

High-resolution atlas of the human hippocampal formation from *postmortem* 9.4T MRI and reconstructed histology

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Introduction

We present a computational atlas of the human hippocampal formation (HF) constructed from ***postmortem*, high-resolution 9.4T MRI and histology**. The atlas template image is generated by normalizing 25 postmortem MR images in a diffeomorphic registration framework. Histology reconstructed in 3D serves as the primary source for labeling structures in the atlas, including the hippocampal subfields. Our atlas will serve important purposes for study of the HF:

- Prior model for automatic *in vivo* MRI segmentation
- Reference space for anatomical and functional studies [5]
- Anatomy learning resource

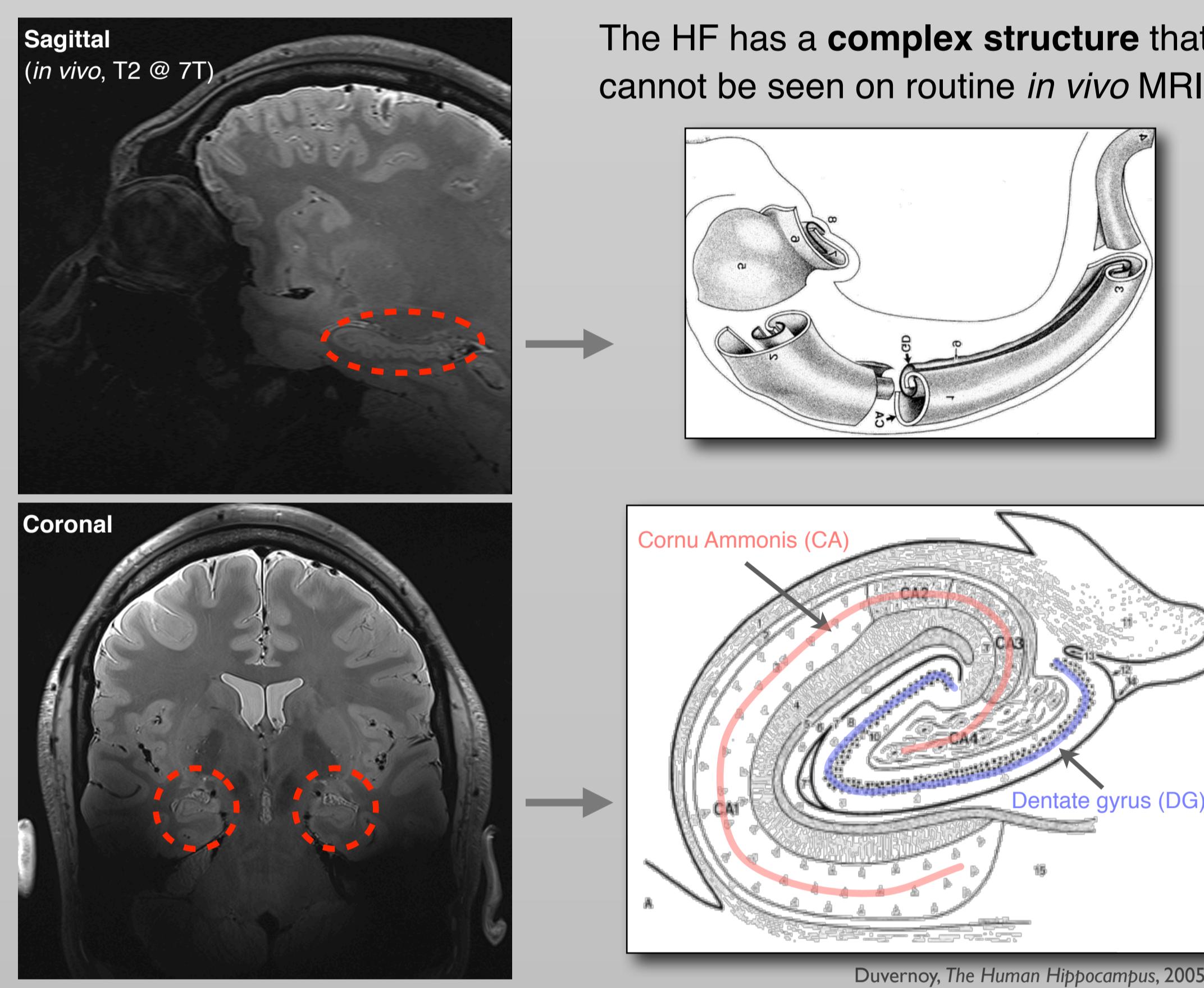
RESEARCH HYPOTHESIS: Our atlas will permit **subfield-specific measures** of hippocampal structure and function in MRI, which will yield more sensitive and specific biomarkers of disease than whole-hippocampal measures.

Background

The **human hippocampal formation (HF)** consists of several structures of the medial temporal lobe that play important roles in declarative memory. The formation comprises the hippocampus proper, as well as the main structures to which its neurons are connected. The HF is divided into microscopically-defined **anatomical subfields** that serve different roles in the memory system and that are differentially affected by the processes of aging and neurological and psychiatric disorders (e.g. dementias, epilepsy, schizophrenia).

MRI is the primary tool for biomarker discovery in the hippocampus, since it is

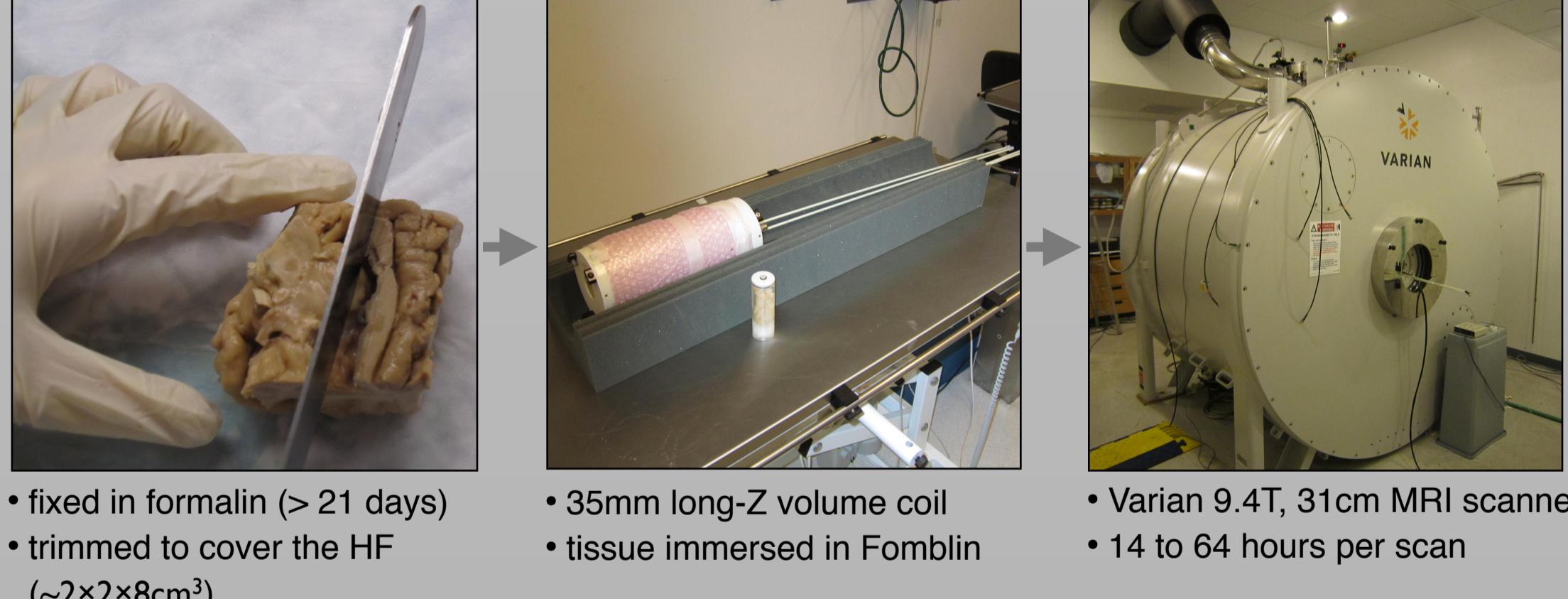
- sensitive to small changes in shape/volume
- robust to repeat measures over time



Data Acquisition

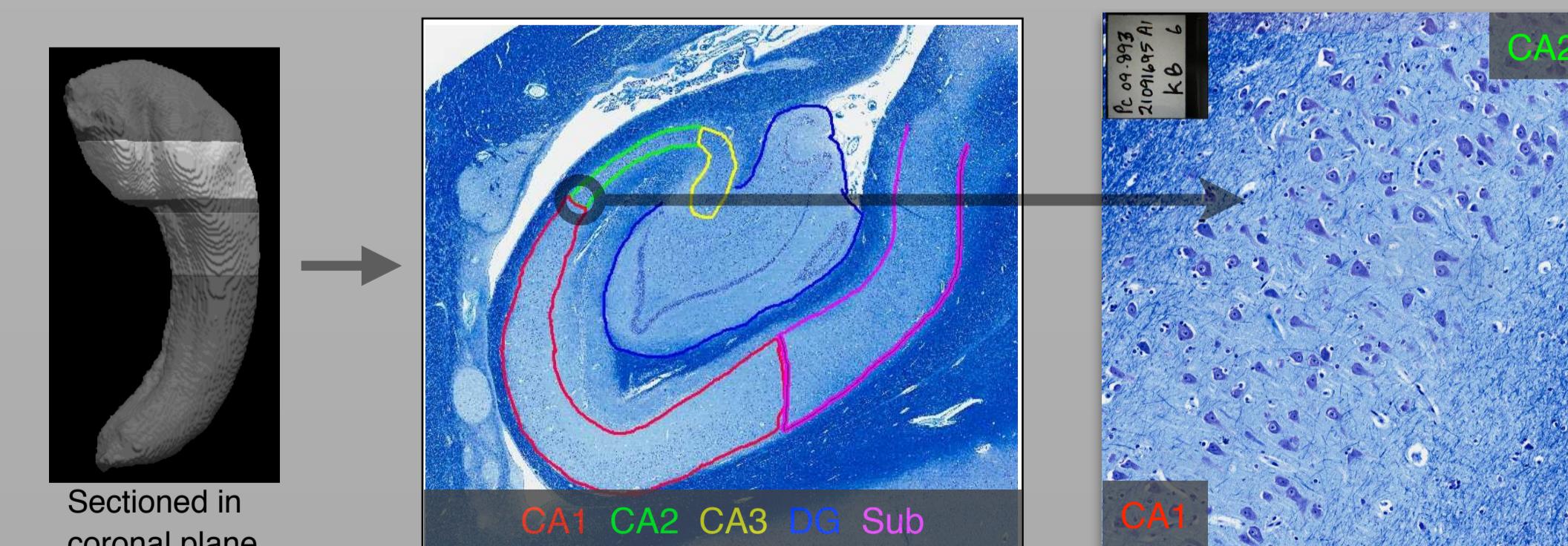
Ultra-high resolution MR imaging of 25 whole hippocampi:

- From 15 autopsy cases: 10 without abnormal neuropathology; 5 with AD
- 0.2mm isotropic resolution (0.2x0.2x0.2mm)
- Spin-echo multi-slice sequence (TR / TE = 4-5s / 23-26ms, >30 averages)



Histology is used to define the HF subfields:

- Tissue sectioned at 5μm thickness and 200μm spacing (to match MRI)
- Klüver-Barrera stain (luxol fast blue + cresyl violet) for **myelin** and **cell bodies**
- Slides digitally scanned at 0.5 μm/pixel



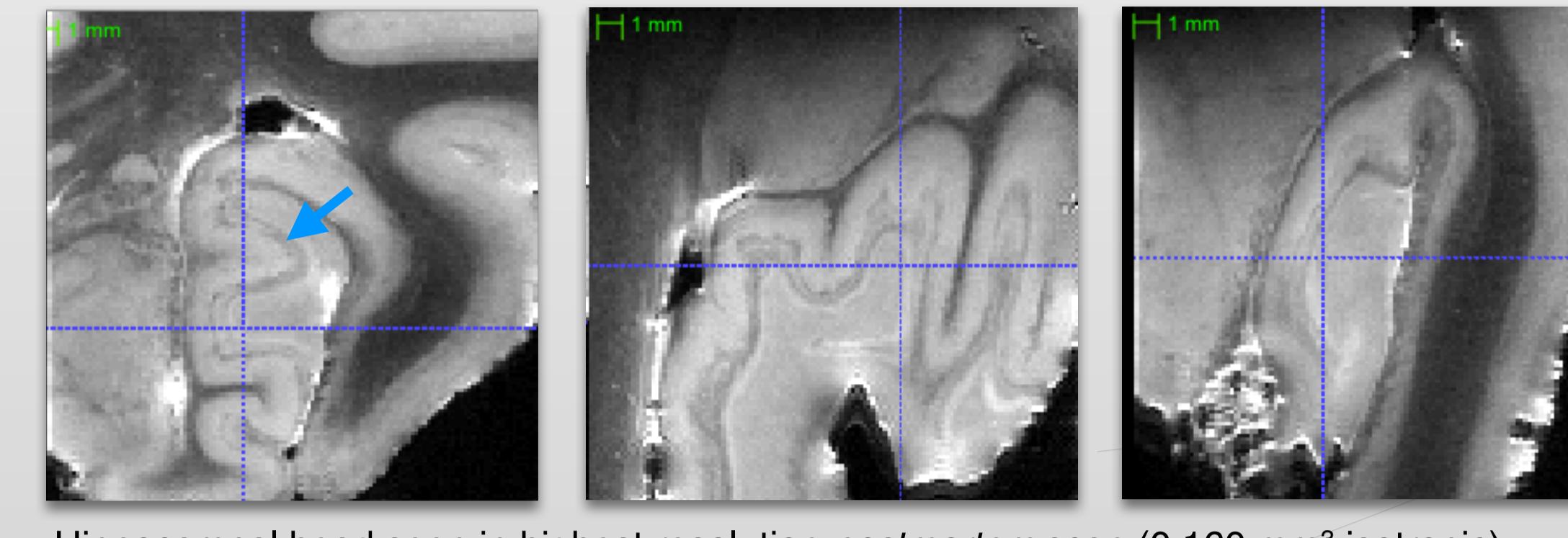
The hippocampal subfields, subiculum, and entorhinal cortex are manually segmented on each histology slice using microscopic cellular features.

References

- [1] Avants, B. and Gee, J.C. (2004), "Geodesic estimation for large deformation anatomical shape averaging and interpolation", *NeuroImage* 23(S1):S139–150.
- [2] Avants, B., et al. (2008), "Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain", *MIA* 12(1):26–41.
- [3] Yushkevich, P.A., et al. (2006), "Continuous medial representation for anatomical structures", *IEEE TMI* 25(2):1547–1564.
- [4] Yushkevich, P.A., et al. (2006), "3D mouse brain reconstruction from histology using a coarse-to-fine approach", *LNCS (WBIR)* 4057:230–237.
- [5] Yushkevich, P.A., et al. (2009), "A high-resolution computational atlas of the human hippocampus from postmortem magnetic resonance imaging at 9.4 T", *NeuroImage* 44(2):385–398.

MRI Template Creation

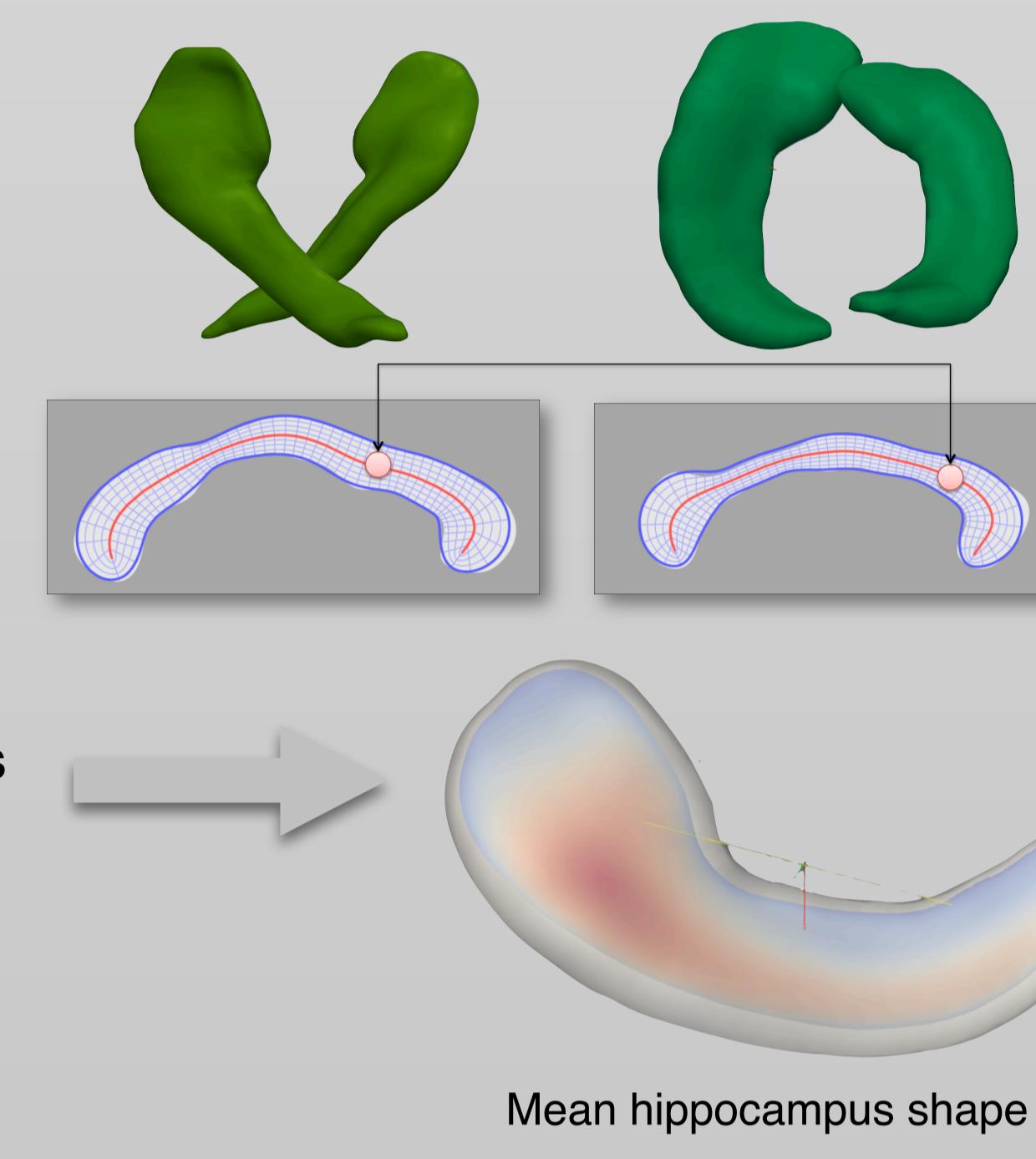
The postmortem MR images show good contrast of structures that cannot be seen on routine clinical MRI, such as the dark band (arrow):



Hippocampal head seen in highest resolution *postmortem* scan (0.160 mm³ isotropic)

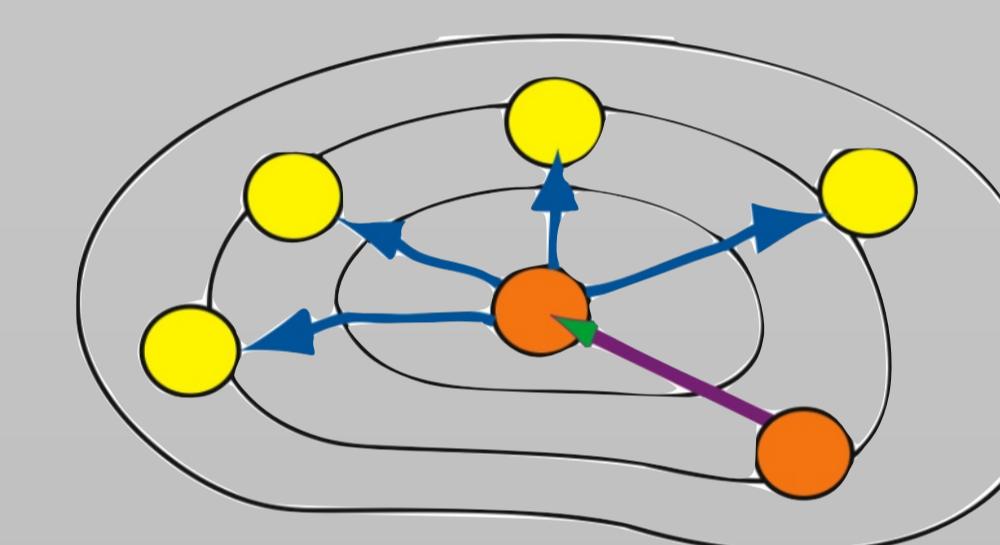
1) The hippocampi are initially aligned using the **continuous medial model representation** (cm-rep) [3]

- Fit cm-rep deformable models to manually-defined hippocampus masks of all subjects
- cm-reps establish geometric correspondence between the hippocampus shapes
- Warp the hippocampus images into a mean shape using the cm-rep coordinate system



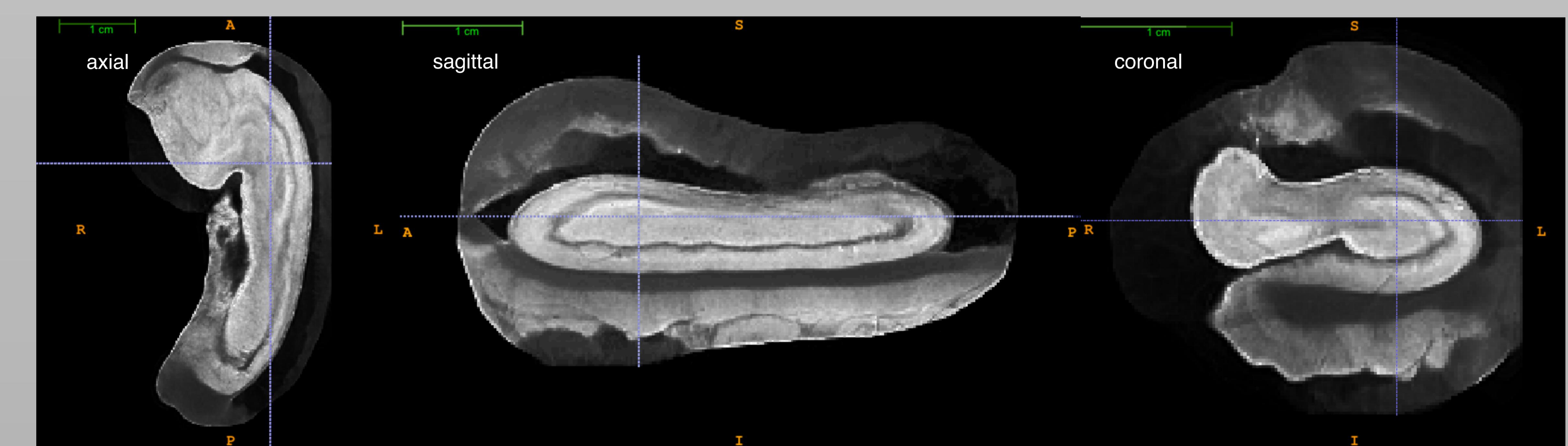
2) Next, the hippocampus images are registered to the initial template above via minimization of geodesic distance [1] with a **symmetric diffeomorphic transformation model** (Advanced Normalization Tools, ANTs) [2]

- Unbiased diffeomorphic averaging creates a template image (orange) that can be registered to each input MRI (yellow) with minimal total deformation

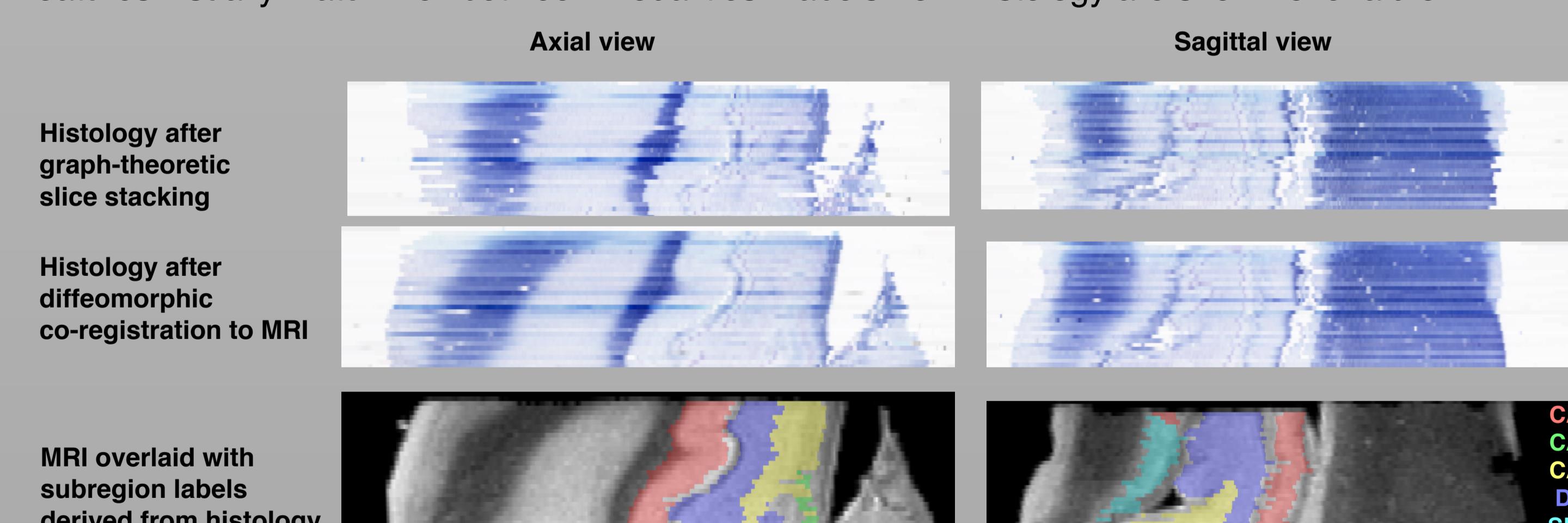


Results

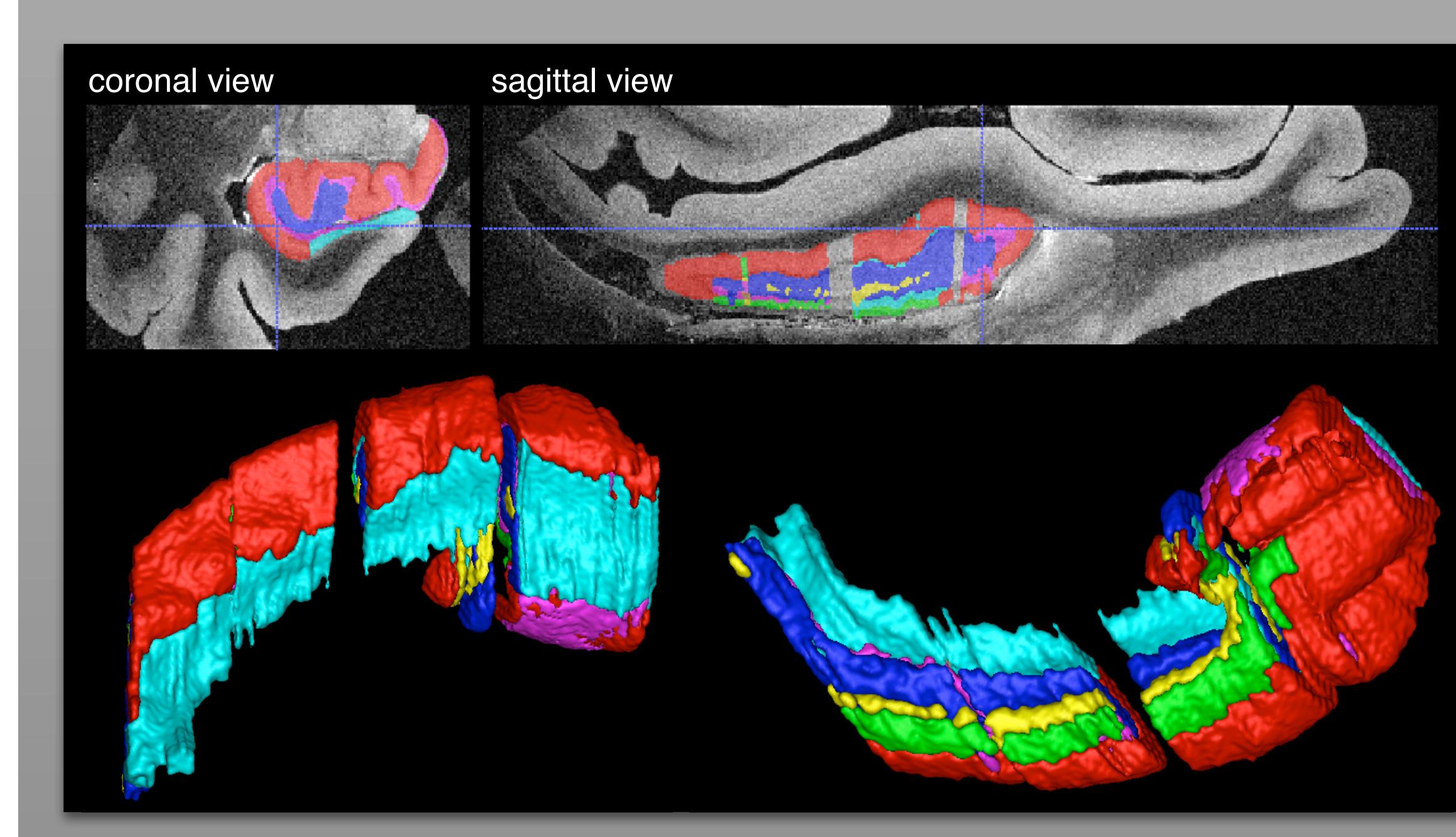
Orthogonal views of MRI atlas template image are shown below. It has similar intensity and shape characteristics to the input images.



Histology reconstructions are compared with MRI following two stages of the pipeline. Co-registration of histology with MRI improves the 3D continuity of structures in the histology volume, and anatomical features visually match well between modalities. Labels from histology are shown overlaid on MRI:

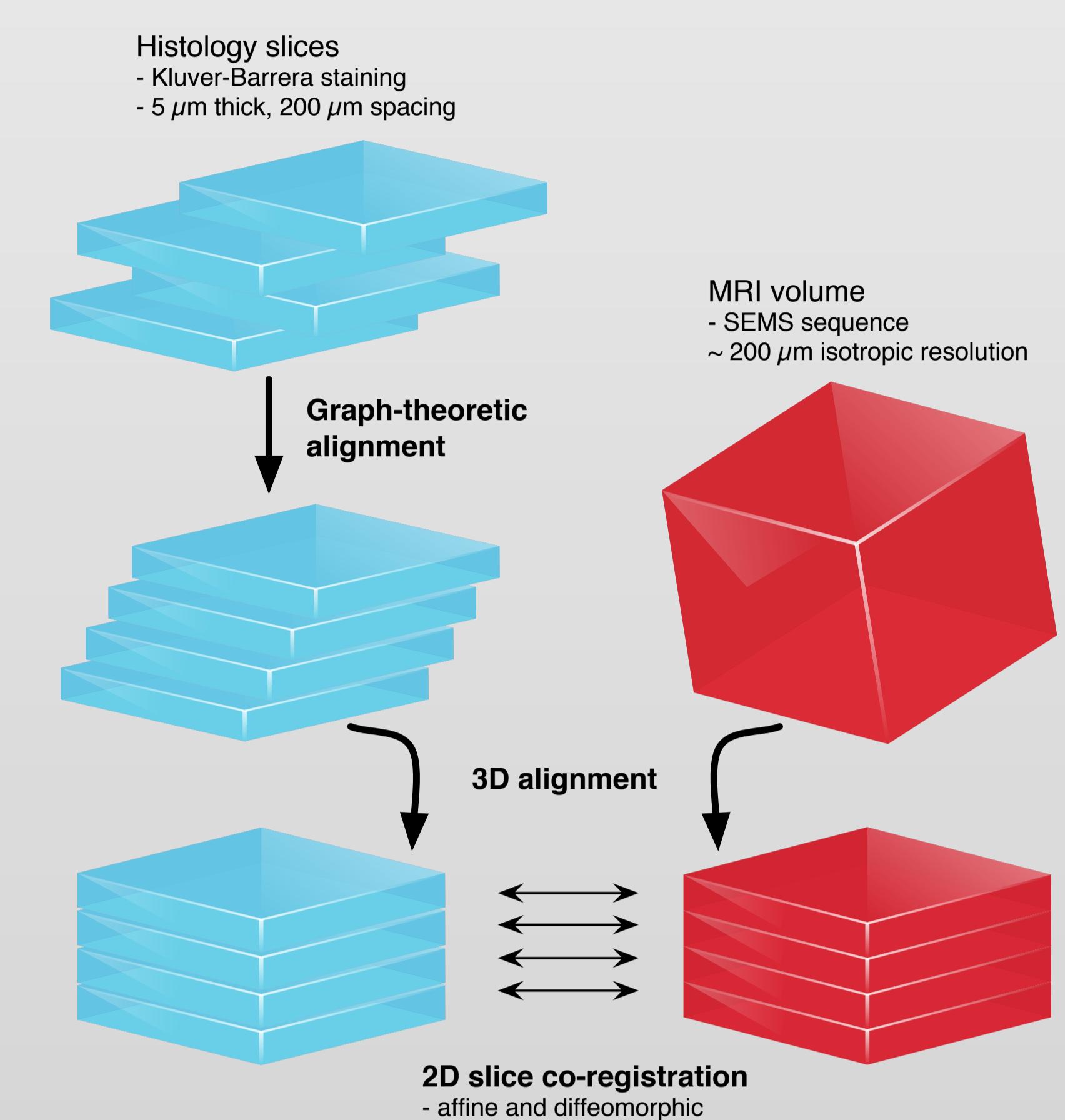


Histology labels from one subject are shown overlaid on the corresponding MRI, along with 3D renderings of the segmentations:

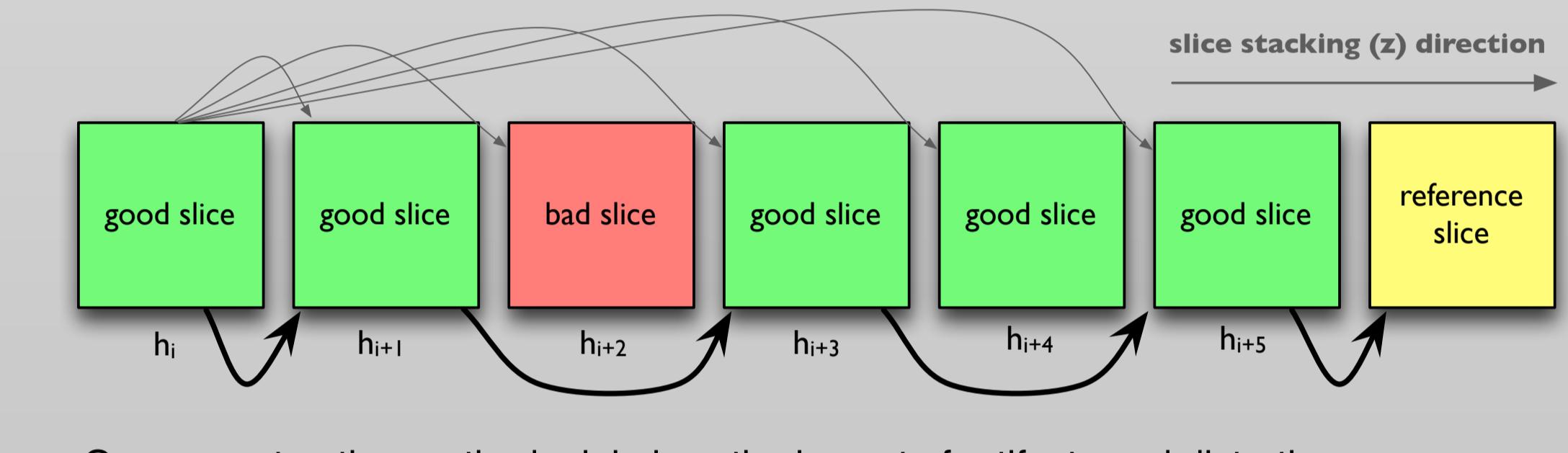


Histology Reconstruction

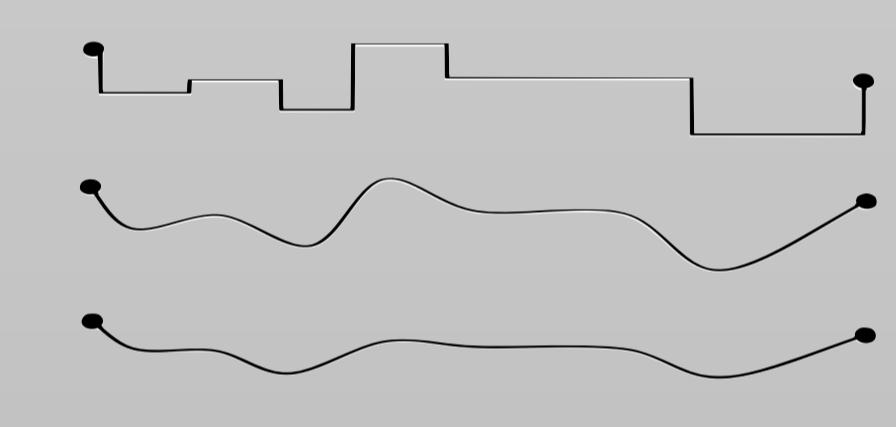
While MRI is advantageous for studying anatomy in 3D, it cannot match the level of cellular detail visible on histology. Thus, we segment the HF subfields on histology. The **histology is then reconstructed in 3D and co-registered with the MR images**. Finally, we transfer the histology labels to MRI space.



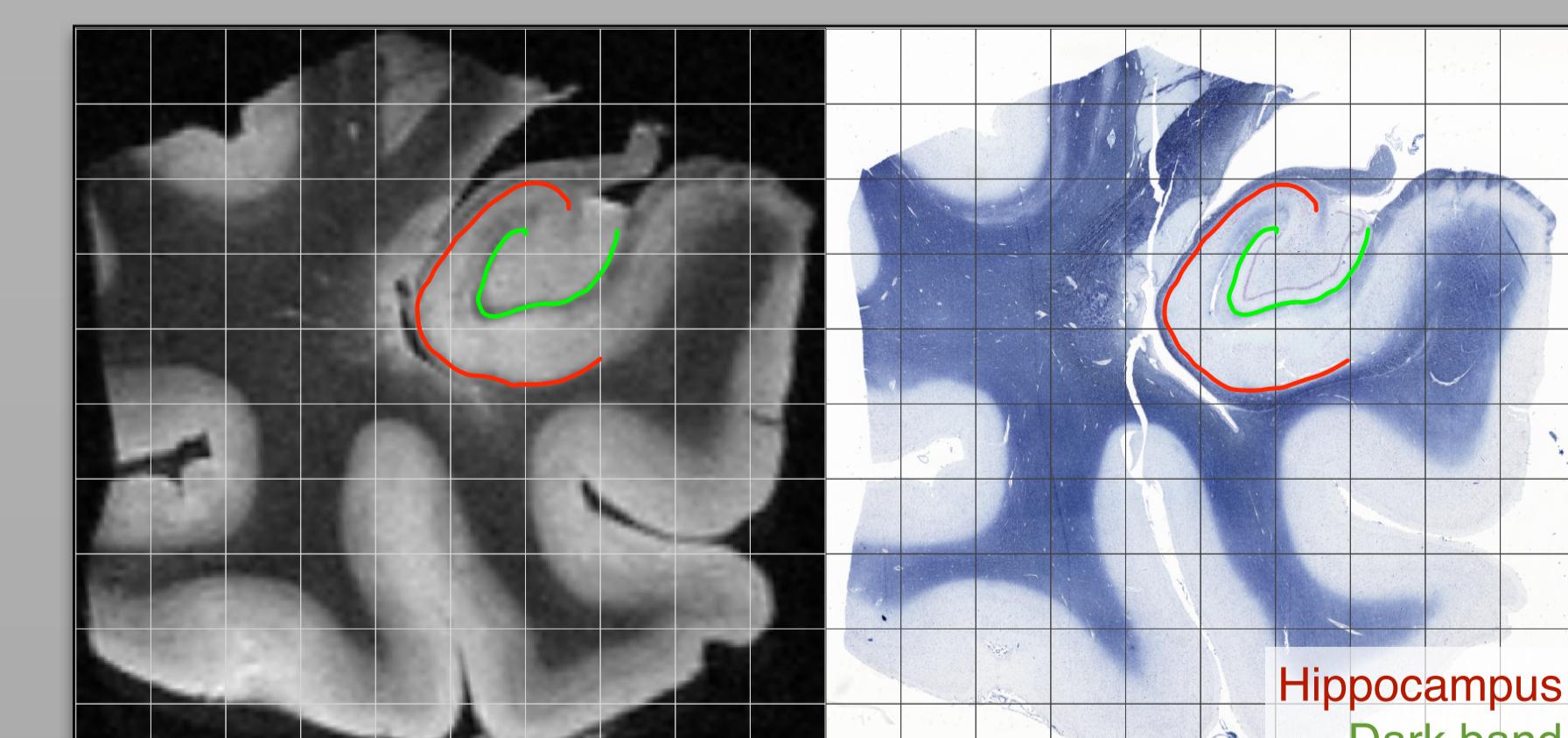
1) Graph-theoretic alignment of slices: compute a sequence of transformations between each slice and a reference slice [4]



2) The reconstruction is refined by iterative affine and diffeomorphic co-registration between histology and MRI



Quantitative evaluation of reconstruction was performed by comparing the distances between corresponding anatomical boundaries in histology and MRI slices:



Conclusions

This is the first work showing hippocampal subfield labels from histology warped into MRI space. We expect our postmortem atlas to serve as a valuable resource for *in vivo* studies by providing prior knowledge on the shapes and distributions of the subfields.

For example, it could serve as a prior anatomical model for MRI segmentation, thereby allowing one to describe subfield volume, thickness, and shape changes in subjects. In Alzheimer's Disease research, this may lead to more sensitive and specific biomarkers of atrophy than are possible with whole-hippocampus volume and shape measures, leading to better cohort selection and treatment effect monitoring in clinical pharmaceutical trials.