



The Neurogenic Fence:

A Spatial Transcriptomic Blueprint of Hippocampal Neurogenic Niche Maintenance and Implications for Alzheimer's Pathogenesis

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Background

Critical Gap: No spatial map of healthy glial–neuronal boundaries before Alzheimer's Disease (AD) onset exists.

- Reactive gliosis drives late-stage AD, yet the spatial logic maintaining healthy glial–neuronal separation before disease onset is entirely undefined.^{1,2}
- The dentate gyrus (DG) is the hippocampus's primary neurogenic zone and one of the earliest site of AD tau pathology.³
- No study has quantified the molecular architecture segregating immune-active glia from DG neurons in the healthy pre-symptomatic brain.

Methods

65,956

12

1,122

Single Cells
Profiled

Cell Type
Subclasses

Gene
Panel

1 Data Acquisition

Allen Brain Cell Atlas MERFISH (Zhuang-ABCA-1) · 65,956 cells · Mouse hippocampus CA1 + DG

2 QC & Dimensionality Reduction

Scanpy · UMAP embedding · Leiden clustering · All 65,956 cells retained

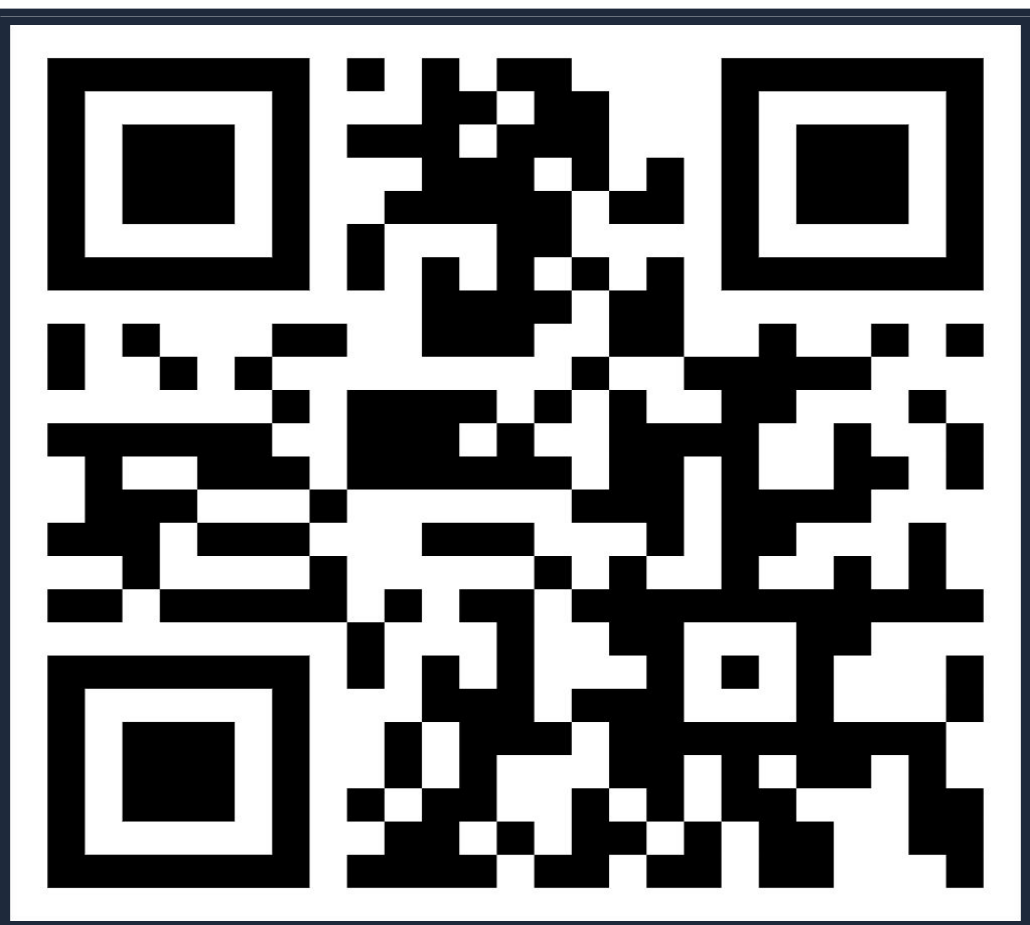
3 Spatial Analysis

Squidpy · Neighborhood enrichment scores · KDTREE interface definition · SciPy

4 DGE & GO Enrichment

Wilcoxon rank-sum · adj-p < 0.05 · GProfiler (mmusculus)

Explore the Data Live



Scan to explore spatial maps & gene expression models.

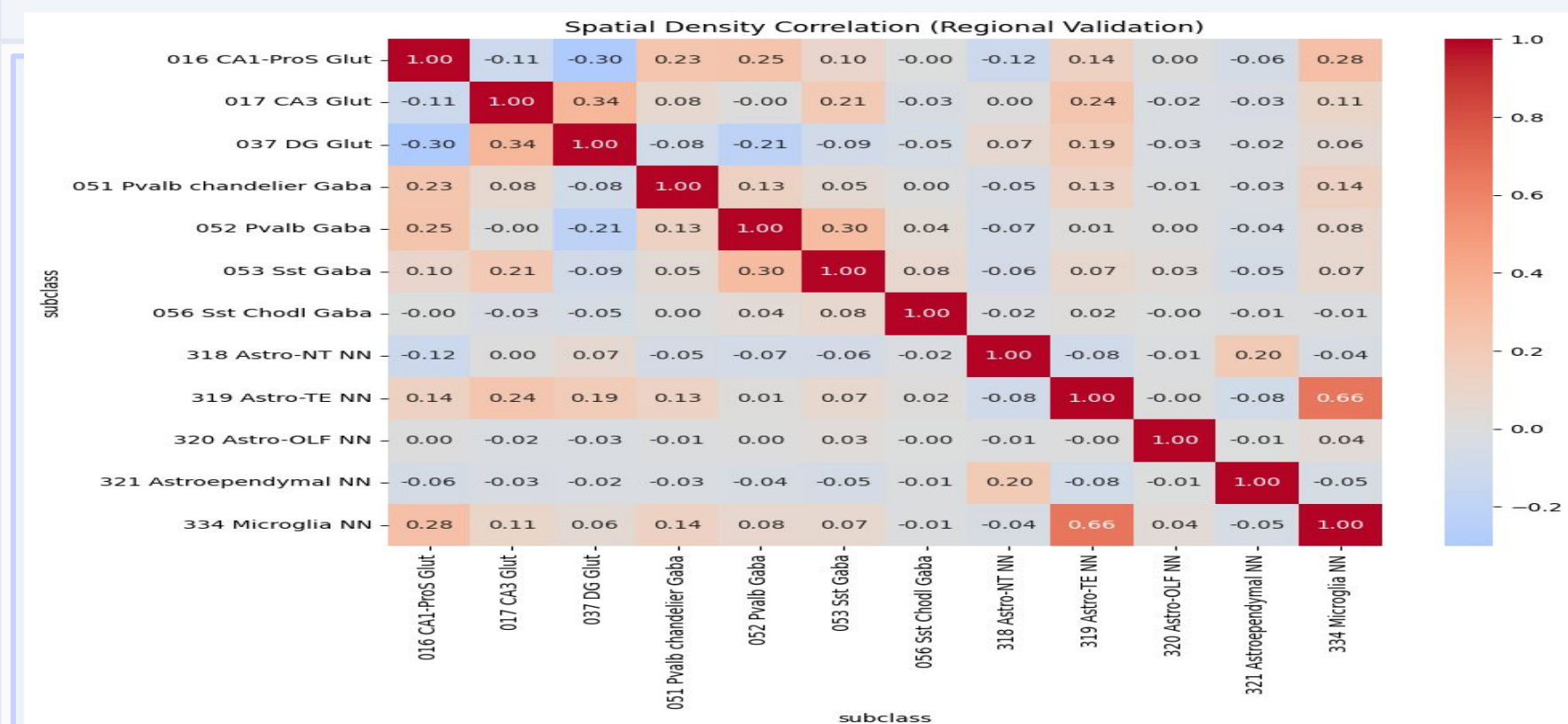
Results

Fig. A Neighborhood Enrichment Heatmap (Z-Scores)



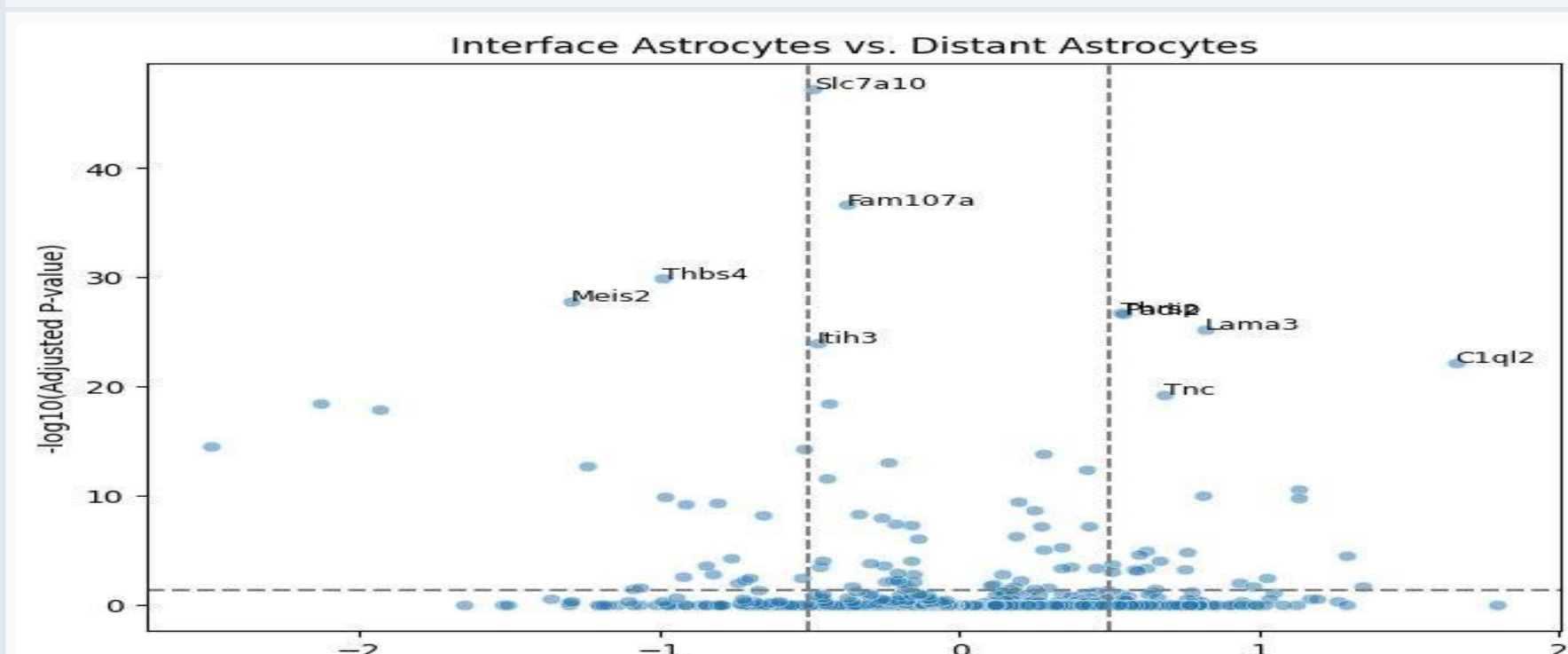
Sharp exclusion zone ($Z < -200$) confirms an active non-random boundary — astrocytes & microglia excluded from DG neuronal core.

Fig. B Spatial Density Correlation ($r = 0.66$)



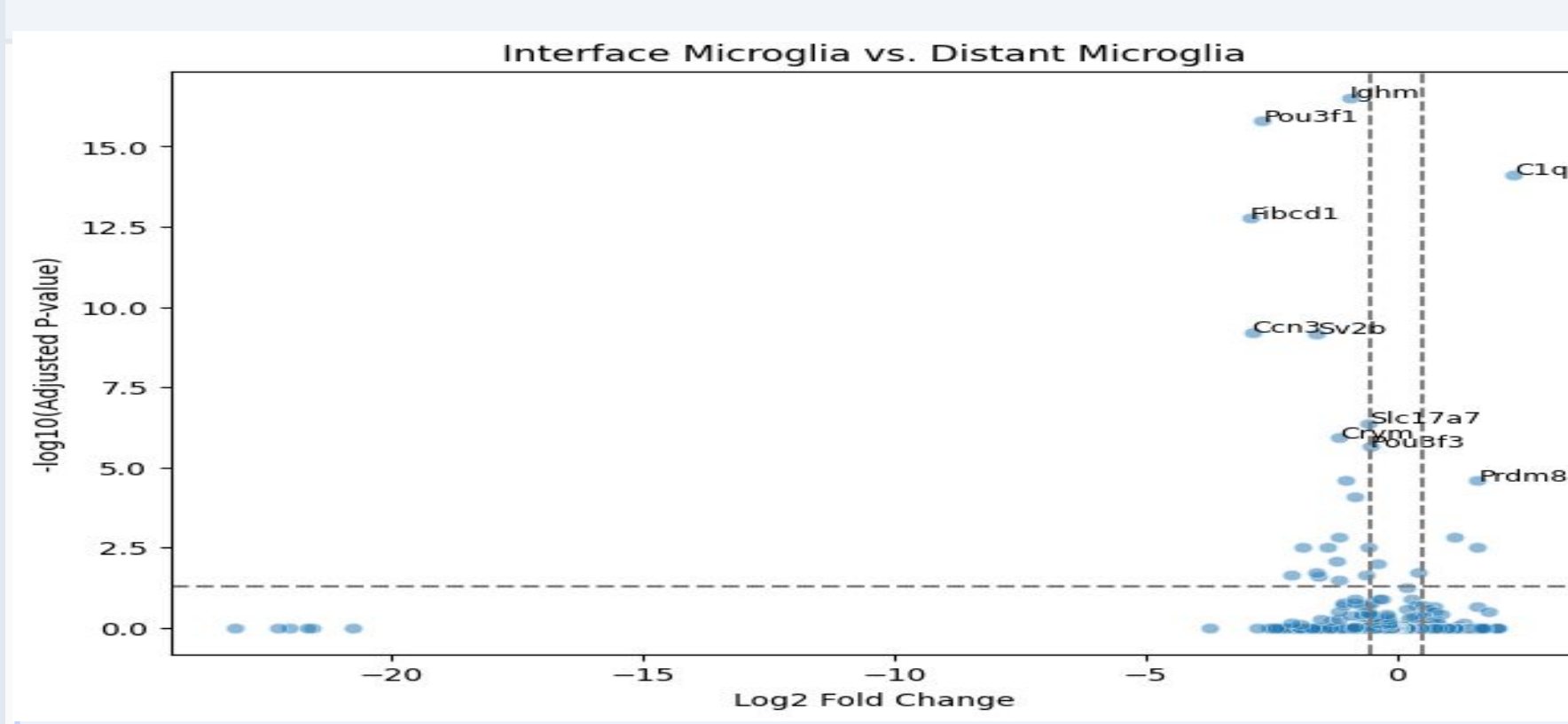
Astrocyte–microglia co-enrichment ($r = 0.66, p < 0.001$) outside DG independently validates fence topology across hippocampal regions.

Fig. C DGE: Interface vs. Distant Astrocytes



TNC & C1QL2 significantly upregulated at interface ($\log_{2}FC > 1.5, adj-p < 10^{-11}$) — primary fence-enforcing molecules.

Fig. D DGE: Interface vs. Distant Microglia



C1QL2 upregulated in interface microglia ($\log_{2}FC \approx 2, adj-p < 10^{-11}$) — shared boundary-enforcement programme across glial types.

Key Molecular Enforcers of the Neurogenic Fence

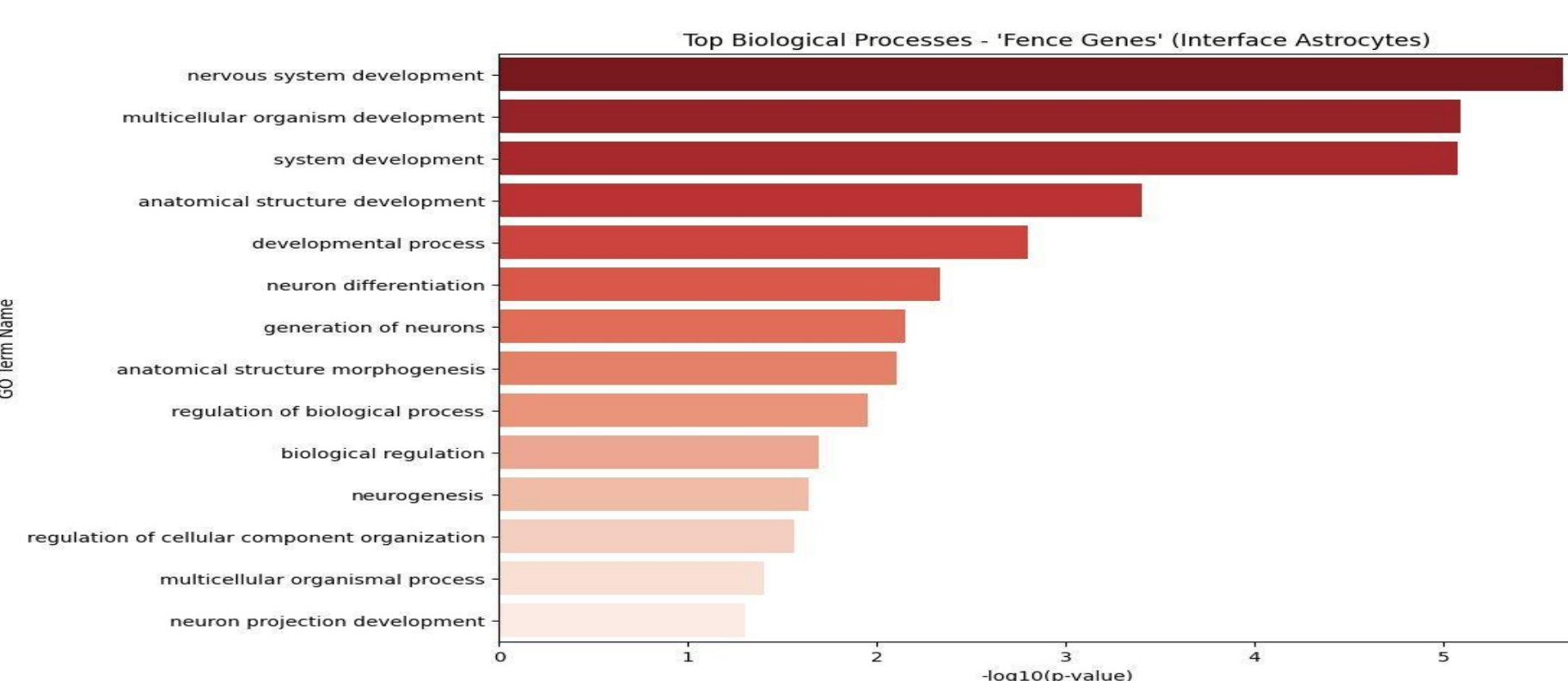
TNC — Tenascin-C · ECM Repulsion Scaffold

$\log_{2}FC = 2.87$ · $adj-p < 10^{-30}$ · Boundary-specific · Blocks glial invasion

C1QL2 — Complement-related Synaptic Organizer

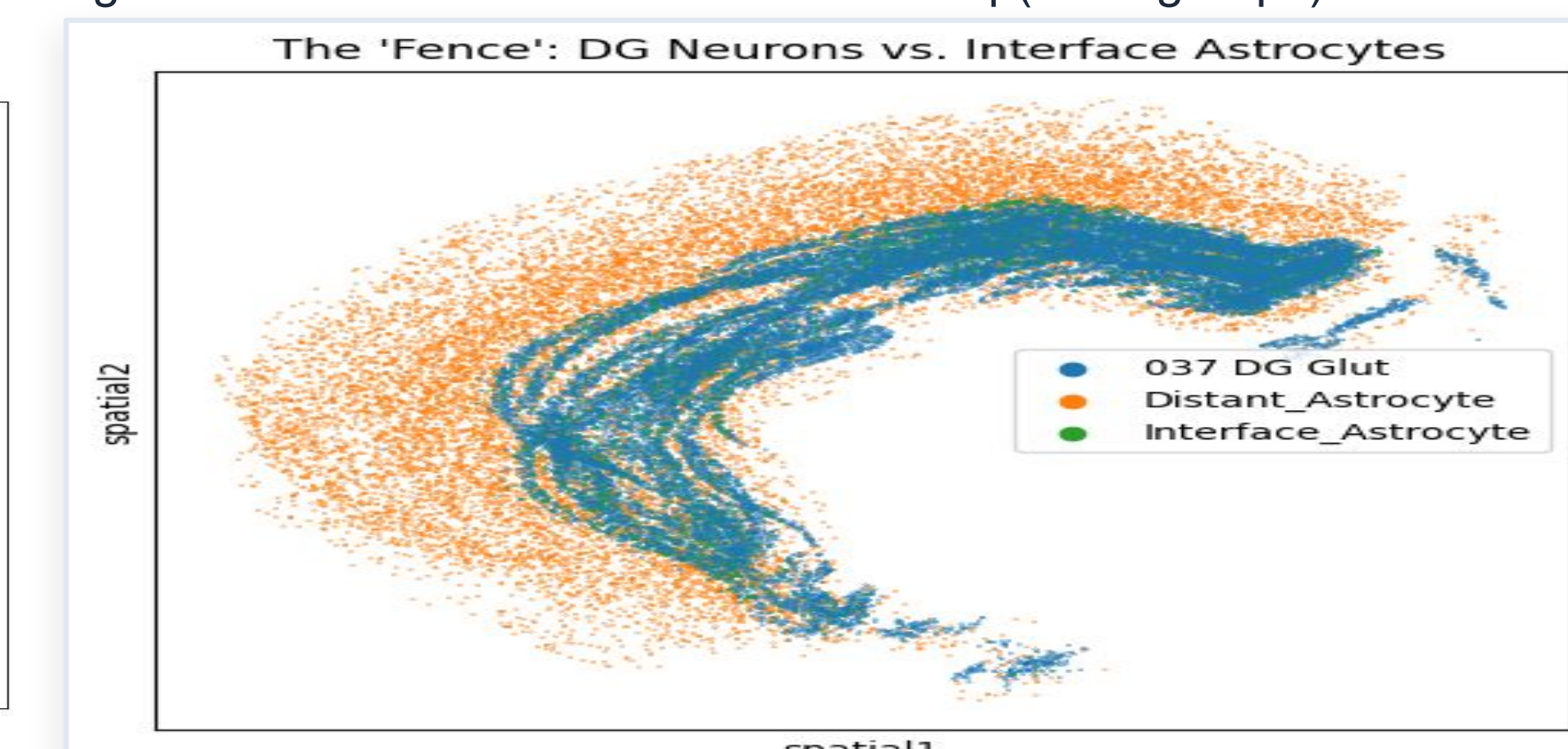
$\log_{2}FC = 1.82$ · $adj-p < 10^{-25}$ · Shared Astrocyte + Microglia enforcement

Fig. E — GO Biological Process Enrichment: Interface Astrocyte Fence Genes



Fence genes enriched for nervous system development & neuron differentiation ($-\log_{10}p > 5$), linking boundary integrity to active neurogenic support programmes.

Fig. F — Visual Confirmation of Fence Map (Cells groups)



Conclusions & AD Implications

01 The Neurogenic Fence is a quantifiable, active boundary. Molecularly enforced by TNC and C1QL2; not a passive anatomical artifact. Provides a precise, measurable target.

02 Fence failure may precede amyloid plaque deposition. Downregulation of boundary-enforcing genes could allow early glial infiltration, opening a pre-symptomatic biomarker detection window.

03 TNC / C1QL2 are novel therapeutic targets. Strategies restoring or mimicking their activity at the DG interface represent a precision neuroprotective approach for early-stage AD intervention.

Proposed Pathogenic Cascade

• **Healthy:** TNC + C1QL2 active → fence intact → neurogenesis preserved
Fence gene downregulation (presymptomatic AD)
↓
Glial infiltration of the neurogenic niche
↓
Loss of DG neurogenesis · Synaptic dysfunction
↓
Amyloid plaque deposition · Clinical Alzheimer's Disease

Next Steps

- Validate TNC / C1QL2 expression in human post-mortem AD hippocampus (ROSMAP / MSBB cohorts)
- Longitudinal spatial analysis in 5xFAD mouse model, track fence integrity before plaque onset
- Develop TNC expression score as a candidate CSF biomarker for pre-symptomatic AD screening

Acknowledgments

Allen Institute for Brain Science, open-access MERFISH dataset; developers of **Scanpy** and **Squidpy**, open-source spatial analysis tools.

Reference

- Moreno-Jiménez EP, et al. *Nat Med.* 2019;25(4):554–560.
- Morabito S. *Diss. UC Irvine.* 2024.
- Lazic A, et al. *Int J Mol Sci.* 2022;23(9):4995.