

Sex-specific hypothalamic glucose metabolism defines divergent metabolic trajectories in Alzheimer's disease

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Alzheimer's disease drives sex-specific metabolic trajectories in the hypothalamus: females experience a precipitous collapse from a preserved prodromal state that might be due to impaired mitochondrial pyruvate metabolism, while males demonstrate metabolic resilience with a slower, more gradual decline and preserved neuronal mitochondrial pyruvate metabolism.

INTRODUCTION

Brain Glucose

Hypometabolism is a core biomarker of Alzheimer's disease (AD).

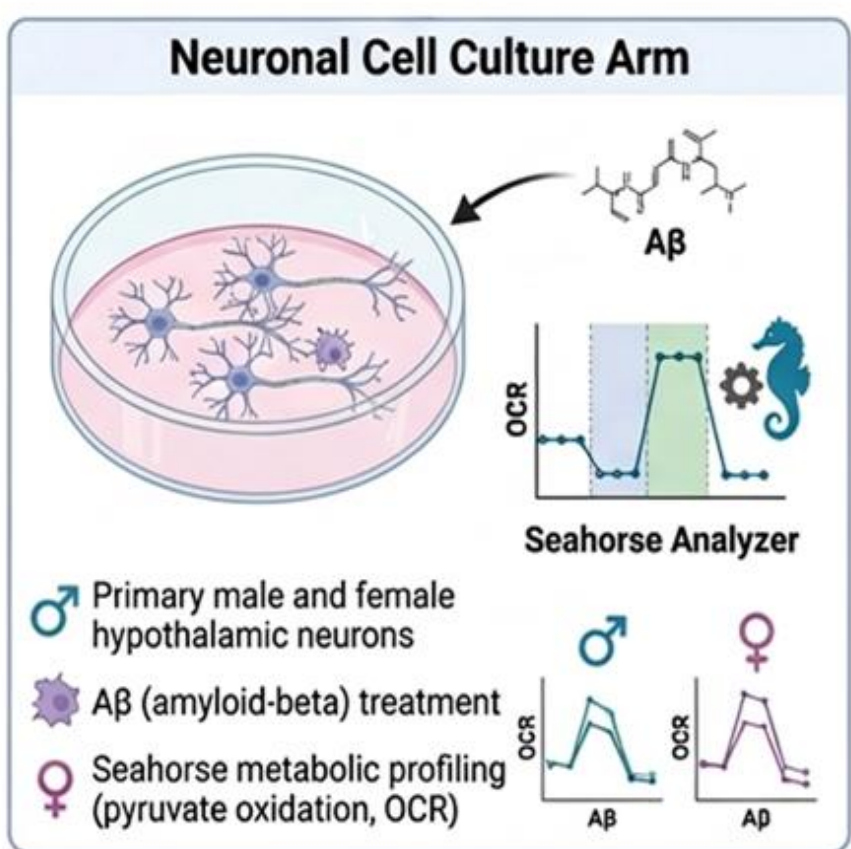
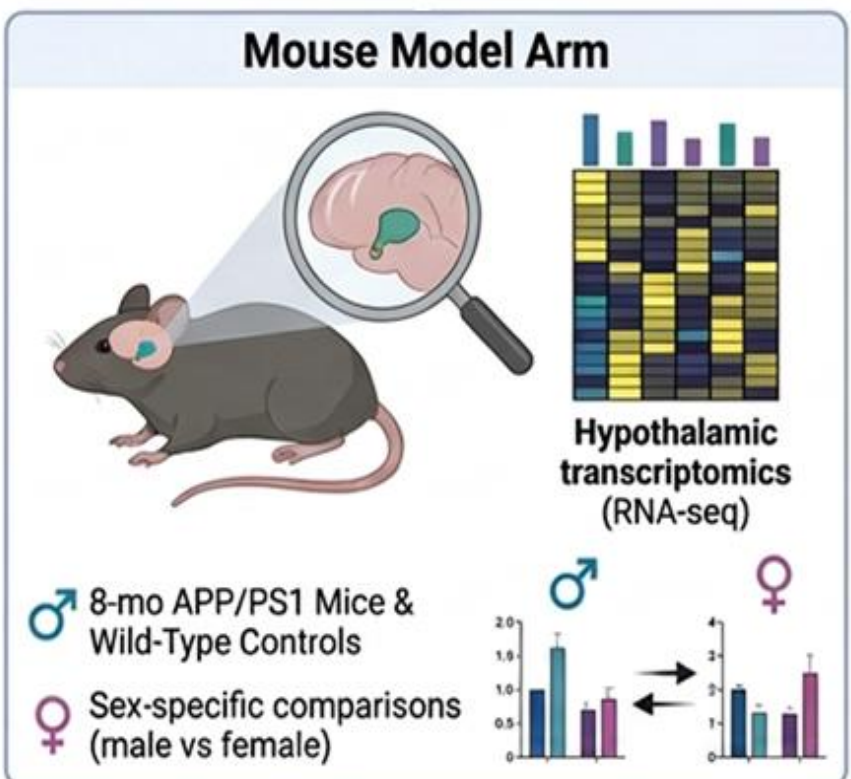
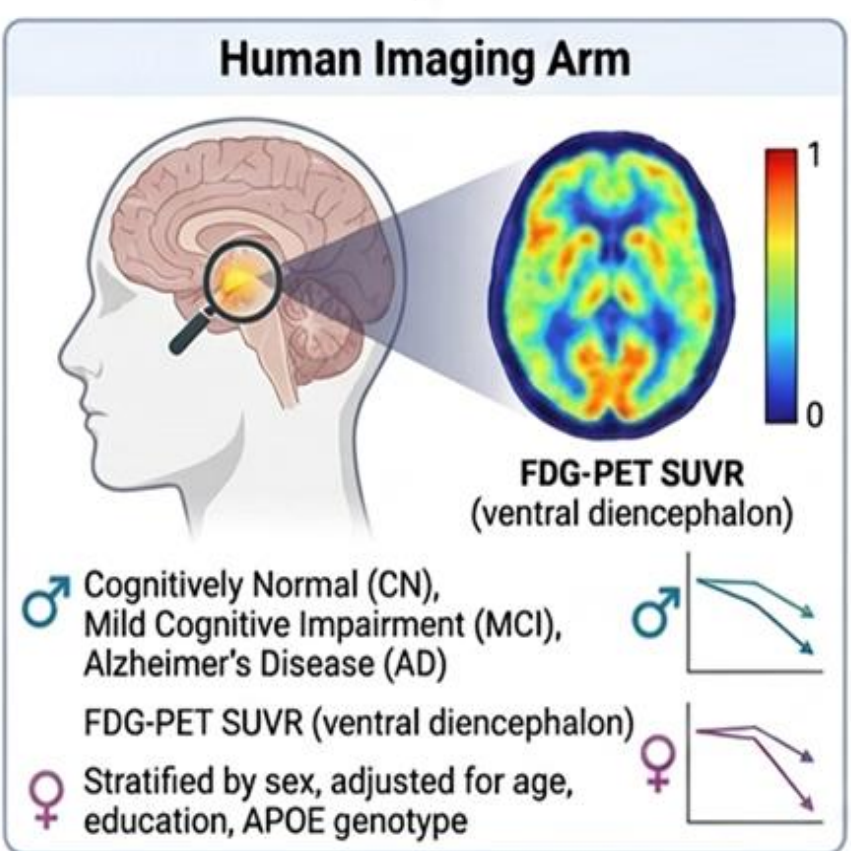
The **hypothalamus** is one of the earliest brain regions to show metabolic abnormalities in AD, yet its sex-specific metabolic vulnerability remains poorly understood.

Limitations of Prior Studies:

Previous FDG-PET research has primarily focused on cortical brain regions, rarely modeling sex-dependent metabolic trajectories or resolving the cellular mechanisms behind these imaging phenotypes.

Study Objective: This study investigates how male and female hypothalamic glucose metabolism diverges in response to AD pathology across human, animal, and cellular models.

METHODS



RESULTS

Hypothalamic FDG-PET shows a graded decline in men and an early preservation in MCI with a sharp decline to AD in women

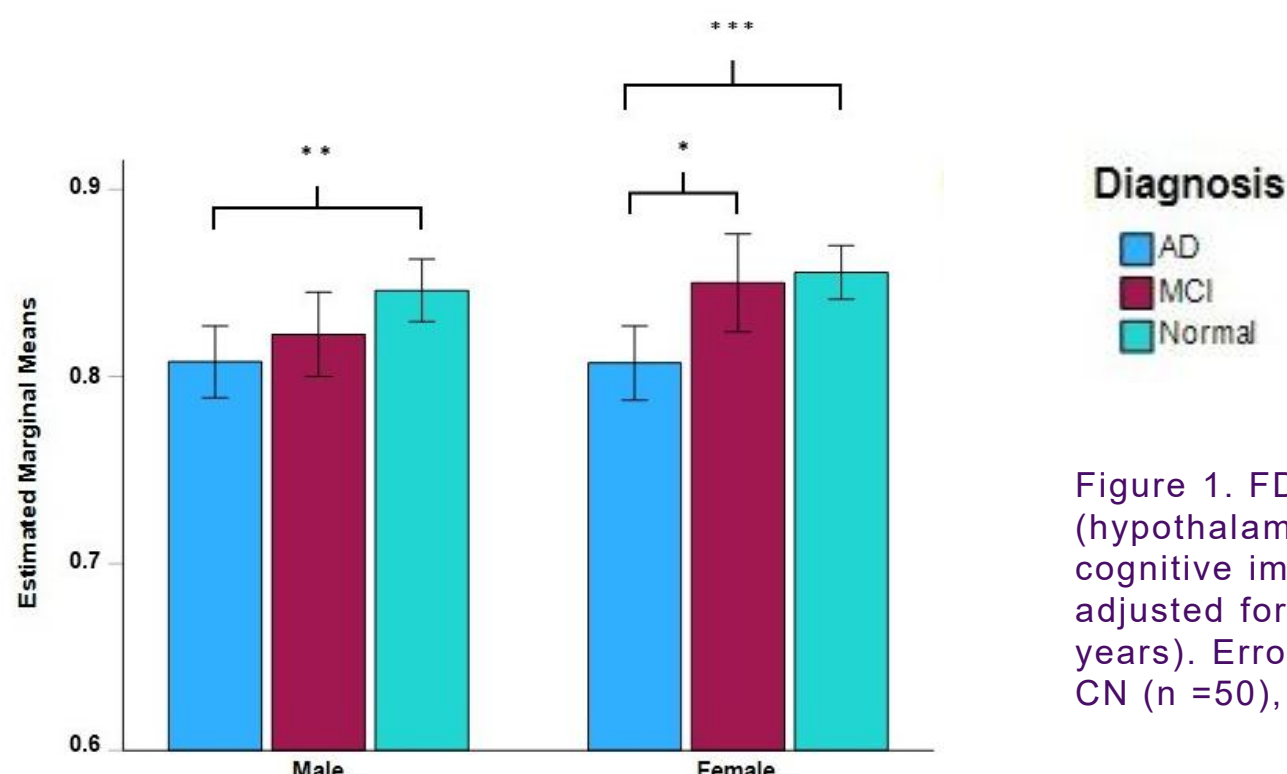


Figure 1. FDG-PET standardized uptake value ratio in the ventral diencephalon (hypothalamic region), normalized to whole cerebellum in cognitively normal, mild cognitive impairment, and Alzheimer's disease participants, stratified by sex and adjusted for age and education (mean age = 72.71 years; mean education = 16.40 years). Error bars represent +2 standard errors. *p<0.05, ** p<0.01, *** p<0.001. Men: CN (n =50), MCI (n =27), AD(n=37); Women: CN (n=67), MCI (n=20),AD (n=37).

Female AD mice showed a hypothalamic glycolytic transcriptional shift vs. male AD

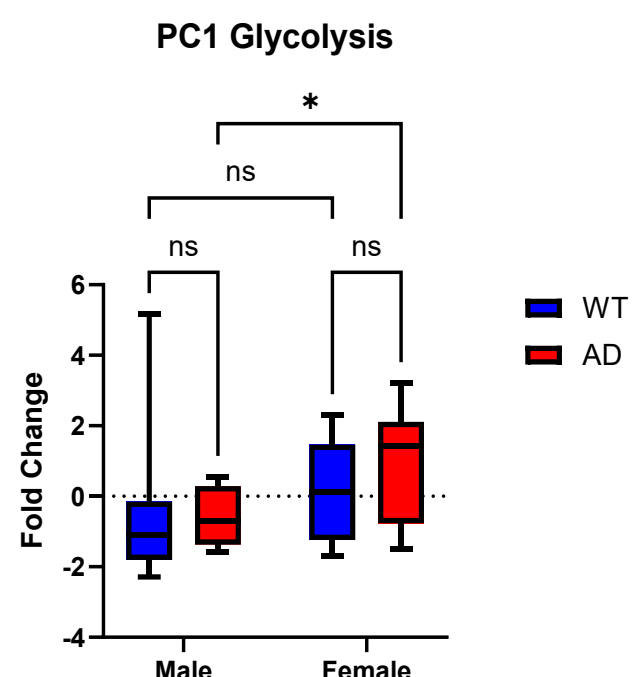


Figure 2. Box-and-whisker plots show fold-change in PC1 (glycolysis-related gene expression) derived from principal component analysis of hypothalamic transcriptomic data in 8-month-old APP/PS1 mice, stratified by sex. Data are expressed relative to WT males (dashed line at 0). * p < 0.05, n=10 per group.

Mitochondrial pyruvate oxidation is impaired in female but not male neurons in response to Aβ

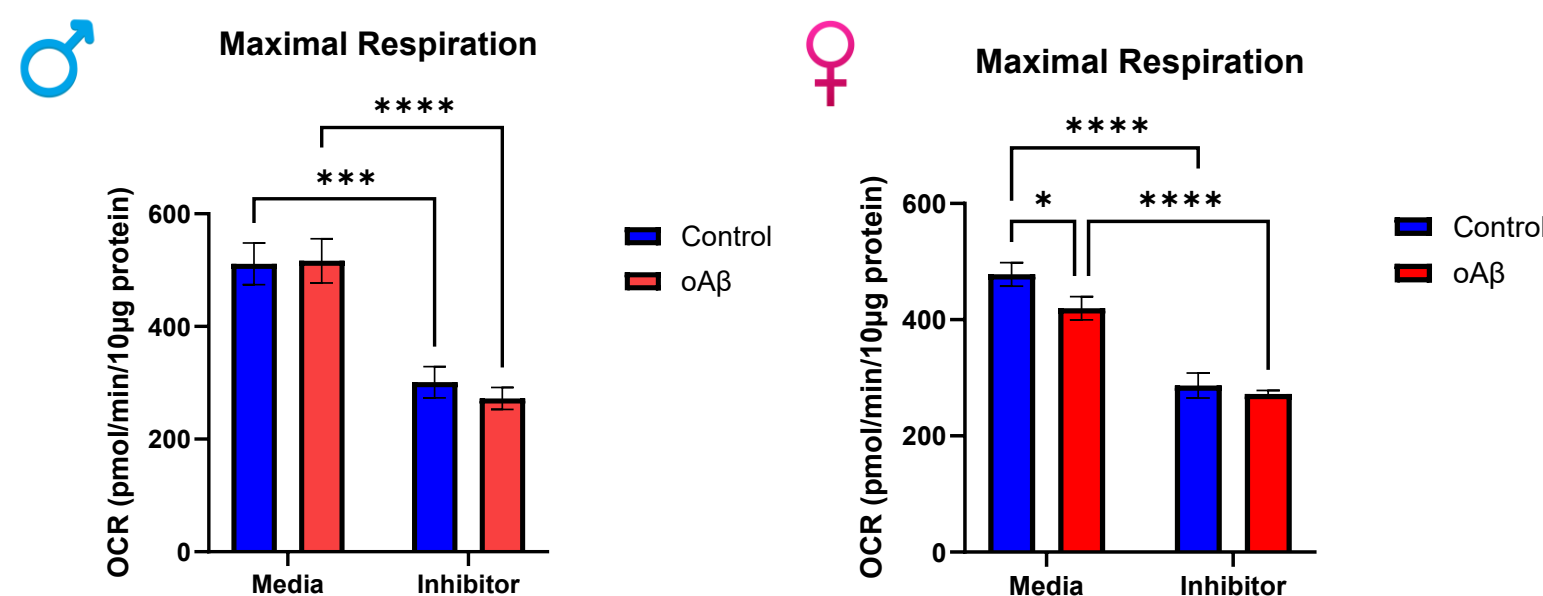


Figure 3. Maximal oxygen consumption rate (OCR), normalized to protein content, is shown for male (a) and female (b) mhypo-BMAL1 hypothalamic neuronal cells treated with vehicle (Control) or 5 μM oligomerized amyloid-β (oAβ) during a Seahorse pyruvate oxidation stress test. In response to oAβ exposure, male neurons maintained maximal respiration in the presence and absence of pyruvate inhibitor whereas female neurons exhibited a significant reduction in the absence but not presence of pyruvate inhibitor, indicating a female-specific OXPHOS reduction that is dependent on pyruvate oxidation. Data are presented as mean ± SEM. n=5 per group.

CONCLUSION

- The female hypothalamus transitions from prodromal preservation of glucose metabolism to a collapse with a decline in mitochondrial pyruvate catabolism and a compensatory glycolytic shift.
- The male hypothalamus shows a slower, regulated decline of glucose metabolism supported by preserved pyruvate metabolism.
- The hypothalamus can be a sex-specific therapeutic target, with the MCI-to-AD transition as a critical window for precision metabolic intervention.

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