

A Volume-Based Alternative for classifying ATN: Data from the Tau Propagation over Time (T-POT) cohort

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Abstract

Background: Alzheimer's disease (AD) is characterized by the cerebral accumulation of amyloid-beta (A), tau (T), and progressive neurodegeneration (N). The widely used ATN system, with regard to positron emission tomography (PET) biomarkers, categorizes AD based on the mean signal in specific regions of interest (ROI). However, this procedure disregards the spatial extent of pathology and neurodegeneration. Here, we propose an alternative quantification of the volume, i.e., fill states, of A, T and N in (pre)-clinical AD.

Method: We analyzed data from the *Tau Propagation over Time (T-POT)* study, including cognitively unimpaired individuals (CU, n = 58), and patients with mild cognitive impairment (MCI, n = 20) or AD dementia (n = 4). C11-PIB-PET (A), 18F-AV1451 (T) and perfusion-phase 18F-AV1451 scans (N) were spatially and intensity-normalized (reference: cerebellum). To quantify the volume of A, T and N, we z-standardized and subsequently binarized all scans within-modality using a z-score threshold. Fill states were then computed as the sum of abnormal voxels relative to a whole-brain mask. Finally, mean fill states were compared across groups of clinical status (CU, MCI, AD) and partial correlations of either fill states or mean PET signal in established, tracer-specific ROIs with cognitive performance (MMSE) were computed, adjusting for age, sex and education.

Result: Mean fill states reflected clinical status, as they increased with disease progression (CU: A = 4%, T = 4%, N = 3%; MCI: A = 15%, T = 11%, N = 4%; AD dementia: A = 20%, T = 23%, N = 5%). Moreover, A and T fill states were negatively associated with MMSE ($\rho_A = -0.299$, $p < .001$; $\rho_T = -0.318$, $p < .01$; $\rho_N = -0.147$, $p = .20$), while associ-

ations of mean PET signal and MMSE tended to be weaker ($\rho_{A(\text{global})} = -.255, p = .03$; $\rho_{T(\text{temporalmetaROI})} = -.275, p = .01$; $\rho_{N(\text{metaROI})} = .179, p = .12$).

Conclusion: We present a competitive quantification scheme for ATN that is associated with both, clinical status and cognitive performance. These results, while currently validated in a larger sample, suggest that the spatiotemporal dynamics of pathology and neurodegeneration in the AD continuum are well captured by our multi-parametric approach, which is possibly superior compared to classification from mean PET signal intensity.

