

TARGETING MICROGLIA WITH CHRONIC CSF1R ANTAGONISM:
EFFECTS ON SUBTYPES, TAU, AND BEHAVIOR IN AMYLOID-
ENHANCED TAUOPATHY

P4-227

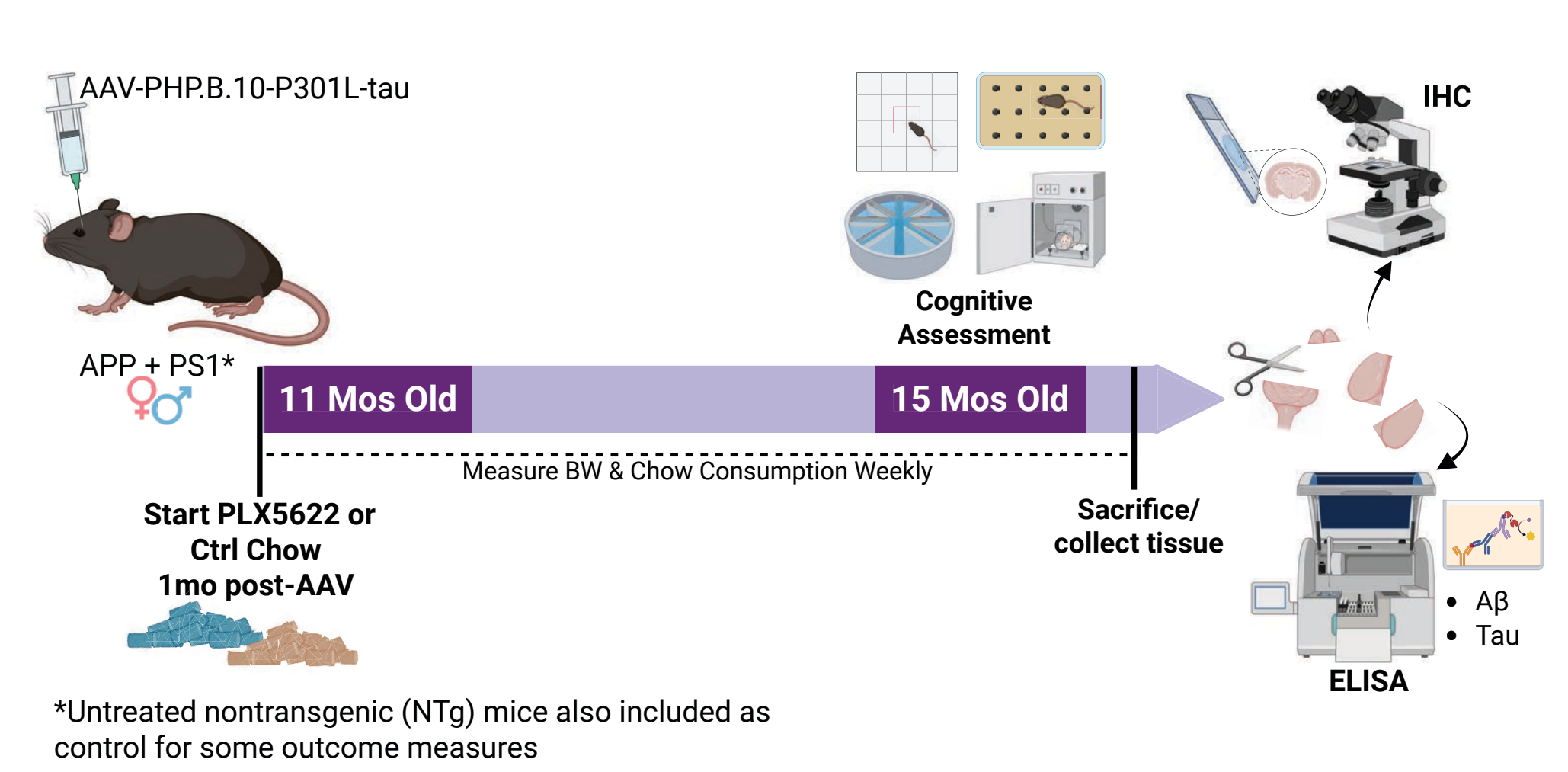
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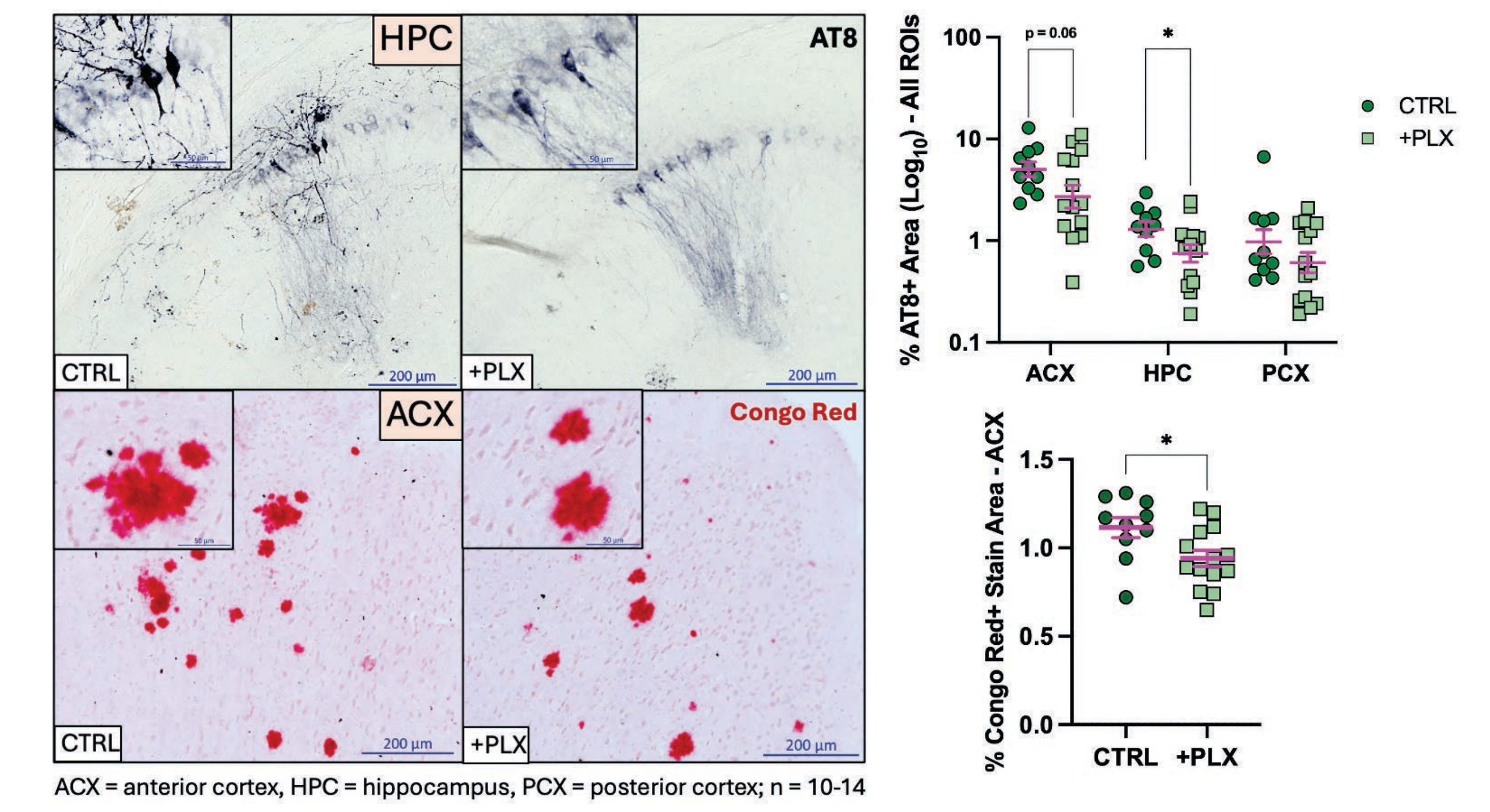
Microglia mediate neuroinflammation in AD, but their relationship with tau pathology remains unclear. We used chronic CSF1R inhibition to deplete microglia in APP+PS1 mice with timed delivery of hP301L tau (APP+PS1^{TAU}) to test whether microglia are required for development of tau pathology in the presence of established amyloidosis.

METHODS

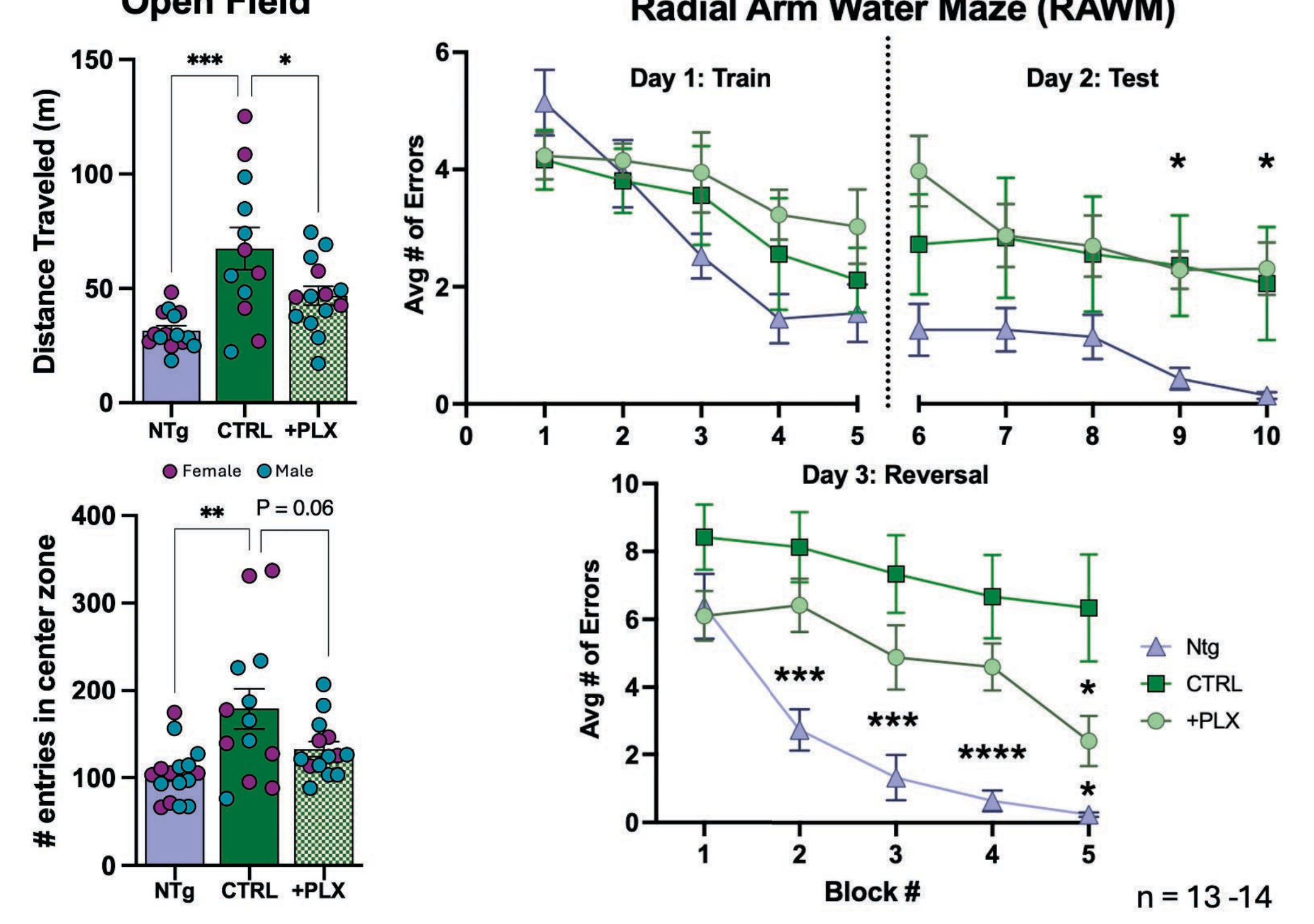


All data were analyzed by t-test or one-way ANOVA +Tukey's, as appropriate. A priori log₁₀ transformation applied when needed to satisfy normality. Presented as mean ± SEM; *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

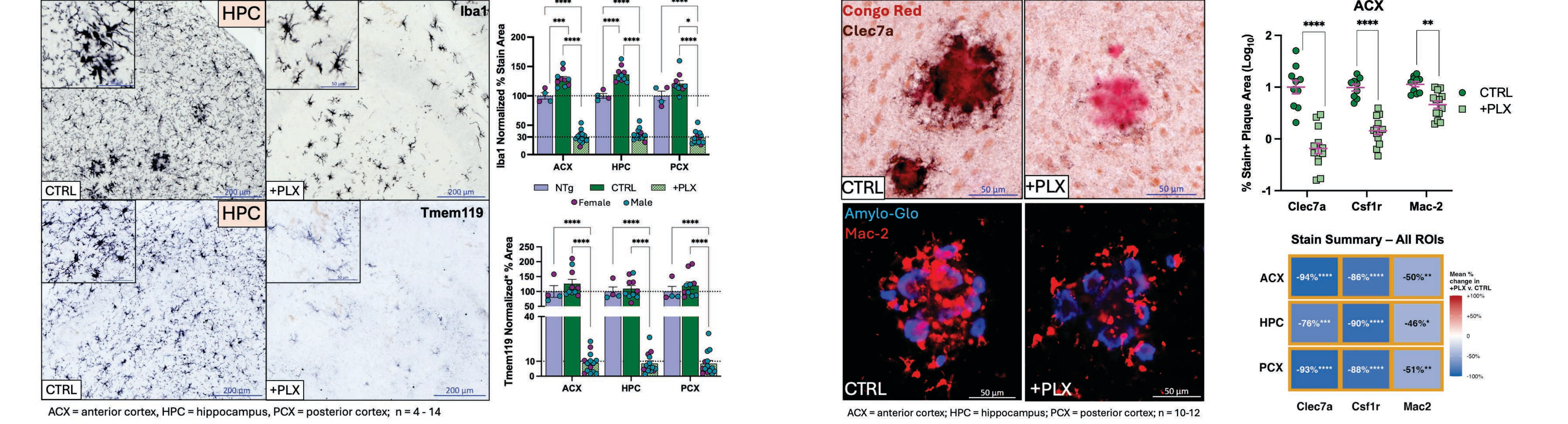
1) Chronic CSF1R inhibition modestly reduces hippocampal pTau and cortical plaque burden



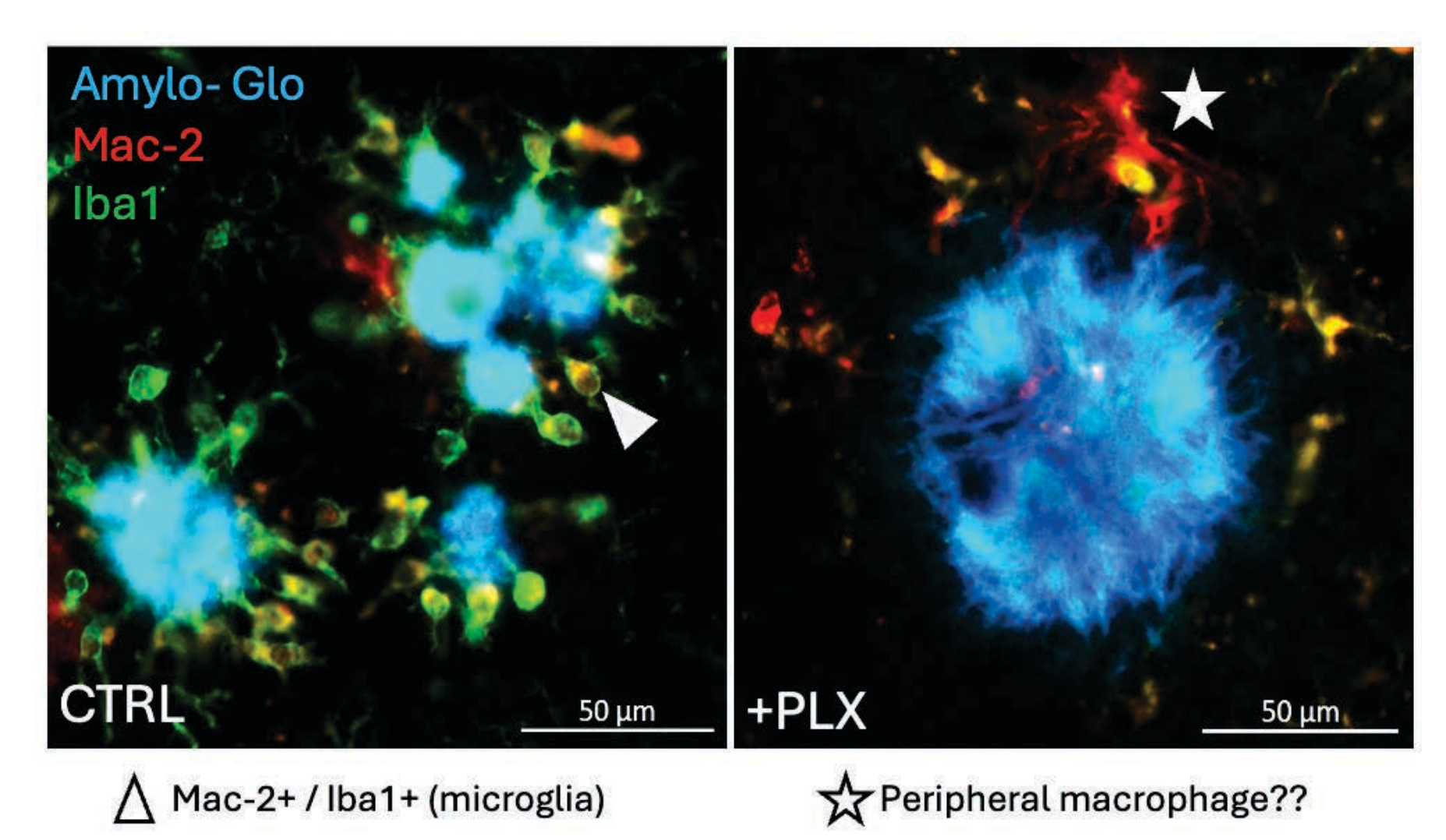
2) Chronic inhibition partially rescues the APP+PS1^{TAU} behavioral phenotype



3) Chronic CSF1R inhibition depletes Tmem119+ homeostatic microglia and Clec7a+ disease-associated microglia (DAM) more robustly than cells labeled by broader myeloid markers



4) Depletion-resistant Mac-2+/Iba1- cells near plaques may reflect peripheral macrophage infiltration



CONCLUSIONS

Microglial response to plaque pathology may contribute to downstream p-tau accumulation

Lower hippocampal p-tau and NP-tau in the near-absence of plaque-associated DAM identifies microglial response as a potential mechanistic link between amyloid and tau

Depletion yields mild functional improvement via regional reductions in pathology

Lower hippocampal p-tau, NP tau and cortical plaque burden are accompanied by mild improvement in cognitive flexibility and anxiety-like behaviors

Microglial subtypes have differential therapeutic vulnerability

Homeostatic microglia and DAM are more sensitive to chronic CSF1R inhibition than total Iba1+ and plaque-associated Mac-2 cell populations

Chronic depletion may promote peripheral infiltration

Depletion-resistant Mac-2+/Iba1- cells at plaques may represent macrophages recruited to compensate for lost microglia

CONTACT/FUNDING

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