Delivering an Accurate Economically Viable Human Connectome through Four Major Technology Advances

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LRDC BOV Nov 4, 2023

Background

Mapping the human connectome, the long distances of the human brain will be a major scientific accomplishment of 21st century science. Although Connectome projects have made maps of connectivity the accuracy in terms of input output mapping is near chance in most anatomical studies such as the fasciculi in the optic nerve. There is no recognized global accuracy specification for a connectome map that is recognized and accepted by the research community after 14 years of the program.

There are severe accuracy problems and cost problems with Connectome science in its failure to achieve the needed accuracy and scalability to map a whole brain at a viable accuracy, cost, and throughput. There have been a substantial number of reviews that highlight the lack of accuracy and repeatability. After 14 years and over $100 million in diffusion connectome mapping programs, the current accuracy is poor (e.g. hit-false alarms of 13%, d'=0.38[Maier-Hein 2014]). By contrast, the genome accuracy was 99.98%, d'=7.44. Tomas and Pierpaoli, in a PNAS 2014 review of connectome diffusion imaging, stated "diffusion tractography technique that produces anatomically accurate results remains an elusive goal even with DWI data of exceptional quality … (that) would require thousands of hours of scan time…. (Projected improvements) may not overcome the inherent ambiguities in inferring long-range axonal connectivity based on local diffusion displacement profiles." The 669 citations of the PNAS paper detail attempts and failures of MRI head coil methods to replicate established anatomy. The connectivity of eye to LGN has been established since the classic work of Malpeli in 1975. However, this settled anatomy has not yet been replicated by any connectome mapping group. No connectome method can accurately map a full nerve containing 1.2 million of axons over centimeters to accurately link the input output map.

We have learned why the accuracy of most diffusion imaging is limited to near chance. In the visual system fasciculi are in the 0.1 mm size range with "birth order" topology making it so separating the lateral and medial field or M and P systems is near chance with greater than 0.5 mm voxel human clinical MRI.

Costs of mapping the connectome vary greatly with method. The cost of a serial EM of the human brain would cost $12 trillion dollars well above viable budget levels. We use multiple methods and scale to control accuracy and cost.

Novel multiscale multimethod methods

Accurate brain connectome mapping requires tracking fasciculus bundles of thousands of axons with a common path entry and exit to the tract with punctate changes in position within the tract. This project focuses on pioneering the Fasciculus Axon Collagen Tract Multiscale Imaging (FACTMI).

FACTMI technology is capable of delineating axonal routes, myelin and collagen matrices in the human and non-human primate (NHP) brains, with an unparalleled resolution of full brain 20 microns in MRI 2 micron CT, 1 micron light sheet and 0.2 microns Magnify in optical patch imaging. We have developed cutting-edge high-field micro coil MRI, deep learning, and high-throughput histology for an intricately detailed reconstruction of the connectome, validating biologically precise phantoms and our novel tissue-specific imaging techniques.

The resulting intricate mapping of long-distance neural connections and micro-structural features will advance our understanding of the brain's architecture, pathology and function. In large mammals (pig, primates, humans) in optic nerve harvested tissue we are succeeding with multi centimeter tracking.

We synergistically use four methods each with specific strengths:

1. **Micro coil array MRI 16 to 144 channels -** diffusion 100/50 micron resolution, structural 29/20 micron on 7T/14T
2. **Micro CT -** 2.5 micron with connective tissue in high contrast PTA connective tissue stains
3. **Light sheet microscope histology** - 1 micron with connective tissue or myelin stains and
4. **Magnify histology -** 0.2 micron expansion of tissue histology with high accuracy axon distributions in stained tissue of connective tissue, myelin, and vasculature.

Imaging cost are estimated to be $9000 per optic system full human brain in 2026 $60,000 creating a data set of 17 terabytes for early visual system and 194 terabytes for a full human connectome.

Learn More

Contact Walter Schneider wws@pitt.edu videos of the methods are available on request

See ISMR$M 2023 power pitch #1189

Results

We imaged and quantified the tissue with T_2WT MRI and diffusion tractography of a pig, rhesus and human brain. The white matter and gray matter exhibited general integrity, indicating good tissue preservation. White matter tracts are preserved well. The optic nerves displayed different orientations at different depth inside the chiasm. MRI of the dissected optic system has successfully followed optic nerve bundles through optic chiasm and entering LGN. Once entered LGN, the optic nerve projections fan out to form topological organization longitudinally and transaxially. The high resolution T2WT structural images of the optic nerve display clear trackable fasciculi boundaries. The MRI segmented fasciculi of about 0.1 – 0.7 mm in diameter, providing a tube for an estimated 35,000 – 192,000 axons traveling as an MRI tractable bundle. We quantify axonal diffusion signals with parallel traveling fasciculi.

We found that axons travel with no evidence of crossing fasciculi walls. This suggests FACTMIC imaging can provide full mapping of connectivity between cortical sources, supporting comprehensive and accurate mapping of connectivity in large mammal tract systems at viable cost. Fasciculi do migrate within the tract blurring projection paths of fiber tracking with voxel sizes of over 100 microns.

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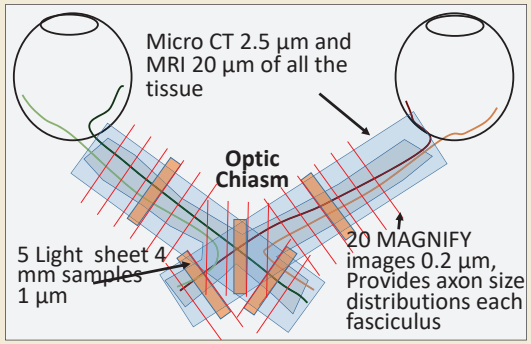
Conclusions & Next steps

Multiscale FACTMIC imaging of the tract holds the potential for full mapping of each axon path from eye to LGN at viable cost on existing animal scanners. We expect to be able to follow groups of clustered fasciculi from the eye to LGN in non-invasive human imaging with quantification of fasciculus and axonal integrity with diffusion and myelin imaging.

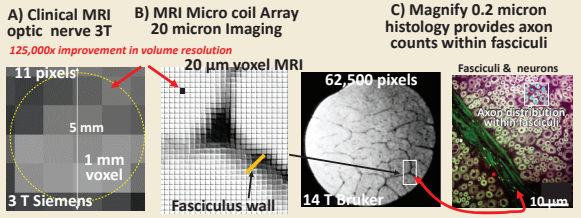
Future steps include parallel array micro coil imaging with 16 and 98 channels. The imaging with the microcells is expected to provide a 13 million time speed up in relative to what it would take do the imaging with a 3T clinical scanner. We expect this to allow full mapping of EVS of the path of every axon eye to LGN to understand visual system anatomy and pathology in large mammals including pig, sheep, rhesus, and human.

Fasciculus Axon Collagen Tract Multiscale Imaging Connectome (FACTMIC)

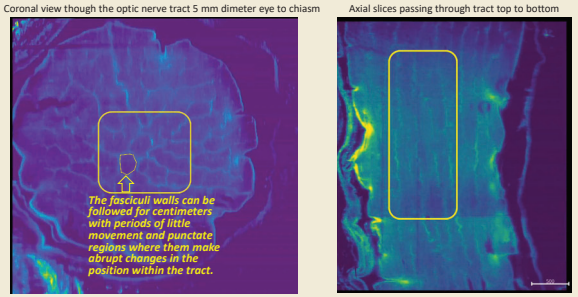
Follow 2.4 million axons within 400+ fasciculi
53,178 images 17 TB data set



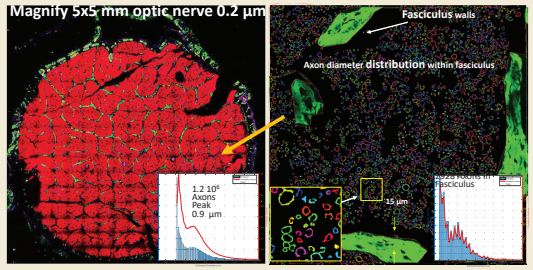
Micro coil delivering 125,000x improvement over clinical MRI optic nerve spatial resolution to follow fasciculi walls



Light sheet following of the fasciculus wall optic nerve 4 mm Z



Magnify tissue expansion 0.2 micron resolution stains of connective, myelin and vascular tissue



Optic Chiasm Crossing phantom structural tensor segmentation into 4 classes of fasciculi based on path left and right eye ipsi or contralateral