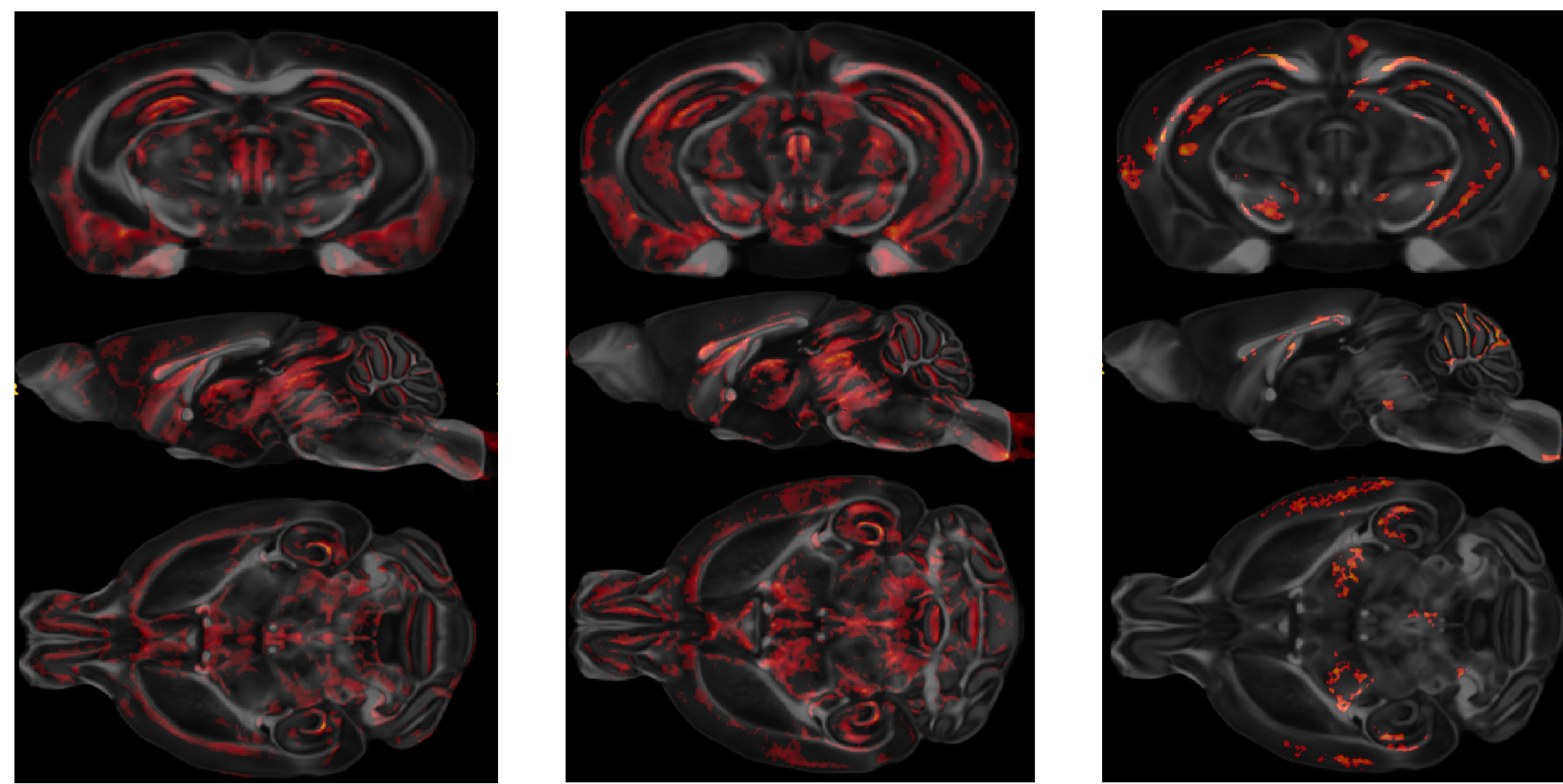


## Introduction

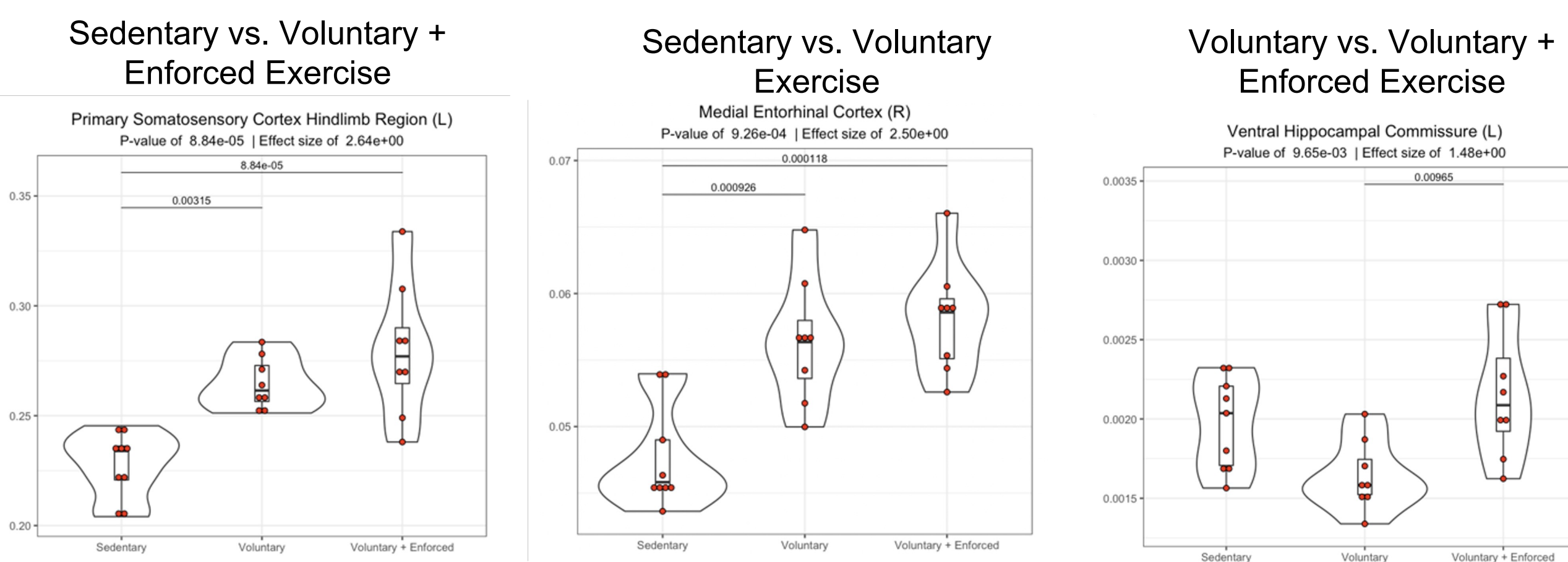
- Alzheimer's Disease (AD) is the most common form of dementia worldwide, and impacts 6.5 million people within the US today.
- There are two forms of Alzheimer's Disease: familiar and sporadic
  - Familiar AD was modeled with CVN mice
  - Sporadic AD was modeled with mice with homozygous targeted replacement of the murine APOE gene with human APOE which has been shown to confer different levels of risk
    - APOE2: confers protection against AD
    - APOE3: normal level of risk for AD
    - APOE4: greatest genetic risk for AD
- Females are at greater risk for AD, influenced by the loss of ovarian function during menopause and corresponding hormonal changes
  - Estrogens can reduce inflammation and increase neuroplasticity.
- Lifestyle factors such as a high fat diet linked to memory deficits.
- Exercise therapies have been shown to reduce neuroinflammation and increase neurogenesis.

## Exercise has positive effect sizes on brain structure and connectivity

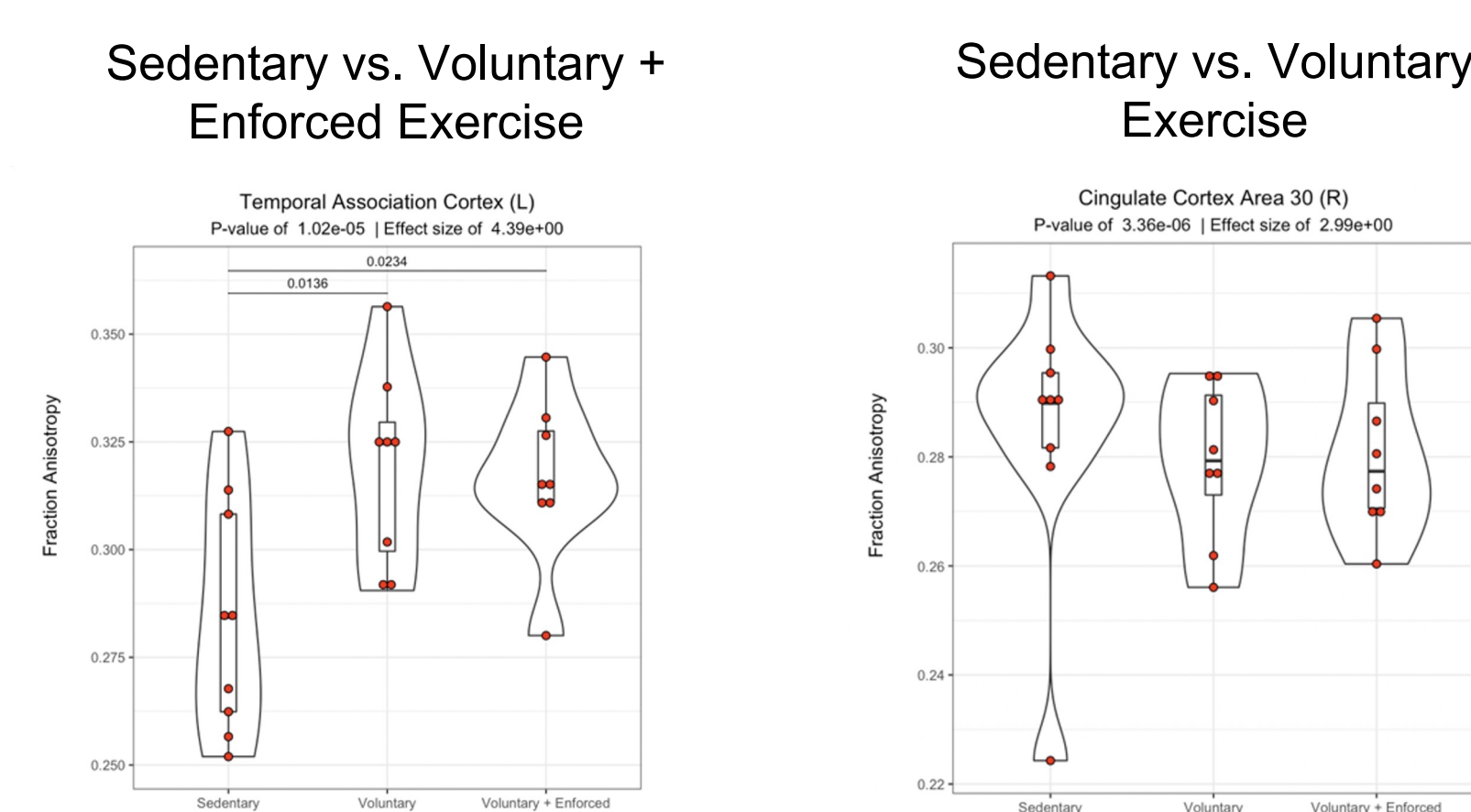


Voxel-Based Analysis (VBA) Fractional Anisotropy (FA) results for sedentary vs. voluntary exercise (left), sedentary vs. voluntary + enforced exercise (middle), and voluntary vs. voluntary + enforced exercise (right) post-hoc comparison (positive effect size)

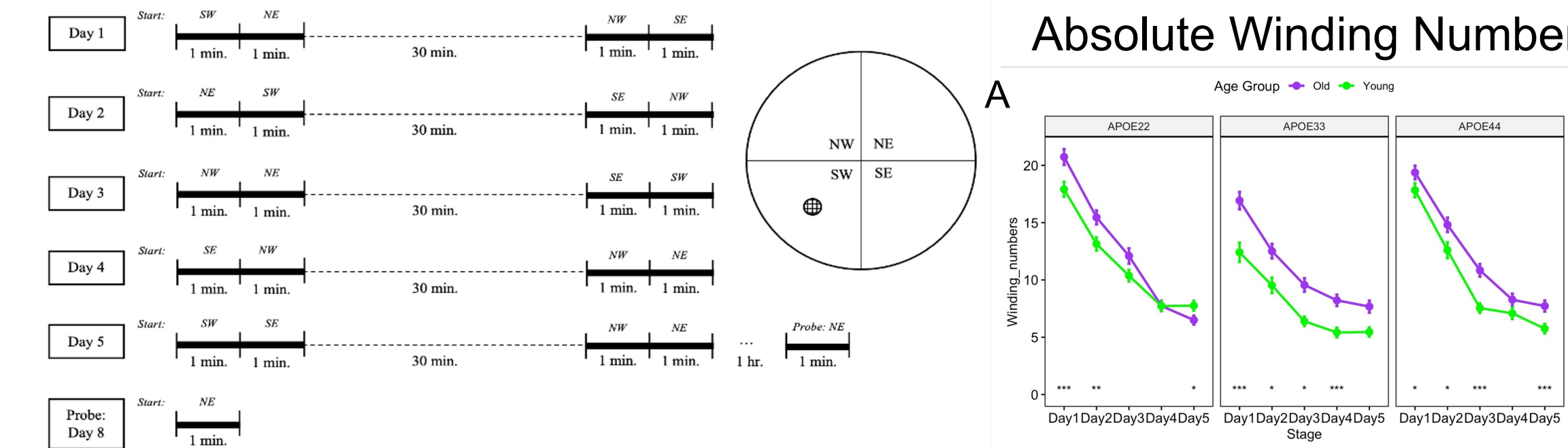
### Regional Volume Changes of Significance following Post-Hoc Analysis (Positive Effect Size)



### Regional FA Changes of Significance following Post-Hoc Analysis (Positive Effect Size)



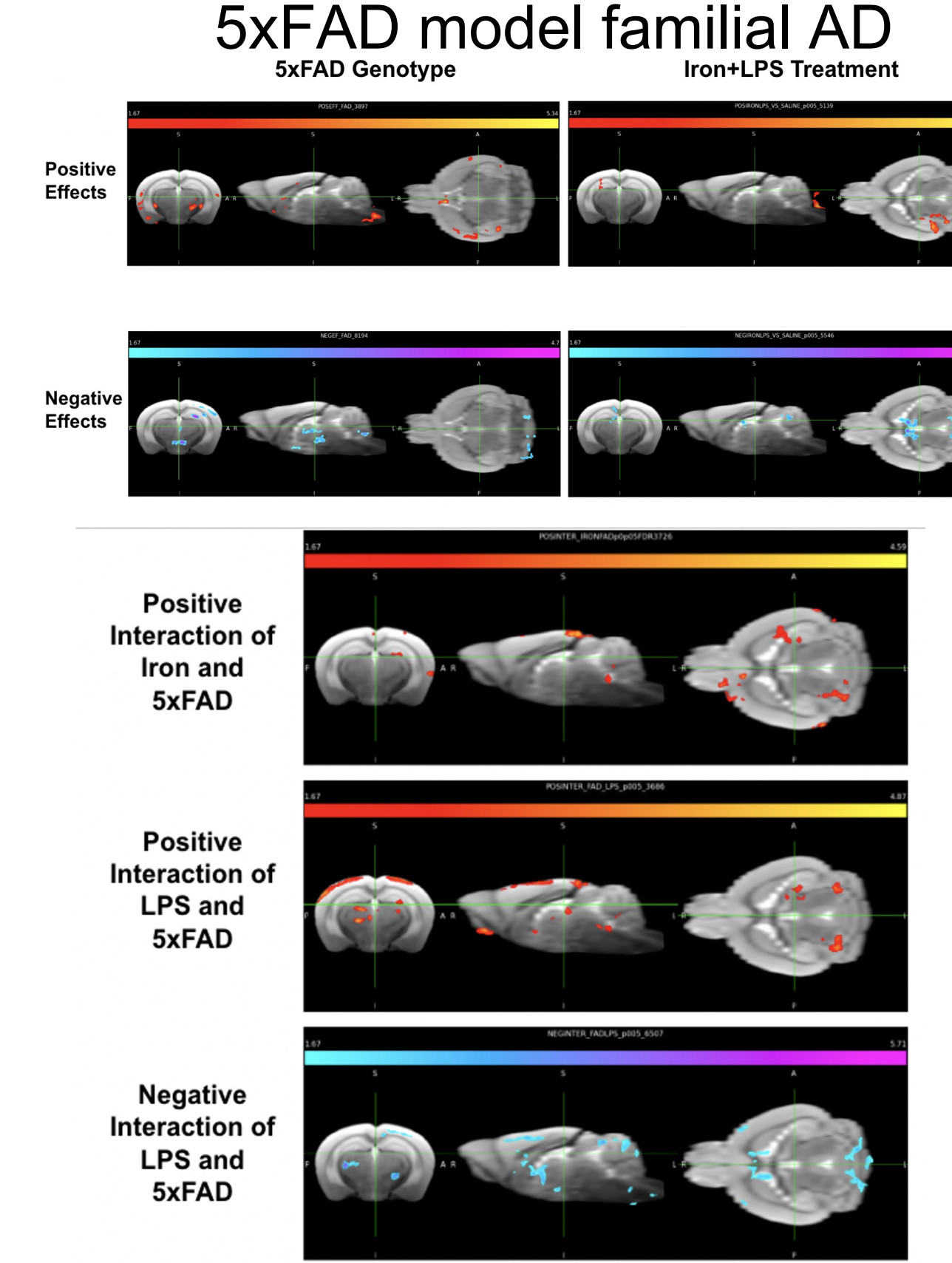
## Effect of age and diet in Morris water maze task in APOE model of AD



The Morris water maze task evaluates **spatial learning and memory**. Absolute winding number characterizes the swim trajectory.

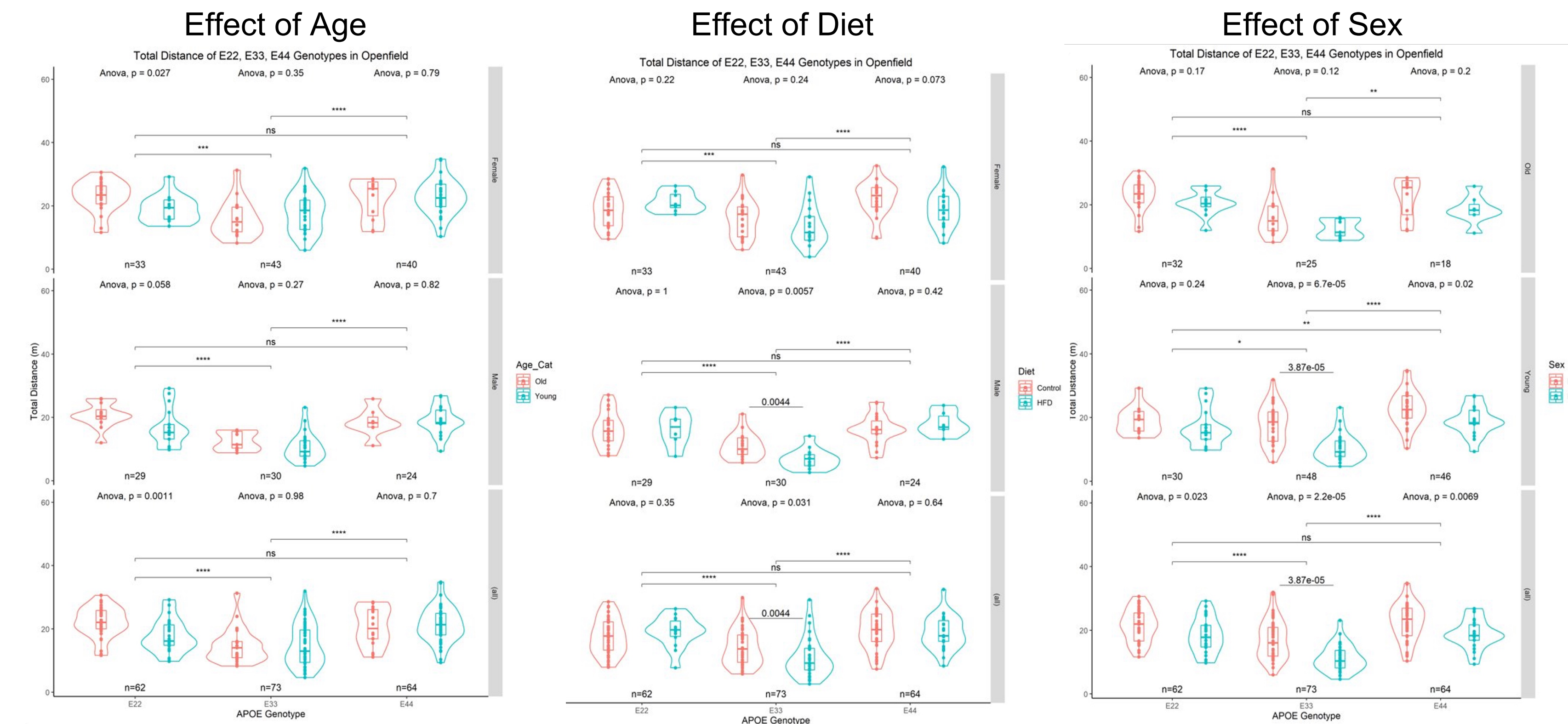
- Significant **effect of age** with the younger mice performing better than the older mice, as expected (Figure A).
- Significant **effect of diet** with mice on the control diet performing better than the mice on a high fat diet, as expected (Figure B).
- No effect of sex, likely because menopause was not induced in this mouse model (Figure C).

## Effect of treatment on 5xFAD model



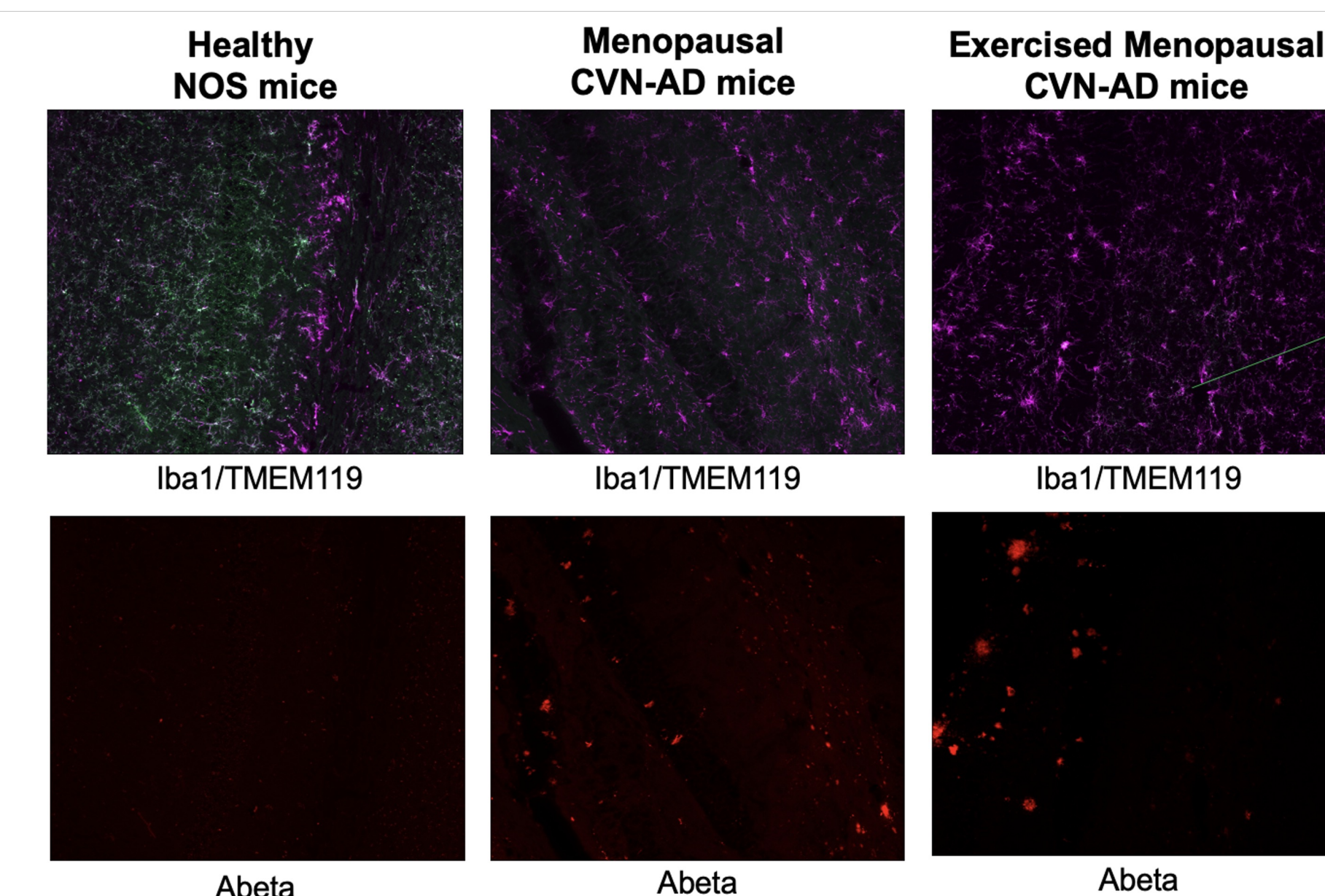
Differences in effects for 5xFAD vs. Wild Type genotypes as well as Iron+LPs vs. Saline Treatments

## Genotype, sex, and diet affect general activity levels



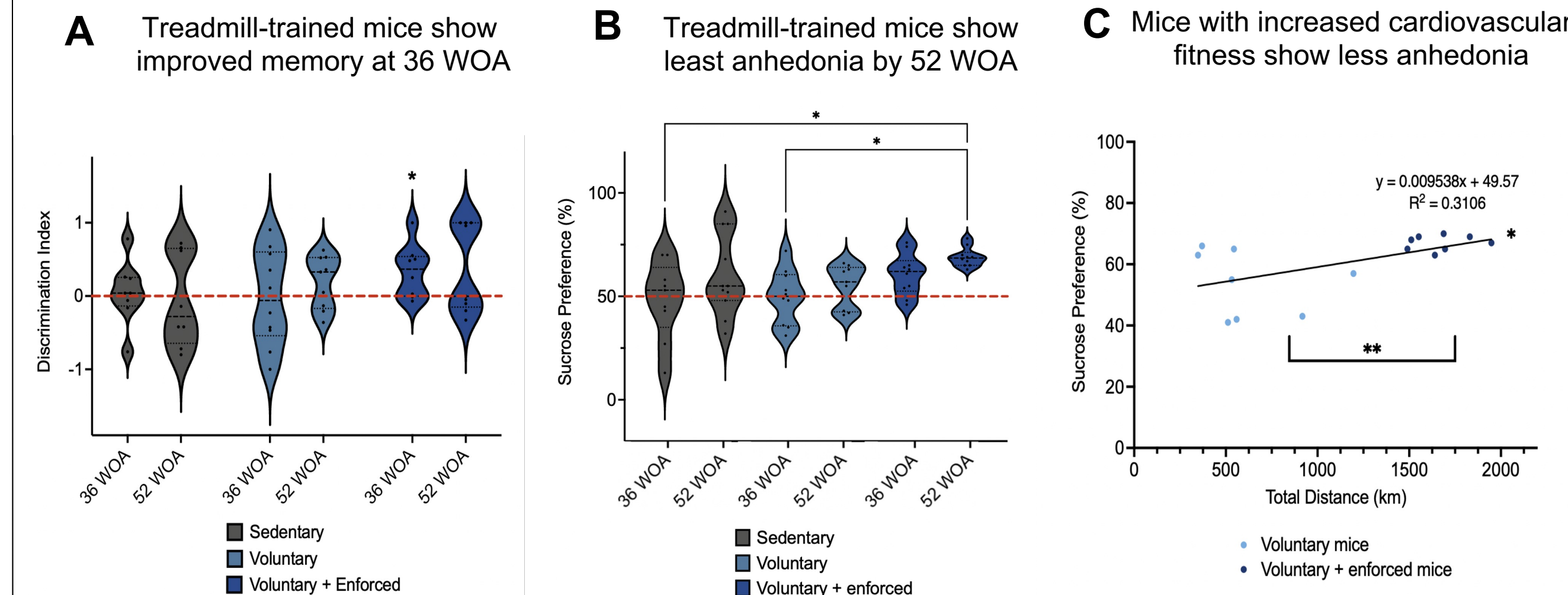
The Open Field task is a simple sensorimotor test used to determine general activity levels, gross locomotor activity, and exploration habits in rodent models. Significant effects were observed with sex, diet, and genotype in APOE model of AD.

## Exercise partially rescues microglia in CVN mice



- Iba1 (purple) is a general microglia stain.
- TMEM119 (green) only stains microglia in a homeostatic state.
- Disease-associated microglia that become dysfunctional due to Alzheimer's pathology may show significant reduction in homeostatic state.
- Menopausal AD mice tend to show no homeostatic microglial expression, while exercise treatment seems to partially rescue microglial functioning.
- This effect may be independent of effect on amyloid beta plaque (red) deposition.

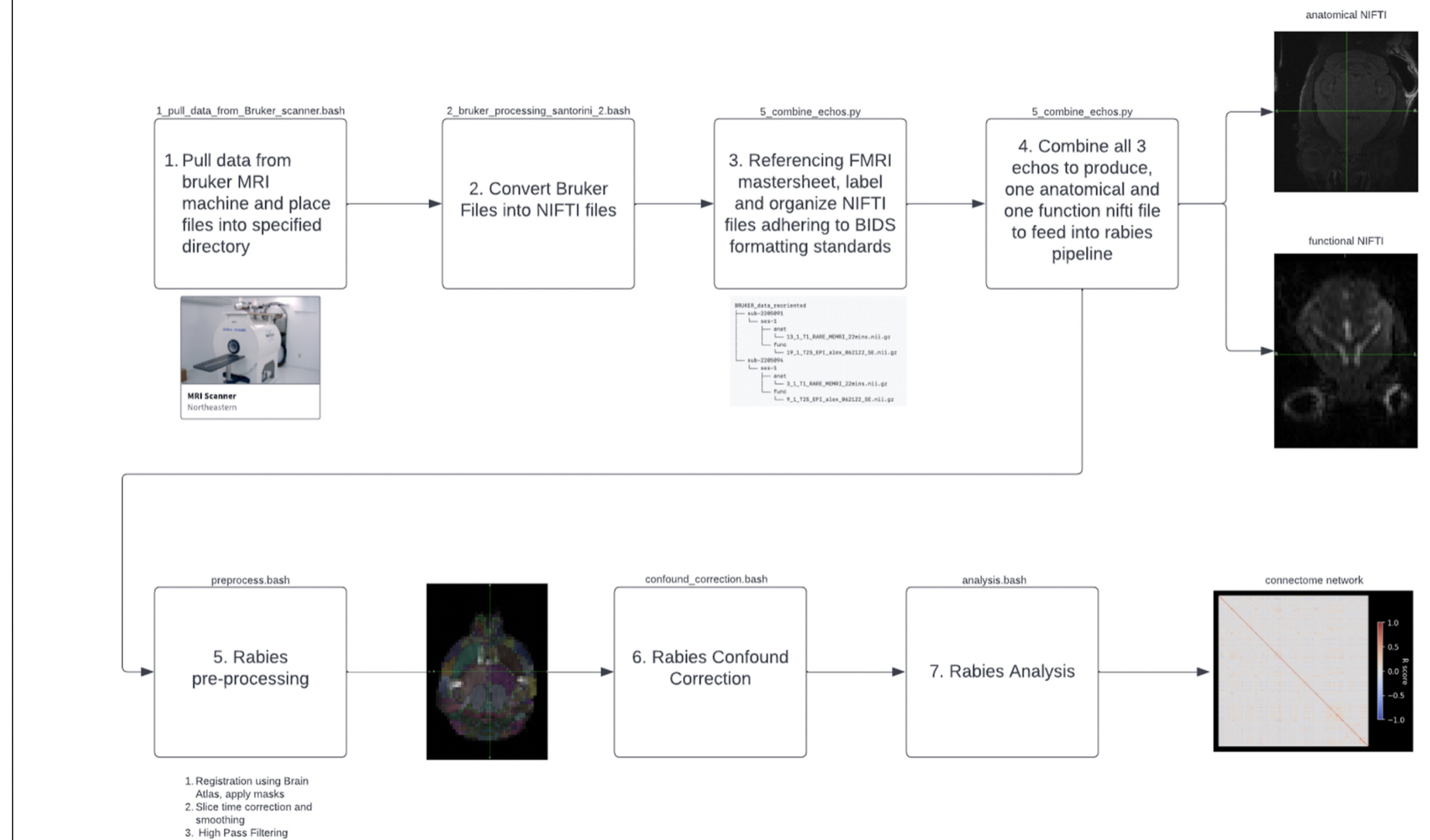
## High intensity exercise reduces memory deficits and anhedonia



Mice underwent either no exercise, voluntary wheel running, or voluntary wheel running as well as treadmill training.

- The treadmill-trained mice show **decreased memory deficits** (Figure A).
  - This increased cardiovascular activity condition was also best in **reducing anhedonia**, with a significant positive correlation between total amount of exercise and preference for sucrose (Figures B and C).
- Overall, the highest-intensity exercise condition was the best in reducing memory impairments and reducing anhedonia, two key symptoms of AD.

## Imaging the AD Brain



Process of obtaining connectomes from fMRI data

## Discussion

- An effect of age, diet, sex, and genotype was demonstrated in behavioral tasks, suggesting an impact on learning memory. The different components of learning and memory were evaluated with the use of behavior tasks, examining spatial and affective learning and memory as well as general activity.
- Brain structure and connectivity was also impacted by genotype and iron + LP versus saline treatment.
- We can compare functional connectomes from fMRI down to voxel level with fractional anisotropy used as a metric of tissue integrity and microstructural changes.
- Exercise can reduce behavioral symptoms and structural brain changes observed in AD
- The effects of AD are exacerbated through menopause, yet have been demonstrated to be mediated with exercise.

### Acknowledgements

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