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Comparative transcriptomics reveals human-specific cortical features

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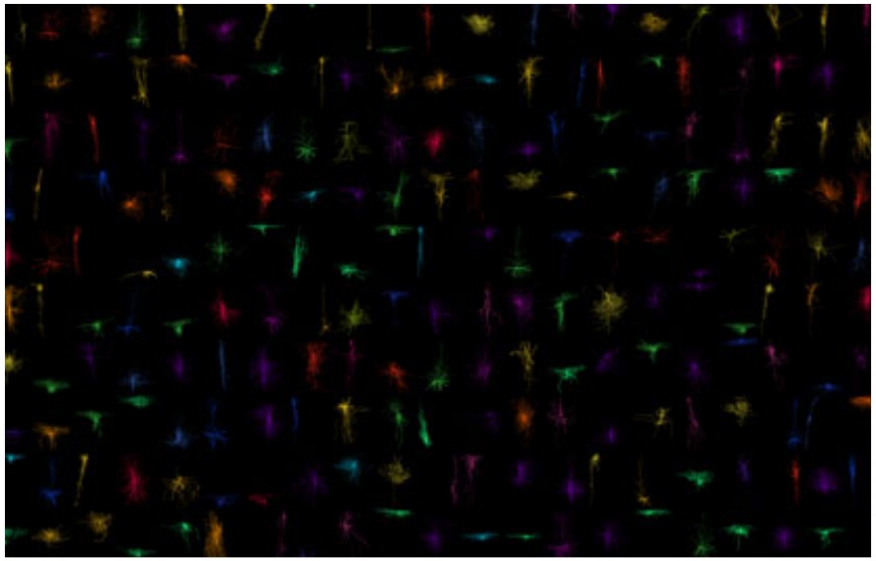

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Single-nucleus and single-cell transcriptomes compared in matched cortical cell types TE Bakken, RD Hodge, JA Miller, Z Yao, TN Nguyen, B Aevermann, ... PloS one 13 (12), e0209648	565	2018
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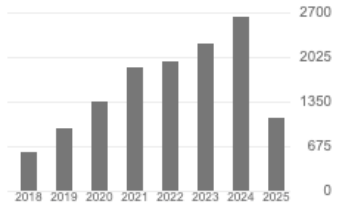

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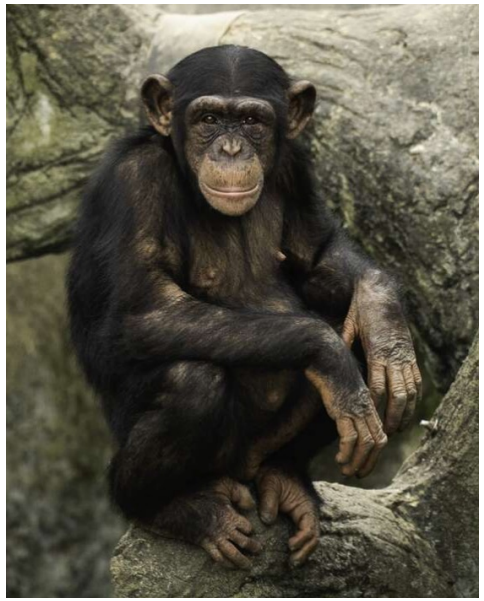
Why do I want to share this article? Why do they chose these primates?



Chimpanzee (C)

Gorilla (G)

Marmoset (M)

Rhesus (R)

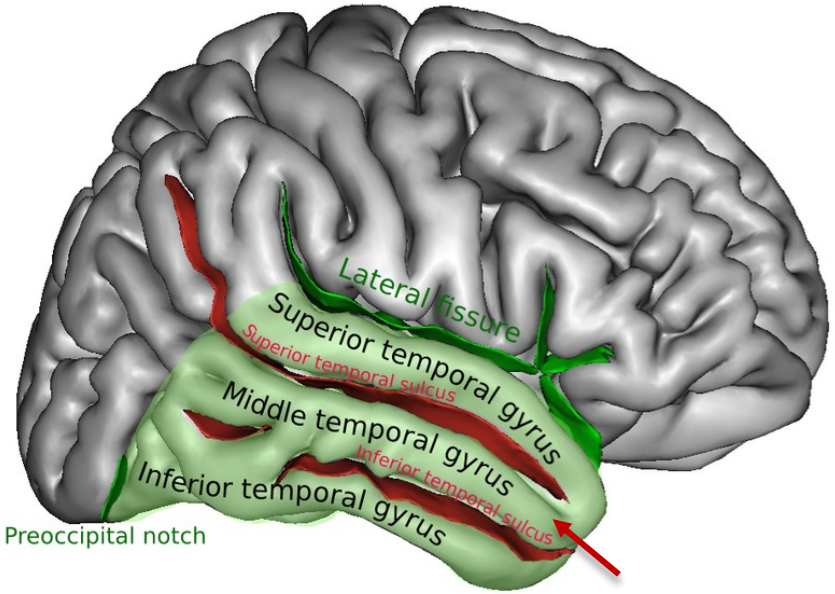
- Gorillas as a third great apes species
- Infer which differences between humans and chimpanzees are newly evolved in humans

- Two phylogenetically diverse monkey species
- Identify the cellular specializations that **humans share with other great apes**
- Contribute to our enhanced cognitive abilities

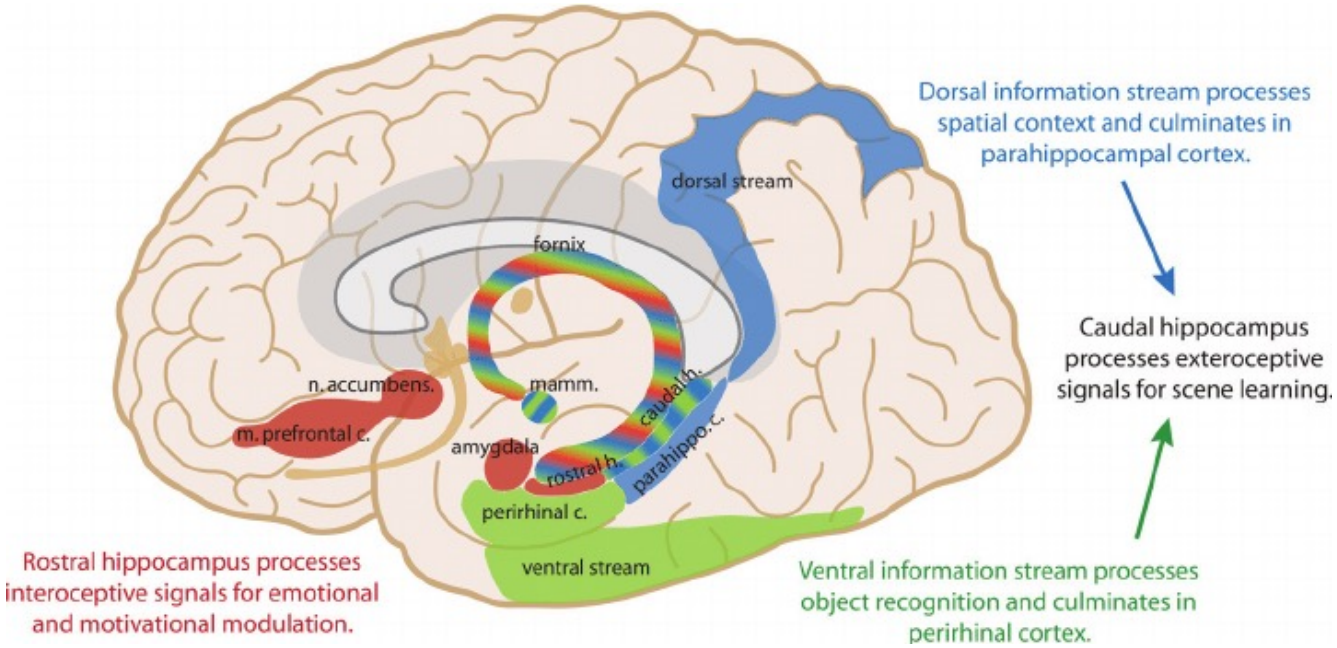
Scientific questions:

What are the molecular and cellular mechanisms underlying the distinctive cognitive abilities of humans compared to other primates?

Anatomical differences change in the molecular programs of cortical neurons and non-neuronal cells



MTG (颞中回): for snRNA-seq



Raslau et al., 2014, American Journal of Neuroradiology

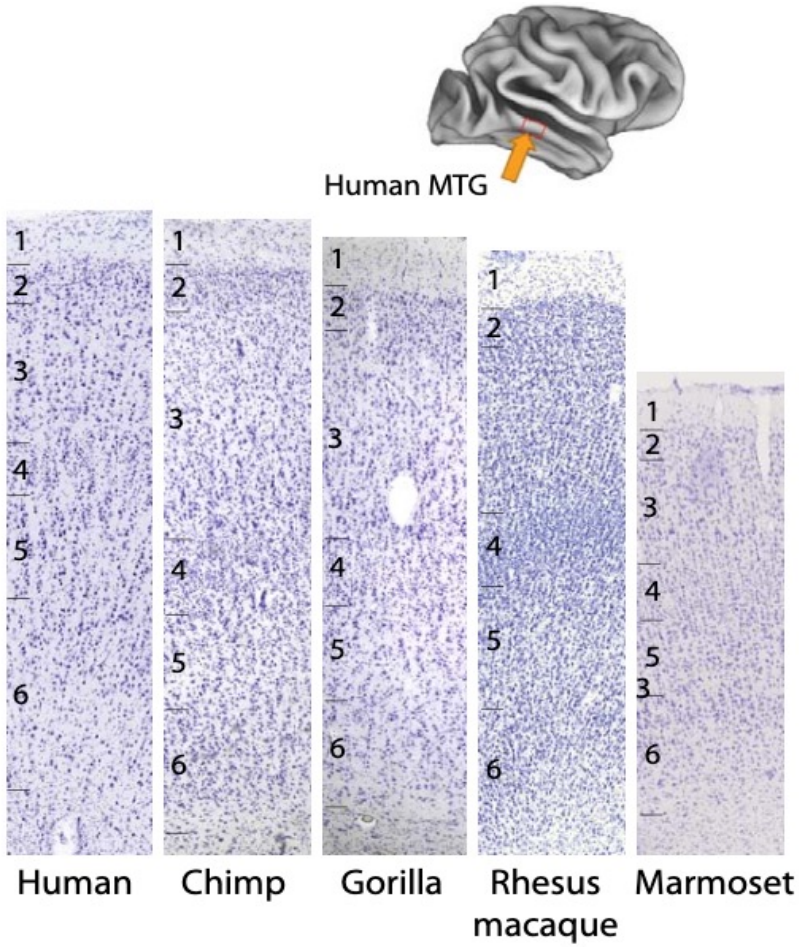
Anatomical differences:

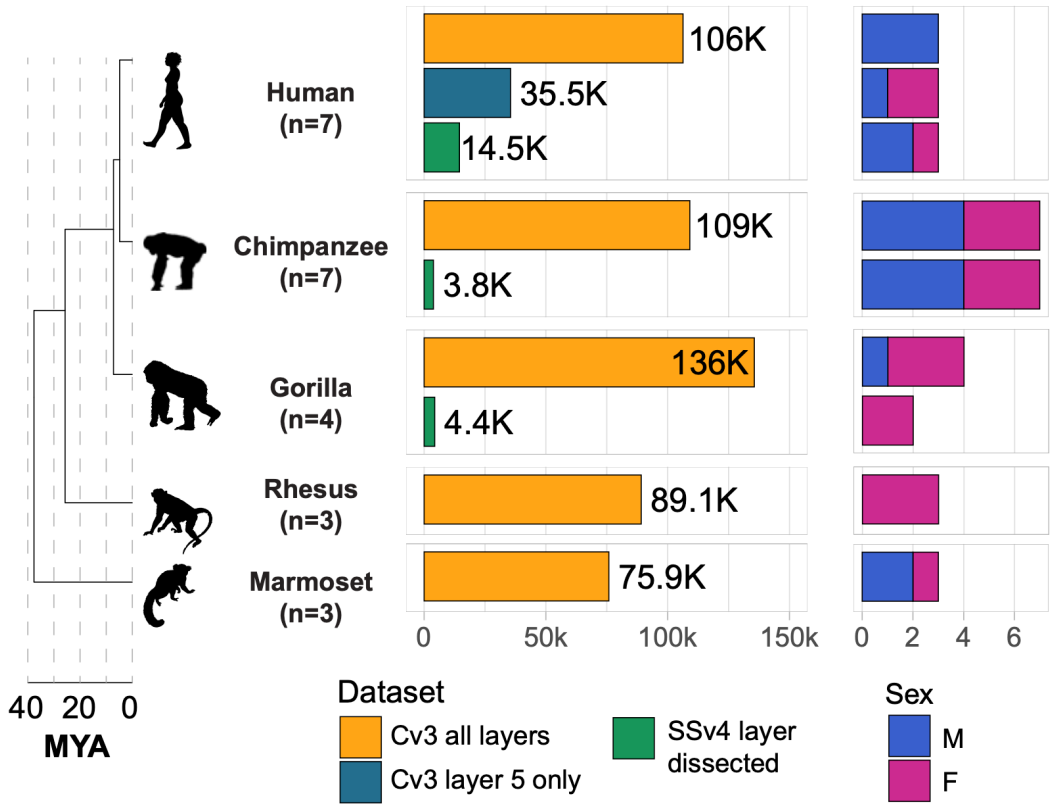
- MTG is larger in human
- More connected to language-associated cortical areas

MTG Functions:

- Integrates multimodal sensory information
- Critical for visual and auditory language comprehension

Profiled more than 570,000 single nuclei from MTG

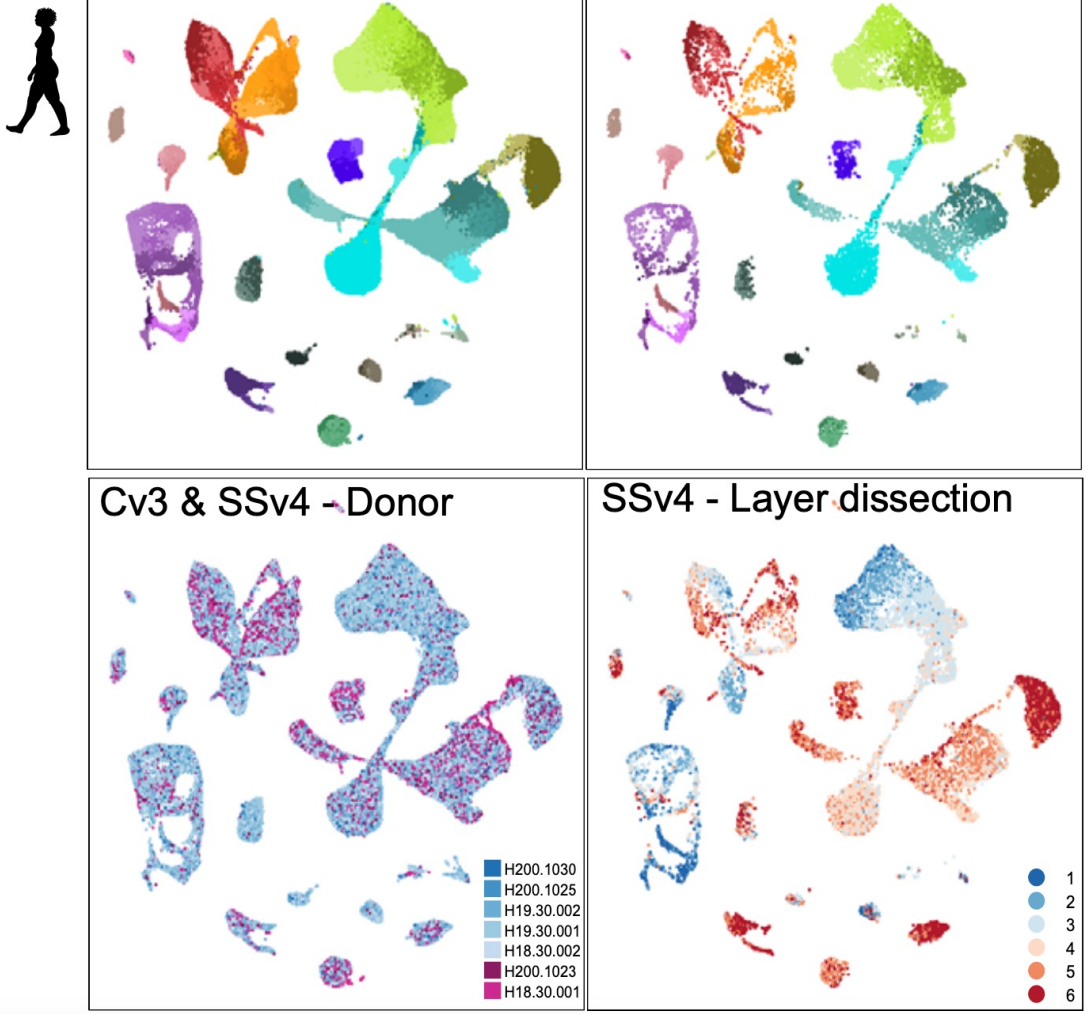




- Using RNA sequencing from the MTG
- Layer dissections for laminar distribution study

- Transcriptomic profiling of more than 570,000 nuclei
- Microdissected layer 5 to capture rare excitatory neuron

Each species was independently analyzed, all nuclei were well mixed across datasets and across individuals



Cell types were grouped into five neighborhoods

✨ were analyzed separately

✨Excitatory neurons

- ①IT: intratelencephalic (IT)–projecting excitatory neurons 内脑投射兴奋性神经元
- ②Non-IT: non–IT-projecting excitatory neurons 非IT投射的兴奋性神经元

✨Inhibitory neurons

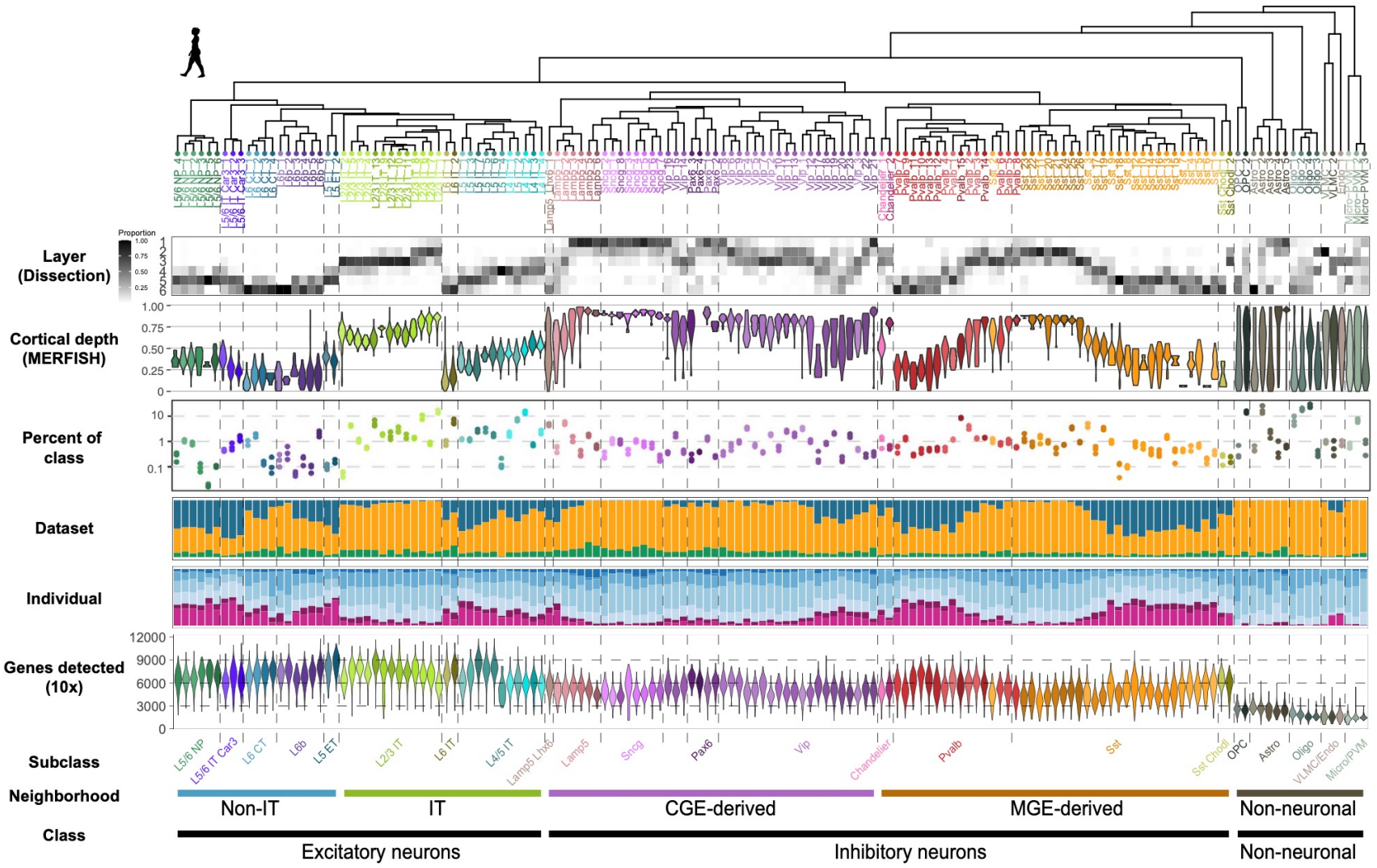
- ③CGE-derived: caudal ganglionic eminence-derived interneurons 尾状神经节隆起
- ④MGE-derived: medial ganglionic eminence-derived interneurons 内侧神经节隆起

✨⑤Non-neuronal cells 非神经元细胞

- astrocytes 星形胶质细胞
- oligodendrocytes 少突胶质细胞
- micro/PVMs 微胶质细胞和血管周围巨噬细胞

…

Species cell types were hierarchically organized into dendrograms based on transcriptomic similarity



Humans had the most cell-type diversity (151 clusters)

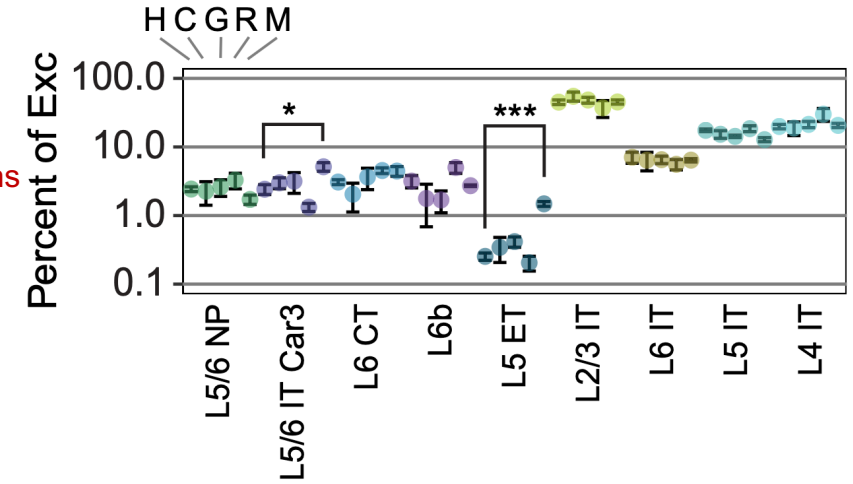
MERFISH: in situ spatial distributions

- Robust gene detection
Neuronal, median 3000 to 9000 genes
Non-neuronal, median 1500 to 3000 genes

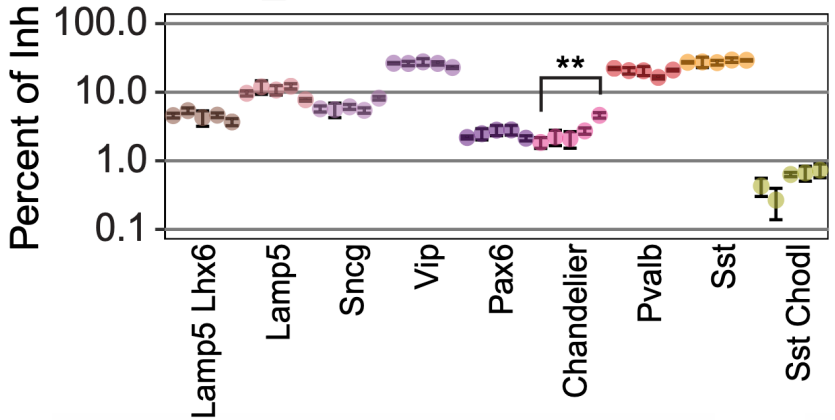
24 conserved subclasses
(18 neuronal, 6 non-neuronal)

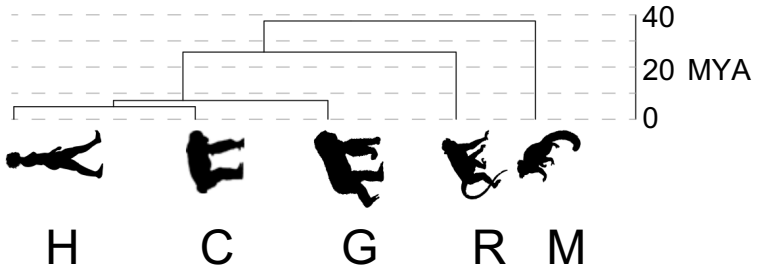
MTG cell types are largely conserved

Excitatory neurons
兴奋性神经元



Inhibitory neurons
抑制性神经元

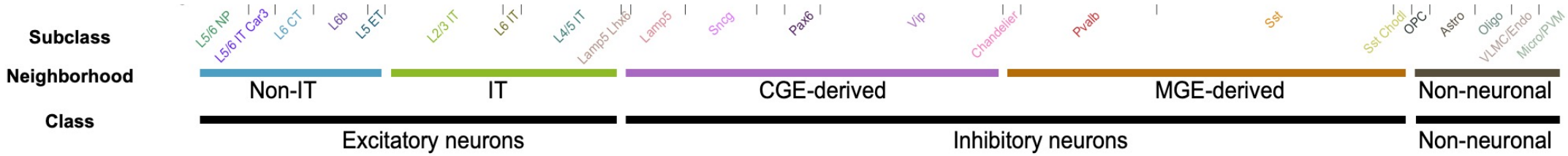




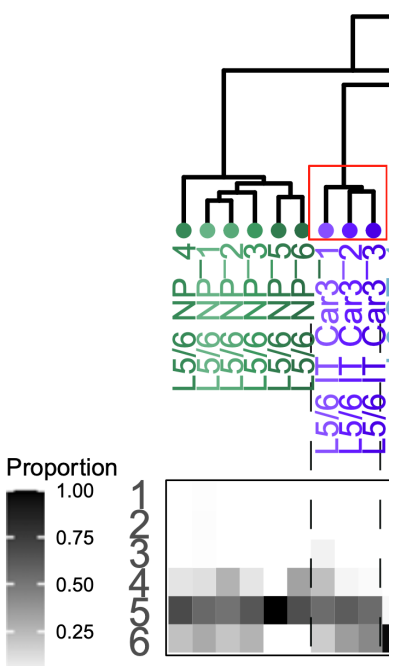
Methods: Post hoc pairwise t tests

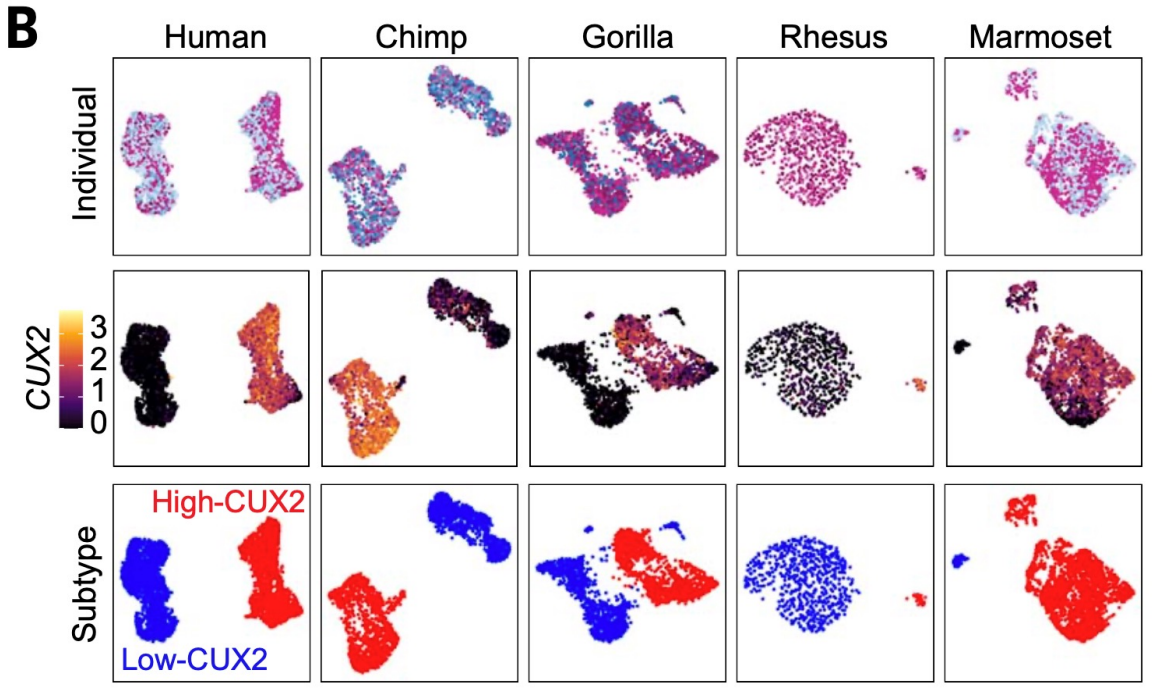
Results:

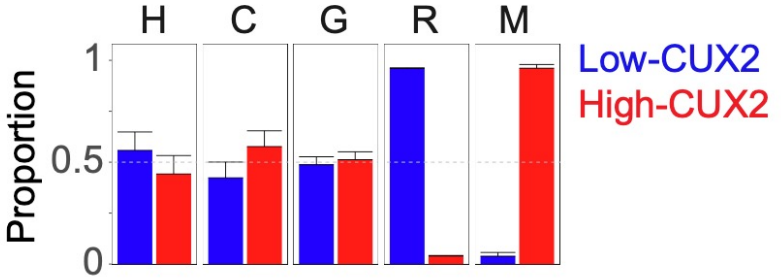
- Within each species, Subclass proportions were highly consistent across individuals.
- Varied significantly across species identified up to **fivefold** more **L5/6 IT CAR3**, L5 ET, and Chandelier in marmosets.



Great apes have similar proportions of two major subtypes of L5/6 IT CAR3 neurons that have high or low CUX2 expression



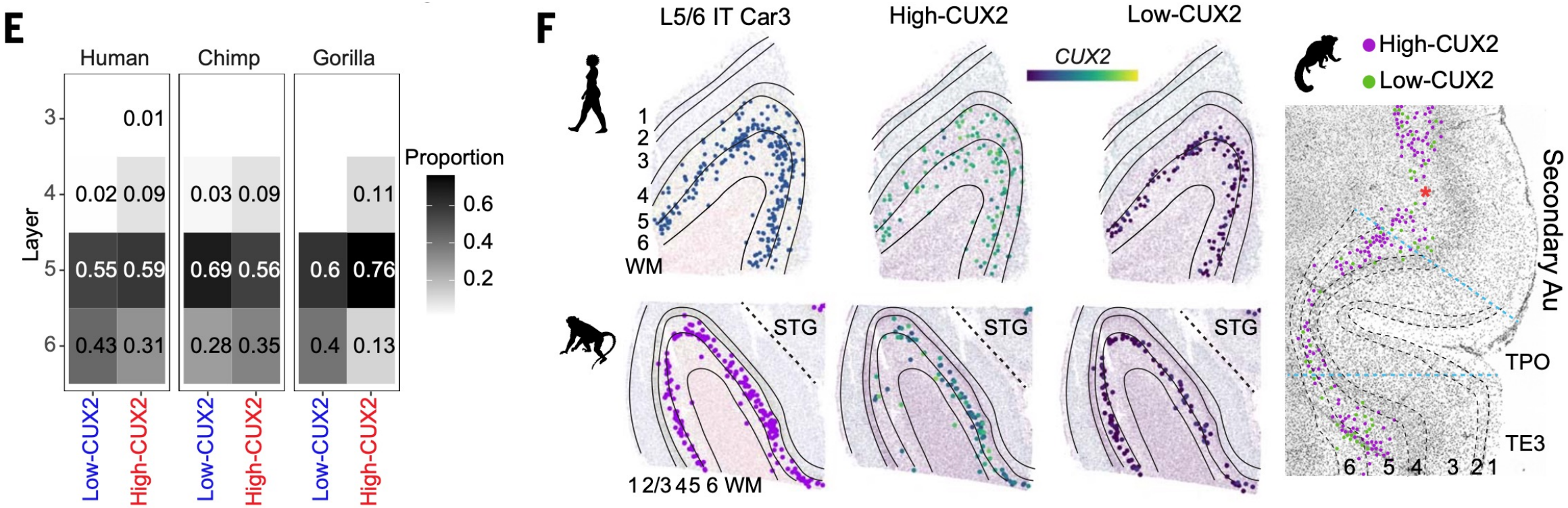




BG: Among L5/6 IT CAR3 neurons, two distinct subtypes had high and low CUX2 expression.
High-CUX2 neurons are enriched in language-related regions in temporal (颞叶) and parietal (顶叶) cortex.

Results: - Subtype proportions were balanced in great apes.
- Mostly low-CUX2 in rhesus.
- Mostly high-CUX2 in marmosets.

Low-CUX2 neurons were consistently more enriched in deeper layers

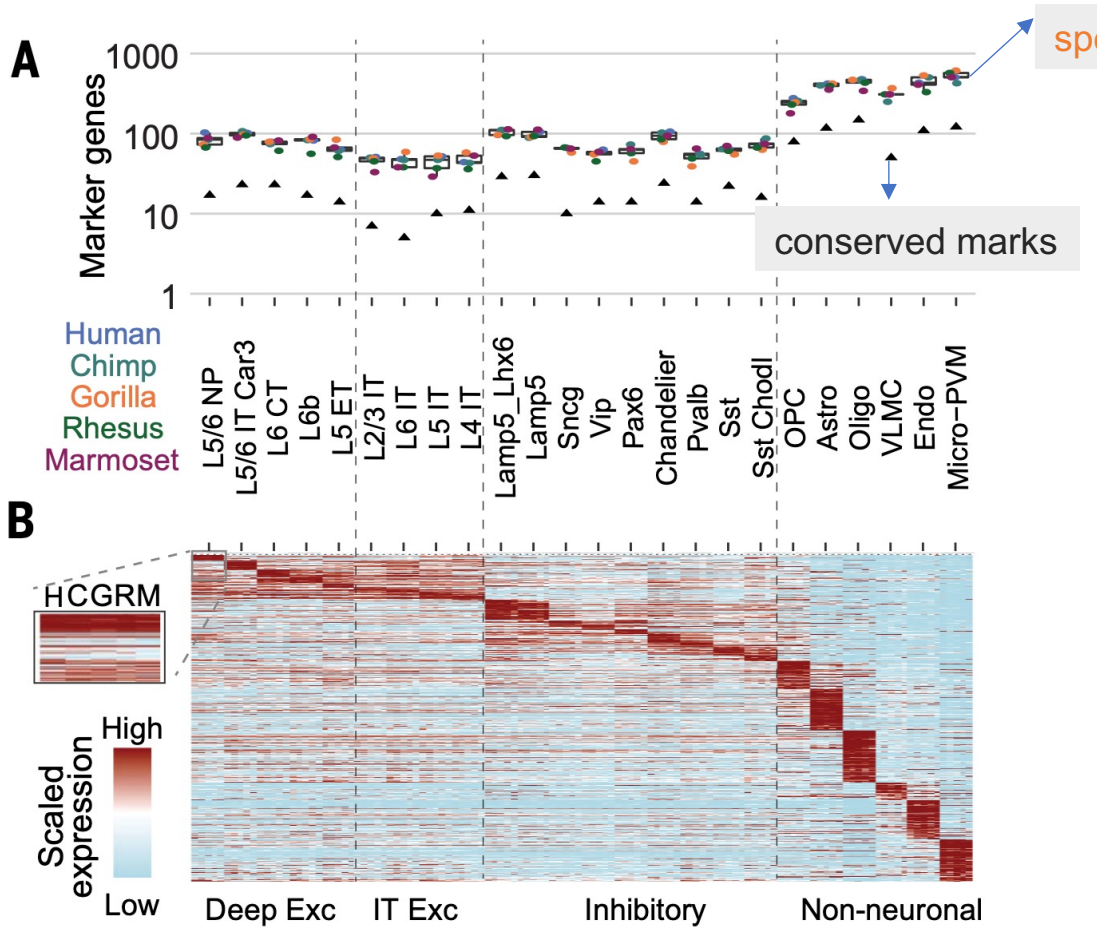


Methods: MERFISH

Results:

- In human, the high-CUX2 subtype extended from upper layer 6 through layer 5. The low-CUX2 subtype was enriched at the border of layers 5 and 6.
- In rhesus MTG, high-CUX2 neurons varied along the **gyrus** with little on the ventral side (腹侧), and more on the **dorsal** side (背侧).

Each subclass had a similar number of markers in all species

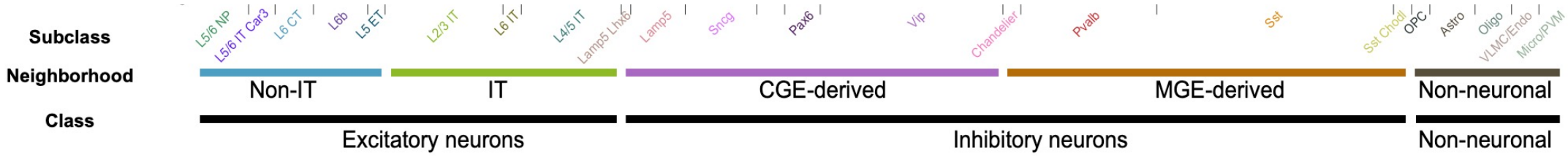


Goal: To compared the transcriptomic similarity

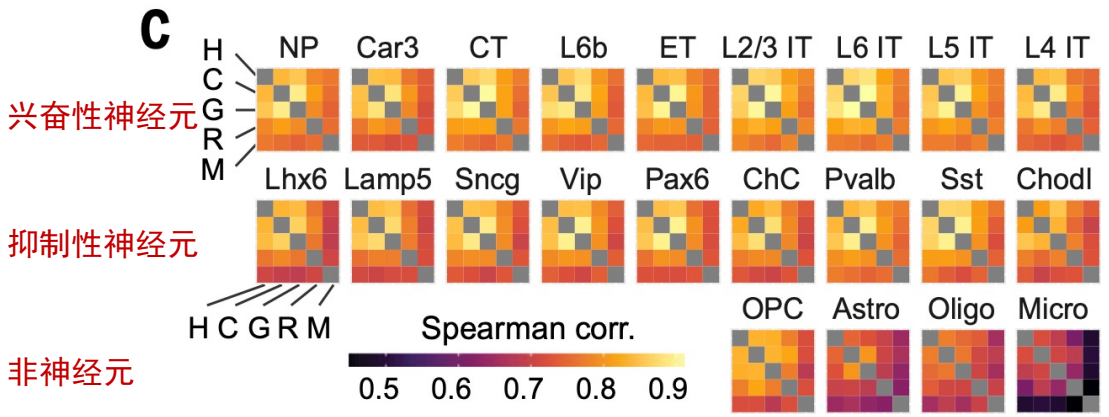
Methods: Defined gene markers, filtered to include one-to-one orthologs

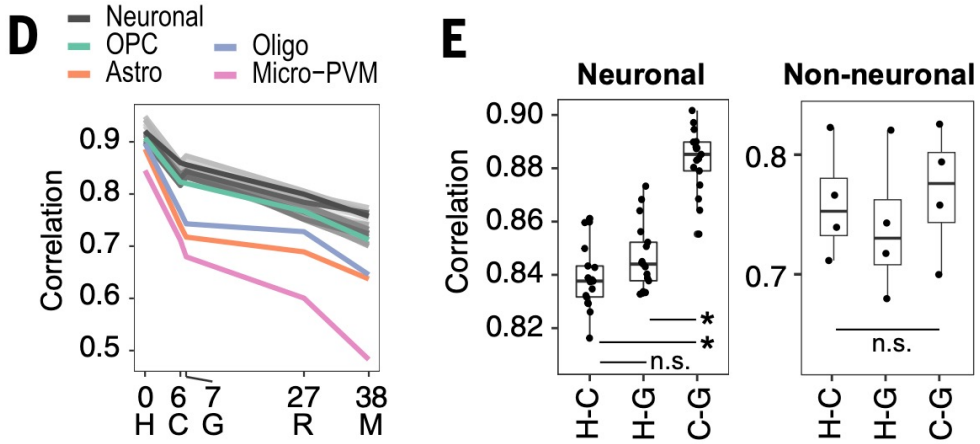
Results:

- Non-neuronal subclasses demonstrated greater distinction than neuronal subclasses.
- Only 10 to 20% had strongly conserved specificity.



Expression similarity decreased with evolutionary distance, faster in Non-neurons

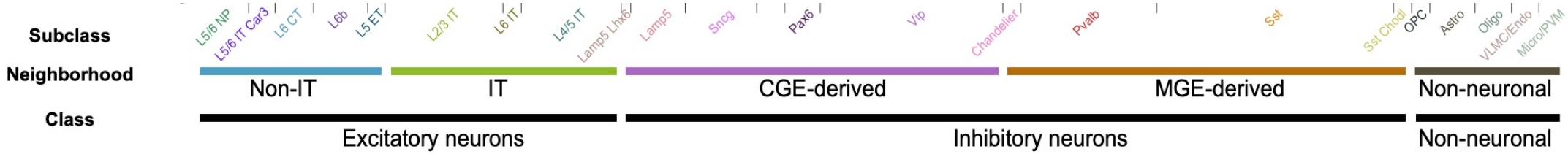




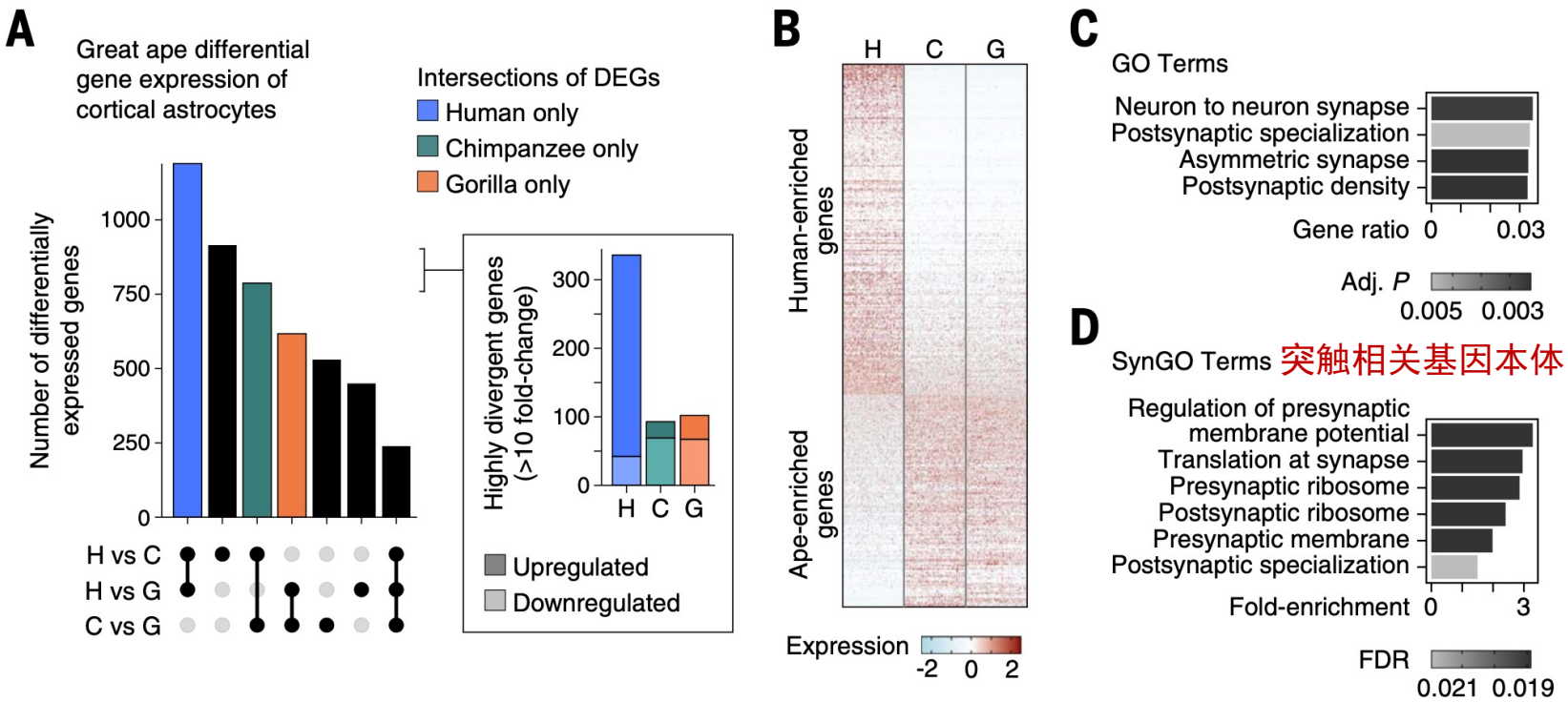
Goal:
To compare the global expression profile of subclasses

Method:
Correlated normalized median expression

Results:
- Glial cells (except OPCs) had greater expression changes between species compared with neurons.
- Expression similarity decreased with evolutionary distance at a similar rate across neuronal subclasses and OPCs, faster in Non-neuronal cells.
- Chimpanzee neuronal subclasses were more similar to gorillas.
- Neuronal expression diverged more rapidly in the human lineage.



Human astrocyte DEGs were enriched in synaptic signaling

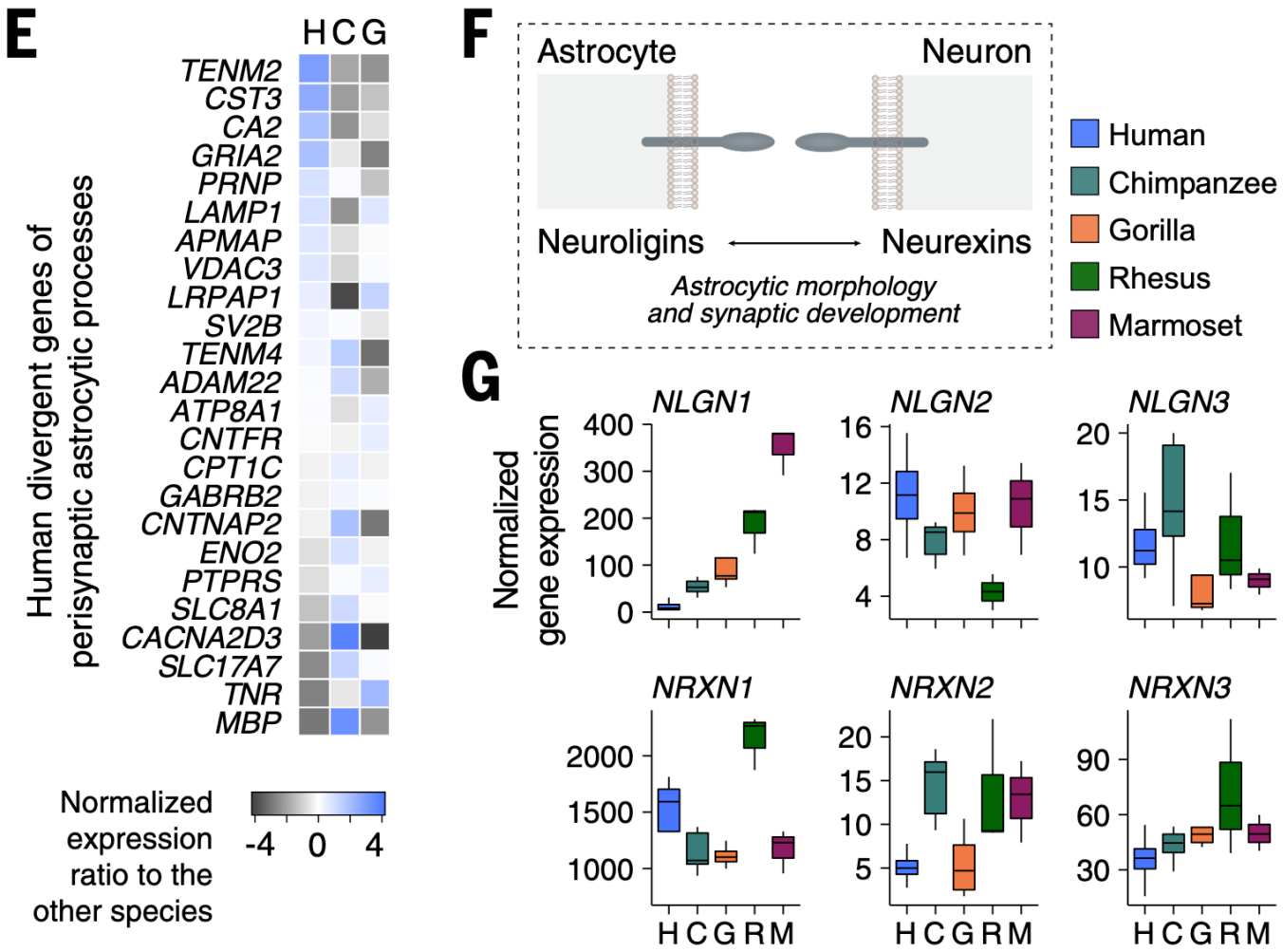


BG: Glial cells (胶质细胞-非神经元) exhibited the most divergent gene expression changes

Goal: To uncover their specialized transcriptional programs

Result: - More human DEGs (1189) than chimpanzee (787) or gorilla (617) DEGs.
- Human DEGs: three times more highly divergent (>10-fold).
- Enriched in synaptic signaling and protein translation pathways.

Neuroligins and neurexins showed divergent expression patterns across great ape

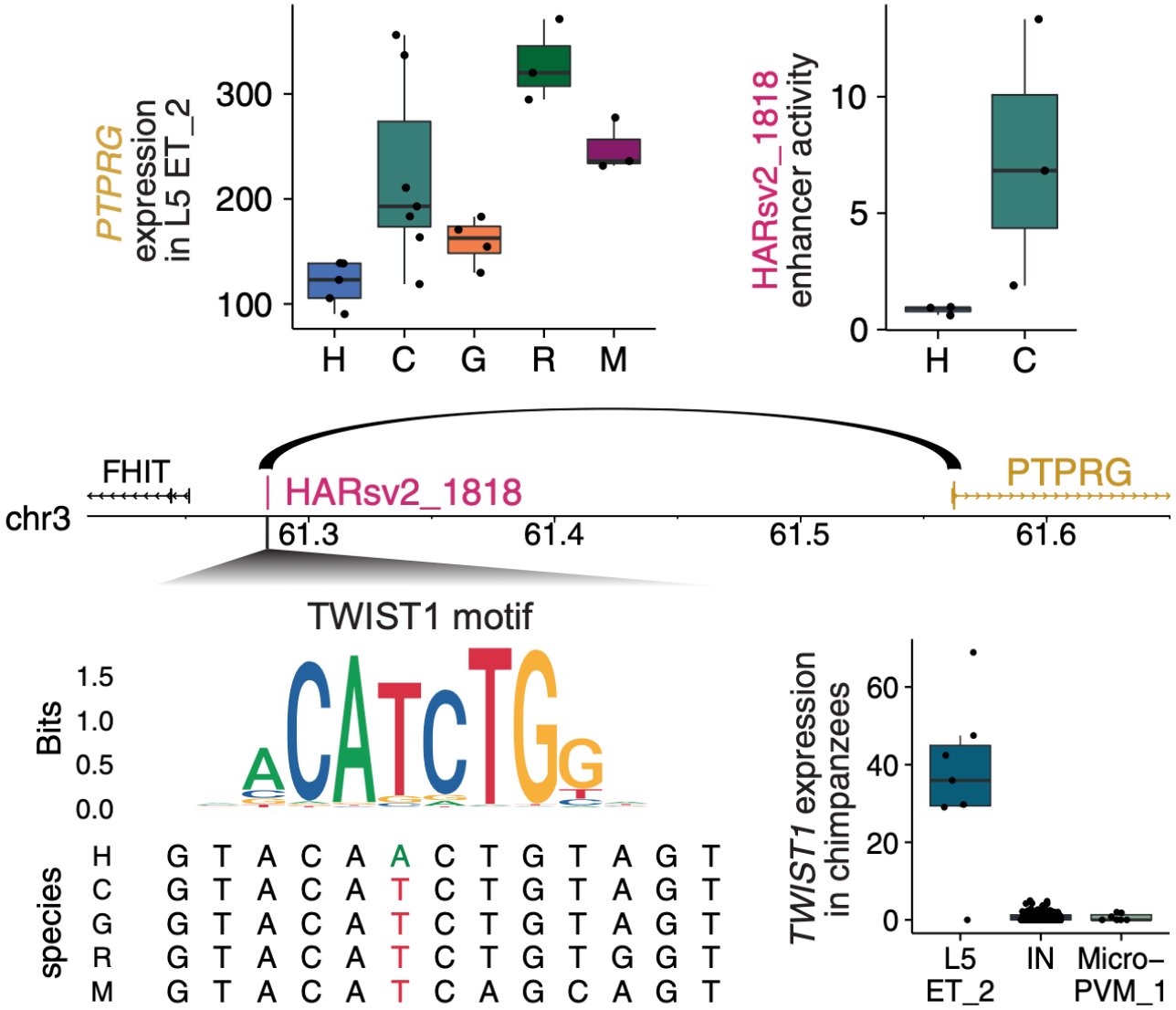


BG: Neuroligins and neurexins: ligand-receptor pairs that play a key role in astrocytic morphology and synaptic development

Goal: To study synapse-related astrocytic gene programs

Results:
- 24 genes (20%) were differentially expressed in human astrocytes, involved in synaptic signaling.
- Genes related to neuroligins and neurexin showed divergent expression patterns across great ape species.

hDEG near HARs play critical roles in synapse establishment, elimination, and maintenance



Genomic regions:
HARs: highly conserved across mammals and have higher substitution rates in the human lineage

BG: PTPRG is a member of the PTP receptor family that acts as presynaptic organizers for synapse assembly.

Results:
- had lower expression in humans than in NHPs.
- PTPRG is located near HARsv2_1818, decreased enhancer activity.

Suppose: decreased enhancer activity from HARsv2_1818 in humans may have decreased PTPRG expression specifically in the excitatory neuron consensus type L5 ET_2.

In support of this hypothesis: base-pair substitution removes a binding site for TWIST1, a basic helix-loop-helix transcription factor.

What problem does this article want to solve? What is the core conclusion?

Questions: How do cellular gene expression changes link to human cognitive uniqueness?

The cognitive abilities of humans are distinctive among primates, but their molecular and cellular substrates are poorly understood.

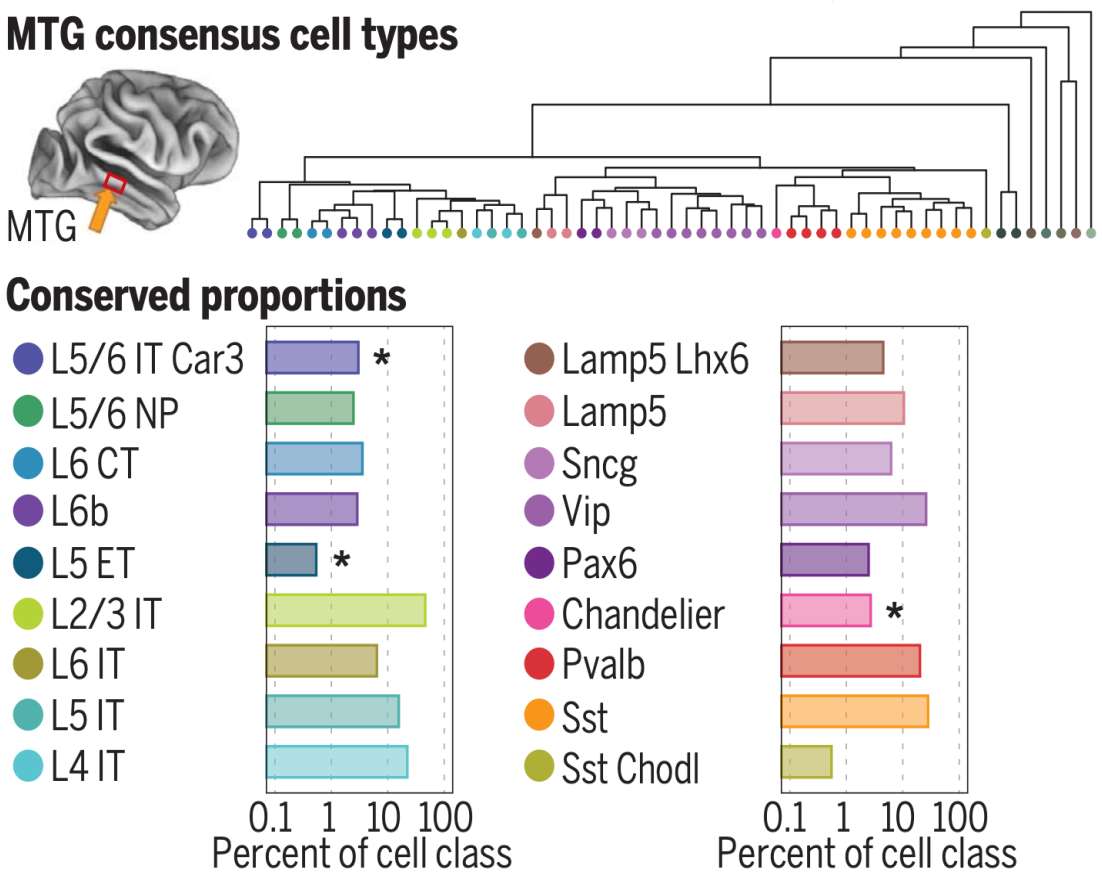
Through the integration of diverse datasets, we identified gene expression changes that may be linked to human adaptive evolution.

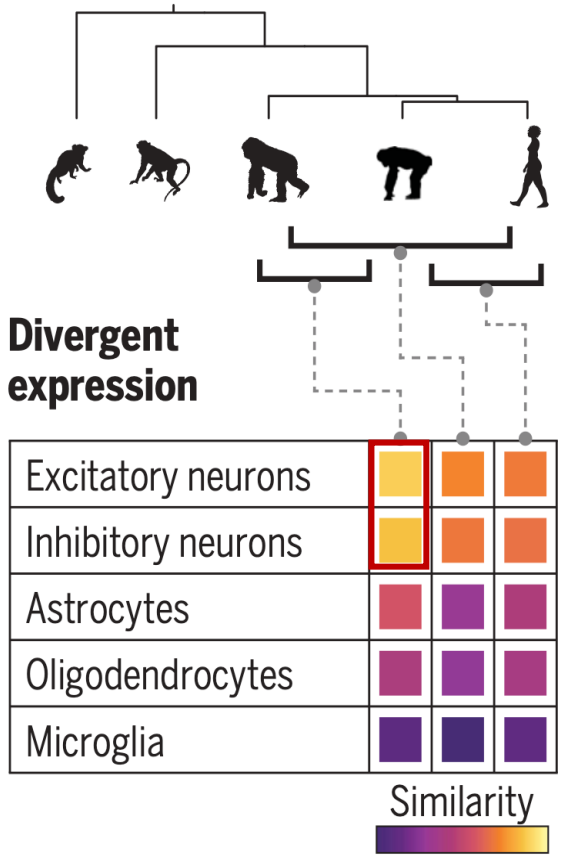
Conclusions:

- **Shared patterns**: Our study found that MTG cell types are largely conserved across approximately 40 million years of primate evolution.
- **Shared patterns**: The composition and spatial positioning of cell types are shared among great apes.
- **Special features**: In each species, hundreds of genes exhibit cell type–specific expression changes, particularly in pathways related to neuronal and glial communication.
- **Special features**: Human-specific DEGs are enriched near likely adaptive genomic changes and are poised to contribute to human-specialized cortical function.

Take home messages

- Human, chimpanzee, and gorilla MTG showed highly similar cell-type composition and laminar organization as well as a large shift in proportions of deep-layer intratelencephalic-projecting neurons compared with macaque and marmoset MTG.
- Microglia, astrocytes, and oligodendrocytes had more-divergent expression across species compared with neurons or oligodendrocyte precursor cells, and neuronal expression diverged more rapidly on the human lineage.
- Only a few … d molecular changes distinctivel…
- Human-sp… to human-specialized cortical fun…





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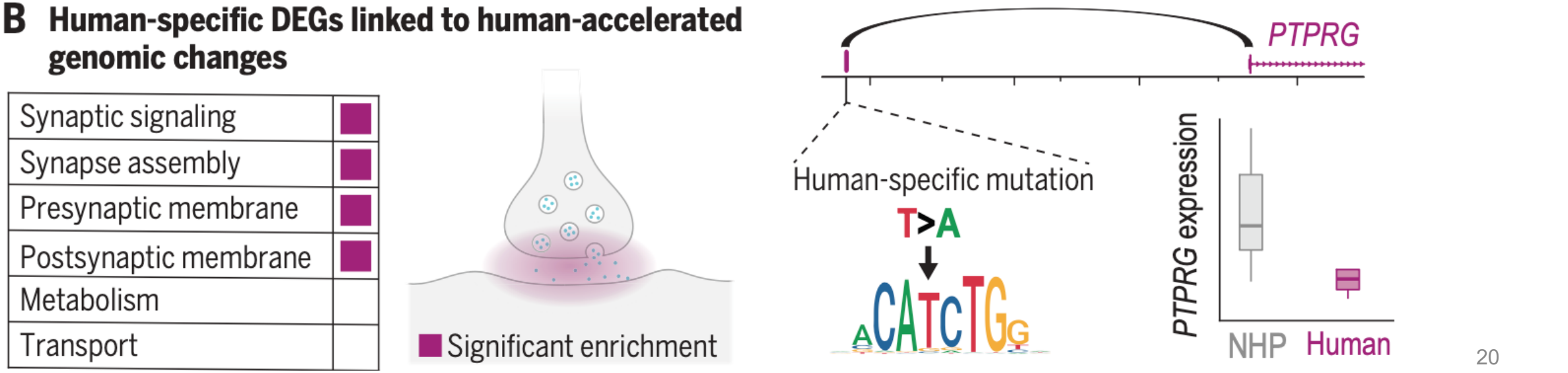
- Microglia, astrocytes, and oligodendrocytes had more-divergent expression across species compared with neurons or oligodendrocyte precursor cells, and neuronal expression diverged more rapidly on the human lineage.
- Only a few hundred genes showed human-specific patterning, suggesting that relatively few cellular and molecular changes distinctively define adult human cortical structure.
- Human-specific DEGs are enriched near likely adaptive genomic changes and are poised to contribute to human-specialized cortical function



Limitations

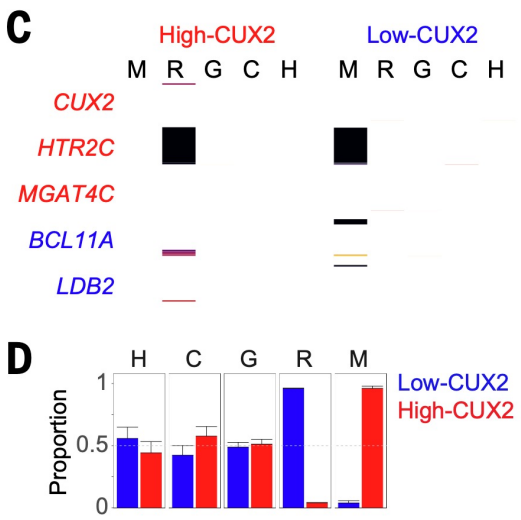
- Unbalanced sample size for rare cell types
- Lack of species diversity

- Insufficient functional verification
- The dynamic changes of cell states have not been fully explored

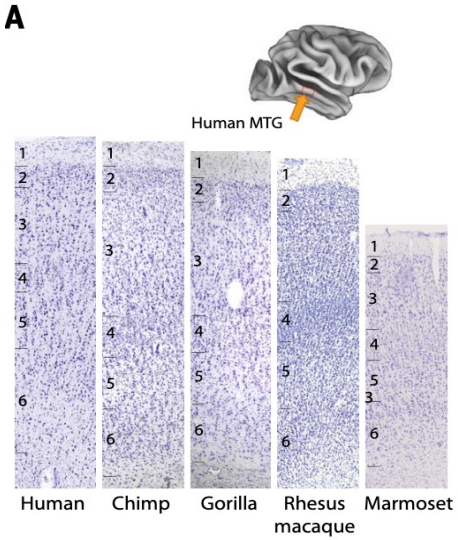
Typos in this article

1.细胞亚类名字写错：Post hoc pairwise t tests between humans and each NHP identified up to fivefold more L5/6 IT CAR3, L5 ET, and PVALB-expressing chandelier interneurons in marmosets.
2.没有该图表：Of note, four members of the neuregulin-ErbB signaling pathway showed differential gene expression in great ape astrocytes, with two receptors (EGFR and ERBB4) displaying expression changes in opposite directions (Fig. 5, I and J)
3.没有该图表：Up-regulation of human ERBB4 expression was higher in protoplasmic and fibrous astrocytes than in interlaminar astrocytes (Fig. 3J and fig. S5G)

4.图和结论不符：



5.皮层数字标错：



Thank you for your attention !

Q & A

RESEARCH ARTICLE SUMMARY

BICCN

Comparative transcriptomics reveals human-specific cortical features

Aoyue Bi 2025.May.23

Human-Specific Features of the Neocortex: Gene Expression and Cellular Insights

为了解决什么问题 Research Objective

- Understand human-specific features of the neocortex
- Identified a subset of changes that may be adaptive
- Found putative links between human accelerated regions (HARs) and human conserved deletions (hCONDELs) and human expression specializations

做了什么分析 / 实验 Methods

- Used comparative single-nucleus transcriptomics
- Analyze samples of the middle temporal gyrus (MTG) from adult humans, chimpanzees, gorillas, rhesus macaques, and common marmosets

结果和现象是怎样 Results and Phenomena

- Human, chimpanzee, and gorilla MTG showed highly similar cell-type composition and laminar organization as well as a large shift in proportions of deep-layer intratelencephalic-projecting neurons compared with macaque and marmoset MTG.
- Microglia, astrocytes, and oligodendrocytes had more-divergent expression across species compared with neurons or oligodendrocyte precursor cells, and neuronal expression diverged more rapidly on the human lineage.
- Only a few hundred genes showed human-specific patterning, suggesting that relatively few cellular and molecular changes distinctively define adult human cortical structure.