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RESEARCH ARTICLE

Explaining variability in early stages of [18F]-flortaucipir tau-PET binding: Focus on sex differences

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Abstract

INTRODUCTION: Female sex is associated with increased [18F]-flortaucipir signal, which may be affected by amyloid pathology, age, and off-target binding in skull and meninges.

METHODS: In this cross-sectional study comprising 52 females and 52 matched males, we examined sex-related differences in regional tau-positron emission tomography (PET) with and without considering off-target binding. We assessed the respective contributions of sex, age, amyloid-PET burden, and off-target binding to tau-PET signal. We explored associations between age at menopause and hormone replacement therapy (HRT) use with regional tau-PET signals.

RESULTS: Female sex was associated with increased regional tau both independently and interactively with amyloid, but amyloid-independent associations were largely reduced when controlling for off-target binding. Age but not age*sex interactions explained a small but significant amount of tau-PET signal in temporoparietal regions. Considering the sample size and limited range of amyloid-PET burden, no clear associations between regional tau-PET signals and age at menopause or HRT use could be found.

DISCUSSION: Female sex is associated with increased [18F]-flortaucipir signal mainly through its interaction with amyloid.

KEYWORDS
age at menopause, Alzheimer's disease, amyloid pathology, hormone replacement therapy, off-target binding, tau pathology

1 | BACKGROUND

The aggregation and accumulation of hyperphosphorylated tau in neurofibrillary tangles is a central process in the pathogenesis of Alzheimer's disease (AD). The brain regions where tau accumulates serve as reliable predictors of regional atrophy,[1] cognitive deterioration,[2] and align with the progression of dementia symptoms.[3] The advent of tau-specific positron emission tomography (PET) tracers has enabled the detection of tau pathology in early disease stages in cognitively healthy individuals.[4] Tau-PET thus allows studying the

underlying factors influencing tau pathology in the aging brain. Among these factors, amyloid-beta (Aβ) pathology stands out as the primary driver, while older age represents another factor that may act independently of Aβ.[5,6] Furthermore, there is substantial evidence pointing to the significant role of sex in the deposition of tau pathology.[7,8] However, particularly in the initial phases of the disease, the tau-PET signal is weak, and accurate quantification of the tau-PET signal is critical if the contributions that these factors make to the tau-PET signal are to be investigated.

Sex-related differences in tau-PET signals have been documented in several studies, wherein female individuals exhibit consistently higher tau-PET signal.[7–10] Particularly in the setting of increased Aβ pathology, females show higher tau-PET burden in temporal brain regions.[7,8] Even when Aβ burden is low, tau-PET burden has been observed to be higher in females, not only in regions typically linked to tau pathology in AD[5,9,10] but also in regions not typically associated with early AD-related tau pathology, for instance in the frontal lobe.[11] Thus, there is evidence suggesting that female sex not only influences the amyloid-tau relationship but also acts as an Aβ-independent driver of tau pathology. Sex-specific risk factors such as early menopause may underlie some of these sex differences in tau-PET signal.[12,13] Advanced age is another factor linked to increased tau-PET burden. Some individuals exhibit elevated tau-PET signal, especially in the medial temporal lobe regions, in the absence of significant Aβ-PET burden,[14,15] which may be related to primary age-related tauopathy (PART), a condition neuropathologically characterized by neurofibrillary tangles without substantial Aβ pathology.[16] Some evidence also suggests, that age-related tau accumulation is not only confined to medial temporal regions, but can also be observed in several neocortical regions.[6]

Among the first-generation tau-PET tracers, [18F]-flortaucipir (AV-1451)[17] holds widespread use in research and has been employed in a large phase III trial of the anti-Aβ monoclonal antibody donanemab.[18] [18F]-Flortaucipir exhibits binding to substances or structures in the brain that are not the primary target of interest ("off-target binding"), for instance, in the choroid plexus or the basal ganglia.[19] Another region where off-target binding has been observed is in the skull and meninges.[20–22] Of particular note, the signal within a skull/meningeal mask tends to decrease with older age but remains consistently higher in females than in males.[20] Although the off-target signal is not excessively elevated, it may affect signal quantification in some regions of interest (ROIs) due to spill-in of off-target signal. Especially in cases where the tau-PET signal is weak, for instance, in most middle-aged individuals or when Aβ pathology is low, this may influence the interpretation of sex-related differences in [18F]-flortaucipir signal.

In this study, we investigated the regional accumulation of tau in a community-based cohort including participants aged 50 years and above. The primary focus of this work is on the contribution of sex to early-stage, regional [18F]-flortaucipir binding. First, we specifically focused on whether considering partial volume effects and skull/meningeal off-target binding influences the detection of sex-related differences in tau-PET signal, both independently and in interaction with global Aβ-PET. Next, we examined how Aβ burden, age, skull/meningeal off-target binding, and sex contribute to the variability in regional tau-PET signal. Finally, we explored whether sex differences in tau-PET signal can be attributed to female-specific risk factors, such as earlier age at menopause and hormone replacement therapy (HRT).

RESEARCH IN CONTEXT

1. **Systematic review**: Relevant articles were identified using Google Scholar and by reviewing cited works. Studies consistently reported sex differences in tau burden, with some suggesting sex main effects and some sex*amyloid interaction effects. However, sex*age interactions and the influence of off-target binding have not been thoroughly examined, despite their potential significance for improving signal quantification.
2. **Interpretation**: Our findings emphasize that female sex, particularly through its interaction with amyloid, is associated with higher tau-PET signal in regions commonly affected by AD-related tau pathology. Statistical adjustment for skull/meningeal off-target binding may improve signal quantification in early-stage tau-PET assessments.
3. **Future directions**: Future research should seek to extend our results to second-generation tau-PET tracers and incorporate longitudinal study designs. As skull/meningeal off-target signal decreases with older age, emphasis should be placed on participant's age. Efforts should be made to identify female-specific factors contributing to tau accumulation in the presence of amyloid.

2 | METHODS

2.1 | Study design and participants

In the current study, we analyzed baseline data from an observational longitudinal clinical study (NCT02958670) at the University of Zurich, Switzerland. This single-center, population-based study aims to assess the regional tau-PET signal using [18F]-flortaucipir (AV-1451) and investigate its correlates in elderly individuals. Participants were recruited from earlier cohort studies conducted at our institute,[23,24] with a prerequisite of already existing data on cerebral amyloid deposition ([11C]-Pittsburgh Compound-B, [18F]-flutemetamol). All participants were volunteers and were initially recruited through newspaper advertisements. Participants from these cohorts who consented to participate in the current study underwent tau-PET imaging with the tracer [18F]-flortaucipir. To be enrolled in the study, participants had to be at least 50 years of age and German-speaking. Exclusion criteria included evidence for cognitive impairment mainly attributed to a non-neurodegenerative underlying medical condition (e.g., medication, brain tumor, severe heart insufficiency, hepatic encephalopathy, acute

psychiatric disease [upon clinical decision]), evidence of larger cerebral infarcts or lacunes in critical memory structures, ongoing infection with human immunodeficiency virus or any hepatitis virus, previous or current participation in anti-Aβ or anti-tau therapeutic trials, presence of factors that may interfere with MRI or PET procedures, and presence of diseases that would likely interfere with study procedures in subsequent years. Female participants had to be without childbearing potential. In addition, for the present analysis, we excluded participants in whom the time between amyloid and tau-PET was more than 5 years and in whom the quality of the T1-weighted image did not allow accurate ROI delineation. Participants were classified as cognitively normal or having mild cognitive impairment (MCI) according to consensus criteria.[25]

2.2 | Protocol approvals and patient consents

The study was approved by the ethics committee of the canton Zurich (Kantonale Ethikkommission Zürich) and the Swiss authority responsible for the authorization and supervision of therapeutic products (Swissmedic). The study was conducted according to the principles expressed in the Declaration of Helsinki.[26] All participants gave written informed consent prior to the first study procedure.

2.3 | Aβ-PET acquisition and processing

Aβ-PET images were acquired with two different radiotracers. Specifically, 40 participants underwent Aβ-PET imaging using the [11C]-PiB radiotracer scanned on a whole-body PET/CT system (Discover RX/VCT, GE Healthcare, Waukesha, WI, USA), and 99 participants underwent Aβ-PET imaging using the [18F]-flutemetamol tracer scanned on a Signa PET/MR (GE Healthcare, Waukesha, WI, USA). The acquired [11C]-PiB and [18F]-flutemetamol data were reconstructed into 4 × 5-min frames, within post-injection intervals of 50–70 min and 90–110 min, respectively. The injected dose of tracer was approximately 140 MBq of [18F]-flutemetamol or 350 MBq of [11C]-PiB. A global neocortical Aβ-standardized uptake value ratio (SUVR) was estimated from frontal, parietal, temporal, and occipital cortices using the cerebellar cortex as the reference region. The global Aβ-SUVR values were then converted to non-standard Centiloid (CL) values as described in Section 2.4.

2.4 | Centiloid calibration of the new global Aβ ROI

Aβ burden is relatively low in most participants of our cohort. Specifically, among female participants, only nine participants had a CL level of >12, indicating subtle Aβ pathology, and three of them had a CL level of >30, indicating established Aβ pathology (Table 1). To increase the variability while enabling a direct comparison between the two Aβ radiotracers, we expanded the conventional CL ROI defined by Klunk et al.[27] to encompass the whole neocortex, thus capturing a broader region of Aβ pathology. To achieve this, we downloaded the [18F]-flutemetamol calibration datasets[28] from the Global Alzheimer's Association Interactive Network (GAAIN) website (http://www.gaain.org/centiloid-project). Following the calibration procedures outlined by Klunk et al. for calibrating a new method to the CL scale,[27] we converted Aβ-SUVR for the whole neocortex into global CLs, hereafter noted as CL^{global}. Our calibration method fulfilled the quality control criteria suggested by Klunk et al. Details regarding the calibration are provided in the supplementary methods (Tables S1 and S2; Figures S1, S2, and S3).

We tested the new CL^{global} in a linear regression model that incorporated age and APOE4 status – recognized as the two main risk factors associated with elevated Aβ pathology in late-onset AD – as independent variables, and either standard CL or CL^{global} as the dependent variable. Both age and APOE4 status demonstrated a stronger predictive capacity for CL^{global} than for the standard CL (Table S2). We interpret these findings as supporting evidence that the CL^{global} scale effectively approximates the underlying Aβ stage in our study participants.

2.5 | Tau-PET acquisition and processing

Tau-PET images were acquired with approximately 200 MBq of [18F]-flortaucipir using the 80- to 100-minute post-injection interval. Each tau-PET image was rigidly co-reregistered to a high-resolution T1-weighted fast spoiled gradient recalled (FSPGR) acquisition with inversion recovery scanned on a 750 W 3T (32-channel coil) or Premier 3T (48-channel coil) scanner (0.5 mm isotropic voxel size).[5] FreeSurfer (version 7.1.1 for CentOS8 (Linux), surfer.nmr.mgh.harvard.edu) parcellation of the T1-weighted MRI scan was applied to the PET data to calculate mean regional SUVR values for ROI from the Desikan-Killiany atlas[29] using an eroded inferior cerebellar gray matter mask as a reference region.[30] T1-weighted images used for parcellation were performed a maximum of 6 months prior to the tau-PET scan. Partial volume effect correction (PVEc) was conducted using the geometric transfer matrix method in PMOD 4.4, with the point-spread-function set to be an isotropic Gaussian with full-width at half-maximum = 4.5 mm.[31] SUVR values of the left and right ROIs were averaged. The global SUVR was computed by taking the average SUVR values across all neocortical ROIs defined in the Desikan-Killiany atlas. For a better comparison of the tau-PET burden in our cohort with other cohorts, we also generated the tau-PET temporal meta-region (entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal ROIs) as previously described.[32] Temporal-meta tau-PET burden is provided solely for descriptive purposes and is not used in any of our statistical analyses.

2.6 | Creation of skull/meningeal ROI

To assess the effect of skull/meningeal off-target binding on regional neocortical tau-PET signal, we applied a mask that encompasses

TABLE 1 Participant characteristics overall and separately for women and men.

Parameter	Overall ($n = 132$)	Men ($n = 80$)	Matched men ($n = 52$)	Women ($n = 52$)
Age at tau PET visit, years mean (SD) [range]	70.1 (8.6) [51–95]	70.9 (8.3) [51–91]	68.9 (8.0) [51–90]	69 (9.0) [54–95]
Education, years mean (SD)	16.0 (2.9)	17.0 (2.5)	17.4 (2.3)	14.5 (2.7)***
APOE-ε4 carriers, *n* (%)	28 (21)	13 (16.3)	13 (25.0)	15 (28.8)
APOE-ε2 carriers, *n* (%)	25 (18.9)	13 (16.3)	8 (15.4)	12 (31.1)
MCI, *n* (%)	32 (24.2)	22 (27.5)	15 (28.8)	10 (19)
MCI with CL > 12, *n* (%)	12 (9.1)	9 (11.3)	5 (9.6)	3 (5.8)
MMSE, mean (SD)	29.2 (1.2)	29.2 (1.0)	29.1 (1.1)	29.2 (1.4)
BMI, mean (SD)	25.3 (3.9)	26.2 (3.3)	25.6 (2.9)	23.9 (4.4)
Diabetes, *n* (%)	6 (4.5)	4 (5)	1 (1.9)	2 (3.8)
Hypertension, *n* (%)	49 (37.1)	39 (48.8)	19 (36.5)	10 (19.2)
CL, mean (SD) [range]	9.3 (17.1) [−11.4–94.9]	10.0 (18.0) [−11.8–94.9]	8.5 (18.6) [−11.4–94.9]	8.1 (15.7) [−8.8–76.7]
CL > 12, *n* (%)	34 (25.8)	25 (31.3)	9 (17.3)	9 (17.3)
CL > 30, *n* (%)	10 (7.6)	7 (8.8)	3 (5.8)	3 (5.8)
Temporal meta tau, SUVR mean (SD)	1.13 (0.11)	1.1 (0.09)	1.1 (0.09)	1.17 (0.13)**
Entorhinal cortex tau, SUVR mean (SD)	1.05 (0.14)	1.01 (0.11)	1.02 (0.11)	1.11 (0.17)**
Skull/meningeal SUVR, mean (SD)	0.64 (0.15)	0.58 (0.11)	0.58 (0.11)	0.73 (0.15)***
Neocortical thickness, mm mean (SD)	2.26 (0.07)	2.26 (0.06)	2.27 (0.06)	2.26 (0.07)
Episodic memory, z-score mean (SD)	0 (0.73)	−0.11 (0.67)	−0.11 (0.68)	0.11 (0.8)
Age at menopause, *n* (%) (NA = 2)				
< 40 years				4 (7.7)
40–45 years				3 (5.7)
46–50 years				8 (15.4)
51–55 years				25 (48.1)
> 55 years				10 (19.2)
HRT use, *n* (%)				11 (21.1)

Note: The male sample was matched to the female sample based on age, APOE4 carrier status, and standard Centiloid positivity (CL > 12 and CL > 30). All tau-PET SUVR values are based on non-PVEc PET data. Neocortical thickness corresponds to the mean thickness of all cortical ROIs from the Desikan-Killiany atlas. Indicated are statistical differences between women and matched men.

Abbreviations: APOE, apolipoprotein; BMI, body mass index; CL, Centiloid; HRT, hormone replacement therapy; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation.

$^{**}p < 0.01$; $^{***}p < 0.001$.

the skull/meninges surrounding the brain. The mask was created by dilating and eroding individual whole brain masks as previously described.[20] Figure 1 shows an example of a skull/meningeal mask, depicted on a participant's T1-weighted image.

2.7 | Age at menopause

Age at menopause and use of HRT were used as female-specific predictors of [18F]-flortaucipir binding as they have been previously linked to tau pathology.[12] Data on these factors were gathered during the assessment of the patient's medical history. Participants provided information on age at final menstruation, from which we added 1 year to derive the age at menopause. For our analysis, participants were categorized into "early age at menopause" if their age at menopause was <51 years or "late age at menopause" if their age at menopause was ≥51 years.[10] The chosen cutoff aligns approximately with the average age at menopause among women in Europe[33] and divides our cohort into two roughly equal-sized groups (early: $n = 22$, late: $n = 28$). In a sensitivity analysis, participants were categorized into three groups based on their age at menopause: <40 years, 40–49 years, and ≥50 years.[34] Information about HRT was captured through simple "yes" or "no" responses; thus, additional information on the specific type, initiation, and duration of the intervention was not available.

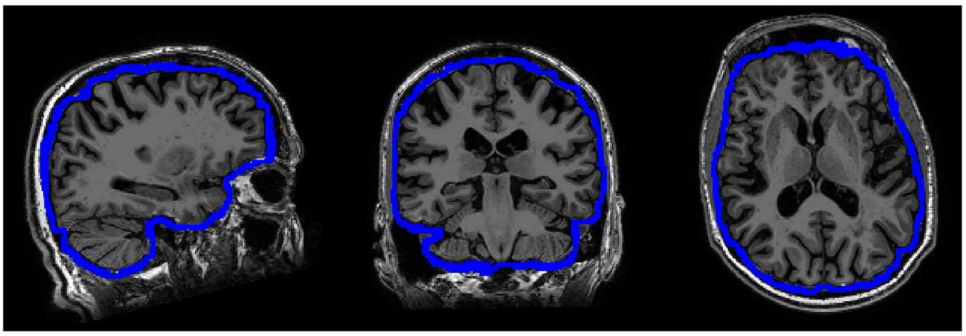

FIGURE 1 Skull/meningeal mask on a participant's T1-weighted image.

2.8 | Cognitive measures

A composite score for episodic memory performance was based on seven cognitive tests: CERAD words [learning, recall, and recognition], VLMT (German version of the RAVLT) [learning, late recall, and recognition], and CERAD figures [recall]. We converted each individual test score to z-scores using the mean and standard deviation of the cohort, and then averaged the z-scores to create the episodic memory score scores.

2.9 | Statistical analysis

Analyses were performed in R version 4.2.2. Demographic characteristics between female participants and matched male participants were compared using Student's t-test for continuous variables and the chi-squared test for categorical variables. Associations between skull/meningeal SUVR, regional tau-PET, mean global tau-PET, and age within the full sample and sex-stratified samples were explored using Pearson's correlations.

As our study sample included disproportionally more males than females (52 females vs. 80 males), we used a matched male sample for the analyses that follow. The *MatchIt* package (v4.5.3) was used to match male participants and female participants based on age at tau PET, APOE4 carrier status, and equal number of individuals with standard CL >12 and >30. Standard CL and not CL^{global} were used as these cutoff values have been identified in a previous study using standard CLs.[35] We obtained the best match when we used the optimal pair matching method with the default distance argument "glm."

Multiple linear regression models were used to investigate sex differences in amyloid-independent and interactive associations with regional tau-PET. Four models were tested using non-PVEc and PVEc regional tau-PET data:

$$\text{Model 1: } tau_{ROI} \sim age\_at\_tauPET + CL^{global} + sex$$
$$\text{Model 2: } tau_{ROI} \sim age\_at\_tauPET + skull\_binding + CL^{global} + sex$$
$$\text{Model 3: } tau_{ROI} \sim age\_at\_tauPET + CL^{global} * sex$$
$$\text{Model 4: } tau_{ROI} \sim age\_at\_tauPET + skull\_binding + CL^{global} * sex$$

Additionally, we explored sex main effects in a model adjusted for age but not for CL^{global}. Statistical significance was assumed at $p < 0.05$ (two-sided), and the results are reported with and without Benjamini-Hochberg false-discovery rate (FDR) correction for 34 ROIs. ROIs for further analysis were selected based on the results of this analysis.

We used the *relaimpo* package (v2.2.6) to evaluate the relative importance of sex, age, CL^{global}, skull binding, and their interactive effect with sex in explaining regional tau-PET signal.[36] The "lmg" method within the package was used to estimate the proportion of explained variance attributable to each variable.

Associations between age at menopause and HRT with tau-PET signal in the selected ROIs were examined using multiple linear regression models:

$$\text{Model 5: } tau_{ROI} \sim age\_at\_tauPET + CL^{global} + age\_at\_menopause$$
$$\text{Model 6: } tau_{ROI} \sim age\_at\_tauPET + CL^{global} * age\_at\_menopause$$

in which "age_at_menopause" stands for binarized age at menopause or HRT use. Skull/meningeal SUVR was not included as a covariate in these models as this analysis was conducted in the female-only sample. FDR adjustment was applied to correct for four comparisons. In sensitivity analyses, all models were adjusted for time between Aβ and tau-PET scan, APOE4 carrier status, or years of education. Additionally, we repeated the analysis by categorizing age at menopause into three distinct groups, as described in Section 2.7.

Last, we aimed to investigate whether accounting for skull/meningeal off-target binding could enhance the ability of the tau-PET signal to predict episodic memory performance. For this analysis, we used the PVEc entorhinal cortex tau-PET signal, as it is a reliable predictor of memory performance in early disease stages.[5,37] We employed multiple linear regression to test whether entorhinal cortex tau predicts episodic memory performance and whether this association can be improved by regressing out the influence of skull/meningeal SUVR from the entorhinal cortex SUVR. We explored potential sex differences by using a sex*tau-PET burden interaction term in our regression model.

2.10 | Data availability

Data from this study are available on request.

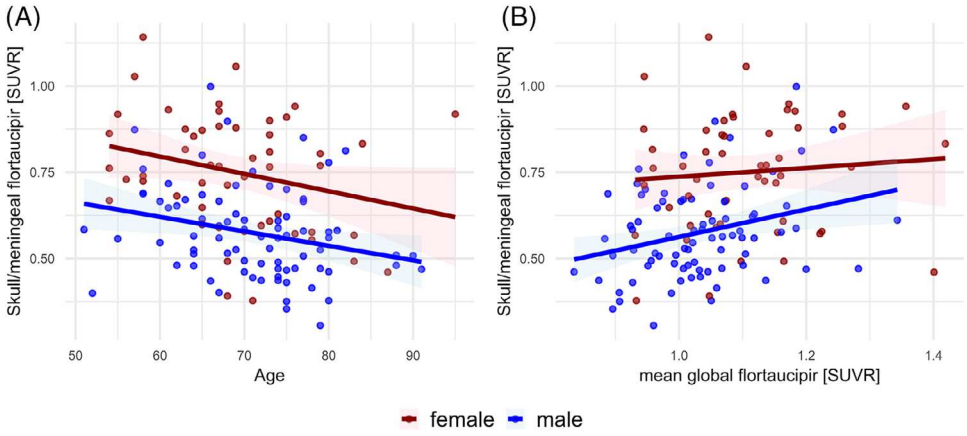

FIGURE 2 Correlations of skull/meningeal [18F]-flortaucipir standardized uptake value ratio (SUVR) and age (A) and mean global [18F]-flortaucipir SUVR (B) for female and male participants.

3 | RESULTS

3.1 | Participant characteristics

The study cohort consists of 141 participants. Of these, five participants were excluded due to a time gap exceeding 60 months between the Aβ and tau-PET scans, two were excluded due to insufficient quality of the T1-weighted images, and two were excluded because of errors during the tau-PET acquisition. Thus, 132 individuals, comprising 52 females and 80 males, were eligible for the matching procedure. The final sample included 52 females and 52 males, matched for age at tau PET, apolipoprotein E4 (APOE4) carrier status, and Aβ-PET burden. Table 1 presents the characteristics of the study cohort.

3.2 | [18F]-Flortaucipir off-target binding in the skull/meningeal ROI

Figure 2 shows off-target binding for male and female participants as a function of age and mean global [18F]-flortaucipir SUVR. All [18F]-flortaucipir SUVRs are based on PVEc PET data. As reported previously in a subsample of this cohort[5] and in line with previous studies,[20,38] female participants showed higher [18F]-flortaucipir SUVR in the PVEc skull/meningeal ROI than men. In stratified analyses, we found similar declines in off-target binding with age in both female and male participants, although the correlation did not reach statistical significance in females (female: $r_{Pearson} = -0.27$, $p = 0.057$; male: $r_{Pearson} = -0.26$, $p = 0.019$). Skull/meningeal SUVR correlated with mean PVEc global tau SUVR in male but not in female participants (female: $r_{Pearson} = 0.08$, $p = 0.552$; male: $r_{Pearson} = 0.29$, $p = 0.009$). When examining individual ROIs, we observed that male participants tended to exhibit stronger correlations between regional [18F]-flortaucipir SUVR and skull/meningeal SUVR than female participants, but lateral occipital, postcentral, pars orbitalis, and lateral orbitofrontal ROIs were among the regions that showed the highest correlations in both groups (Table S3). The stronger association observed between neocortical tau-PET signal and skull/meningeal signal in male individuals suggests that skull/meningeal SUVR in males primarily reflects the spill in signal from the neocortical tau-PET signal. In contrast, in female individuals, stronger tau-PET signal from off-target binding may make such an association less pronounced.

3.3 | Aβ-independent and Aβ-interactive effects of sex on regional tau-PET signal

Our subsequent aim was to examine sex-related differences in regional [18F]-flortaucipir SUVR, both independently and in interaction with CL^{global}. In addition, we examined whether the use of PVEc data and control for skull/meningeal SUVR influenced regional differences. The results of this analysis are presented in Figure 3 and Tables S4–S7. Overall, female sex demonstrated notable associations with elevated [18F]-flortaucipir SUVR across nearly all ROIs. Higher [18F]-flortaucipir signals in female participants were particularly evident in the analysis of the primary effect and were also evident when an interactive effect with CL^{global} was examined. When using PVEc data, there was an observed increase in the β-estimates and a change in the number of ROIs exhibiting sex differences in [18F]-flortaucipir SUVR compared to the non-PVEc data. The increase in [18F]-flortaucipir SUVR within many ROIs was no longer apparent after accounting for skull/meningeal SUVR in the regression model. However, this diminishing effect was less pronounced when considering the interaction between CL^{global} and sex on regional [18F]-flortaucipir SUVR, but additional ROIs survived FDR correction when skull/meningeal SUVR was included in the regression model. Sex main effects in a model that did not adjust for CL^{global} mirror those observed when CL^{global} is taken into account (Figure S4).

Based on these results, we selected four ROIs for our subsequent analyses: the parahippocampal cortex, the inferior temporal cortex, and the isthmus cingulate as regions showing Aβ-dependent sex differences and the rostral anterior cingulate as a region showing potential Aβ-independent sex differences in tau pathology. These regions were

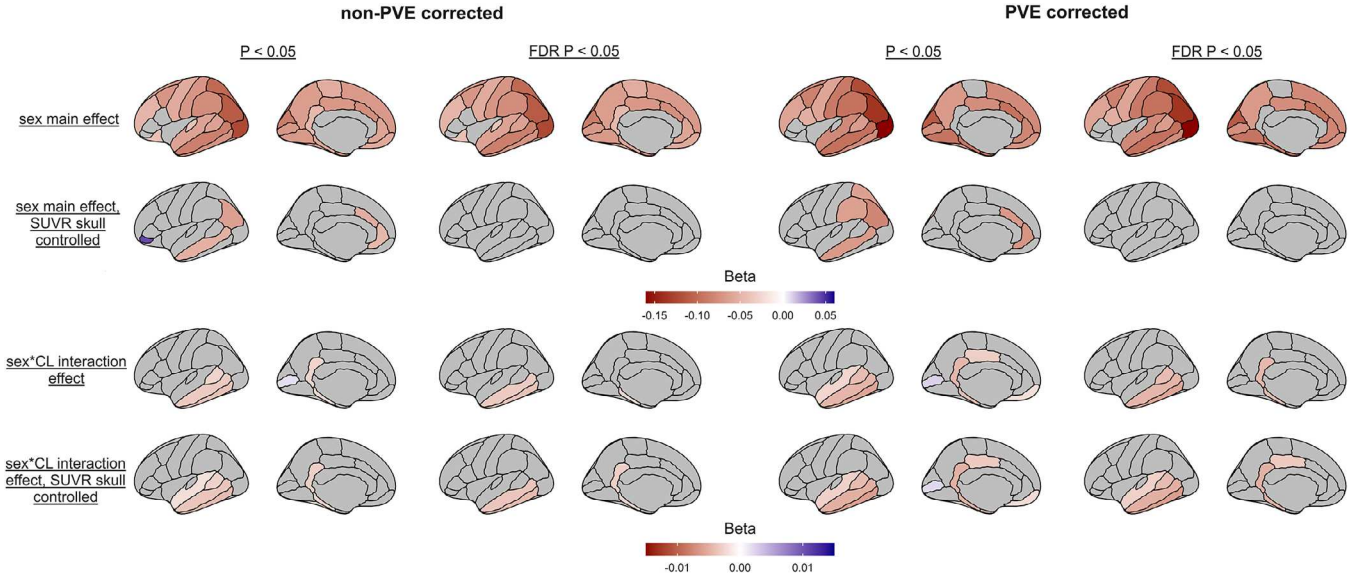

FIGURE 3 Cortical regions showing significant sex differences in [18F]-flortaucipir standardized uptake value ratio (SUVR). In the regression models, sex was coded as female = 0 and male = 1; thus, negative beta estimates (red) indicate higher [18F]-flortaucipir SUVR in females, and positive estimates (blue) indicate higher [18F]-flortaucipir SUVR in males. Compared to male individuals, female individuals exhibit elevated [18F]-flortaucipir SUVR in cortical regions, both independently and interactively with CL^{globa}l.

selected among those that showed significant sex-related differences and were chosen from distinct brain areas to minimize inter-region correlations. Sex differences in the relationship between CL^{global} and tau-PET within the four selected regions are presented in Figure 4. Closer examination of scatterplots before and after accounting for the influence of skull/meningeal SUVR indicates the most pronounced changes when CL^{global} is low and tau-PET signal is weak. Scatterplots for the lateral occipital ROI, which showed the largest sex main effect in the off-target signal uncorrected analysis, are shown in Figure S5. The PVEc data were used in all subsequent analyses.

3.4 | Relative importance of sex, age, amyloid, and skull/meningeal binding in explaining regional [18F]-flortaucipir signal

We then examined the extent to which the variance in the [18F]-flortaucipir signal within the four chosen ROIs could be explained by the variables sex, age, CL^{global}, and skull/meningeal [18F]-flortaucipir signal. The model that included all variables, including the interaction between sex and CL^{global} (Figure 5A–D), explained the most variability in the [18F]-flortaucipir SUVR, which was evident in the (A) parahippocampal cortex (R^2: 0.457), (B) inferior temporal cortex (R^2: 0.498), (C) isthmic cingulate cortex (R^2: 0.389), and (D) rostral anterior cingulate cortex (R^2: 0.219). In contrast to the other three ROIs, the four variables explained considerably less variance within the rostral anterior cingulate. Within this region, sex emerged as the predominant factor contributing to the explained variance, whereas in the other three ROIs, CL^{global} typically played a more prominent role in accounting for variability, as indicated by the bars in the plot. While significant sex*age interactions were observed in all ROIs except the rostral anterior cingulate cortex, we considered that these interactions might be influenced by a positive correlation between age and CL^{global}. To test this hypothesis, we incorporated both interaction terms into a model with inferior temporal [18F]-flortaucipir SUVR as the dependent variable. The results confirmed that sex interacts with CL^{global} ($\beta = -0.70$, $p < 0.001$) but not with age ($\beta = -0.17$, $p = 0.31$), although the power to detect effects was probably limited in this model. In an exploratory analysis, we examined whether carrying an APOE4 allele explains [18F]-flortaucipir SUVR variability using two models – one that included APOE4 status only and another that included all variables plus a sex*APOE4 interaction term. Neither of these analyses showed a significant effect of APOE4 status ($p > 0.83$) or its interaction with sex ($p > 0.33$) on tau-PET signal in any of the four regions.

3.5 | Associations between age at menopause and regional tau

Adjusting for age and CL^{global}, we found no main association between age at menopause or HRT use and tau-PET in any of the four ROIs. In the context of elevated Aβ levels, female participants who reported HRT use showed lower tau levels in the parahippocampal, inferior temporal, and isthmus cingulate ROIs than those who did not report HRT use (Table S8, Figure S6). However, it is important to note that the number of female participants reporting HRT use is relatively small ($n = 11$ (21%)), and as depicted in Figure S6, there is limited variability in Aβ burden within this group, with the highest CL^{global} reaching ~28. No significant interaction between age at menopause and CL^{global} on regional tau-PET was found. The results remained largely unchanged

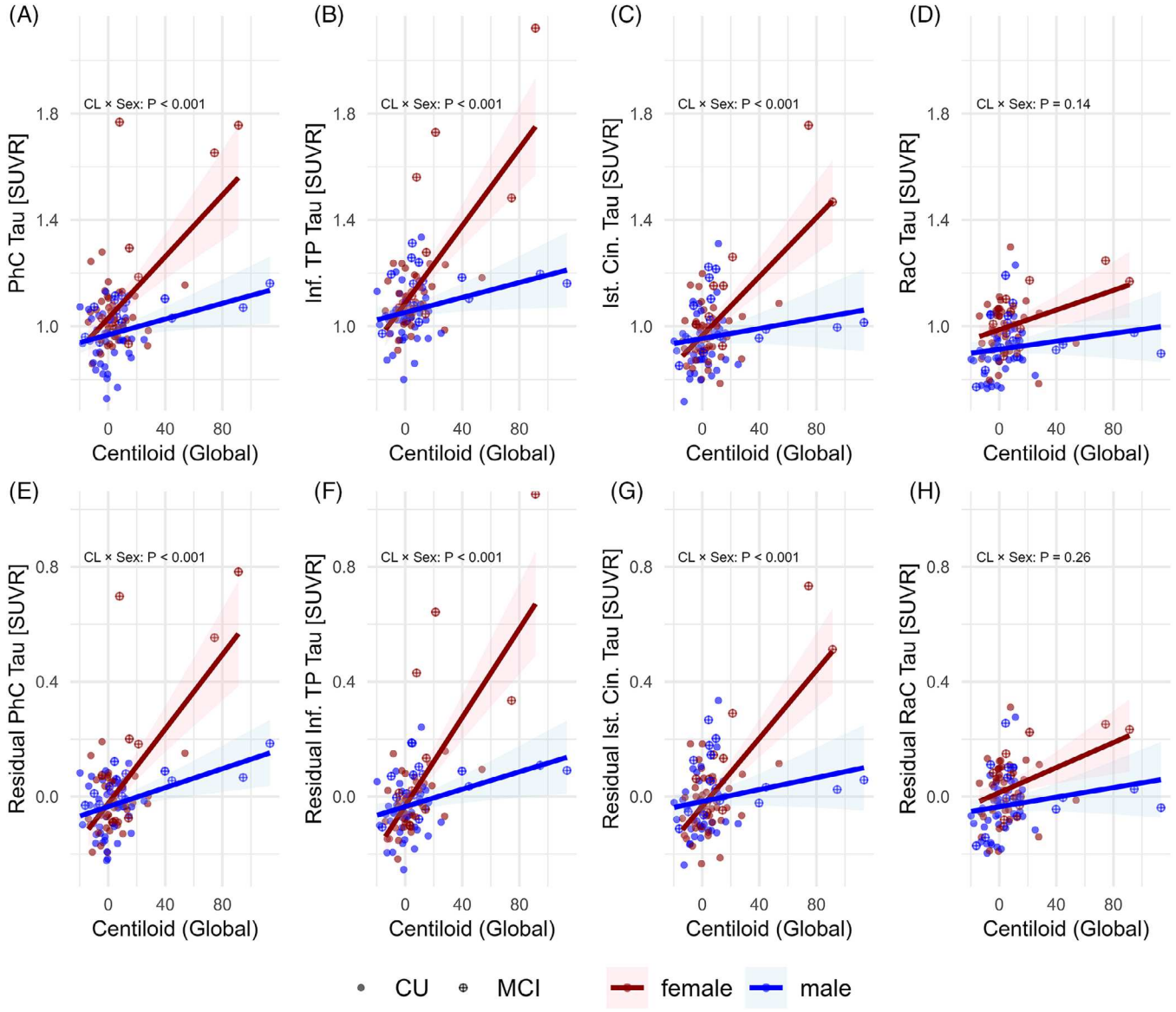

FIGURE 4 [18F]-flortaucipir standardized uptake value ratio (SUVR) in four selected ROIs in female and male individuals as a function of CL^{global} before (A–D) and after (E–H) regressing out the effect of skull/meningeal SUVR.

in sensitivity analyses. Figure S7 displays the associations between HT use or age at menopause and the remaining ROIs. Figure S8 shows the results when participants were grouped by age at menopause into three categories.

3.6 | Entorhinal cortex tau as a predictor of episodic memory performance

Finally, we used entorhinal cortex [18F]-flortaucipir SUVR to explore its associations with episodic memory, based on prior evidence indicating its role as a predictor of memory performance in the early stages of tau pathology.[5] Male sex ($\beta = -0.486$, $p < 0.001$) and higher entorhinal cortex [18F]-flortaucipir SUVR ($\beta = -0.408$, $p < 0.001$) were strong predictors of lower episodic memory performance when controlling for age, education, and number of neuropsychological assessments. No interaction between sex and entorhinal cortex [18F]-flortaucipir SUVR on episodic memory performance ($\beta_{interaction} = -0.086$, $p = 0.537$) was found. We obtained virtually identical results when we used the residuals of entorhinal cortex [18F]-flortaucipir SUVR after regressing out the association with skull/meningeal SUVR.

4 | DISCUSSION

In this cross-sectional, community-based cohort study, we investigated in detail the role of sex in explaining variability in regional [18F]-flortaucipir SUVR, independently and interactively with Aβ burden, age, and off-target binding in a skull/meningeal mask outlining the brain. Overall, our results confirm that female sex, particularly

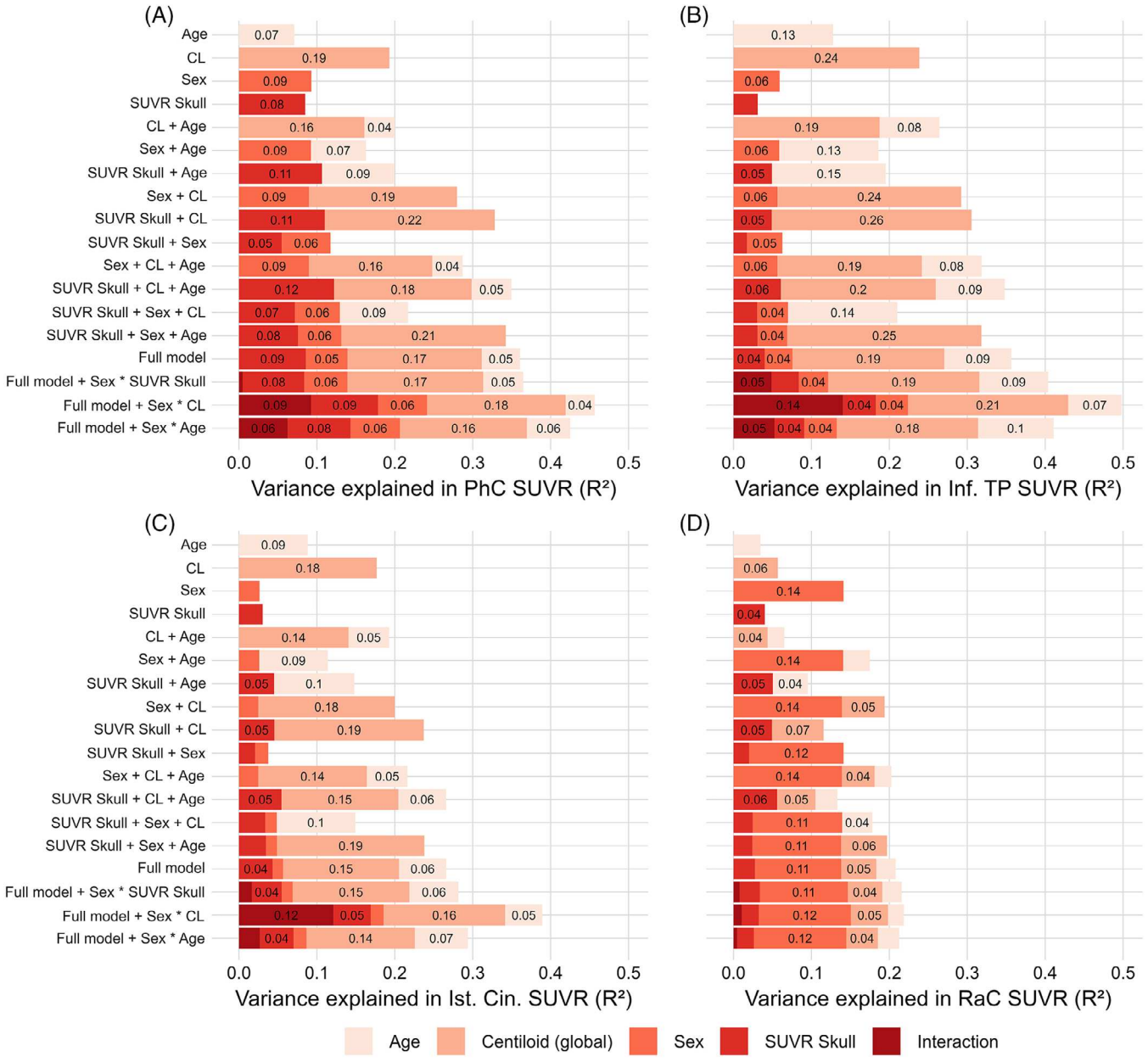

FIGURE 5 Amyloid and sex contribute most to explaining variability in [18F]-flortaucipir standardized uptake value ratio (SUVR) in parahippocampal (A), inferior temporal (B), isthmus cingulate (C), and rostral anterior cingulate (D) regions of interest (ROIs). In the *Full model*, all four variables were included. Values within the plots denote the R^2 contribution of each variable in each model, with R^2 values below 0.04 omitted from the plot for clarity.

in the presence of Aβ pathology, is associated with increased [18F]-flortaucipir SUVR in regions typically associated with AD-related tau pathology. An Aβ-independent elevation in [18F]-flortaucipir SUVR in female individuals can be primarily attributed to higher off-target binding in the skull/meninges compared to male individuals. Furthermore, age but not age*sex interactions explain a small but significant amount of [18F]-flortaucipir SUVR binding in temporoparietal ROIs. Finally, we did not observe a main association between age at menopause and HRT with regional tau-PET signal. Given the limited number of participants with high Aβ-PET burden in the small group of HRT users, our finding of a significant interaction between HRT use and Aβ burden on tau-PET signal in parahippocampal and inferior temporal ROIs should be interpreted with caution.

When we examined only the main effects, the collective influence of Aβ load, age, sex, and skull/meningeal off-target binding accounted for approximately one-third of the variability in tau PET signal within the parahippocampal and inferior temporal regions and roughly one-quarter of the variance in the isthmus-cingulate cortex. Aβ burden was the most substantial contributor to regional tau-PET signal, aligning with evidence that Aβ plays a central role in driving tau pathology[39] and is the primary predictor of tau accumulation.[40] This was most pronounced in the inferior temporal cortex, which is consistent with

previous studies that observed the strongest tau accumulation in the inferior temporal region in individuals with increased Aβ burden.[41] Age emerged as another significant factor contributing to tau-PET signal in these regions. The relative importance of age in explaining tau-PET signal decreased when Aβ burden was taken into account, indicating that a large part of the age-related influence on tau-PET signal is related to its association with increased Aβ pathology.[5] Nonetheless, age remained a contributor to variance even when considering its association with increased Aβ pathology, suggesting that some proportion of tau-PET signal can be attributed to Aβ-independent age-related tau accumulation. The observation that this effect is notably less pronounced compared to Aβ burden aligns with findings in PART, a condition typically characterized by a more gradual clinical progression, as opposed to conditions in which Aβ is present.[16,42] This is further supported by a recent imaging study, which showed subtle longitudinal changes in tau-PET among individuals who were Aβ negative but exhibited elevated medial temporal tau-PET signal.[14] Importantly, we identified significant interactions between sex and Aβ burden on tau-PET signal within temporoparietal brain regions. These interactions consistently indicated that, in regions typically associated with early AD-related tau pathology, females exhibited higher tau-PET signal for a given burden of Aβ than males. Including a sex*Aβ burden interaction enhanced the model's explanatory capacity and contributed substantially to the variance explained. In contrast, the interaction between sex and age turned out to be non-significant when we accounted for the sex*Aβ burden interaction in the model, suggesting that both males and females exhibit similar age-related effects on tau-PET signal. However, given that an age-related tau-PET increase is subtle, a larger sample size may be needed to detect such an interaction.

Another important finding was that the detection of sex*Aβ interactions is largely unaffected by skull/meningeal off-target binding. Figure 2 indicates that when using PVEc data and incorporating skull/meningeal off-target binding as a covariate, β-estimates are larger across regions, and significant sex differences are evident in two additional regions that typically exhibit early AD-related tau pathology, which were not found in a model that did not account for off-target binding. Considering this finding in light of the study cohort, which primarily consists of participants in early Aβ stages when tau-PET signal is typically low,[43] this may suggest that using PVEc data and including skull/meningeal off-target binding as a covariate is a method slightly more sensitive to detect regional sex*Aβ interactions on tau-PET signal compared to using non-PVEc data and not accounting for skull/meningeal off-target binding. In turn, accounting for skull/meningeal off-target binding does not seem to enhance the predictive capability of entorhinal cortex tau-PET signal for episodic memory performance.

Previous studies reported higher tau-PET signal in female individuals that was independent of Aβ burden.[9,10] Based on our first analysis, we suggest two explanations for this finding. First, while females do tend to exhibit higher tau pathology, this difference is better explained by an interaction with Aβ, but detecting this interaction can in some circumstances be difficult because of inherent limitations of Aβ and tau PET imaging. Second, particularly in the setting of low Aβ pathology, this sex-related difference may largely stem from increased off-target binding in the skull/meninges in female compared to male individuals, as in many regions, no significant main effect of sex was observed once the influence of off-target binding was considered. Despite adjusting for off-target binding, a sex main effect remained in some regions, although none of them survived FDR correction. Visual inspection of the correlation plots for the rostral anterior cingulate ROIs (Figure 3), a region in which the main effect of sex persisted even after accounting for off-target binding, also indicates sex differences in tau-PET signal in the lowest CL stages. Given the low burden of tau pathology typically observed in these regions during early disease stages[3,44] and the almost consistently increased tau-PET signal in female compared to male participants in Figure 3D,H, it is unlikely that this discrepancy reflects physiological differences in tau accumulation.

One crucial aspect to consider is the age of the study cohort. While male individuals tend to exhibit lower off-target binding across a broad age range compared to female individuals, it is likely that, in an older cohort, this disparity would not substantially impact neocortical tau-PET signals, as the signal in the skull/meninges is generally weak in older individuals of both sexes. This may have contributed to a higher, Aβ-independent tau-PET burden in female individuals, which was found in younger cohorts (mean age <66 years) examined in previous studies,[9,10] including our own.[5] Accounting for skull/meningeal off-target binding may thus be important when the aim is to investigate sex differences in tau-PET signal that are potentially unrelated to Aβ pathology in older middle-aged adults. The creation and utilization of a mask such as the one used in a previous study,[20] and integrated into our current investigation, could offer a viable strategy for addressing off-target binding in a sensitivity analysis.

We did not identify sex-specific risk factors that increase tau pathology independently from Aβ, which reinforces our interpretation that the elevated tau pathology observed in females primarily depends on Aβ pathology. We did, however, observe a significant interaction between Aβ-PET and HRT use on regional tau-PET. Although this finding is supported by previous studies,[12] it must be noted that the limited range of Aβ burden within the HRT user group limits our ability to draw conclusions from these data. Additionally, in contrast to work by Coughlan et al.,[12] we did not observe higher tau pathology in participants with elevated Aβ-PET burden who reported earlier menopause compared to those with later menopause. Nevertheless, our results do not necessarily contradict their study. Coughlan et al. reported that a global Aβ-PET burden threshold of ~20 CLs or higher is necessary to observe a significant association between age at menopause and tau PET in several ROIs. In our cohort, only five females crossed this threshold, making it likely that detecting such an association was not possible.

Some limitations should be considered when interpreting the results of the present study. First, our interpretation of [18F]-flortaucipir signal in the skull/meningeal mask as off-target signal might not be entirely accurate, as signal spill-over from the brain ROIs to the skull/meningeal ROI is likely not completely eliminated through PVEc, leaving residual spill-over signal. Therefore, it is possible that we have corrected for some tau-PET signal reflecting "true" tau pathology. This

consideration may be particularly important in cohorts with increased tau pathology; thus, correction for skull/meningeal off-target binding is probably more appropriate for cohorts in the early stages of tau pathology when neocortical tau-PET signal is generally weak. Second, it is important to note that our findings concerning off-target binding may not directly apply to second-generation tau-PET tracers. Exploring this aspect is crucial because skull/meningeal off-target binding is more pronounced with the tracers [18F]-MK6240 and [18F]-RO948.[20,45] Third, the study cohort is a highly educated sample that is not fully representative of more clinically and ethnically diverse populations. Fourth, the sample size, especially for the female-specific analyses, was relatively small, and the limited Aβ-PET burden in the HRT use group restricts our ability to draw definitive conclusions. Fifth, unfortunately we lacked additional information about HRT use and reproductive factors. Factors such as HRT initiation, age at menarche, or reproductive years are important components to consider in such analyses.[46]

Sex is an important factor influencing tau-PET signal, particularly in interaction with Aβ-PET burden but also in off-target binding. It is crucial to elucidate the factors and underlying mechanisms driving these sex differences in the presence of Aβ pathology. Particularly in the early stages of tau pathology, when interventions may be most effective,[18] accurate quantification of tau-PET signal is essential for this research.

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CONFLICT OF INTEREST STATEMENT

Christoph Hock and Roger M. Nitsch are employees and shareholders of Neurimmune AG, Switzerland. Dario Bachmann, Andreas Buchmann, Sandro Studer, Antje Saake, Katrin Rauen, Esmeralda Gruber, Anton Gietl, and Valerie Treyer declare no relevant conflicts of interest. Author disclosures are available in the supporting information

CONSENT STATEMENT

All participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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