

Sex differences in susceptibility to synapse loss and cognitive decline after immune challenge in a mouse model of Alzheimer's disease



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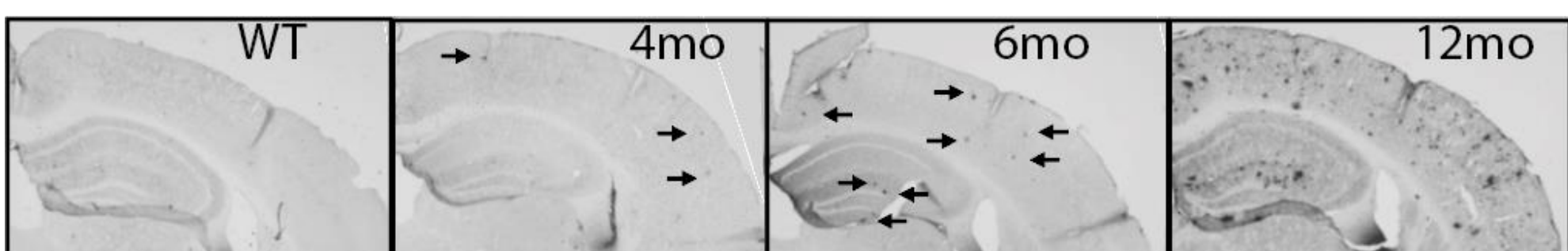
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INTRODUCTION

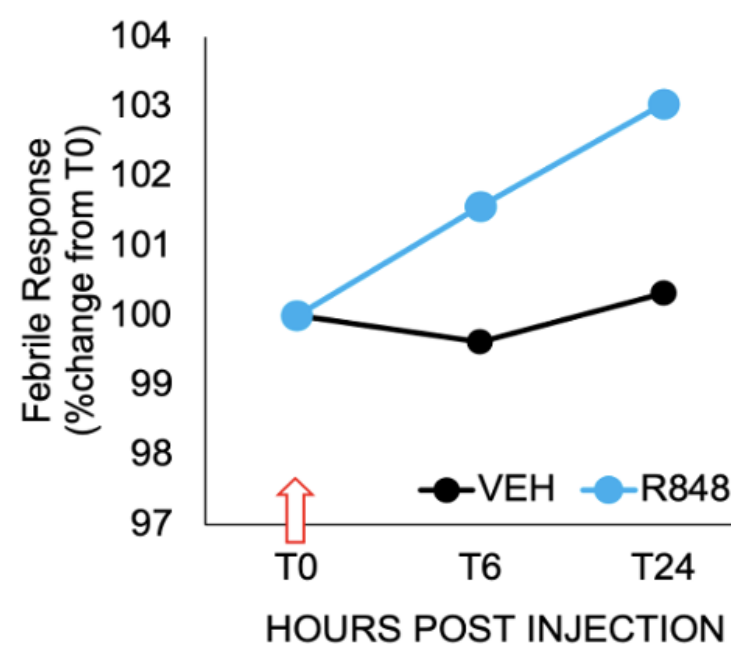
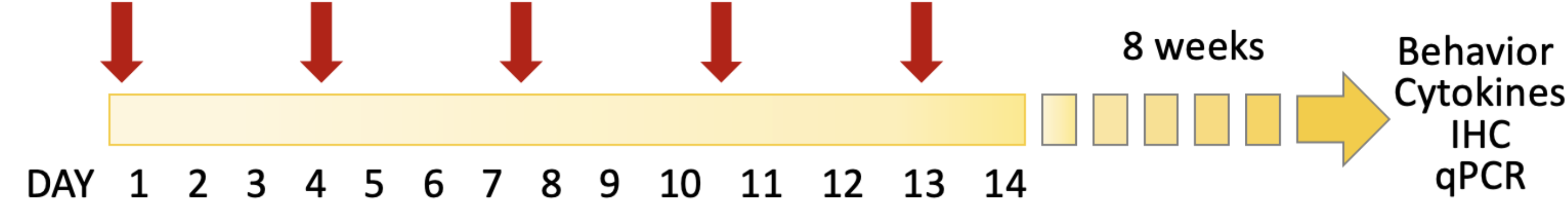
Inflammatory events significantly contribute to Alzheimer's disease pathogenesis. Growing evidence suggests midlife as a period of unique susceptibility to factors that can confer protection or susceptibility to later cognitive health or dementia. In humans, inflammation during midlife is associated with risk for cognitive decline and AD that emerge decades later. In addition, transient viral infections can lead to long lasting post-viral syndromes that emerge after a transient illness. Some viral illnesses (e.g., COVID-19, influenza, and shingles), are also associated with faster progression of AD and elevated AD risk later in life We have previously demonstrated that in young adult mice, short term / transient inflammation causes long lasting cognitive decline in both sexes and sex-specific changes in hippocampal gene expression (Tchessalova & Tronson 2019, 2020). Others have demonstrated that a single immune challenge via lipopolysaccharides injection accelerates progression of amyloid β ($A\beta$) and memory decline in transgenic AD mice. Here, new data demonstrates the impact of transient viral-like immune challenge in midlife (9-12 months) male and female mice on cognitive decline and AD progression.

METHODS

MICE **MIDLIFE MICE:** Male and female C57Bl6/N retired breeders (ENVIGO) , 9-10mo on arrival
APP/PS1 MICE: Male and female APP/PS1 Mice, backcrossed to C57Bl6/N background, 9-11 mo at the beginning of experiments



SUBCHRONIC IMMUNE CHALLENGE (R848)
R848 (resiquimod) i.p. 1000ug/kg in 4% DMSO/PBS



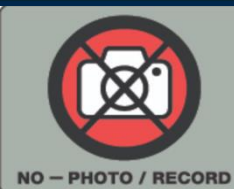
BEHAVIORAL TASKS

MEMORY: Novel Object Recognition; Context Fear Conditioning, **ANHEDONIA:** Sucrose preference

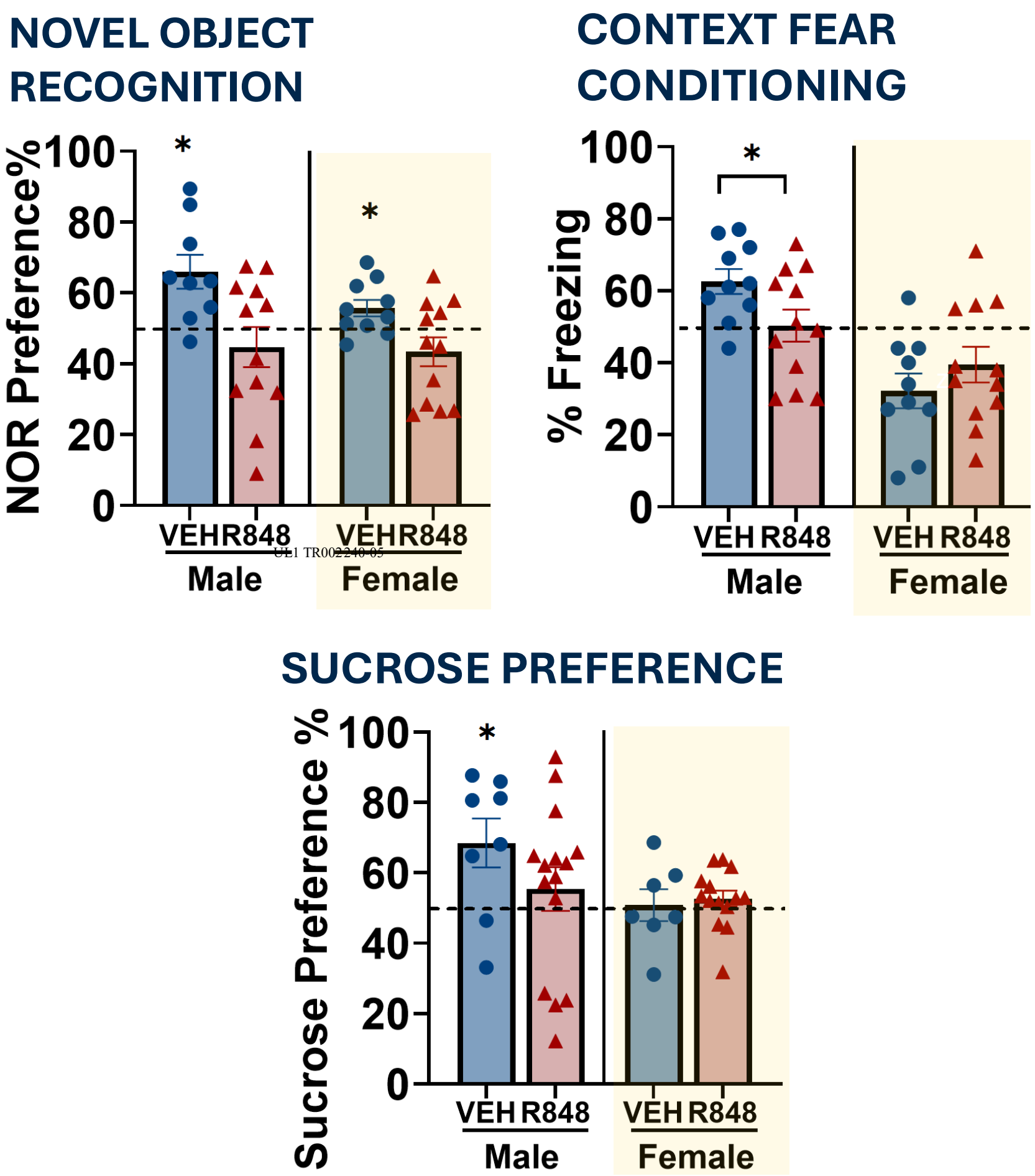
CYTOKINES, IHC, qPCR

Luminex (Magplex) was used for cytokine ELISA, IHC with IBA1 for microglia and $A\beta$ 40 for plaques, qPCR for synaptic markers

RESULTS

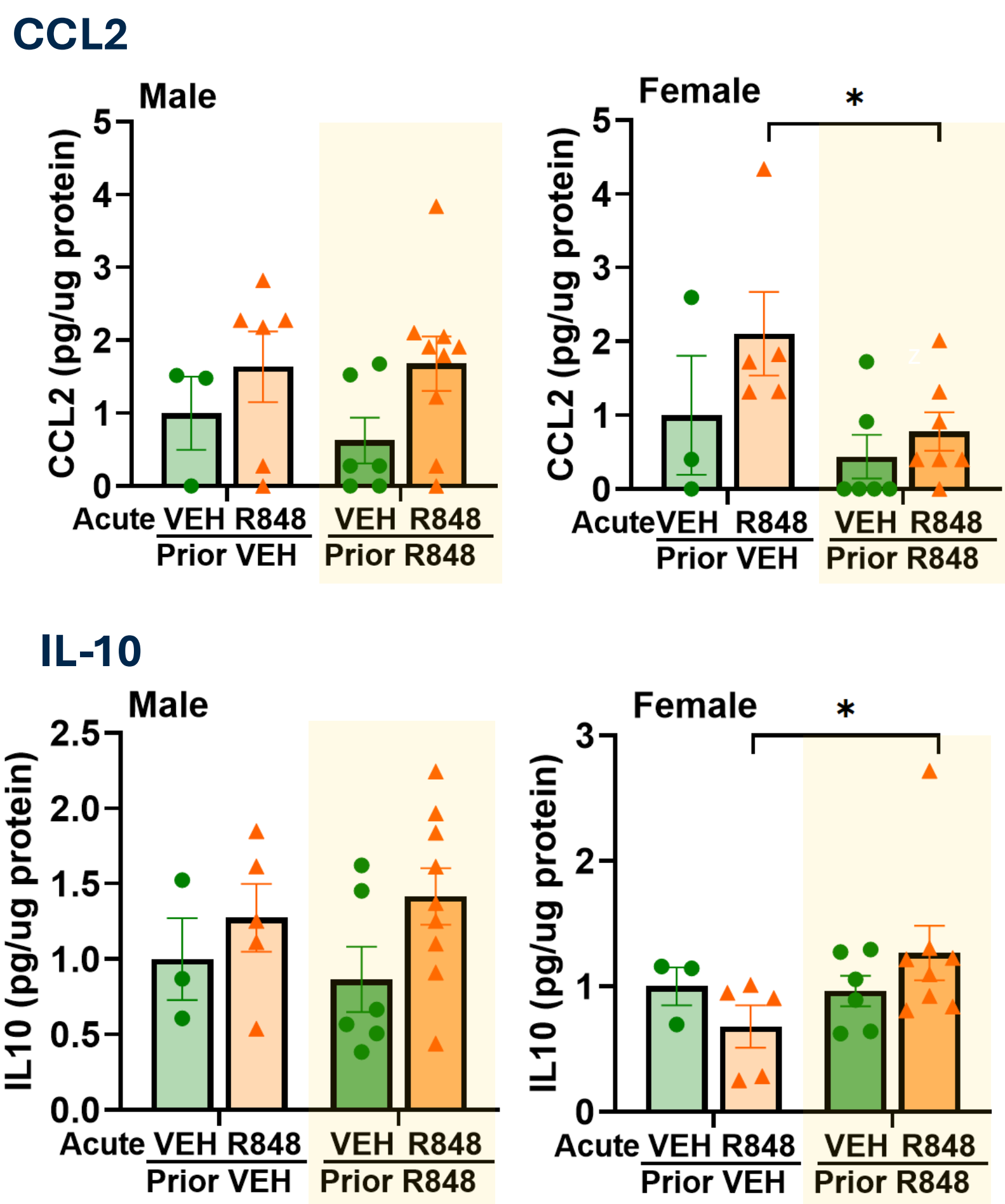


BEHAVIORAL IMPAIRMENTS



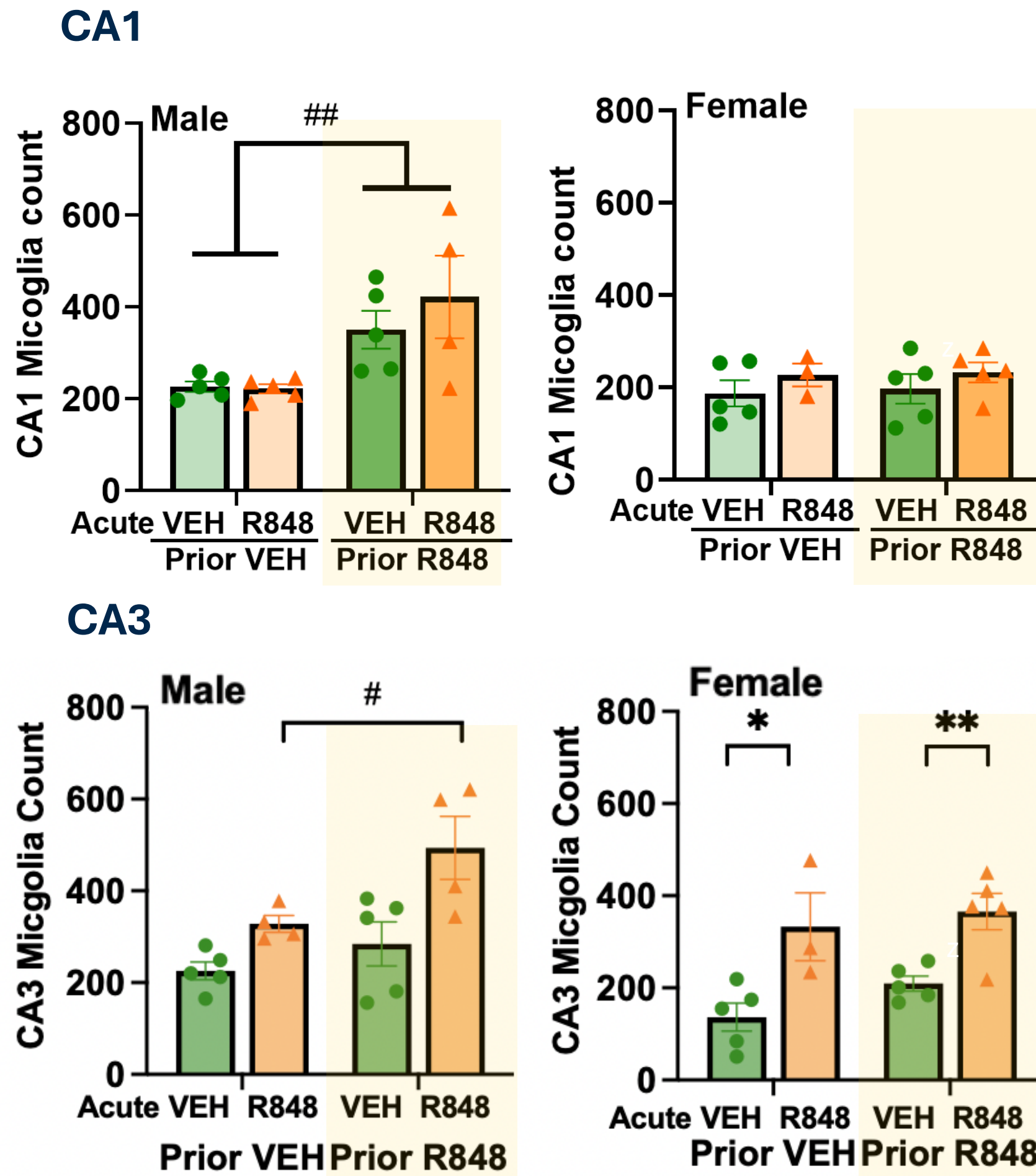
2 months after scR848, males and females show memory impairments. Both sexes show NOR deficits, Males show deficits in CFC. Males also show reduced sucrose preference suggesting persistent anhedonia-like effects.
*p < 0.05

HIPPOCAMPAL CYTOKINES



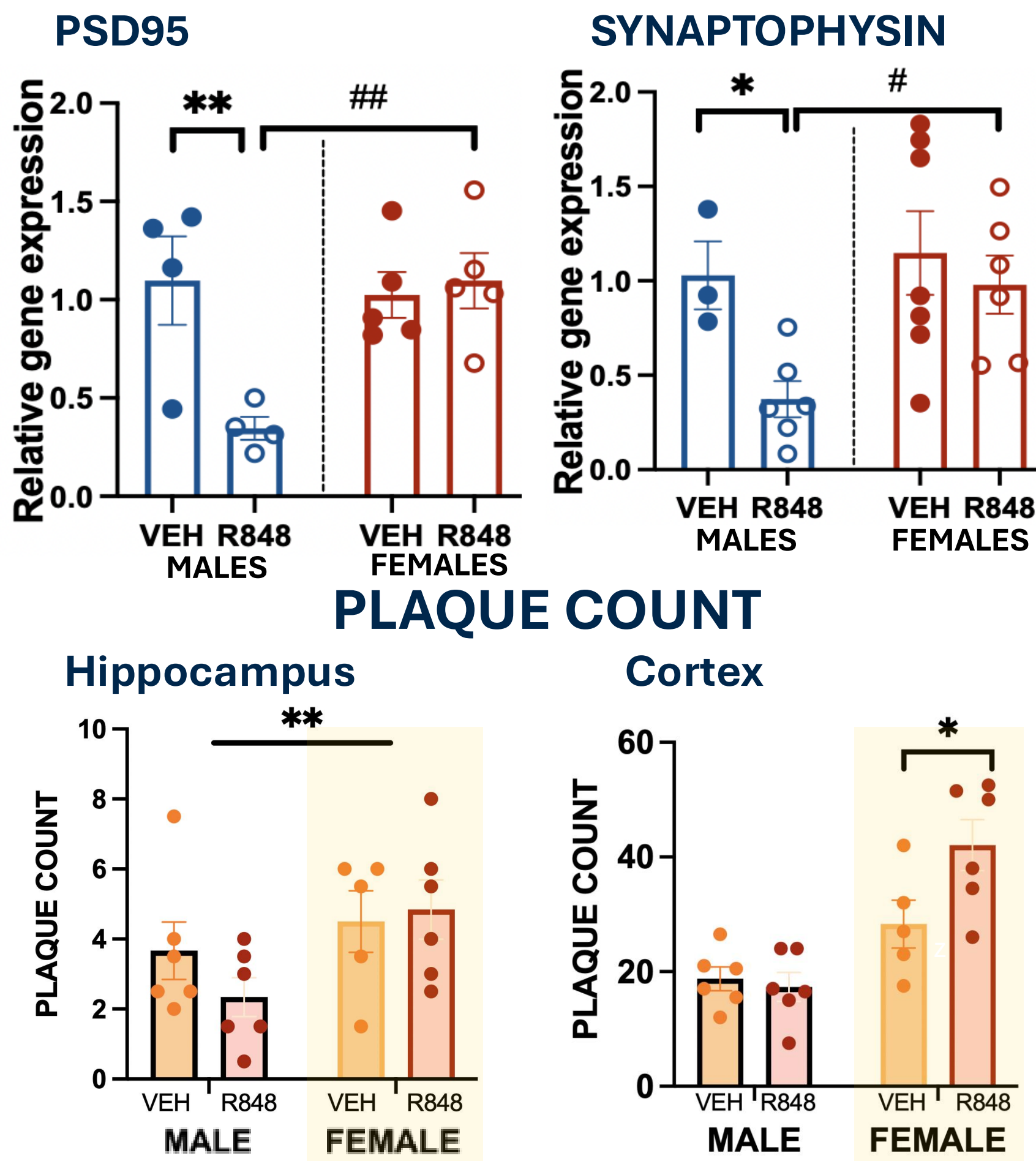
Across 32 cytokines, females but not males, show hippocampal cytokine reprogramming >2 months after scR84. Some cytokines (e.g., CCL2) show tolerance, others (e.g., IL-10) exhibit priming, many cytokines show no changes after scR848 and a subsequent acute challenge. *p < 0.05

MICROGLIA COUNT



Only males show sustained increase in microglia number after scR848 in CA1. In CA3, females show elevated microglia number after acute R848, whereas males show priming after scR848 + acute challenge.
*p < 0.05 cf veh; # p < 0.05, ## p < 0.01 cf prior VEH

SYNAPTIC MARKERS

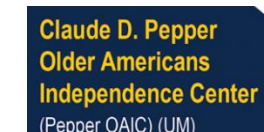


2 months after scR848, males, but not females, show decreased synaptic markers in dorsal hippocampus. In APP/PS1 mice, females but not males, show increased plaque deposition 2 months after scR848.
*p < 0.05 **p < 0.01; #p < 0.05, ##p < 0.01

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CONCLUSIONS

- Subchronic immune challenge during MIDLIFE contributes to cognitive decline in both sexes
- Males have broader effects, greater microglia priming, and more synaptic loss – But what contributes to cognitive decline in females?
- Females are more susceptible to plaque production – but how?

REFERENCES



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