Building a 3D Atlas of the Human Hippocampus From Postmortem Magnetic Resonance Imaging

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Introduction

The study of human hippocampal morphometry is common in neuroimaging due to the important role that the hippocampus plays in episodic memory and in neurodegenerative diseases that affect memory. In most such studies, *in vivo* MRI is used to characterize the size and shape of the hippocampus. Due to the limitations of *in vivo* MRI resolution, the hippocampus is typically represented as a homogeneous structure with a thicker head, an elongated body and a curved thin tail. However, the hippocampus is a very complex structure, formed by multiple layers that fold and twist and whose boundaries with nearby grey matter structures are not clearly visible at *in vivo* MRI resolution. To facilitate the study of *in vivo* hippocampal morphometry, we are developing a detailed 3D atlas of the hippocampus using *postmortem* imaging. Using a high-field animal scanner, we are imaging the hippocampus and surrounding structures at ~0.01mm^3 resolution, at which the boundaries between hippocampal subfields can be distinguished. Using diffeomorphic image normalization methodology, we are combining data from multiple specimens into a single atlas. This atlas will support model-based automatic *in vivo* MRI segmentation algorithms and the analysis of differential neurodegeneration across hippocampal subfields in *in vivo* MRI studies.

Materials and Methods

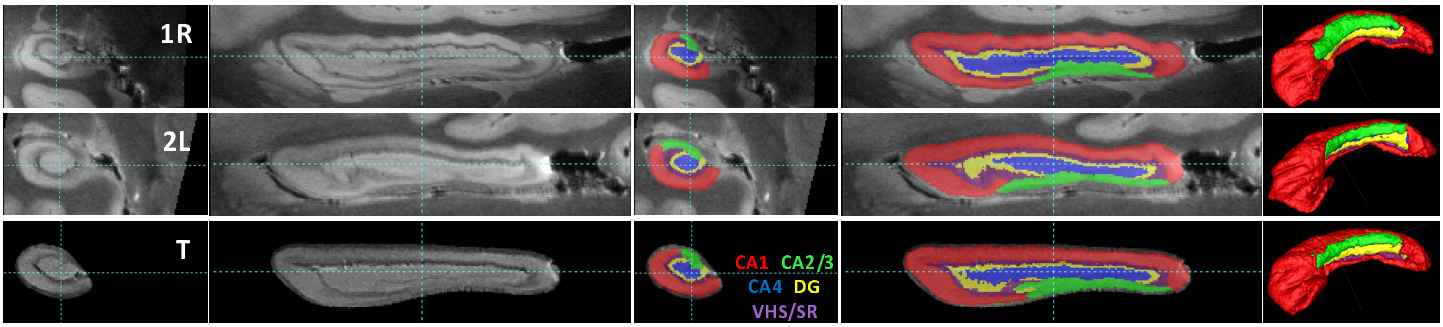
Specimens and Imaging. Three formalin-fixed brain specimens (21+ days) from autopsy cases with no abnormal neuropathological findings were studied so far. Samples containing the whole hippocampus and fitting into the 70mm coil were extracted from each hemisphere. Samples were placed in plastic bags and wrapped with bubble-wrap so that they fit snuggly into the coil. The alternative of placing samples in Fomblin was not adopted due to the difficulty of extracting air bubbles and motion of the sample due to gradient vibrations. Imaging took place on a 9.4 Tesla Varian 31cm horizontal bore scanner (Varian Inc, Palo Alto, CA) using a 70mm ID TEM transmit/receive coil (Insight Neuroimaging Systems, Worchester, MA). A standard multi-slice spin echo sequence with TR/TE=5000/25ms was used. An oblique slice plane was chosen so as to allow the entire hippocampus to be covered with fewest possible slices. Around 130 interleaved slices with 0.2mm thickness were acquired. Phase encode direction was from left to right and the read out direction followed the long axis of the hippocampus. The field of view was typically 60mm x 90mm, with matrix of size 300x300, yielding 3D images of 0.2mm x 0.3mm x 0.2mm resolution. Most samples were scanned overnight (15-16 hours) with 32-44 averages. One sample was scanned with 160 averages over a weekend, with 0.2mm isotropic resolution.

Manual Segmentation. In three of the samples, the hippocampus was labeled by a trained expert using ITK-SNAP (itksnap.org) and using the Duvernoy atlas of the hippocampus as a reference (Duvernoy, 2005). Five labels were used: cornu Ammonis fields CA1, combined CA2 and CA3, and CA4; dentate gyrus (DG); and a label combining the vestigial hippocampal sulcus and the stratum radiatum of the cornu Ammonis (VHS/SR). Segmentation required 1-2 weeks per sample due to the complexity of hippocampal subfields and the high resolution of the images.

Atlas-Building. Postmortem MRI images are difficult to normalize because of differences in field of view and presence of artifacts. Initial rigid alignment of the hippocampal anatomy in the MRI images was obtained by landmark matching. An atlas-building technique based on diffeomorphic symmetric image registration (Avants et al., 2007) was used to combine images of the samples into a single atlas (the atlas is an artificial image, which requires the least total deformation to warp to each of the input images). A consensus segmentation of the atlas was generated by warping the manual segmentations to the atlas and using the STAPLE algorithm (Warfield et al., 2005) to assign a label to each voxel.

Results

The figure below shows cross-sections through a corresponding point in MRI images of two specimens (1R and 2L) and the template (T). The right-most column shows the 3D rendering of the subfield masks. Notice the consistency in the shape of the folds in CA1 in the head of the hippocampus.



To evaluate the consistency of segmentation and registration, we evaluated the match between the template segmentation computed by STAPLE and the warped manual segmentations. The average Dice overlaps are 0.91 for CA1, 0.68 for CA2/3, 0.79 for CA4, 0.64 for DG and 0.66 for VHS/SR.

Discussion

Future research will involve validating the segmentation protocol using histology, increasing the number of samples used to build the hippocampus atlas, building population-specific atlases in dementia, and fitting the atlas to *in vivo* imaging data. The latter will leverage T2-weighted images with 0.5mm x 0.5mm x 2.0mm voxels, in which the separation between hippocampal layers is partially detectable.

References

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