

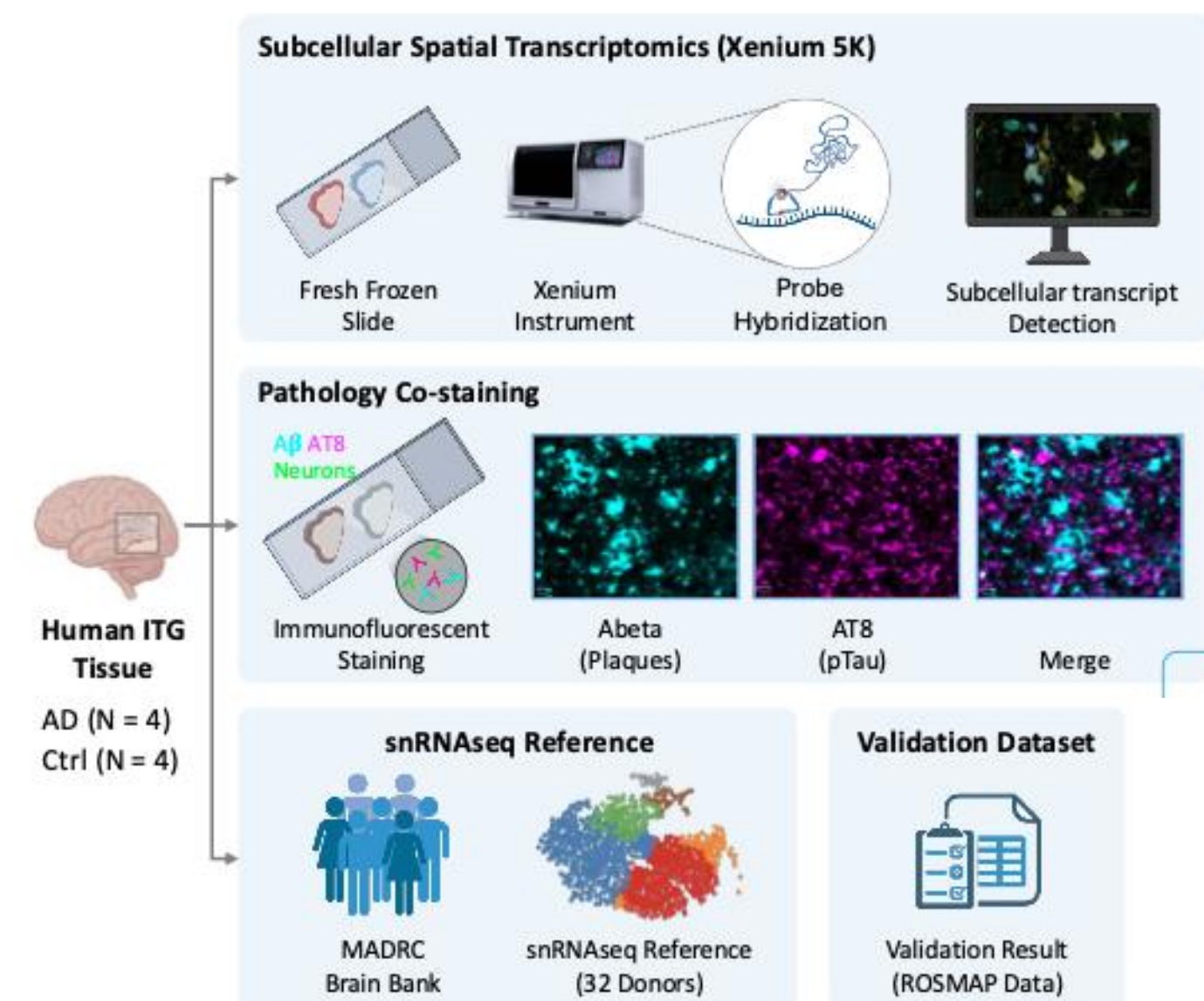
1 Background / Question

- A β Plaques, in particular neuritic plaques, function as localized microenvironments that facilitate tau aggregation^{1,2,3,4}.
- A β plaques are broadly distributed, whereas neuronal somatic tau accumulation are selective⁵.

Whether, how, and in which neuronal populations local plaque-associated neuritic stress is converted into somatic tau burden?

Which neuronal programs resist or amplify the transition from neuritic plaque tau stress to soma pTau?

2 Methods



Xenium subcellular ST + A β /AT8 IF (4 Control, 4 AD)

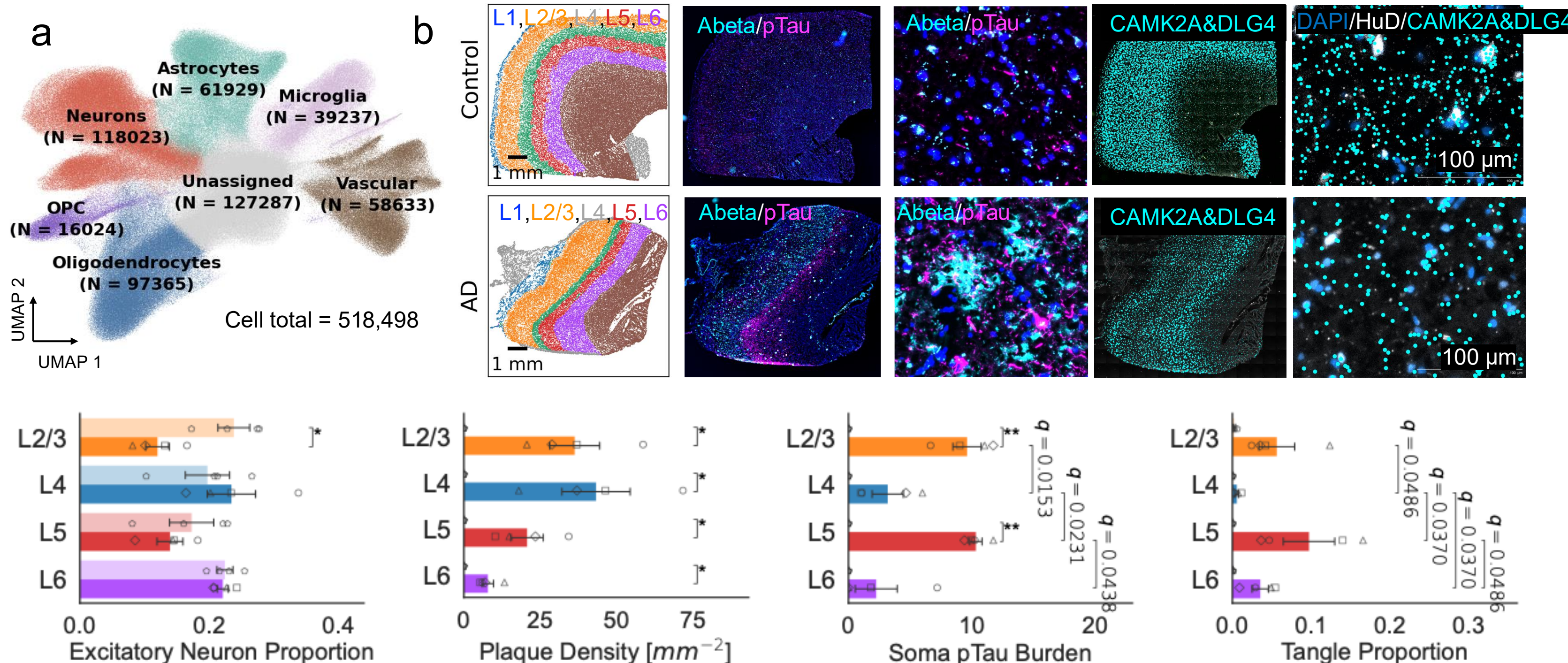
Cell-type, subtype, and layer annotation

Neuritic plaque (NP) pTau & layer-wise association with soma pTau

Excitatory neurons trajectory analysis & pTau vulnerability score

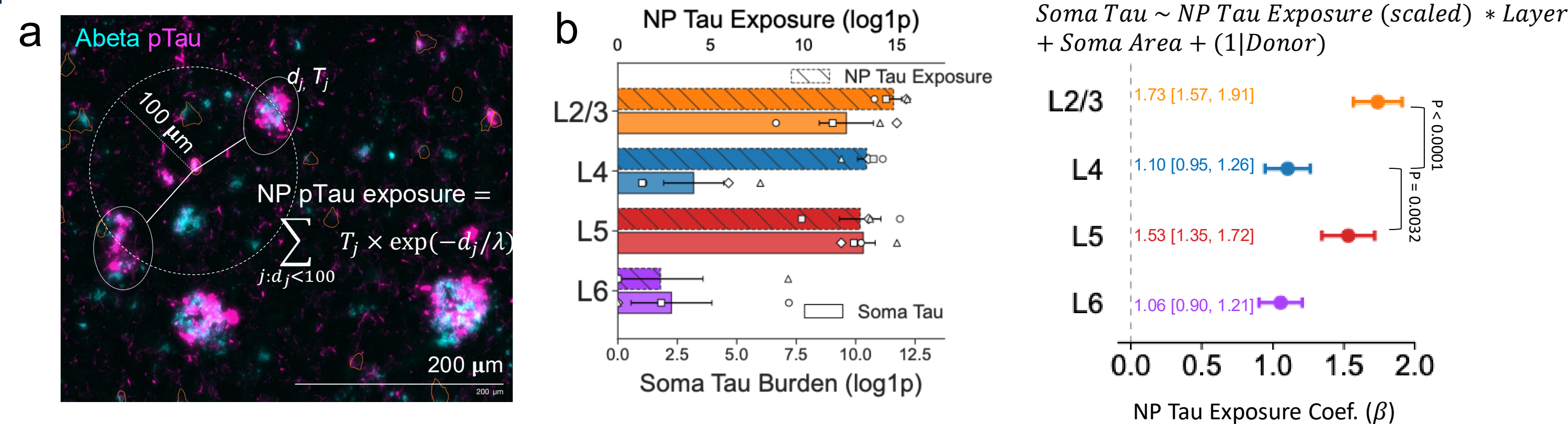
Molecular program identification

3 Result 1: Spatial atlas of cortical architecture, gene expression, and AD pathology in human ITG



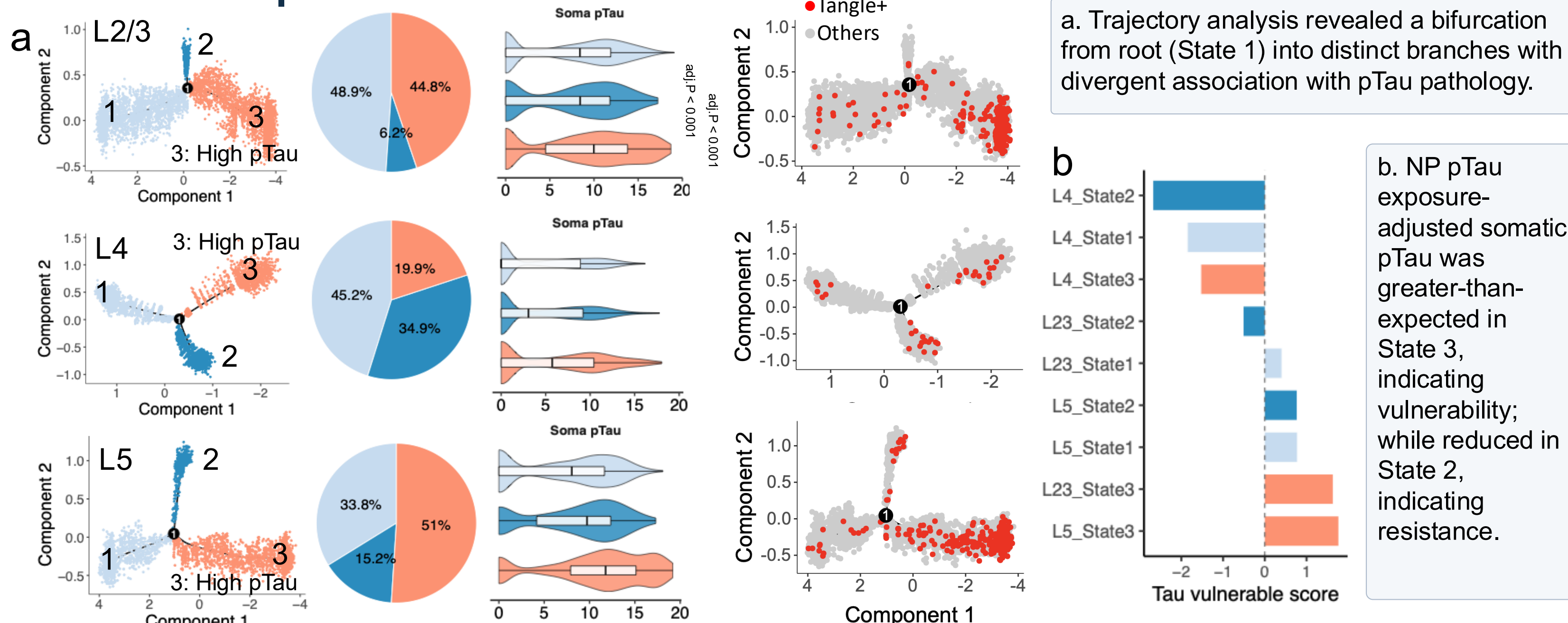
- Subcellular spatial transcriptomics robustly recovered both neuronal and non-neuronal compartments across control and AD tissues.
- Control cortex exhibited minimal pathology, whereas AD cortex showed widespread plaque deposition but selective somatic tau accumulation in L2/3 and L5 neurons.

4 Result 2: Layer-specific dissociation between neuritic plaque pTau and somatic pTau accumulation

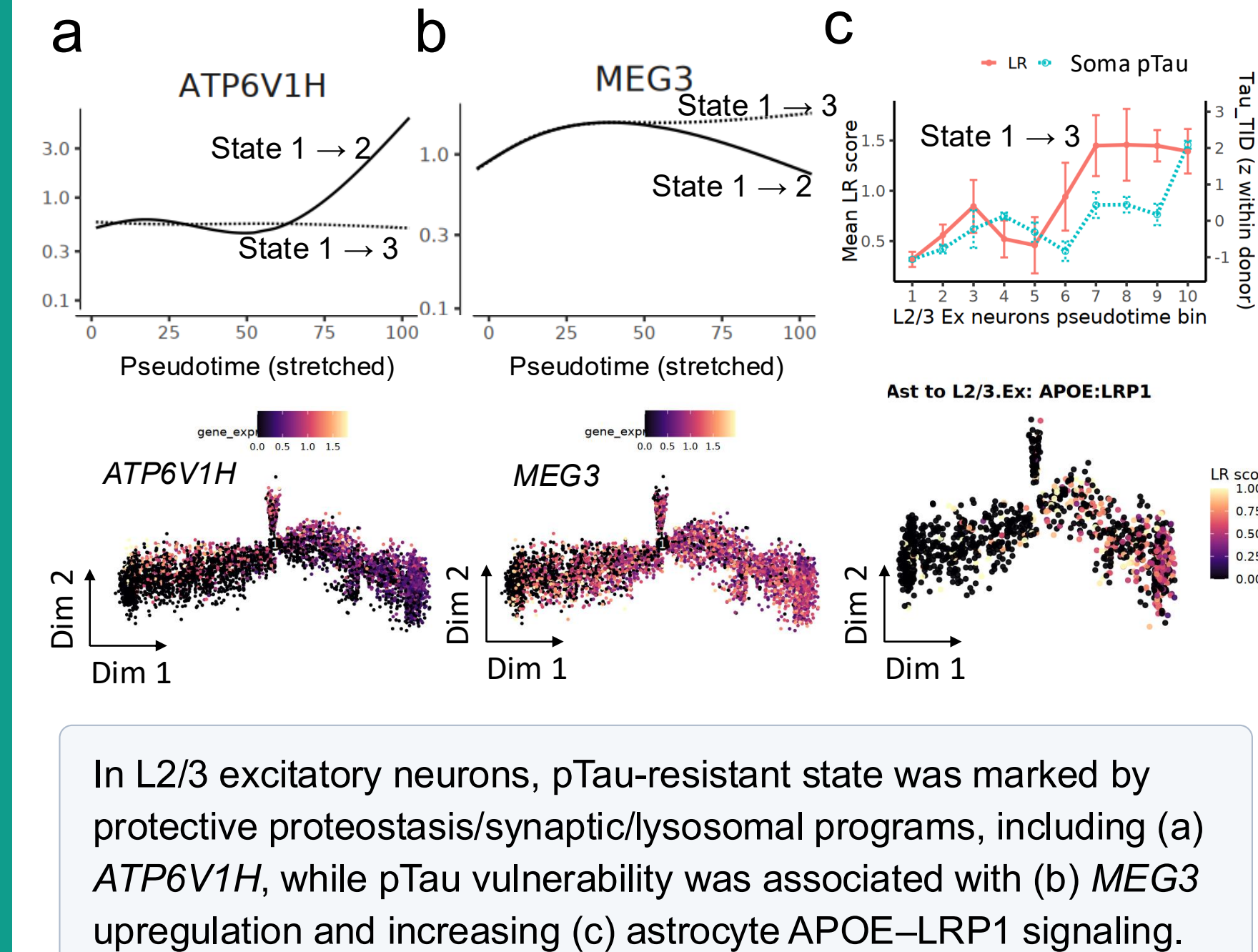


- Neuritic plaque (NP) pTau exposure defined as distance-decayed plaque toxicity exposure score.
- L4 excitatory neurons displayed substantially lower somatic tau burden despite experiencing comparable NP pTau exposure.

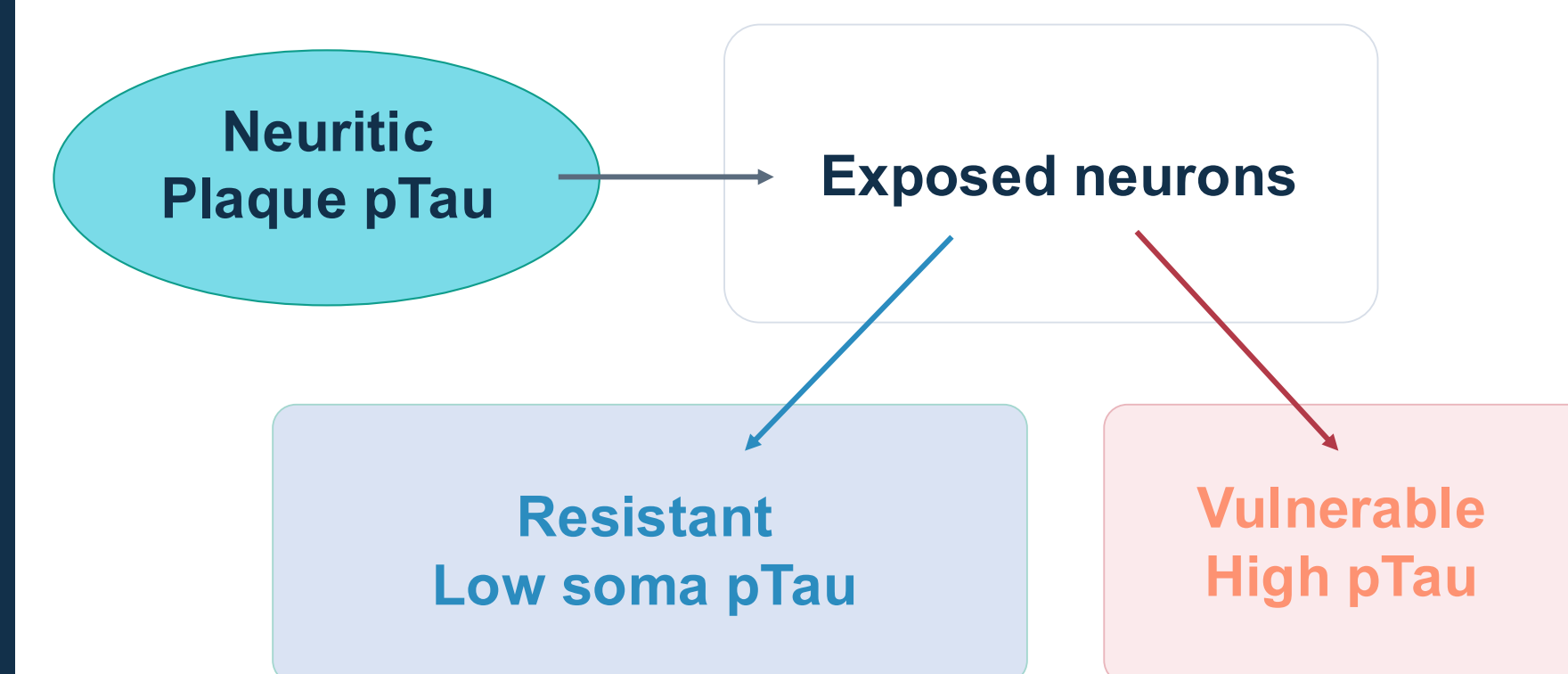
5 Result 3: Intrinsic neuronal states modulate the plaque-associated stress into somatic pTau accumulation



6 Molecular program



7 Conclusion



Conclusion:

- Subcellular spatial transcriptomics with co-registered A β /AT8 pathology identifies neuritic plaque pTau-associated niches and links local plaque toxicity to neuronal responses.
- Somatic pTau accumulation is layer- and state-selective rather than plaque toxicity exposure-only driven.
- Resistant states buffer plaque toxicity stress, whereas vulnerable states are associated with greater somatic pTau accumulation.

8 References

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