

Assessment of core biomarkers efflux from the brain in Alzheimer’s Disease: the Delta study

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Background

Evaluating the rate at which the pathological proteins of amyloid-beta (Aβ) and phosphorylated tau (pTau) flow from the brain to the periphery can contribute to an understanding of the metabolic mechanism of Alzheimer’s disease (AD) biomarkers and facilitate research on blood biomarker-based diagnosis and intervention measures.

Methods

A total of 371 participants were enrolled from the Chongqing Aging and Dementia Study. Blood samples were concurrently collected from the internal jugular vein (IJV) and median cubital vein (MCV), along with PET scans. Our previous data showed no significant differences in core biomarker levels between radial artery (RA) and MCV samples. For better clinical accessibility, we used MCV measurements as a surrogate for RA levels in analyses. MRI data were obtained from subsets (n=122). Plasma Aβ42 and pTau217 were measured using Lumipulse G1200. Key Delta formulas: $\Delta = C_{IJV} - C_{MCV}$; $\Delta\% = (C_{IJV} - C_{MCV}) / C_{MCV}$; Total global cerebral blood flow (CBF)=mean global CBF×brain volume×1.03/100; Net brain efflux rate (N_BER)=Total global CBF×Δ; Relative brain efflux rate (R_BER)=Total global CBF×Δ%. Statistical analyses used Mann–Whitney U, Spearman correlation, and ridge regression in R 4.2.2.

Results

The physiological efflux rate of core biomarkers from the brain was estimated to be 4478.4 ng/day for Aβ42 and 9.8 ng/day for pTau217 in cognitively normal and Aβ-negative participants (CN). Compared with CN, AD patients demonstrated a markedly reduced Aβ42 efflux rate (320.8 ng/day, $p < 0.001$) but an elevated pTau217 efflux rate (119.8 ng/day, $p < 0.001$). Aβ42 N_BER and R_BER were lower in AD than in CN ($p < 0.001$), and they worsened with Braak stage. Compared with CN, pTau217 N_BER increased ($p < 0.001$), while R_BER remained unchanged ($p = 0.448$) in AD. Aβ42 efflux was inversely correlated with brain Aβ and Tau burden ($\rho = -0.420$ and -0.307 , both $p < 0.001$). N_BER, rather than R_BER, of pTau217 was positively correlated with Aβ and Tau burden ($\rho = 0.473$ and 0.590 , both $p < 0.001$). Ridge regression revealed that the central Aβ burden and peripheral factors each contributed approximately 50% to Aβ42 efflux variation. For pTau217, central contributions diminished after normalization, and the overall explanatory power of the pTau217 Δ and Δ% models was low (24.01% and 8.30%, respectively).

Conclusions

In AD, the efflux rate of Aβ42 from the brain is reduced and is dually regulated by both central and peripheral factors. The increased efflux rate of pTau217 from the brain primarily reflects an elevated central production, with relatively stable efflux characteristics in AD.

Figure 1. Brain efflux rates of core pathological proteins across AD pathological stages

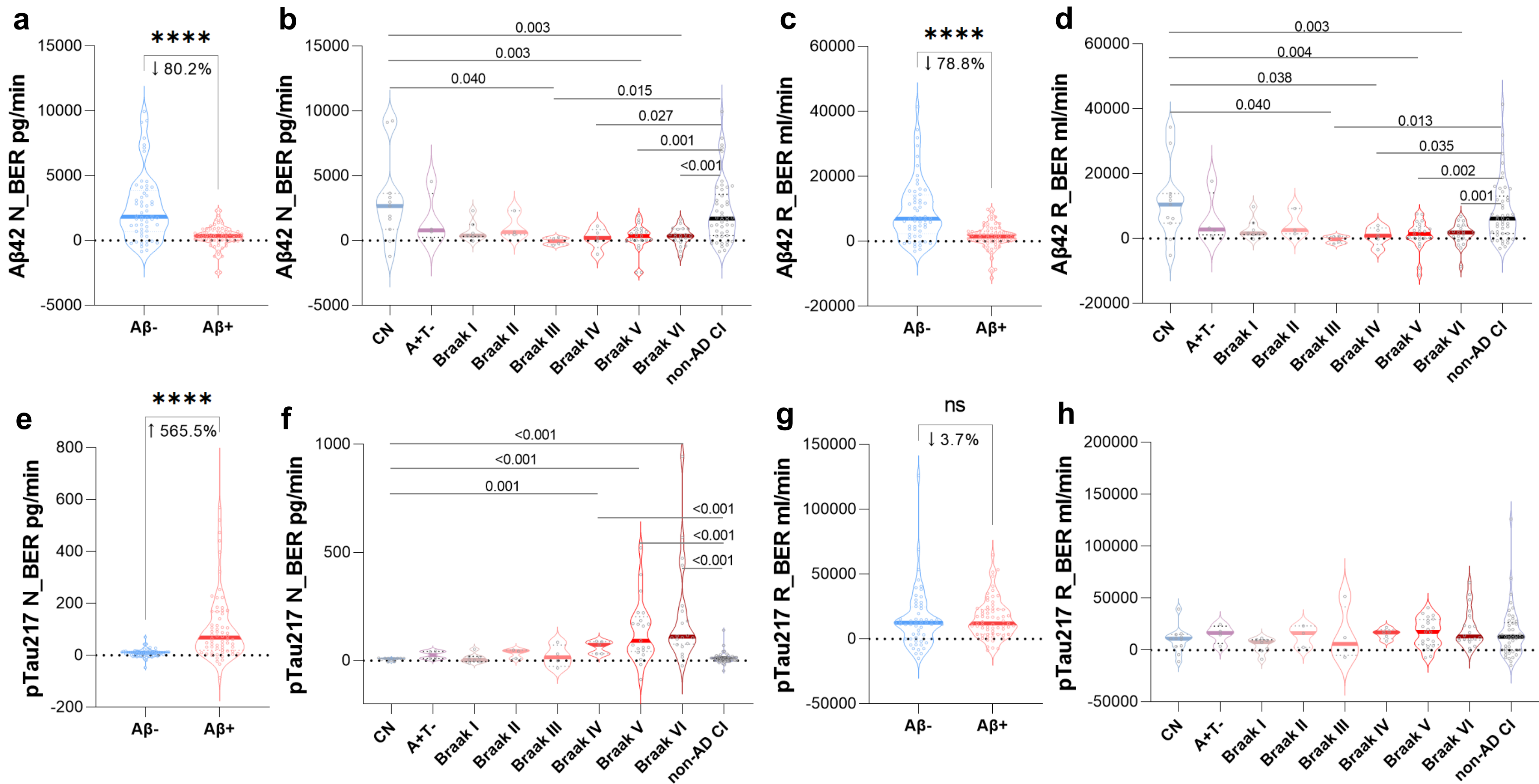


Figure 2. Correlation between brain efflux rates of core pathological proteins and central pathological burden in AD

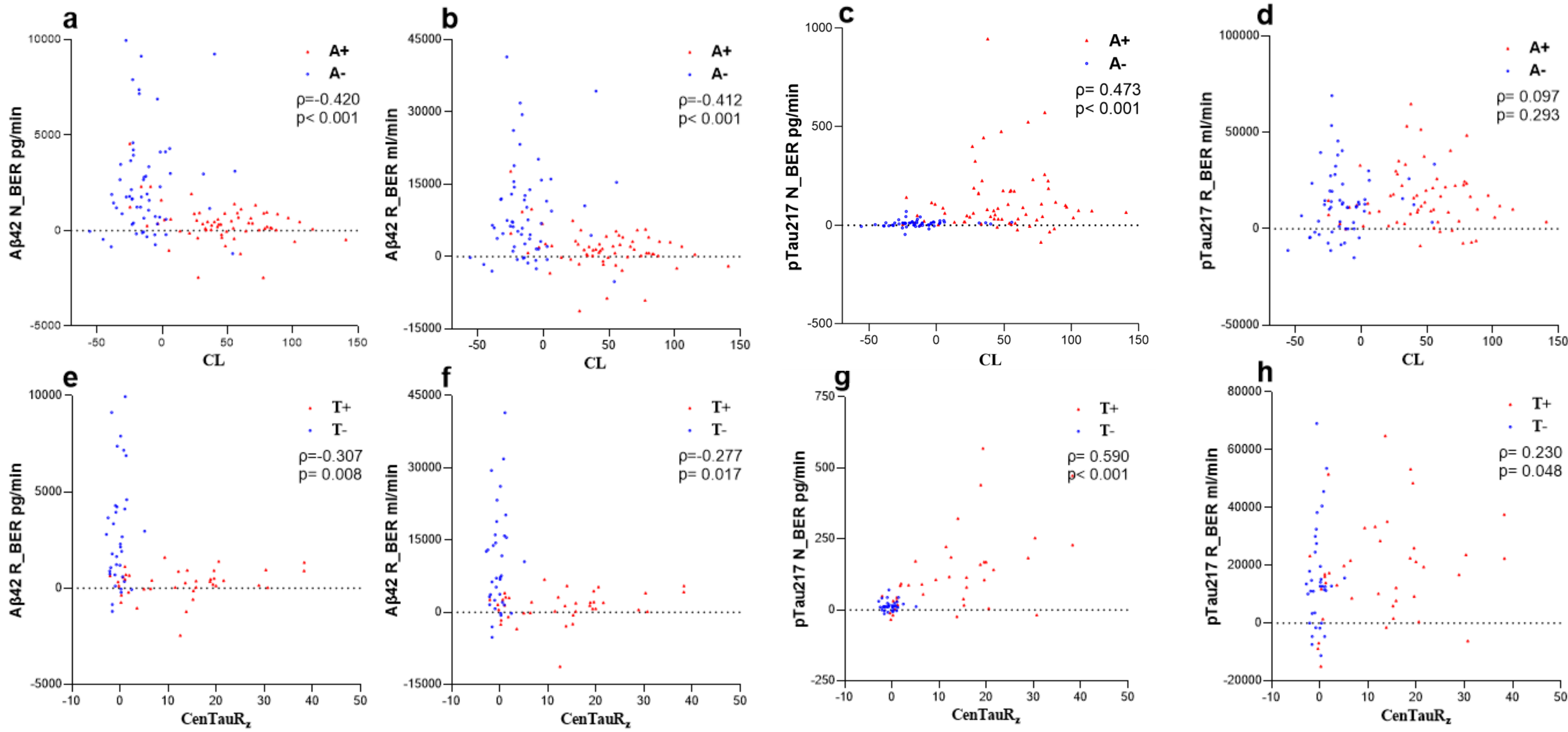
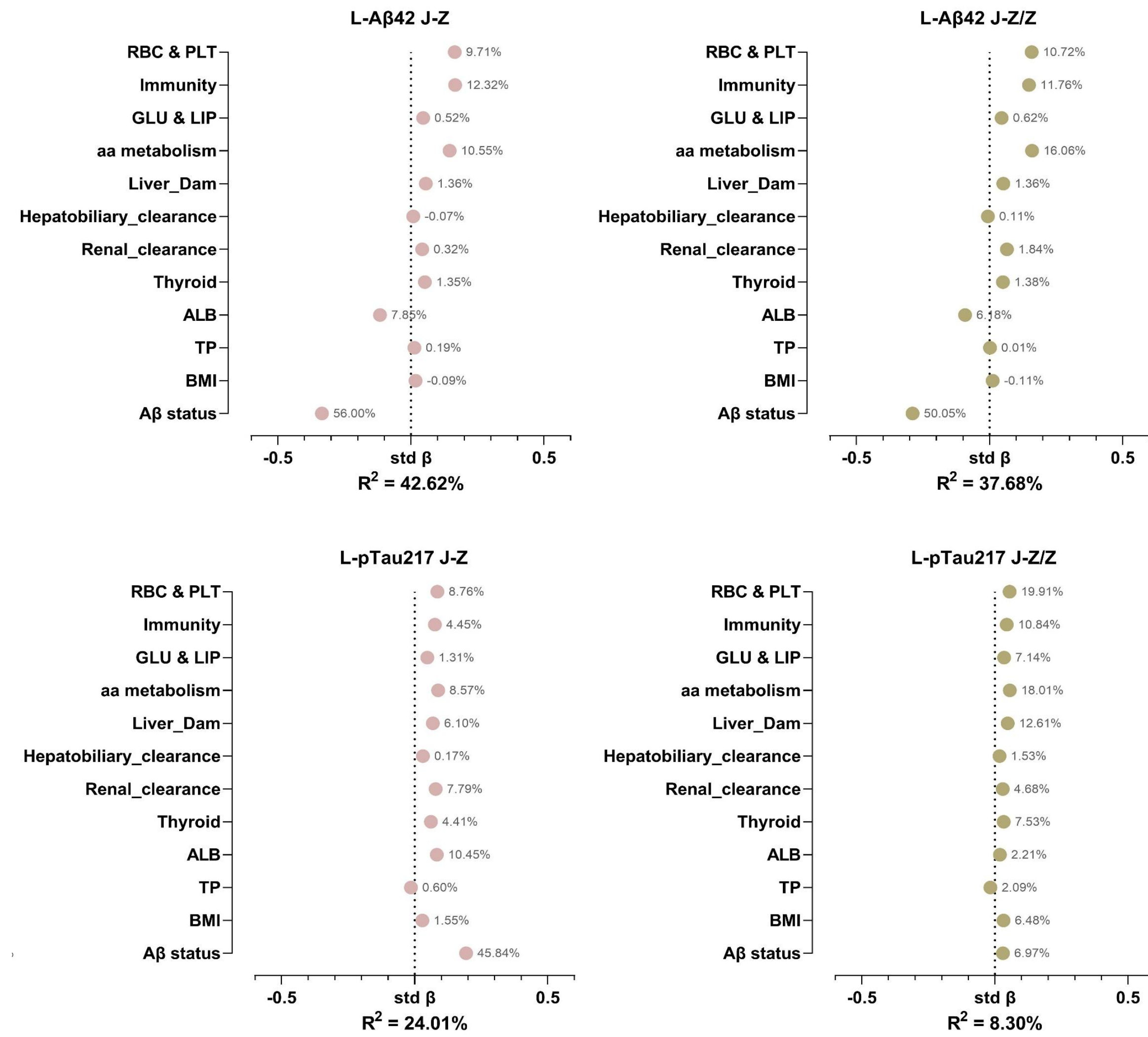
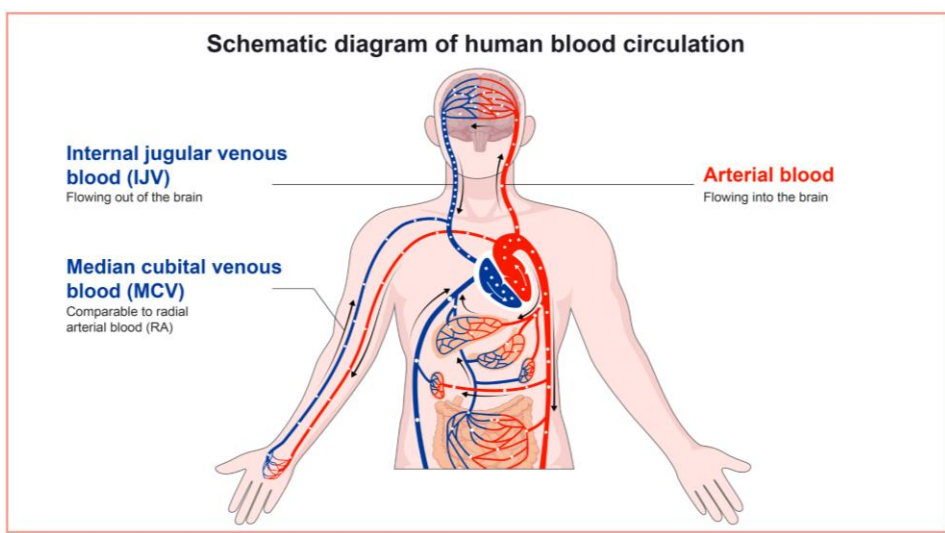


Figure 3. Contribution of systemic factors to Delta/Delta% of core pathological proteins



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