Polarization-sensitive optical coherence tomography of the human brain connectome

David A. Boas, Hui Wang, Caroline Magnain, and Bruce Fischl

High-resolution ex vivo imaging of the brain is achieved with a novel technique that will enable studies of normal brain structure and the effects of neurological disorders.

The human brain is composed of approximately 100 billion neurons that ‘communicate’ through an intricate network of axons and dendrites. The difficulty of tracing these 3D neuronal pathways, however, has been a critical barrier for standard histology (the study of microscopic anatomy) over the past 100 years. Indeed, there is still no technology that can be used to acquire microscopic images in undistorted 3D space for mapping human brain connectivity.

Currently available techniques for 3D brain mapping include histological staining and polarized light imaging. In these approaches, 2D image slices are obtained, but these must be physically cut and hence distorted, which makes 3D reconstruction extremely labor intensive and prone to irreducible errors.

Over the past two decades, diffusion magnetic resonance imaging (dMRI) has been used to improve the understanding of regional connectivity and its functional importance in the living human brain. The millimeter-scale resolution of dMRI, however, means that it is challenging to obtain images when fibers from multiple directions come together in relatively compact regions (e.g., the confluence of different bundles, or fan-in regions of the internal capsule or the cerebellar peduncles).

In our work, we have therefore been developing a new method—known as automatic serial-sectioning polarization-sensitive optical coherence tomography (as-PSOCT)—with which it is possible to resolve human neuronal fiber projections and orientations, with 3.5 μm in-plane resolution and better than 50 μm through-plane resolution. In our approach we conduct the imaging in a tissue block-face before cutting induces any distortions. In this way, we can maintain volumetric microscopic registration and enable neuronal fiber tracing over long distances.

A schematic illustration of the envisioned imaging system for mapping the whole human brain connectome is shown in Figure 1.

At present, we have configured our system to image a volume on the order of 10 cm³ rather than the whole human brain (about 1200 cm³). We can thus demonstrate our technology as a proof-of-principle (i.e., a prelude to scientific investigations of the human brain’s structure) and, to date, we have acquired volumetric images that span up to 1 cm³. We have also validated our images against standard Nissl and Gallyas histological staining (see Figure 2). Our PSOCT images have good contrast, which arises from the alignment and density of cell populations and myelinated fibers. In addition, with as-PSOCT, it is possible to resolve the confluence of fiber bundles in brain regions that cannot be distinguished with dMRI (see Figure 3).

Continued on next page
There are, however, currently three main challenges to using our approach for imaging the entire human brain. First, it is necessary to achieve at least a 100-fold increase in the data acquisition rate. Indeed, with our current spectral-domain PSOCT system, we can acquire only 50,000 A-lines per second.\textsuperscript{9} For comparison, previously demonstrated OCT systems have an acquisition rate that is 20 times greater (1MHz).\textsuperscript{10, 11} Second, we need to reduce the amount of speckle noise corruption that plagues all OCT imaging (without sacrificing too much speed or resolution). Third, we need to cut larger sections of tissue so that the optical contrast can be maintained. At present, we use a vibratome to cut agarose-embedded fixed human tissue. The width of the cuts we can achieve is limited to 2cm, but blades do exist for cutting widths of up to 7cm. To image the entire human brain, however, 15cm cuts are necessary. A microtome and hardening of the tissue are thus required. Tissue hardening can be achieved by freezing or by embedding paraffin, but the main challenge is to find a tissue-hardening procedure with which the tissue optical contrast of interest can be maintained.

We are also working to develop our method further so that we can perform neuronal fiber tractography over the whole ex vivo human brain, with a volumetric resolution that is 350,000 times greater than dMRI (i.e., 3.5 $\times$ 3.5 $\times$ 10$\mu$m versus 350 $\times$ 350 $\times$ 350$\mu$m, respectively). This should thus enable the study of human brain connections with unprecedented detail.

Our technology should have broad scientific and clinical relevance, that is, by providing the ability to accurately image both local and long-range circuitry. With our approach there is the potential to elucidate the biological basis of disorders such as autism, as well as to better understand how the interplay of distant brain regions underlies human cognitive capabilities. The as-PSOCT method also provides a novel and important way to validate and train improved dMRI tractography algorithms that are used on in vivo human data.

In summary, we have developed a novel imaging method—as-PSOCT—for ex vivo brain imaging. So far, we have demonstrated this approach with a proof-of-principle setup and have validated the images against standard histological staining techniques. We can currently achieve an in-plane resolution of 3.5$\mu$m and a through-plane resolution of better than 50$\mu$m. By making further developments in our image processing technique, however, we aim to achieve a through-plane resolution that is better than 10$\mu$m (i.e., 350,000 times better than dMRI). In our ongoing efforts we are also working to overcome the major hurdles to using our technique to map the entire human brain. Namely, we wish to substantially increase the data acquisition rate and to find a tissue-hardening method that allows large (15cm) brain cuts to be made. We are confident that with time and sufficient

\textit{Continued on next page}
resources we will meet these challenges, and that within the next
decade we will be capable of using as-PSOCT to provide veridi-
cal images of the whole human brain at unprecedented reso-
lution and contrast. Our work will thus lead to an improved
understanding of normal human brain structure and function,
and of the effects of neurological disorders.

Author Information

David A. Boas, Hui Wang, Caroline Magnain, and Bruce Fischl
Department of Radiology
Massachusetts General Hospital/Harvard Medical School
Charlestown, MA

References

1. S. Herculano-Houzel, The human brain in numbers: a linearly scaled-up primate
2. K. Amunts, C. Lepage, L. Bourdet, H. Mohlberg, T. Dickscheid, M.-È Rousseau,
S. Bludau, et al., BigBrain: an ultrahigh-resolution 3D human brain model, Science 340,
Hütz, et al., High-resolution fiber tract reconstruction in the human brain by means
4. V. Arsigny, X. Pennec, and N. Ayache, Polyrigid and polyaffine transformations: a
novel geometrical tool to deal with non-rigid deformations—application to the registration
5. P. J. Basser, J. Mattiello, and D. LeBihan, Estimation of the effective self-diffusion
Clare, P. M. Matthews, J. M. Brady, and S. M. Smith, Characterization and propagation
other fallacies: the do’s and don’ts of diffusion MRI, Neuroimage 73, pp. 239–254, 2013.
8. D. A. Boas, H. Wang, E. Komukoglu, B. Fischl, S. Sakadzie, and C. V. Magnain,
Imaging human brain cytoarchitecture with quantitative optical coherence tomography,
Presented at SPIE Photonics West 2017.

Continued on next page
