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Hippocampal subfield deformation shows unique patterns associated with amyloid-beta, TDP-43, and PHF-TAU burden

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Background: Alzheimer's dementia (AD) is the most common form of dementia in adults over the age of 65, however, current tools for diagnosing the disease need to be improved. The relationships between clinical syndromes and pathological causes are complex, which makes accurate diagnosis difficult. Further, as treatment agents with potential disease-modifying effects are developed, sensitive and specific biomarkers will be needed, so that they can be tested and then eventually used in the appropriate patient populations. The goals of the current project are to develop an *in vivo* hippocampal surface atlas from structural MRI that is predictive of postmortem β-amyloid, paired helical filament (PHF-tau) neurofibrillary tangles (NFTs) and transactive response DNA-binding protein-43 (TDP-43) neuropathologies.

Methods: Using a sample of 101 older adults from two longitudinal cohort studies conducted by the Rush Alzheimer's Disease Center, we used hippocampal shape analysis of ante-mortem T1-weighted structural magnetic resonance to generate surfaces for the whole hippocampus and zones approximating the underlying subfields using a previously developed automated image-segmentation pipeline (Freesurfer-Initiated Large Deformation Diffeomorphic Metric Mapping; FSLDDMM). Multivariate linear regression models were constructed to examine the relationship between shape and pathology measures while accounting for covariates which include co-existing pathologies and other neuropathological variables (hippocampal sclerosis, Lewy bodies, gross infarcts, atherosclerosis, arteriosclerosis, and cerebral amyloid angiopathy), with relationships mapped onto hippocampal surface locations. In a previous sample of 42 subjects from the same cohort, univariate models were not able to be examined due to low power.

Results: Results show a significant and unique pattern of deformation for each neuropathology when accounting for covariates including age and sex. Specifically, β-amyloid was associated

with a significant inward deformation in zones approximating the subiculum, where PHF-tau NFTs were associated with a significant inward deformation along the left hippocampal tail within the subiculum. TDP-43 inclusions were associated with a significant inward deformation in the body of the hippocampus along the CA1/subiculum border. Results were corrected for multiple comparisons using the random field theory (RFT) with a family-wise error rate (FWER) < 0.05.

Discussion: These results indicate a unique pattern of deformation due to individual neuropathology, after accounting for covariates. Deformation regions associated with β-amyloid and PHF-Tau replicate previously published results on a smaller subset of the sample. With the presented increased sample size, a significant TDP-43 signature arose. Results indicate that hippocampal deformation may be used to represent a biomarker of individual post mortem disease which could allow for the early and accurate diagnosis of disease and aid in the selection for clinical trials.

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