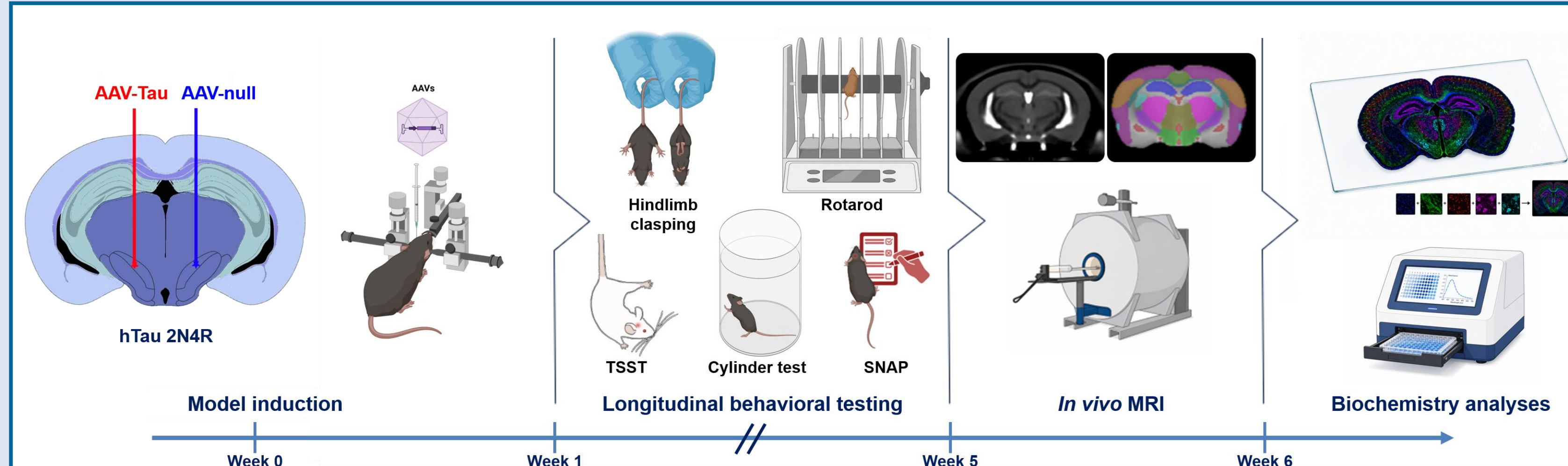




Introduction

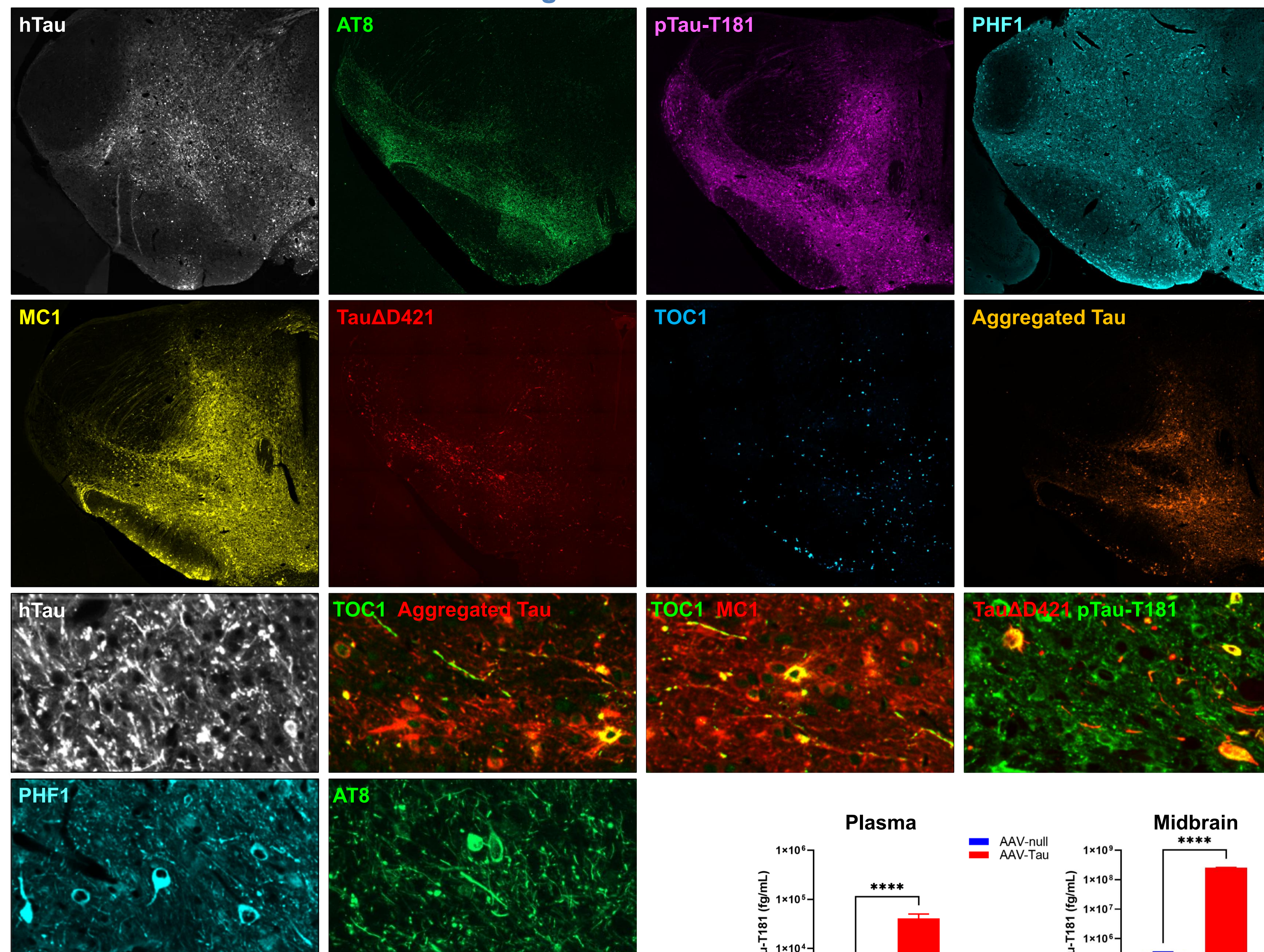
- Tau pathology in the substantia nigra (SN) has been recognized as a key feature in tauopathies with Parkinsonian features, where abnormal tau protein accumulation is associated with neurodegeneration.
- Understanding the role of tau in this subcortical brain region is essential for developing better animal models and therapies for 4R tauopathies.
- AAV-Tau rodent models can be developed utilizing adeno-associated viruses (AAVs) to induce tau expression in specific brain regions, thereby enabling the study of tau-related neurodegeneration *in vivo*.
- We have characterized a novel mouse model utilizing AAV-induced human wild-type tau (2N4R) expression specifically targeting the substantia nigra and midbrain, designed to model the tau-related neurodegeneration of neurons observed in tauopathies with Parkinsonian features, such as Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD).

Methods

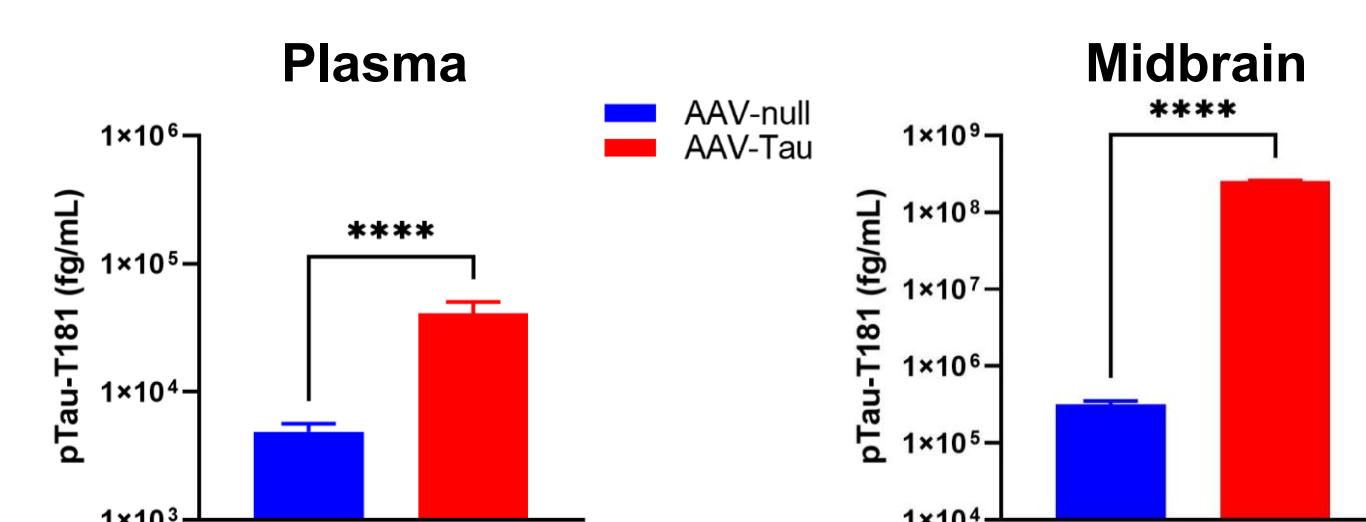


Results

Pathological Tau Accumulation

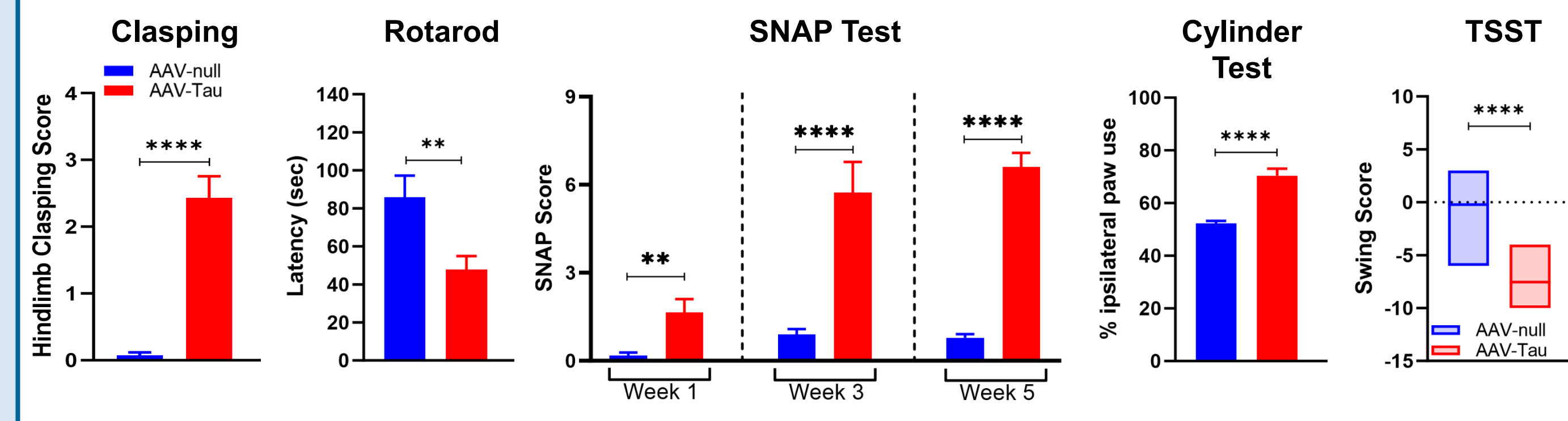


Tau accumulation and pathological Tau species in the ipsilateral midbrain of AAV-Tau-injected animals, shown by hTau, AT8 (pTau-S202/T205), MC1 (conformationally altered Tau), pTau-T181, PHF1 (pTau-S396/404), TOC1 (Tau oligomers), TauAD421 (Tau cleaved at D421), and aggregated Tau immunostaining. No immunoreactivity was observed in AAV-Null brains.



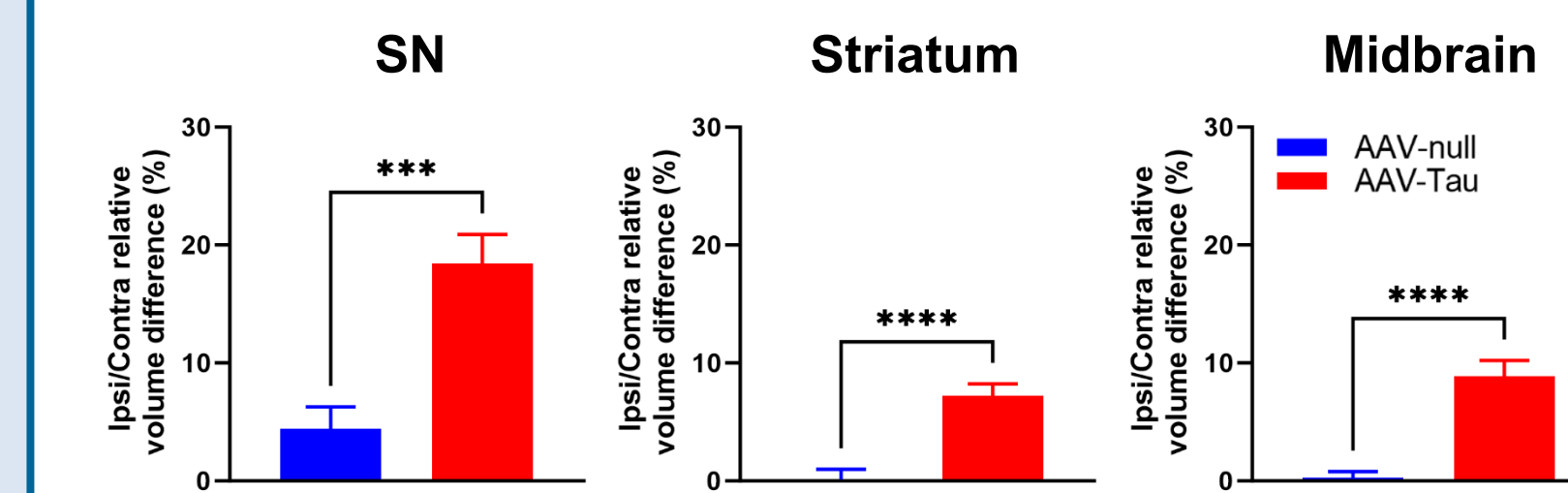
Increased ipsilateral midbrain pTau-T181 levels in AAV-Tau-injected animals assessed by immunoassay (Mean $\pm$ SEM; t-test; *p<0.05; ****p<0.0001).

Progressive Locomotor Impairments



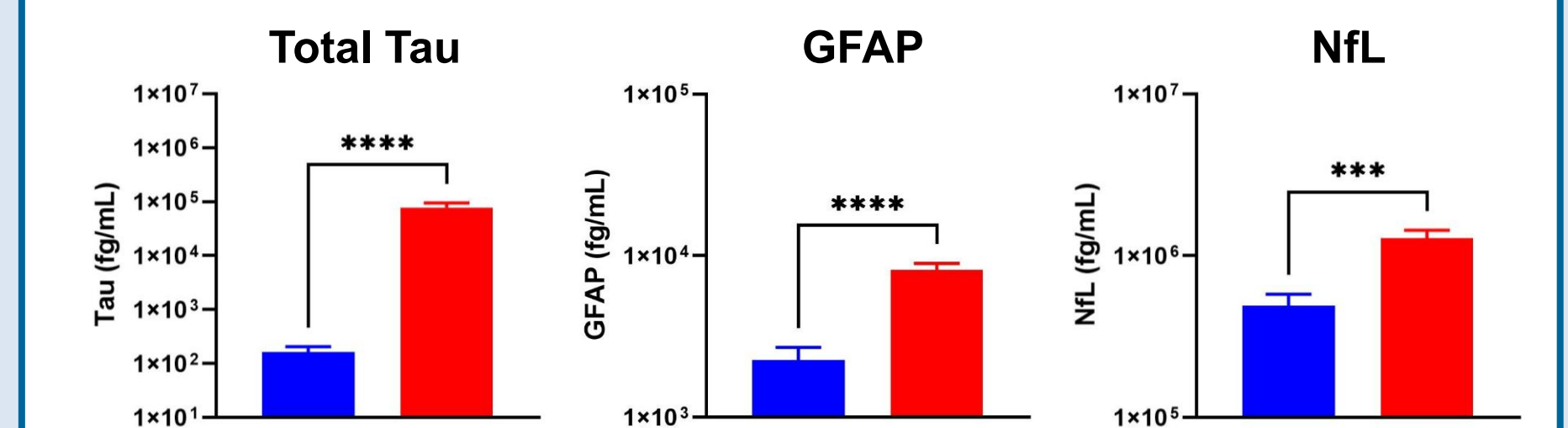
AAV-Tau-injected mice displayed statistically significant hindlimb clasp, impaired rotarod performance, increased SNAP (Simple Neuroassessment of Asymmetric Impairment) scores, preferential use of the ipsilateral forelimb paw in the cylinder test and significantly biased swing contralateral to the lesioned hemisphere compared to AAV-Null controls (Mean $\pm$ SEM; t-test; **p<0.01; ****p<0.0001).

MRI Brain Atrophy



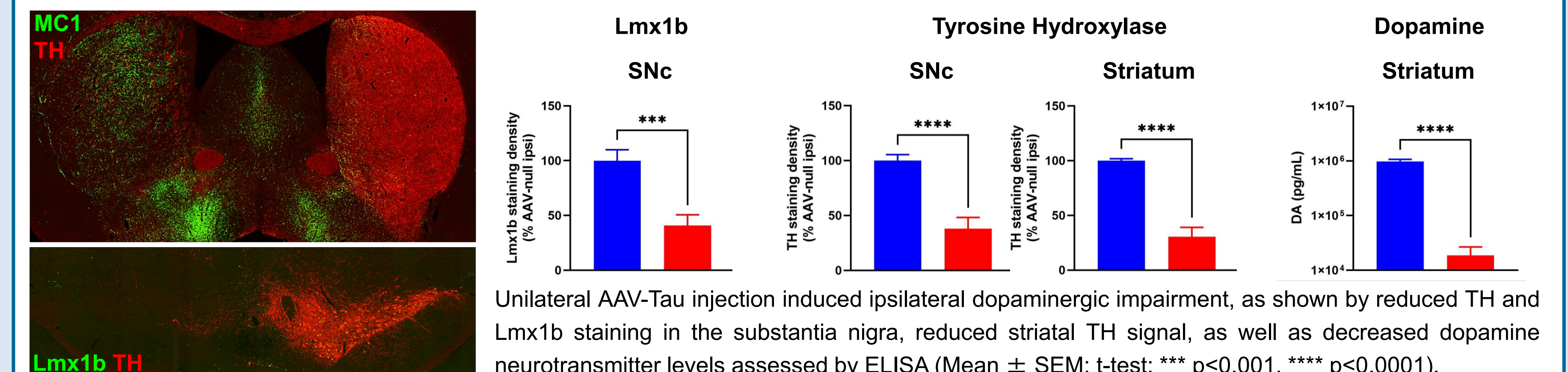
AAV-Tau-injected mice showed significant atrophy in ipsilateral brain regions compared to the contralateral hemisphere (Mean $\pm$ SEM; t-test; ***p<0.001, ****p<0.0001).

Terminal Plasma Neurodegeneration Biomarkers



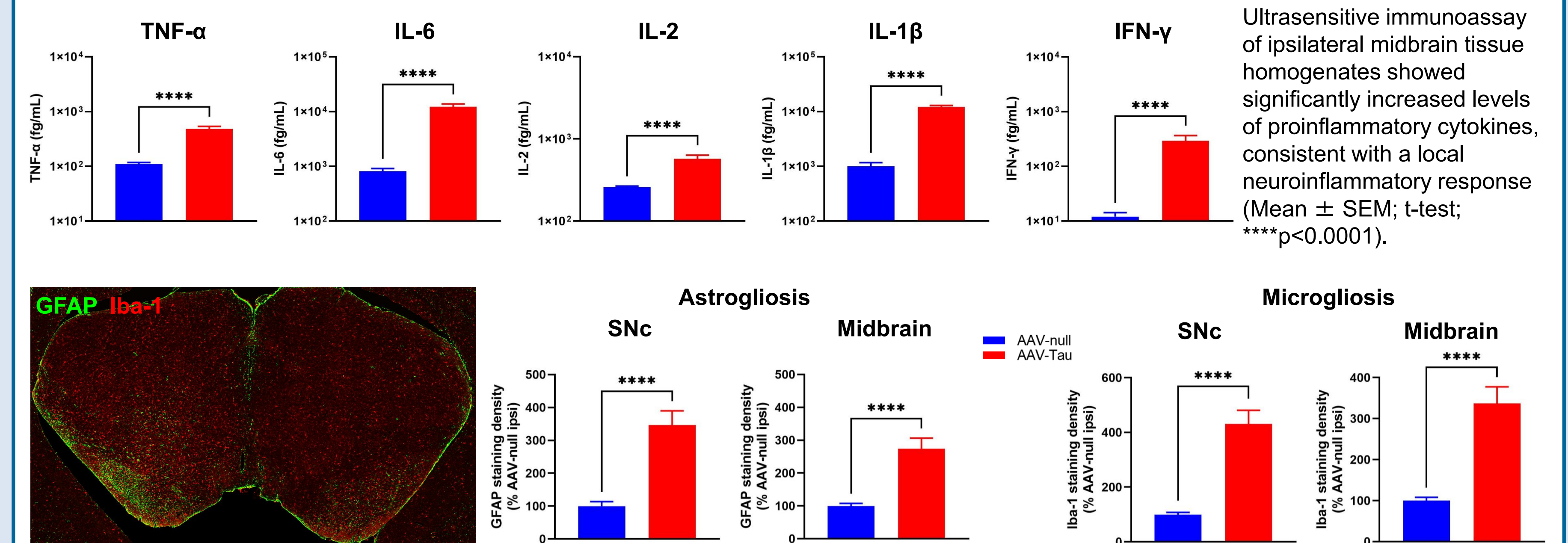
Ultrasensitive immunoassay analysis revealed significantly increased terminal plasma total Tau, GFAP, and NfL levels in AAV-Tau-injected mice (Mean $\pm$ SEM; t-test; ***p<0.001, ****p<0.0001).

Dopaminergic Markers Loss and Dopamine Deficit



Unilateral AAV-Tau injection induced ipsilateral dopaminergic impairment, as shown by reduced TH and Lmx1b staining in the substantia nigra, reduced striatal TH signal, as well as decreased dopamine neurotransmitter levels assessed by ELISA (Mean $\pm$ SEM; t-test; ***p<0.001, ****p<0.0001).

Neuroinflammation & Proinflammatory Cytokines



Ultrasensitive immunoassay of ipsilateral midbrain tissue homogenates showed significantly increased levels of proinflammatory cytokines, consistent with a local neuroinflammatory response (Mean $\pm$ SEM; t-test; ****p<0.0001).

Quantitative immunofluorescence analysis of mouse brain sections stained for GFAP and Iba-1 showed increased astrocytic and microglial reactivity in the ipsilateral midbrain and substantia nigra pars compacta (SNc) following unilateral AAV-Tau injection (Mean $\pm$ SEM; t-test; ****p<0.0001).

Conclusion

The early development of motor deficits, tau pathology, regional brain atrophy, neurodegeneration, and neuroinflammation observed in AAV-Tau-injected mice makes this translational model a valuable and reliable tool for preclinical efficacy studies aimed at accelerating the development of disease-modifying therapeutic interventions for tauopathies with Parkinsonian features, such as PSP and CBD.