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Sex differences in Alzheimer's disease: do differences in tau explain the verbal memory gap?

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ABSTRACT

To determine if sex differences in verbal memory in AD are related to differences in extent or distribution of pathological tau, we studied 275 participants who were amyloid PET positive and carried clinical classifications of normal cognition, mild cognitive impairment (MCI) or dementia, and had tau (AV1451) PET. We compared tau distribution between men and women, and as a function of genetic risk. In MCI we further explored the relationship between quantity and distribution of tau in relation to verbal memory scores. Women had more tau burden overall, but this was driven by sex differences at the MCI stage. There was no significant difference in tau load by *APOE* e4 status. Within the MCI group the association between tau and performance in verbal memory tasks was stronger in women than men. The topography of the associations between tau and verbal memory also differed in MCI; women demonstrated stronger relationships between tau distribution and verbal memory performance, especially in the left hemisphere. These findings have implications for understanding tau distribution and spread, and in interpretation of verbal memory performance.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, with prevalence of tens of millions worldwide, and rising (Holtzman et al., 2011). Women are often reported to have higher prevalence than men (Brookmeyer et al., 2011; Rocca et al., 1991) but there are also differences in how each sex expresses symptoms of the disease.

AD affects the cognition of men and women differently. For example, when cognitive decline begins, women retain verbal memory reserve longer than men (Caldwell et al., 2017; Sundermann et al., 2016). Despite this, most studies of AD, including clinical trials, test memory exclusively through the verbal modality (Rogers et al., 1998; Rösler et al., 1999) (e.g., word lists of the ADAS-Cog, Rey Auditory Verbal Learning Test). It has been suggested that the verbal memory reserve may lead to an important delay in diagnosis in women (Sundermann et al., 2017). Furthermore, using verbal tests, it appears that women decline more quickly than men, once impairment is established (Kramer et al., 2003).

Why would this difference in course, with limited verbal memory decline followed by accelerated decline in women but not men, occur? One explanation is a difference in the amount or regional distribution of pathology. Amyloid β (Aβ) and tau proteins are considered to synergistically impair brain function in AD. Aβ plaques are deposited in extracellular space fairly diffusely and early in the disease with no specific sex differences noted (Buckley et al., 2018). By contrast, tau generally follows

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a regional predilection where pathology begins in transentorhinal cortex, then spreads throughout the limbic system and eventually into the neocortex more widely (Braak and Braak, 1997), with concomitant loss of ability in cognitive domains dependent on the integrity of those regions. Women demonstrate more pathological tau burden overall at death (Oveisgharan et al., 2018). Data from CSF studies suggests that women, especially those who carry an *APOE* e4 allele, demonstrate higher levels of pathological tau in the MCI stage of the disease specifically (Altmann et al., 2014; Oveisgharan et al., 2018), potentially tying to the timing of more rapid decline of cognition in women than men.

The anatomical distribution of tau may also differ in men and women: Another recent pathological study replicated the finding of more tau in women, and further reported sex differences in distribution. Men were more likely to have hippocampal sparing subtype, whereas women were more likely to have a limbic predominant distribution (Liesinger et al., 2018). Now with tau PET, we are able to investigate the quantity and distribution of cerebral tau pathology in vivo. An earlier PET study in cognitively normal individuals, 30% of whom were amyloid positive, reported higher levels of entorhinal tau in women but not men (Buckley et al., 2019b). Given that tau is closely linked to cognition, sex differences in tau burden and tau distribution may underlie the sex differences in the clinical and neuropsychological expression of AD.

While we know that carrying an *APOE* e4 allele increases risk of developing AD (Poirier et al., 1993), it has more recently become evident that genetic risk differs by sex (Riedel et al., 2016), with higher conversion to MCI and AD in female carriers of the *APOE* e4 allele (Altmann et al., 2014). In addition, women decline more quickly with AD, especially those carrying an *APOE* e4 allele (Lin et al., 2015). Women with MCI decline more rapidly than men on the ADAS-Cog, and women with an *APOE* e4 allele decline fastest (Holland et al., 2013) and have higher pathological tau concentrations. *APOE* e4 has also been shown to be associated with both Aβ and tau deposition, with *APOE* e4 positive individuals having reduced ability to clear Aβ, as well as increased accumulation of tau (Riedel et al., 2016). However, no sex differences are found in the increased rates of Aβ positivity associated with carrying an *APOE* e4 allele (Jack et al., 2015), supporting the notion that the sex difference in the effect of *APOE* e4 on AD may be mediated by tau. Indeed, a more recent paper showed trend levels for higher tau accumulation in the CSF in amyloid positive cognitively unimpaired women e4 carriers, but not men (Buckley et al., 2019a). The location of tau may differ by *APOE* e4 status too, with Emrani and colleagues finding in a literature review that *APOE* e4 carriers tended to have a more typical medial temporal pattern while noncarriers had more distributed tau (Emrani et al., 2020).

In the current study we initially use tau PET to better understand sex differences in quantification and distribution of this pathology across the AD spectrum (i.e., in Aβ+ individuals with clinical classifications of normal cognition (NC), mild cognitive impairment (MCI) or AD Dementia (ADD)), and how this relates to sex-differences in cognition and genetic risk. We expected there to be more tau evident in women's brains compared with men's, and that this might be influenced by their *APOE* e4 status. We further expected differences in the pattern of tau related to verbal memory performance. Understanding how underlying tau distribution is reflected in cognitive performance is important, both in elucidating the natural history of the disease, and how to interpret cognitive tests. Furthermore, given that tau is now becoming a potential target of new AD medications (Cummings et al., 2018), we need a comprehensive understanding of how it behaves in different groups of patients.

2. Materials and methods

2.1. Participants

Participants were from AD Neuroimaging Initiative (ADNI) phases 2 and 3. Inclusion and clinical diagnosis criteria for ADNI have been described previously (Aisen et al., 2010; Weiner et al., 2017). In this cross-sectional study, we specifically included subjects from ADNI who received tau (AV1451) PET, Aβ PET (florbetapir- or florbetaben-PET), and had neuropsychological data (delay between neuropsychology visit and Tau PET: mean: 0.60 years, SD: 0.78 years). We further restricted our sample to Aβ positive participants (as determined by standard thresholds of 1.11 and 1.20 summary cortical SUVr for florbetapir-PET and florbetaben-PET, respectively (Landau et al., 2014, 2013)) because we were interested in the spectrum of disease in AD. Selected data comprised 1031 visits in total, from 737 individuals. Out of those, 339 individuals had at least one Aβ positive scan. Of these, 295 individuals had a tau-PET at or following their Aβ positive scan date. 16 of these individuals had processing and/or QC issues, and 4 lacked sufficient neuropsychological data. The final sample was thus comprised of 275 participants with a positive Aβ status. For the purposes of this analysis, participants with normal cognition and significant memory concern were grouped together in the normal cognition (NC) group, and participants with early and late mild cognitive impairment were grouped together in the mild cognitive impairment (MCI) group.

2.2. Standard protocol approvals, registrations and patient consents

ADNI is a multisite study. Local Institutional Review Boards approved all protocols and consent procedures. All participants provided written informed consent at their institution.

2.3. Data Availability

ADNI data are available to eligible researchers through the LONI website (adni.loni.usc.edu).

2.4. Cognitive testing

Verbal memory tests were the focus of the current investigation. ADNI uses the Rey Auditory Verbal Learning Test (RAVLT (Rey, 1958)) and Logical Memory (LM (Reynolds and Powel, 1988)) test. We included the RAVLT sum of all correctly recalled words across trials 1 through 5 (RAVLT learning), RAVLT total recall after a 30-minute delay (RAVLT delay), LM immediate recall, and LM delayed recall. Tests were also completed in other domains but we focused on the verbal memory tests given the known sex differences in this domain, and the importance of verbal memory tests in the diagnosis of MCI and AD.

2.5. Imaging analysis

The processing of neuroimaging data was as follows: raw T1 MR images were downloaded in DICOM format from the ADNI data portal. Then, MRIs were processed with FreeSurfer (version 6.0) to automatically segment and parcellate each structural MRI, and reconstruct the cortical surface (Dale et al., 1999; Fischl et al., 1999). Tau PET images were downloaded from the ADNI portal in the most preprocessed form: realigned to the first frame, averaged across frames, voxel sizes standardized, and resolution made

uniform. The preprocessed images were co-registered to the subject's temporally closest MRI. The co-registered Tau PET images were then converted into standard uptake value ratio (SUVr) images, by normalizing the images to mean AV1451 uptake in the FreeSurfer-defined cerebellar gray matter. The individual SUVr volumes were then projected onto each individual's cortical surface model by sampling from points half-way between the white and pial surfaces.

As an estimation of overall tau load, we calculated the mean SUVr of AV1451 within the cortical grey matter. This includes the entire cortical mantle (specifically codes 1000-1035 and 2000-2035 at https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/AnatomicalROI/FreeSurferColorLUT). The hippocampus is excluded due to noise resulting from off target binding in adjacent regions. We refer to this measure as "average SUVr" in the rest of the report.

2.6. Processing for vertex-wise analyses

Prior to conducting surface-based vertex-wise analyses (see below), the individual Tau PET surface maps were registered into a common space (fsaverage space) and smoothed using a 5 mm kernel.

2.7. Statistical analysis

2.7.1. Comparison of cognitive test scores between groups

T-tests were used to determine differences in age and years of education between men and women. ANCOVAs were used to compare performance in cognitive tests between men and women, controlling for age, education, and diagnostic category. Chi Squared tests were used to determine differences in distribution of ApoE4 carriers, Race, and Diagnostic category between men and women.

2.7.2. Overall level of tau: Do women have more tau in their brains? Does ApoE affect this relationship?

Average SUVR was used as a dependent variable in a univariate general linear model with sex, ApoE status (binarized to presence or absence of an ApoE4 allele), and diagnosis as independent variables and age as a covariate. We also assessed the interactions of all independent variables in a separate model. We performed pairwise t-tests on significant effects using the Holm-Bonferroni method. We repeated these analyses within each diagnostic group (NC, MCI, ADD). Based on results from these analyses, and previous studies (Altmann et al., 2014; Oveisgharan et al., 2018), we limited the following analyses to the MCI diagnostic group to reduce the number of tests performed.

2.7.3. Distribution of tau: Does tau distribution generally differ between women and men with MCI?

Surface-based group analysis was performed in FreeSurfer to assess the topography of the sex difference in tau load. Our contrasts were designed to test, at each vertex on the cortical mantle, whether women had more tau than men. Age was included as a covariate in these analyses and multiple comparisons correction was performed using Monte Carlo simulation methods (Hagler et al., 2006) with a cluster-forming threshold of $p < 0.001$ and a cluster-wise probability of $p < 0.05$.

2.7.4. Strength and topography of tau-cognition relationships in MCI

We then performed surface-based general linear model (GLM) analyses to assess the relationship between tau and cognition. A vertex-wise analysis was performed between Tau PET and each cognitive test score. Model contrasts were designed to test whether more tau was associated with worse cognitive performance, after regressing out the effects of age and years of education (YOE). The surface-based GLM analyses were conducted separately for men and women. Multiple comparisons correction was performed using the same simulation methods and thresholds noted in the previous subsection. All statistical surface maps are displayed at a threshold of $-\log_{10}(p)>3$ unless otherwise specified.

We were interested in comparing and contrasting the statistical maps from the tau-cognition analyses in women with those of men. We compared the statistical maps in two ways. First, to assess the similarity in the *topography of the associations*, we computed Dice coefficients between the statistical maps produced in the sex-stratified surface-based GLM analysis. Dice's coefficients assess the overlap between two regions, with zero being no overlap and 1 being total overlap (Dice, 1945). Dice's coefficients were calculated for left and right hemisphere separately, and then for the whole brain.

In addition to analyzing the similarities in the topography of the associations, we also assessed the differences in the *strength of the associations*. To this end, we performed z-tests to compare, at each vertex, whether the strength of the tau-cognition association differed between men and women. A z-statistic at each vertex was calculated using the following:

$$z_{observed} = \frac{\operatorname{arctanh}(r_{women}) - \operatorname{arctanh}(r_{men})}{\sqrt{\frac{1}{n_{women}-3} + \frac{1}{n_{men}-3}}}$$

Where arctanh is the inverse hyperbolic tangent function (i.e., Fisher's z-transformation), r_{women} and r_{men} are the partial correlations between tau and cognition at that particular vertex for women and men, respectively, and n_{women} and n_{men} are the number of women and men in our sample. This $z_{observed}$ corresponds to the difference in strength of the tau-cognition associations in women versus men. We report our results by binarizing the $z_{observed}$ maps with a threshold $z = 1.96$, which corresponds to $p = 0.025$, 2-sided. In order to reduce the number of vertices examined, this z-test procedure was restricted to vertices that were within significant clusters in the tau-cognition surface-based analysis for either men or women.

3. Results

3.1. Demographic details and test scores

Men were significantly older and more educated than women. Women also performed better on RAVLT Learning in the overall group. The diagnostic distribution also differed significantly, with the male group having a higher proportion of mildly cognitively impaired individuals. There were no other significant differences between sexes in terms of demographic details or test scores (Table 1).

Within the MCI subgroup ($n = 89$), men ($n = 56$) were significantly older ($p = 0.002$) and more educated than women ($p = 0.028$), and performed better on LM Delayed Recall ($p = 0.032$). There were no other significant differences between sexes on verbal memory tests (Table 2).

3.2. Overall level of tau: Do women have more tau in their brains?

In the overall sample, women had significantly higher average tau PET SUVR ($F(1, 243) = 4.24$, $p = 0.041$. There was a main effect of diagnosis ($F(2,24) = 27.949$, $p < 0.0001$) with lower SUVR in NC compared with ADD ($t = 6.39$, $p < 0.0001$) and MCI ($t = 5.21$, $p < 0.0001$), and lower SUVR in MCI compared with ADD ($t = 3.65$, $p = 0.0003$). There was a main effect of age ($F(1,243) = 14.46$, $p =$

Table 1
Demographics and cognitive test scores for women and men.

	Men (n = 139)	Women (n = 135)	*p* value
Age	77.87 ± 7.60	74.64 ± 7.28	**<0.001**
YOE	16.81 ± 2.55	15.93 ± 2.38	**0.003**
RAVLT Delay (Men n = 137, Women n = 135)	4.26 ± 4.44	6.36 ± 5.12	0.084
RAVLT Learning	34.26 ± 13.23	41.08 ± 14.94	**0.017**
RAVLT Recognition	10.63 ± 4.06	11.27 ± 4.26	0.235
LM Delayed Recall	8.96 ± 6.30	10.20 ± 6.46	0.494
LM Immediate Recall	10.71 ± 5.98	11.99 ± 5.76	0.915
Days between RAVLT Delay Score and Tau PET (Men n = 137, Women n = 135)	38.87 ± 55.29	38.24 ± 63.395	0.931
Days between RAVLT Learning/RAVLT Recognition Scores and Tau PET	35.84 ± 46.71	38.24 ± 63.40	0.720
Days Between LM Delayed Recall/LM Immediate Recall Scores and Tau PET	44.62 ± 54.51	52.09 ± 64.56	.301
ApoE4 carriers (%) (Men n = 124, Women n = 124)	68 (54.84)	76 (61.3)	0.367
Race (%white)	97%	89%	0.107
Diagnosis			**0.004**
ADD (%)	18 (12.95)	12 (8.89)	
MCI (%)	56 (40.29)	33 (24.44)	
NC (%)	65 (46.76)	90 (66.67)	

Note: Two men were missing RAVLT Delay data, 15 men and 11 women were missing ApoE data. Cognitive test score comparisons were corrected for age, education and diagnosis. Time between cognitive test and tau PET scan was a mean of 37–48 days (depending on the test, maximum 343 days).

Table 2
Demographics and cognitive test scores for women and men with MCI.

	Men (n = 56)	Women (n = 33)	*p* Value
Age	*78.29 ± 7.23*	*73.01 ± 8.18*	***0.002***
YOE	*16.43 ± 2.76*	*15.15 ± 2.35*	***0.028***
RAVLT Delay (Men n = 54, Women n = 33)	*2.98 ± 4.04*	*2.12 ± 3.16*	*0.065*
RAVLT Learning	*30.82 ± 12.08*	*28.15 ± 11.33*	*0.127*
RAVLT Recognition	*9.82 ± 4.13*	*7.94 ± 4.34*	***0.019***
LM Delayed Recall	*6.88 ± 6.04*	*4.3 ± 5.47*	***0.032***
LM Immediate Recall	*9.02 ± 5.61*	*7.39 ± 5.27*	*0.199*
ApoE4 carriers (%) (Men n = 54, Women n = 31))	*33 (61.11)*	*25 (80.65)*	*0.105*

Note: Two men were missing RAVLT Delay data, two men and two women were missing ApoE data..

0.0002), reflecting higher SUVR with older age. Although sex distributions of ApoE status varied between diagnostic groups (APOE e4 presence was found in 51.4% NC women, 47.54% NC men, 80.65% MCI women, 61.11% MCI men, 100% ADD women, 66.66% ADD men) there was no main effect of ApoE status, or an interaction between sex and ApoE status on SUVR values. There was a significant interaction between diagnosis and ApoE ($F(1,237) = 5.38$, $p = 0.005$, such that carriers with MCI had the highest tau levels), and between diagnosis and sex ($F(2,237) = 11.65$, $p < 0.0001$), such that women had significantly higher average SUVR than men ($F(1,81) = 8.79$, $p = 0.004$) in the MCI group only. Given this finding, the remaining of the analyses were limited to patients with MCI, as this is where the main differences appear to be, consistent with prior research.

We addressed if there was more tau in those with an APOE e4 allele in the MCI group specifically, and found no main effect of carrier status ($F(1,85) = 0.007$, $p = 0.935$) or sex*APOE interaction effect ($F(1,85)=0.605$, $p=0.439$).

Addressing regional tau deposition in the MCI group, there was no main effect of APOE, nor sex*APOE interaction effect in regions associated with Braak Stages I, III, IV, V, or VI in the MCI group.

3.3. Distribution of tau: Do men and women with MCI have different tau distributions?

The topographic distribution of tau in the MCI women and men of our sample is displayed in Fig. 1a. In the surface-based analysis, there was one cluster, in the medial occipital lobe, where there was significantly more tau in women (Fig. 1b).

3.4. Comparison of strength and distribution of tau-verbal memory associations between men and women

Visual inspection of the statistical maps from the sex-stratified surface-based analyses, revealed several sex differences (Fig. 2a), with women with MCI showing more left-hemisphere specific relationships, particularly in the temporal and pareital regions. Men tended to show more bilaterali relatinships and more frontal relationships, especially during the learning phases (RAVLT Learning and LM Immediate). The Dice Score Coefficient (DSC; see Table 3) on the RAVLT Delay (DSC = 0.01) indicated little to no overlap between sex-stratified statistical maps. For the remaining tests, the DSCs indicated moderate topographic similarity between maps, with RAVLT Learning (DSC = 0.483), LM Delayed Recall (DSC = 0.503), and LM Immediate Recall (DSC = 0.651) showing more overlap. There was generally more overlap in the left hemisphere than the right with men showing a more bilateral distribution in the correlations between regional tau and learning and immediate memory tasks, compared with women.

Differences in the tau-cognition relationships were further exemplified in the z-test analyses (Table 4, Fig. 2b) which identified how sex differences in the strengths of these relationships were widespread, almost always stronger in women than men, and more so in the left than right hemisphere. The only clusters of significance that were stronger in men were for RAVLT learning, and existed in the right parietal and frontal lobes.

4. Discussion

We analyzed sex difference in tau PET in amyloid-positive ADNI participants with normal cognition, MCI, or dementia. Given the biomarker characterization, and in the symptomatic groups, late onset and predominance of amnestic symptoms, our study likely comprised individuals with underlying late onset AD across a continuum of severity. As expected, women performed better overall on verbal memory tests than men, and had higher levels of tau PET uptake overall than men. The difference was greatest in MCI in this amyloid-positive cohort, and we thus focused on the MCI participants for more detailed analyses. Aside from a single cluster in the right medial occipital lobe, there were no significant sex differences in the topographic distribution of tau in men and women with MCI. While women appeared to lose their cognitive reserve at the MCI stage, not differing from men on performance four of five verbal memory measures, sex difference were evident in regional relationship between tau distribution and cognition, with women showing more left lateralized relationships. Women had stronger relationships between tau and verbal memory measures than men, notably in the left hemisphere.

The finding that women had higher levels of tau *in vivo* overall is consistent with earlier reports (Liesinger et al., 2018; Oveisgharan et al., 2018) from studies of *post mortem* brain tissue.

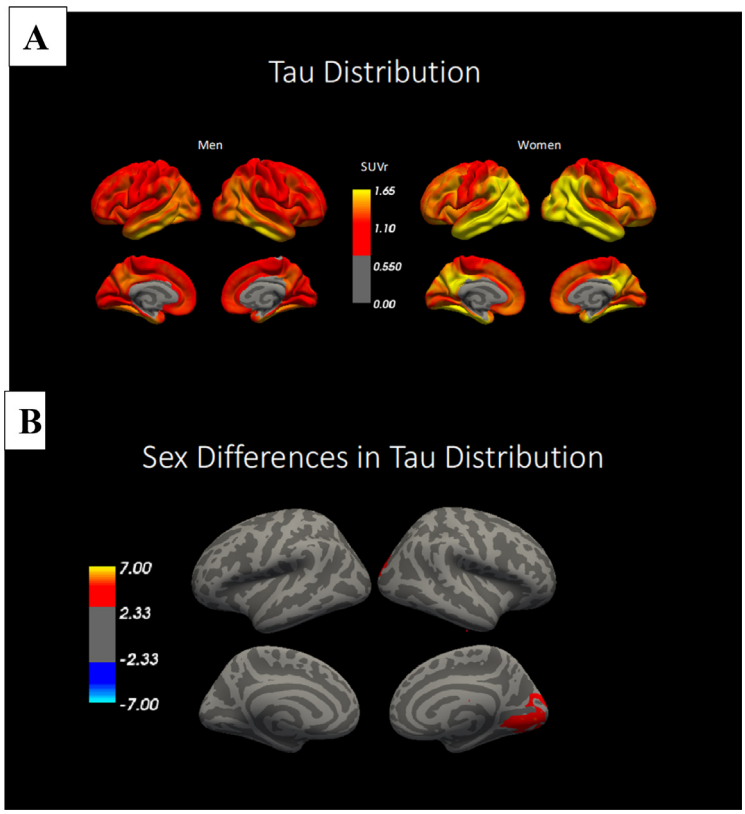

Fig. 1. (A) Average tau distribution in men and women with MCI. All maps are rendered on the fsaverage semi-inflated brain and are on an identical scale: SUVr 0.7 to 1.65, and covaried for age. Abbreviations: SUVr, Standard Uptake Value Ratio. (B) Sex differences in tau distribution in men and women with MCI. Map rendered on the fsaverage inflated brain and shown in units of -log10(p) at threshold of 3–7.

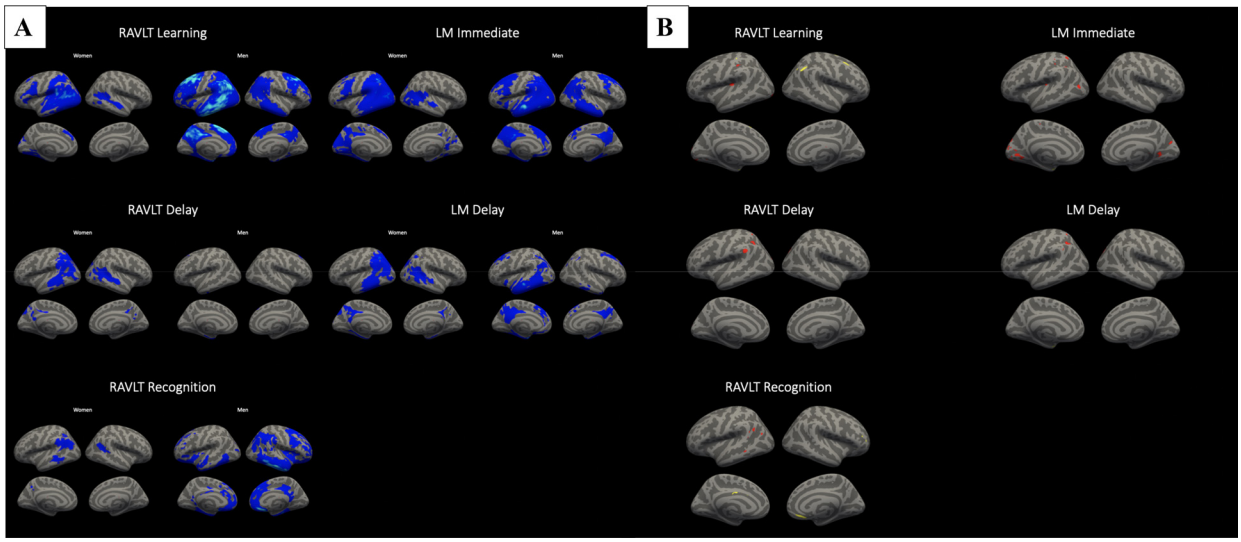

Fig. 2. (A) Statistical maps from sex-stratified surface based analyses between cognitive performance and Tau PET in MCI. All maps are shown in units of -$\log_{10}$(p) and are at identical thresholds of 3–7 and covaried for age and education. (B) Statistical maps showing clusters of significance to assess the relative strength of vertex-wise associations between task performance and tau in men and women. Red clusters are stronger in women, yellow clusters are stronger in men. Abbreviations: LM, logical memory; RAVLT, rey auditory learning test.

Consistent with earlier studies investigating pathological tau in CSF (Altmann et al., 2014), we found elevated tau levels in women with MCI. In this sample, this was not explained by the presence of an ApoE e4 allele. Prior research points to a role of ApoE in rate of cognitive decline in women (Holland et al., 2013). However, other studies have not isolated amyloid positive participants. In our study, where all participants were amyloid positive, most women and many of the men carried an e4 allele. The typically identified sex-effect of ApoE on decline may have been masked by its over-representation in this sample. Furthermore, there may be other genes that are important in sex-specific AD risk (Fan et al., 2020). Sex differences in the effect of ApoE on tau and cognitive decline may be further explored in the future by longitudinal tau PET studies.

Table 3
Dice score coefficients to assess the overlap in the tau-cognition statistical maps from sex-stratified GLM analysis.

Cognitive test	Left hemisphere	Right hemisphere	Whole brain
RAVLT Learning	0.612	0.183	0.485
RAVLT Delay	0.000	0.000	0.000
RAVLT Recognition	0.044	0.050	0.035
LM Immediate	0.762	0.404	0.651
LM Delay	0.608	0.253	0.499

Dice coefficients were generated separately for the left and right hemisphere, and then for the whole brain.
Abbreviations: LM, logical memory; RAVLT, rey auditory learning test.

A sex difference in tau PET in the occipital lobe was also identified in a study combining cognitively unimpaired and MCI participants from ADNI and the Harvard Aging Brain study, but only in APOE e4 carriers (Buckley et al., 2020). This combined cohort included amyloid negative participants as well, and the great majority were cognitively unimpaired. It could be that the occipital region represents the watershed of tau spread that is greater in women in the MCI stage compared with men.

Despite the lack of sex differences in overall performance on most verbal memory tasks in MCI participants, consistent with our prior findings (Caldwell et al., 2017), we found strong sex differences in the association of tau with verbal memory. Women demonstrated more left hemisphere-specificity of tau in relation to reduced verbal memory, and had stronger relationships between verbal memory and regional tau. Given that overall performance on verbal memory test did not differ between men and women in the MCI group, this provides additional support for the notion that women can bear a bigger burden of tau while maintaining cognitive performance (Digma et al., 2020; Ossenkoppele et al., 2020). We noted more differences in the left hemisphere, which may be especially involved in verbal tasks, and particularly so in women (Banks et al., 2012). Further studies in cohorts with nonverbal memory tasks may show different results, as these tasks may involve more right hemisphere involvement (Banks et al., 2012). An additional line of research might be to assess non-tau changes as potentially linked to memory changes in men with AD. Men have been shown to have more vascular brain changes with aging (Ropele et al., 2010) as well as more neocortical Lewy bodies (Nelson et al., 2010), which could contribute to non-tau pathways for cognitive decline in older men with AD.

We tend to measure progression in AD with tests that demonstrate sex differences. The ADNI dataset, used here, uses mostly tests which are performed at a higher level in healthy women compared with healthy men. This may bias our understanding of AD in men and women, and the results of the current study suggest that exploring cognition with measures which are more sex-agnostic may be beneficial. An alternative is to run more sex-specific research, as AD may be different enough

Table 4
Z-test clusters of significance to assess the relative strength of vertex-wise associations between task performance and tau in men and women.

Test	Hemisphere	Direction	Size (mm^2)	X	Y	Z	Location
RAVLT Learning	Left	W>M	412.70	−14.3	−89.3	−4.0	Lateral Occipital
		W>M	257.46	−30.5	−79.2	−9.0	Lateral Occipital
		W>M	153.05	−11.7	−94.4	19.8	Lateral Occipital
	Right	M>W	250.84	52.0	−50.7	44.7	Inferior Parietal
		M>W	201.96	33.8	15.6	51.3	Caudal Middle Frontal
		M>W	82.84	31.3	3.3	62.8	Superior Frontal
RAVLT Delay	Left	W>M	199.32	−32.5	−48.9	35.2	Superior Parietal
		W>M	171.84	−58.8	−40.7	30.6	Supramarginal Gyrus
		W>M	103.20	−11.7	−93.8	20.3	Lateral Occipital
	Right	W>M	390.73	24.2	−83.6	34.5	Superior Parietal
RAVLT Recognition	Left	W>M	88.56	−50.8	−55.8	24.9	Inferior Parietal
	Right	M>W	157.83	4.0	31.3	−13.1	Medial Orbitofrontal
LM Immediate	Left	W>M	438.59	−4.8	−71.8	9.8	Lingual
		W>M	289.90	−14.8	−88.6	−3.4	Lateral Occipital
		W>M	248.98	−12.4	−94.8	20.6	Lateral Occipital
	Right	W>M	167.04	25.9	−55.1	5.3	Lingual
		W>M	73.92	13.9	−73.0	25.9	Cuneus
		W>M	65.85	20.2	−84.5	35.3	Superior Parietal
LM Delayed	Left	W>M	262.36	−46.6	−52.3	43.4	Supramarginal Gyrus
		M>W	89.34	−22.1	0.1	−20.2	Entorhinal
	Right	W>M	332.45	22.6	−84.6	34.2	Superior Parietal

Clusters larger than 50 mm^2 were included. In the case that multiple clusters were above this threshold, the three largest clusters were included.

in men and women to argue against combining the sexes in studies.

There are limitations to this study, including the restricted cognitive data available. It would be of particular interest to see cognition-tau relationships in memory tests that do not rely on verbal inputs, given the known female advantage with these materials. The sample sizes in the current study were also relatively small, especially to identify differences by diagnosis, with the most apparent divergence by sex at the MCI level. Future studies with larger samples will be important to see if our findings replicate. In addition, this cohort is largely white and highly educated, future studies in more diverse samples are needed.

There are translational implications for differences in tau between the sexes. Specifically, it is important to take into account sex differences when we are using cognitive measures to define, diagnose and track disease. At the same time, it is important to also take biomarker differences into account. Differences in tau between the sexes will become especially important if the tau-targeting agents in the current therapeutic pipeline (Cummings et al., 2018) show promise, as the type of cognitive change which could be seen in successful trials may differ between men and women.

Author Contribution

Sarah J. Banks PhD: Conceptualization, writing (all drafts), supervision. Murray J. Andrews, BA, Formal analysis, methodology, writing (all drafts). Leonardino Digma BA, Formal analysis, methodology, writing (all drafts). John Madsen BS, Formal analysis. Emilie T. Reas PhD, Writing (reviewing and editing). Jessica Caldwell PhD, Writing (reviewing and editing). Linda K. McEvoy PhD, Writing (reviewing and editing). Chun Chieh Fan MD PhD, Methodology. Anders M. Dale PhD, Methodolgy. James B. Brewer MD PhD, Methodology, writing (reviewing and editing), conceptualization.

Disclosure statement

S.J.B, M.J.A, L.D., J.Z.K.C., E.T.R. and J.M. have no competing interests to declare. C.C.F. is a consultant for CorTechs Labs, in addition to his research appointment at the University of California, San Diego. L.K.M. holds stocks in CorTechs Labs. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He also receives research funding from General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. J.B.B has served on advisory boards for Elan, Bristol-Myers Squibb, Avanir, Novartis, Genentech, and Eli Lilly and holds stock options in CorTechs Labs, Inc., Impact Biomedicines, and Human Longevity, Inc. The terms of these arrangements have been reviewed and approved by UCSD in accordance with its conflict of interest policies.

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Verification

This manuscript represents an original paper which is not under consideration elsewhere. All authors have approved of the manuscript in its final form.

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