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Neuroimaging: Sex and ethnoracial differences – Biomarkers

Sex-associated differences in pathology burden in early-onset Alzheimer's disease

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Abstract

Background: Previous research has suggested that, compared to males, females are at greater risk for and have greater pathology burden in late onset. However, sex differences in early onset AD (EOAD) have not yet been studied.

Method: We included 167 participants [28 cognitively normal (CN, 68% females), 98 early onset AD (EOAD, 55% females), and 41 cognitively impaired amyloid-negative (EOnonAD, 31% females] subjects from the Longitudinal Early-Onset AD Study (LEADS) with available Flortaucipir PET, Florbetaben PET, and MRI data. Multiple linear regression (MLR) models including age and MMSE as covariates were used in the pooled sample to examine the effects of sex on hippocampal and white matter hyperintensity volume, mean cortical thickness, mean tau distribution by Braak regions and mean cortical amyloid SUVR. We also ran voxelwise MLR with sex as the predictor and cortical thickness, amyloid SUVR normalized to whole cerebellum, tau SUVR normalized to cerebellar crus, respectively, as the outcome measures while controlling for age, MMSE, and total intracranial volume (MRI only). Results are displayed at a cluster-level FWE correction of $p<0.05$.

Result: There were no significant demographic differences between males and females in any diagnostic group. Across the pooled sample females showed significantly greater atrophy of the hippocampus ($p=0.0001$), greater tau SUVR in Braak regions 3&4 ($p=0.05$) and 5&6 ($p=0.04$) and trend for greater global amyloid uptake ($p=0.074$) (Table 2). The analyses in imaging space confirmed these findings and showed that the effects are driven by the EOAD group. Females showed greater amyloid deposition globally and greater tau deposition in the frontal, inferior parietal and temporal lobes (Figure 3).

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Conclusion: Female sex is associated with greater pathology burden in EOAD. Longitudinal studies will be needed to establish whether such difference translates in faster rates of progression in women relative to men.

Figure 1: Structural MRI measure by sex

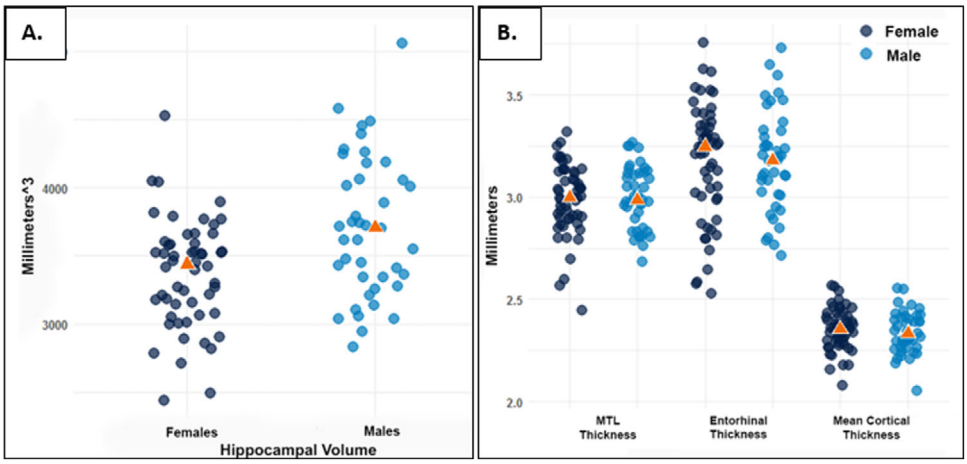

FIGURE 1

TABLE 1

Table 1: Demographic comparisons

	CN	EOAD	EO non-AD
N	62	99	39
Age	54.4 (6.12)	58.8 (3.82)	57.3 (-6.42)
Sex (M/F)	20/42	44/55	27/12
Education (yrs)	16.8 (2.17)	15.5 (2.46)	15.6 (-2.6)
MMSE	29.3 (0.75)	21.7 (4.99)	25.8 (-3.15)
CDR Global (<0.5/ >=0.5)	40/0	1/60	0/14
FBB SUVR	1.00 (0.05)	1.55 (0.17)	0.98 (-0.06)

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Figure 2: Amyloid and tau PET SUVR measures by sex

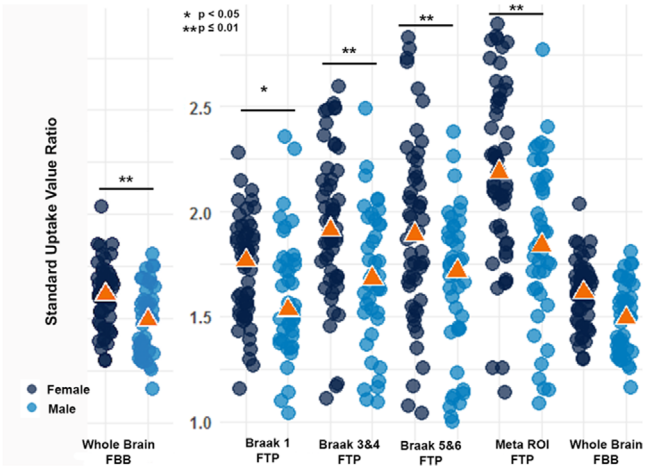

FIGURE 2

Figure 3: Voxelwise multiple linear regression models

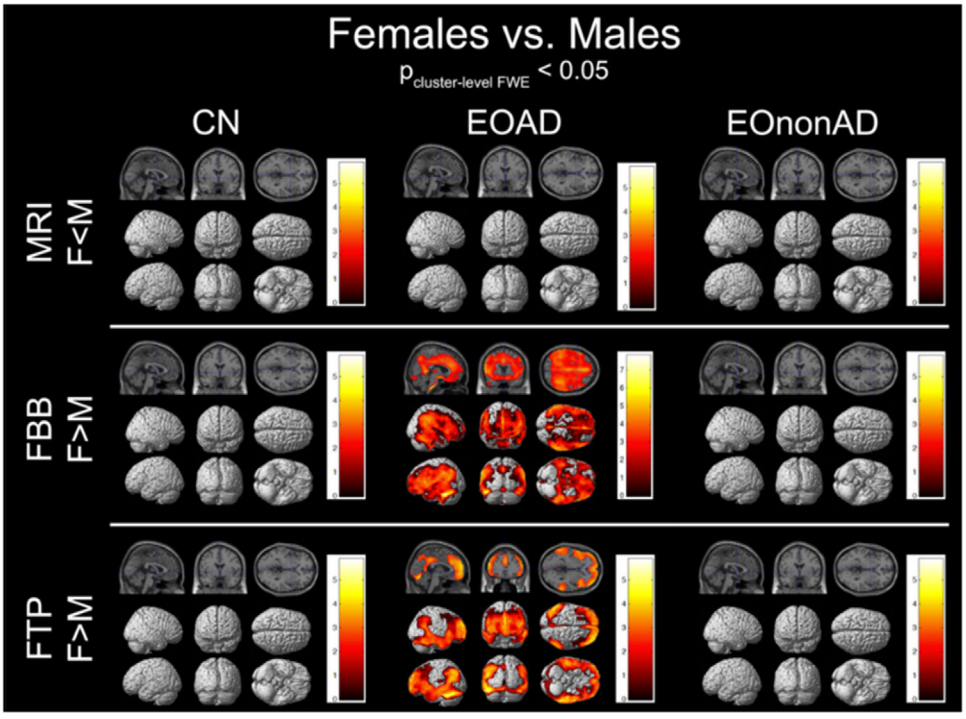

FIGURE 3

TABLE 2

Table 2: Multiple linear regression models

	Model 1: Age	Model 2: Age, MMSE	Model 3: Age, Dx
MTL	0.0007 (0.980)	-0.013 (0.613)	0.006 (0.833)
Entorhinal cortex	0.006 (0.899)	-0.017 (0.674)	0.015 (0.718)
Hippocampal volume	289.6 **(<.0001)**	251.5 **(0.0001)**	320.8 **(<.0001)**
Mean Cortical Thickness	-0.012 (0.493)	-0.022 (0.114)	-0.012 (0.421)
WMH volume	239.7 (0.383)	320.6 (0.235)	66.77 (0.810)
BRAAK12	-0.019 (0.628)	0.009 (0.786)	-0.012 (0.675)
BRAAK34	-0.151 **(0.018)**	-0.087 **(0.049)**	-0.150 **(0.0006)**
BRAAK56	-0.168 **(0.015)**	-0.101 **(0.040)**	-0.164 **(0.0007)**
Mean Cortical Amyloid SUVR	-0.095 **(0.030)**	-0.065 **(0.074)**	-0.075 **(<.0001)**