

Sex- and Region-Specific Associations Between Tau, Amyloid, Neuroinflammation, NMDA Receptors, and Cognition in Alzheimer's Disease



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Tau and NMDAR couple more strongly to cognition in men across the full cohort and most prominently within AD, where women additionally show medial-temporal sensitivity to neuroinflammation and amyloid burden.

INTRODUCTION	METHODS	RESULTS	SUMMARY & CONCLUSIONS
Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which older age and female sex are major risk factors. AD pathological hallmarks are amyloid-β plaques and tau-based neurofibrillary tangles, with additional contributions from neuroinflammation and loss of NMDA glutamate receptors (NMDAR). Here we asked how regional densities of tau, amyloid, the neuroinflammation marker TSPO, and NMDAR in postmortem hippocampus, entorhinal cortex (EC), and parietal cortex relate to antemortem cognition (MMSE), and whether these relationships differ by sex and clinical diagnosis. This work extends prior sex-stratified analyses of AD pathology by measuring four mechanistically distinct targets on the same set of cases, in adjacent sections in brain regions implicated in AD. We hypothesized that the strength — not just the presence — of biomarker–cognition coupling would differ between men and women and that the largest sex-specific signal would emerge in the AD subgroup, where pathology load is highest.	Frozen postmortem hippocampus (CA1, dentate gyrus (DG), subiculum), EC, and parietal cortex were obtained from 154 individuals with a clinical diagnosis of AD, mild cognitive impairment (MCI), or cognitively normal (CN) ≤ 18 months prior to death (24–27/sex/diagnosis). Cryostat sections were processed for quantitative autoradiography of amyloid, Tau, neuroinflammation (TSPO) and NMDA receptors with [³H]Pib, [¹⁸F]T807, [³H]PK11195 or [³H]MK801 respectively, utilizing published methodology. Marker densities were quantified in FIJI. Multiple linear regression models tested whether the association between each biomarker and MMSE differed by sex (biomarker $\times$ sex interaction) and, in a second model, whether that sex-specific relationship further varied by diagnostic group (biomarker $\times$ sex $\times$ diagnosis interaction; AD vs MCI vs CN). MMSE was modeled as $\log(\text{MMSE} + 1)$ to satisfy normality. Models were adjusted for covariates significantly associated with MMSE in univariate analyses ($p < 0.05$): diagnosis, Braak stage, and APOE status. Coefficients are reported as exponentiated estimates ($\exp \beta$) with 95% CIs: $\exp \beta < 1$ indicates that higher biomarker density associates with lower MMSE (detrimental); $\exp \beta > 1$ indicates higher MMSE (protective). Type 3 T tests assessed individual coefficients; type 3 F tests assessed the overall interaction. α was preset at 0.05 for all tests.	A. Biomarker associations with MMSE vary by sex and region across diagnoses B. Tau and NMDAR associations with MMSE are strongest in AD	Across all diagnoses (Fig. A): - Higher tau in CA1, subiculum, and EC was associated with lower MMSE in both sexes, with steeper slopes in men. - Higher NMDAR density in CA1, DG, and EC was associated with higher MMSE, with a stronger protective effect in men. In the AD subgroup (Fig. B): - Tau and NMDAR sex differences were most pronounced; in EC, the tau–MMSE link was significant in men only. - Higher TSPO (DG, subiculum) and higher Pib (DG, subiculum) were associated with lower MMSE in women; EC TSPO was associated with lower MMSE in both sexes. Sex differences did not reach significance for TSPO or Pib. Thus, sex shapes how AD pathology maps onto cognition across medial-temporal circuits.