

THE ROLE OF PTAU IN DRIVING NEURO-METABOLIC AND VASCULAR UNCOUPLING

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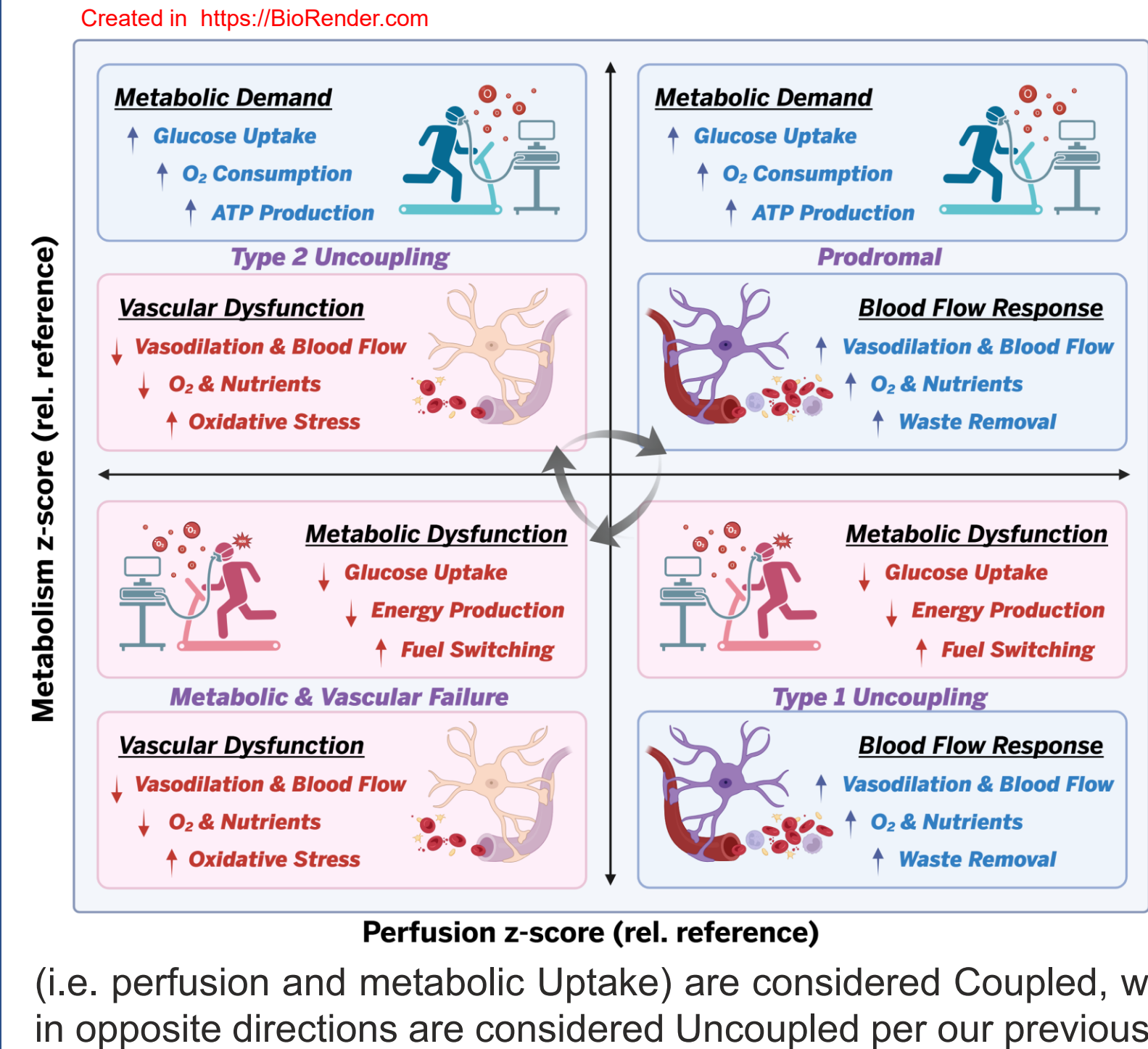
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BACKGROUND

Phosphorylated tau (pTau) is a major pathological hallmark of Alzheimer's disease (AD) and contributes to neurodegeneration [1]. Neuro-metabolic and vascular dysregulation (MVD) has been shown to occur before amyloid beta accumulation in both preclinically [2] and clinically [3] and is thought to contribute to AD disease progression. Evaluating the combined effects of MVD and pTau pathology may help establish mechanistic links between tau accumulation and vascular dysfunction. **Hypothesis: Accumulation of ptau triggers MVD through the disruption of cellular metabolism and vascular dysfunction, ultimately leading to progressive decline in AD.**

GRAPHICAL ABSTRACT



MATERIALS AND METHODS

PS19 Transgenic mice, which retain MAPT*P301S, were randomized by sex and genotype, and were assessed at 3, 6, and 9 months according to IUSM IACUC and ARRIVE guidelines [5]. At the aforementioned time points, the mice were imaged with [18F]-FDG to assess neuronal glucose metabolism and [64Cu]-PTSM to quantify cerebral perfusion, followed by image registration and segmentation. PET data are represented as z-scores relative to age-matched WT controls, per our previous methods [2,3]. After euthanasia, the hemi-brains were harvested for IFA and WB per our previous methods [2,3].

CONCLUSION

By reviewing our results, the mechanistic changes are significant across time, genotype, and sex. 3-Mos Het relative to WT displays Type 1 and Type 2 Uncoupling. 6-Mos Het relative to WT displays Type 2 and Prodrumal changes. 9-Mos Het relative to WT displays Prodrumal and Neurometabolic Failure, which is in line with our previous work in other mouse models and clinical populations, as indicated by our uncoupling and trajectory charts.

REFERENCES

- [1] Miao J et al. 2019 (10.3389/fnagi.2019.00034)
- [2] Onos KD et al. 2024 (10.1002/alz.13842)
- [3] J.K. Chong et al. 2025 (<https://doi.org/10.1002/alz.70790>)
- [4] Allen Institute for Brain Science. Allen Mouse Brain Atlas. <https://mouse.brain-map.org/>
- [5] Percie du Sert N, et al. PLoS Biol. 2020. DOI: 10.1371/journal.pbio.3000410

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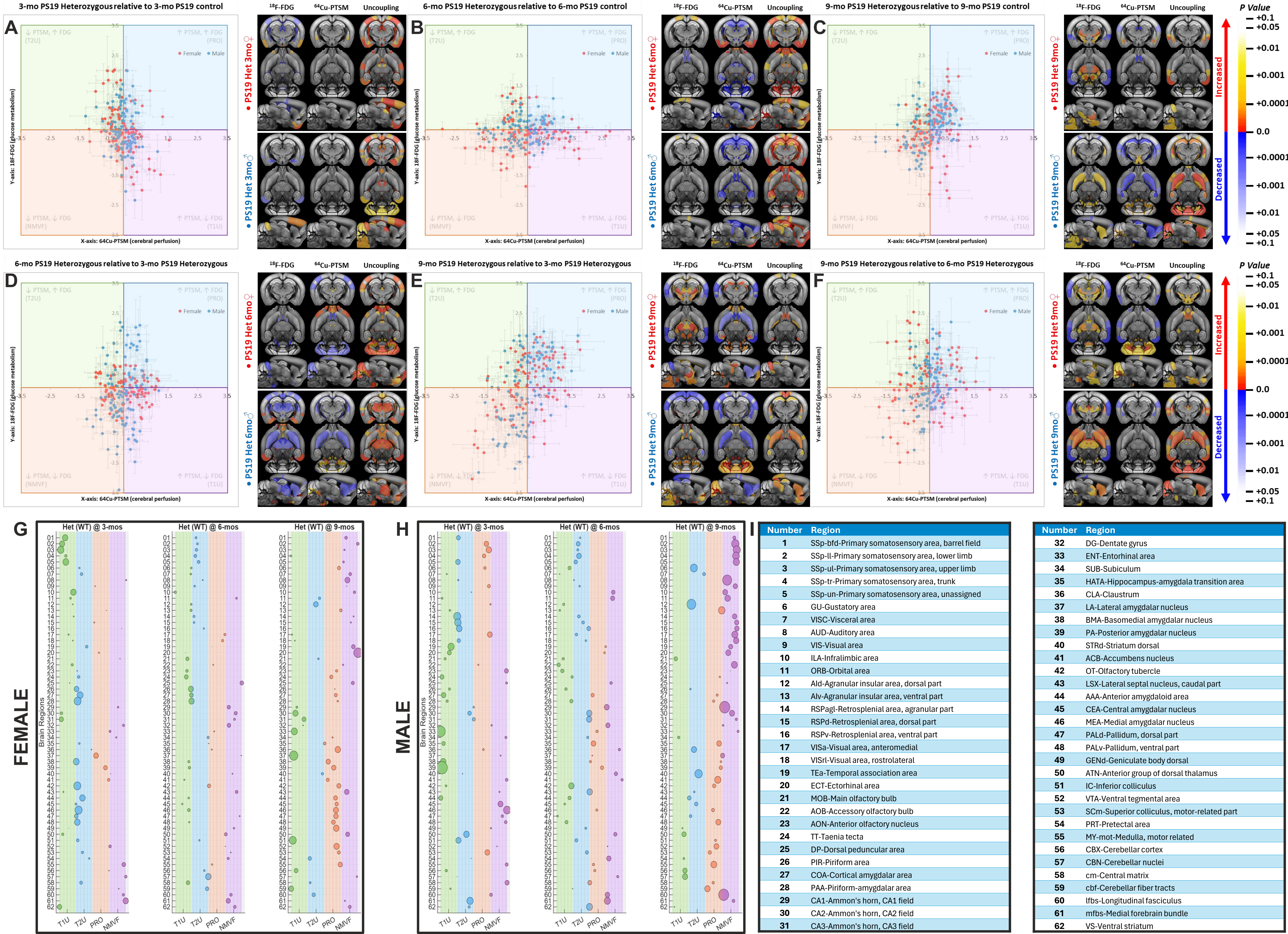
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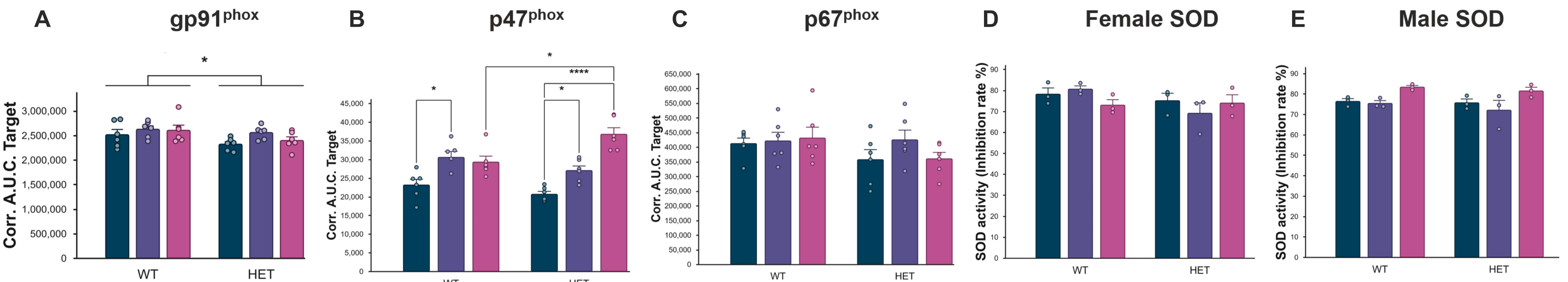
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