Characterizing the glymphatic peri-vascular connectome and its disruption in AD

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Characterizing the glymphatic peri-vascular connectome and its disruption in AD

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1

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Alzheimer's disease & other dementias

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Research Abstract

We are proposing a novel approach to diagnosing early Alzheimer's disease (AD) and predicting progression via a robust biomarker that captures 'glymphatic' pathway transport on a systems level. The glymphatic pathway is a brain-wide system, which was recently discovered to function as a clearance pathway for toxic brain waste proteins including soluble amyloid beta (A?) and tau similarly to the classical body-wide lymphatic system. As such, the glymphatic pathway comprises a previously overlooked and unique compartment of the brain vasculature, the peri-vascular space wherein cerebrospinal fluid (CSF) is flowing and streaming into the brain interstitial fluid (ISF) space thereby forcing waste solutes out of the brain. Except for rare familial AD, where excessive A? production and deposition in the brain clearly drives cognitive decline, there is limited evidence in the more common sporadic AD that cerebral A? accumulation is the result of A??overproduction. In fact, emerging evidence suggests that parenchymal A? accumulation in sporadic AD is driven by reduced A? clearance. The glymphatic pathway is thus a prime candidate for linking disruptive clearance of A? to AD, and we will use this opportunity to develop new tools and computational analysis aimed explicitly at capturing global glymphatic pathway function and serve as a novel diagnostic AD biomarker. Currently there is no method available to capture all of the intricate and dynamic components of glymphatic transport, in particular, parenchymal transport and clearance pathways. We propose to integrate imaging techniques and develop novel computational analysis including optimal mass transport to characterize the glymphatic pathway as a brain-wide dynamic 'unit'. The ultimate goal of the proposed investigation is to apply the glymphatic biomarker and track its disruption in progressing vascular and parenchymal amyloid pathologies. The proposed studies are based on novel preliminary findings that 1) glymphatic transport can be visualized as an integrative system through perivascular and interstitial spaces; 2) that state dependent changes induced by specific anesthetic regimens which dramatically affect the glymphatic transport can be captured by optimal mass transport analysis; and 3) a new transgenic rat model of cerebral amyloid angiopathy (rTg-SwDI) which will be used for specific hypothesis testing against the transgenic rat AD model (rTgF344-AD36) in the proposed studies. The specific aims are the following: (1) To develop biomarkers to visualize and functionally quantify macroscopic, glymphatic transport based on computational analysis of MRI and macroscopic optical imaging of CSF tracers in normal young (3 month old) rats and (2) to determine how and when normal aging and specific AD-like cerebral vascular and parenchymal amyloid pathologies influence glymphatic transport in the brain using the computational pipeline developed in SA1. Successful completion of the proposed highly innovative experiments will yield an entirely new and promising biomarker to track reduced Aß clearance via the glymphatic pathway which is key to the propagation of CAA and AD.

Lay Summary

PROJECT NARRATIVE We propose to develop an imaging "biomarker" to identify the changes in the 'glymphatic' system that occur due to normal aging and, in particular, following deposition of amyloid plaques. Pre-clinical studies show that the glymphatic system is involved with brain-wide metabolic waste clearance, including removal of beta- amyloid. The glymphatic biomarker will be used to detect early-stage disease such as vascular amyloidosis with deposits in the small blood vessels and/or within the brain tissue itself. The goal is to understand how dysfunction of the glymphatic system contributes to further amyloid buildup evident in Alzheimer's disease and to cognitive deficits. The novel studies will be performed in two different (and new) transgenic rat models of amyloid disease which closely mimic the human

conditions of cerebral vascular or parenchymal amyloid pathologies.

Further information available at:

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