Deep Cervical Lymphovenous Anastomosis (dcLVA) Expedites Glymphatic Drainage In Alzheimer's Disease Rat Model

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- dcLVA alleviates glymphatic stasis by accelerating tracer clearance in AD brains.
- ULM shows dcLVA restores microvascular arterial and venous perfusion toward normal levels.
- dcLVA increases AQP4 polarization and promotes neuroreparative glial phenotypes.
- dcLVA affects the coupled axis of brain clearance, perfusion, and homeostasis.

INTRODUCTION

Alzheimer's disease (AD) is increasingly linked to dysfunction of the meningeal lymphatic and glymphatic systems, contributing not only to impaired waste clearance but also to neurovascular and microenvironmental dysregulation. Deep cervical lymphovenous anastomosis (dcLVA) is a microsurgical strategy to improve cervical lymphatic outflow, but its mechanisms in AD remain unclear.

METHODS

We established a dcLVA surgical intervention in App^{NL-G-F} rats and applied a multi-modal imaging and histological framework to assess clearance-related tracer transport, cerebral microvascular morphology and perfusion, and AD-related tissue changes. Dynamic contrast-enhanced MRI was used to evaluate tracer transport kinetics, ultrasound localization microscopy to characterize microvascular structure and hemodynamics, and histological analyses to examine amyloid-β (Aβ) deposition, AQP4 polarization, and glial phenotypic markers.

RESULTS

The dcLVA procedure maintained high short-term patency and improved exploratory behavior and spatial learning in AD rats. MRI tracer kinetic modeling showed that dcLVA alleviated glymphatic stasis through accelerated clearance and increased parenchymal influx. Hemodynamic analyses further demonstrated that dcLVA restored arterial and venous perfusion toward normal levels. At the tissue level, dcLVA increased cortical AQP4 polarization and was accompanied by marker-based shifts in microglia and astrocytes toward a less inflammatory and more reparative profile.

CONCLUSIONS

Our study demonstrates that dcLVA influences AD-related brain dysfunction by modulating downstream cervical lymphatic outflow and thereby reshaping coordinated aspects of clearance-related transport, microvascular perfusion, and glial homeostasis. These findings provide a preclinical rationale for lymphatic-targeted intervention in AD.

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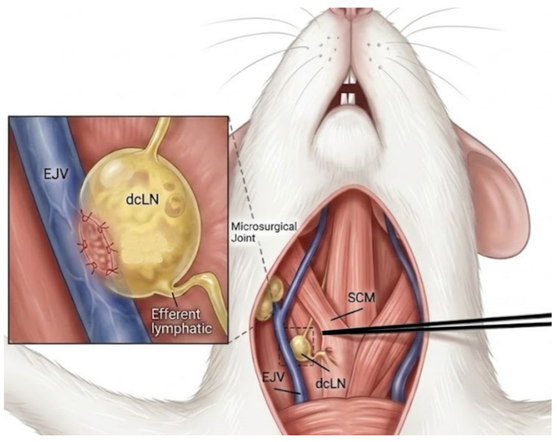
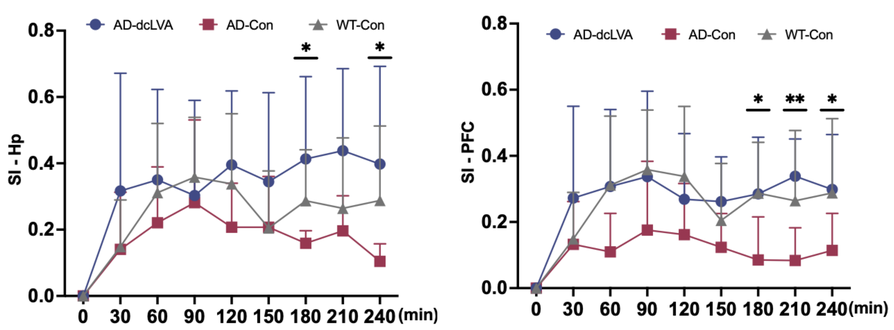
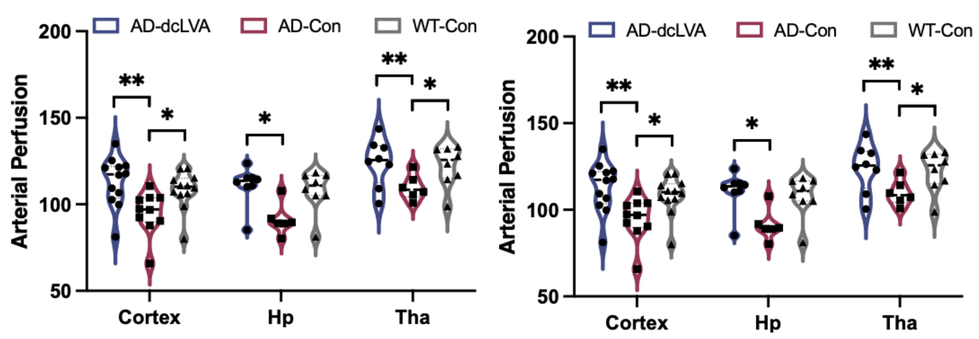


Schematic diagram of the deep cervical lymphovenous anastomosis (dcLVA) surgery EJV: external jugular vein; SCM: sternocleidomastoid muscle; dcLN: deep cervical lymph node



Post-injection changes of Signal Intensity fold change in Hippocampus (Hp), Prefrontal Cortex (PFC) among dcLVA, WT-Con and AD-Con groups.



Group comparisons of arterial and venous perfusion in cortex, hippocampus and thalamus among dcLVA, WT-Con and AD-Con groups.