

A Multimodal Approach To Characterizing Molecular Interactions Between Traumatic Brain Injury And Alzheimer's Disease

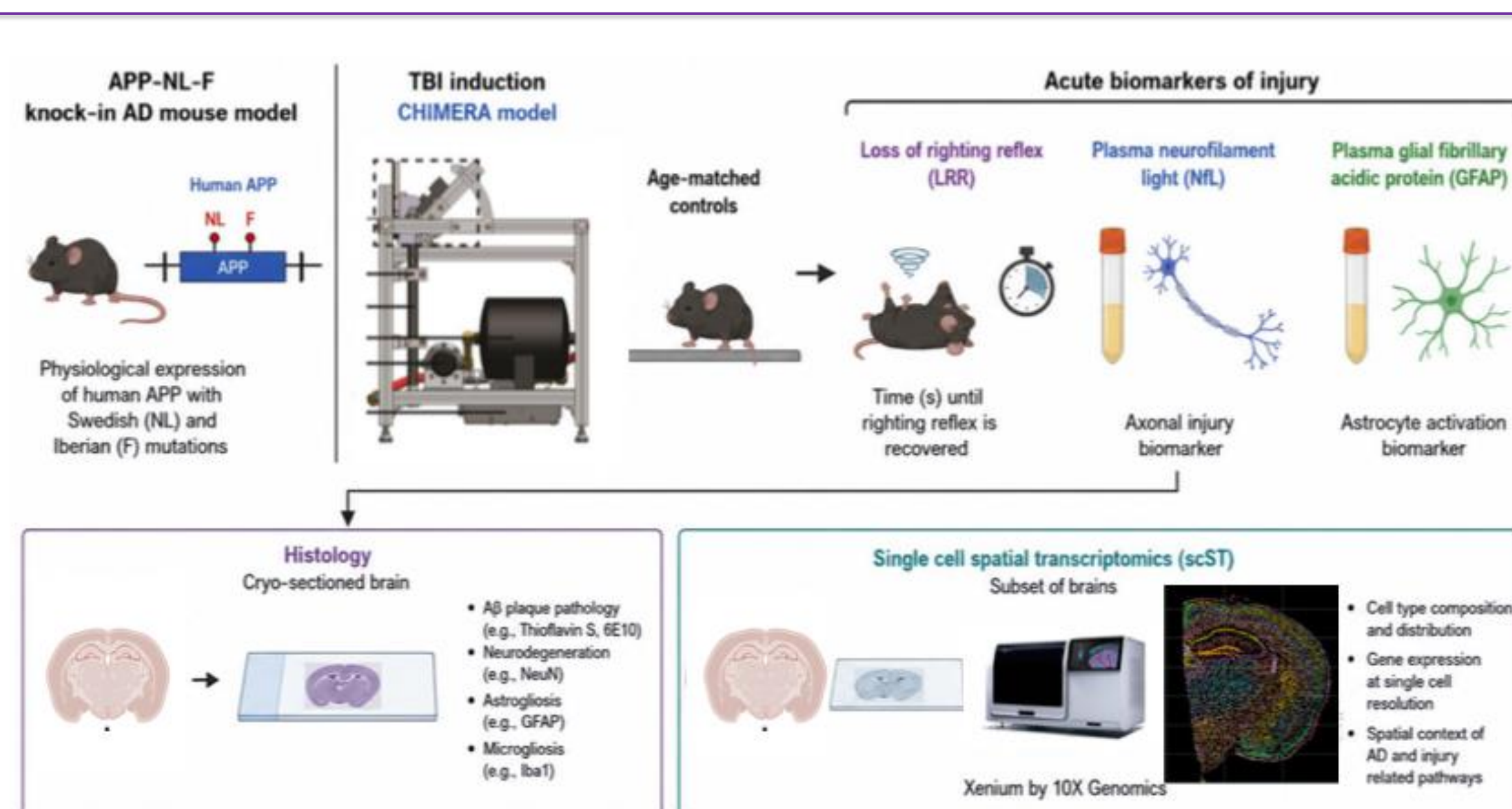
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INTRODUCTION

Alzheimer's disease (AD) risk and progression may be significantly modified by traumatic brain injury (TBI). TBI results in multifaceted neuropathology including neuroinflammation, neuronal loss, axonal damage and cerebrovascular damage.

While age at injury is linked to worse outcomes, the molecular mechanisms underlying interactions between TBI and AD remain unclear. *Analysis of molecular and cellular changes that occur in injured brain is crucial to understand TBI's contributions to dementia and AD.*

METHODS

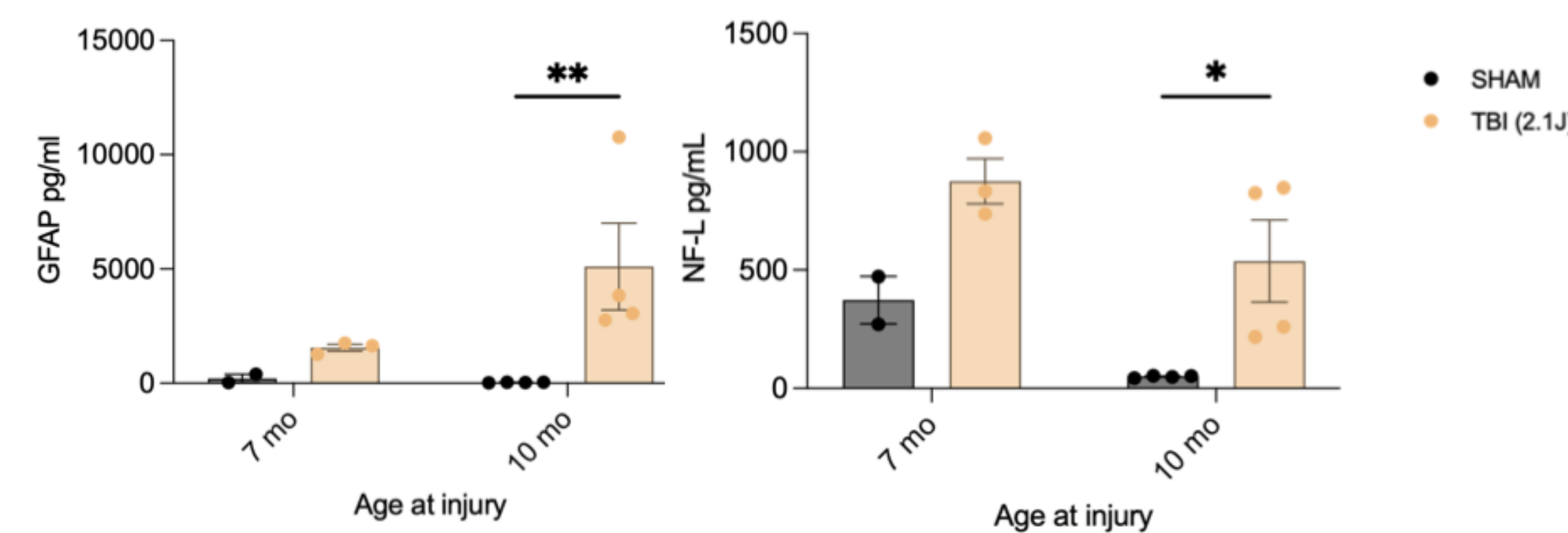


We used APP knock-in NLF AD mouse model, that express physiological levels of human APP containing the Swedish (NL) and Iberian (F) mutations, and studied them at 7, 10, 12, 14, 16, 18 and 20 months of age. TBI was induced using the Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA) model and age matched uninjured controls were included. Acute loss of righting reflex as well as plasma biomarkers were quantified. Brains were cryo-sectioned for histology and spatial transcriptomics analysis.

RESULTS

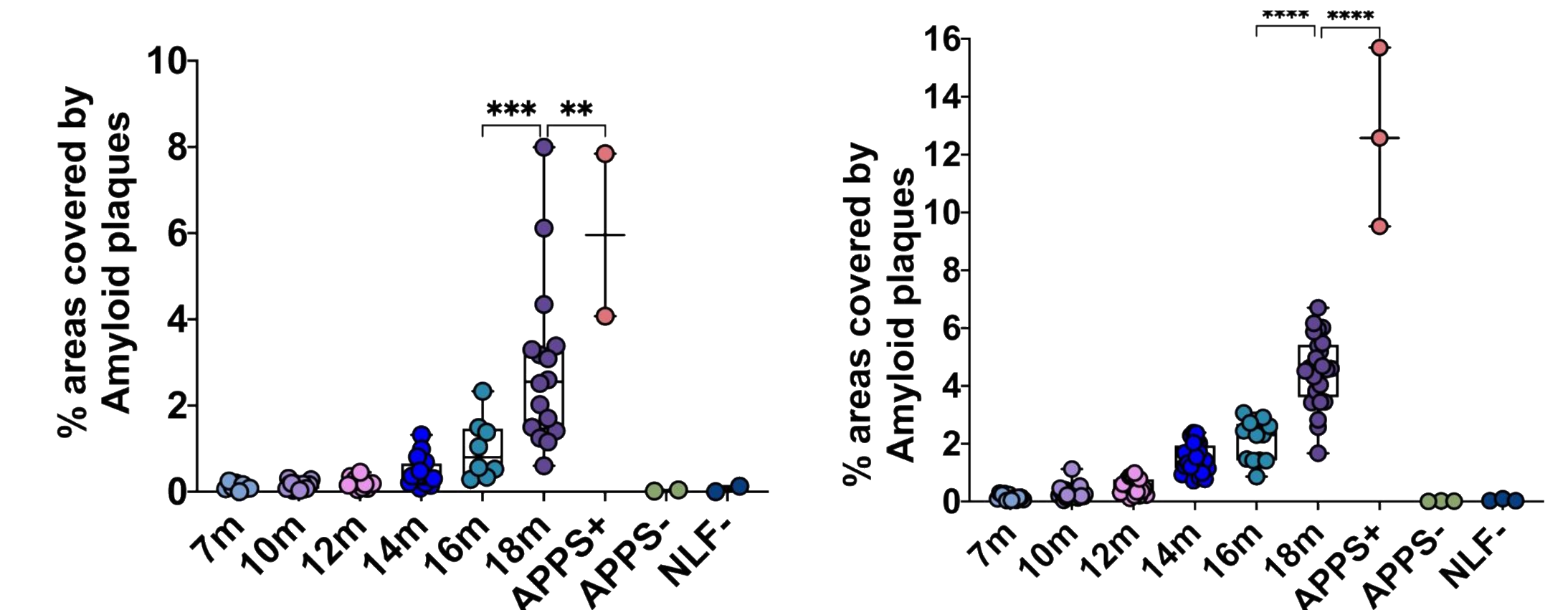
Behaviour and Biomarkers

Injured AD mice showed delayed righting reflex recovery and had higher plasma GFAP and NfL levels as compared to shams, with GFAP levels demonstrating an age-dependent increase in the injured group.



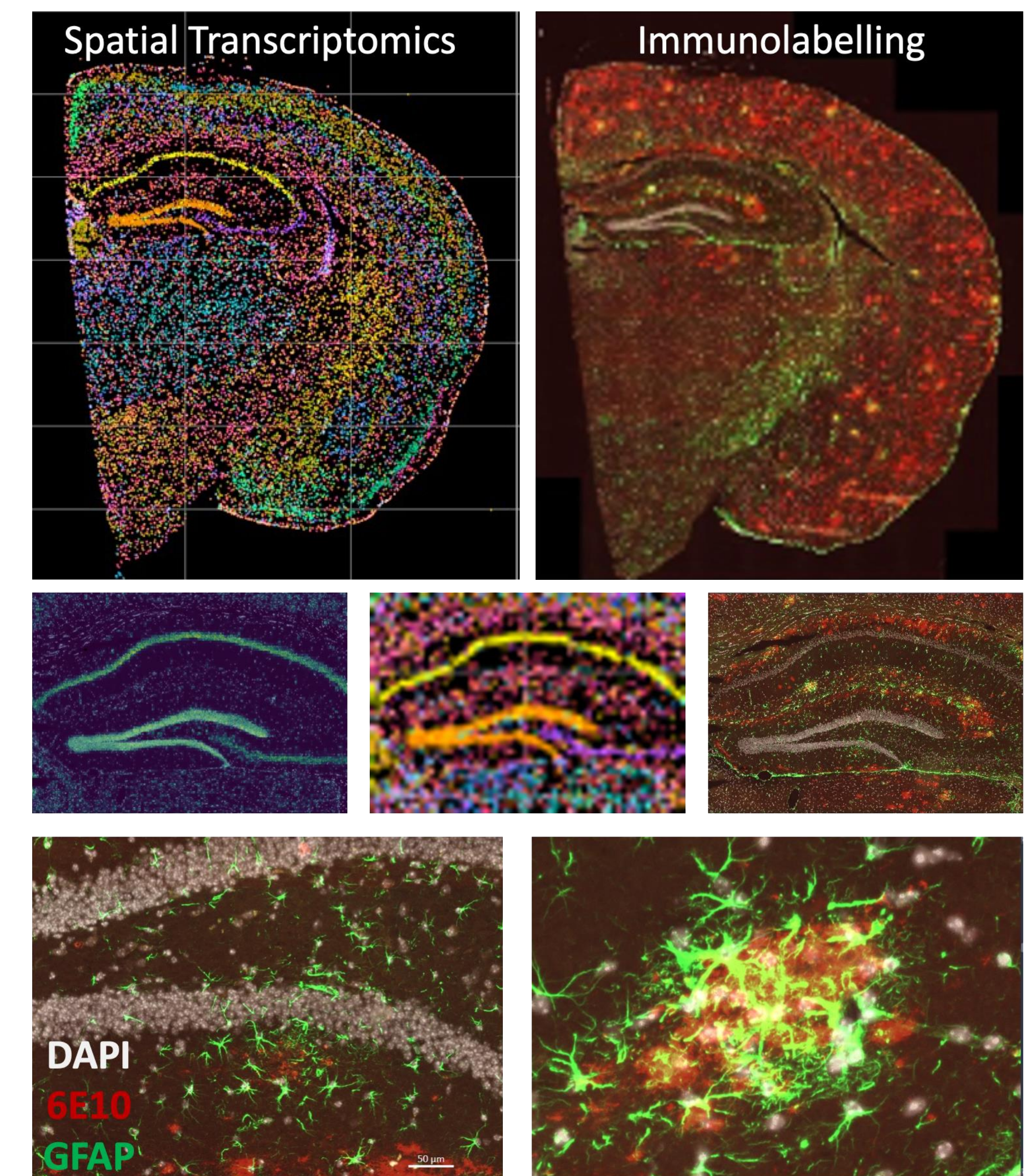
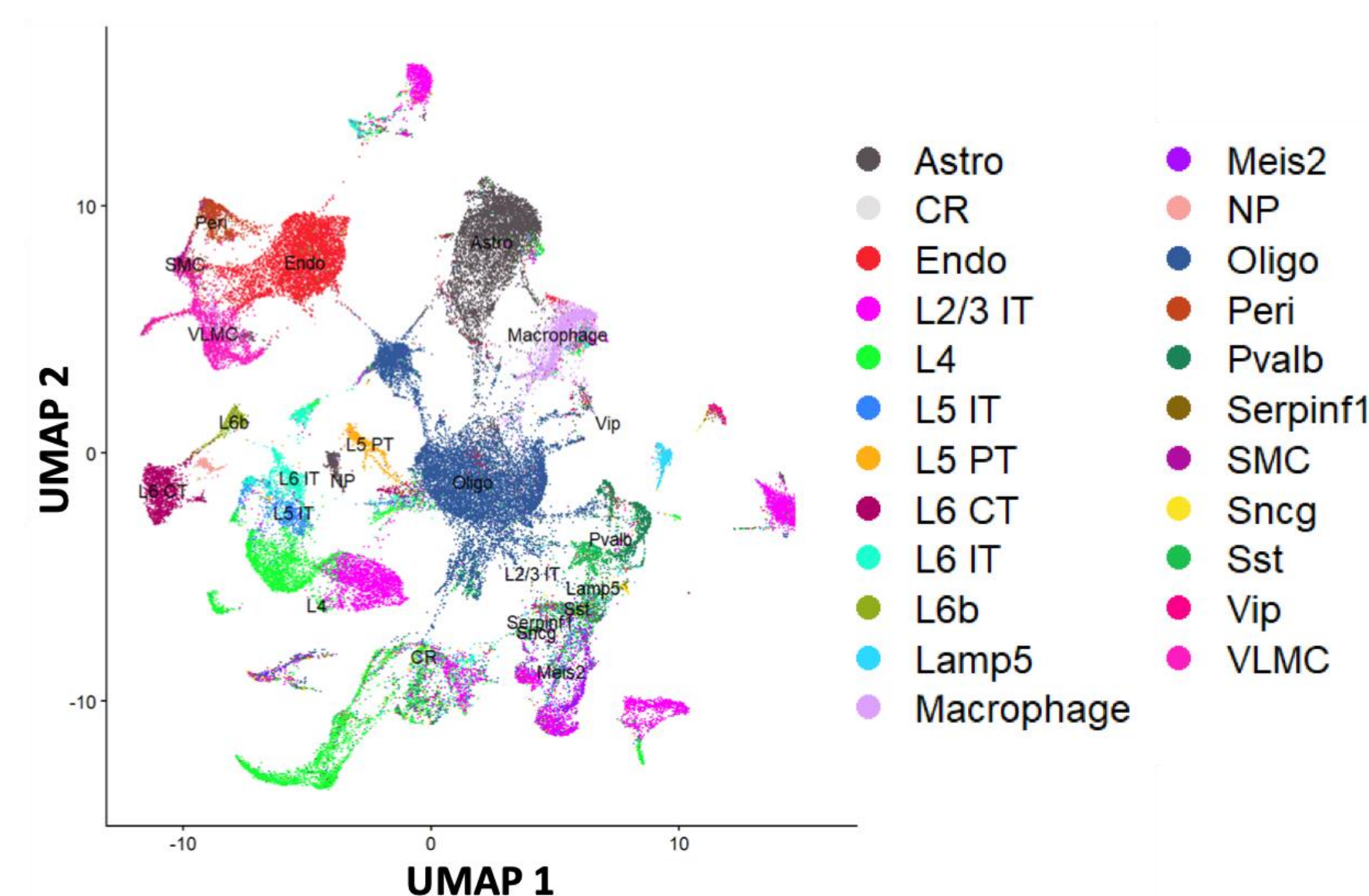
Histology

Amyloid-beta immunostaining (6E10) in brain showed an age-related temporal progression of amyloid deposition in all NLF brains. APP/PS1 sections were included as amyloid positive and negative controls.



Spatial Transcriptomics

Using a 246 gene panel, our initial dataset mapped 545,695 cells (277,681,932 transcripts) in 18 months old male and female sham and TBI mice spanning several AD-relevant brain regions. We conducted multiplexed immunostaining on same sections after acquiring transcriptomic data. Astroglia and microglia was observed in all brains and injured AD brains showed distinct immunoreactivity in optic tract and hippocampus. Dimensionality reduction and clustering identified multiple cell-types specific clusters which will be analysed for differential gene expression next.



CONCLUSION

Our preliminary study provides a spatiotemporal framework for understanding TBI-AD interactions by integration of high throughput transcriptomics with plasma biomarkers and histological validation. Elucidating these interactions is essential for defining shared and distinct mechanisms across trauma and dementia.