Tau Proteinopathy

Tau proteinopathy refers to a group of neurodegenerative diseases characterized by abnormal accumulation, misfolding, or hyperphosphorylation of tau protein within neurons or glial cells. Tau is a microtubule-associated protein that stabilizes microtubules in neurons. In disease states, tau becomes dysfunctional and forms neurofibrillary tangles (NFTs), leading to neuronal dysfunction and death.

Tau Proteinopathy vs Tau Pathology

Both terms are correct but used in different contexts. Below is a comparative summary:

Term	Definition	Typical Use Context
Tau proteinopathy	A neurodegenerative disease characterized by abnormal tau aggregation.	Neuropathological diagnosis, disease classification
Tau pathology	The presence of abnormal tau protein (e.g., hyperphosphorylated, aggregated), regardless of specific disease.	Imaging, biomarkers, histological reports

Tau Proteinopathy

Definition: A class of neurodegenerative diseases characterized by tau protein misfolding, hyperphosphorylation, and aggregation into neurofibrillary tangles (NFTs).

Examples:

- Alzheimer's disease (mixed proteinopathy)
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Pick's disease

Use:

- In diagnostic classifications
- In neuropathology reports
- In research defining disease entities

Tau Pathology

Definition: Refers to the histological or biochemical presence of abnormal tau in the brain tissue, cerebrospinal fluid (CSF), or via PET imaging.

Examples:

- Elevated phospho-tau in CSF
- Positive tau-PET imaging
- Detection of neurofibrillary tangles on microscopy

Use:

- Describing findings in research or clinical imaging
- Monitoring disease progression
- Biomarker studies

Summary Table

Aspect	Tau Proteinopathy	Tau Pathology
Scope	Disease entity	Pathological process
Formality	More specific and formal	Descriptive and broad
Field	Neuropathology, taxonomy	Clinical, biomarker, imaging studies
Usage example	“CBD is a 4R tau proteinopathy.”	“Tau pathology was evident in PET scan.”

Tau PET positivity in individuals with and without cognitive impairment varies with age, amyloid-β status, APOE genotype and sex

Type of study: Observational, large-scale multisite neuroimaging (tau PET) meta-analysis **First author et al.:** Ossenkoppele et al. **Affiliation:** Amsterdam UMC, Alzheimer Center Amsterdam (Amsterdam, The Netherlands) **Journal:** Nature Neuroscience **Purpose:** To quantify how tau PET positivity varies by age, cognitive status (CU, MCI, dementia), Aβ status, APOE ε4 carriage, and sex, using 12,048 participants across 42 cohorts. **Conclusions:**

- Among cognitively unimpaired (CU), tau positivity increases modestly with age: from 1.1 % to 4.4 % in Aβ–, versus 17.4 % to 22.2 % in Aβ+.
- In MCI and dementia, tau positivity decreases with age (e.g., MCI: 68 → 53 %; dementia: 91.5 → 74.6 %).
- APOE ε4 accelerates onset of both Aβ and tau pathology by decades.
- Female sex also confers higher tau positivity risk across groups.
- Findings were validated using an independent autopsy dataset (n ≈ 5,072).

Critical Review

Strengths: - Extremely large, international sample (n = 12,048), with independent replication (n = 5,072) — excellent statistical power and generalizability. - Multi-variable modeling allows disentangling effects of age, Aβ, APOE, and sex. - Use of both in vivo PET and autopsy data strengthens validity.

Concerns: - **Heterogeneity and harmonization:** Forty-two cohorts used various tracers, PET protocols, and tau positivity thresholds. The authors note harmonization efforts but residual bias may remain. - **Cross-sectional design:** Unable to track individual progression; age-related decline in positivity among MCI/dementia may reflect cohort effects or survival bias, not actual biology. - **Covariate control:** It's unclear if vascular risk, education, or clinical severity were adjusted; these could influence tau deposition. - **Sex difference interpretation:** Higher tau PET in women may reflect hormonal or social factors; causality remains untested here. - **Threshold effects:** Reporting across positivity thresholds can amplify small measurement variances—continuous measures might yield more nuanced insights.

Overall, while methodologically robust, the paper's translation into clinical prognostication requires attention to inter-cohort variability and longitudinal dynamics.

Final Verdict

- **Score:** 8.0/10

1. Large scale and replication are major strengths; cross-sectional design and heterogeneity limit mechanistic inference.

Takeaway for neurosurgeons

- APOE ε4 carriers and Aβ+ individuals, especially women over 60, have elevated risk of early tau accumulation—consider when interpreting PET scans and risk stratification. - Modest tau positivity in older CU may signal preclinical Alzheimer's disease; high positivity in MCI/dementia supports AD pathology, but age-specific prevalence should inform biomarker interpretation.

Bottom Line

This study delivers a refined, population-based template for tau PET positivity, stratified by key risk modifiers. While providing valuable benchmarks, longitudinal validation and standardization are needed to translate findings into routine diagnostics.

CITATION: Tau PET positivity in individuals with and without cognitive impairment varies with age, amyloid-β status, APOE genotype and sex. Ossenkoppele R et al. *Nat Neurosci*. 2025 Jul 16. doi: 10.1038/s41593-025-02000-6. Online ahead of print. **Corresponding author:** R. Ossenkoppele r.ossenkoppele@amsterdamumc.nl **PubMed PMID:** 40670684