**O2-11-02: Definition of harmonized protocol for hippocampal segmentation**

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**Background**
Heterogeneity of landmarks among protocols leads to different volume estimates, hampering comparison of studies and clinical use. There is an urgent need to define a harmonized protocol for manual hippocampal segmentation from magnetic resonance scans. Landmark differences among the 12 most common protocols were extracted, operationalized, and quantitatively investigated. The results were presented to the Delphi panel, consisting of seventeen researchers with substantial expertise in hippocampal segmentation, in order to reach an evidence-based consensus on segmentation landmarks.

**Methods**
The Delphi panel participated in iterative anonymous voting sessions where feedback from previous rounds was utilized to progressively facilitate panelists' convergence on agreement. Panelists were presented with segmentation alternatives, each associated with quantitative data relating: (i) reliability, (ii) impact on whole hippocampal volume, and (iii) correlation with AD-related atrophy. Panelists were asked to choose among alternatives and provide justification, comments and level of agreement with the proposed solution. Anonymous votes and comments, and voting statistics of each round were fed into the following Delphi round. Exact probability on binomial tests of panelists' preferences was computed.

**Results**
Sixteen panelists completed four Delphi rounds. Agreement was significant on (i) inclusion of alveus/fimbria (P = 0.021); inclusion of the whole hippocampal tail (P = 0.013); (iii) segmentation of the medial border of the body following visible morphology as the first choice (P = 0.006) and following a horizontal line in the absence of morphological cues (P = 0.021); inclusion of the minimum hippocampus (comprising head and body) (P = 0.001); and inclusion of vestigial tissue in the segmentation of the tail (P = 0.022) (Figure). Significant agreement was also achieved for exclusion of internal cerebrospinal fluid pools (P = 0.004). Based on previous quantitative investigation, the hippocampus so defined covers 100% of hippocampal tissue, captures 100% of AD-related atrophy, and has good intra-rater (0.99) and inter-rater (0.94) reliability.

**Conclusions**
A Harmonized Protocol for Manual Segmentation has been agreed among an international panel of experts. The protocol will be validated with neuropathological data and its accuracy will be compared with protocols currently used in Alzheimer's disease research.