Tauopathies and neuronal connectivity: diffusion imaging and CLARITY

https://neurodegenerationresearch.eu/survey/tauopathies-and-neuronal-connectivity-diffusion-imaging-and-clarity/

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USA

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Research Abstract

? DESCRIPTION (provided by applicant): Bridging an understanding of neuroanatomy from the cellular level of microns to the systems level of millimeters is both challenging and important at this time. We are uniquely poised to undertake this multidisciplinary research topic applied to the human postmortem brain, because we have two PI's: Dr. Carol Miller, M.D., with expertise in the neuropathology and cell and molecular biology of neurodegenerative diseases, such as

tauopathies, especially Alzheimer’s disease (AD), and FTLD-tau variants, using the new CLARITY preparation method for large tissue volume; and Kristi Clark, Ph.D., a neuroscientist with expertise in developing novel neuroimaging methods of high angular and spatial resolution diffusion MRI (dMRI). AIM 1 Examines tau protein detection and effects of axonal aggregates in the human postmortem corpus callosum in AD, and in disease controls, e.g. progressive supranuclear palsy (PSP) a tauopathy, and in neurologically normal, age-matched controls. First, tissues (~1cm blocks) are imaged with dMRI followed by three dimensional (3D) 2-photon microscopy imaging of CLARITY processed tissue immunostained for tau, phospho-tau and neurofilament. Then, we will spatially co-register the dMRI data with the 3D 2-photon microscopy and superimpose the maps to evaluate the sensitivity and specificity of several dMRI metrics for the detection of tau. In AIM 2, cross-sections of hippocampus, one of the earliest sites affected in AD, will be analyzed by dMRI models followed by CLARITY-processed tissues to determine effects of tau aggregation on neuronal connectivity. With the CLARITY protocol applied to formalin-fixed, hippocampal cross-sections, we have already achieved immunolabeling with neuronal subtype markers in 500?m tissue sections. Similarly, we have successfully acquired our dMRI acquisition on the ex vivo human hippocampus, achieving delineation of hippocampal sub-regions and the connectivity among the sub-regions. These studies could potentially lead to development of an in vivo, non-invasive imaging protocol for clinical use in the early diagnosis and monitoring of treatment responses in a myriad of neurodegenerative diseases where protein aggregates form. In future studies, companion, unfixed tissue samples could be examined for molecular correlates pinpointing changes in RNA processing and post-translational modifications, which cannot be done in disease model systems.

Further information available at:

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