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Sex mediates relationships between regional tau pathology and cognitive decline

Running head: Sex, regional tau pathology and cognitive decline

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Abstract

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 (Female, 58%; 73.8[8.5] years) and 55 individuals with MCI (Female, 38%; 76.9[7.3] years) from the Harvard Aging Brain Study and the Alzheimer's Disease Neuroimaging Initiative. We examined ¹⁸F-Flortaucipir (FTP)-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* $A\beta$ -PET(+/-) and sex*APOE ϵ 4 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: Females showed significantly higher FTP-signal than males across multiple regions of the cortical mantle ($p < 0.007$). $A\beta$ -moderated sex differences in tau signal were localized to medial and inferior-lateral temporal regions ($p < 0.007$); $A\beta+$ females exhibited greater FTP-signal than other groups. APOE ϵ 4-moderated sex differences in FTP-signal were only found in the lateral occipital lobe. Females with higher FTP-signal in composite ROI exhibited faster cognitive decline than males ($p = 0.04$).

Interpretation: Tau vulnerability in females is not just limited to the medial temporal lobe and significantly contributed to greater risk of faster cognitive decline. Interactive effects of sex and $A\beta$ were predominantly localized in the temporal lobe, however, sex differences in extra-temporal tau highlights the possibility of accelerated tau proliferation in females with the onset of clinical symptomatology.

Introduction

Growing evidence suggests females exhibit higher levels of tau burden than males¹⁻⁷; this is particularly apparent in those with genetic risk for sporadic Alzheimer's disease (e.g., apolipoprotein ϵ 4 [APOE ϵ 4] carriers)³ or with elevated levels of β -amyloid (A β) burden⁵. Levels of both CSF total tau and p-tau are higher in female APOE ϵ 4 carriers across the cognitive impairment spectrum¹, including those who are clinically normal³. Post-mortem findings also observe a greater amount of tau tangles in females than males^{6,7}, as supported by a recent meta-analysis of post-mortem samples across multiple cohorts³. While in vivo CSF findings are consistent, this modality does not provide regionally specific information about tau burden.

Relatively few tau-PET findings reports have focused on topographical sex differences in tau signal⁸. We recently found that clinically-normal older females with higher levels of global A β exhibit higher levels of entorhinal tau burden than males⁵. 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 metabolism⁹ or APOE ϵ 4 status¹⁰. 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 A β levels and APOE ϵ 4 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 (e.g., age, inflammation, cardiovascular, hormones, 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 A β and APOE ϵ 4 carriage. We hypothesized that females 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 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 Female, 58%; 74[8.5] years, range: 50-94yrs) and 55 individuals with MCI (21 Female, 38%; 77[7.3] years, range: 60-92yrs) 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 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 $\text{A}\beta$ -PET scan was a median (interquartile range) of 43 (7-112) days (max=3= yrs). For ADNI, the interval was 7 (2-32) days (max=4.8 yrs). 21 participants had a lag of longer than one 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.

APOE Genotyping

A blood sample was collected in each study for direct genotyping of APOE (heterozygotes and homozygotes for the $\epsilon 4$ allele were collapsed into one category, with $\epsilon 2$ - $\epsilon 4$ individuals removed).

Magnetic Resonance Imaging

Structural T1-weighted anatomical 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-Killiany cortical and aseg subcortical ROI parcellations¹³, with quality control measures previously described¹¹.

$\text{A}\beta$ Positron Emission Tomography

HABS used ^{11}C Pittsburgh compound-B (PiB), while ADNI used ^{18}F -Florbetapir (FBP). The PET acquisition parameters for each study have been published previously¹⁴⁻¹⁶. Distribution volume ratios (DVRs) were computed using Logan plotting 40 to 60 minutes post injection, and summary measures were computed from a weighted average within a large 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 grey¹⁷. 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 cerebellum¹⁴. As each cohort used different tracers and processing pipelines, $\text{A}\beta$ -PET signal was expressed dichotomously using a 1.11 SUVr threshold in ADNI¹⁸ and a 1.185 DVR threshold in HABS¹⁹, although $\text{A}\beta$ -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 elsewhere²⁰ (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 in-house processing pipelines²⁰. SUVrs were created by referencing to cerebellar grey^{20, 21}. All FTP ROI data are partial volume corrected using the Geometric Transfer Matrix method (GTM)²², although associations involving non-PVC data were also explored. Due to off-target binding with FTP-PET²³, 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 method²⁴.

Tau Analysis

Analyses were run in R v3.3.3 (The R Foundation) and MATLAB vR2018b (MathWorks, Inc., 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 SUVr across 41 cortical and sub-cortical ROIs. For 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 further investigate the spatial distribution of sex effects, we examined surfaced-based vertex wise maps (full sample, and in A β + or APOE ϵ 4 carriers). As with our previous study⁵, we did not include a three-way sex*A β *APOE ϵ 4 interactions due to low statistical power. The models were:

Model 1: FTP ~ Sex + Age + Cohort*

Model 2A: FTP ~ Sex + A β Group + Age + Cohort* [main effects only]

Model 2B: FTP ~ Sex $\times$ A β Group + Age + Cohort* [fully factorial]

Model 3: FTP ~ Sex $\times$ APOE ϵ 4 + 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 males and females. We also examined a composite of regions that highlighted sex*A β 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 [$n_{\text{observations}}=1626$] and prospective [$n_{\text{observations}}=965$]), 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 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 A β -PET scans greater than one 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 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 Table 1 (Supplementary Table A displays diagnostic demographic comparisons). Within HABS, female participants were younger than males. For ADNI, females exhibited slightly higher continuous A β -PET SUVR than males. Comparison between cohorts revealed that HABS females were marginally younger, had higher MMSE scores and a lower proportion of A β + individuals relative to ADNI females. There were no significant follow-up differences for neuropsychological assessments between men ($t = 6.01$ (SE=2.5) years) and women ($t = 5.38$ (2.4) years).

---Table 1---

Main effect of sex

Females showed significantly higher FTP SUVR signal 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 s < .007; Fig 1, with model R^2 included). Estimated SUVR differences between males and females can be found in Supplementary Table B (and for subsequent models). Adjusting for dichotomous A β -PET attenuated the sex effect in the pars orbitalis, caudal middle frontal, postcentral, lingual, inferior temporal, and entorhinal gyrus to non-significant (p s < .05). As a post-hoc analysis, we examined a sex*age interaction but found no effect on any ROIs.

---Figure 1---

Sex and A β interaction on FTP signal

There was no difference in A β +/- status between males and females ($t(392)=1.66$, $p=0.10$). A β + females 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 males and females in A β +/- groups are shown in Figure 3. These regions were recapitulated within each cohort when examining continuous A β .

---Figure 2---

Sex and APOE ϵ 4 interaction on FTP signal

Female APOE ϵ 4 carriers exhibited higher FTP SUVR in the lateral occipital lobe than any other group (Fig 4).

---Figure 3---

Effects on cognitive decline

Using a composite of the sex differentiated ROIs (gathered from all significant Model 1 outputs), females with higher FTP signal exhibited faster cognitive decline than males ($t_{\text{sex*tau composite*time}}=-2.49$, $p=0.01$; Fig 5 and Supplementary Table C 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*A β interaction (gathered from all significant Model 2B outputs; $t_{\text{sex*tau composite*time}}=-2.34$, $p=0.02$). We found no sex*A β_{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.

---Figure 4---

Sex differences in tau ROI signal in clinically-normal individuals

Findings were largely recapitulated in clinically-normal individuals (see Fig 6), and adjusting for A β -PET exerted little influence. For the sex*A β status interaction, a significant effect was observed in the fusiform, inferior temporal, entorhinal, accumbens area and the amygdala; clinically-normal A β + females exhibited higher FTP signal than any other group. Clinically-normal female APOE ϵ 4 carriers exhibited higher FTP SUVR 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, $t_{\text{sex*tau composite*time}}=-1.64$, $p=0.10$, and the sex*A β composite, $t_{\text{sex*tau composite*time}}=-1.72$, $p=0.08$. There were no sex*A β *tau interactions on cognitive decline, which may have reflected low statistical power for detection.

Sensitivity Analyses

Excluding individuals with A β -PET scans greater than one 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 a $p \sim 0.007$. 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, females had greater signal than males ($\beta = 0.83$ (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 (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 females exhibited higher FTP SUVR than males in many temporal and extra-temporal regions. These comprised the parietal, middle frontal, lateral occipital, fusiform, supramarginal, cuneus, banks of the STS, and frontal/temporal pole regions. Many of these regions remained significantly different between the sexes even after adjusting for A β status. Amyloid-moderated sex differences in tau signal (sex*A β interaction) were largely restricted to the temporal lobe. A β + females showed higher FTP signal than A β + males and A β - 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 A β + females show higher signal than A β + males. In clinically-normal individuals, A β + females displayed elevated signal only in temporal regions of the fusiform, inferior temporal and entorhinal cortices. By contrast, female APOE ϵ 4 carriers only showed elevated signal in the occipital region relative to male APOE ϵ 4 carriers and non-carriers, 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 APOE ϵ 4-moderated sex effects on tau signal arose from previous studies showing that female APOE ϵ 4 carriers have higher levels of CSF tau than male carriers³. Interestingly, a sex*APOE ϵ 4 interaction did not mirror sex*A β findings in this study in that female APOE ϵ 4 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*APOE ϵ 4 interaction, and/or there may simply be different sources of variance driving these two markers. Finally, a collection of regions (predominantly extra-temporal) appear to be sex divergent but are unexplained by

A β 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 females. The interpretation of our cognitive findings are varied: a) that females 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 b) 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 signal^{9, 25, 26} and show associations with greater cortical thinning and CSF p-tau levels²⁶, supporting the notion that they are proximal to neurodegenerative processes. Previous studies also show higher FTP signal in these regions in those with elevated A β burden^{27, 28}, supporting the notion of a female vulnerability to tau in AD vulnerable regions. Some regions that showed sex differences (e.g. frontal and temporal pole) are small and attract signal-to-noise issues. We found smaller effect sizes associated with these regions, and unsurprisingly were more affected by partial-volume correction. 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 work⁵, we found that clinically-normal older A β + females showed greater tau in medial temporal regions than males, suggesting that A β -related susceptibility follows the early topographical patterns of the AD pathological cascade²⁹⁻³³. 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*APOE ϵ 4 interactive effects on FTP SUVR⁵. Another rationale for elevated FTP SUVR in females may be due to non-specific binding²³. Binding in extra-cortical hotspots such as the lateral occipital, middle temporal, and superior and inferior parietal lobes have been reported beyond the common FTP-related culprits (e.g., choroid plexus, skull, meninges)²³. It remains unclear why females might express additional susceptibility to non-specific 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 signal in regions of interest. A comprehensive exploration and assessment of the extent to which other contributors may drive sex differences in FTP 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 females 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 A β 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 A β -PET signal^{19,38}, although it may be possible that A β differences may occur earlier, such as during menopause³⁷, which may have a downstream effect on tau deposition. A recent pilot clinical-trial showed that women treated with transdermal 17 β -estradiol exhibited slightly lower levels of A β -PET signal than an age-matched placebo group (particularly female APOE ϵ 4 carriers)³⁹. There is also a possibility that tau vulnerability may be a direct result of estrogen depletion post-menopause, and animal models support this hypothesis.^{34,40} Without direct human-model evidence, this remains unclear. Sex differences exist in 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 females 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 (Figure 2D) highlights that females showed higher levels of tau across all these regions and not greater numbers of females at higher tau levels. That is, males 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-old clinically-normal A β + individuals⁴⁵. Further, males with higher levels of tau in these regions may not be included for various reasons: (1) stringent study inclusion criteria (i.e. lower cardiovascular risk), (2) faster rates of progression to dementia or death in males with higher temporal tau, or (3) males 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 females exhibit higher FTP signal than males in multiple brain regions, in earlier stages of disease. Higher FTP signal in these regions translated to accelerated cognitive decline in females relative to males. Examining these findings within the context of longitudinal FTP-PET studies could help to address whether males and females with medial temporal tau, or who are A β +, have different FTP-PET trajectories across the brain.

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Author contributions

Study concept and design was carried out by RFB, MRS, REA, ECM, HILJ, BJH, DMR, KAJ, RAS. Data acquisition and analysis was carried out by RFB, MRS, MJP, TJH, APS, DVM, ZBR, LM. Drafting the manuscript and figures was conducted RFB, MRS, RAS.

Conflict of interest

Nothing to report

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Table 1. Demographic comparisons between HABS and ADNI cohorts

Figure 1. Main effects of sex on FTP SUVr after adjusting for age and cohort (A) with 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 $F > M$).

Figure 2. Interactive effects of sex and $A\beta$ +/- on FTP SUVr after adjusting for age and cohort (A) with ROI-based analyses within $A\beta$ + participants only ($n = 129$; corrected $p < 0.007$), (B) β standardized and SE for each ROI with corresponding model R^2 (bars to the right denoting $F > M$), and (C) model estimates of FTP SUVr in the inferior temporal cortex (with 95% CI) in males and females with $A\beta$ -PET +/-

Figure 3. Density maps depicting the distributions of FTP-signal in regions that are differentiated by a sex* $A\beta$ interaction

Figure 4. Interactive effects of sex and APOE ϵ 4 on FTP SUVr after adjusting for age and cohort (A) with ROI-based analyses within APOE ϵ 4 carriers only ($n = 109$; corrected $p < 0.007$), (B) β standardized and SE for each ROI with corresponding model R^2 (bars to the right denoting $F > M$), and (C) model estimates (with 95% CI) of FTP SUVr in males and females with and without APOE ϵ 4 carriage.

Figure 5. Spaghetti plot of cognitive trajectories over time in clinically-normal individuals (0th time represents the first FTP-PET scan) and faceted by a tertile split of composite FTP-PET signal (top = meta-ROI, middle = meta temporal ROI, bottom = reference-ROI) with quadratic fit curves stratified by sex

Figure 6. Main effects of sex on FTP SUVr signal in clinically-normal individuals only, showing beta weights and standard errors for each ROI with corresponding model R^2 (bars to the right denoting $F > M$). Red indicates multiple comparison significance $p < .007$, purple indicates $p < .05$ and blue indicates sub-threshold estimates.

Figure 7. Main effect of sex on FTP SUVr after adjusting for age and cohort [ROI-based analyses]: (A) ADNI uncorrected (B) ADNI corrected, (C) HABS uncorrected, and (D) HABS corrected

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Table 1. Demographic comparisons between HABS and ADNI cohorts

	HABS		Test Statistic	<i>p</i>	ADNI		Test Statistic	<i>p</i>	All
	F	M			F	M			
N (% subsample)	152	99			68	79			398
<i>APOE</i> ε3ε4 Haplotype	34 (22)	18 (18)	$X^2 = 0.64$	.42	24 (35)	19 (24)	$X^2 = 2.23$	.14	95 (24)
<i>APOE</i> ε4ε4 Haplotype	3 (2)	1 (1)	$X^2 = 0.36$	.55	3 (4)	7 (9)	$X^2 = 1.14$	.29	14 (4)
High Aβ	42 (28)	26 (26)	$X^2 = 0.06$	.81	32 (47)	29 (38)	$X^2 = 1.61$	.20	129
Global CDR 0.5	8 (5)	6 (6)	$X^2 = 0.07$	.79	23 (34)	34 (43)	$X^2 = 1.31$	.25	71 (18)
Median [IQR]									
CDR Sum of Boxes	0 [0-0]	0 [0-0]	$Z = 0.47$	.64	0 [0-0.5]	0 [0-1.375]	$Z = -0.66$	.51	0 [0-0.5]
Mean (SD)									
Age	72.2 (9.5)	74.8 (8.3)	$t(249) = -2.21$	.02*	74.7 (6.2)	76.7 (7.4)	$t(145) = -1.82$	.07#	74.2 (8.5)
MMSE	29.3 (1.0)	29.1 (1.1)	$t(249) = 1.30$	.20	28.7 (1.6)	28.4 (2.0)	$t(144) = 0.96$	.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)	$t(249) = -0.85$	.40	15.8 (2.7)	16.8 (2.6)	$t(145) = -2.34$	.02*	16.2 (2.8)
Aβ DVR/SUVr	1.2 (0.2)	1.2 (0.2)	$t(247) = 0.59$	.55	1.2 (0.2)	1.1 (0.2)	$t(145) = 2.66$	.008*	1.2 (0.2)

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