Neuroimaging Bridge to CLARITY

Kristi Clark[1], Farshid Sepehrband[2,3], Alexander Talishinsky[4], Samuel Barnes[5], Russell Jacobs[5], Shagun Mehta[4], Celia Williams[4], and Carol Miller[4]

[1]*Institute for Neuroimaging and Informatics, University of Southern California, Los Angeles, CA, United States,* [2]*Centre for Advanced Imaging, The University of Queensland, Brisbane, Australia,* [3]*Queensland Brain Institute, The University of Queensland, Brisbane, Australia,* [4]*Department of Pathology, University of Southern California, Los Angeles, CA, United States,* [5]*Beckman Institute, California Institute of Technology, Pasadena, CA, United States*

Target audience: This abstract is intended for quantitative and microstructural imaging communities.

Purpose: Bridging an understanding of neuroanatomy in the human brain from the cellular level of microns and nanometers to the systems level of millimeters is both challenging and important at this point in history. This project seeks to bridge this knowledge gap by generating and superimposing quantitative models of three-dimensional (3D) connectivity profiles within the human hippocampus at both the cellular level, with the CLARITY method, and at the systems level, with diffusion MRI (dMRI) tractography.

Methods: *Human specimens and tissue preparation.* Human hippocampal tissues were obtained from the USC Alzheimer's Disease Research Center (ADRC) Brain Research Study from patients characterized neurologically and psychometrically and followed to autopsy.

MRI acquisition. MRI data were acquired with a 7T Bruker Biospec system. For dMRI, we acquired 5 non-diffusion-weighted images and 60 diffusion-weighted directions for each of six shells with the following b-values: 1000s/mm^2, 3000s/mm^2, 4000s/mm^2, 8000s/mm^2, 12000s/mm^2, and 16000s/mm^2. The spatial resolution was 200µm x 200µm x 400µm.

CLARITY and immunohistochemistry. Our methods, closely model the description of methods for human brain imaging from the original CLARITY publication (4) with few minor alterations for archived human tissue staining and clearing. Immunostains included anti-neurofilament for axons and DAPI for nuclei.

Co-localization of CLARITY and dMRI. We inserted 3 glass capillary tubes (0.5mm internal diameters) into samples prior to imaging. These tubes are filled with a mixture of fluorescent dye marker for visualization in the two-photon microscopy and MRI contrast agent.

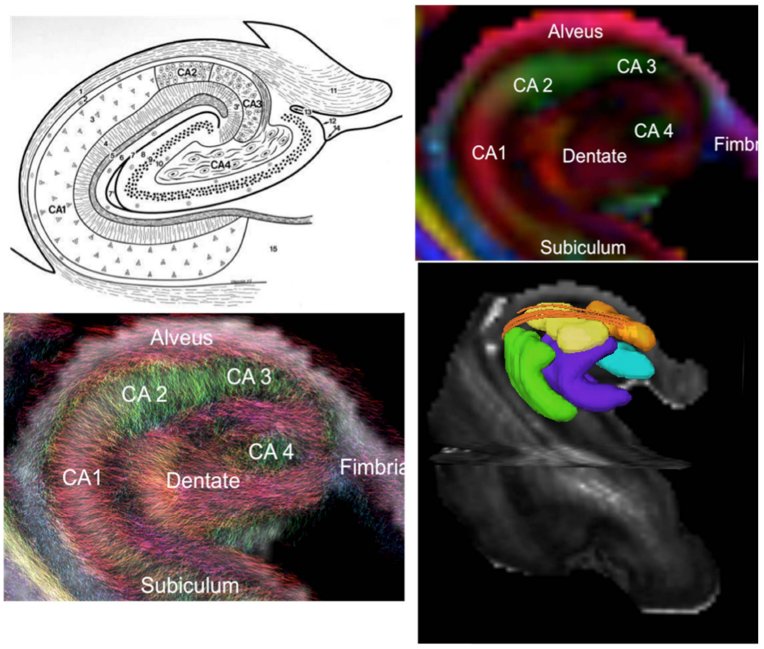

Figure 1. Localization of hippocampal sub-fields. Top left: diagram of hippocampal subfields (1). Top right: identification of major subfields overlaid onto a color-coded RBG map from the diffusion tensor model. Red indicates left-right, green: anterior-posterior; blue: superior-inferior. Bottom left: subfields overlaid on a tract density image (2). Bottom right: Schaffer collaterals (orange lines) identified between CA3 (orange) and CA1 (green) using a streamline tractography algorithm (3). CA2 (yellow), CA4 (cyan) and the dentate (purple) are shown for reference.

Results: Localization of hippocampal subfields was possible in the dMRI data, and the Schaffer collaterals were identified with fiber tracking (Fig 1).

Discussion and conclusions: By downsampling the microscopy results to the same spatial resolution as the dMRI results, we are able to superimpose the two to validate microstructural models of dMRI and tractography.

References

1. Duvernoy HM. The Human Hippocampus : Functional Anatomy, Vascularization and Serial Sections with MRI. 3rd edition ed. Berlin: Springer-Verlag; 2005.
2. Calamante F, Tournier JD, Jackson GD, Connelly A. Track-density imaging (TDI): super-resolution white matter imaging using whole-brain track-density mapping. Neuroimage. 2010;53(4):1233-43. Epub 2010/07/21. doi: 10.1016/j.neuroimage.2010.07.024. PubMed PMID: 20643215.
3. Yeh FC, Verstynen TD, Wang Y, Fernandez-Miranda JC, Tseng WY. Deterministic diffusion fiber tracking improved by quantitative anisotropy. PloS one. 2013;8(11):e80713. doi: 10.1371/journal.pone.0080713. PubMed PMID: 24348913; PubMed Central PMCID: PMC3858183.
4. Chung K, Deisseroth K. CLARITY for mapping the nervous system. Nature methods. 2013;10(6):508-13. doi: 10.1038/nmeth.2481. PubMed PMID: 23722210.