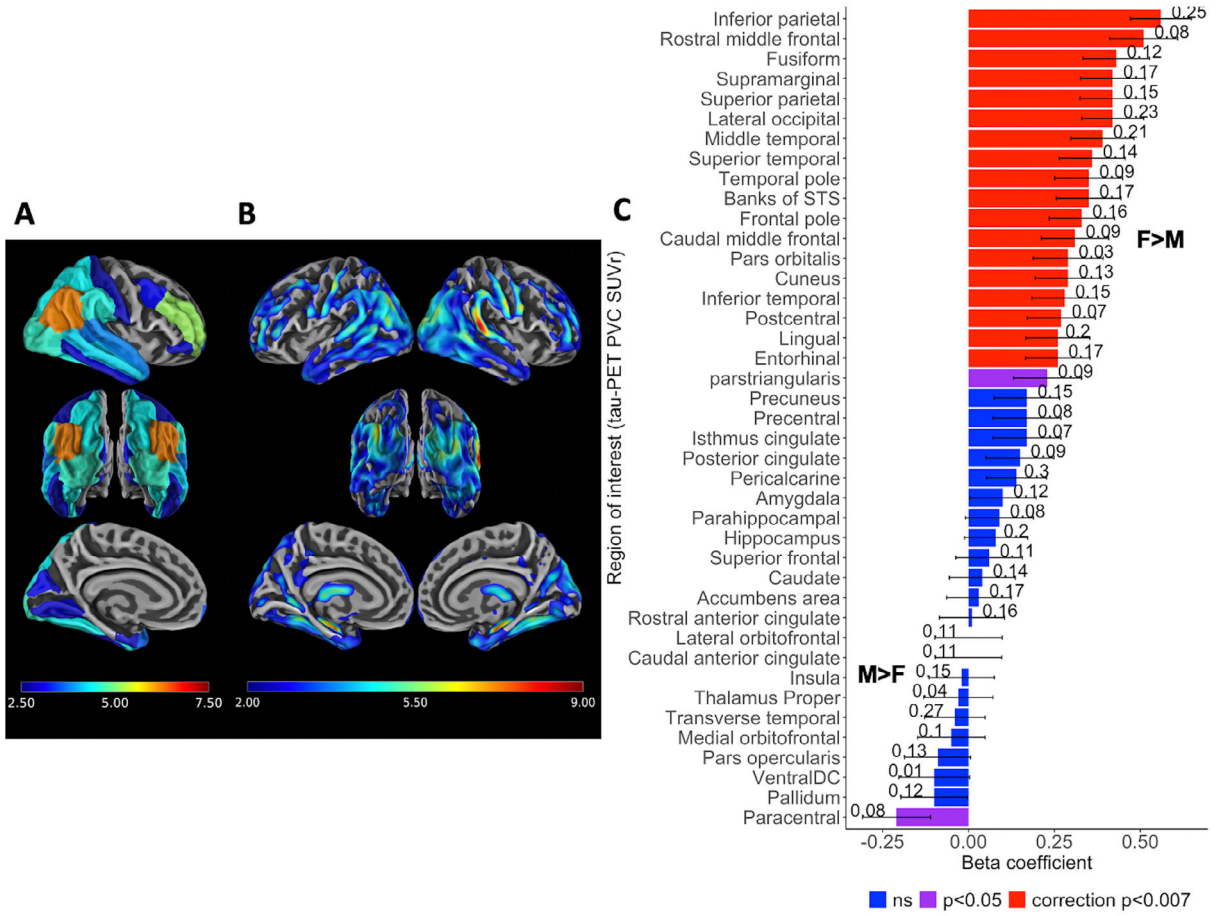

FIGURE 1: Main effects of sex on ^{18}F-Flortaucipir (FTP) standardized uptake value ratios (SUVrs) after adjusting for age and cohort (A) with region of interest (ROI)-based analyses across all participants (corrected $p < 0.007$), (B) showing vertex-wise (false discovery rate [FDR] corrected $p = 0.016$), and (C) showing beta weights and standard errors for each ROI with corresponding model R^2 (bars to the right denoting female > male [F > M]). ns = not significant; PET = positron emission tomography; PVC = partial volume corrected; STS = superior temporal sulcus.

further investigate the spatial distribution of sex effects, we examined surfaced-based vertex wise maps (full sample, and in Aβ + or APOEε4 carriers). As with our previous study,[5] we did not include a three-way sex*Aβ*APOEε4 interaction due to low statistical power. The models were:

Model 1: FTP ~ Sex + Age + Cohort*.

Model 2A: FTP ~ Sex + Aβ Group + Age + Cohort* (main effects only).

Model 2B: FTP ~ Sex × Aβ Group + Age + Cohort* (fully factorial).

Model 3: FTP ~ Sex × APOEε4 + Age + Cohort*.

*A dichotomous indicator for either HABS or ADNI.

Multiple Comparison Correction

Principal component analysis was used to determine the parameter for multiple comparison correction. We observed 7 eigenvalues ≥ 1, thus a correction $\alpha < 0.007$ was used for multiple comparisons. False discovery rate (FDR) correction was used for vertex-wise maps.

Effects on Cognitive Decline

To examine the effect of elevated FTP-PET signal on cognitive decline, we created a composite of the tau ROIs that differentiated significantly between men and women. We also examined a composite of regions that highlighted sex*Aβ regions, as well as a composite that contained regional signal with no sex differences for reference. We then examined the moderating effect of sex on the relationship between these tau composites and cognitive decline on the Preclinical Alzheimer's Cognitive Composite (PACC).[25] We included individuals with at least two neuropsychological assessments (n = 388). As FTP-PET was introduced mid-way through both studies, we examined time relative to PET scan (both retrospective [$n_{observations}$ = 1,626] and prospective [$n_{observations}$ = 965]), with first assessment occurring approximately 3.5 years (SD = 2.2 years) prior to the tau scan and final assessment approximately 2.3 years (SD = 1.7 years) after. We covaried for age, diagnosis at time of tau scan, years of education, and cohort, with

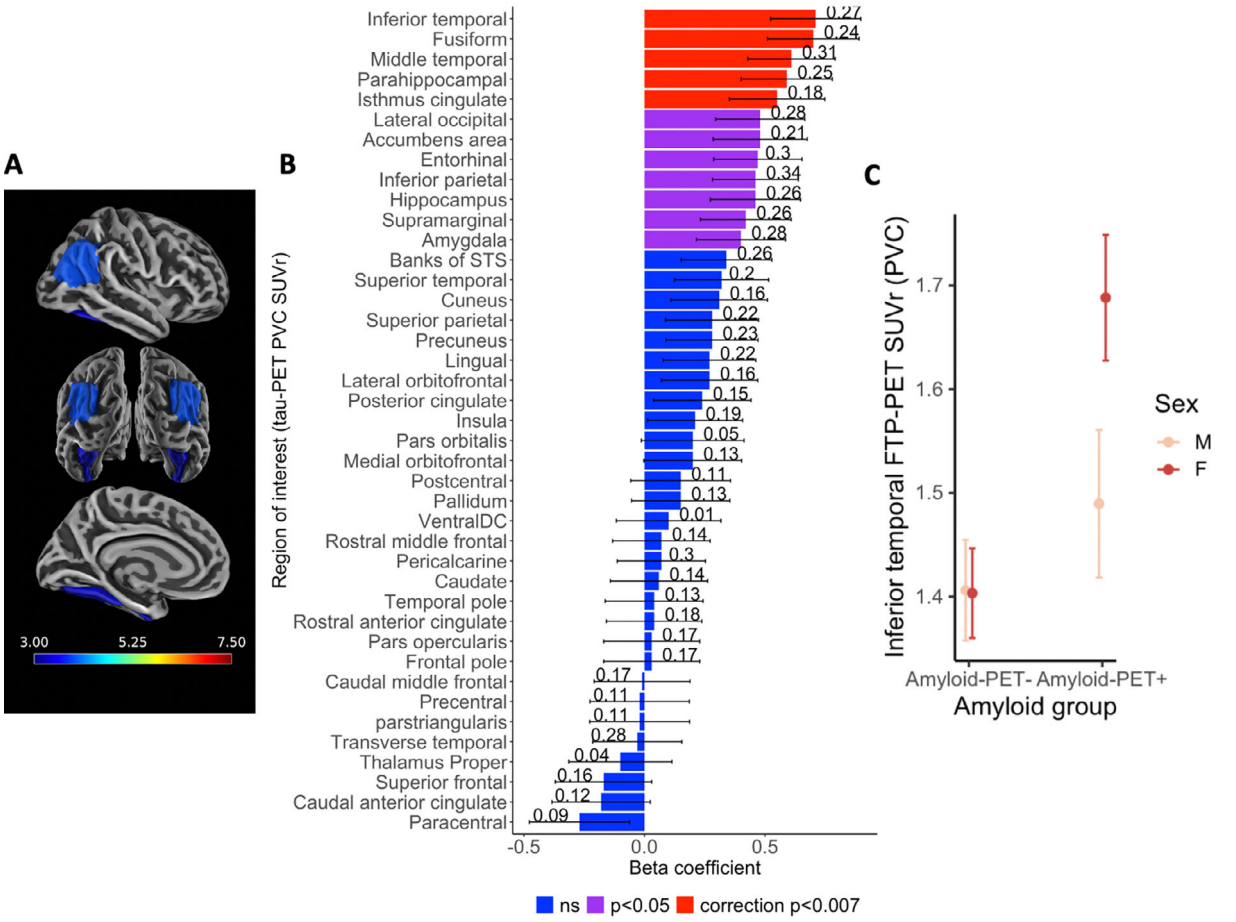

FIGURE 2: Interactive effects of sex and β-amyloid (Aβ) positive / negative (+ / –) on ^{18}F-Flortaucipir (FTP) standardized uptake value ratios (SUVrs) after adjusting for age and cohort (A) with region of interest (ROI)-based analyses within Aβ + participants only (n = 129; corrected $p < 0.007$), (B) β standardized and standard error for each ROI with corresponding model R^2 (bars to the right denoting female > male [F > M]), and (C) model estimates of FTP SUVrs in the inferior temporal cortex (with 95% confidence intervals) in men and women with Aβ-positron emission tomography (PET) +/–. ns = not significant; PVC = partial volume corrected; STS = superior temporal sulcus.

random intercepts and slopes. We examined PACC change from baseline and included a quadratic time term.

Sensitivity Analyses

We examined the effect of removing individuals with Aβ-PET scans greater than 1 year from their FTP-PET scan. In addition, we examined findings in only clinically normal individuals, when using non-PVC FTP-PET, and also when covarying for regional bihemispheric cortical thickness or brain volume within each ROI. We also examined interactions between sex*age. Finally, we separately explored the main effects of sex within each cohort, covarying for age, to understand the recapitulation of our findings across samples.

Results

Demographics

Participant characteristics within each cohort are presented in the Table (Supplementary Table S1 displays diagnostic demographic comparisons). Within HABS, female participants were younger than male participants. For ADNI, women exhibited slightly higher continuous Aβ-PET SUVrs than men. Comparison between cohorts revealed that HABS women were marginally younger, had higher Mini-Mental State Examination (MMSE) scores and a lower proportion of Aβ + individuals relative to ADNI women. There were no significant follow-up differences for neuropsychological assessments between men (t = 6.01 [SE = 2.5] years) and women (t = 5.38 [SE = 2.4] years).

Main Effect of Sex

Women showed significantly higher FTP SUVr signals in the following ROIs (listed by decreasing magnitude of effect): inferior parietal, rostral middle frontal, fusiform, supramarginal, superior parietal, lateral occipital, middle temporal, superior temporal, temporal pole, banks of the superior temporal sulcus, frontal pole, pars orbitalis, caudal middle frontal, pars orbitalis, cuneus, inferior temporal, postcentral, lingual, and entorhinal gyrus (p values

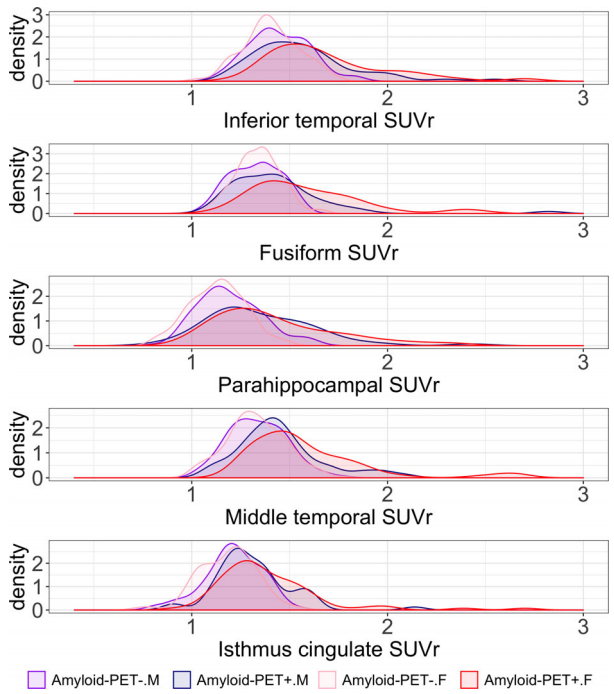

FIGURE 3: Density maps depicting the distributions of ^{18}F-Flortaucipir (FTP)-signal in regions that are differentiated by a sex*Aβ interaction. Aβ = β-amyloid; PET = positron emission tomography; SUVr = standardized uptake value ratio.

< 0.007; Fig 1, with model R^2 included). Estimated SUVr differences between men and women can be found in Supplementary Table S2 (and for subsequent models). Adjusting for dichotomous Aβ-PET attenuated the sex effect in the pars orbitalis, caudal middle frontal, postcentral, lingual, inferior temporal, and entorhinal gyrus to nonsignificant (p values < 0.05). As a post hoc analysis, we examined a sex*age interaction but found no effect on any ROIs.

Sex and Aβ Interaction on FTP Signal

There was no difference in Aβ +/− status between men and women (t(392) = 1.66, p = 0.10). Aβ + women, however, exhibited higher FTP-signal in the inferior temporal, fusiform, middle temporal, parahippocampal, and isthmus cingulate regions than any other group (Fig 2). Density maps showing the distributions of tau signal across men and women in Aβ +/− groups are shown in Figure 3. These regions were recapitulated within each cohort when examining continuous Aβ.

Sex and APOEε4 Interaction on FTP Signal

Female APOEε4 carriers exhibited higher FTP SUVr in the lateral occipital lobe than any other group (Fig 4).

Effects on Cognitive Decline

Using a composite of the sex differentiated ROIs (gathered from all significant model 1 outputs), women with higher FTP signal exhibited faster cognitive decline than men ($t_{sex*tau\ composite*time}$ = −2.49, p = 0.01; Fig 5 and Supplementary Table S3 for model estimates), after adjusting for covariates, including diagnostic status. We also found a similar effect when examining a composite of the significant regions from the sex*Aβ interaction (gathered from all significant model 2B outputs; $t_{sex*tau\ composite*time}$ = −2.34, p = 0.02). We found no sex*$Aβ_{status}$*tau interaction on cognitive decline (t = −0.92, p = 0.36). When examining a composite of tau regions that did not show sex differences (anterior and posterior cingulate and precuneus), we did not find an effect of sex*tau on cognitive decline.

Sex Differences in Tau ROI Signal in Clinically Normal Individuals

Findings were largely recapitulated in clinically normal individuals (see Fig 6), and adjusting for Aβ-PET exerted little influence. For the sex*Aβ status interaction, a significant effect was observed in the fusiform, inferior temporal, entorhinal, accumbens area, and the amygdala; clinically normal Aβ + women exhibited higher FTP signal than any other group. Clinically normal female APOEε4 carriers exhibited higher FTP SUVrs in the lateral occipital lobe. Examining the effects on cognitive decline in this group (n = 335), we found only trend-level effects in the sex-differentiated composite, $t_{sex*tau\ composite*time}$ = −1.64, p = 0.10, and the sex*Aβ composite, $t_{sex*tau\ composite*time}$ = −1.72, p = 0.08. There were no sex*Aβ*tau interactions on cognitive decline, which may have reflected low statistical power for detection.

Sensitivity Analyses

Excluding individuals with Aβ-PET scans > 1 year in duration from the FTP-scan did not alter findings. Using non-PVC FTP signal, significant main effects of sex were observed in similar regions than with PVC, albeit with slightly stronger effects in some cases. When covarying regional cortical thickness or volume in the non-PVC analyses, the only ROI to show attenuated effects was the entorhinal cortex, which maintained approximately p = 0.007. Similarly, covarying for diagnosis or PACC had little influence on the main effect of sex. We examined sex differences in off-target FTP-binding regions, such as the skull; for this ROI, women had greater signals than men (β = 0.83 [0.1], p < 0.001). Covarying for skull FTP signal (whether PVC or non-PVC), however, did not markedly change the pattern of findings, and, in some instances, magnified the sex effect. No significant

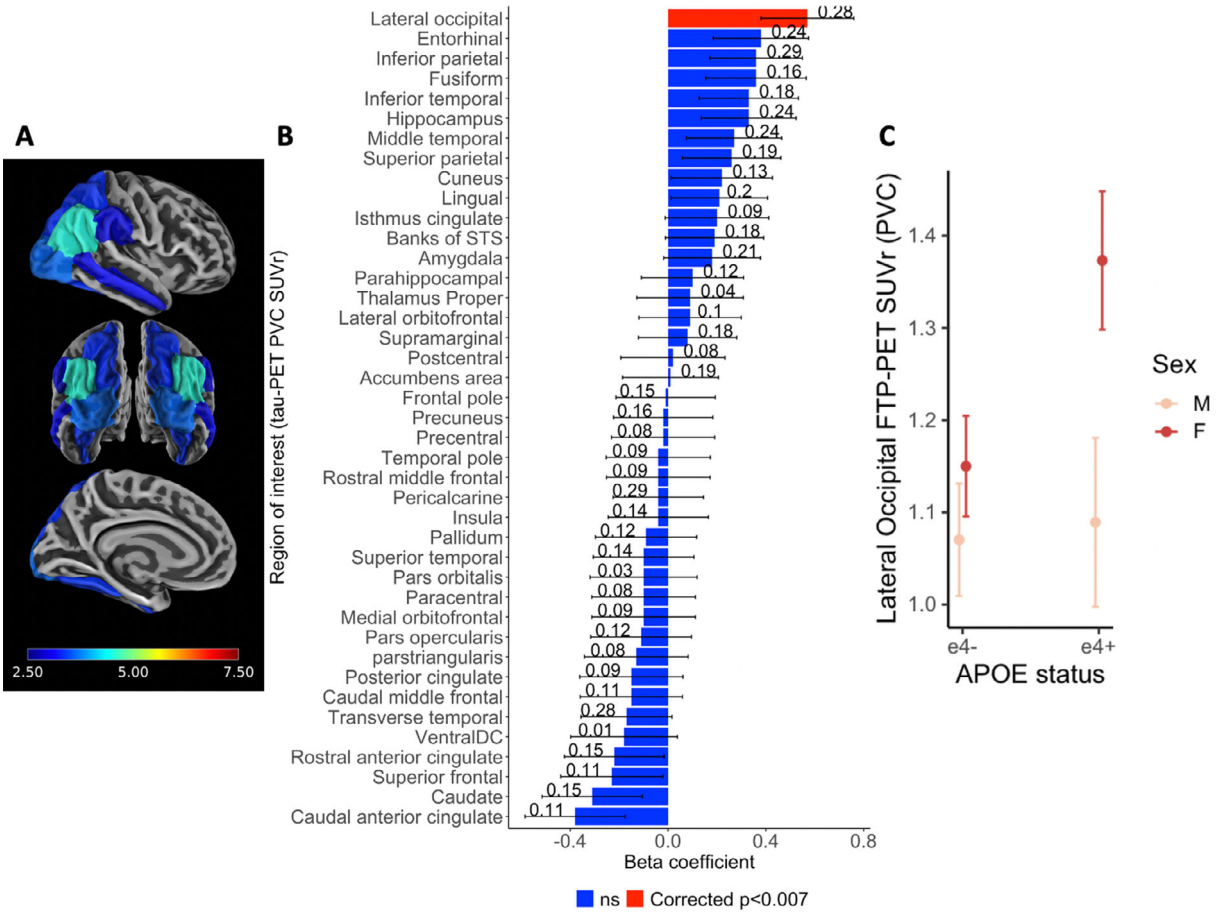

FIGURE 4: Interactive effects of sex and apolipoprotein ε4 (APOEε4) on ^{18}F-Flortaucipir (FTP) standardized uptake value ratio (SUVr) after adjusting for age and cohort (A) with region of interest (ROI)-based analyses within APOEε4 carriers only (n = 109; corrected $p < 0.007$), (B) β standardized and standard error for each ROI with corresponding model R^2 (bars to the right denoting female > male [F > M]), and (C) model estimates (with 95% confidence interval) of FTP SUVr in men and women with and without APOEε4 carriage. ns = not significant; PET = positron emission tomography; PVC = partial volume corrected; STS = superior temporal sulcus.

(corrected or uncorrected) sex*age effect was observed across all FTP-PET PVC ROIs. Moreover, the only sex*age effect in non-PVC FTP signal was limited to the precentral gyrus (uncorrected). Finally, we found that examining each cohort individually largely recapitulated the main effects of sex that were reported when combining both cohorts (Fig 7).

Discussion

Examining broad sex-related tau vulnerability revealed that women exhibited higher FTP SUVrs than men in many temporal and extratemporal regions. These comprised the parietal, middle frontal, lateral occipital, fusiform, supramarginal, cuneus, banks of the superior temporal sulcus (STS), and frontal/temporal pole regions. Many of these regions remained significantly different between the sexes even after adjusting for Aβ status. Amyloid-moderated sex differences in tau signals (sex*Aβ interaction) were largely restricted to the temporal lobe. Aβ + women showed higher FTP signals than Aβ + men and Aβ – individuals in regions such as the inferior and middle temporal gyrus, the fusiform gyrus, and parahippocampus. Some regions exhibited both main sex effects and amyloid-moderated sex effects on tau signal, such as the inferior temporal, middle temporal, and fusiform gyrus. These findings reveal an AD-specific female vulnerability to temporal lobe tauopathy, such that Aβ + women show higher signals than Aβ + men. In clinically normal individuals, Aβ + females displayed elevated signal only in temporal regions of the fusiform, inferior temporal, and entorhinal cortices. By contrast, female APOEε4 carriers only showed elevated signal in the occipital region relative to male APOEε4 carriers and noncarriers, regardless of clinical status. Our interpretation of these findings is that AD pathology-related exists to explain sex differences in FTP-PET signal, but this is largely confined to the temporal lobe. Our intention of examining APOEε4 moderated sex effects on tau signal arose from previous studies showing that female

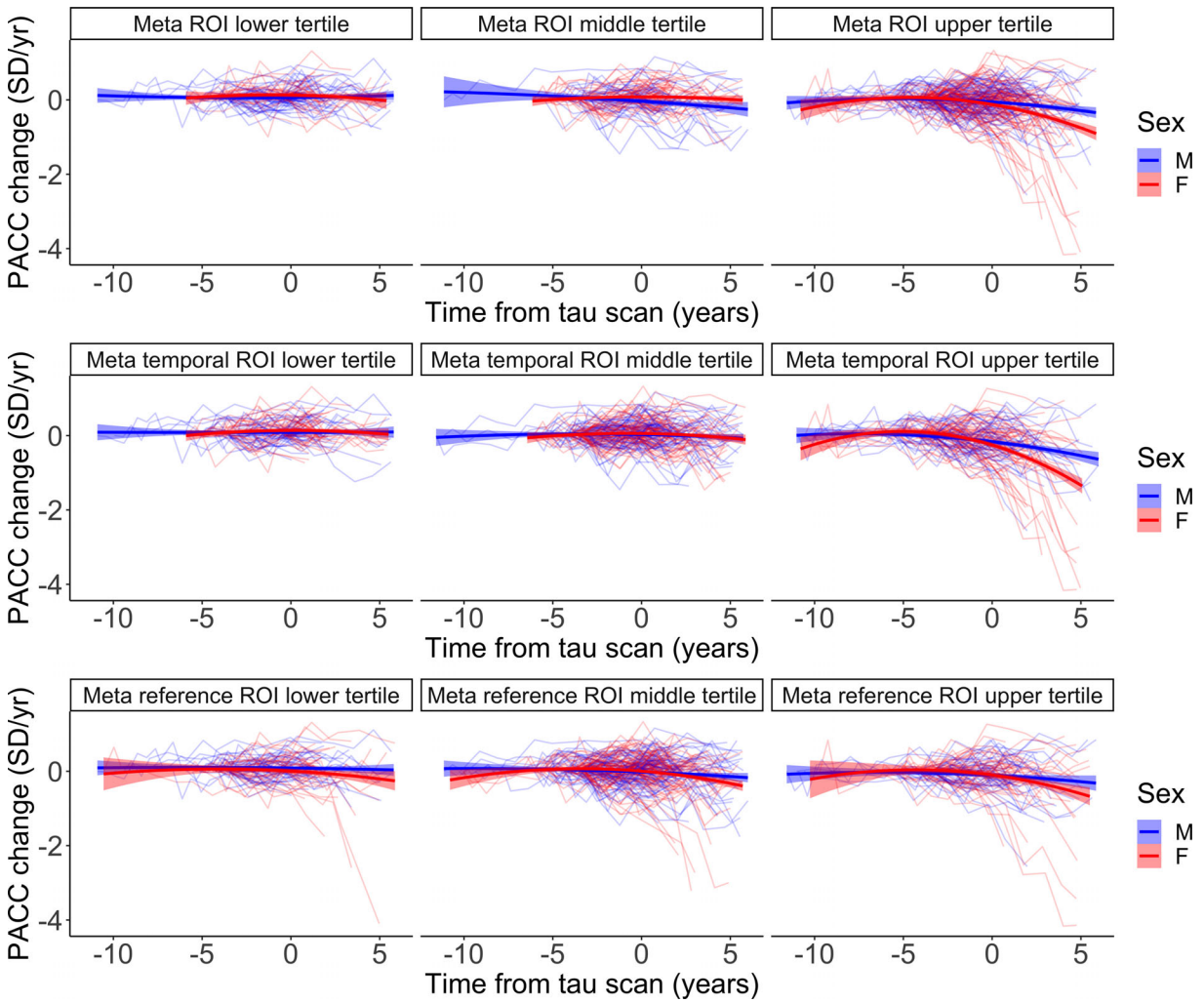

FIGURE 5: Spaghetti plot of cognitive trajectories over time in clinically normal individuals (0th time represents the first ^{18}F-Flortaucipir [FTP]-positron emission tomography [PET] scan) and faceted by a tertile split of composite FTP-PET signal (top = meta-region of interest [ROI], middle = meta temporal ROI, and bottom = reference-ROI) with quadratic fit curves stratified by sex. PACC = Preclinical Alzheimer's Cognitive Composite.

APOEε4 carriers have higher levels of CSF tau than male carriers.[3] Interestingly, a sex*APOEε4 interaction did not mirror sex*Aβ findings in this study in that female APOEε4 carriers did not show higher tau signal in the temporal lobe. It is possible that there was not enough statistical power to reliably observe a sex*APOEε4 interaction, and/or there may simply be different sources of variance driving these two markers. Finally, a collection of regions (predominantly extratemporal) appear to be sex divergent but are unexplained by Aβ burden or AD genetic risk, suggesting other biological mechanisms at play or a potential source of error.

We also found that sex-differentiated cortical patterns of FTP signal translated to faster cognitive decline in women. The interpretation of our cognitive findings are varied: (1) that women can "survive" (without diagnosis) for longer with medial temporal tau deposition, but once tau has spread to the neocortex, an accelerated pattern of decline is expected, or (2) that men with neocortical tau distribution have already progressed to a dementia diagnosis and are not represented in these models.

Findings in larger ROIs were largely consistent within each sample and were found to exist in analyses examining PVC or non-PVC, whether or not brain atrophy was covaried. Many of the aforementioned regions have been posited as particularly susceptible to higher FTP signals[9,25,26] and show associations with greater cortical thinning and CSF p-tau levels,[26] supporting the notion that they are proximal to neurodegenerative processes. Previous studies also show higher FTP signals in these regions in those with elevated Aβ burden,[27,28] supporting the notion of a female vulnerability to tau in AD vulnerable regions. Some regions that showed sex differences (eg, frontal and temporal poles) are small and attract signal-to-noise issues. We found smaller effect sizes associated with these regions, and unsurprisingly were more affected by

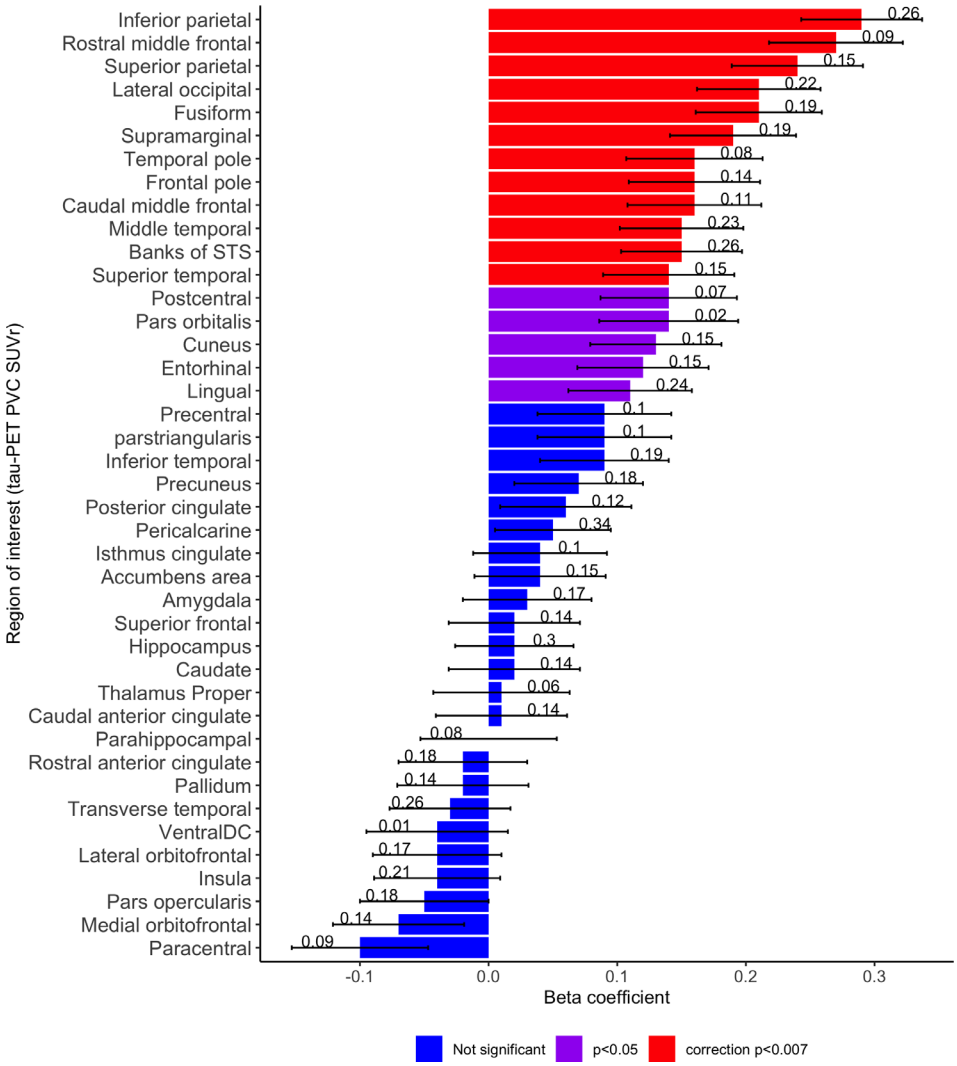

FIGURE 6: Main effects of sex on ^{18}F-Flortaucipir (FTP) standardized uptake value ratio (SUVr) signal in clinically normal individuals only, showing beta weights and standard errors for each region of interest (ROI) with corresponding model R^2 (bars to the right denoting female > male [F > M]). Red indicates multiple comparison significance $p < 0.007$, purple indicates $p < 0.05$, and blue indicates subthreshold estimates. PET = positron emission tomography; PVC = partial volume corrected; STS = superior temporal sulcus.

PVC. As such, findings in these regions should be interpreted with caution. Importantly, clinically normal individuals could recapitulate the overall pattern of findings, suggesting that they were not solely driven by cognitive impairment.

Similar to our previous work,[5] we found that clinically normal older Aβ + women showed greater tau in medial temporal regions than men, suggesting that Aβ-related susceptibility follows the early topographical patterns of the AD pathological cascade.[29–33] Although studies of CSF total tau and p-tau have often reported a sex-APOE effect, we did not find any regions to robustly show this effect, except in the lateral occipital lobe. This was supported by our previous analysis of a priori regions that only showed weak sex*APOEε4 interactive effects on FTP SUVrs.[5] Another rationale for elevated FTP SUVrs in women may be due to nonspecific binding.[23] Binding in extracortical hotspots, such as the lateral occipital, middle temporal, and superior and inferior parietal lobes, have been reported beyond the common FTP-related culprits (eg, choroid plexus, skull, and meninges).[23] It remains unclear why women might express additional susceptibility to nonspecific binding. Additional sensitivity analyses revealed sex differences in skull FTP signal in both cohorts, although covarying for this signal did not appreciably change our findings. This does raise some interesting questions about whether this difference is arising from off-target binding or spillover from signals in ROIs. A comprehensive exploration and assessment of the extent to which other contributors may drive sex differences in FTP

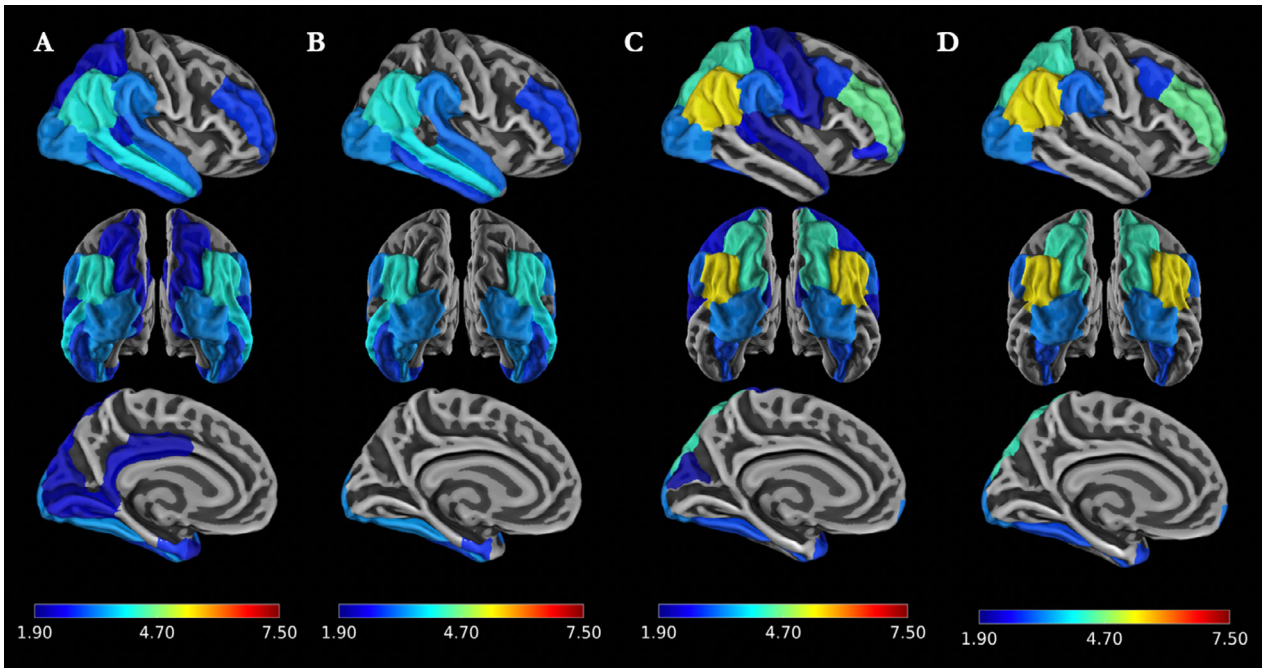

FIGURE 7: Main effect of sex on ^{18}F-Flortaucipir (FTP) standardized uptake value ratio (SUVr) after adjusting for age and cohort (region of interest [ROI]-based analyses): (A) Alzheimer's Disease Neuroimaging Initiative (ADNI) uncorrected, (B) ADNI corrected, (C) Harvard Aging Brain Study (HABS) uncorrected, and (D) HABS corrected.

signal is critical to interpreting the biological underpinnings of such.

One question that this study cannot answer is the potential biological mechanism that might drive female vulnerability to tau deposition. Changes in estrogen exposure in postmenopausal women are one potential rationale.[8,34,35] Studies have yet to report on the relationship between endogenous or exogenous estrogen levels and regional tau deposition, however, there are some studies linking Aβ with changes in estrogen, suggesting this might have a downstream effect on tau vulnerability.[36,37] Observational studies, however, do not show sex differences in Aβ-PET signal,[19,38] although it may be possible that Aβ differences may occur earlier, such as during menopause,[37] which may have a downstream effect on tau deposition. A recent pilot clinical trial showed that women treated with transdermal 17β-estradiol exhibited slightly lower levels of Aβ-PET signals than an age-matched placebo group (particularly female APOEε4 carriers).[39] There is also a possibility that tau vulnerability may be a direct result of estrogen depletion postmenopause, and animal models support this hypothesis.[34,40] Without direct human model evidence, this remains unclear. Sex differences exist in the risk for metabolic syndrome in this age group, and sex dimorphism in inflammatory markers are well-established[41,42]; considering their link with AD dementia risk,[43,44] these factors could play a role in female tau vulnerability. In addition, it remains unclear the impact of age on these models: it is possible that younger women with higher amyloid burden may express a more aggressive progression of pathology. We were cautious about testing such complicated multi-way interactions when statistical power was lacking, however, we believe a natural next step is to interrogate this question, particularly in light of the fact that the menopausal phase begins, on average, at 42 years of age in the general population.

Finally, it is important to address the issue of survival bias and competing risk for mortality that may be driving sex differences. An examination of density plots of tau deposition in temporal regions (Fig 2D) highlights that women showed higher levels of tau across all these regions and not greater numbers of women at higher tau levels. That is, men with higher tau did not exist in either sample. Women were slightly younger than men in the current study, and recent evidence suggests that tau paradoxically increases in younger and older clinically normal Aβ + individuals.[45] Further, men with higher levels of tau in these regions may not be included for various reasons: (1) stringent study inclusion criteria (ie, lower cardiovascular risk), (2) faster rates of progression to dementia or death in men with higher temporal tau, or (3) men may be less likely to join observation studies or opt in for PET scanning.

The strength of this study is a combined analysis of two independent cohorts, which can provide statistical power to examine effects that may appear across multiple

ROIs. One limitation, however, is the extent to which sex differences are a representation of PET methodological effects. We examined morphological differences, PVC, and non-PVC FTP metrics, however, and did not find evidence of major biases. Another limitation is the lack of generalizability to community populations; individuals from HABS and ADNI have high education, socioeconomic status, and low racial and ethnic diversity. Examining sex differences in regional tau deposition will be critical in more diverse populations.

In conclusion, our findings suggest that women exhibit higher FTP signals than men in multiple brain regions in earlier stages of disease. Higher FTP signals in these regions translated to accelerated cognitive decline in women relative to men. Examining these findings within the context of longitudinal FTP-PET studies could help to address whether men and women with medial temporal tau, or who are Aβ +, have different FTP-PET trajectories across the brain.

Acknowledgments

The authors thank the participants who volunteered their valuable time to these studies. The Harvard Aging Brain Study is funded by the National Institute on Aging (P01AG036694) with additional support from several philanthropic organizations. The Alzheimer's Disease Neuroimaging Initiative is funded by the NIA (U19AG024904), the NIBIB, the Canadian IHR, and several philanthropic organizations. Several co-authors' contributions were also supported by career development awards: R.F.B. is supported by a K99/R00 award from NIA; H.I.L. is supported by a Marie-Sklodowska-Curie Global Fellowship within the European Union's Horizon 2020 Research and Innovation Programme; and T.J.H. is supported by a K01 award from NIA.

Author Contributions

R.F.B., M.R.S., R.E.A., E.C.M., H.I.L.J., B.J.H., D.M.R., K.A.J., and R.A.S. were responsible for study concept and design. R.F.B., M.R.S., M.J.P., T.J.H., A.P.S., D.V.M., Z.B.R., and L.M. were responsible for data acquisition and analysis. R.F.B., M.R.S., and R.A.S. were responsible for drafting the manuscript and figures.

Potential Conflicts of Interest

The authors declared no conflict of interest.

References

1. Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol 2014;75:563–573.
2. Damoiseaux JS, Seeley WW, Zhou J, et al. Gender modulates the APOE ε4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. J Neurosci 2012;32:8254–8262.
3. Hohman T, Dumitrescu L, Barnes L, et al. Sex-specific effects of Apolipoprotein E on cerebrospinal fluid levels of tau. JAMA Neurol 2018;75:989–998.
4. Buckley RF, Mormino EC, Chhatwal J, et al. Associations between baseline amyloid, sex, and APOE on subsequent tau accumulation in cerebrospinal fluid. Neurobiol Aging 2019;78:178–185.
5. Buckley R, Mormino E, Rabin J, et al. Sex differences in the association between regional tau and global amyloid PET. JAMA Neurol 2019;76:542–551.
6. Barnes LL, Wilson RS, Bienias JL, et al. Sex differences in the clinical manifestations of Alzheimer disease pathology. Arch Gen Psychiatry 2005;62:685–691.
7. Oveisgharan S, Arvanitakis Z, Yu L, et al. Sex differences in Alzheimer's disease and common neuropathologies of aging. Acta Neuropathol 2018;136:887–900.
8. Ferretti MT, Iulita MF, Cavedo E, et al. Sex differences in Alzheimer disease—the gateway to precision medicine. Nat Rev Neurol 2018; 14:457–469.
9. Ramanan VK, Castillo AM, Knopman DS, et al. Association of Apolipoprotein E ϵ4, educational level, and sex with tau deposition and tau-mediated metabolic dysfunction in older adults. JAMA Netw Open 2019;2:e1913909.
10. Paranjpe M, Liu M, Paranjpe I, et al. Sex modulates the ApoE ε4 effect on tau 18F-AV-1451 PET imaging in individuals with Normal aging and mild cognitive impairment. J Nucl Med 2019;60:253–253.
11. Dagley A, LaPoint M, Huijbers W, et al. Harvard aging brain study: dataset and accessibility. Neuroimage 2017;144:255–258.
12. Aisen P. Cognitive/clinical endpoints for pre-dementia AD trials. J Prevent Alzheimer's Dis 2015;2:82.
13. Mormino EC, Betensky RA, Hedden T, et al. Synergistic effect of β-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. JAMA Neurol 2014;71:1379–1385.
14. Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann Neurol 2012;72:578–586.
15. Landau SM, Lu M, Joshi AD, et al. Comparing positron emission tomography imaging and cerebrospinal fluid measurements of β-amyloid. Ann Neurol 2013;74:826–836.
16. Mormino EC, Betensky RA, Hedden T, et al. Amyloid and APOE ε4 interact to influence short-term decline in preclinical Alzheimer disease. Neurology 2014;82:1760–1767.
17. Joshi AD, Pontecorvo MJ, Clark CM, et al. Performance characteristics of amyloid PET with florbetapir F 18 in patients with Alzheimer's disease and cognitively normal subjects. J Nucl Med 2012;53: 378–384.
18. Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and APOEe4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. Alzheimers Dement 2018;14:1193–1203.
19. Johnson KA, Schultz A, Betensky RA, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. Ann Neurol 2016;79:110–119.
20. Becker JA, Hedden T, Carmasin J, et al. Amyloid-β associated cortical thinning in clinically normal elderly. Ann Neurol 2011;69: 1032–1042.

21. Rousset OG, Ma Y, Evans AC. Correction for partial volume effects in PET: principle and validation. J Nucl Med 1998;39:904.

22. Baker SL, Maass A, Jagust WJ. Considerations and code for partial volume correcting [18F]-AV-1451 tau PET data. Data Brief 2017;15: 648–657.

23. Greve DN, Salat DH, Bowen SL, et al. Different partial volume correction methods lead to different conclusions: an 18 F-FDG-PET study of aging. Neuroimage 2016;132:334–343.

24. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol 2014;71:961–970.

25. Schultz SA, Gordon BA, Mishra S, et al. Widespread distribution of tauopathy in preclinical Alzheimer's disease. Neurobiol Aging 2018; 72:177–185.

26. Maass A, Landau S, Baker SL, et al. Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. Neuroimage 2017;157:448–463.

27. Fortea J, Vilaplana E, Alcolea D, et al. Cerebrospinal fluid β-amyloid and phospho-tau biomarker interactions affecting brain structure in preclinical Alzheimer disease. Ann Neurol 2014;76:223–230.

28. Schöll M, Lockhart SN, Schonhaut DR, et al. PET imaging of tau deposition in the aging human brain. Neuron 2016;89:971–982.

29. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18:351–357.

30. Delacourte A, David J, Sergeant N, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–1165.

31. Braak H, Rub U, Schultz C, Del Tredici K. Vulnerability of cortical neurons to Alzheimer's and Parkinson's diseases. J Alzheimers Dis 2006; 9:35–44.

32. Duyckaerts C. Tau pathology in children and young adults: can you still be unconditionally baptist?. Acta Neuropathologica. 2011;121: 145–147. http://dx.doi.org/10.1007/s00401-010-0794-7.

33. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259.

34. Brinton RD, Yao J, Yin F, et al. Perimenopause as a neurological transition state. Nat Rev Endocrinol 2015;11:393–405.

35. Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: a think tank convened by the Women's Alzheimer's research initiative. Alzheimers Dement 2016; 12:1186–1196.

36. Schönknecht P, Pantel J, Klinga K, et al. Reduced cerebrospinal fluid estradiol levels are associated with increased β-amyloid levels in female patients with Alzheimer's disease. Neurosci Lett 2001;307: 122–124.

37. Mosconi L, Berti V, Quinn C, et al. Sex differences in Alzheimer risk: Brain imaging of endocrine vs chronologic aging. Neurology 2017; 89:1382–1390.

38. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924–1938.

39. Kantarci K, Lowe VJ, Lesnick TG, et al. Early postmenopausal transdermal 17β-estradiol therapy and amyloid-β deposition. J Alzheimers Dis 2016;53:547–556.

40. Grimm A, Biliouris EE, Lang UE, et al. Sex hormone-related neurosteroids differentially rescue bioenergetic deficits induced by amyloid-β or hyperphosphorylated tau protein. Cell Mol Life Sci 2016;73:201–215.

41. Zore T, Palafox M, Reue K. Sex differences in obesity, lipid metabolism, and inflammation—a role for the sex chromosomes? Mol Metab 2018;15:35–44.

42. Khramtsova EA, Davis LK, Stranger BE. The role of sex in the genomics of human complex traits. Nat Rev Genet 2019;20:173–190.

43. Ferreira ST, Clarke JR, Bomfim TR, De Felice FG. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimers Dement 2014;10:S76–S83.

44. Frisardi V, Solfrizzi V, Seripa D, et al. Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. Ageing Res Rev 2010;9:399–417.

45. Jack CR Jr, Wiste HJ, Schwarz CG, et al. Longitudinal tau PET in ageing and Alzheimer's disease. Brain 2018;141:1517–1528.