Data-Driven Thresholding Statistically Biases ATN Profiling across Cohort Datasets

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Background: While the amyloid/tau/neurodegeneration (ATN) framework has found wide application in Alzheimer's disease research, it is unclear if thresholds obtained using distinct thresholding methods are concordant within the same dataset and interchangeable across cohorts.

Objectives: To investigate the robustness of data-driven thresholding methods and ATN profiling across cohort datasets.

Design and Setting: We evaluated the impact of thresholding methods on ATN profiles by applying five commonly-used methodologies across cohort datasets. We assessed the generalizability of disease patterns discovered within ATN profiles by clustering individuals from different cohorts who were assigned to the same ATN profile.

Participants and Measurements: Participants with available CSF amyloid-β 1–42, phosphorylated tau, and total tau measurements were included from eleven AD cohort studies.

Results: We observed high variability among obtained ATN thresholds, both across methods and datasets that impacted the resulting profile assignments of participants significantly. Clustering participants from different cohorts within the same ATN category indicated that identified disease patterns were comparable across most cohorts and biases introduced through distinct thresholding and data representations remained insignificant in most ATN profiles.

Conclusion: Thresholding method selection is a decision of statistical relevance that will inevitably bias the resulting profiling and affect its sensitivity and specificity. Thresholds are likely not directly interchangeable between independent cohorts. To apply the ATN framework as an actionable and robust profiling scheme, a comprehensive understanding of the impact of used thresholding methods, their statistical implications, and a validation of results is crucial.