HIGH-RESOLUTION IMAGING OF MYELIN LOSS AND DEGRADATION IN NEURODEGENERATIVE DISEASES WITH BIREFRINGENCE MICROSCOPY

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Degeneration or breakdown of the myelin sheath that wraps and insulates axons of the central nervous system, as well as peripheral nerves, is a factor in a large array of neurological disorders. These include multiple sclerosis, stroke, and age-related neurodegenerative diseases like Alzheimer's Disease (AD). The neuropathological diagnosis of AD requires the presence of neuritic amyloid plaques and neurofibrillary tangles [1], and for decades, a variety of medical approaches for the treatment of AD have focused on the reduction of plaques. However, while these approaches have recently been shown to reduce amyloid burden, there are minimal clinical benefits [2]. In the search for more promising avenues for treatment and prevention of dementia due to AD, a number of research teams have pivoted to focus on the status of oligodendrocytes and myelin integrity in association with AD, and their relationships to the pathogenesis of AD [3]. To elucidate those roles, imaging of myelin must be at high-resolution (~300 nm) to resolve structural detail and early stages of breakdown on the individual axon level; and this imaging must be performed over large volumes of brain tissue to enable quantification of the prevalence of myelin structural defects. Established modalities for imaging myelin include electron microscopy, which is not scalable to scanning large areas of brain tissue, or microscopy of myelin histology stains, which invoke technical and practical limitations that impede quantification or imaging of defects [4].

Myelin structure is highly ordered and anisotropic, on both mesoscopic and microscopic scales, exhibiting strong optical birefringence. Using optical birefringence as a contrast mechanism, we have been advancing the application of quantitative birefringence microscopy (qBRM) to image myelin structure and integrity at the single axon level [5]. Our preliminary studies reveal and quantify myelin structural changes associated with AD dementia. In this presentation we will illustrate the design principles of our custom widefield birefringence microscope and describe the high-throughput extraction of quantitative, high-resolution maps of myelin. Examples of generated images are shown in Fig. 1. The correlation between prevalence of myelin defects and disease stages will be discussed, and the potential impact of the generated information on the management of AD will be addressed.

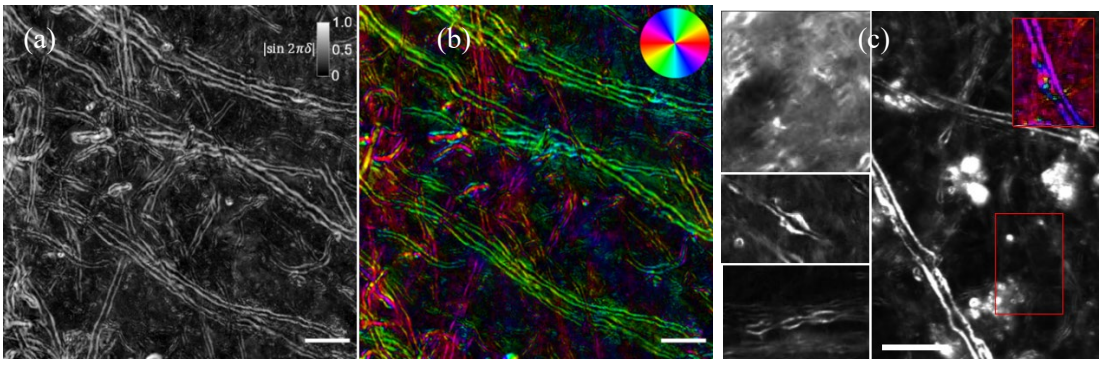

Fig. 1. qBRM images of individual myelinated axons in a rhesus monkey cortex (a & b) and in the human prefrontal cortex of AD patients (c). Edges of the myelin sheathes around axons are visualized. a) a map of the relative retardance of the birefringence signal, which is proportional to the density and thickness of the myelin sheathes; b) an orientation map of the optic axis of the myelin; c) examples of myelin structural defects found with higher prevalence in AD. Scale bars = 15 μm

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