

Effects of early-handling and sex on cognitive resilience in APP/PS1 mice

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Introduction & Methods:

- **Alzheimer’s Disease (AD)** is characterized by changes in brain structure and function.
- Some individuals maintain normal cognitive function despite AD pathology, a phenomenon known as **cognitive resilience (CR)**.
- **APP/PS1 mice** exhibit a relevant mutation for AD, causing the accumulation of amyloid-beta and resulting cognitive deficits.
- CR can be induced in mice by improved maternal care through an **early handling (EH)** paradigm.

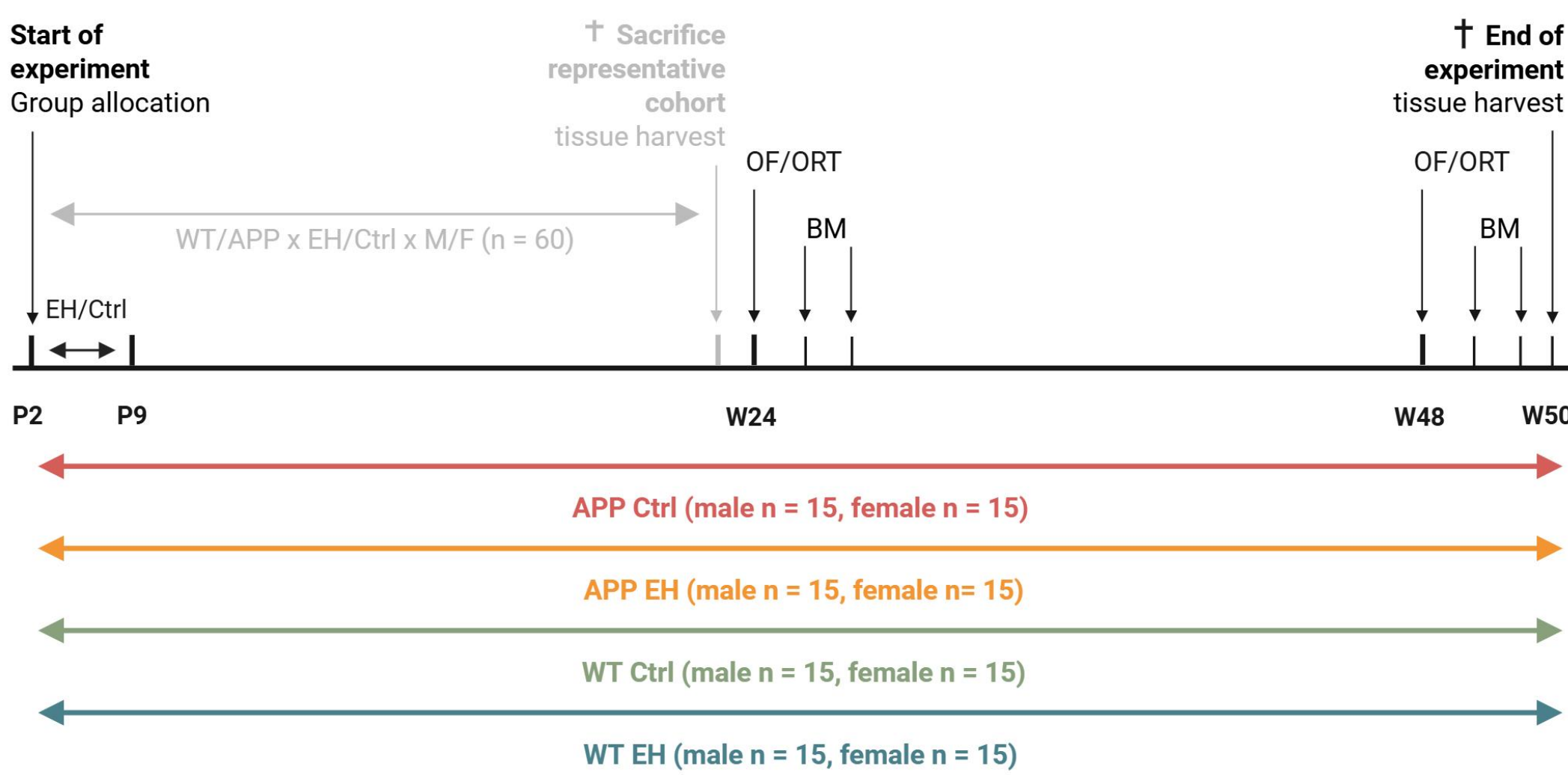


Figure 1: Study overview. Group allocation at postnatal day (P) 2. Early handling (EH) paradigm between P2 and P9. Behavioral testing at 6 and 12 months of age. Tissue harvest at 6 (behavioral testing independent) and 12 months of age. Ctrl = control, WT = wild type, APP = APP/PS1, M = male, F = female, W = week, OF = open field test, ORT = novel object recognition test, BM = Barnes maze.

Aim: Unravel the molecular signature of cognitive resilience and the modulatory role of sex.

Results:

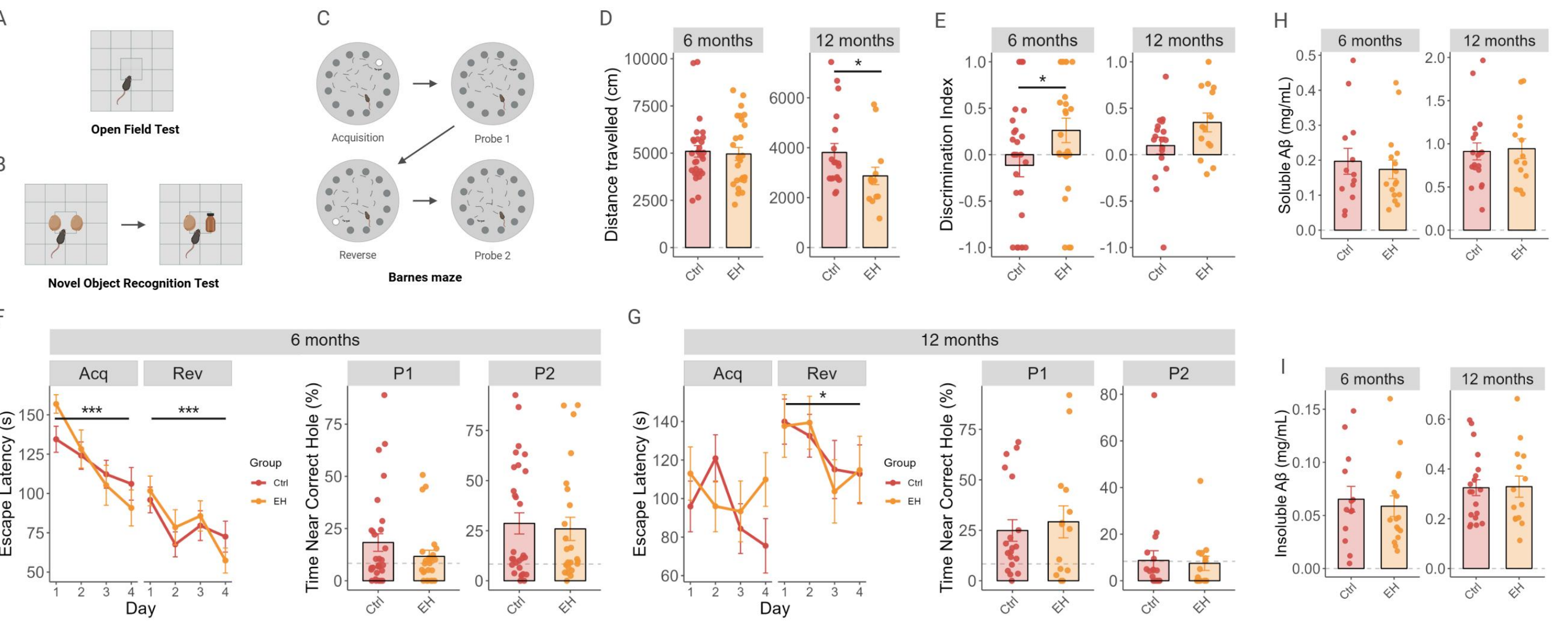


Figure 2: Behavioral outcomes and hippocampal Aβ levels of APP/PS1 mice by condition. A) Open field test (OF). B) Novel object recognition test (ORT). C) Barnes maze (BM). D) EH reduces APP/PS1-induced increase in general locomotion at 12 months in the OF (p<0.05). E) EH show better non-spatial memory at 6 months in the ORT (p<0.05). F) No group differences in spatial learning (Acq), cognitive flexibility (Rev), or memory (P1 & P2) in the BM at 6 or 12 months of age. H) No group differences in whole-hippocampal soluble and I) insoluble Aβ levels.

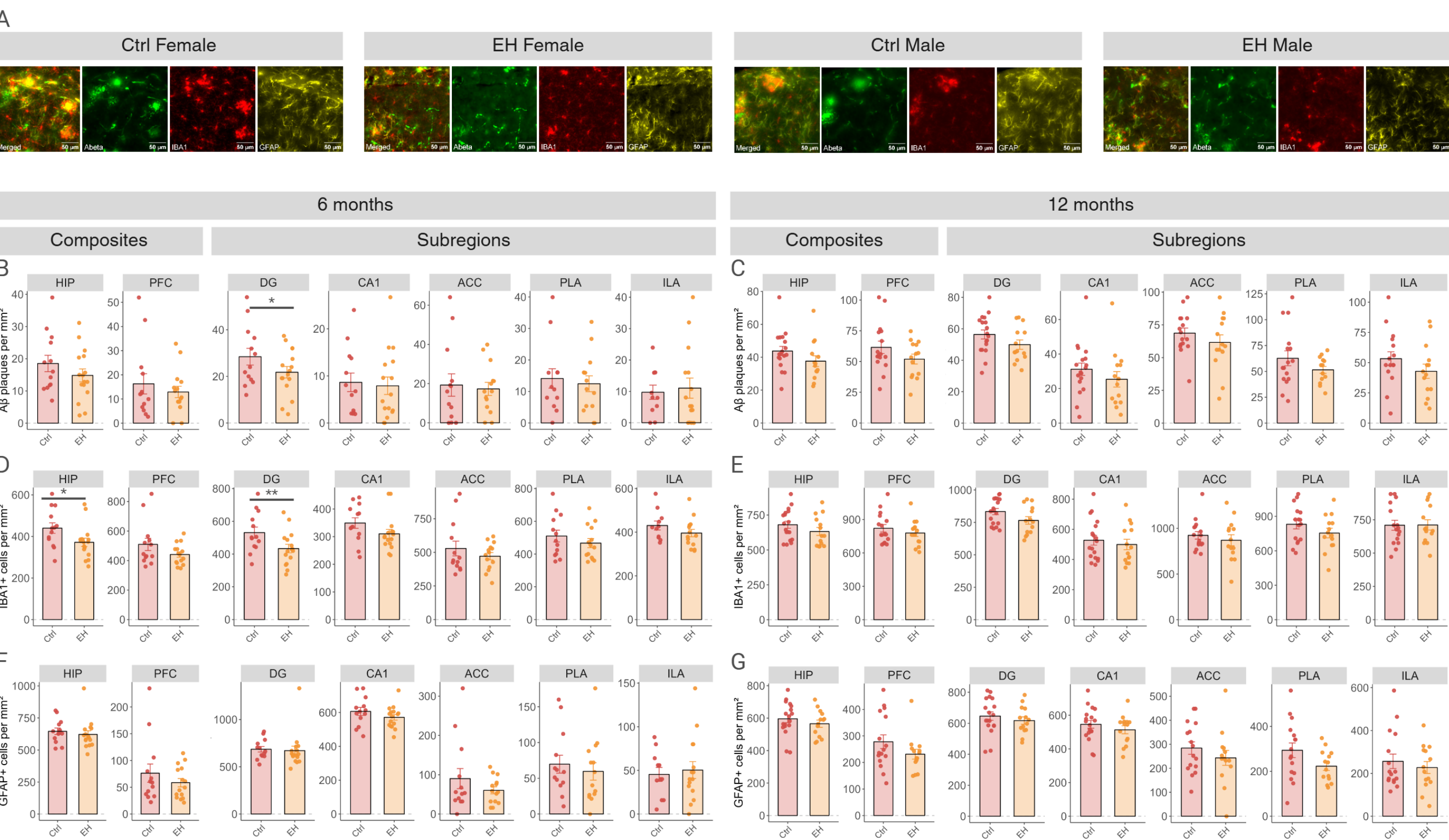


Figure 3: Markers of pathology in APP/PS1 mice by condition. A) representative image of the Aβ-IBA1-GFAP triple staining. B) EH reduced Aβ-plaque density in the DG at 6 months (p<0.05). C) No group differences in Aβ-plaque density at 12 months. D) EH reduced IBA1+ cell density in the hippocampal composite (HIP, p<0.05) and in the DG (p<0.01) at 6 months. E) No group differences in IBA1+ cell density at 12 months. F) No group differences in GFAP+ cell density at 6 or 12 months of age.

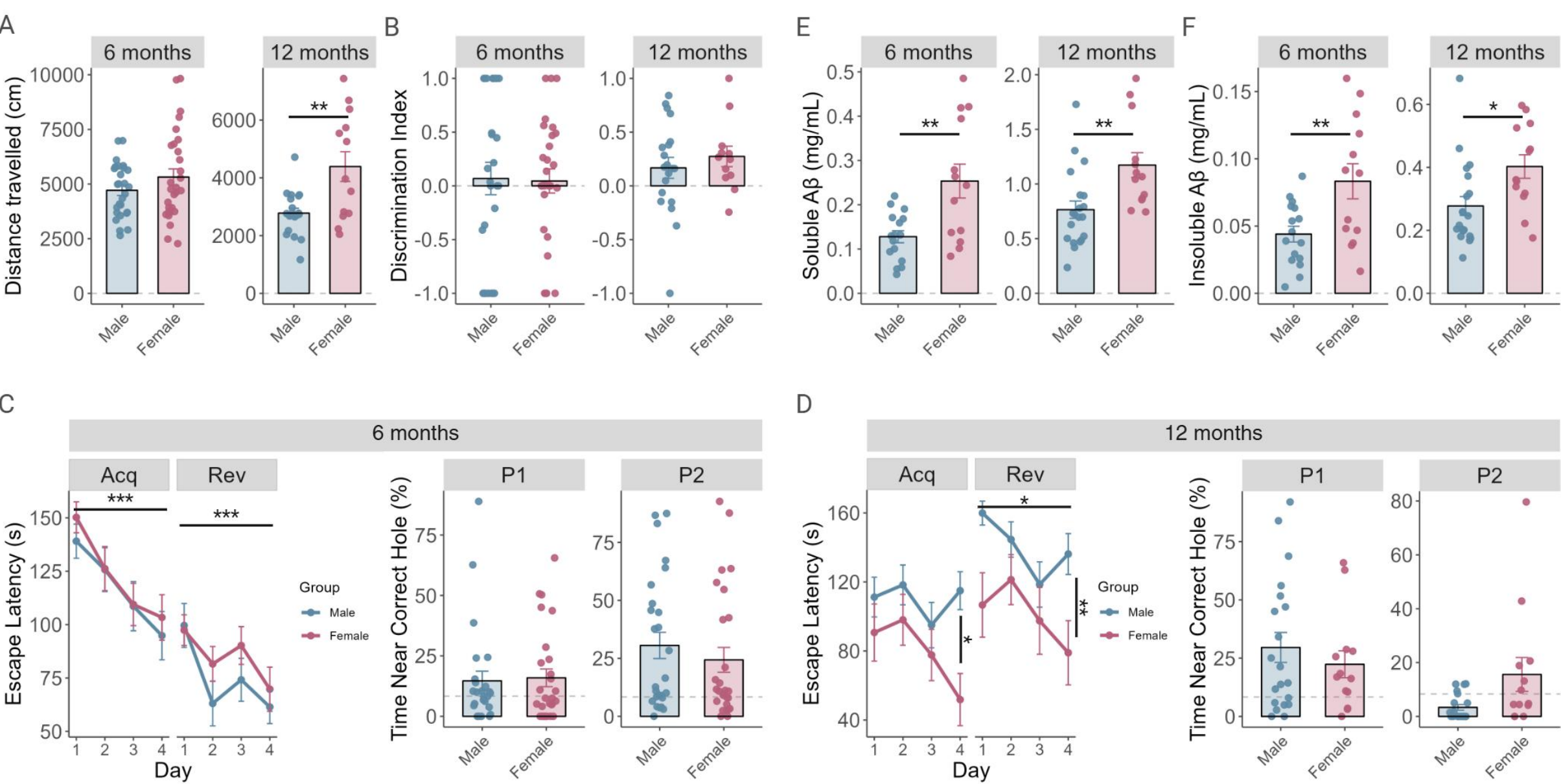


Figure 4: Behavioral outcomes and hippocampal Aβ levels of APP/PS1 mice by sex. A) Female show hyperactivity at 12 months in the OF (p<0.01). B) No sex differences in non-spatial memory in the ORT. C) No sex differences in spatial learning (Acq), cognitive flexibility (Rev), or memory (P1 & P2) in the BM at 6 months. D) Females show faster escapes (Acq, p<0.05) and better spatial learning (Rev, p<0.01) trial. E) females show higher levels of whole-hippocampal soluble (6&12 months: p<0.01) and I) insoluble Aβ (6 months: p<0.01, 12 months: p<0.05) levels.

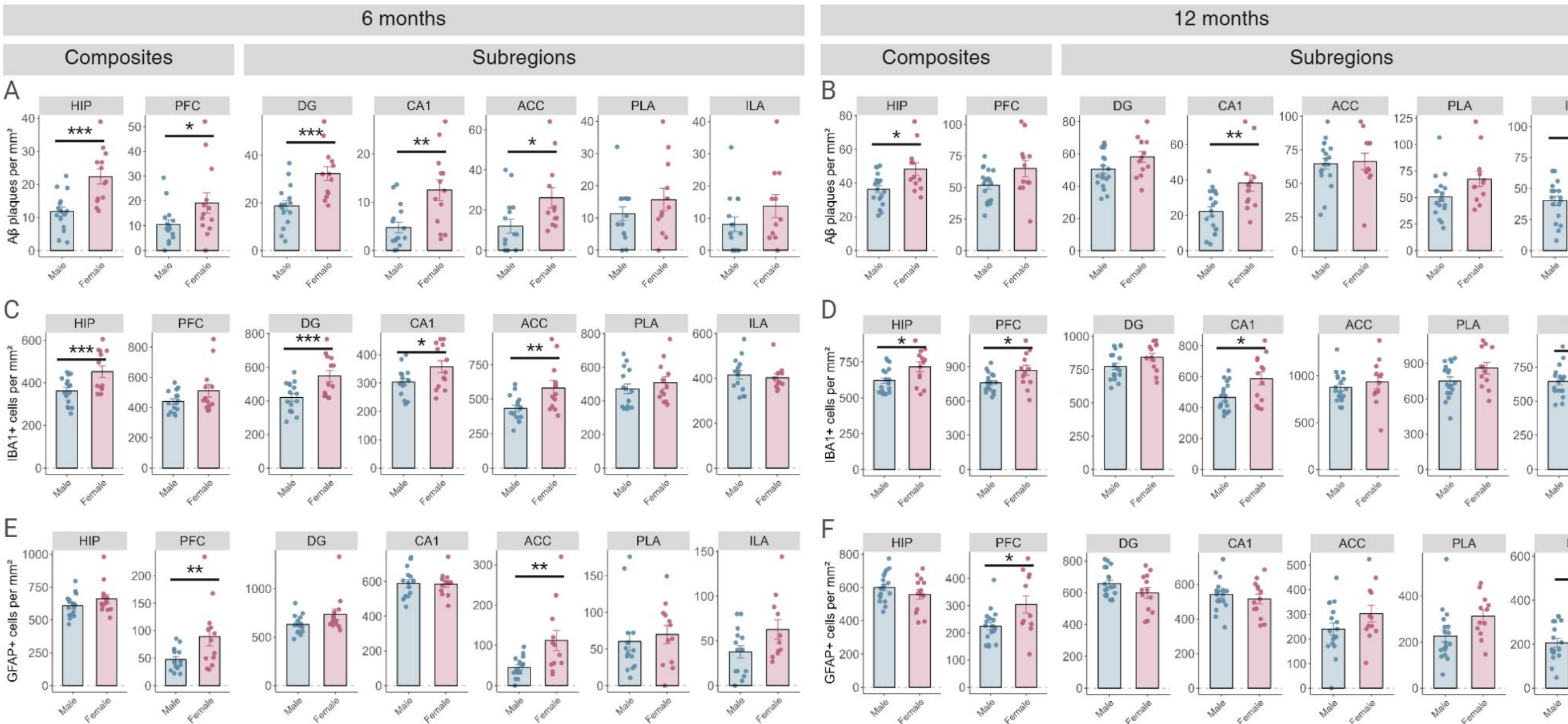


Figure 5: Markers of pathology in APP/PS1 mice by sex. A) Females show higher hippocampal and prefrontal Aβ-plaque density at 6 months (HIP, p<0.001; PFC, p<0.05; DG, p<0.001; CA1, p<0.05), as well as at B) 12 months (HIP, p<0.05; CA1, p<0.01; ILA, p<0.05). C) IBA1+ cell density is higher in females in hippocampal regions (HIP, p<0.001; DG, p<0.001; CA1, p<0.05) and in the ACC (p<0.01) at 6 months, and D) in hippocampal (HIP, p<0.05; CA1, p<0.05) and prefrontal (PFC, p<0.05; ILA, p<0.01) regions at 12 months. E) Females show higher prefrontal GFAP+ cell density (PFC, p<0.01; ACC, p<0.01) at 6 and F) 12 months of age (PFC, p<0.05; ILA, p<0.05).

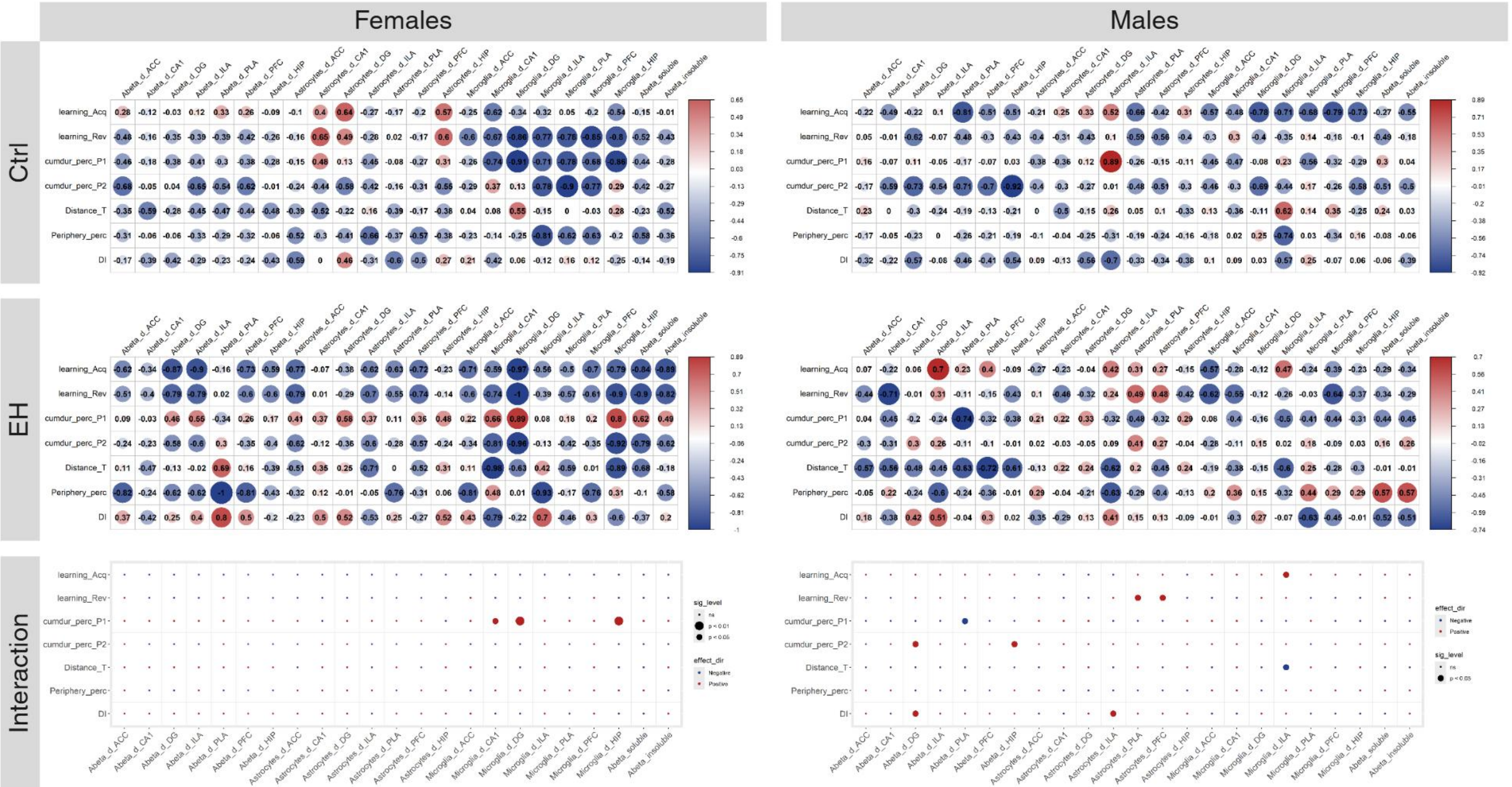


Figure 6: Associations of cognition and pathology at 12 months. Associations between cognition and markers of pathology in APP/PS1 Ctrl females (top left), APP/PS1 Ctrl males (top right), APP/PS1 EH females (middle left) and APP/PS1 EH males (middle right). Interaction between the association of cognition and pathological markers and condition (EH vs Ctrl) among females (bottom left) and males (bottom right). Interaction p-values are raw (non-FDR corrected), using EH as contrast.

Conclusion:

- **EH normalizes** AD-induced changes in locomotion at 12 months and **improves non-spatial memory** at 6 months, concordant with a hippocampal **reduction in amyloid plaques and microglia density**.
- **Females show better spatial learning** at 12 months, despite **higher overall pathological burden** at 6 and 12 months.
- **Among females**, better performance associates with higher microglia density, suggesting that **EH might induce different microglia states**.
- Among males, behavior-pathology associations are less clear, suggesting that effects of **EH differ between sexes**.

Take-home message:

Effects of EH are multifaceted and seem to affect males and females differently. In females, effects are likely driven by differing microglia states. Our findings highlight the critical role of early postnatal experiences in modulating resilience to the development of AD pathology, and the modulatory role of sex.

Let's connect!

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