

Evidence for Sex-Specific Brain Reserve and Progression from Mild Cognitive Impairment to Alzheimer's Dementia

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This study presents multimodal analyses that demonstrate sex differences in neurodegeneration, tau, and CSF GAP-43. Results support the notion that females may have greater initial brain reserve and resilience to AD-related pathology but undergo more rapid decline as disease progresses, underscoring the importance of considering sex in prognosis and drug treatment.

INTRODUCTION

There is increasing recognition of biological sex-related differences in the prevalence, clinical phenotypes, progression, and treatment efficacy of dementia, especially Alzheimer's disease (AD)^{1,2}. However, the specific role of sex remains unclear. Most previous studies have focused on a single modality, while disease development and progression involve multiple interacting modalities, such as amyloid plaques, neurofibrillary tangles, neurodegeneration, and synaptic loss. This study therefore aimed to examine clinical features across multiple modalities to clarify the role of sex in reserve and vulnerability from mild cognitive impairment (MCI) to AD dementia.

METHODS

We examined AD biomarker-positive individuals with MCI or AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (MCI n = 680, AD n = 270) and the National Alzheimer's Coordinating Center (NACC) (MCI n = 436, AD n = 174) datasets. Baseline gray matter volume (GMV) from T1-weighted MRI was compared between sexes in both cohorts. In subsets of participants with available data, sex differences in tau burden (measured by PET) and cerebrospinal fluid (CSF) growth-associated protein 43 (GAP-43), a measure related to synaptic dysfunction, were assessed. Longitudinal analyses examined sex differences in annual brain atrophy and conversion from MCI to dementia.

RESULTS

Females with MCI due to AD exhibited **greater baseline GMV** than males (**Fig 1**) but similar cognition (similar results in ADNI and NACC). These differences were no longer observed at the AD dementia stage. Females with MCI due to AD exhibited **higher baseline GAP-43** ($P = 0.005$), **greater tau burden** in temporal and parietal regions (**Fig 2**), and **more rapid annual hippocampal atrophy** (**Fig 3**). Results were adjusted for age, education, and baseline CDR-SB.

Among participants with longitudinal follow-up, 47.1% converted from MCI at baseline to dementia during follow-up over a mean follow-up of 1290 days. The percentage of participants who converted was not significantly different between sexes ($P = 0.47$).

Fig 1. Gray matter volume (GMV) comparison by sex in participants with MCI

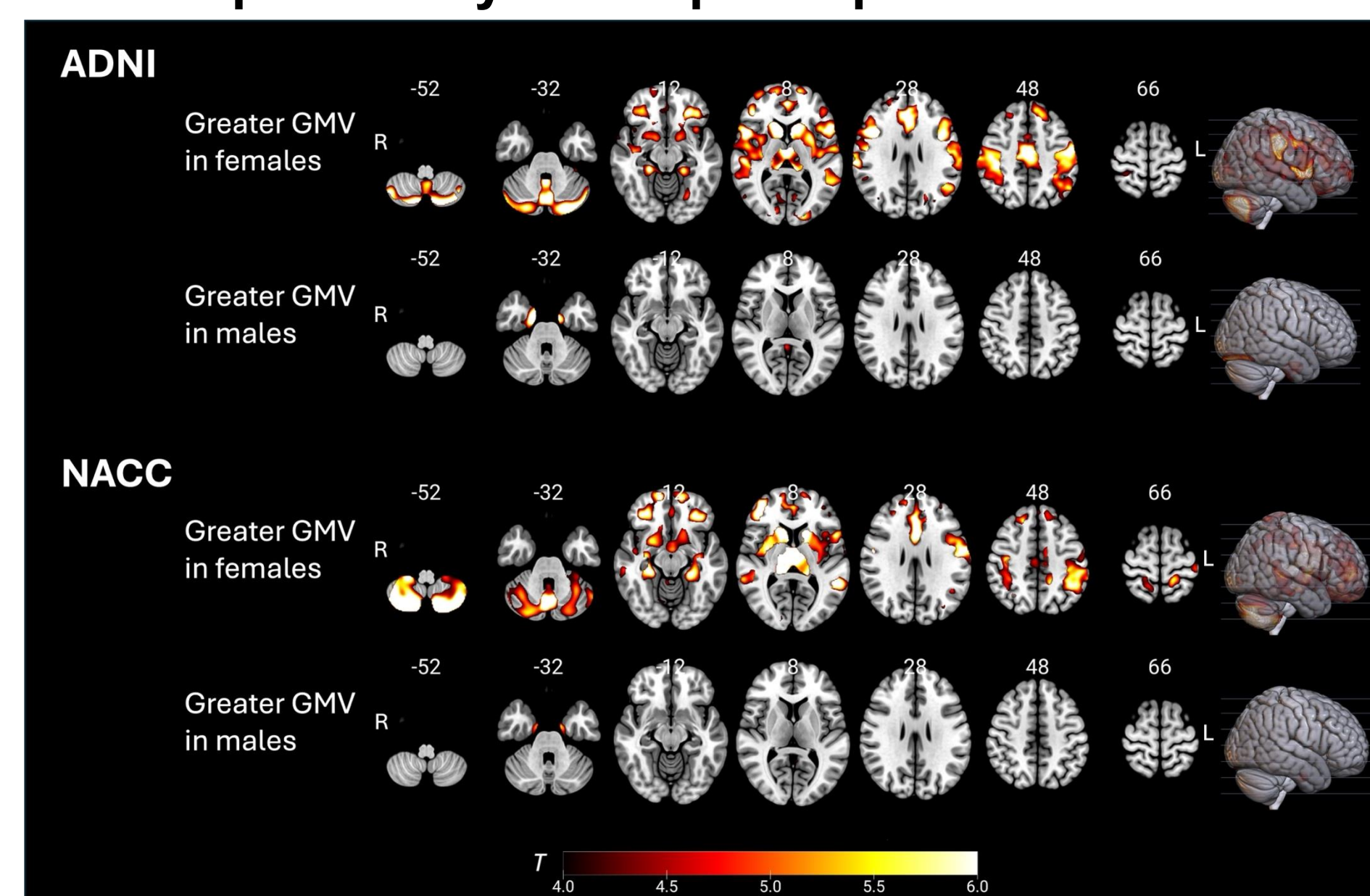


Fig 1. Baseline GMV comparison between females and males in MCI participants with positive AD biomarkers from the ADNI dataset (n = 680) and from the NACC dataset (n = 436). Results are corrected for total intracranial volume, age, education and disease severity measured by CDR-SB.

Fig 2. Tau-PET burden by sex in participants with MCI

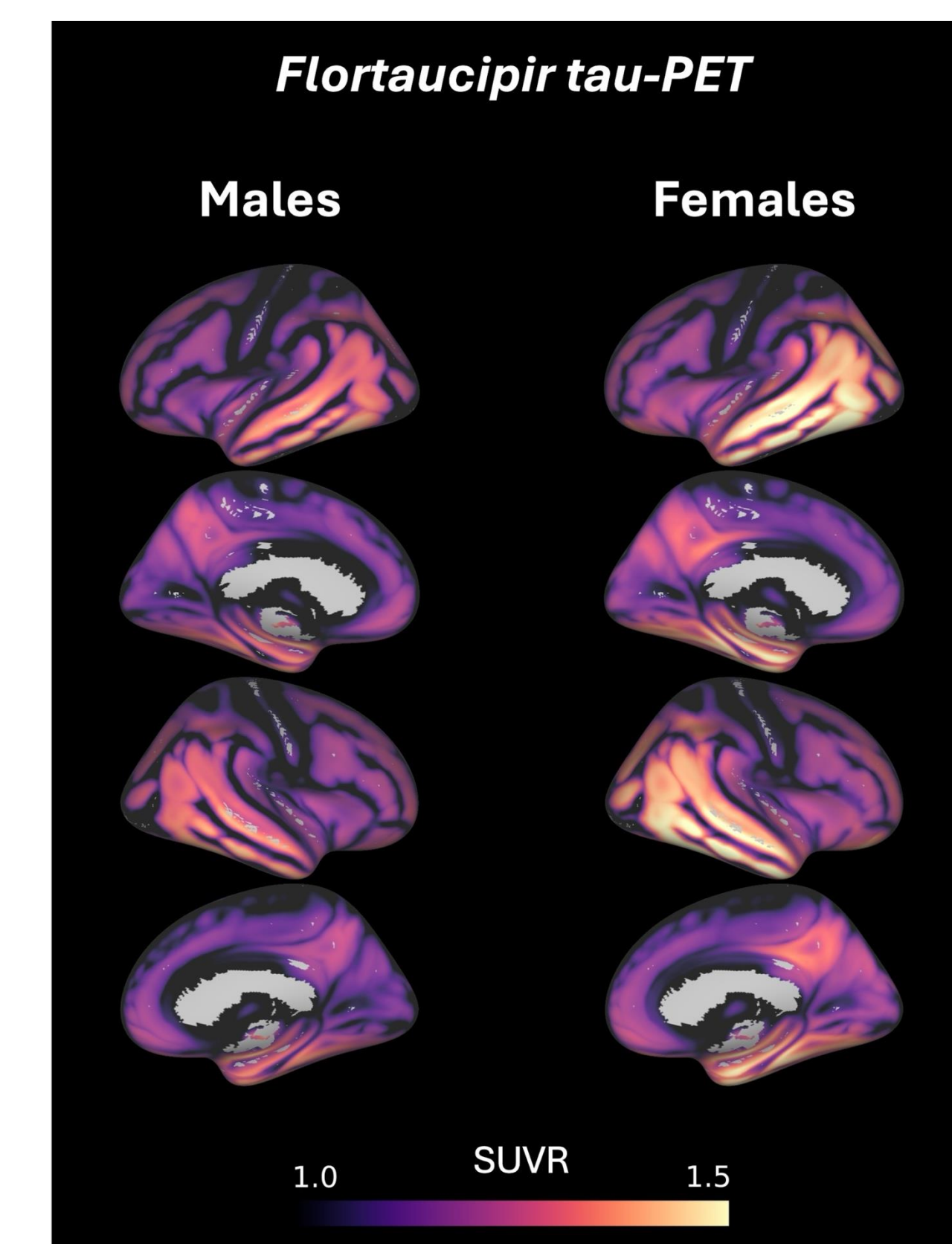


Fig 2. Average standardized uptake value ratio (SUVR) from baseline flortaucipir tau-PET (gray matter masked) stratified by sex in participants with MCI at baseline (n = 164).

Fig 3. Annual atrophy comparison by sex in participants with MCI at baseline

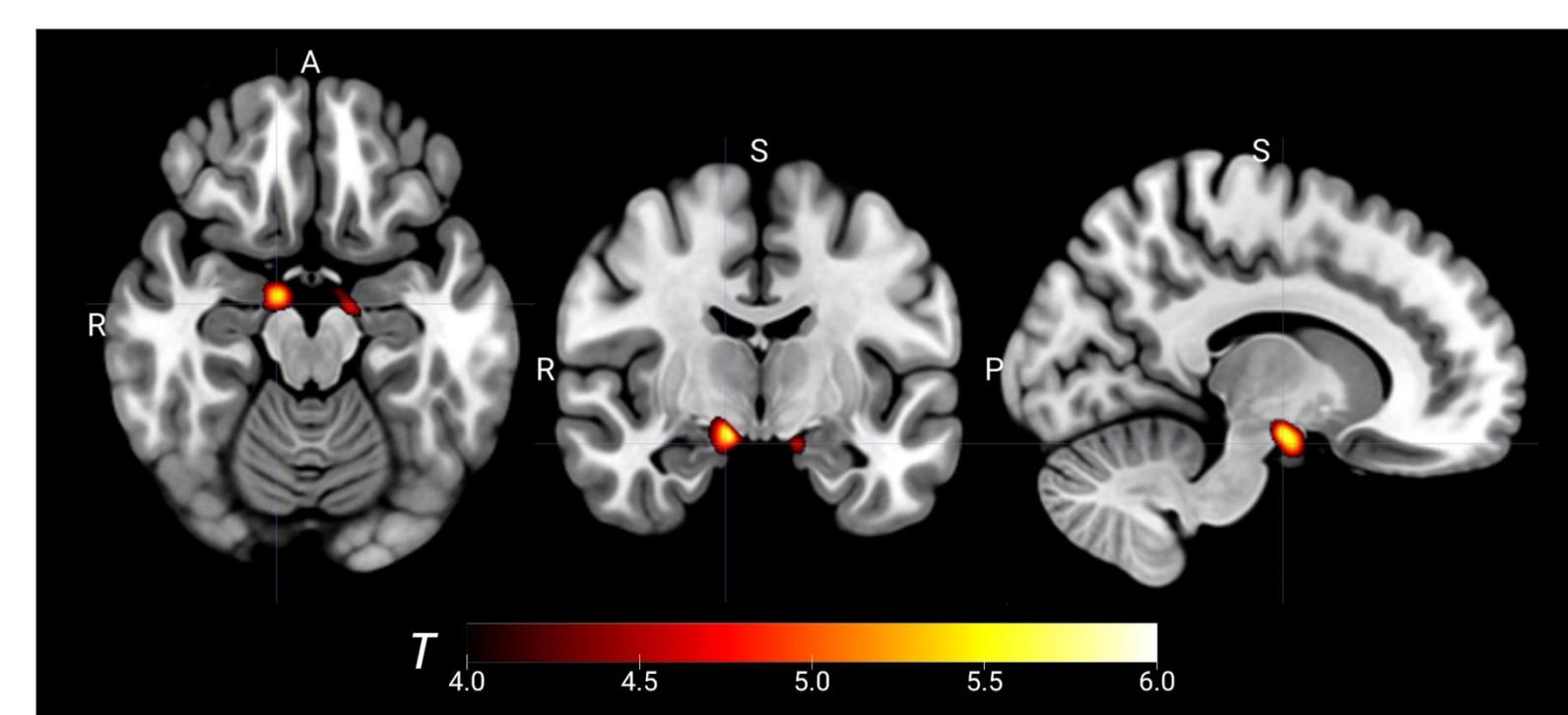


Fig 3. Comparison of annual GMV atrophy between females and males with MCI at baseline (n = 563). Regions in the hot color scheme represent brain regions where females exhibited greater annual atrophy than males. Results are corrected for total intracranial volume, age, education and CDR-SB scores at baseline.

CONCLUSION

Females may start with better brain reserve at earlier stages of MCI but experience accelerated decline once a critical threshold of pathology is reached, which may involve synaptic changes as measured by GAP-43 and tau accumulation. Findings support sex-specific disease trajectories and highlight the need for sex-informed biomarkers.

References: 1. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2022;18:700-89. 2. Ferretti MT et al. Sex differences in Alzheimer disease - the gateway to precision medicine. *Nat Rev Neurol*. 2018;14:457-69.

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