

BLOOD AND CSF PHOSPHORYLATED AND NON-PHOSPHORYLATED TAU PROFILE IN RAPID VS SLOW NEURODEGENERATIVE DISEASES

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TAKE HOME MESSAGE: P-tau is elevated in rapid neurodegeneration, but much less than in AD. Non-phosphorylated tau shows the opposite pattern. Peripheral tau is unchanged in AD, CJD and stroke.

INTRO & METHOD

INTRODUCTION

- In addition to Alzheimer's disease (AD), multiple neurodegenerative and acute conditions, such as Creutzfeldt-Jakob disease (CJD) and stroke, have shown elevated levels of phosphorylated and non-phosphorylated tau species in cerebrospinal fluid (CSF) and blood [1,2,3]
- However, the extent and pattern of these biomarker changes, and their direct comparison with AD, a predominantly slowly progressive neurodegenerative disorder, remain insufficiently characterized.
- This is largely due to reliance on different analytical assays across studies, limiting direct evaluation of disease-specific tau alterations.

METHODS

TAU PROTEIN

1 aa N1 N2 R1 R2 R3 R4 2N4R 441 aa

We applied a targeted mass spectrometry (MS) method [4,5] to simultaneously quantify multiple phosphorylated tau species (p-tau181, p-tau199, p-tau202, p-tau205, p-tau217, and p-tau231) and non-phosphorylated tau peptides (tau195–209, tau212–221) in CSF and blood, and CNS- and PNS-specific peptides in blood.

Phosphorylated tau: p-tau181, p-tau199, p-tau202, p-tau205, p-tau217, and p-tau231

Non-phosphorylated tau (tau195–209, tau212–221)

Non-phosphorylated tau (CNS- and PNS-specific peptides)

Demographics

CSF participants

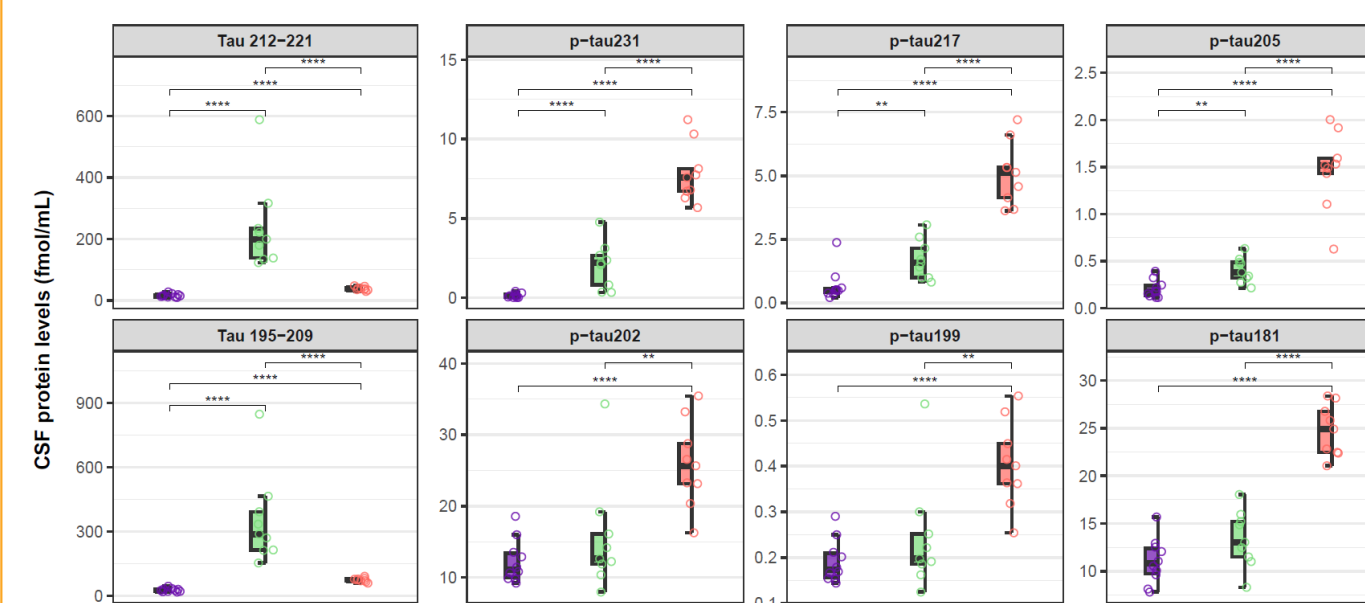
Diagnosis	N	Age, median (IQR)
Control	10	69.5 (64.5–74.4)
CJD	10	68.1 (65.9–78.4)
AD	10	76 (70.6–77.9)

We analyzed two independent cohorts including the following groups: cognitively unimpaired controls, patients with CJD and AD, in CSF and in blood, and additionally stroke in blood.

Plasma participants

Diagnosis	N	Age, median (IQR)	Female, n (%)
Control	10	59.5 (58–61)	3 (30%)
Stroke	15	Not available	Not available
CJD	10	66 (63.2–67.8)	5 (50%)
AD	10	61 (57.2–68.8)	6 (60%)

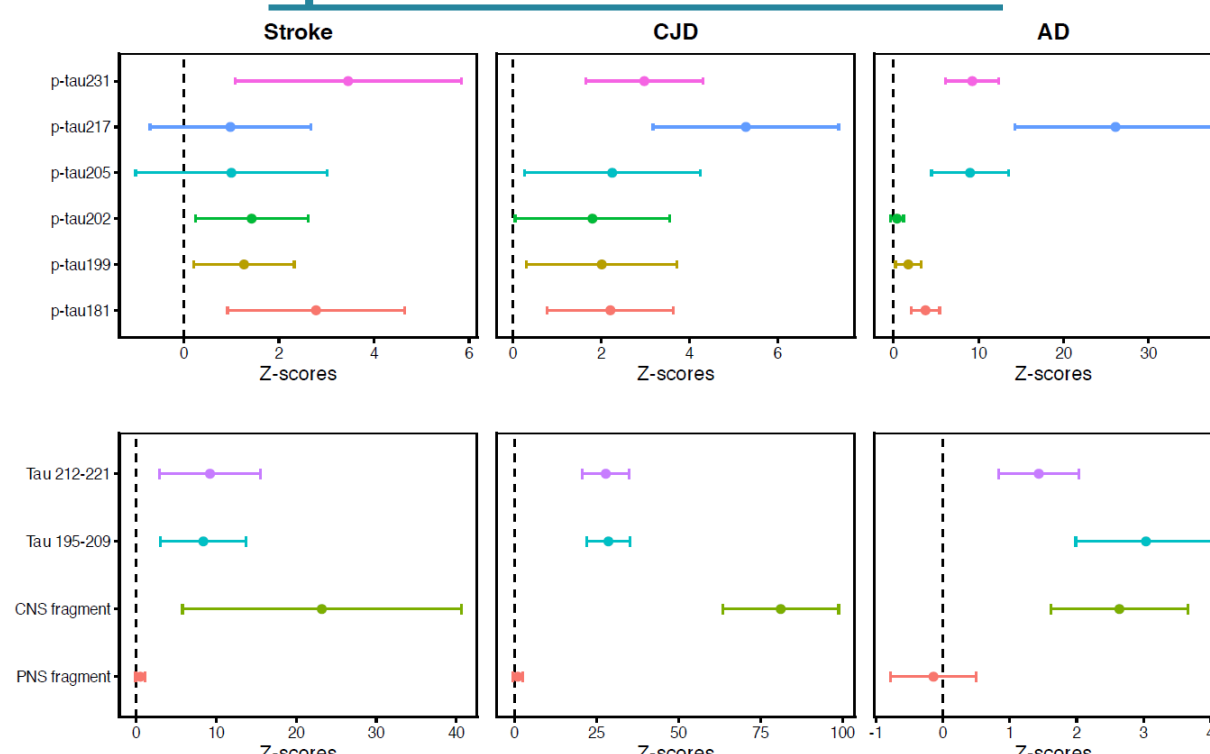
CSF phospho and non-phospho-tau species across conditions



CSF tau concentrations in controls, and patients with CJD and AD. Differences in CSF tau levels by groups were determined by non-parametric Mann-Whitney U test. P-values displayed are not FDR adjusted (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$). The levels of p-tau231, p-tau217 and p-tau205 were higher in both CJD and AD vs controls, while p-tau202, p-tau199 and p-tau181 were only higher in AD. The level of all p-tau species was significantly higher in AD than CJD.

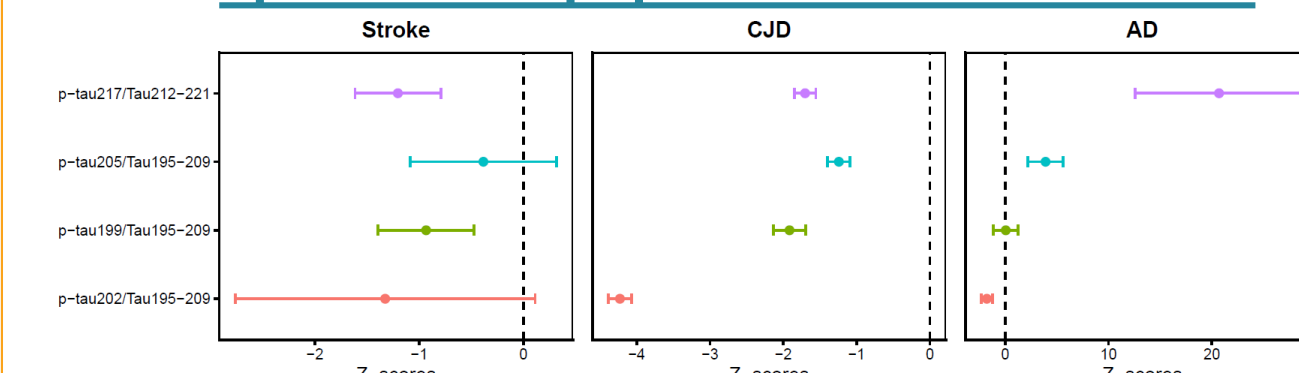
RESULTS

Plasma phospho and non-phospho-tau species across conditions



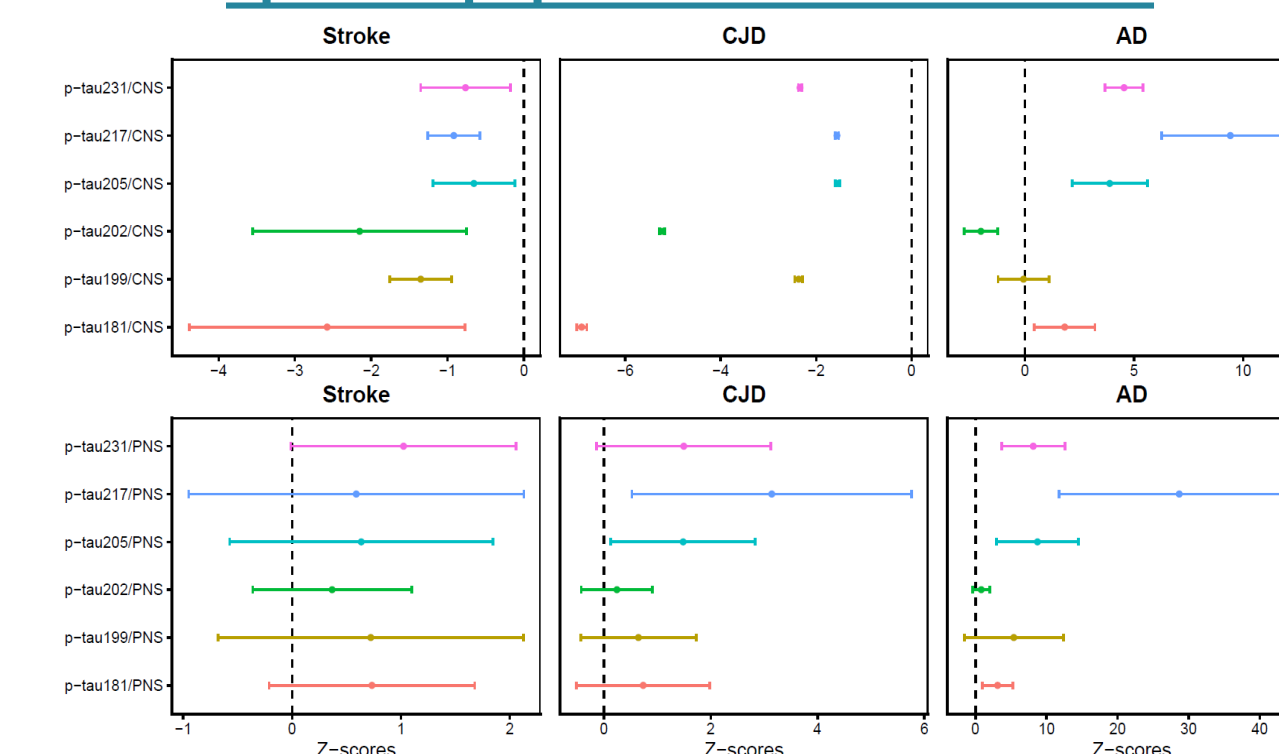
Plasma tau species levels patients with stroke, CJD and AD relative to controls. Values are standardized using controls as a reference. The dot corresponds to the mean z-score for each disease group, with error bars indicating the 95% confidence intervals around the mean. In AD, p-tau231, p-tau217 and p-tau205 present the highest changes, while in stroke and CJD all p-tau species change in a similar manner. The CNS-specific peptide increased the most in stroke and CJD. In AD, the CNS and non-isoform-specific non-phosphorylated tau species presented similar fold-changes. Peripheral tau was not changed in any of the conditions.

Plasma ratios of phospho/non-phospho-specific-tau peptides in each disease



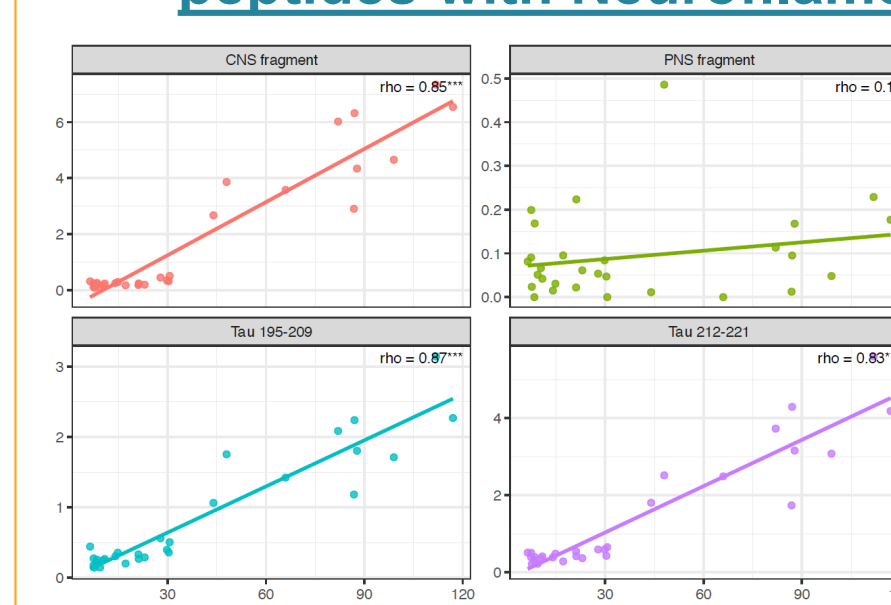
Plasma tau ratios between the phosphorylated peptides and their non-phosphorylated form. Values are standardized using controls as reference. The dot corresponds to the mean z-score for each disease group, with error bars indicating the 95% confidence intervals around the mean. In AD, the ratios remain similar to the p-tau peptides alone, while in stroke and CJD they invert their trend.

Plasma ratios of phospho/ CNS- and PNS-specific peptides in each disease



Plasma tau ratios between the phosphorylated peptides and CNS- and PNS-specific forms. Values are standardized using controls as a reference. The dot corresponds to the mean z-score for each disease group, with error bars indicating the 95% confidence intervals around the mean. In AD, the ratios with the CNS-tau indicated p-tau231, p-tau217 and p-tau205 as the ones with highest fold-changes. For CJD, the ratios presented very low standard deviations. The ratios with PNS-tau did not change the distribution, but increased dispersion.

Associations of non-phosphorylated tau peptides with Neurofilament Light (NfL)



Association between plasma non-phosphorylated tau species and plasma NFL in all participants (Spearman's correlations, unadjusted p-values; ***: $p < 0.001$). NFL correlated with non-isoform specific non-phosphorylated tau and the CNS-specific peptide, but not with PNS-tau.

CONCLUSIONS

Using a unique MS-based approach, we show that:

- (1) Tau hyperphosphorylation at specific epitopes is not unique to AD, although CSF and plasma levels are significantly higher than in other conditions.
- (2) Extreme elevations of non-phosphorylated tau in plasma are characteristic of intense neurodegeneration (CJD) and acute neuronal injury (stroke) likely reflecting secondary tau pathology due to extensive cortical neurodegeneration/damage.
- (3) Peripheral tau markers are not increased in AD, CJD or stroke, whereas CNS-specific tau species show substantially greater increases in CJD and stroke than those observed in AD.

REFERENCES

- [1] Hermann P & Zerr I. Rapidly progressive dementias — aetiologies, diagnosis and management. *Nat Rev Neurology* (2022).
- [2] Stanne TM *et al.* Association of Plasma Brain-Derived Tau With Functional Outcome After Ischemic Stroke. *Neurology* (2024)
- [3] Bentivenga GM *et al.* Clinical value of novel blood-based tau biomarkers in Creutzfeldt-Jakob disease. *Alzheimers Dement* (2025).
- [4] Montoliu-Gaya L *et al.* Mass spectrometric simultaneous quantification of tau species in plasma shows differential associations with amyloid and tau pathologies. *Nat Aging*. (2023)
- [5] Montoliu-Gaya L *et al.* Optimal blood tau species for the detection of Alzheimer's disease neuropathology: an immunoprecipitation mass spectrometry and autopsy study. *Acta Neuropathol.* (2023)

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