Network-based tau deposition patterns are related to functional network failure largely via beta-Amyloid across the Alzheimer’s spectrum

David T. Jones M.D.¹, Val J. Lowe M.D. ¹, Heather J. Wiste¹, Matthew L. Senjem¹, Kejal Kantarci M.D., Bradley F. Boeve M.D. ¹, David S. Knopman M.D. ¹, Ronald C. Petersen M.D. Ph.D. ¹, Clifford R. Jack, Jr. M.D. ¹

¹Mayo Clinic, Rochester, MN, USA

**Background:** The cascading network failure (CNF) model of Alzheimer’s disease (AD) pathophysiology hypothesizes that synaptic activity related to shifts in large-scale functional network organization is causally related to observed beta-amyloid accumulation via alteration in amyloid precursor protein processing. Once the large-scale network reorganization interacts with vulnerable brain systems, a tau-related neurodegenerative process evolves within that system. To test these predications, we investigated the relationship between Tau-PET, task-free fMRI, and beta amyloid-PET in a cross-sectional sample spanning the Alzheimer’s disease spectrum.

**Methods:** Tau-PET (AV-1451), beta amyloid-PET (PiB), and TF-fMRI were obtained in a cohort of subjects across the AD spectrum (n = 218). All subjects that were clinically impaired (n = 41) had PiB SUVR > 1.5. Tau-PET scans were intensity normalized to the cerebellar gray matter, spatially normalized to standard space, and smoothed. Independent component analyses was then performed, with biologically relevant components being identified via a strong amyloid effect for the tau components (Bonferroni corrected p < 0.01). A goodness-of-fit analysis of these components with a functional connectivity atlas was then performed. Tau-PET memory system component scores were included in a mediation analyses with PiB-PET and a marker of functional network failure we term the network failure quotient (NFQ).

**Results:** Five biologically relevant tau-PET components were identified. These components had high GOF scores with visual, executive, and memory-related networks likely reflecting phenotypic heterogeneity in the AD cohort given the visual and executive components were associated with age-of-onset. The memory-related Tau-PET component was associated with PiB-PET (β=0.59, p<0.001) and NFQ (β = 0.30, p<0.001). A mediation analysis showed a strong mediation effect by PiB-PET (mediation effect [95% CI] = 0.85 [0.23, 1.41], p<0.001) on the relationship between NFQ and tau-PET (direct effect [95% CI] = 0.30 [-0.01, 0.57], p = 0.08). Similar results are obtained with individual elements of the NFQ.

**Conclusions:** Tau deposits in visual, executive, and memory-related networks which may reflect heterogeneity in AD phenotypes. Consistent with the CNF model of AD, direct examination of tau-PET and functional connectivity in the same subjects demonstrates a strong association of network failure with tau that is largely mediated by beta-amyloid.