No current imaging technology can directly and without significant distortion visualize the defining microscopic features of the human brain. Ex vivo histological techniques yield exquisite planar images, but the cutting, mounting and staining they require induce slice-specific distortions, introducing cross-slice differences that prohibit true 3D analysis. Clearing techniques such as CLARITY have proven difficult to apply to large blocks of human tissue, and cause dramatic distortions as well. Thus, we have only a poor understanding of human brain structures that occur at a scale of 1-100μm, in which neurons are organized into functional cohorts. This impairs our ability to classify cell types, as the functional properties of any given cell are a function of both its molecular characteristics and the spatial context within which it resides. To date, mesoscopic features such as cortical laminae which are critical components of this spatial context, have only been quantified in studies of 2D histologic images acquired in a small number of subjects and/or over a small region of the brain, typically in the coronal orientation, implying that features that are oblique or orthogonal to the coronal plane are difficult to properly analyze. Our consortium will develop and utilize an imaging infrastructure to create a human brain cell census and instantiate it in a coordinate system that will enable an immediate impact of all in vivo MRI studies of the human brain.

4x4x2 cm tissue blocks will be imaged with serial sectioning polarization sensitive optical coherence tomography (PS-OCT) to obtain 20 μm isotropic resolution images of cyto- and myelo-architectural features and fiber tractography. The issue is to speed up the imaging process. For now the imaging of this single block could take a week to two. One way to speed up is by designing an objective with larger field of view. If we can twice the FOV, the total process time will be