

Evaluation Of Central Tau Pathology Following Intraperitoneal Administration Of P301S-derived Brain Homogenates

Jesus Garcia-Martin¹, Laura Vegas-Gomez¹, Maria Angeles Arredondo-Alcala¹, Antonia Gutierrez^{1,2}, Ines Moreno-Gonzalez^{1,2,3}

¹Dept. Cell Biology, Faculty of Sciences, University of Malaga. IBIMA, Malaga, Spain. ²Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain. ³The University of Texas Health ScienceCenter at Houston, Houston, TX, USA.



Introduction

Alzheimer's disease (AD) progression has been closely linked to the **prion-like spreading of hyperphosphorylated tau (ptau)** along neural networks. While this central propagation has been widely studied, the potential for **peripheral ptau to drive CNS pathology** remains under investigation. Previous studies indicate that systemic administration of blood from tauopathy models exacerbates neurodegeneration; however, **it is unclear whether systemic exposure to other types of ptau-rich sources**, such as ptau-containing brain samples, **is sufficient to drive peripheral-to-central propagation**.

Methods

Subjects: PS19 line overexpresses the P301S mutant human microtubule-associated protein tau (MAPT).

BH inoculation: Intraperitoneal (i.p.) in 2-month-old mice, once a week for 3 weeks (150 µL).

Behavioral tests: Rotarod and Y-maze at 6 months.

IHC: Brain sections from 6-month-old mice were incubated with AT8 antibody.

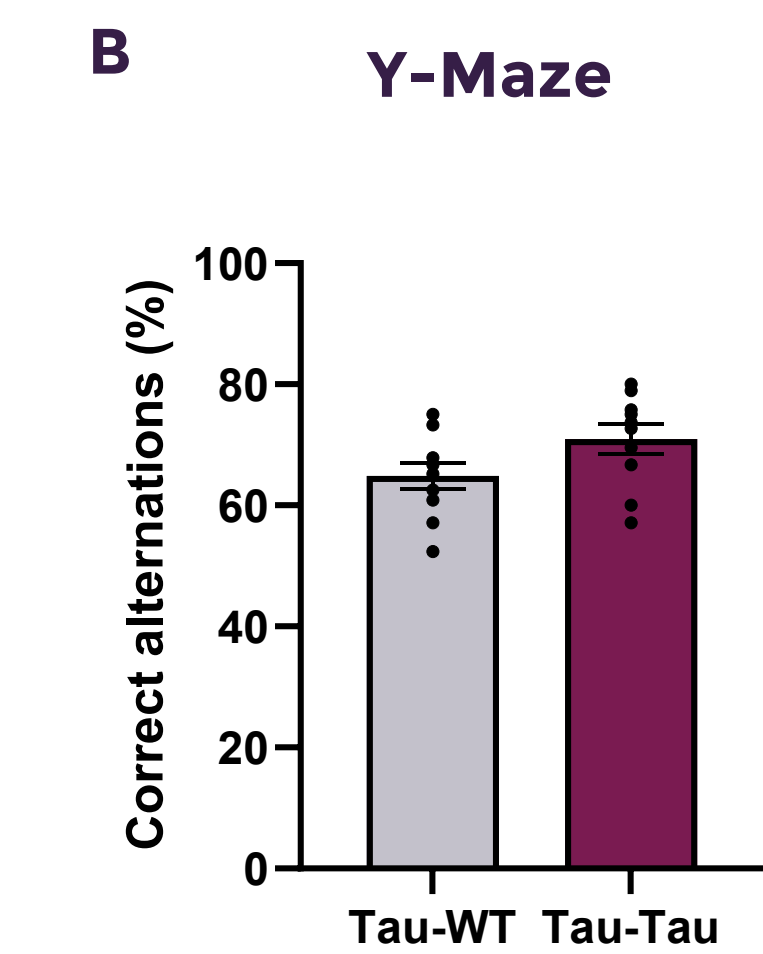
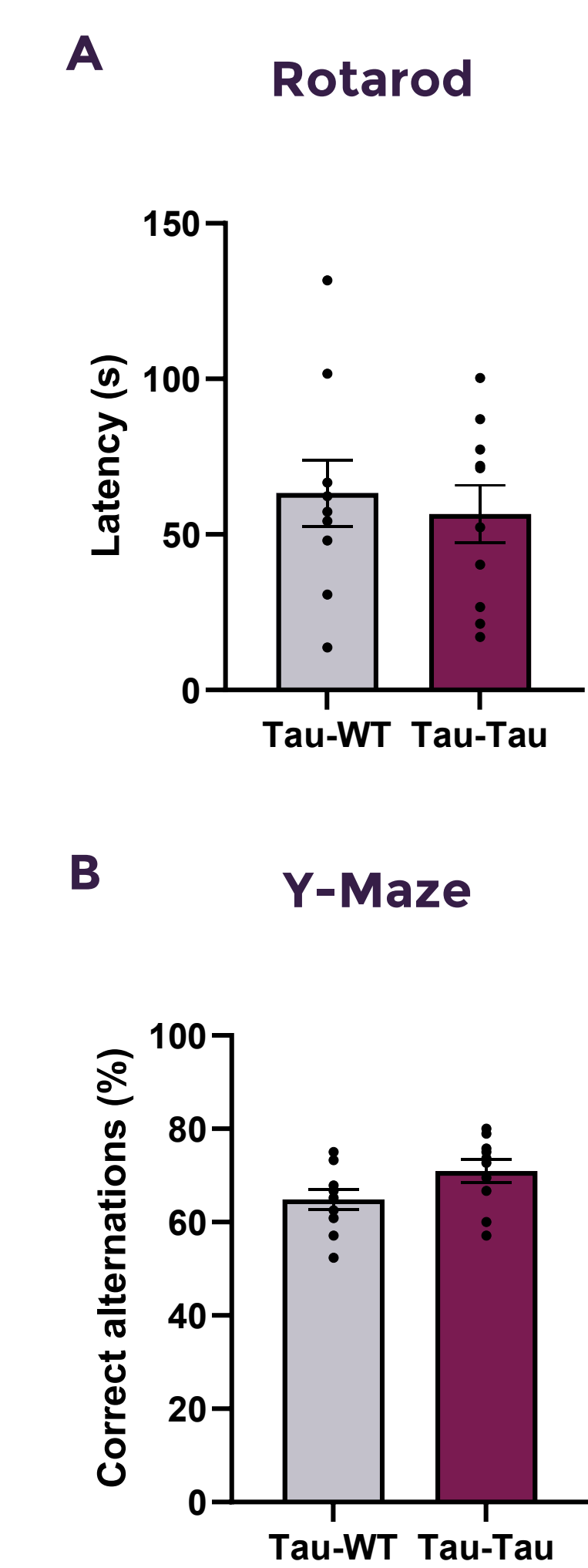
WB: Brain homogenates from 6-month-old mice were incubated with AT8, HT7, and GAPDH antibodies.

ELISA: Plasma and brain homogenates were analyzed for total htau, tau pS199, tau pT181, and tau pT217 markers.

Analysis and quantification: Behavioral tests were analyzed using EthoVision XT17 software (Noldus). Statistical analysis was performed with R and GraphPad Prism v10.

Results

Behavioral analysis



Tau pathology analysis

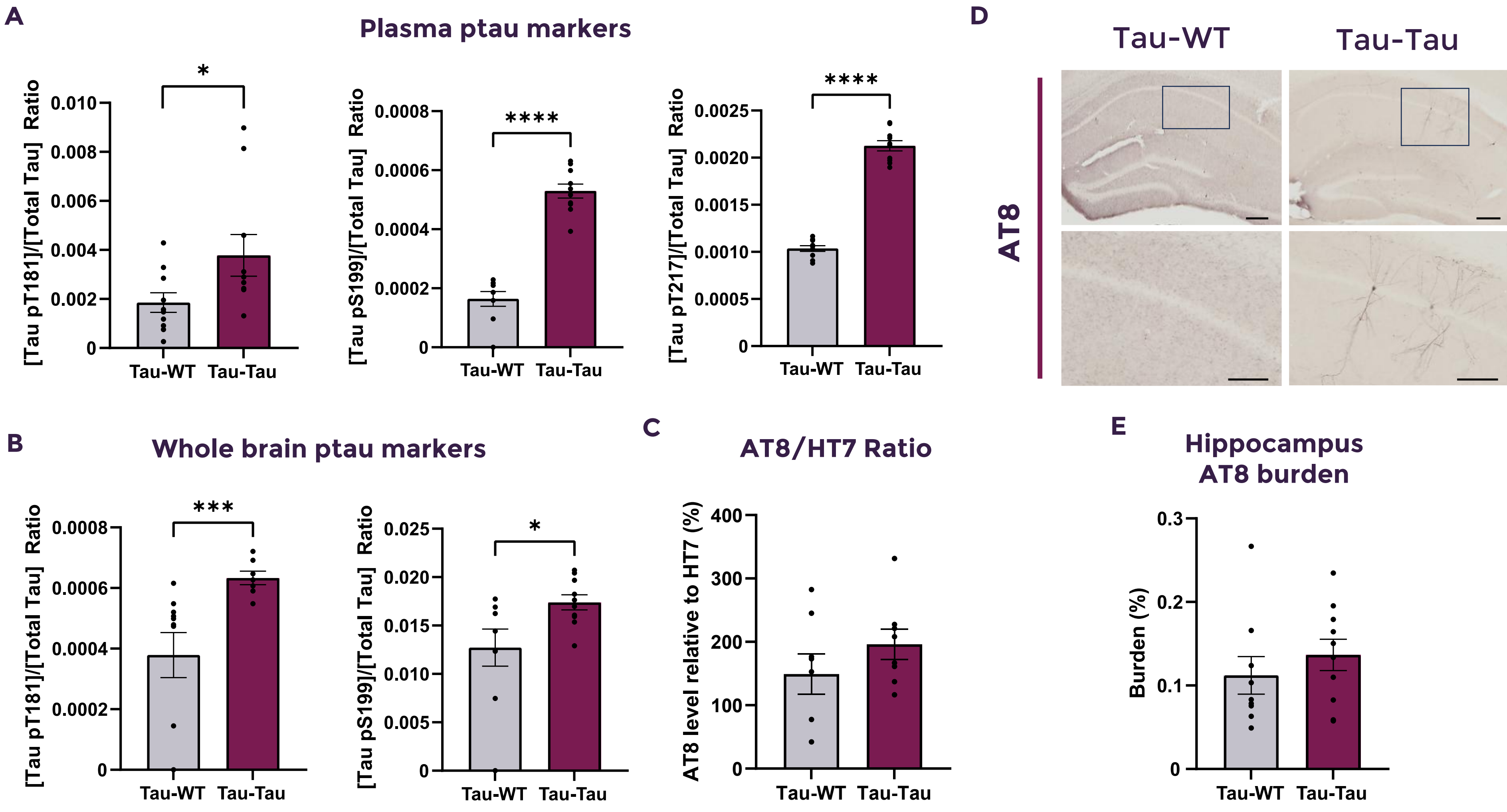


Figure 1. **A** Evaluation of motor activity measured by the Rotarod performance test and **B** evaluation of working memory measured by the Y-Maze test. *Two-tailed t-test* ($\alpha = 0.05$). Data are presented as mean $\pm$ SEM (n = 9 per group).

Figure 2. **A** Quantification by ELISA of pTau markers in plasma samples and **B** whole brain samples. **C** WB quantification of AT8/HT7 ratio (%). **D** Representative bright-field photomicrographs of PS19 animals i.p. injected with BH from WT (left) and PS19 (right) donor animals, immunostained with AT8 (pTau). Scale bars: 200 µm (top) and 50 µm (bottom). **E** Quantitative analysis of the burden (%) in the hippocampus. PS19 animals i.p. injected with BH from PS19 donors exhibited significantly higher levels of ptau markers in plasma and in the whole brain, although AT8 burden in the hippocampus and AT8/HT7 was not increased compared to those injected with WT donor blood. *Two-tailed t-test* or *Mann-Whitney U* ($\alpha = 0.05$). Data are presented as mean $\pm$ SEM (n = 8-9 per group). *p < 0.05; ***p < 0.001; ****p < 0.0001.

Conclusions

Our results indicate that while factors derived from **peripherally administered brain homogenates** can cross biological barriers and induce an increase in peripheral and central ptau levels, such accumulation is **insufficient to trigger robust pathological aggregation or cognitive decline** in the P301S model. These findings contrast with the pathological effects previously observed following peripheral administration of P301S-derived blood, suggesting that the **systemic route or specific co-factors present in circulation are critical** for driving central tau pathology from a peripheral source.

Funding

This work was funded by MICIU/AEI and by European Union NextGenerationEU/PRTR (CNS2022-135424); Ramon y Cajal Program (RYC-2017-21879); the project PID2019-107090RA-I00 funded by MICIU/AEI; Grifols-2025 Albumin Awards Program, Grifols Scientific Awards; and FLC-2026 Fundación La Colmena granted to IM-G.

Contact

