Cytosplore Simian Viewer: Visual Exploration for Multi-Species Single-Cell RNA Sequencing Data

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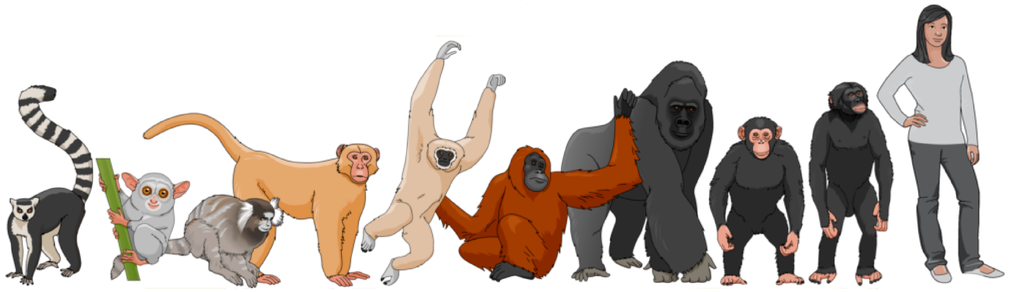
Distinction between human vs other primates



https://news.janegoodall.org/2018/06/27/chimps-humans-monkeys-whats-difference/

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Evolutionary expansion of connectivity between multimodal association areas in the human brain compared with chimpanzees

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Edited by John Morrison, University of California Davis, and accepted by Editorial Board ... October 31, 2018)

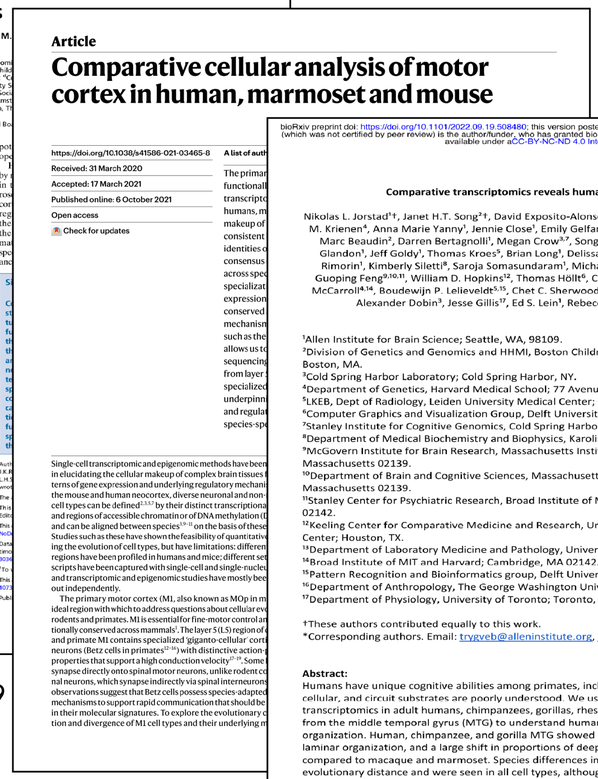
The development of complex cognitive functions during human evolution coincides with pronounced encephalization and expansion of white matter, the brain's infrastructure for region-to-region communication. We investigated adaptations of the human macroscale brain network by comparing human brain wiring with that of the chimpanzee, one of our closest living primate relatives. White matter connectivity networks were reconstructed using diffusion-weighted MRI in humans ($n = 57$) and chimpanzees ($n = 20$) and then analyzed using network neuroscience tools. We demonstrate higher network centrality of connections linking multimodal association areas in humans compared with chimpanzees, together with a more pronounced modular topology of the human connectome. Furthermore, connections observed in humans but not in chimpanzees particularly link multimodal areas of the temporal, lateral parietal, and inferior frontal cortices, including tracts important for language processing. Network analysis demonstrates a particularly high contribution of these connections to global network integration in the human brain. Taken together, our comparative connectome findings suggest an evolutionary shift in the human brain toward investment of neural resources in multimodal connectivity facilitating neural integration, combined with an increase in language-related connectivity supporting functional specialization.

connectome | evolution | chimpanzee | multimodal | comparative connectomics

A key step toward understanding human behavior is to understand how the human brain supports advanced cognitive functions such as social cognition, language, and theory of mind—abilities that are highly developed in humans (1–3). Comparative studies have pointed to several brain adaptations that may have facilitated the emergence of complex cognition during human evolution. The modern human brain is approximately three times larger in volume than that of early hominins, vastly exceeding the predicted brain size for a primate species of the same body size (4–6). Cellular examinations have indicated more pronounced dendritic branching of pyramidal cells in the human brain compared with other primates, suggesting a greater potential for neural integration of information in humans (7–9). Indeed, the human brain allocates relatively more cortex to association areas than to primary sensory and motor areas (4, 10–12), along with proportionally more white matter compared with other primates (13–15). These observed differences suggest that the evolution of advanced cognitive features in humans was accompanied by widespread modifications to the complex architecture of the human brain and its connectivity. The topological organization of these brain connectivity adaptations and their ...

www.pnas.org/cgi/doi/10.1073/pnas.1818512116

Ardesch, et al., National Acad Sciences, 2019



Article

Comparative cellular analysis of motor cortex in human, marmoset and mouse

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Single-cell transcriptomic and epigenomic methods have been ... in elucidating the cellular makeup of complex brain tissues ... terms of gene expression and underlying regulatory mechani... the mouse and human neocortex, diverse neuronal and non-... cell types can be defined[1,2,3,7] by their distinct transcriptiona... and regions of accessible chromatin or DNA methylation [1] ... and can be aligned between species[3,7–10] on the basis of these ... Studies such as these have shown the feasibility of quantitative ... ing the evolution of cell types, but have limitations: differen... regions have been profiled in humans and mice; different se... scripts have been captured with single-cell and single-nuclei... and transcriptomic and epigenomic studies have mostly bee... out independently.

The primary motor cortex (M1, also known as MOp in m... ideal region with which to address questions about cellular ev... rodents and primates. M1 is essential for fine-motor control ar... tionally conserved across mammals[7]. The layer 5 (L5) region of ... and primate M1 contains specialized 'giganto-cellular' cort... neurons (Betz cells in primates[12–14]) with distinctive action ... properties that support a high conduction velocity[15–19]. Some ... synapse directly onto spinal motor neurons, unlike rodent co... nal neurons, which synapse indirectly via spinal interneurons... observations suggest that Betz cells possess species-adapted ... mechanisms to support rapid communication that should be ... in their molecular signatures. To explore the evolutionary c... tion and divergence of M1 cell types and their underlying m...

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Comparative transcriptomics reveals human-specific cortical features

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Abstract:
Humans have unique cognitive abilities among primates, including language, but their molecular, cellular, and circuit substrates are poorly understood. We used comparative single nucleus transcriptomics in adult humans, chimpanzees, gorillas, rhesus macaques, and common marmosets from the middle temporal gyrus (MTG) to understand human-specific features of cellular and molecular organization. Human, chimpanzee, and gorilla MTG showed highly similar cell type composition and laminar organization, and a large shift in proportions of deep layer intratelencephalic-projecting neurons compared to macaque and marmoset. Species differences in gene expression generally mirrored evolutionary distance and were seen in all cell types, although chimpanzees were more similar to

Bakken, et al., Nature, 2021

Jorstad, et al., BioRxiv, 2022

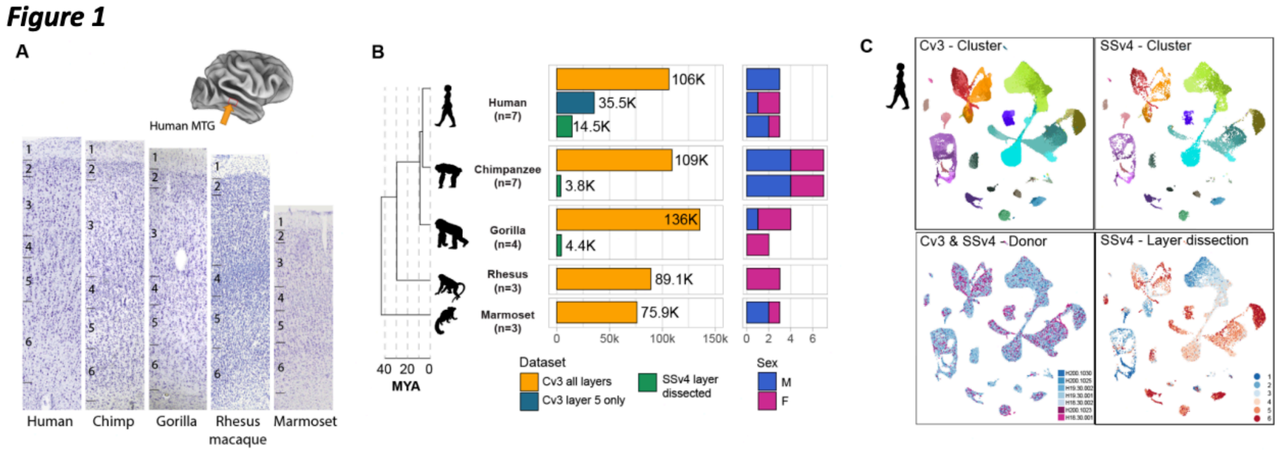
Specialised brain region

Middle Temporal Gyrus

https://radiopaedia.org/articles/middle-temporal-gyrus

Comparative transcriptomics reveals human-specific cortical features

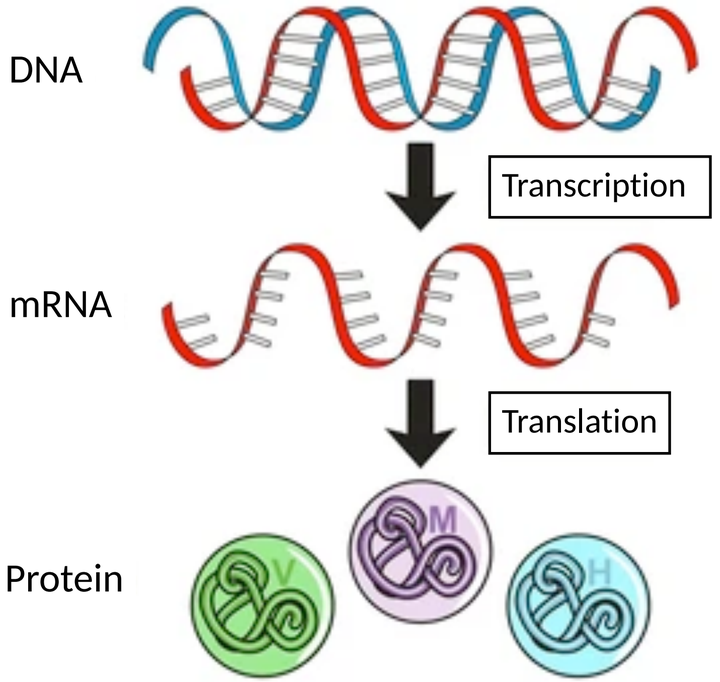
Jorstad, Song, Exposito-Alonso, et al.



Jorstad, et al., BioRxiv, 2022

Transcriptomic data

- Information about the RNA molecules
- Which genes are expressed
- How gene expression varies

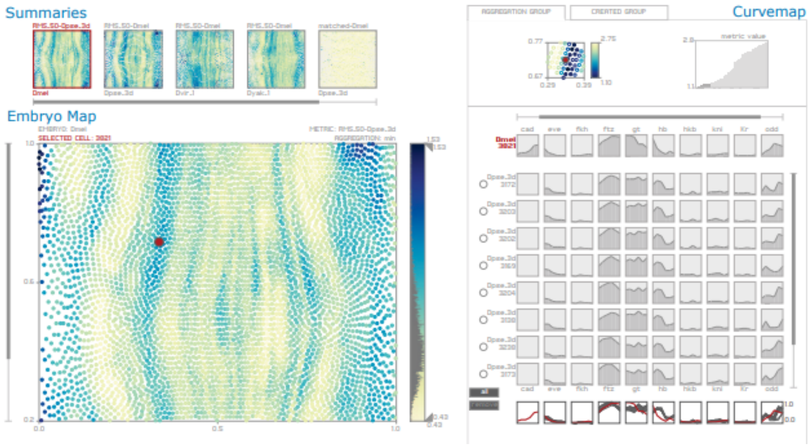


https://www.azolifesciences.com/article/A-Guide-to-Understanding-Gene-Expression.aspx

Omics visualisation tools

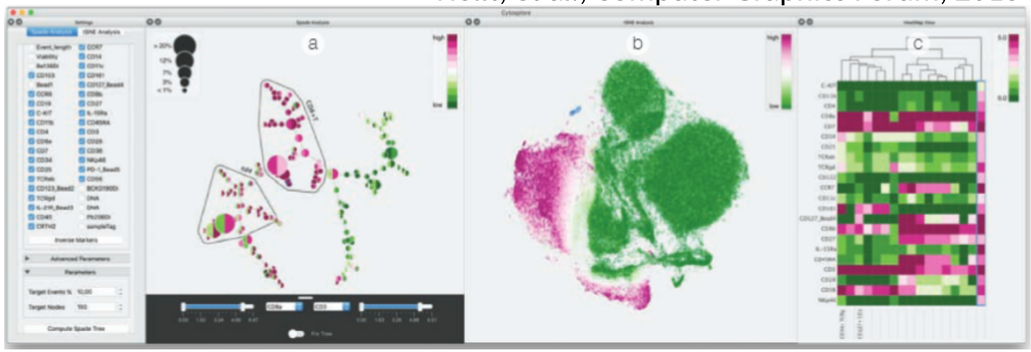
MulteeSum

Meyer, et al., IEEE TVCG, 2010

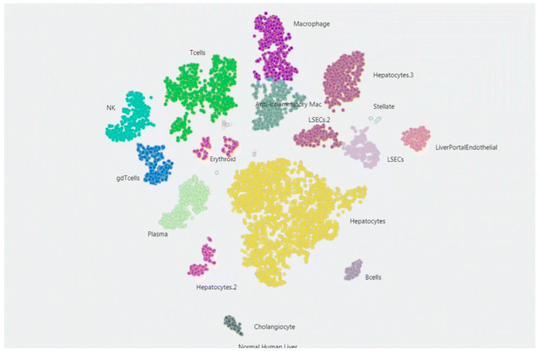


Cytosplore

Höllt, et al., Computer Graphics Forum, 2016



Single Cell Explorer

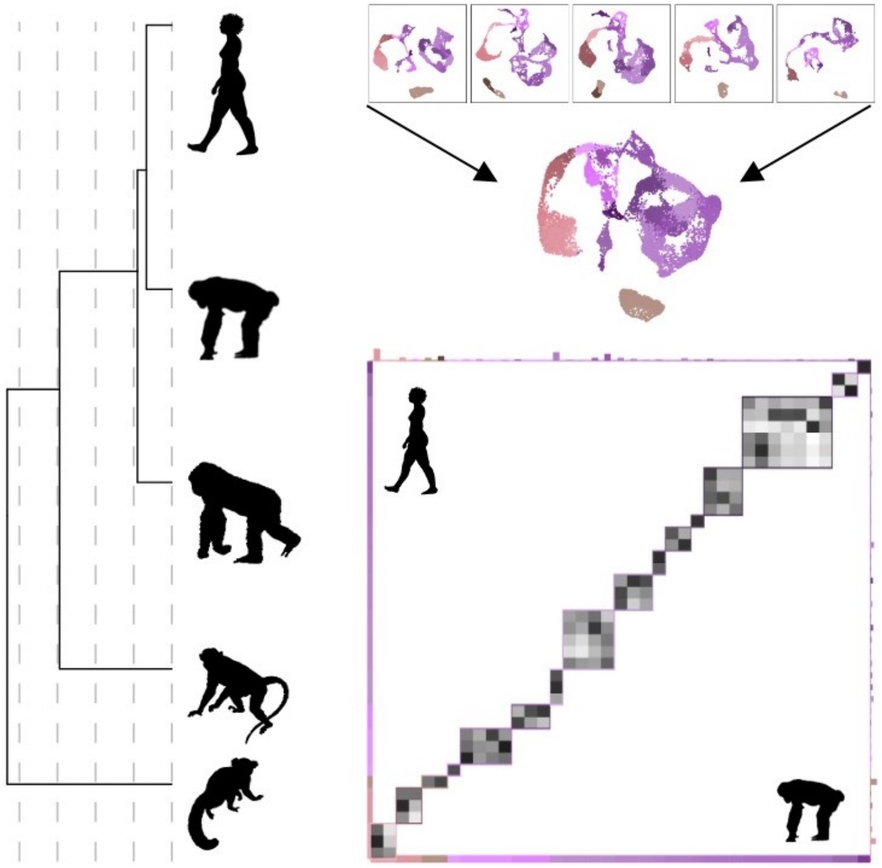


Feng, et al., BMC Genomics, 2019

Comparative analysis

- **Comparative** analysis of **multi-species** single-cell transcriptomic datasets

- Understanding of **cell type** and **gene expression** variations

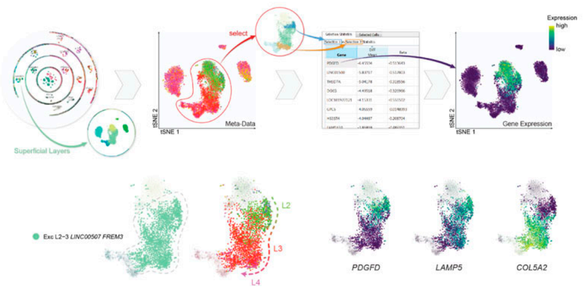


Collaboration and study setup

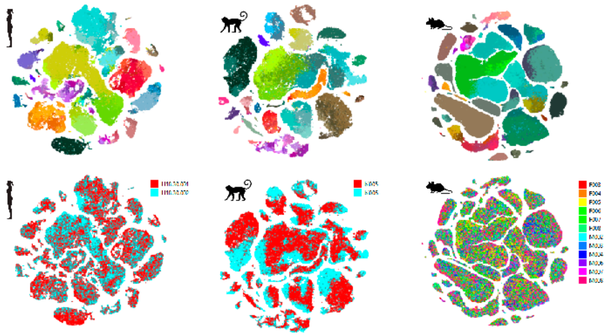
- Long-term collaboration

Tasic, et al., Nature, 2018

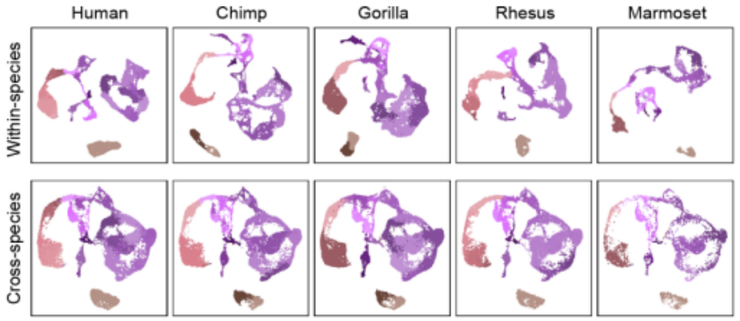
Hodge, et al., Nature, 2019



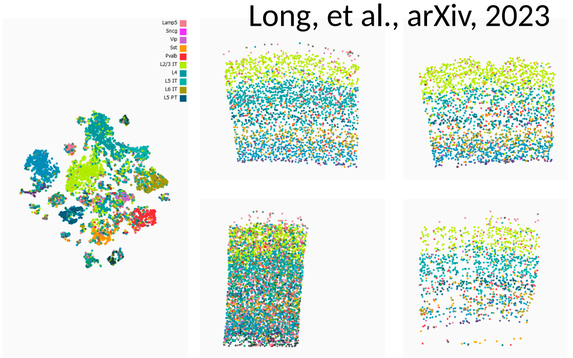
Bakken, et al., Nature, 2021



Jorstad, et al., BioRxiv, 2022



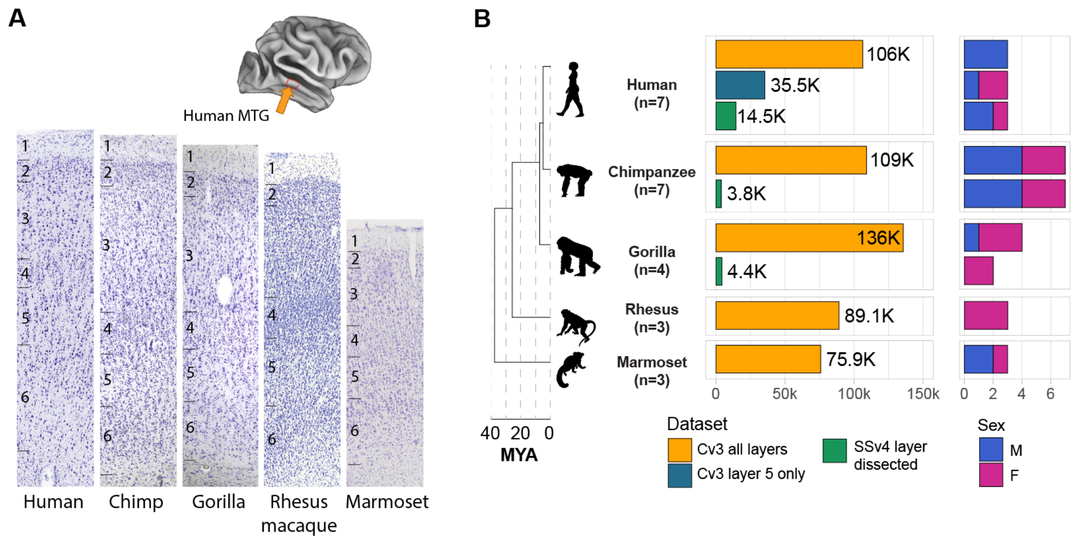
Long, et al., arXiv, 2023



Collaboration and study setup

- Long-term collaboration
- Data generation

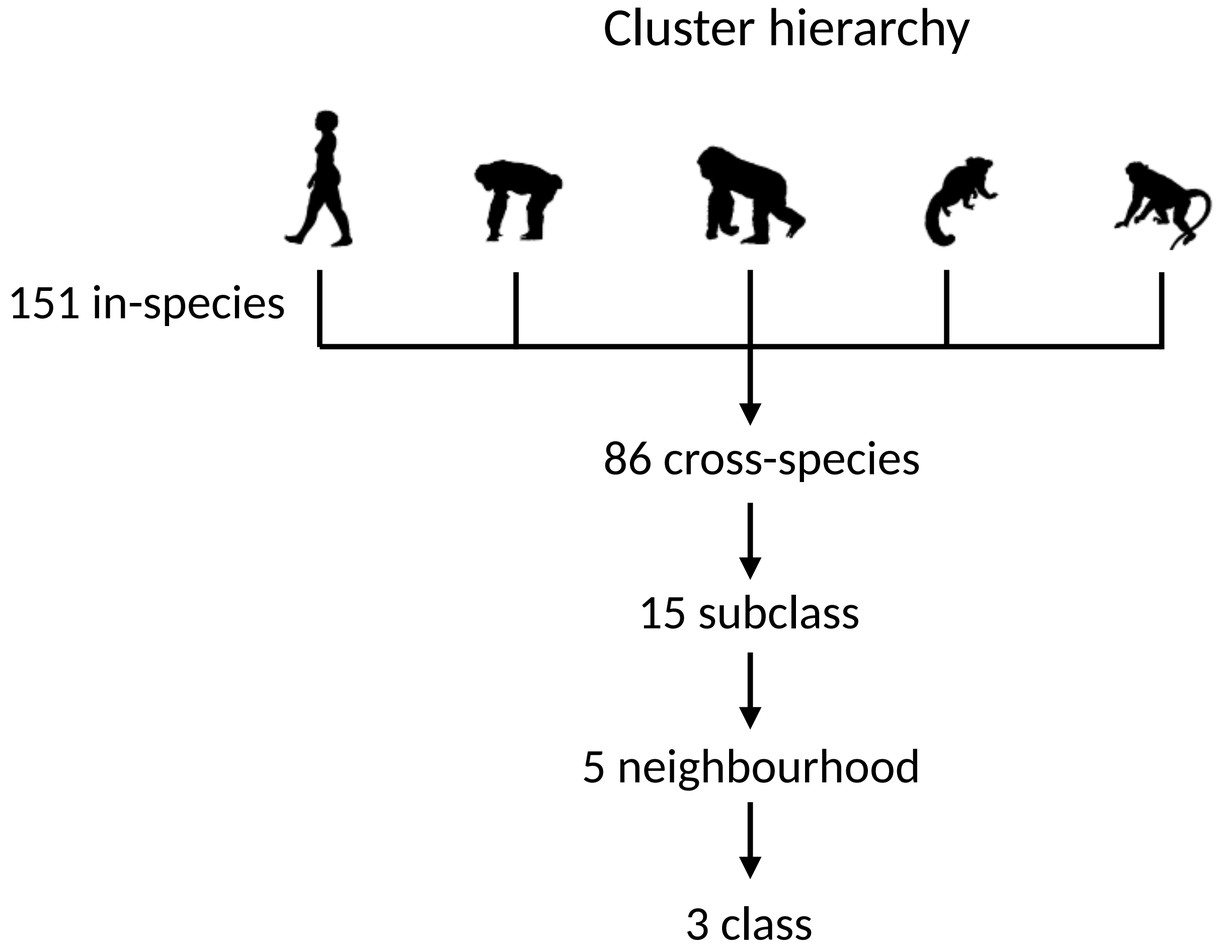
Comparative transcriptomics reveals human-specific cortical features
Jorstad, Song, Exposito-Alonso, et al.



Jorstad, et al., BioRxiv, 2022

Collaboration and study setup

- Long-term collaboration
- Data generation
- Data complexity



Jorstad, et al., BioRxiv, 2022

Collaboration and study setup

- Long-term collaboration
- Data generation
- Data complexity
- Domain specific goals

High level goals

How do cell type characteristics, such as **layer distribution** or **gene expression**, **differ** across species?

Collaboration and study setup

- Long-term collaboration
- Data generation
- Data complexity
- Domain specific goals

High level goals

How do cell type characteristics, such as **layer distribution** or **gene expression**, **differ** across species?

Are there genes that have **comparable expression patterns** across multiple species?

Collaboration and study setup

- Long-term collaboration
- Data generation
- Data complexity
- Domain specific goals

High level goals

How do cell type characteristics, such as **layer distribution** or **gene expression**, **differ** across species?

Are there genes that have **comparable expression patterns** across multiple species?

Are there genes that have highly variable expression patterns **across multiple species**?

Collaboration and study setup

- Long-term collaboration
- Data generation
- Data complexity
- Domain specific goals
- Task abstraction

Tasks

1. I**dentify** cross-species **clusters** of interest by exploring in-species cell cluster attributes

Collaboration and study setup

- Long-term collaboration
- Data generation
- Data complexity
- Domain specific goals
- Task abstraction

Tasks

1. I**dentify** cross-species **clusters** of interest by exploring in-species cell cluster attributes

2. **Identify genes** of interest for the identified cross-species clusters according to their attached meta information

Collaboration and study setup

- Long-term collaboration
- Data generation
- Data complexity
- Domain specific goals
- Task abstraction

Tasks

1. I**dentify** cross-species **clusters** of interest by exploring in-species cell cluster attributes

2. **Identify genes** of interest for the identified cross-species clusters according to their attached meta information

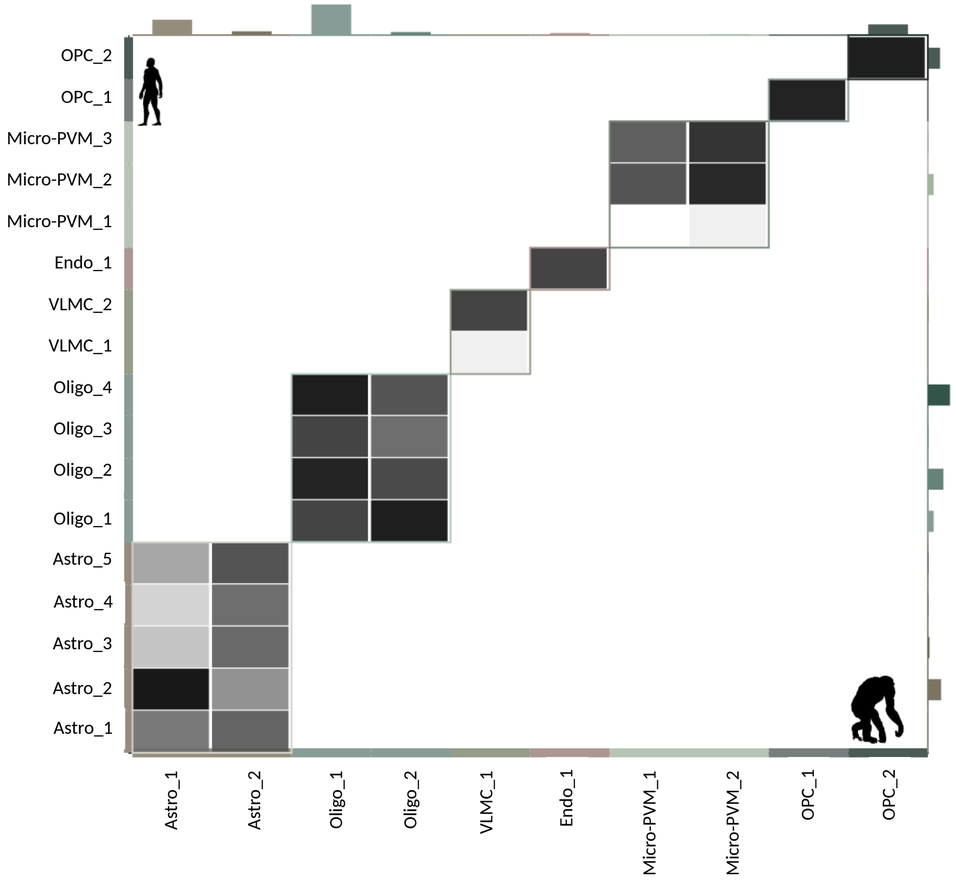
3. **Compare** gene **expression** values between species

Task 1: Cluster identification

Subtask: Attribute exploration

- Distance

Heat map



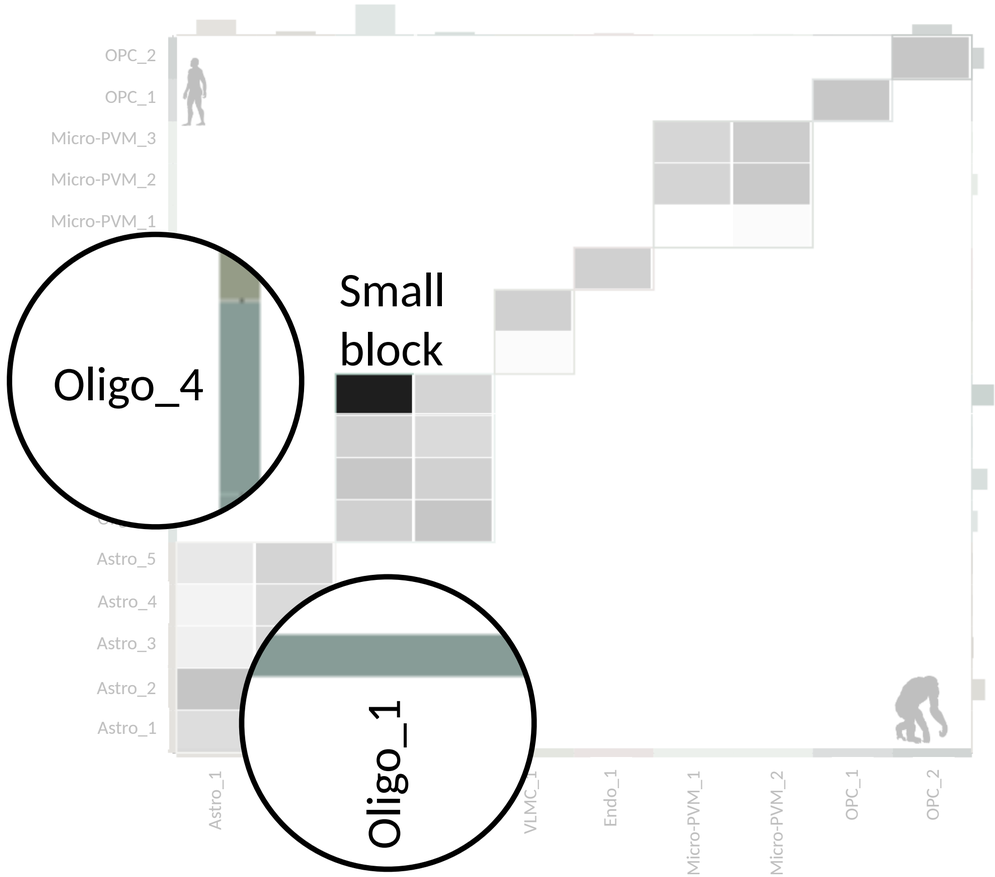
Details on distance measure
by Jorstad et al., BioRxiv, 2022

Task 1: Cluster identification

Subtask: Attribute exploration

- Distance

In-species clusters

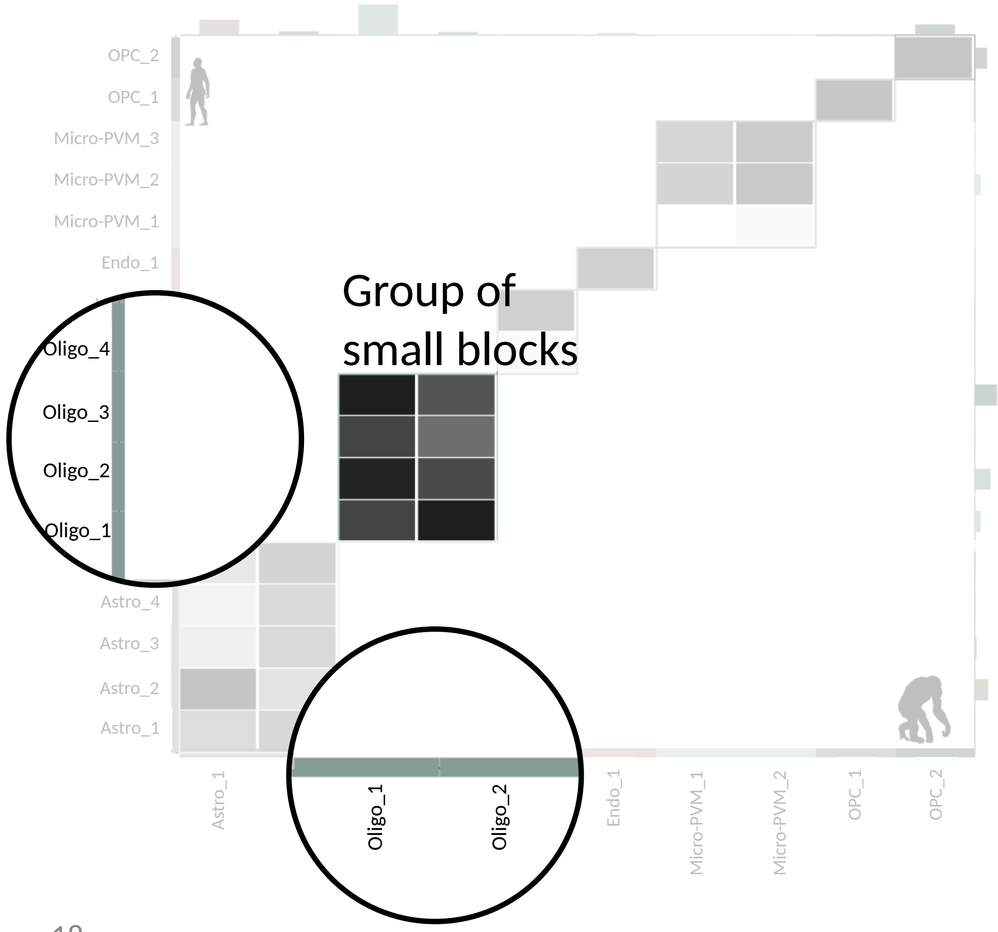


Task 1: Cluster identification

Subtask: Attribute exploration

- Distance

Cross-species clusters

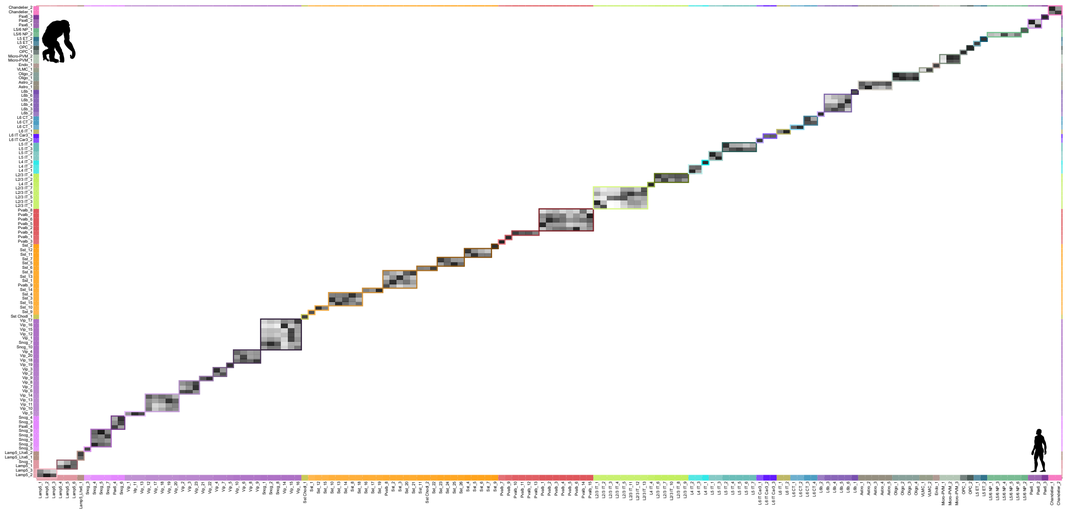


Task 1: Cluster identification

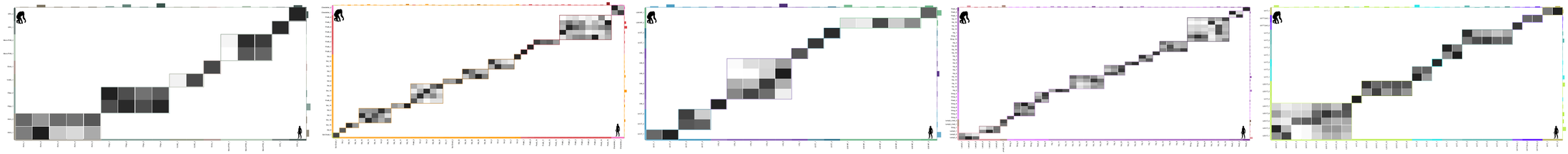
Subtask: Attribute exploration

- Distance

Heat map with all clusters



Heat maps based on neighbourhoods

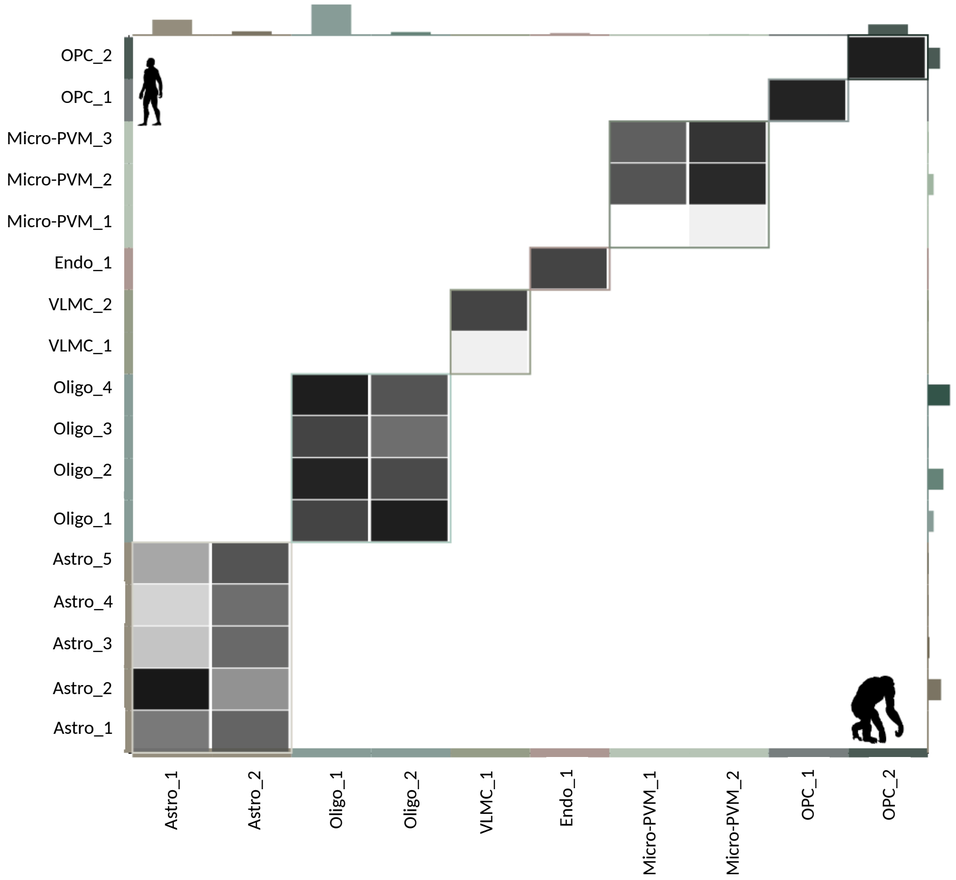


Task 1: Cluster identification

Subtask: Attribute exploration

- Distance
- Size

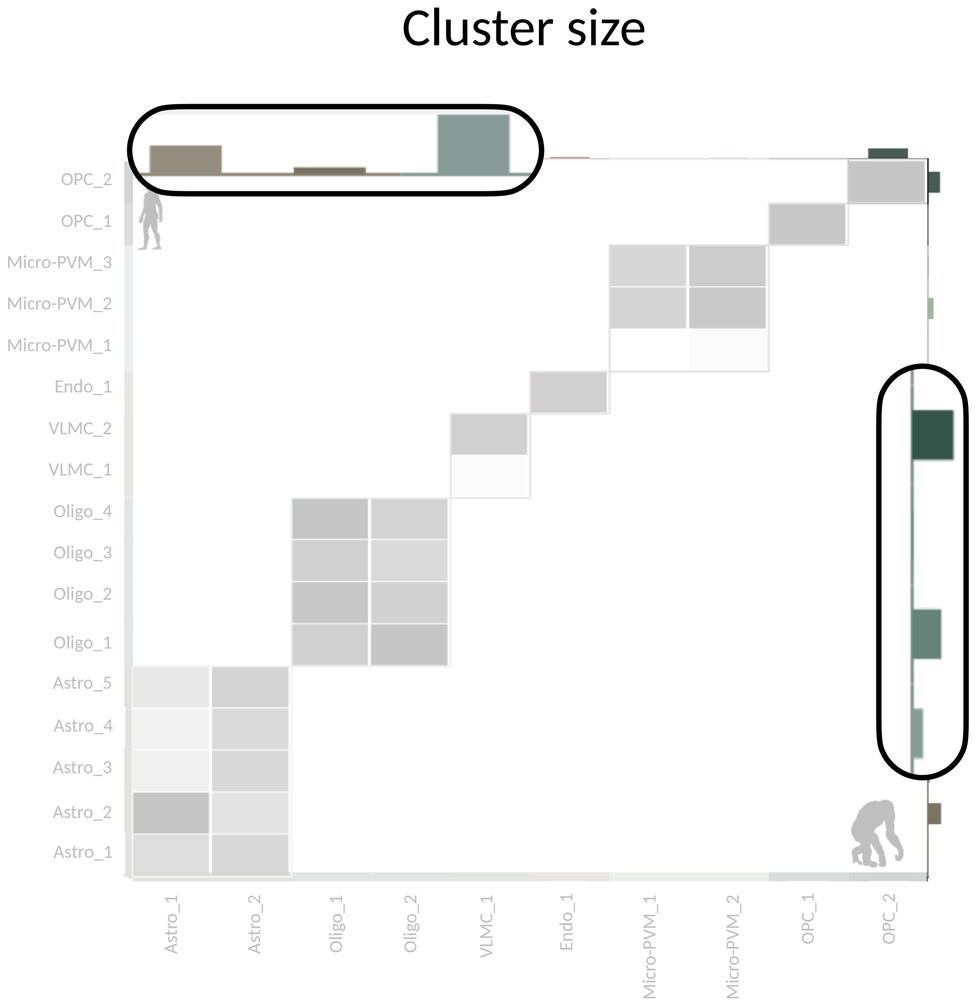
Cluster size



Task 1: Cluster identification

Subtask: Attribute exploration

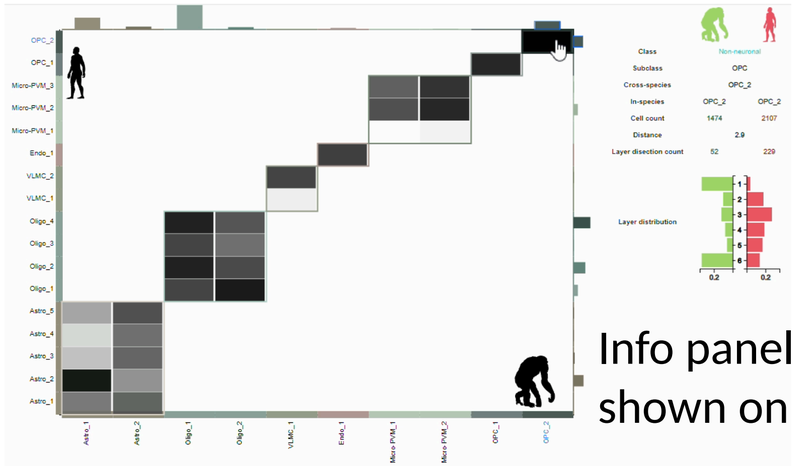
- Distance
- Size



Task 1: Cluster identification

Subtask: Attribute exploration

- Distance
- Size
- Additional metadata

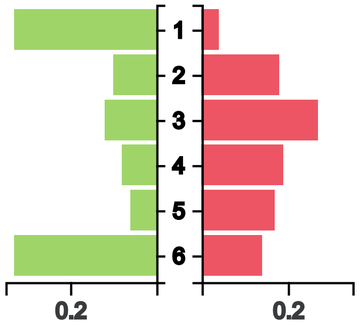


Info panel shown on hover

Info panel

Class	Non-neuronal	
Subclass	OPC	
Cross-species	OPC_2	
In-species	OPC_2	OPC_2
Cell count	1474	2107
Distance	2.9	
Layer disection count	52	229

Layer distribution



Task 1: Cluster identification

Subtask: Attribute exploration

- Distance
- Size
- Additional metadata

Info panel

Class	Non-neuronal	
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Cross-species	OPC_2	
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Cell count	1474	2107
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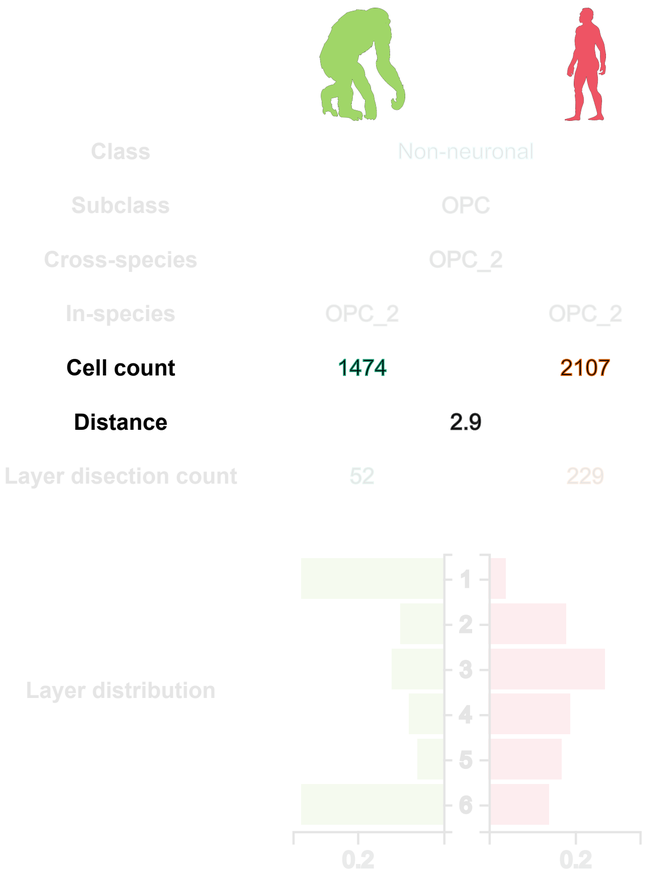
Layer distribution

Task 1: Cluster identification

Subtask: Attribute exploration

- Distance
- Size
- Additional metadata

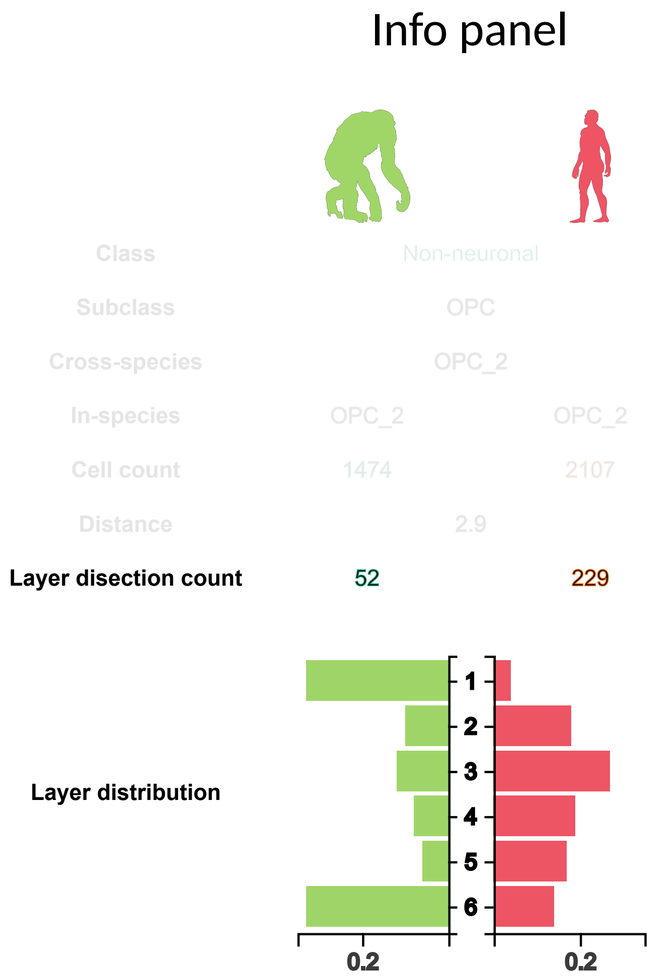
Info panel



Task 1: Cluster identification

Subtask: Attribute exploration

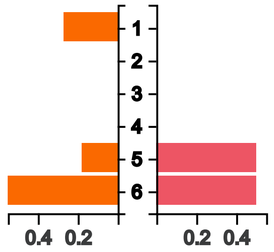
- Distance
- Size
- Additional metadata



Task 1 cluster identification: Example

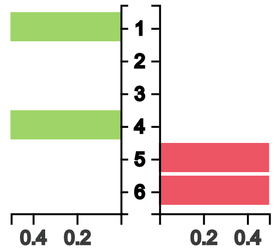
Class	Non-neuronal	
Subclass	OPC	
Cross-species	OPC_1	
In-species	OPC_2	OPC_1
Cell count	377	54
Distance	41.8	
Layer disection count	11	2

Layer distribution



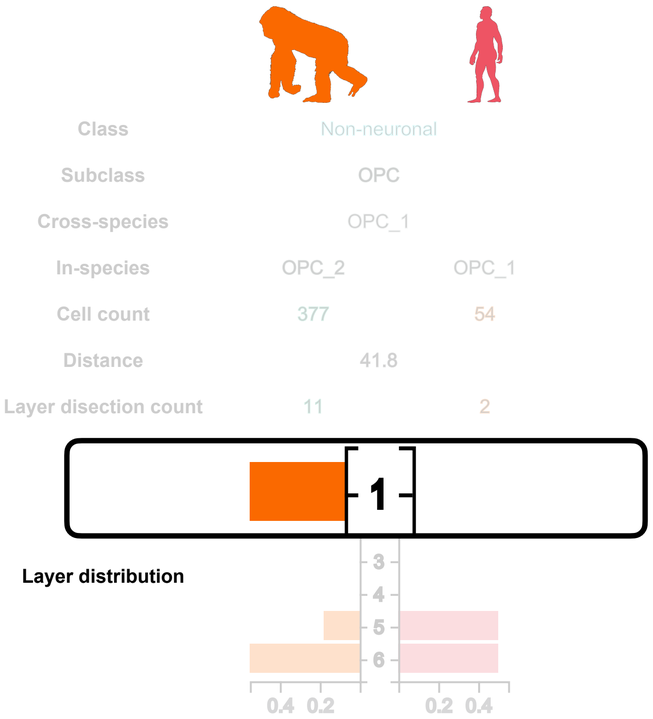
Class	Non-neuronal	
Subclass	OPC	
Cross-species	OPC_1	
In-species	OPC_1	OPC_1
Cell count	32	54
Distance	4.2	
Layer disection count	2	2

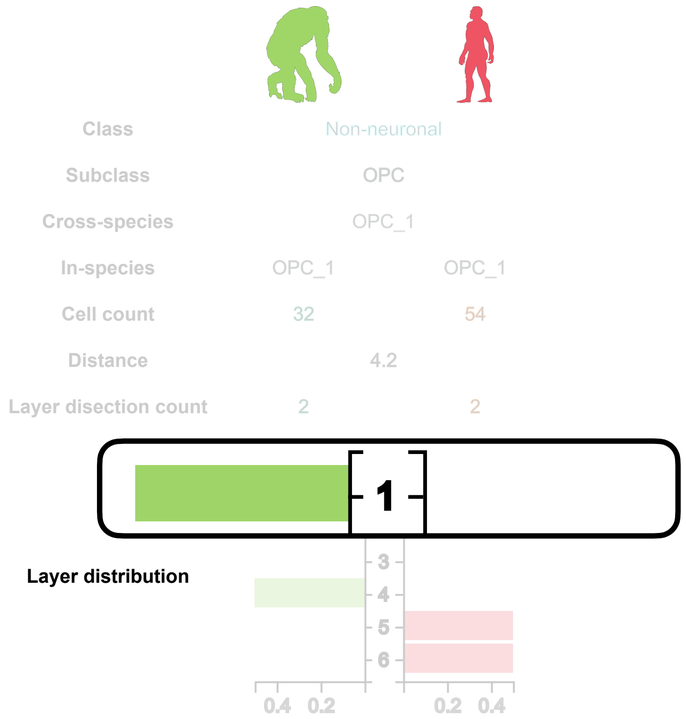
Layer distribution



Task 1 cluster identification: Example

Cells in layer1 in gorilla but not humans



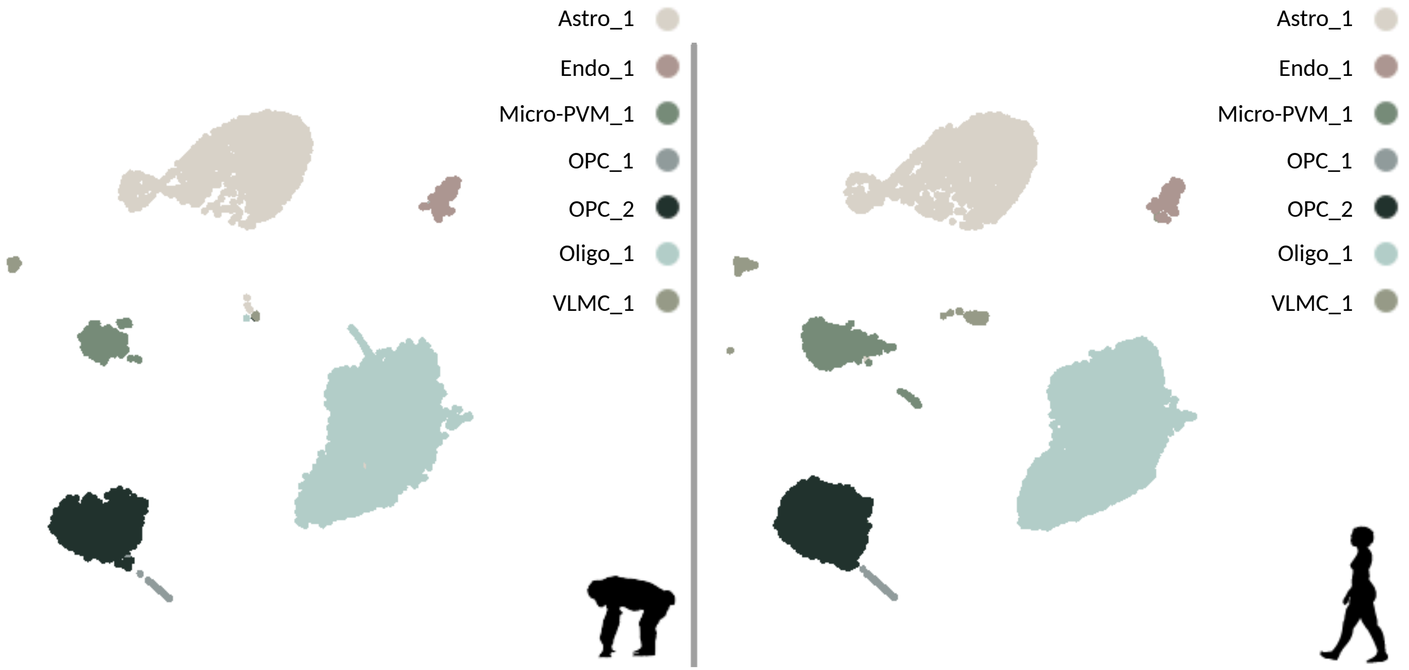


Cells in layer1 in chimpanzee but not humans

Task 1: Cluster identification

Subtask: Attribute exploration

- Distance
- Size
- Additional metadata

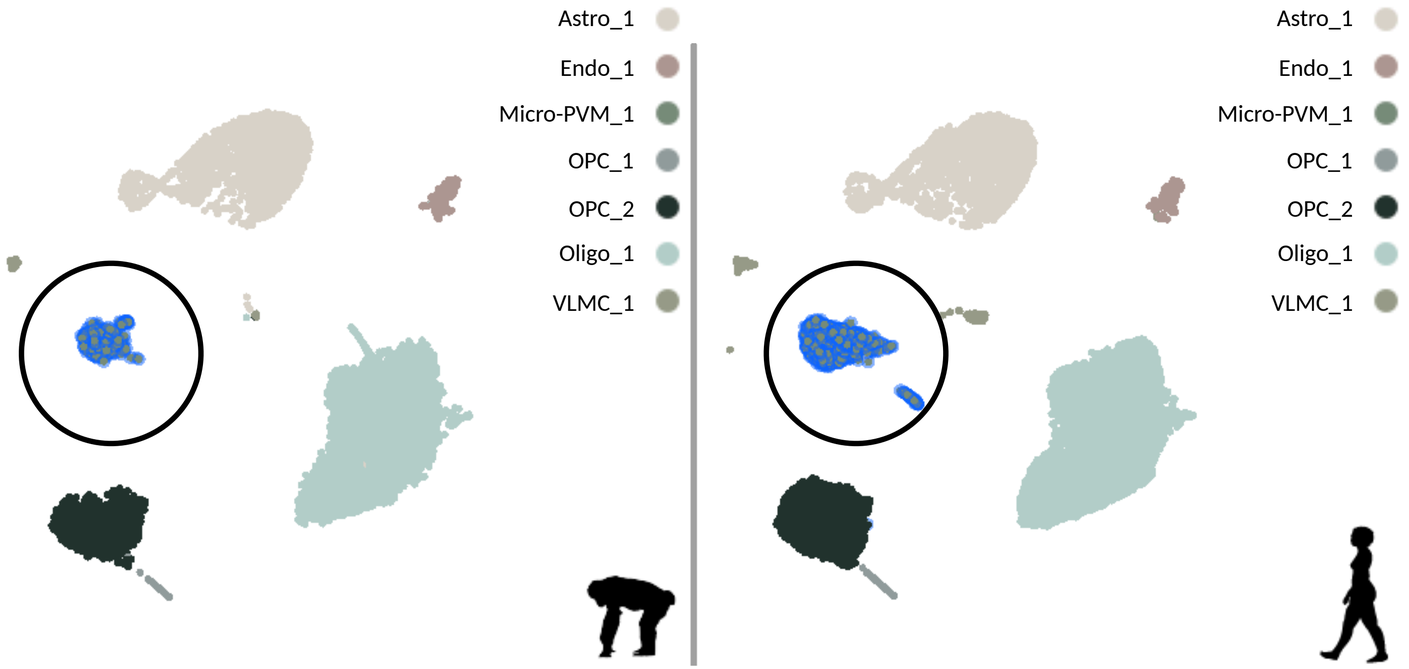


Low dimensional UMAP embeddings

Task 1: Cluster identification

Subtask: Attribute exploration

- Distance
- Size
- Additional metadata



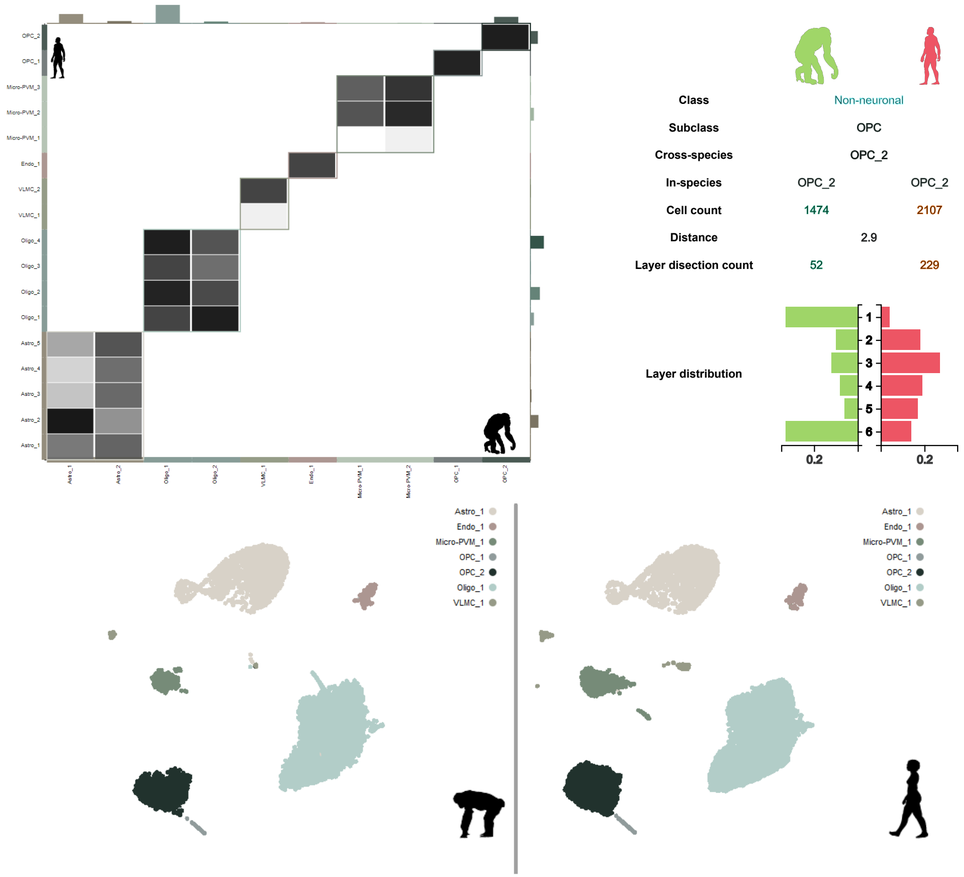
Low dimensional UMAP embeddings

Task 1: Cluster identification

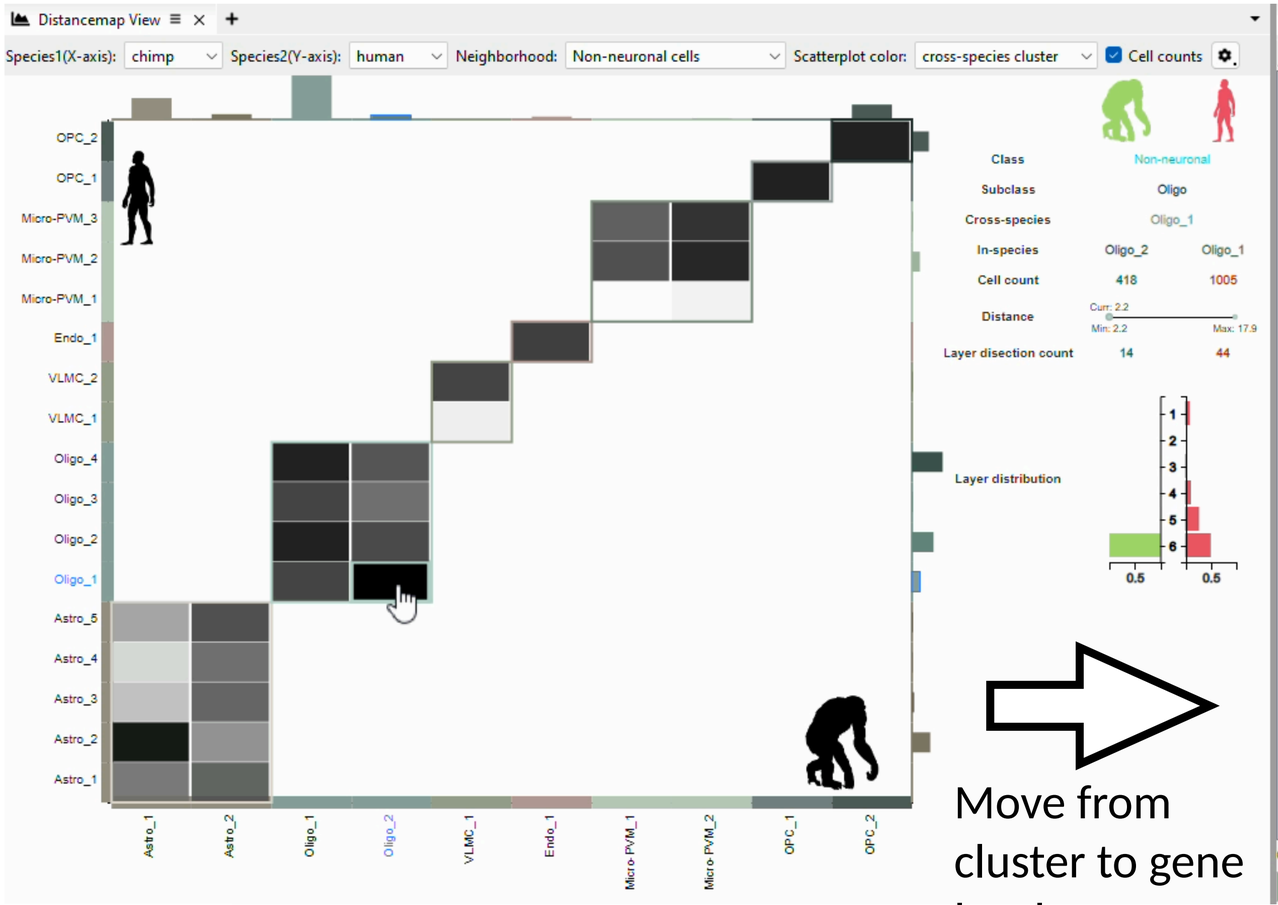
Subtask: Attribute exploration

- Distance
- Size
- Additional metadata

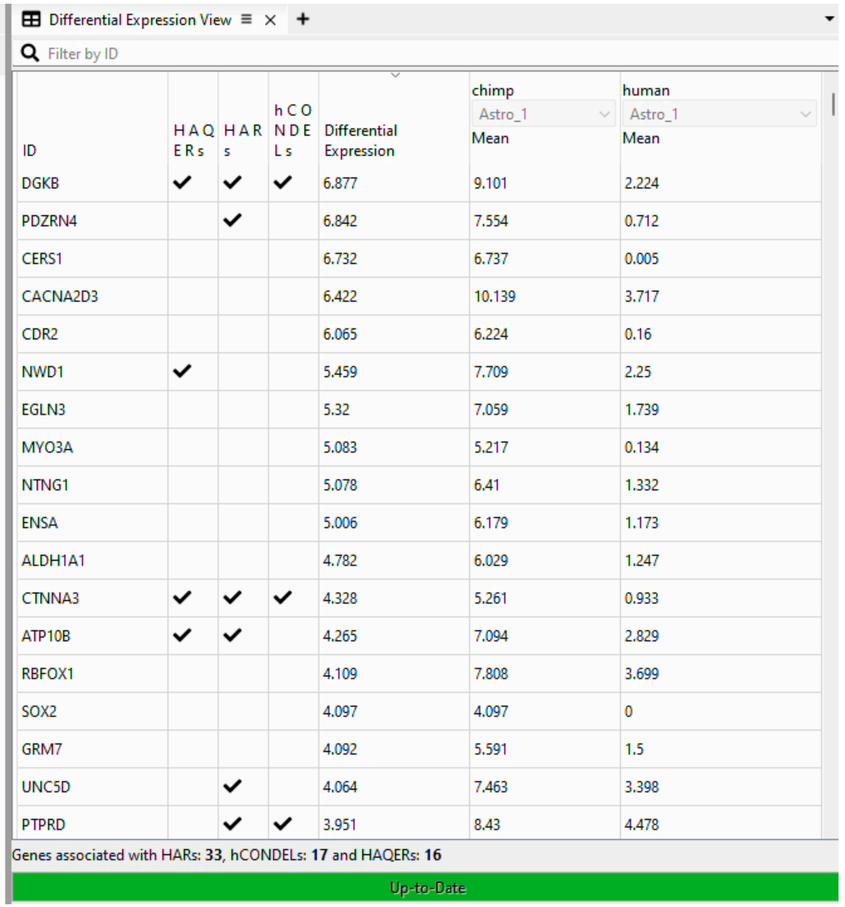
Views for subtasks



Task switching: Cluster to gene level



Move from cluster to gene level



ID	HAQERs	HARs	hCONDELs	Differential Expression	chimp Astro_1 Mean	human Astro_1 Mean
DGKB	✓	✓	✓	6.877	9.101	2.224
PDZRN4		✓		6.842	7.554	0.712
CERS1				6.732	6.737	0.005
CACNA2D3				6.422	10.139	3.717
CDR2				6.065	6.224	0.16
NWD1	✓			5.459	7.709	2.25
EGLN3				5.32	7.059	1.739
MYO3A				5.083	5.217	0.134
NTNG1				5.078	6.41	1.332
ENSA				5.006	6.179	1.173
ALDH1A1				4.782	6.029	1.247
CTNNA3	✓	✓	✓	4.328	5.261	0.933
ATP10B	✓	✓		4.265	7.094	2.829
RBFOX1				4.109	7.808	3.699
SOX2				4.097	4.097	0
GRM7				4.092	5.591	1.5
UNC5D		✓		4.064	7.463	3.398
PTPRD		✓	✓	3.951	8.43	4.478

Task 2: Gene identification

Subtask: Attribute exploration

- Expression differences

Average 12000 genes (rows)

Filter by ID

ID	HAQERs	HARs	hCONDELs	Differential Expression	chimp Oligo_1 Mean	human Oligo_1 Mean
MDGA2				5.847	7.854	2.007
SLIT2				5.646	7.372	1.726
BTBD11		✔		4.96	5.055	0.095
LIPA				4.943	8.008	3.065
CDR2				4.905	4.952	0.047
MAML2				4.76	8.495	3.735
SLC6A20				4.627	4.633	0.005
FRMD4A				4.62	7.179	2.559
POLR2F				4.603	7.62	3.017
SOX2				4.325	4.325	0
SLC25A48				4.301	4.681	0.379
FAM171B				4.173	6.141	1.968
CLDN11				4.107	11.855	7.748
DCC				4.043	5.303	1.26
ADD1				4.034	8.454	4.42
RELN				4.025	4.386	0.361
TMEM178A				3.997	4.42	0.423
PLEKHH2				3.981	4.587	0.606
PLCB4		✔		3.764	3.855	0.091
PID1		✔		3.749	3.881	0.132
KCNMA1				3.742	4.485	0.744
LDLRAD4				3.621	8.077	4.456
DLGAP1				3.612	5.701	2.089
ZDHHC20				3.612	8.464	4.852
KCNIP4				3.471	8.391	4.921
SGCZ	✔	✔		3.388	4.303	0.915
ADAMTS14				3.38	4.027	0.647

Genes associated with HARs: **28**, hCONDELs: **9** and HAQERs: **9**

Up-to-Date

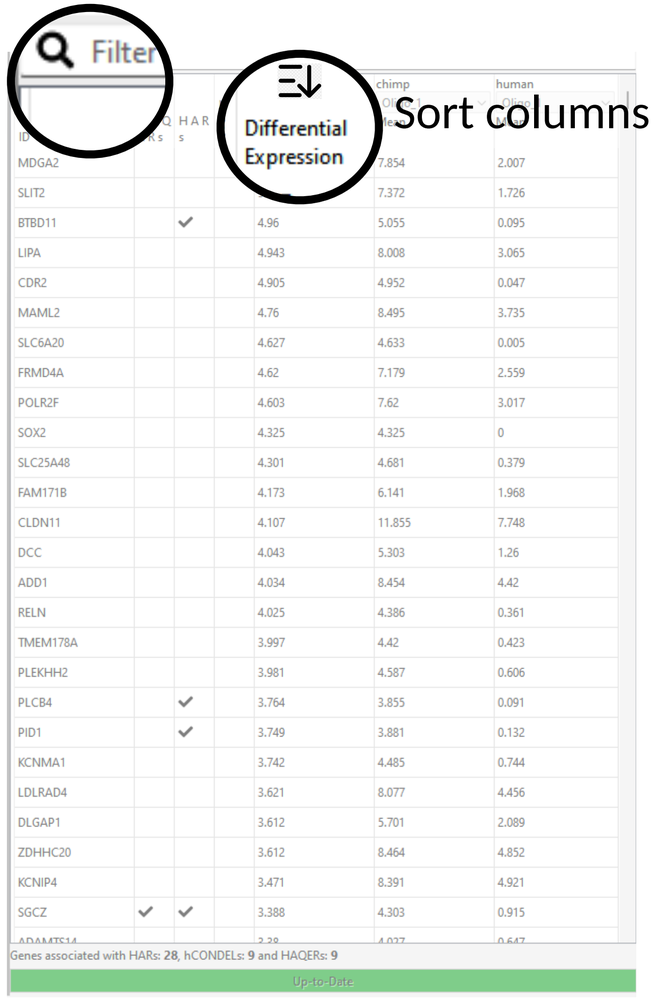
Task 2: Gene identification

Subtask: Attribute exploration

- Expression differences

Filter rows

Sort columns



Task 2: Gene identification

Subtask: Attribute exploration

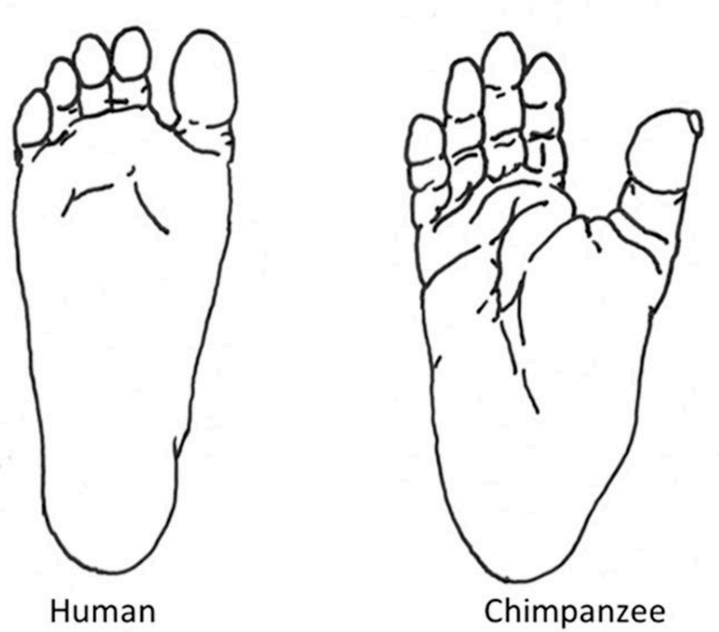
- Expression differences
- Accelerated genomic regions

Task 2: Gene identification

Subtask: Attribute exploration

- Expression differences
- Accelerated genomic regions

Foot comparison human vs chimpanzee



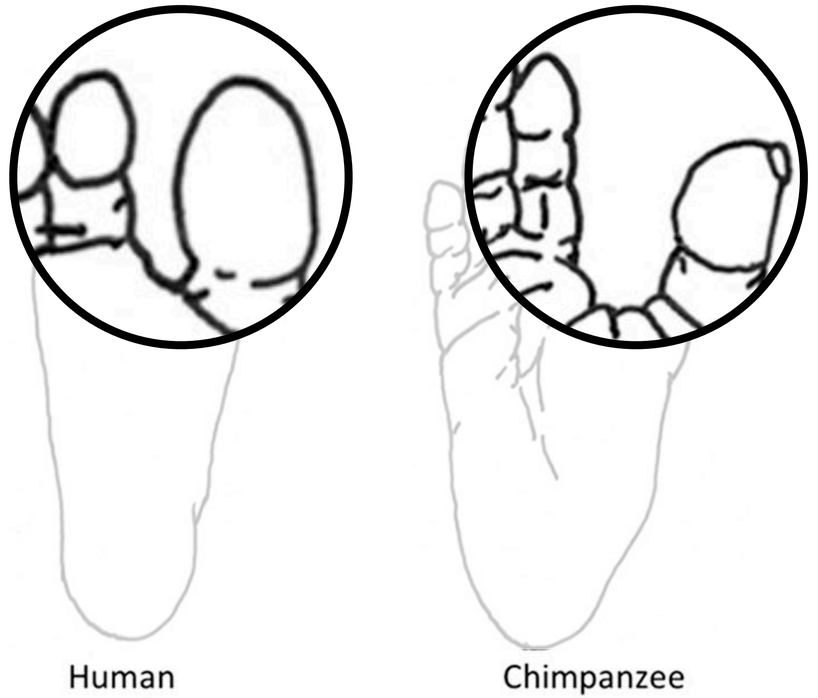
Hunt, et al., Cambridge University Press, 2020

Task 2: Gene identification

Subtask: Attribute exploration

- Expression differences
- Accelerated genomic regions

Foot comparison human vs chimpanzee

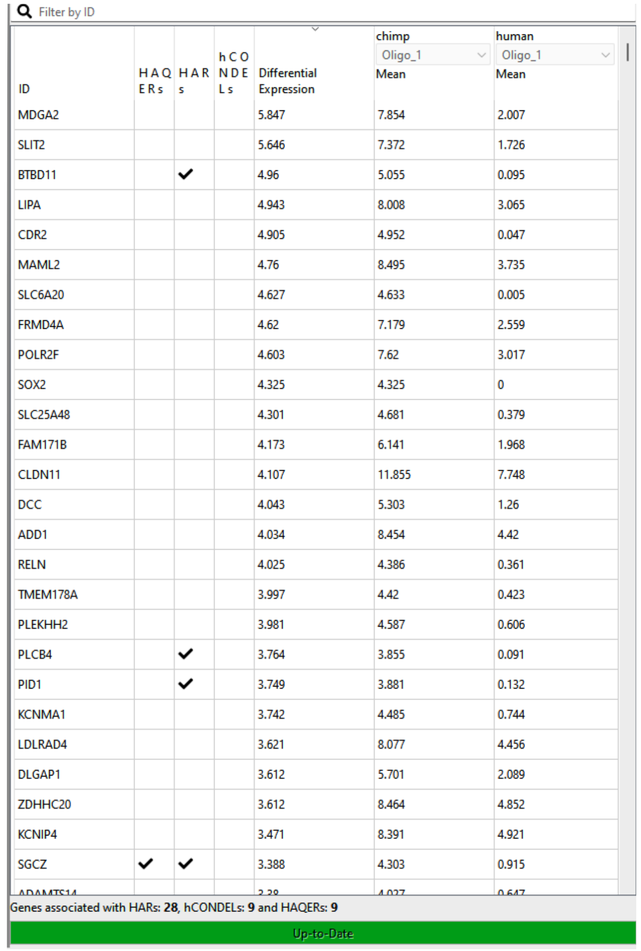


Hunt, et al., Cambridge University Press, 2020

Task 2: Gene identification

Subtask: Attribute exploration

- Expression differences
- Accelerated genomic regions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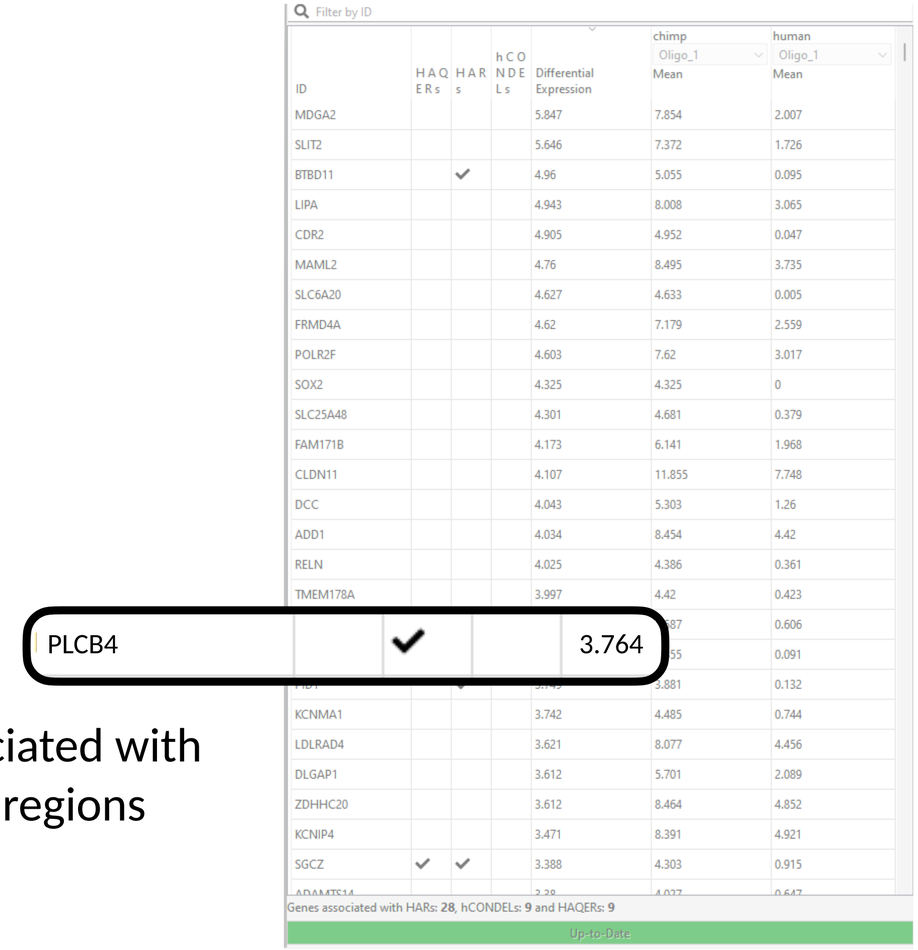
Genes associated with HARs: **28**, hCONDELs: **9** and HAQERs: **9**

Up-to-Date

Task 2: Gene identification

Subtask: Attribute exploration

- Expression differences
- Accelerated genomic regions

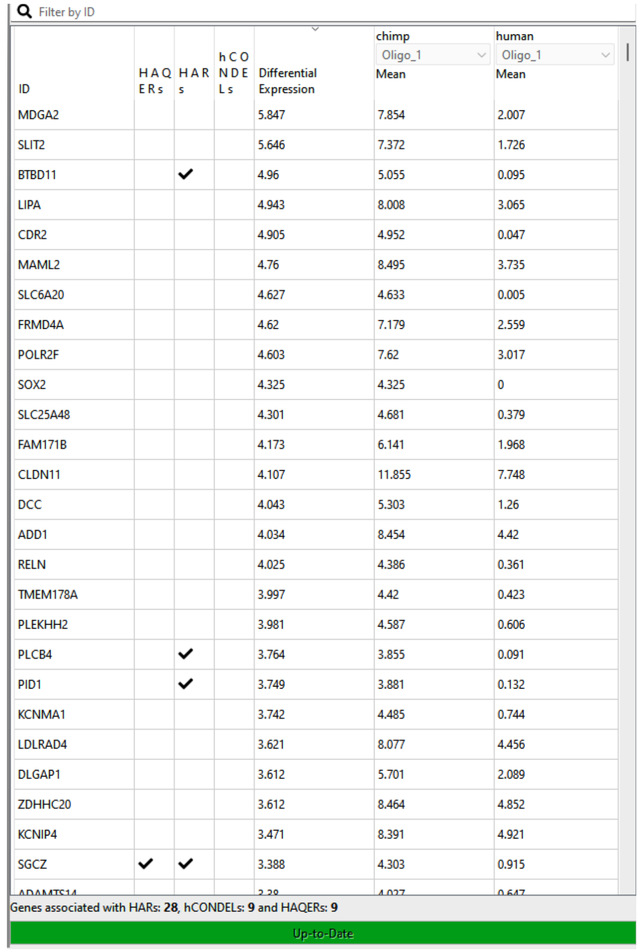


Genes associated with accelerated regions

Task 2: Gene identification

Subtask: Attribute exploration

- Expression differences
- Accelerated genomic regions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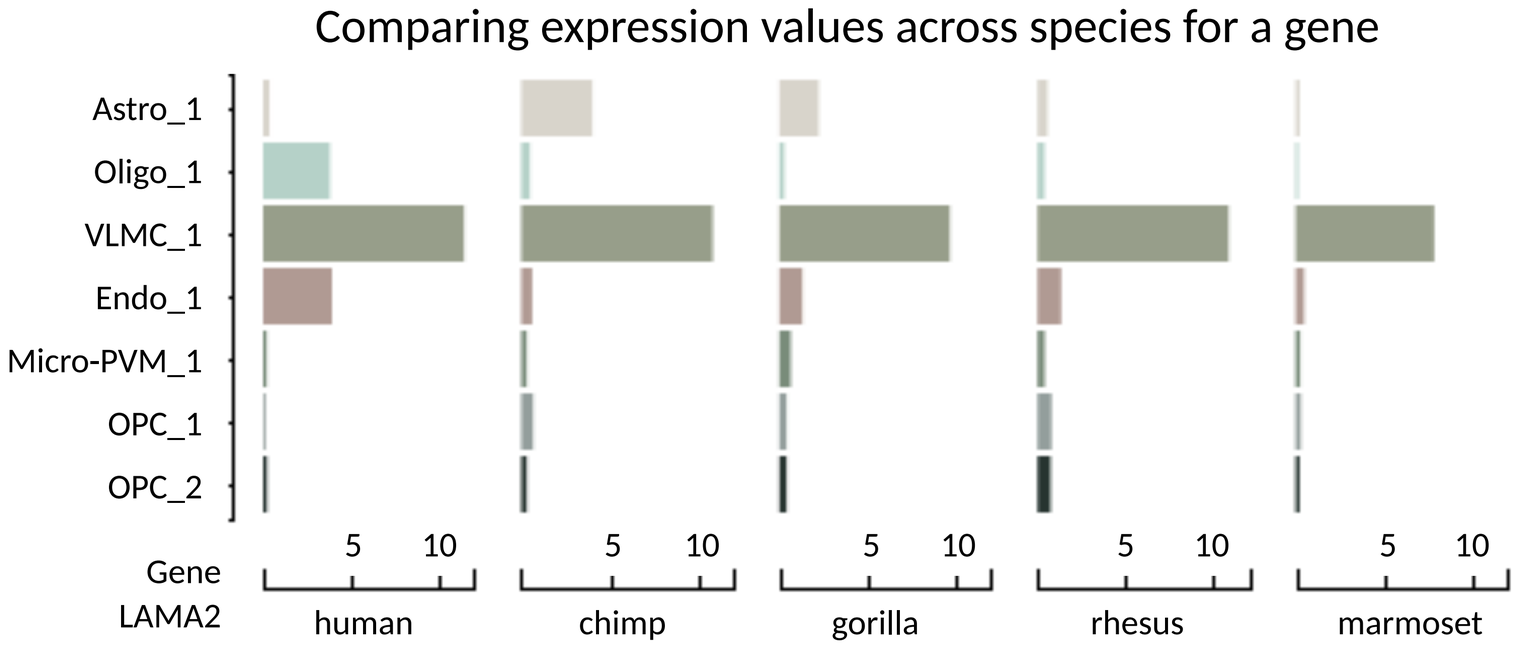
Up-to-Date

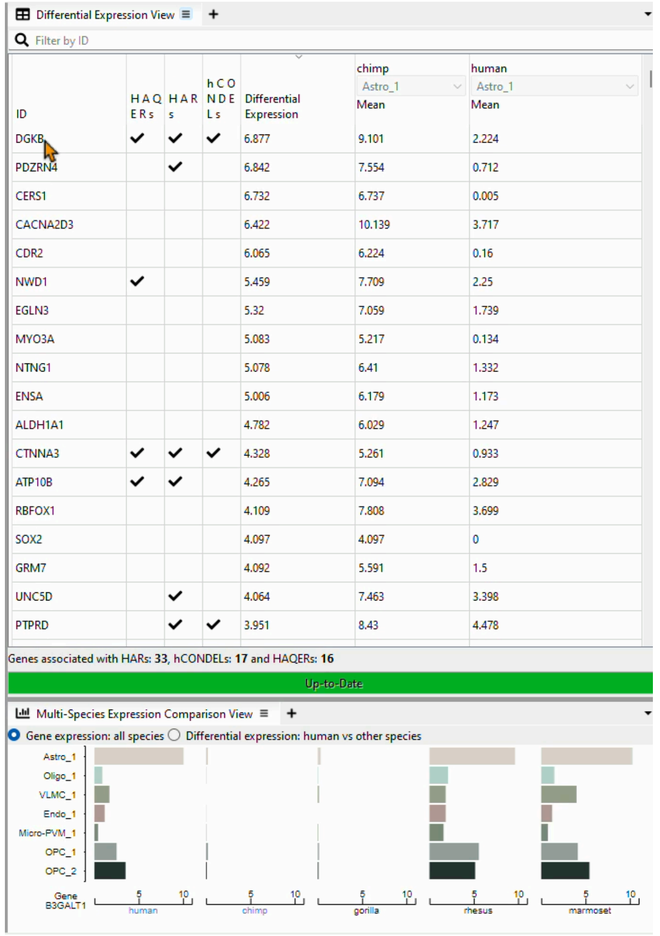
Task 3: Expression comparison

- Multi-species expression comparison



Task 3: Expression comparison

- Multi-species expression comparison

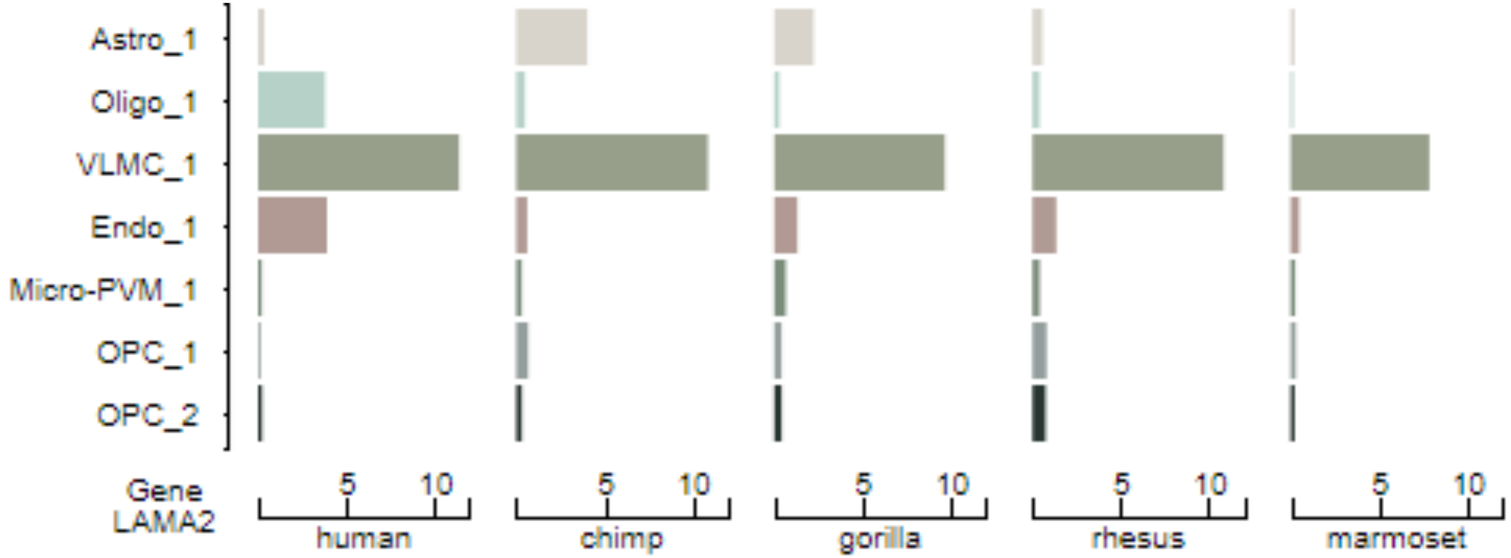


Compared across species

Task 3: Expression comparison

- Multi-species expression comparison

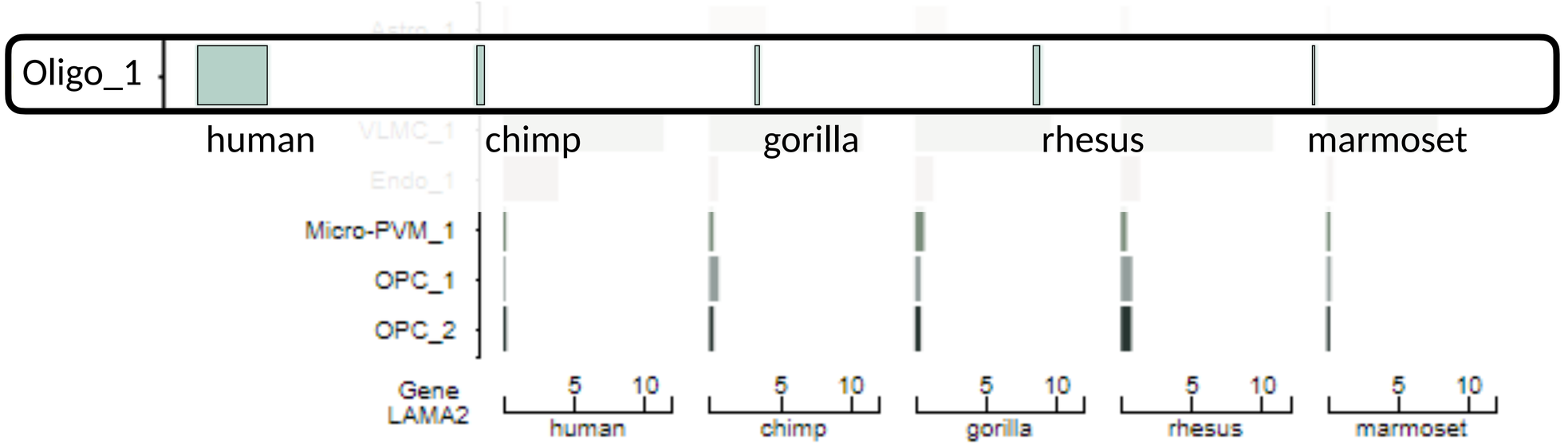
Human has high expression compared to the other primates



Task 3: Expression comparison

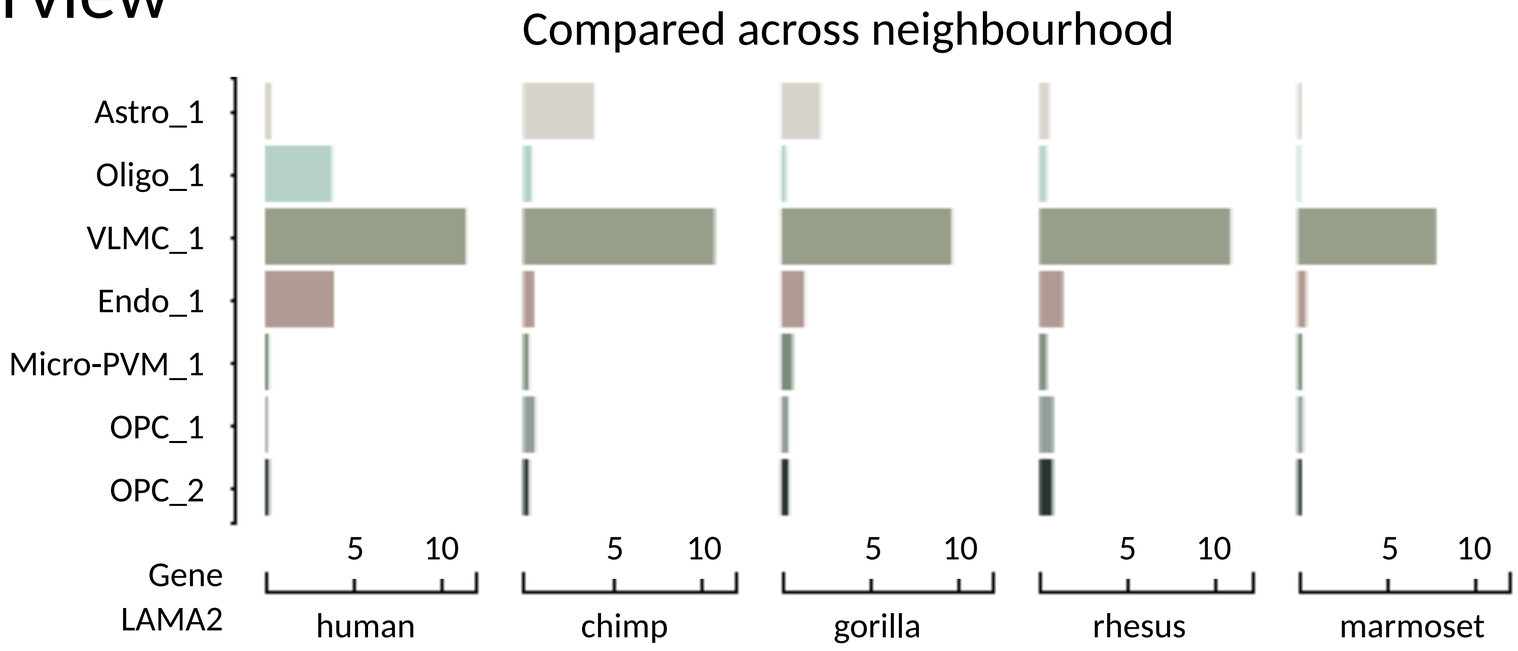
- Multi-species expression comparison

Human has high expression compared to the other primates



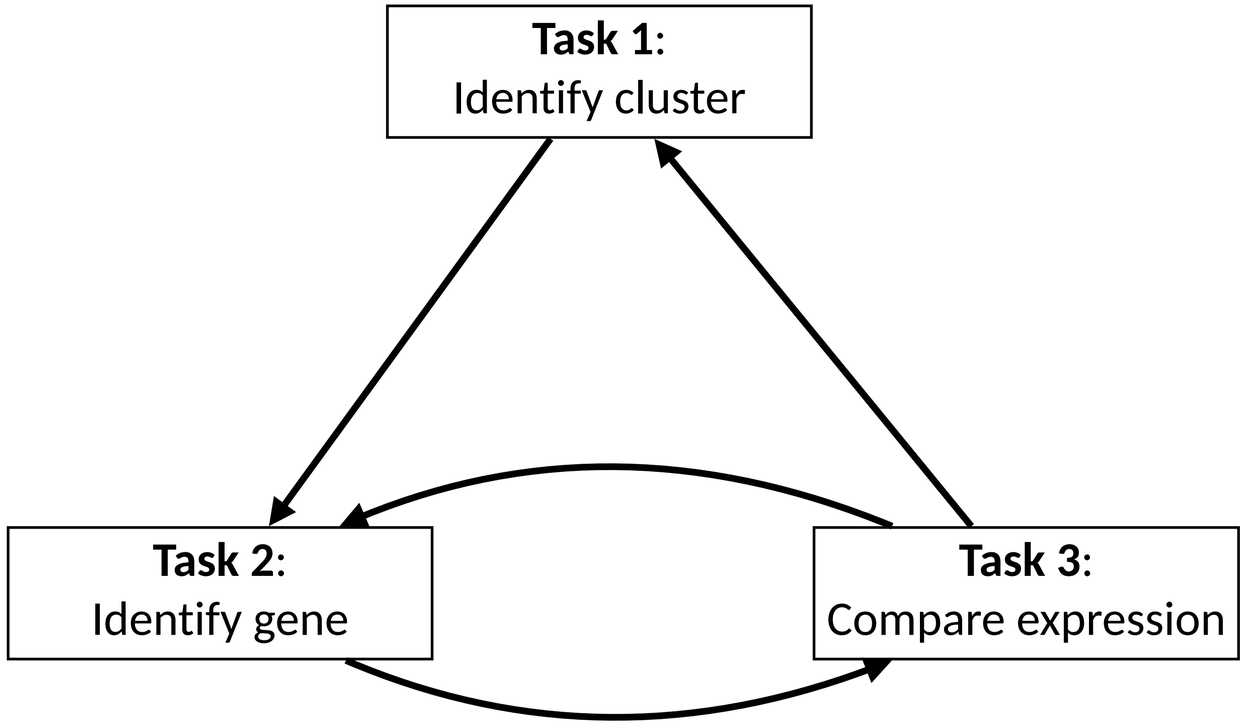
Task 3: Expression comparison

- Multi-species expression comparison
- Neighbourhood overview



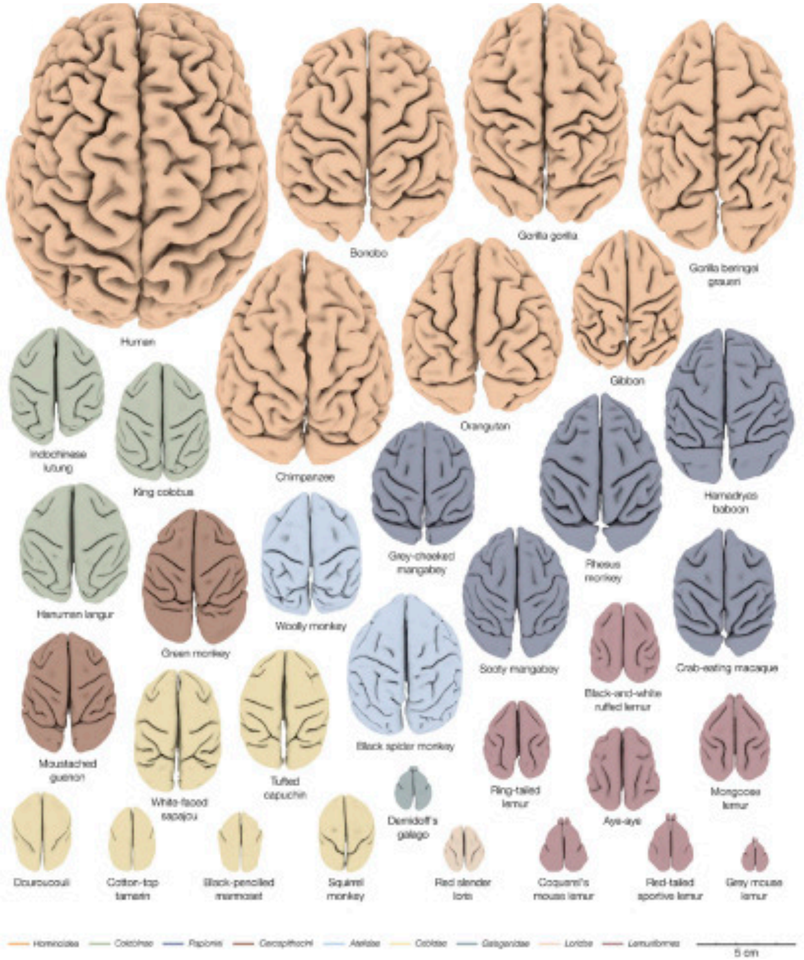
Task 3: Expression comparison

- Multi-species expression comparison
- Neighbourhood overview
- Circular workflow

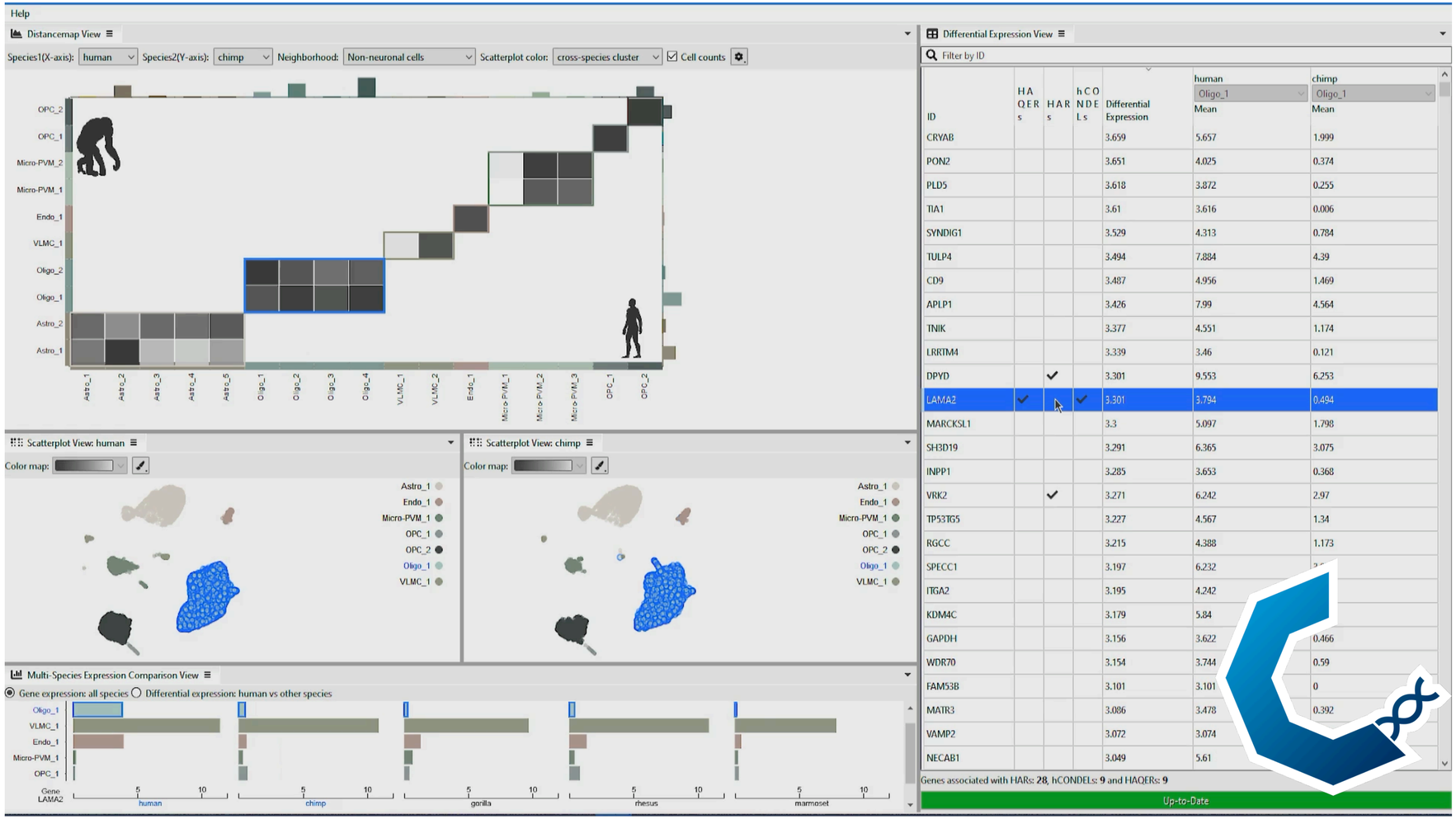


Conclusion

- Comprehensive user study
- Examples indicate potential
- Accommodate more species
- Go beyond pairwise comparison



Friedrich, et al., Elsevier, 2021



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