PATHOLOGIC VALIDATION OF THE HIPPOCAMPAL RADIAL DISTANCE SURFACE MAPPING TECHNIQUE

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Background

Hippocampal atrophy is the most established structural imaging biomarker for Alzheimer's disease (AD). There are two well-established approaches for investigating hippocampal atrophy: the classic hippocampal volumetry approach and the newer 3D shape analytic approach. The hippocampal volumetry approach has been pathologically validated. Our objective was to provide pathologic validation of the 3D hippocampal radial thickness approach.

Methods

The temporal lobes of 9 AD and 7 cognitively normal subjects were scanned post-mortem at 7 Tesla. Pathologic diagnosis of AD was based on Braak and Braak and CERAD criteria. The temporal lobes were scanned for 60 hours on a 7T Bruker Biospec MRI scanner. The hippocampal structures were segmented with the EADC-ADNI Harmonized Protocol for Hippocampal Segmentation (EADC-ADNI HarP) and subjected to 3D radial distance analyses. 6 μm-thick hippocampal slices were stained for amyloid beta (Aβ1-40), tau (PHF-tau) and cresyl violet. The demarcations of each hippocampal subfield were manually drawn with Aperio ImageScope® CS on the digitally scanned stained tissue. Subfield margins were identified based on cytoarchitectonic features. Neuronal counts, Aβ and tau burden for each hippocampal subfield were obtained. The associations between pathology indices and hippocampal radial distance were investigated with linear regression followed by permutation-based correction for multiple comparisons with the stringent cut-off of $p<0.01$.

Results

Kruskal-Wallis comparison of medians showed significant differences between the two groups for total hippocampal tau and Aβ burden ($p=0.01$ for both) but not neuronal count ($p=0.12$). Significant differences in the medians were seen in all subfields for tau and in the subiculum, CA1 and CA3 for Aβ. Hippocampal radial distance was significantly associated with pathologic diagnosis (p corrected<0.0001) and mean Aβ burden (p corrected =0.02). We also found trends for associations with neuronal count (p corrected =0.067) and Braak and Braak staging (p corrected =0.092). While we observed locally significant associations between subfield Abeta and tau burden and neuronal counts, these did not survive our stringent correction for multiple comparisons.

Conclusions

The observed associations provide pathologic validation of 3D hippocampal radial distance methodology and pathologic confirmation of 3D hippocampal analyses as a valid AD biomarker.