Assessing Glymphatic Clearance in a Preclinical Model of Amyotrophic Lateral Sclerosis

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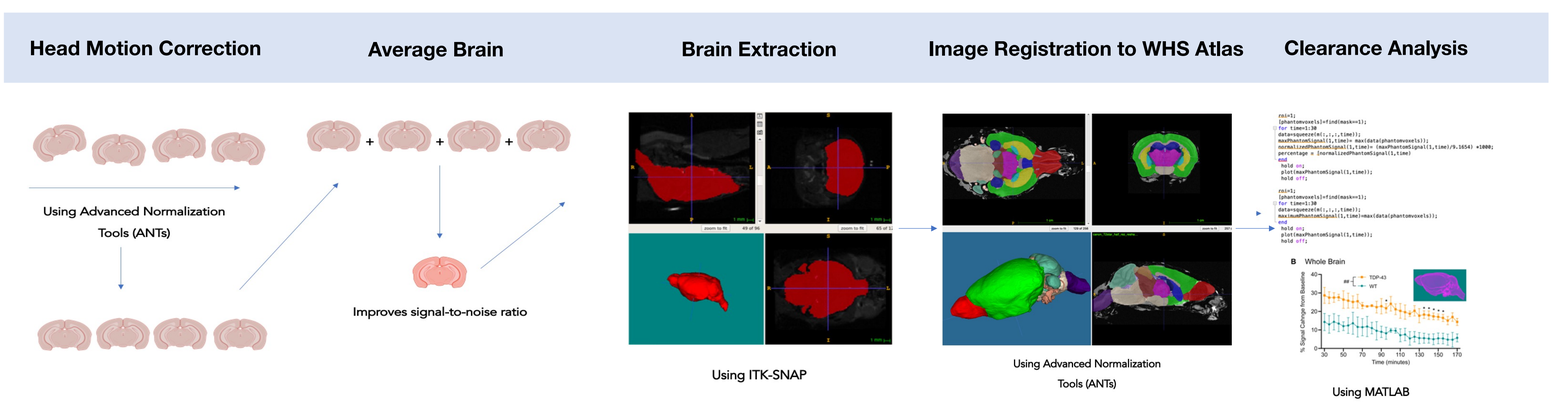
Background

A pathological hallmark of ALS is the presence of insoluble aggregates of abnormally phosphorylated TDP-43 proteins(1,2). Is the glymphatic system, a pathway to clear solutes, impaired in ALS?

- Neurodegenerative diseases are chronic and inexorable conditions characterized by the presence of insoluble aggregates of abnormally ubiquitinated and phosphorylated proteins(1,2).
- Following the discovery of the glymphatic system as a pathway to clear solutes, it has been suggested that impaired glymphatic function may contribute to both the initiation and progression of neurodegenerative diseases. However, this has yet to be demonstrated in ALS.
- This project assesses the function of the glymphatic system in a transgenic mouse model of ALS.

Study design and methods

- This study utilized NEFH/NLS+ double transgenic mice with doxycycline (Dox) regulatable expression of human TDP-43 (hTDP-43), deficient in its nuclear localization sequence (NLS) to allow cytoplasmic aggregation of TDP-43, (referred to as TDP-43 mice).
- The first part of this study aims to investigate the function of the glymphatic system at the symptomatic disease course of ALS while the second part of the study investigates at the asymptomatic disease stage.
- A series of MRI analysis (flow chart below) was done to evaluate glymphatic clearance.



Results

Impaired glymphatic clearance in the whole brain, limbic system, and pons of TDP-43 mice

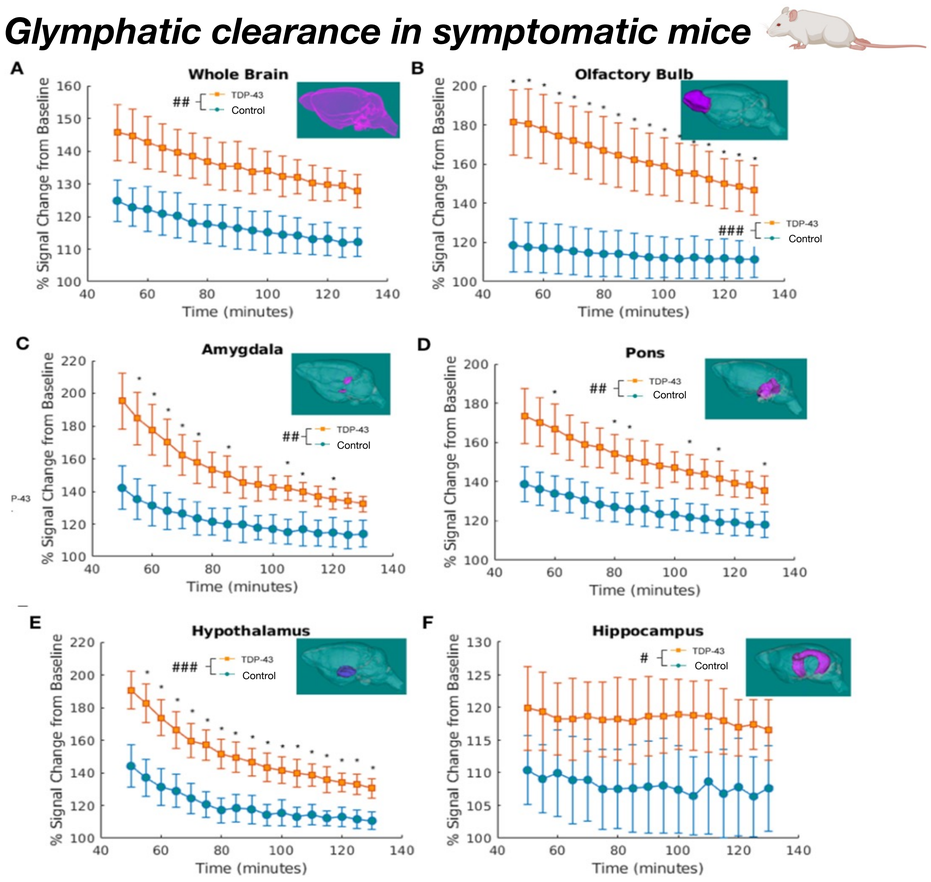


Figure 1. Impaired glymphatic clearance in <u>symptomatic</u> TDP-43 mice. Following overexpression of hTDP-43, DCE-MRI demonstrated increased residual intensity and impaired whole brain (Figure 1A) glymphatic clearance in symptomatic TDP-43 mice. Limbic structures such as the hypothalamus, olfactory bulb, amygdala, and hippocampus (Figure 1B,1C,1E and 1F) showed significant impairment of glymphatic clearance. Impaired glymphatic clearance was also found in the pons of TDP-43 mice (Figure 1D).

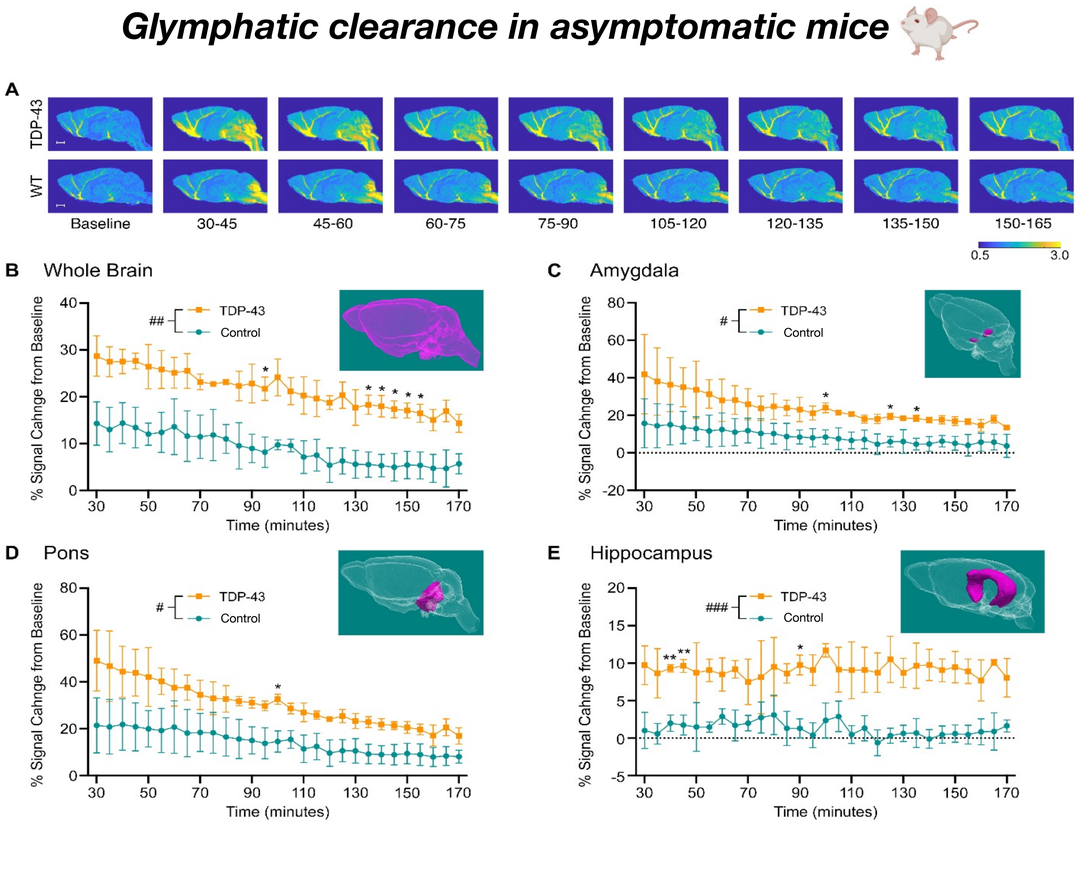


Figure 2. Impaired glymphatic clearance in <u>asymptomatic</u> TDP-43 mice. The representative DCE-MRI images of TDP-43 and control mice overtime (Figure 1A). DCE-MRI also demonstrated increased residual intensity and decreased glymphatic clearance in the whole brain (Figure 1B), limbic system (amygdala and hippocampus, Figure 1C and 1E) and pons (Figure 1D) TDP-43 mice.

Conclusion

The glymphatic system is impaired in both symptomatic and asymptomatic TDP-43 mice.

- Reduced glymphatic clearance observed in TDP-43 mice may be associated with:

Disturbed sleep(3)
↑ Levels of norepinephrine
↓ Interstitial space volume
↑ CSF influx resistance

Impaired respiratory function(4)
↓ Strength of the muscles
↓ function of the respiratory system
↓ CSF flow by respiratory system
↓ Glymphatic influx

Abnormal AQP4 expression(5)
↓ Polarization of AQP-4
↑ CSF flow resistance
↓ CSF-ISF exchange
Possible causes: Genetics and aging factors

BBB breakdown(6)
↓ dysfunction and damage to choroid plexus elements and endothelial cells
↓ glymphatic clearance

- Reduced glymphatic clearance may result in the progressive spread of TDP-43 which leads to reduced transmission of motor information from the brain to the muscles through the corticospinal tract(7) possibly resulting to muscle paralysis.
- Impaired glymphatic clearance in the limbic system may promote psychological issues and dementia as is often found in ALS patients(8).

This study presents a potential role for the glymphatic system as a therapeutic target in ALS disease progression and a sensitive marker for detecting ALS-associated brain abnormalities.

- In ALS, TDP-43 accumulates before brain damage and symptom onset(1,2) and hence, the glymphatic system may be a possible therapeutic target and early disease detection.

References

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