

Sex differences in the gut microbiota are associated with distinct neuropathological responses in the 5xFAD model of Alzheimer's disease

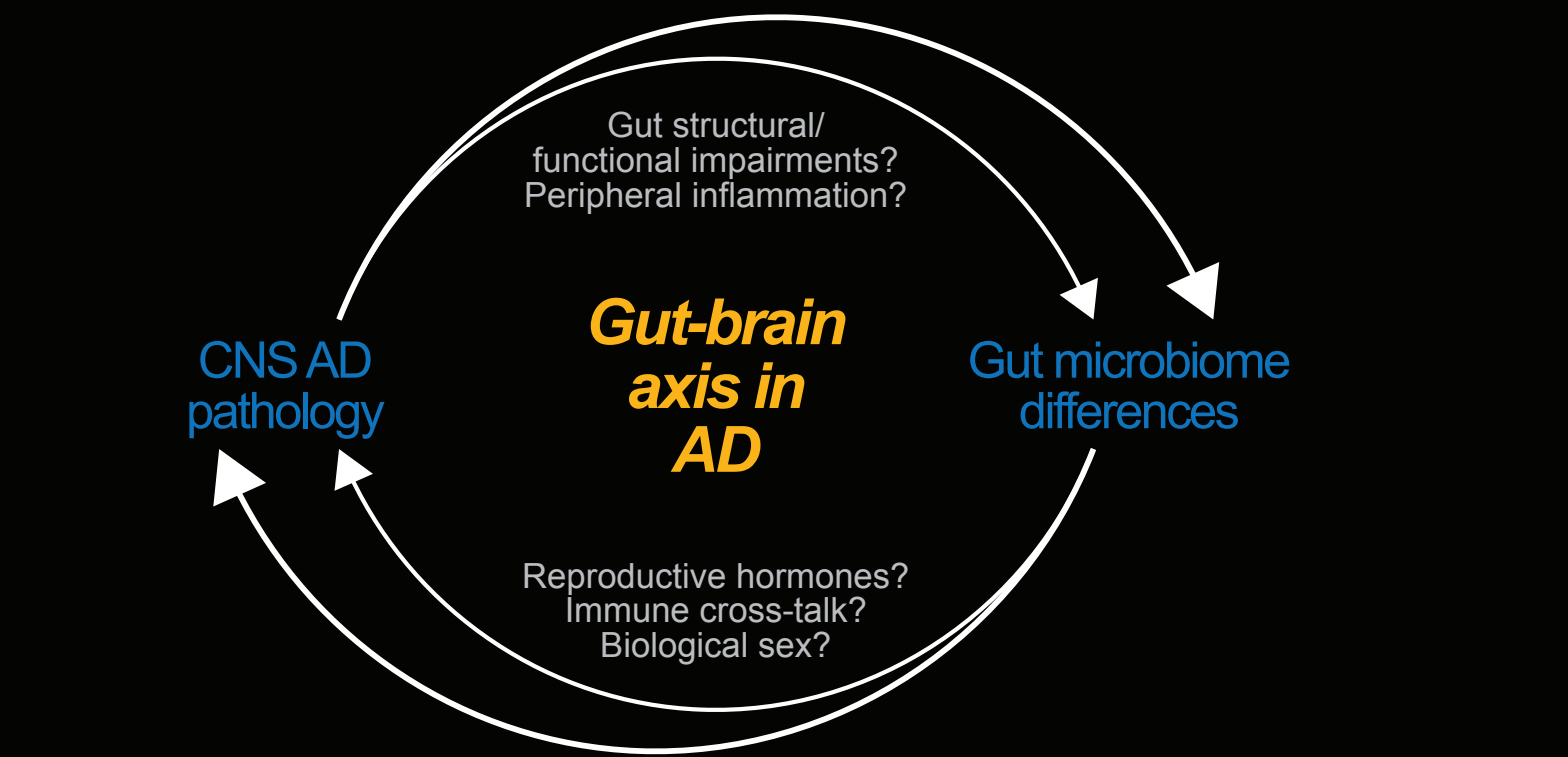
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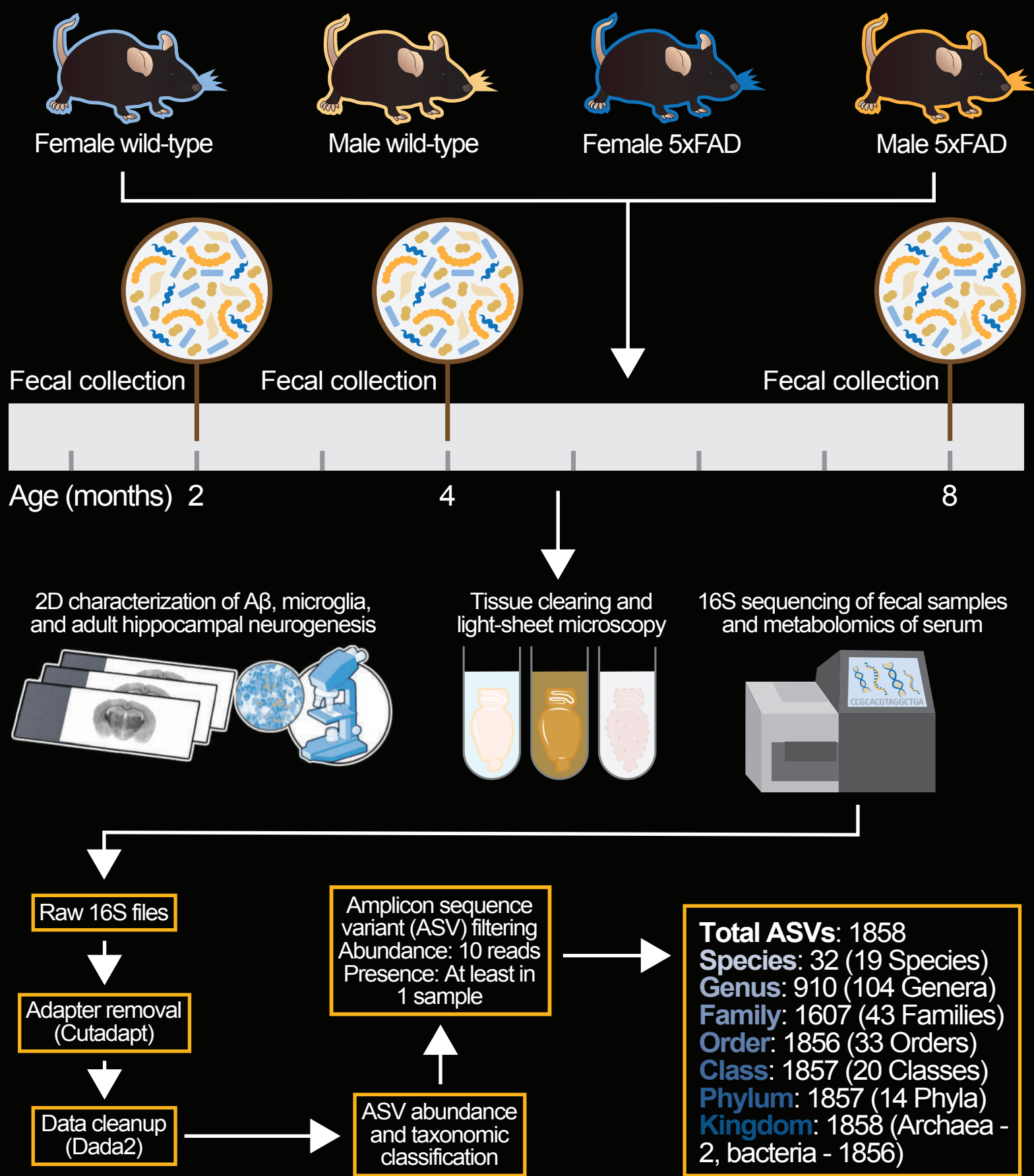
Background

- Women are twice as likely to develop Alzheimer's disease (AD) as men¹ and experience more rapid cognitive decline².
- Many AD mouse models recapitulate such sex differences^{3,4}.
- Reproductive hormones does not fully account for this extent of sex-dimorphic AD neuropathological responses^{5,6}.
- Transferring AD gut microbiota to wild-type rats impaired adult hippocampal neurogenesis (AHN) and memory⁷.
- Sex differences in the gut microbiome composition are detected around the age of onset of AD in humans^{8,9}.

Does the gut microbiome composition contribute to the sex-dimorphic AD neuropathological kinetics?

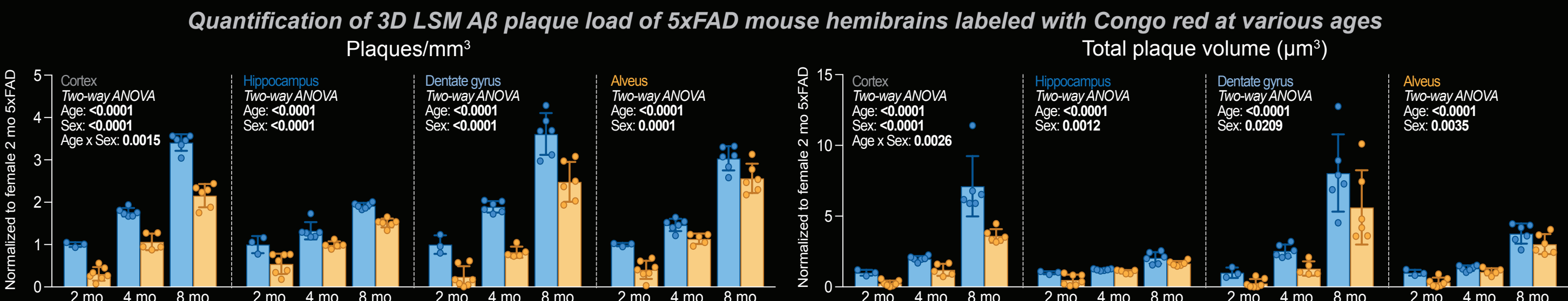
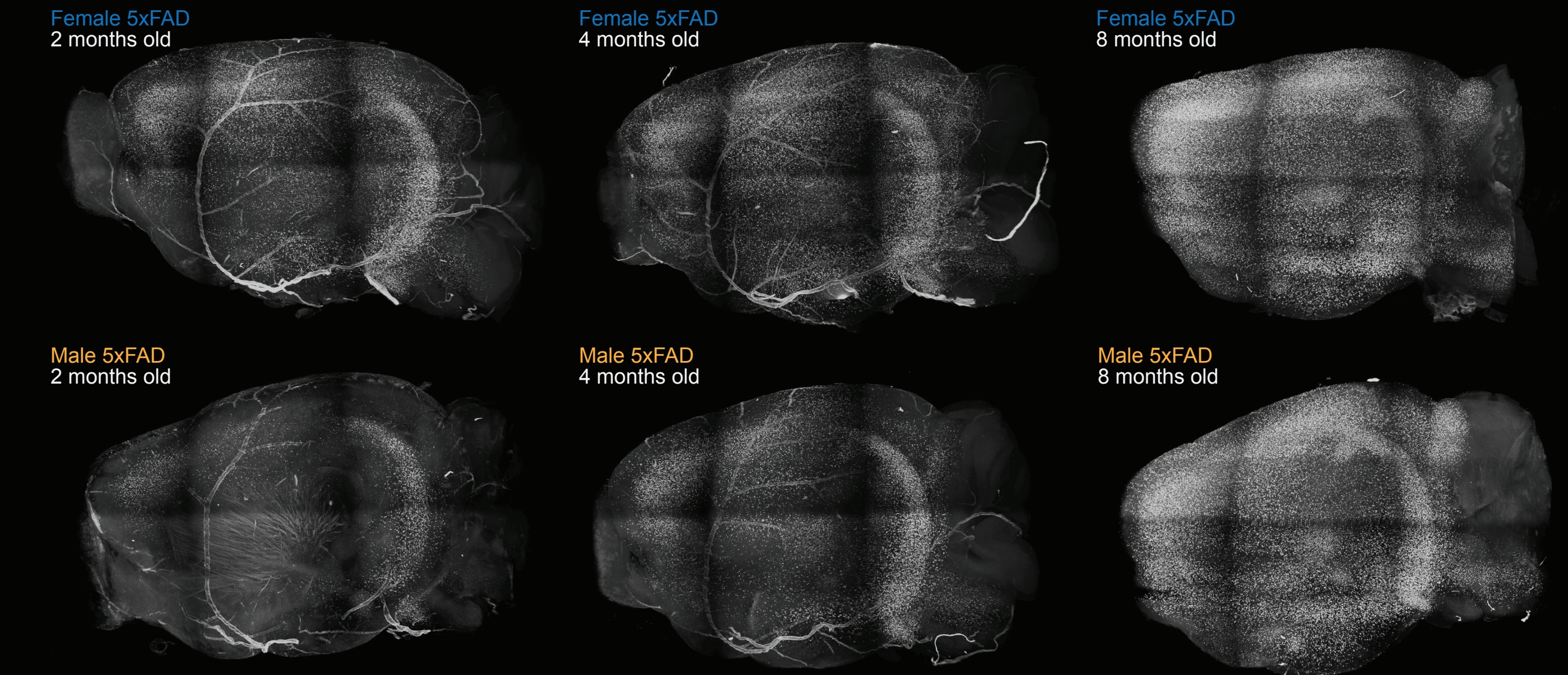


Experimental design

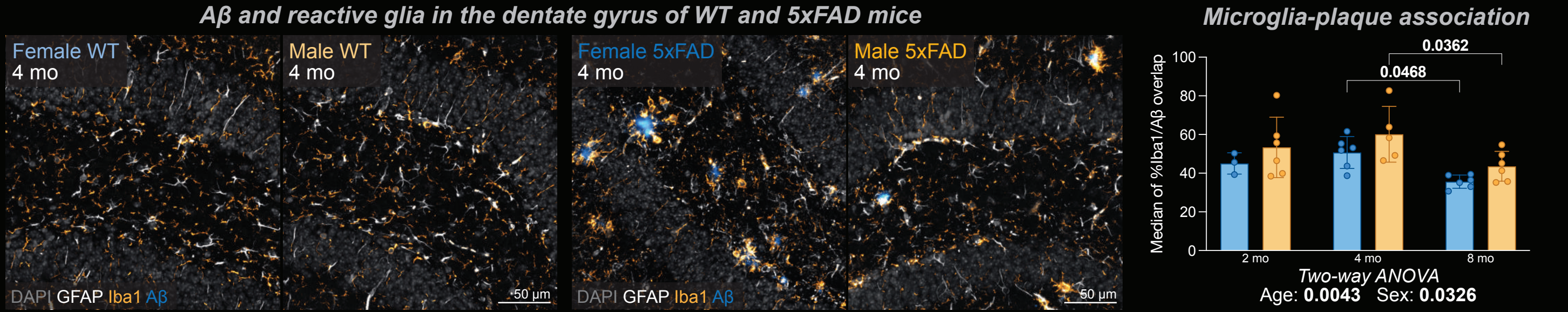


Results

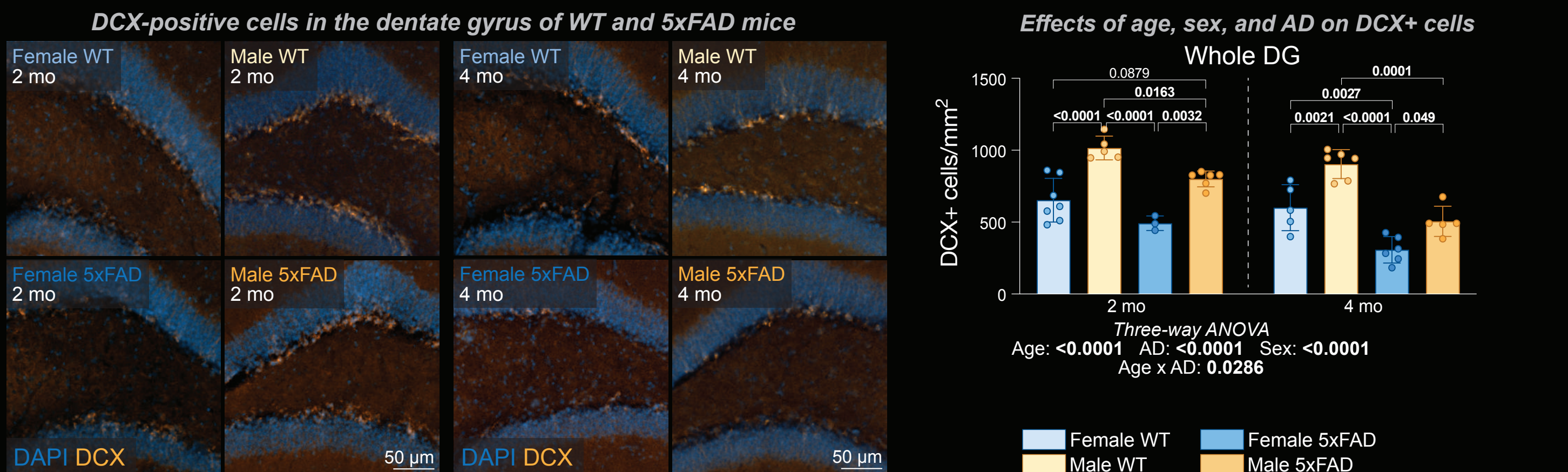
1 Female 5xFAD mice exhibit higher Aβ burden compared to males at the earliest analysis timepoint and this sex dimorphism is sustained through adulthood.



2 Female 5xFAD mice show lower microglial plaque association compared to males in the dentate gyrus.



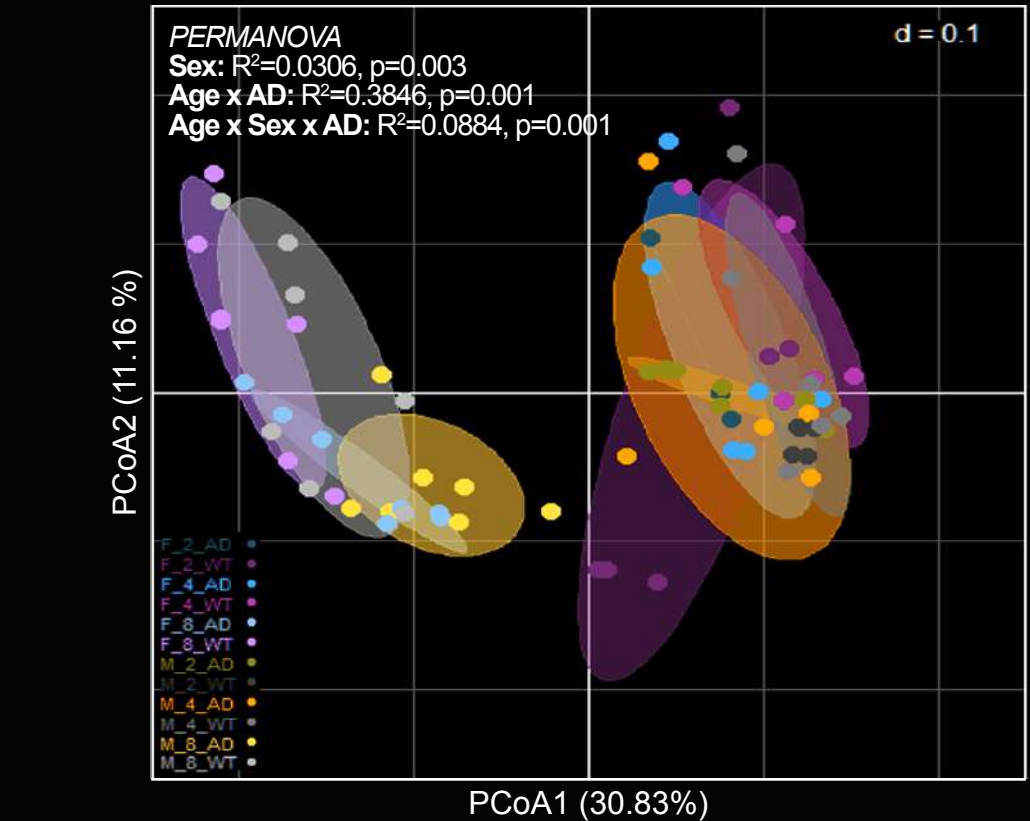
3 Male 5xFAD mice exhibit an earlier impairment in AHN in response to Aβ compared to females.



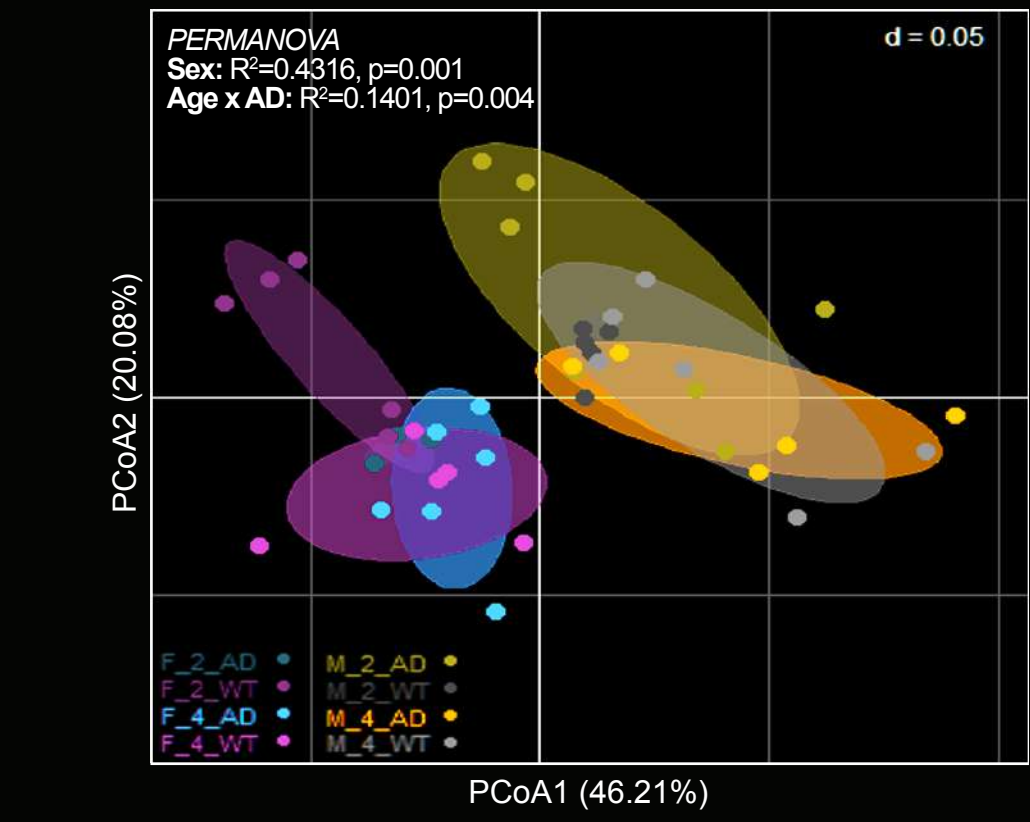
4 Significant sex-specific ASV differences emerge early in WT and 5xFAD mice which coincides with the onset of plaque deposition and subsides with age.



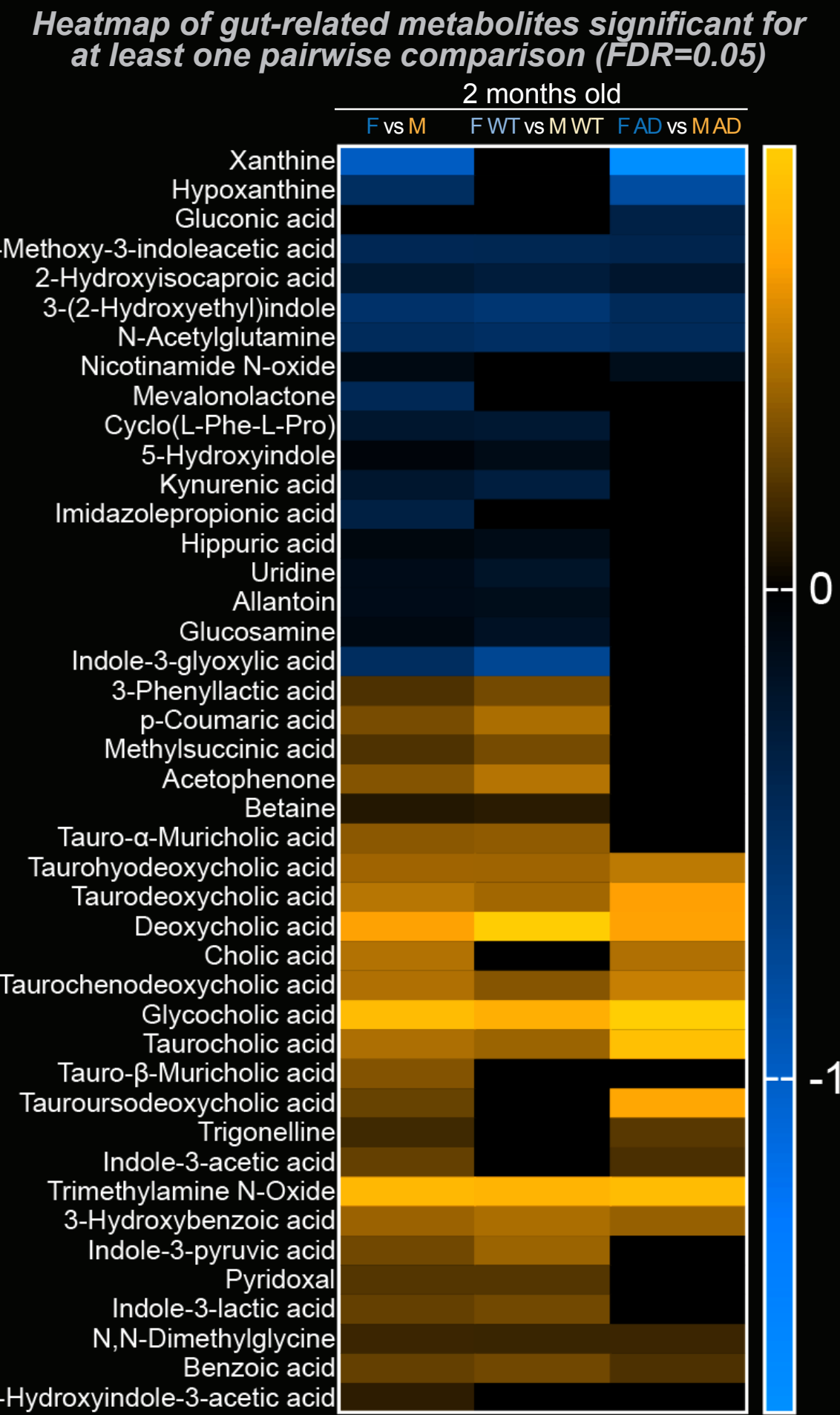
5 Age, sex, and AD drive differences in microbiome composition.



6 Sex primarily separates metabolite profiles in WT and 5xFAD mice.



7 Significant and early sex differences in gut-related metabolites.



Conclusions

- 5xFAD mice recapitulate features of AD sex dimorphism, with earlier emergence and higher Aβ burden in females.
- Male 5xFAD mice exhibit an earlier neurogenic niche vulnerability compared to females.
- The onset of plaque deposition coincides with major sex differences in the gut microbiome.
- Distinction in circulating metabolites, some gut microbiota-derived, are primarily driven by sex.

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