

Inhaled ultrafine particulate matter affects microglial morphology and learning and memory behavior in an Alzheimer's disease mouse model

Inhaled Particles XII

Glasgow

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Alzheimer's Disease and Air Pollution

- Alzheimer's Disease (AD) is the 6th leading cause of death in the US
 - 1 in 9 Americans over 65 yrs of age have AD
- Most cases of AD occur after age 65 and are considered sporadic
 - Role of gene-environment interactions?
- Exposure to particulate air pollution induces lung and systemic inflammation
- Exposure to traffic-related pollution or PM_{2.5} is associated with increased incidence of AD

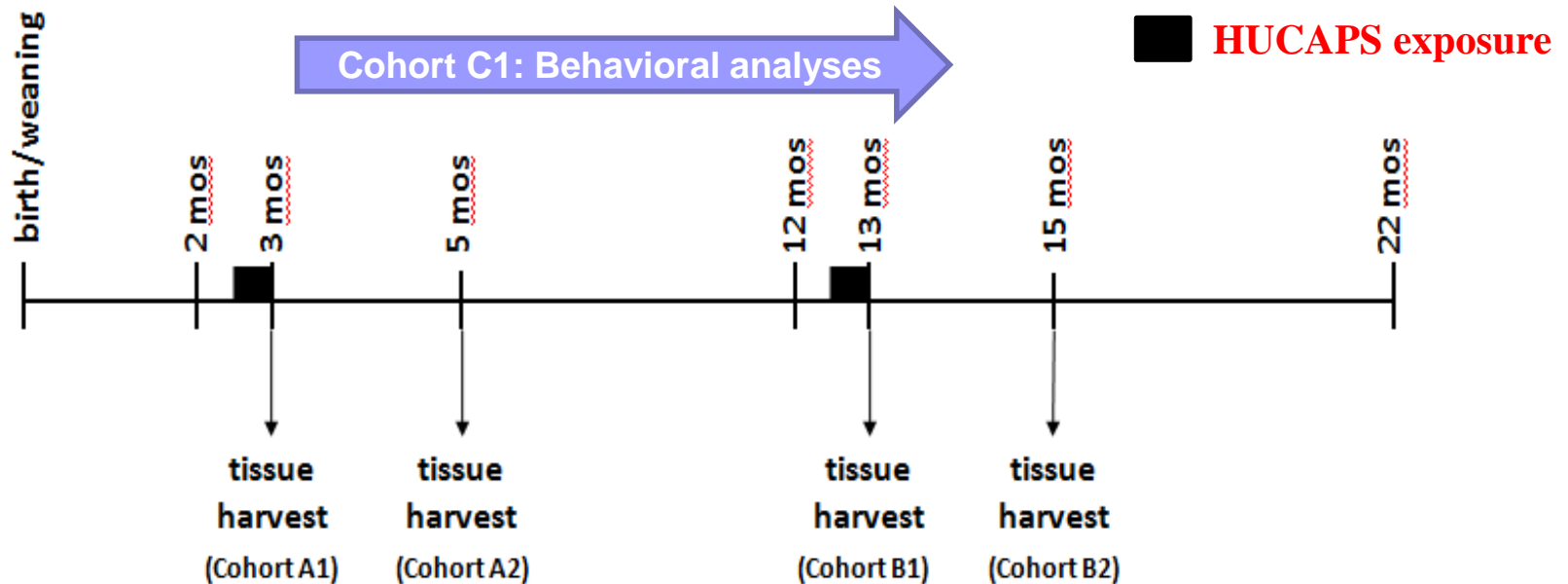
Hypothesis

Repeated ambient UFP exposure will cause chronic inflammatory changes in the brain that will affect the progression of AD-related pathology and memory deficits

Approach

- Use concentrated ambient ultrafine particles as a model of exposure to traffic-related air pollution
- Employ a mouse model of AD (3xTg-AD) that expresses hallmark pathologies of the human disease (age-dependent development of amyloid plaques and tau tangles)

Experimental Paradigm



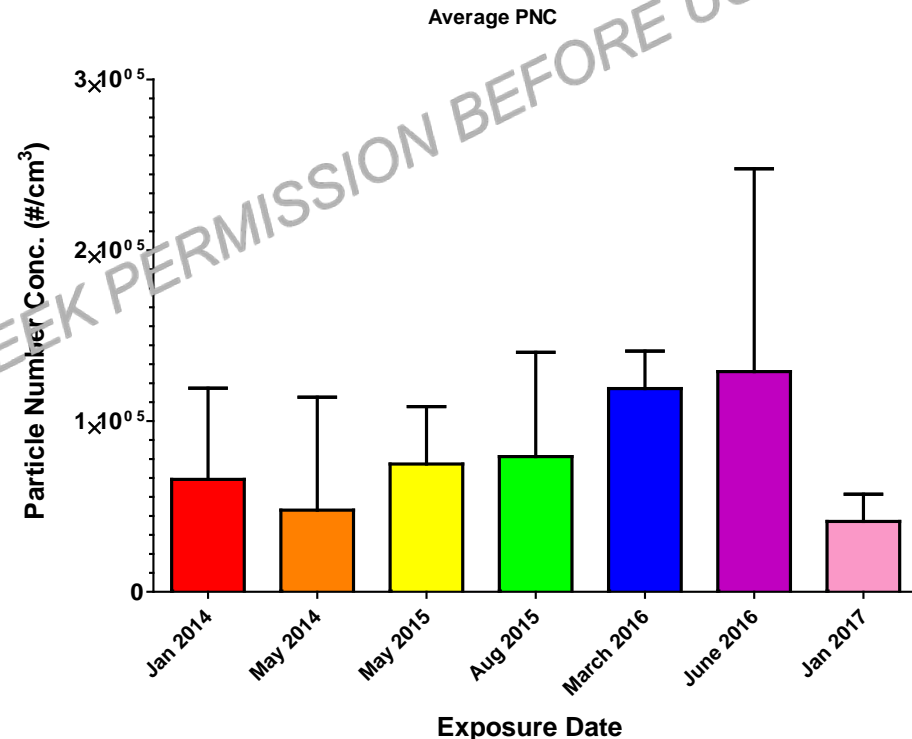
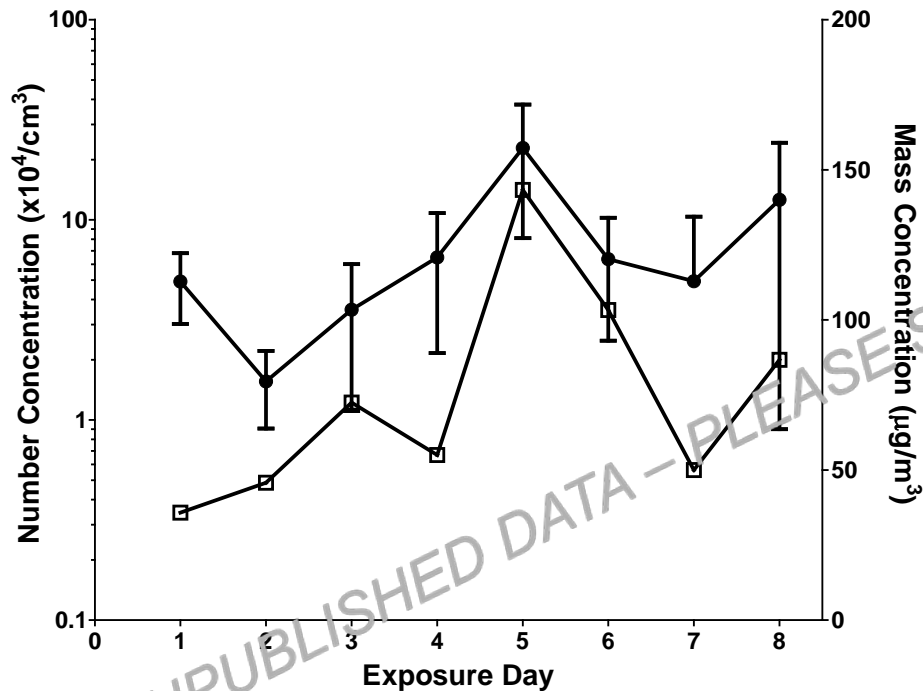
Focus of this talk is on **two** of the cohorts above:

- **C1:** Exposure at 2.5 months (before development of pathology), followed by behavioral testing through ~14 mos
- **B1:** Exposure at 12.5 months (after development of pathology) and immediate harvest

HUCAPS Exposures

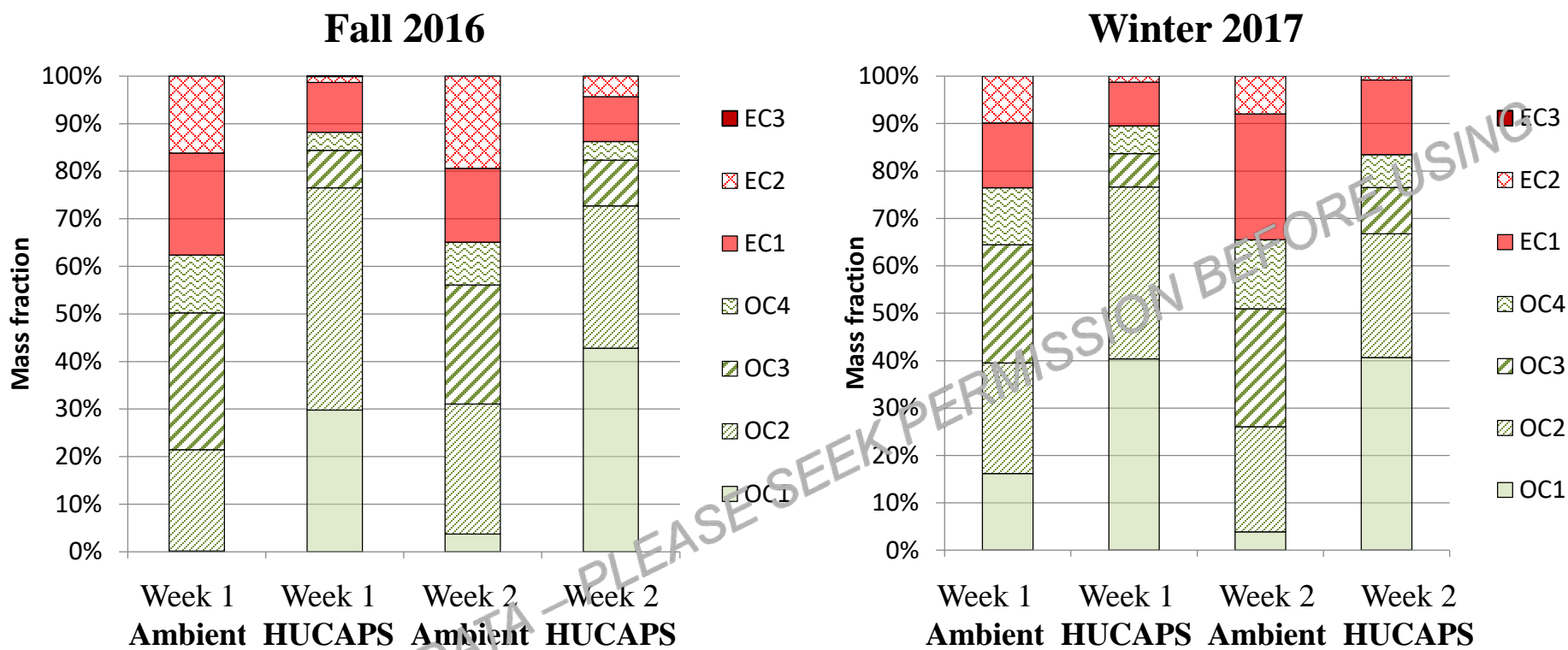
Harvard Ultrafine Concentrator of Ambient Particle System

□ Concentration factor is typically ~10 times ambient



- PNC range = $1.56 \times 10^4 - 2.29 \times 10^5/\text{cm}^3$
- Mass conc. range = $13.9 - 84.7 \mu\text{g}/\text{m}^3$
CMD ~70-90 nm

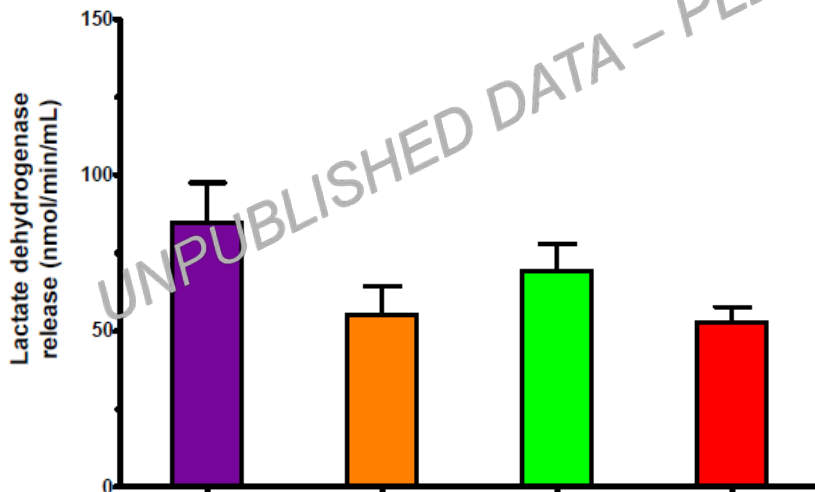
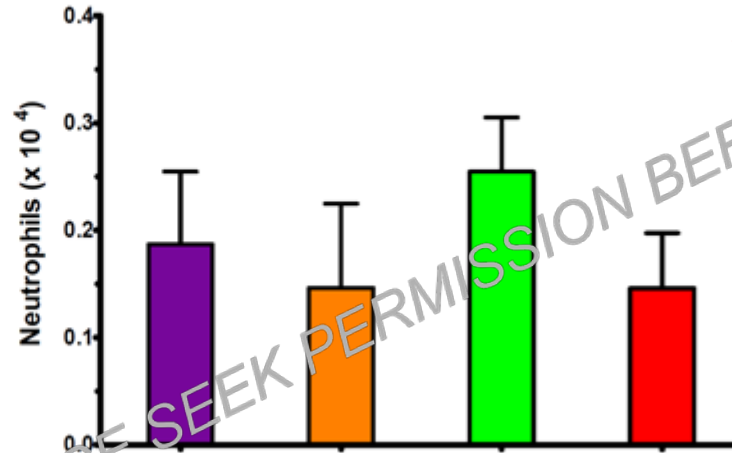
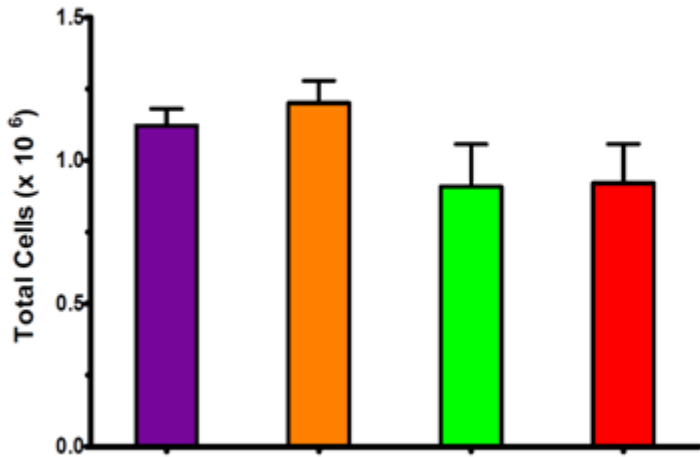
HUCAPS Chemical Composition



- The HUCAPS leads to strong enhancement in particulate organic mass in comparison to inorganic constituents.
- Indicators of fuel burning (S), wood smoke (K), and traffic (Na, Cu, Br; engine, brake, and tire wear) sources were concentrated by the HUCAPS.
- Some elements were neither concentrated nor enriched and some were depleted in the HUCAPS, e.g. Si, Fe.

Inflammatory state of the lung following HUCAPS exposure

NTg filtered air
NTg HUCAPS
3xTgAD filtered air
3xTgAD HUCAPS

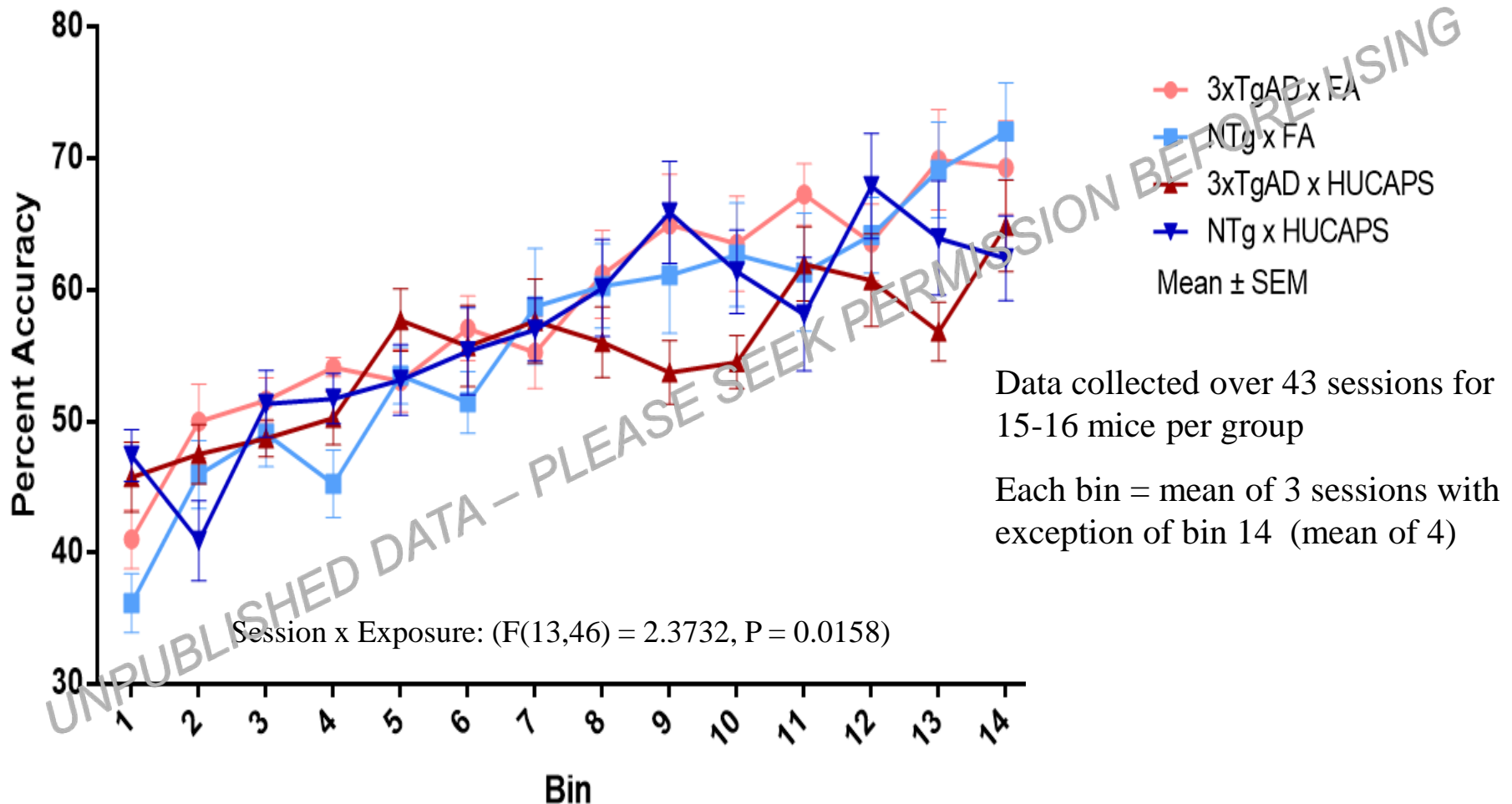


13-14 mo mice

Means \pm SEM (n=4-5)

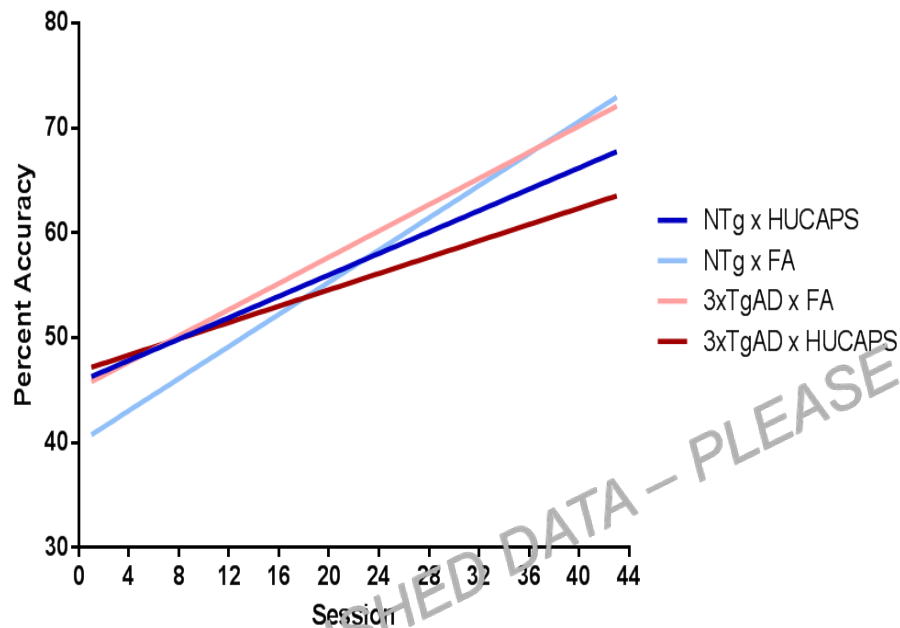
No significant main effects or interactions

Radial Arm Maze Testing (8 armed test of spatial learning and memory, hippocampus-dependent)

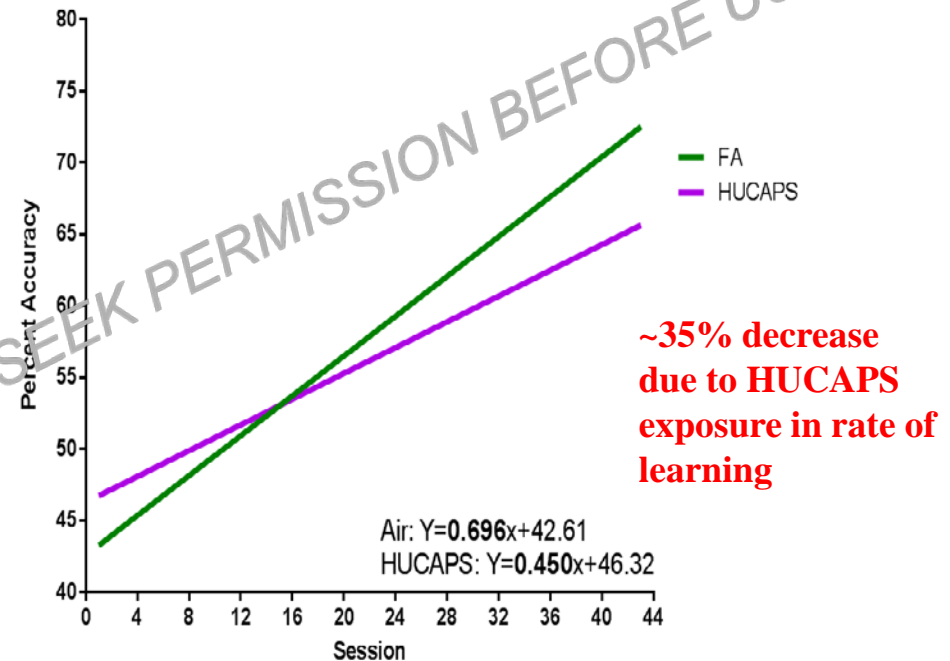


8 Armed Radial Arm Maze: Reference Memory (non-baited incorrect entries)

Average Performance



Summary by Exposure

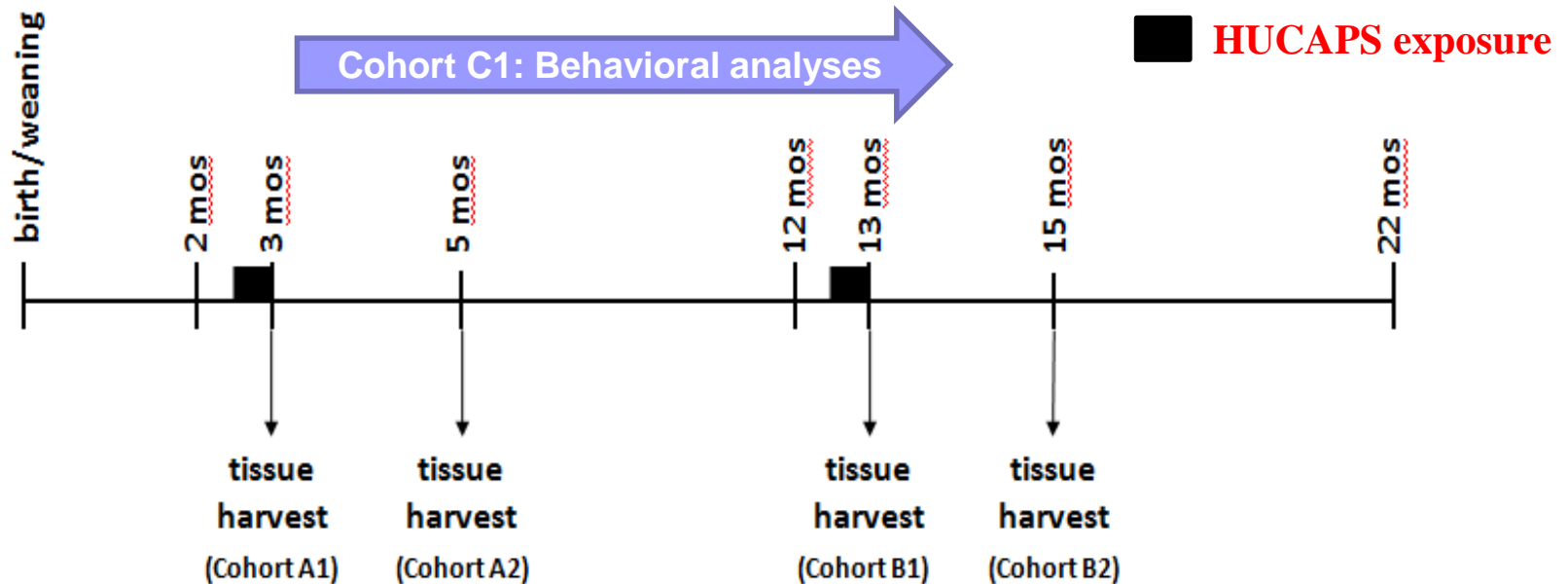


- Effect of treatment on the rate of learning (slope; $p = 0.012$), specifically in deficits in reference memory
- No deficits in working memory (re-entry errors)

Other Behavioral Tests

- Novel object recognition testing
 - Not strictly hippocampus-dependent
 - No significant main effects or interactions that impacted either: 1) time spent with or 2) approaches to the novel object
 - Mice do not demonstrate great preference for the novel object
- Locomotor activity (open field test)
 - Bin*genotype*treatment, $p = 0.0065$
 - Impact on RAM or NOR testing?

Experimental Paradigm



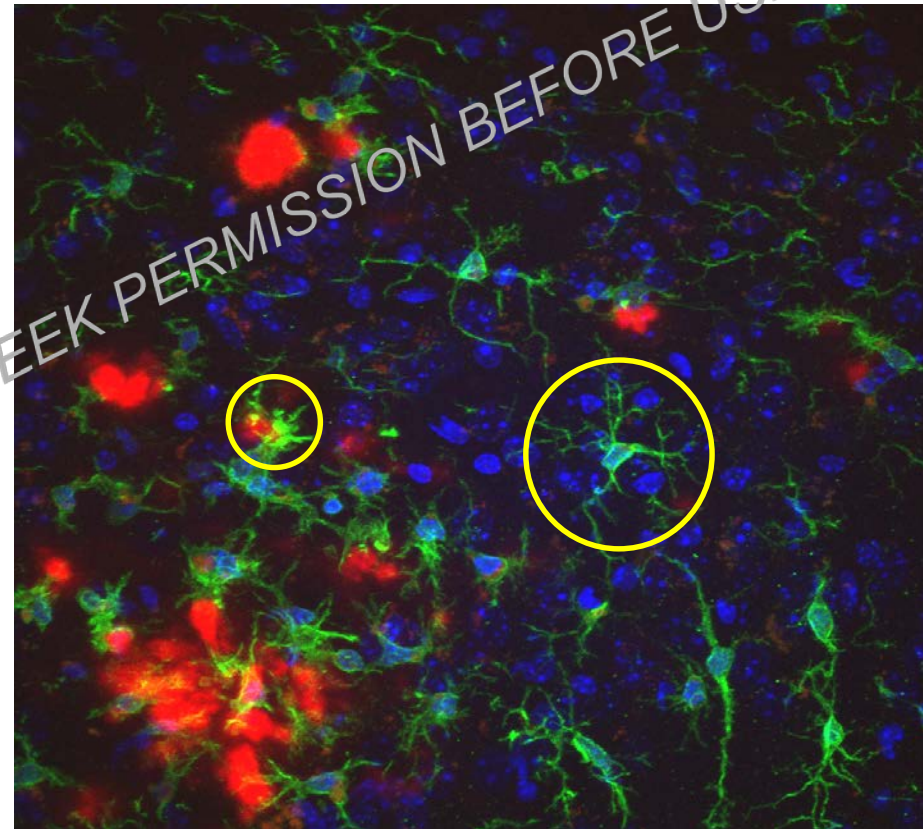
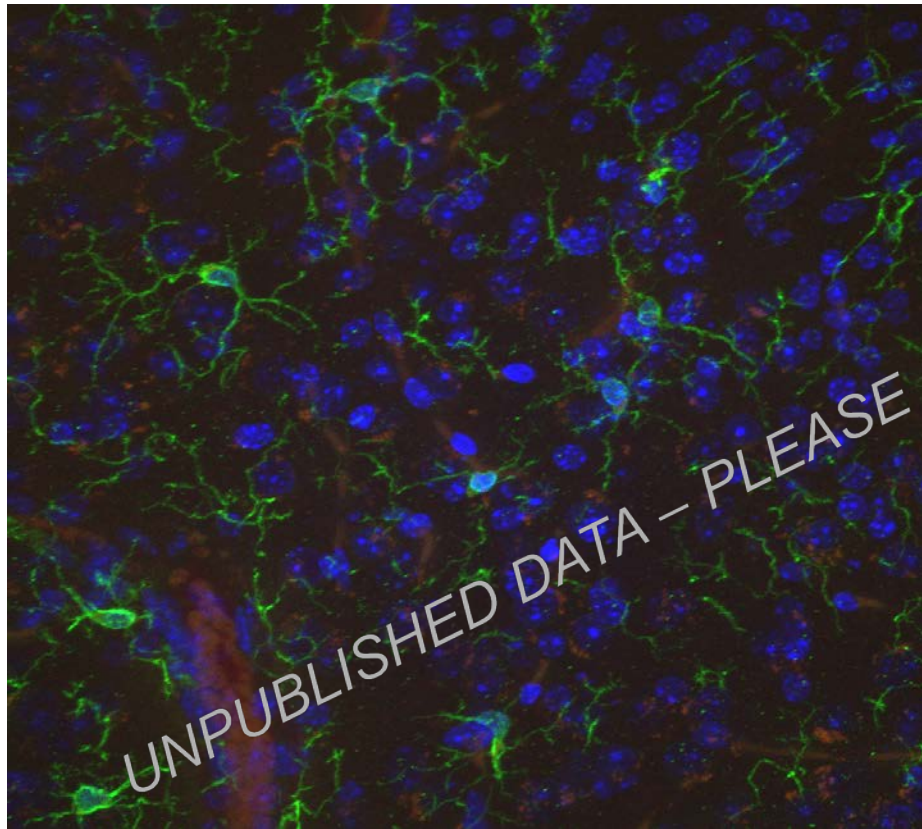
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Microglia-plaque interactions in HUCAPS-exposed 3xTgAD mice (subiculum)

NTg mouse

3xTgAD mouse (area with plaque deposition)



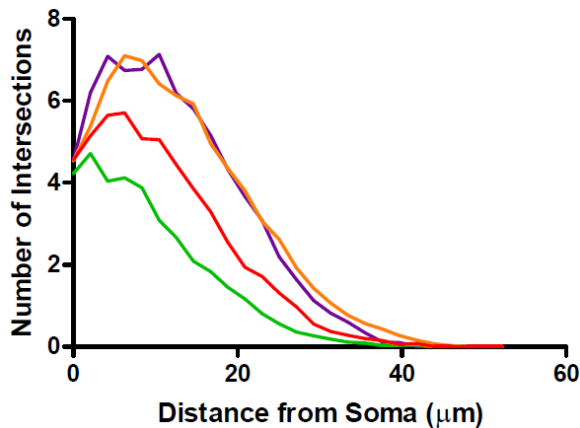
Blue: Hoechst (nuclei)

Green: Iba1 (microglia)

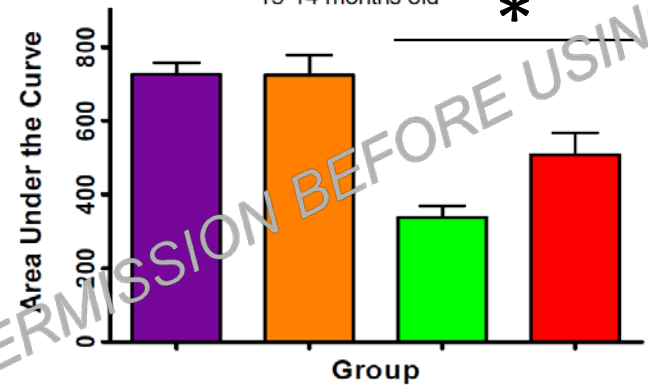
Red: Congo Red (fibrillar plaques)

Microglial morphology changes in HUCAPS-exposed mice (13-14 months old)

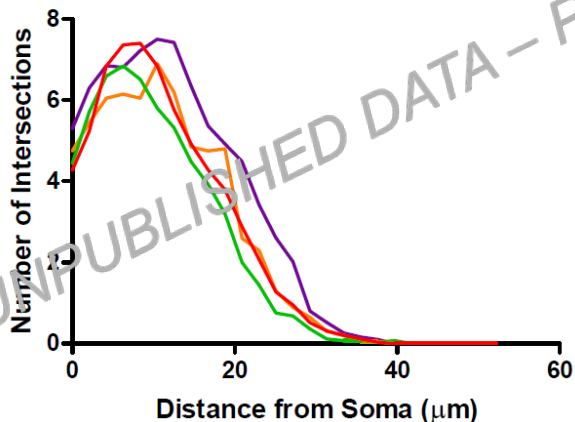
Sholl Analysis Subiculum



Subiculum
13-14 months old



Sholl Analysis Cortex




NTg FA
NTg HUCAPS
3xTgAD FA
3xTgAD HUCAPS

3xTgAD HUCAPS phenotype
closer to that of NTg mice

* No plaque pathology in the cortex

Conclusions

- HUCAPS-exposed mice have deficits in hippocampal-dependent reference memory.
- HUCAPS exposure causes a change in morphology of plaque-associated hippocampal microglia from 3xTgAD mice.
- These effects occur in the absence of overt lung inflammation.



2-week exposures at particle number concentrations that occur in large cities

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