Role of glymphatic-lymphatic system in CNS fluid homeostasis and potential dysregulation in Alcohol Use Disorder

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Recent data show that CNS fluid homeostasis is critically dependent on the interconnected glymphatic and meningeal lymphatic systems. The two systems are considered 'coupled', when the glymphatic outflow of 'dirty' brain fluids collects into the meningeal lymphatic vessels and drains to the deep cervical lymph nodes (dcLN). Impairment of the two systems has been linked to cognitive impairment, however, whether "uncoupling" accelerates neurodegeneration remains controversial. Here we present data based on novel advances in imaging and computational fluid dynamic analysis for tracking the glymphatic-lymphatic functional interplay in the live brain.

Methods: To measure glymphatic-lymphatic system function we used dynamic magnetic resonance imaging (DCE-MRI) with Gd-based contrast injection into the CSF. DCE-MRI data was analyzed using computational fluid dynamics analysis based on unbalanced regularized Optimal Mass Transport (urOMT) theory to generate brain maps of CSF flow dynamics, glymphatic mass gain/loss in relation to drainage to the dcLN (i.e., 'coupling' status) (Chen et al., 2022). We applied our toolbox to a rat model with: i) advanced neurodegeneration in the form of cerebral amyloid angiopathy (CAA type 1) and ii) chronic brain drainage impairment – blocked dcLN drainage - to examine glymphatic-lymphatic coupling status under different pathological conditions.

Results: We observed that the CSF directional flow patterns and mean speed were strikingly different across the two models. In rats with CAA type 1, the mean CSF flow speed was increased by 20% and flow trajectories at the skull base were diverted away from the brain resulting in decreased glymphatic solute flux and time-delayed clearance. In contrast, in rats with blocked dcLN drainage, the CSF directional flow pattern was normal. However, the mechanical stress increased the rat's intracranial pressure and resulted in accelerated glymphatic clearance via engagement of alternate extracranial perivenous drainage pathways.

Discussion: Here we uncovered two different types of glymphatic-lymphatic uncoupling. In the setting of advanced neurodegeneration (CAA type 1) uncoupling manifested as rerouting of CSF flow streams away from the brain resulting in decreased glymphatic transport and time-delayed dcLN drainage. On the other hand, in the context of mechanical stress uncoupling manifested as premature glymphatic solute clearance and engagement of alternate brain drainage routes. Our data provide new insights and show that multiple metrics of glymphatic-lymphatic function must be tracked to interpret pathophysiology related to dysregulation of CNS fluid homeostasis and brain waste clearance. Our new techniques are being applied to bridge the gap in knowledge regarding the status of glymphatic-lymphatic *coupling* in alcohol use disorder.

References: Chen X*, et al.* Cerebral amyloid angiopathy is associated with glymphatic transport reduction and time-delayed solute drainage along the neck arteries *Nature Aging* **2**, 214-233 (2022)

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