Developmental diversification of cortical inhibitory interneurons

Christian Mayer, Christoph Hafemeister, Rachel C. Bandler, Robert Machold, Renata Batista Brito, Xavier Jaglin, Kathryn Allaway, Andrew Butler, Gord Fishell ✉ & Rahul Satija ✉
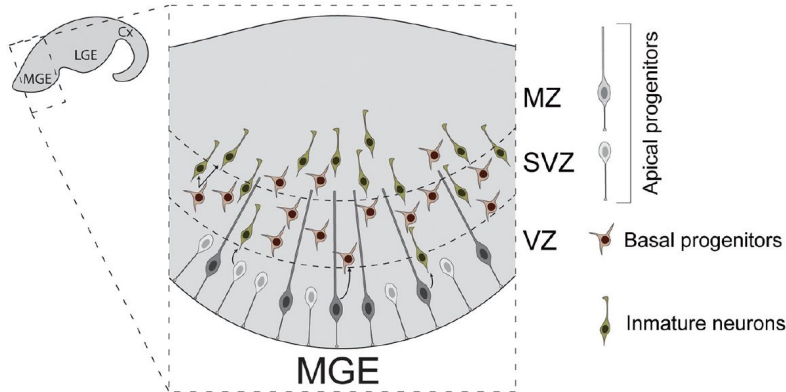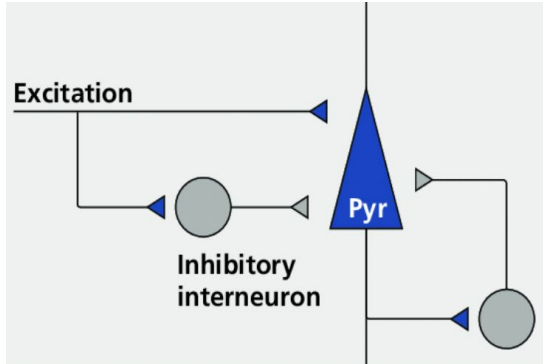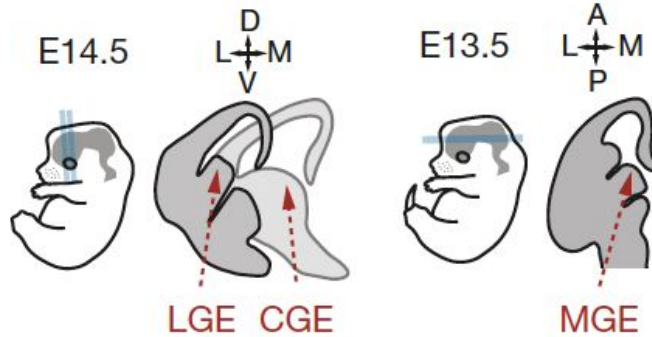
# GABAergic Interneurons Diversity in Neocortex
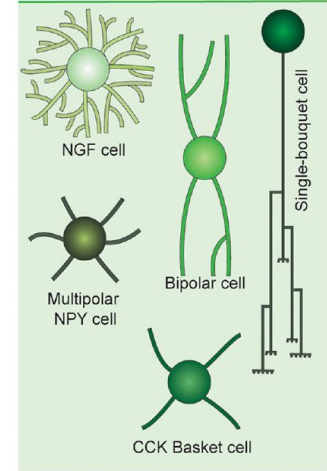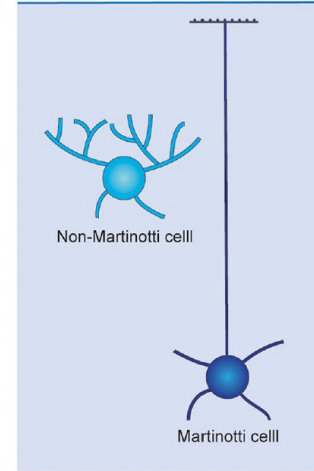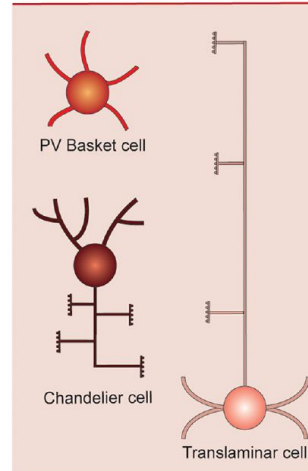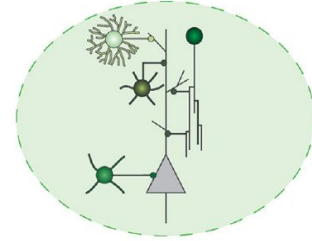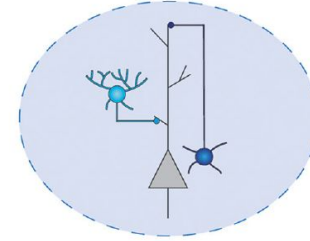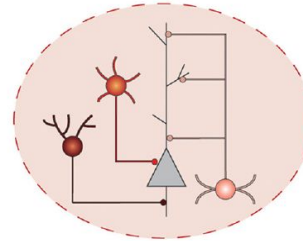
Generation of diversity during cortical development

1. When does the precursors in the ganglion eminences take on the interneuron precursor fate?
2. How does the interneuron precursors give rise to different types of interneuron?

Library Preparation - Drop-seq scRNA Sequencing

1. GE tissues dissected from mouse embryo at peak neurogenesis.
   a. Contain mitotic and postmitotic progenitors
2. Dissociated with papain dissociation system
3. Libraries prepared with Nextera XT DNA Library Preparation Kit.
4. Sequenced with Illumina NextSeq 500
   a. Macosko, E. Z. et al. Highly parallel genome-wide expression profiling of individual cells using nanoliter droplets. *Cell* 161, 1202–1214 (2015).
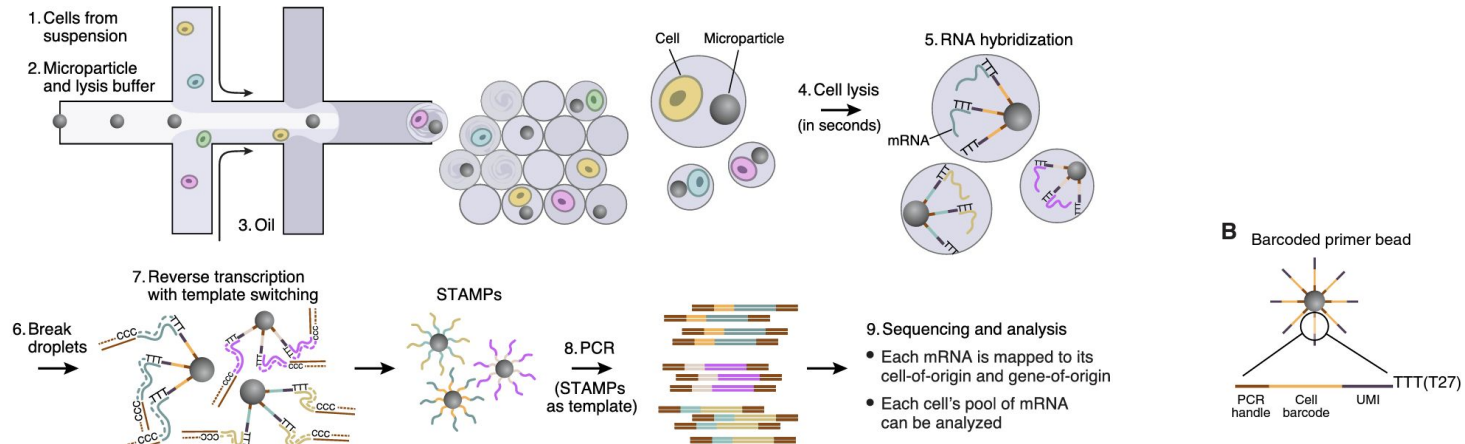
Data Processing:

1. Reads were aligned to 84 Mus musculus genome using STAR.
2. Data filtration by using the quality control metrics:
    a. Removed cells with low number of unique detected gene; low alignment rate; low number of reads; low total UMIs.
3. MGE: 5,622 cells; CGE: 7,401 cells; LGE: 8,543 cells.
    a. Average 1,626 UMIs per cell.
4. Data normalized to remove the effect of sequencing depth and cell cycle stage.

Data and Code Source:

- https://github.com/ChristophH/in-lineage
- https://github.com/mayer-lab/Mayer-et-al-2018_IntegratedAnalysis

Reproduction:
- Maturation Trajectory
- Analysis of Development of Mitotic Cells
- Analysis of Heterogeneity in Postmitotic Cells
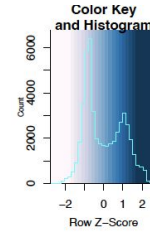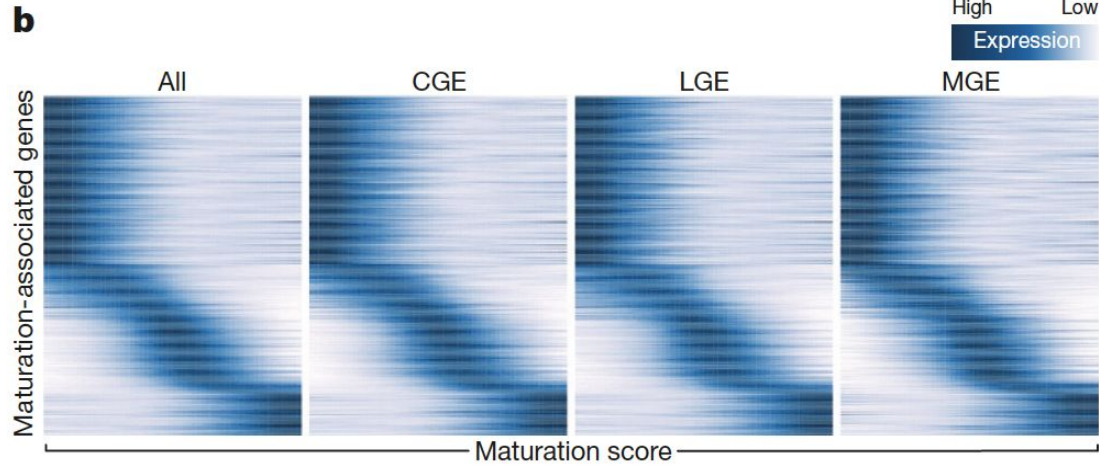- Determining the timeline of subtypes diversification.

New Analysis:
- Comparing heterogeneity between MGE and CGE.
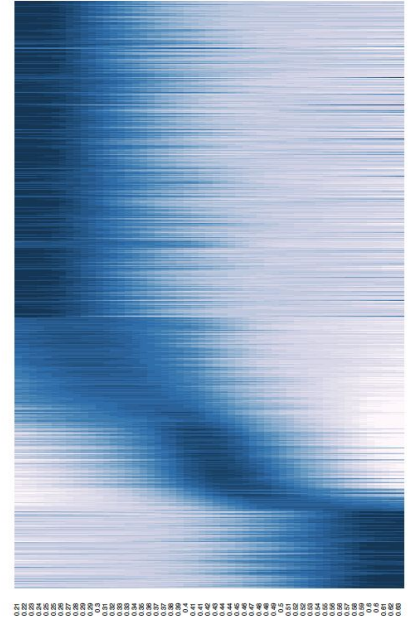
Maturation Trajectory of GE precursors

Reproduced:
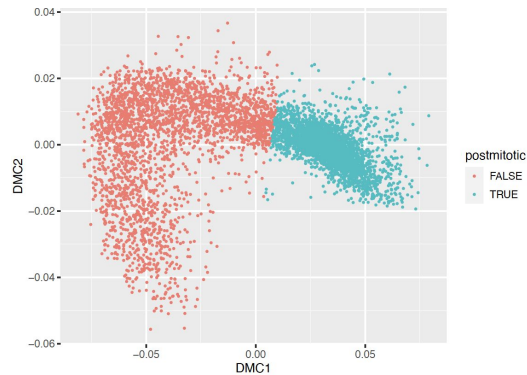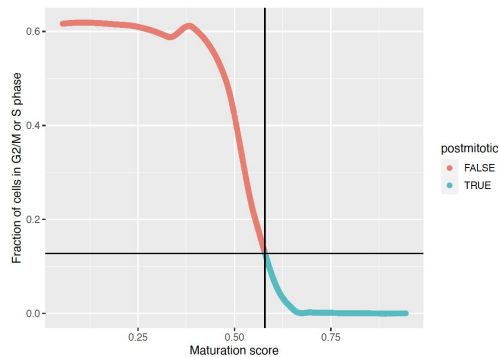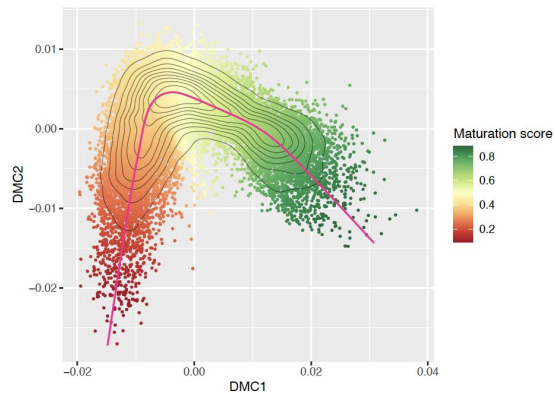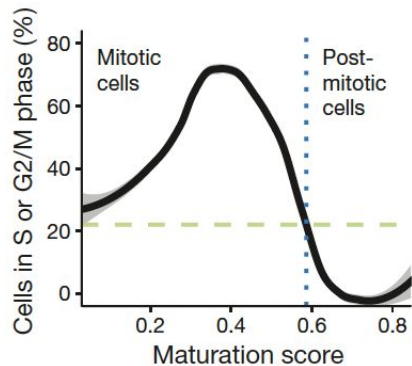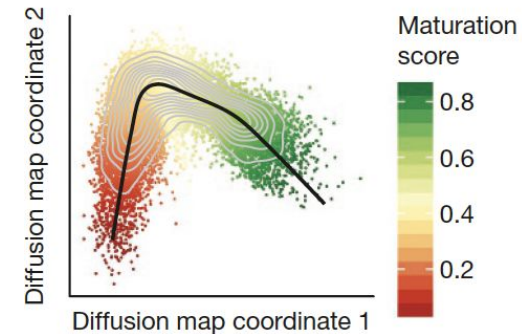
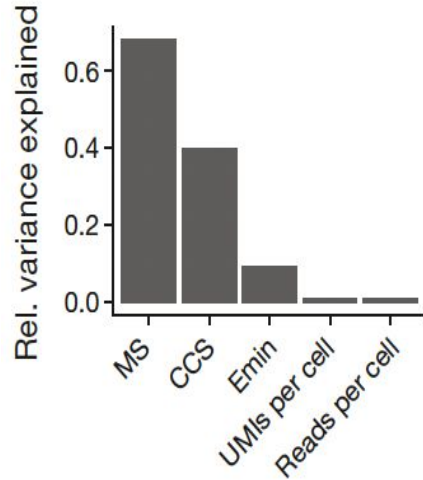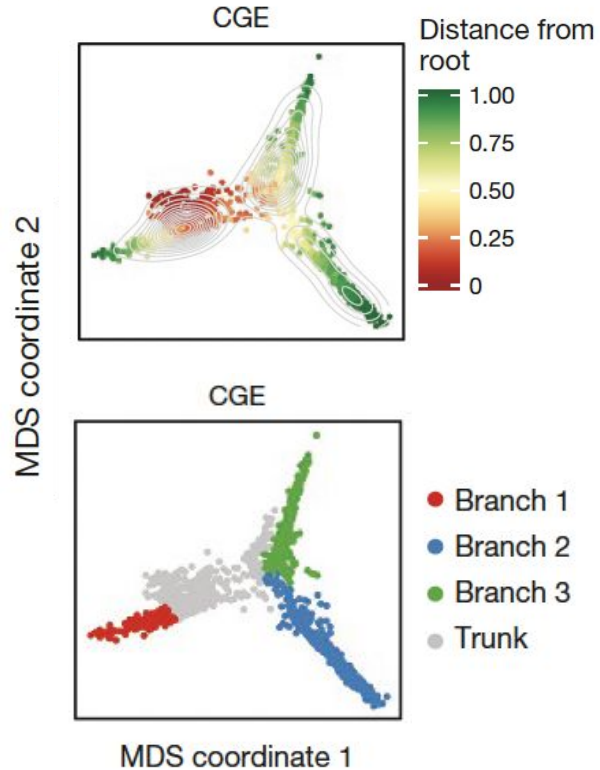# Development of Mitotic Progenitors

Reproduced:

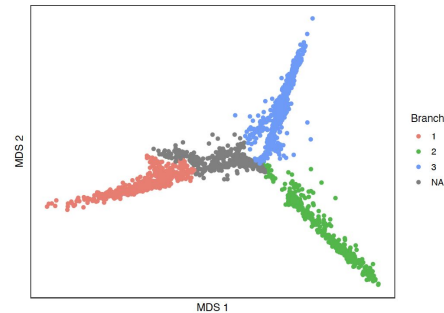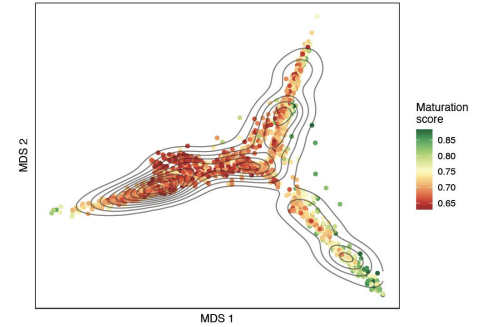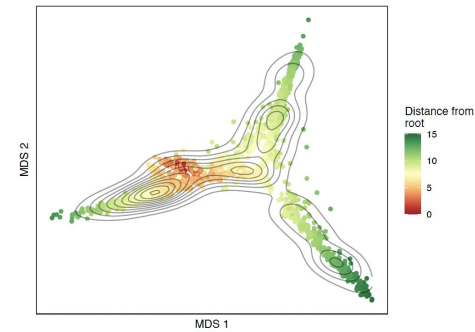# Sources of Heterogeneity in Mitotic Cells

Gene expression trajectory of progenitors in all 3 GEs:

- ○ Stem cell → Proneural → Neurogenics

Postmitotic CGE Analysis

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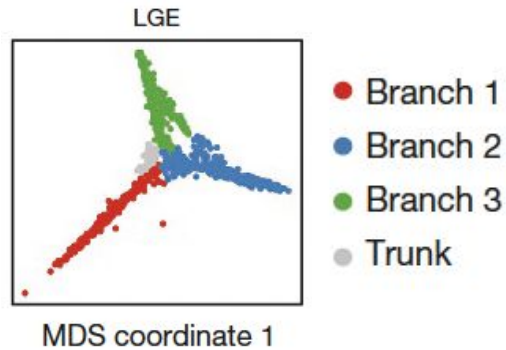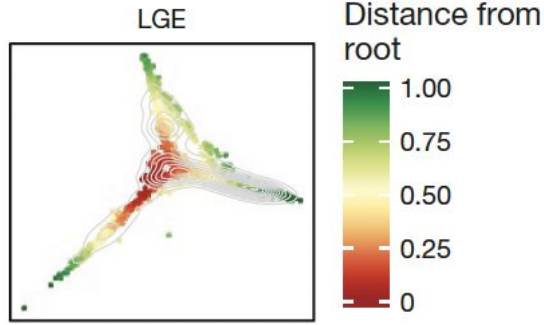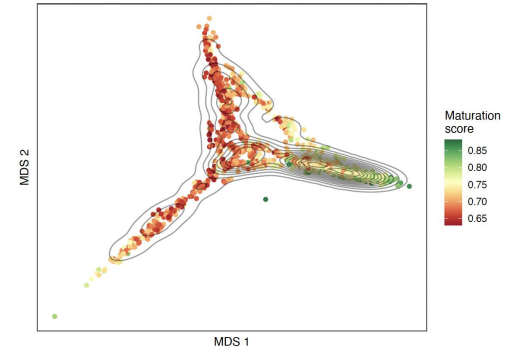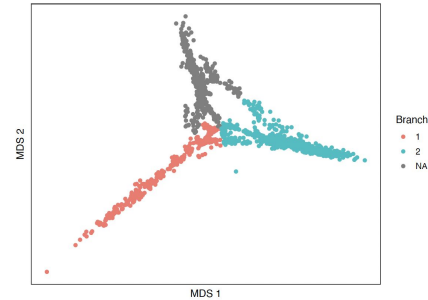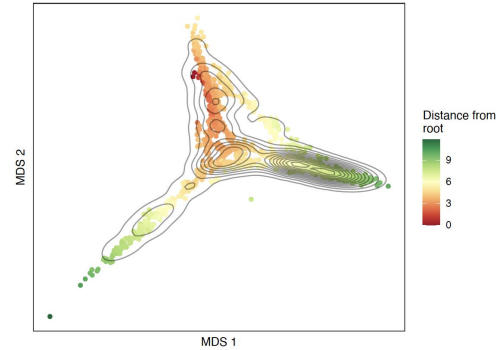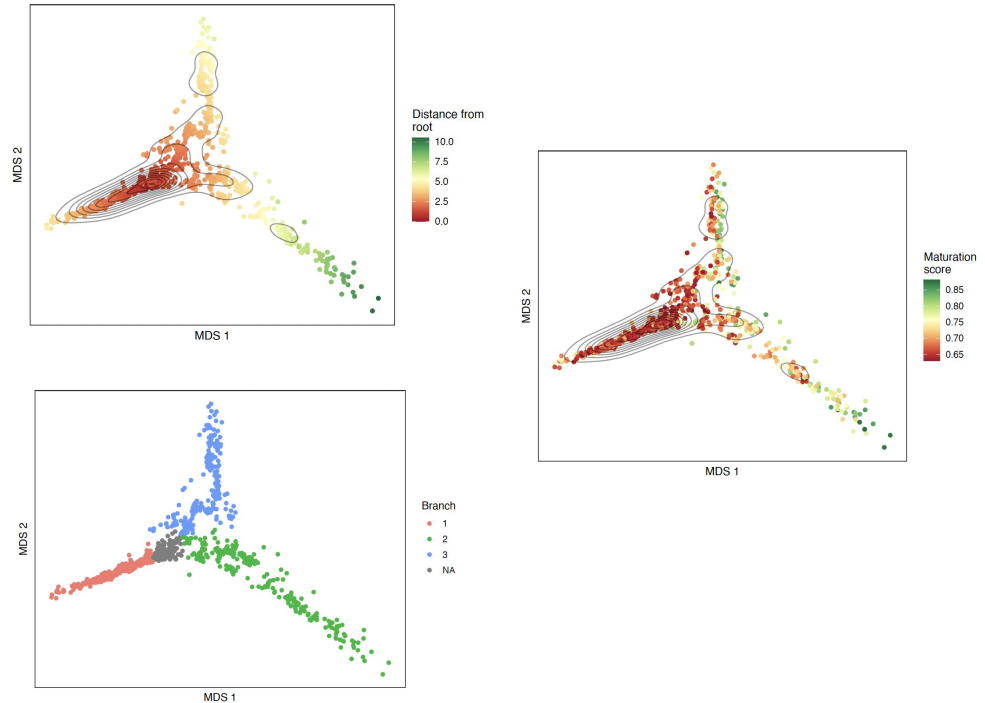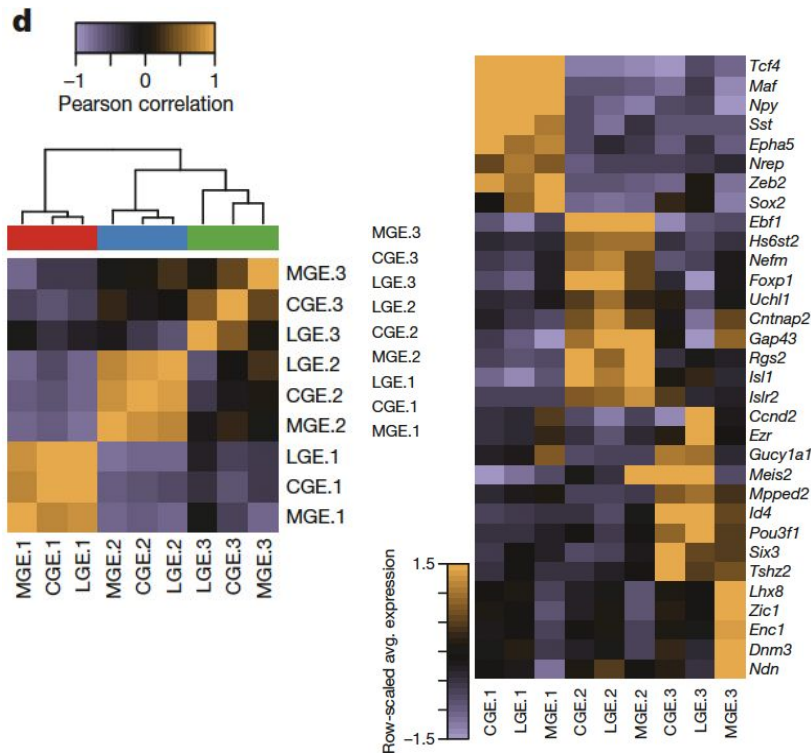# Postmitotic LGE analysis

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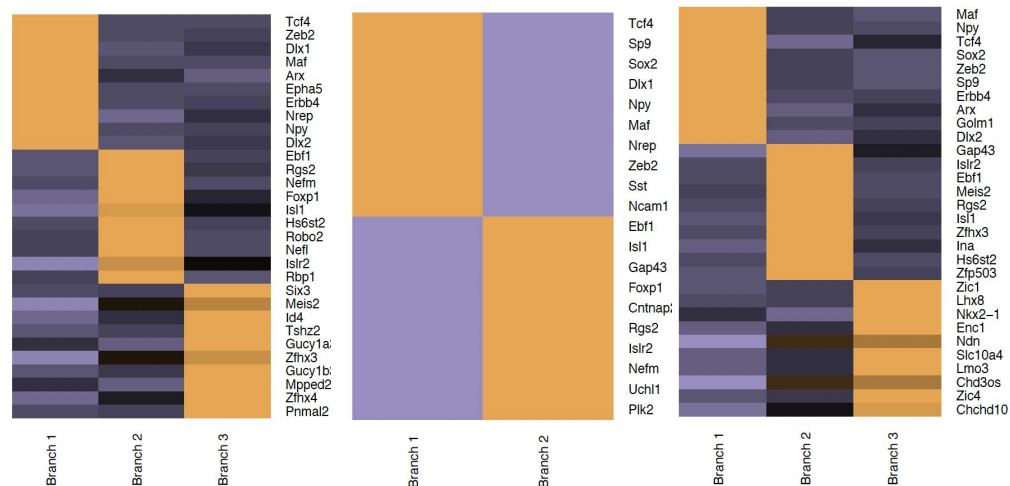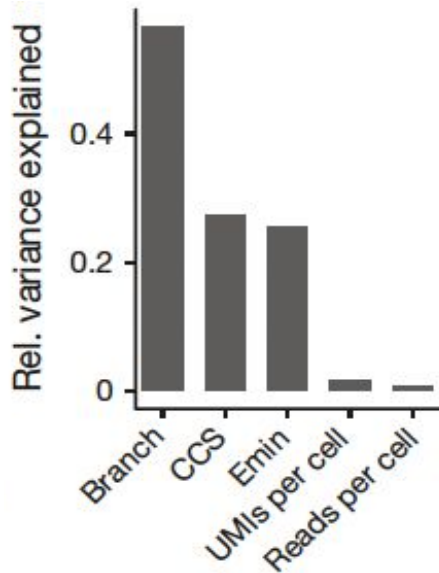
Postmitotic MGE Analysis
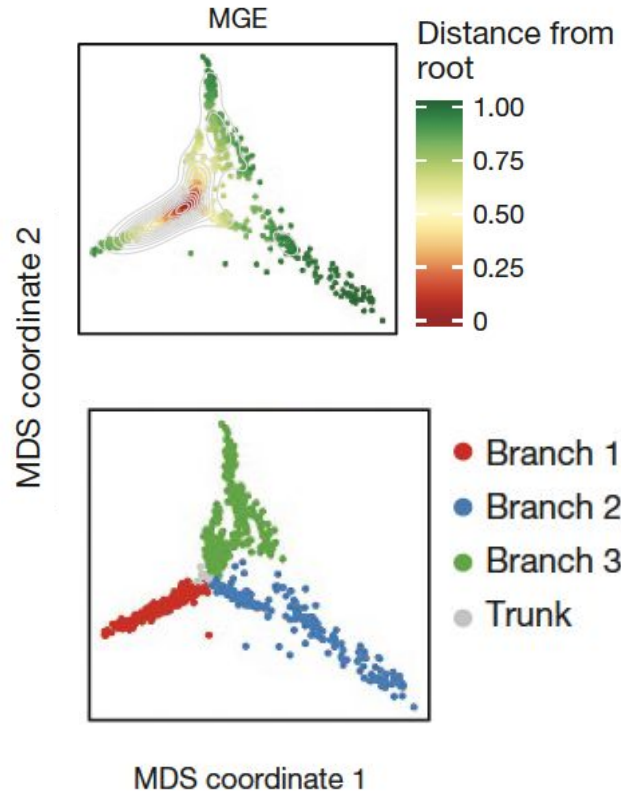
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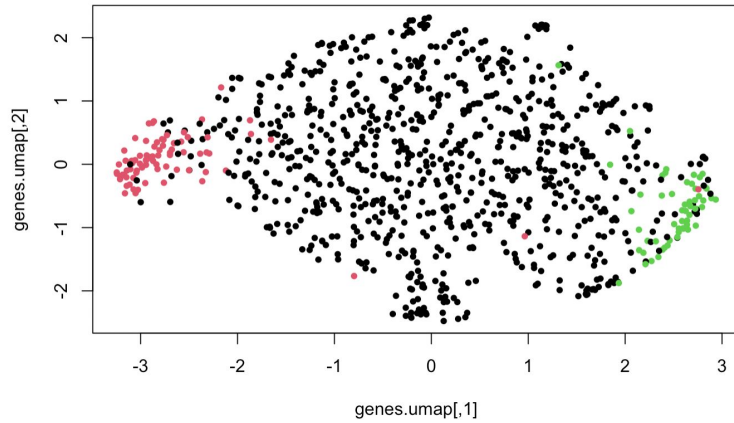# Postmitotic Comparison of 3 Eminences

Reproduced:

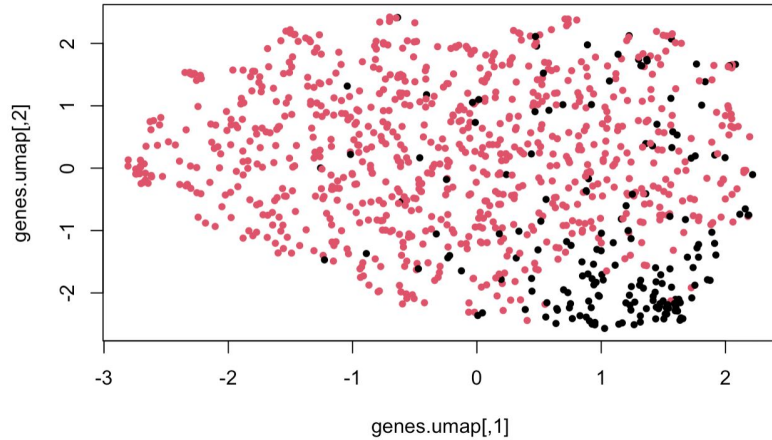# Sources of Heterogeneity in Postmitotic Cells

Cell fate diverge as soon as they're post-mitotic into 3 precursor states, one of which is the interneuron precursor states.
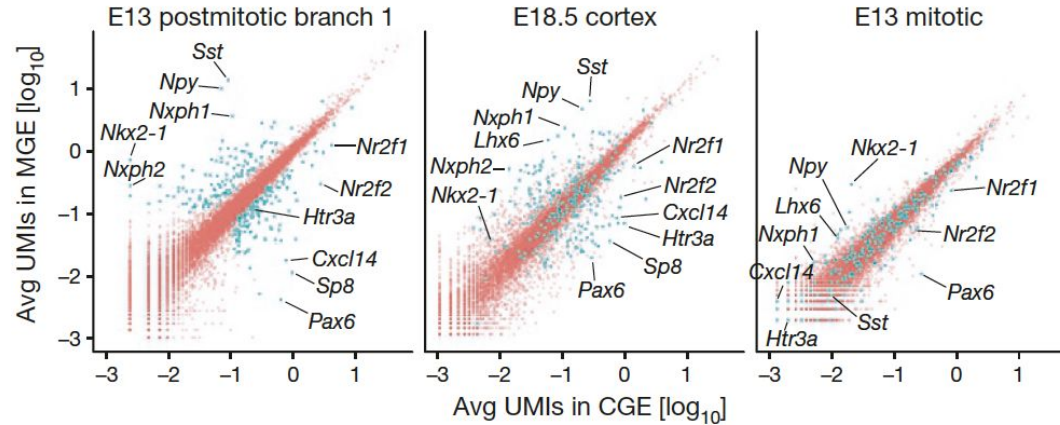
MGE vs CGE Expression Cluster
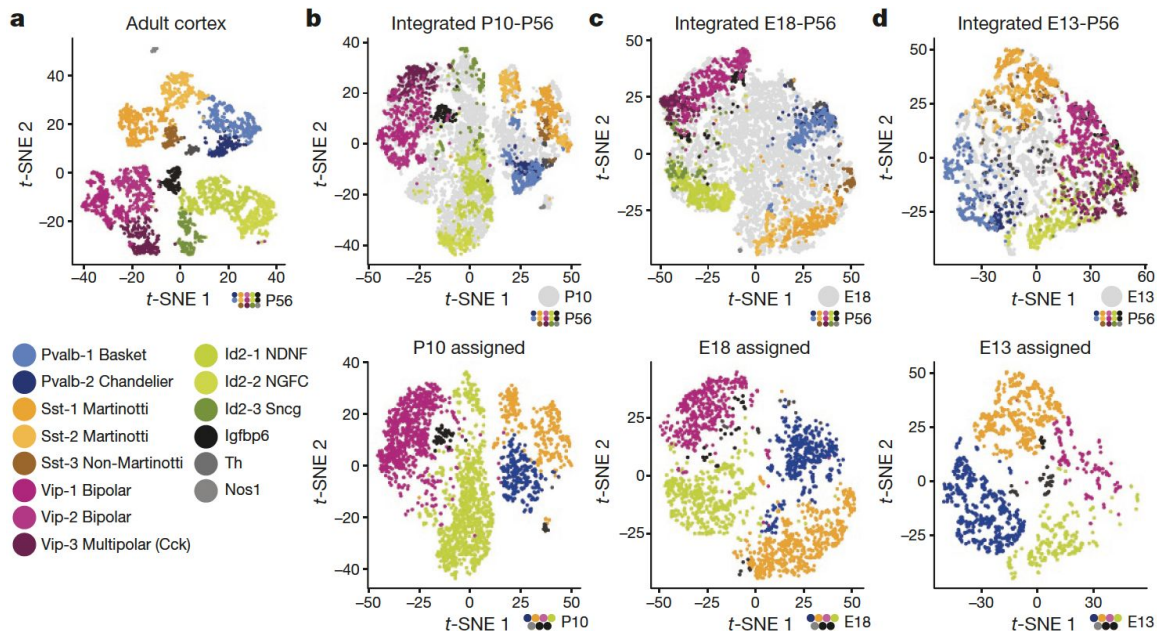

CGE Expression Cluster

MGE Expression Cluster

MGE vs CGE expression profile

Development of Subtypes

- **Diversification trajectory:**
  - E13.5: PV & SOM separation starts
  - E18.5: Separation into all 3 cardinal types. Some subtypes separation in SOM & VIP.
  - P10: Separation of all 3 cardinal types into subtypes.

Results Summary:

- **Interneuron Developmental Model:**
  - Precursor-state genes give common characteristic to all IN precursors (migration to the cortex). Eminence-specific genes give each IN type its unique characteristics (synapse location).

Challenges:

- Quantity of Data
- Pairwise integration required older version of Seurat