

# From genetics to neurobiology through transcriptomic data analysis

Ahmed Mahfouz

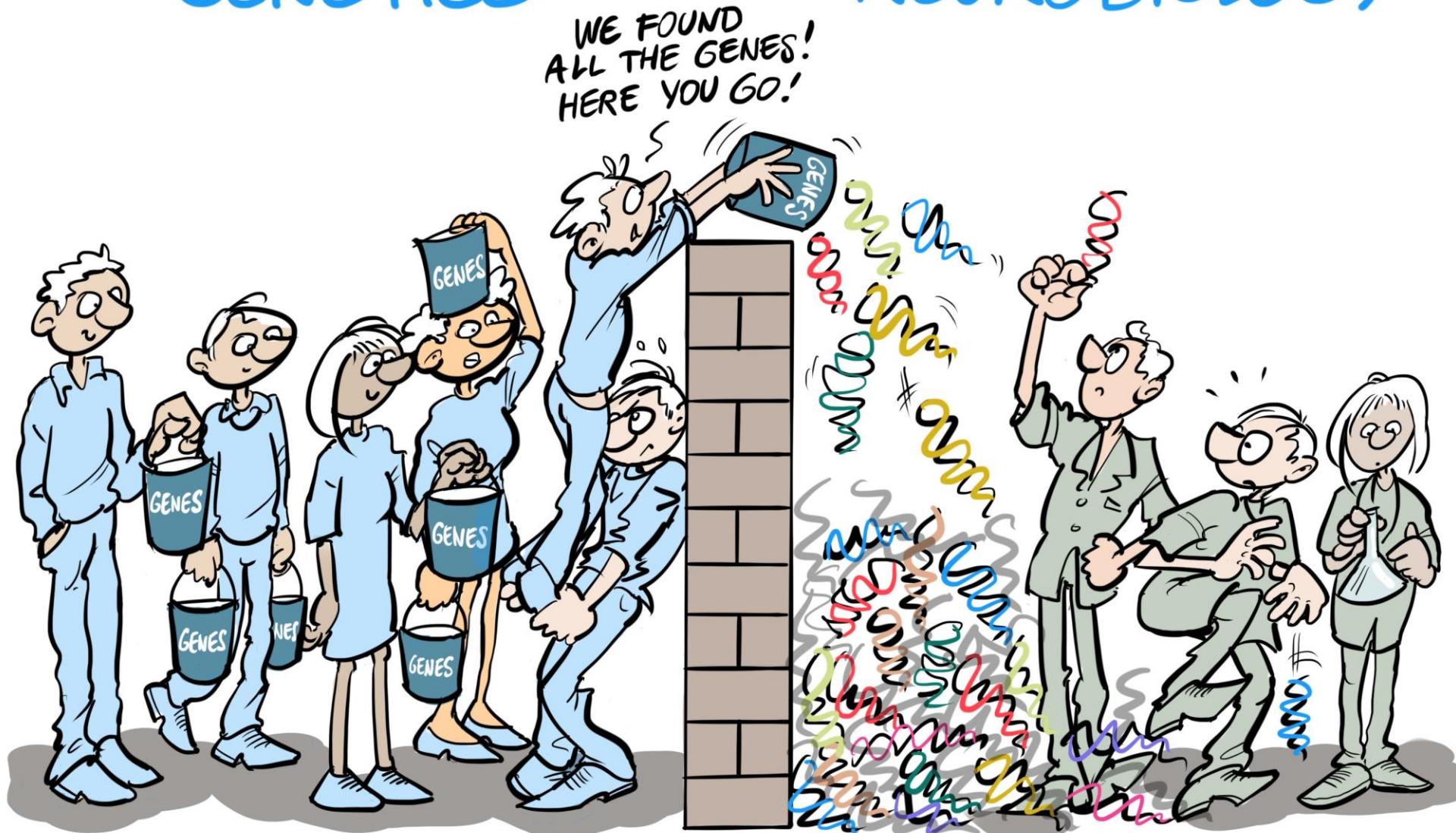
Dept. of Human Genetics, Leiden University Medical Center

Leiden Computational Biology Center, LUMC

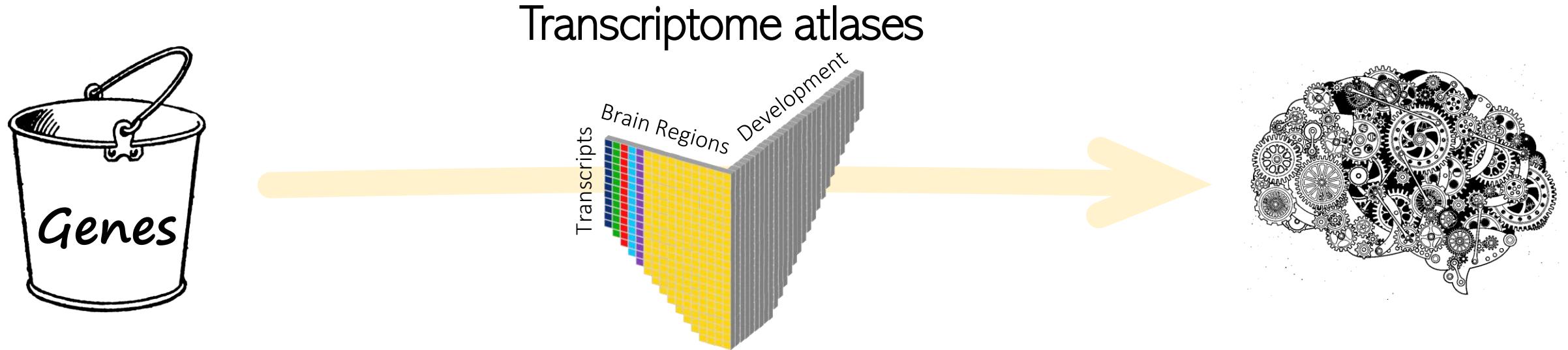
Pattern Recognition and Bioinformatics, TU Delft

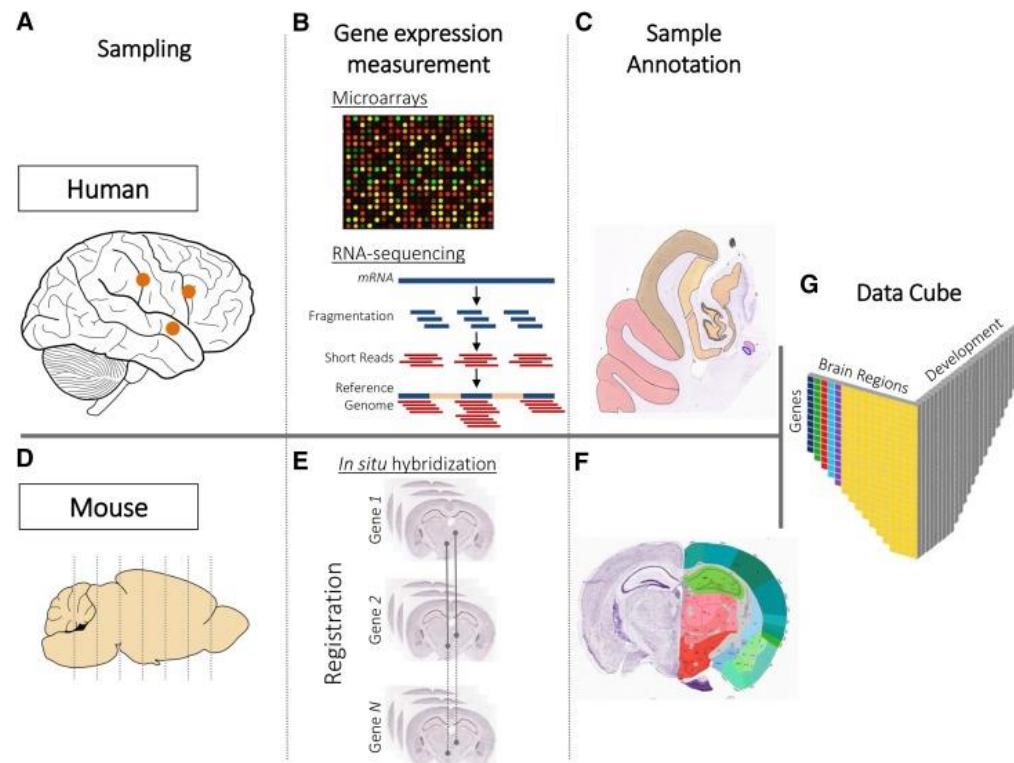
# GENETICS

# NEUROBIOLOGY

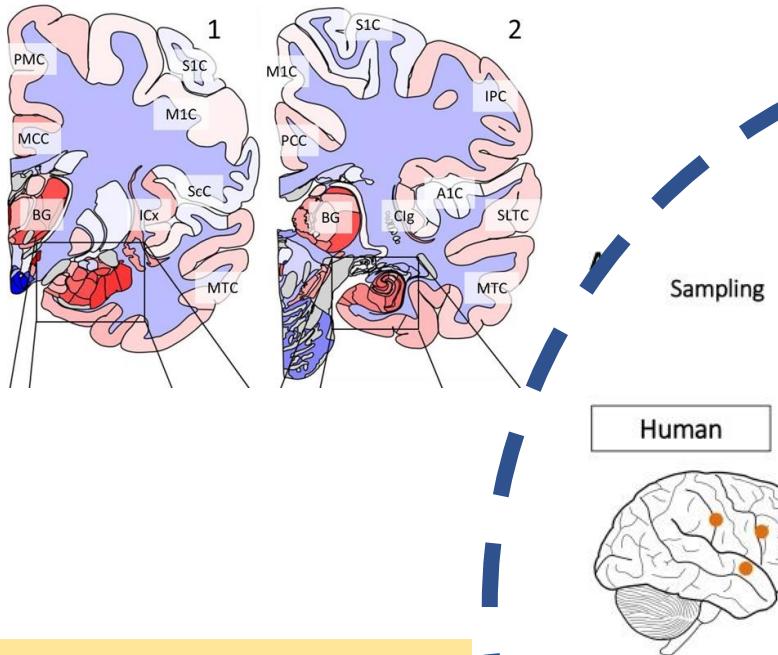


# A functional genomics approach

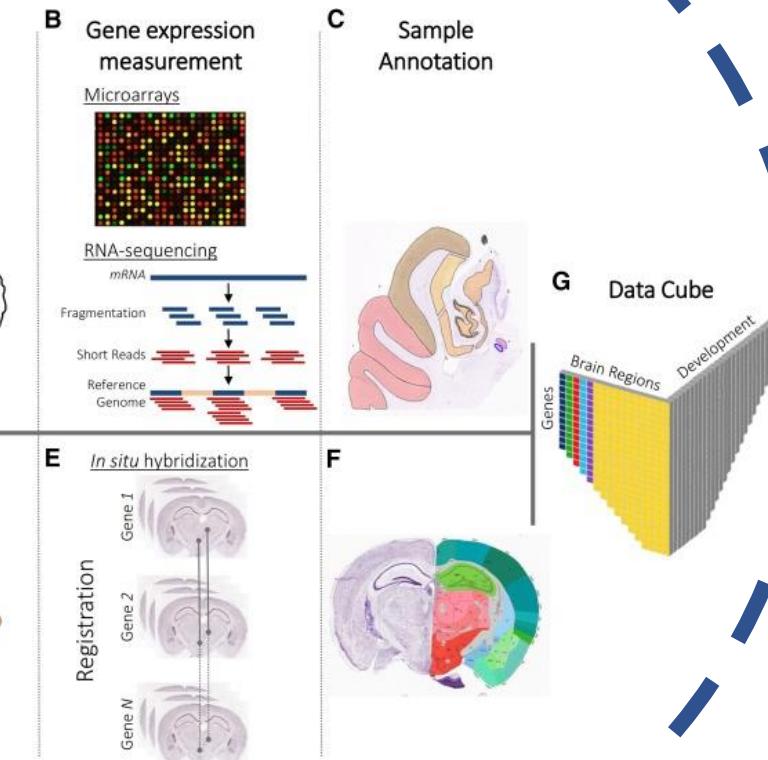
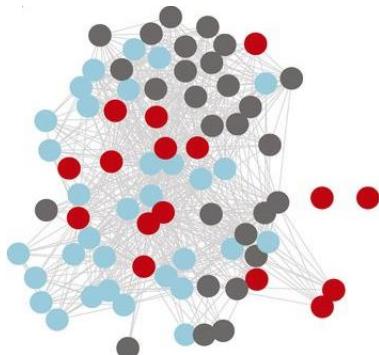




## Spatio-temporal patterns



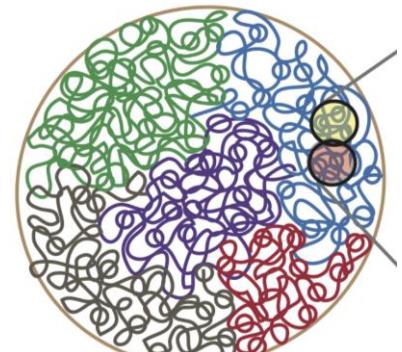
## Regulatory networks



## Interactive visualization



## Data integration





Arlin Keo

ARTICLE

<https://doi.org/10.1038/s42003-020-0804-9>

OPEN

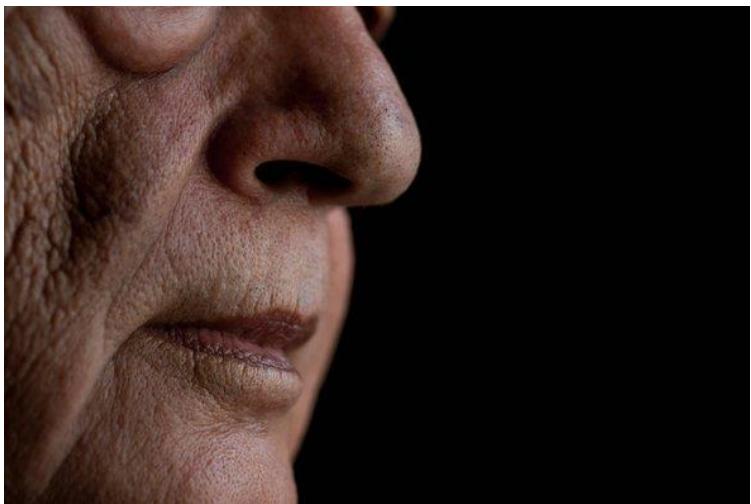
 Check for updates

# Transcriptomic signatures of brain regional vulnerability to Parkinson's disease

Arlin Keo  <sup>1,2</sup>, Ahmed Mahfouz  <sup>1,2</sup>, Angela M.T. Ingrassia<sup>3</sup>, Jean-Pascal Menebooo<sup>4,5</sup>, Celine Villenet<sup>4</sup>, Eugénie Mutez<sup>6,7,8</sup>, Thomas Comptdaer  <sup>6,7</sup>, Boudewijn P.F. Lelieveldt<sup>2,9</sup>, Martin Figeac<sup>4,5</sup>, Marie-Christine Chartier-Harlin  <sup>6,7</sup>✉, Wilma D.J. van de Berg  <sup>3</sup>✉, Jacobus J. van Hilten  <sup>10</sup>✉ & Marcel J.T. Reinders  <sup>1,2</sup>✉

Keo et al. *Communication Biology* 2020

# Parkinson's disease (PD) progression

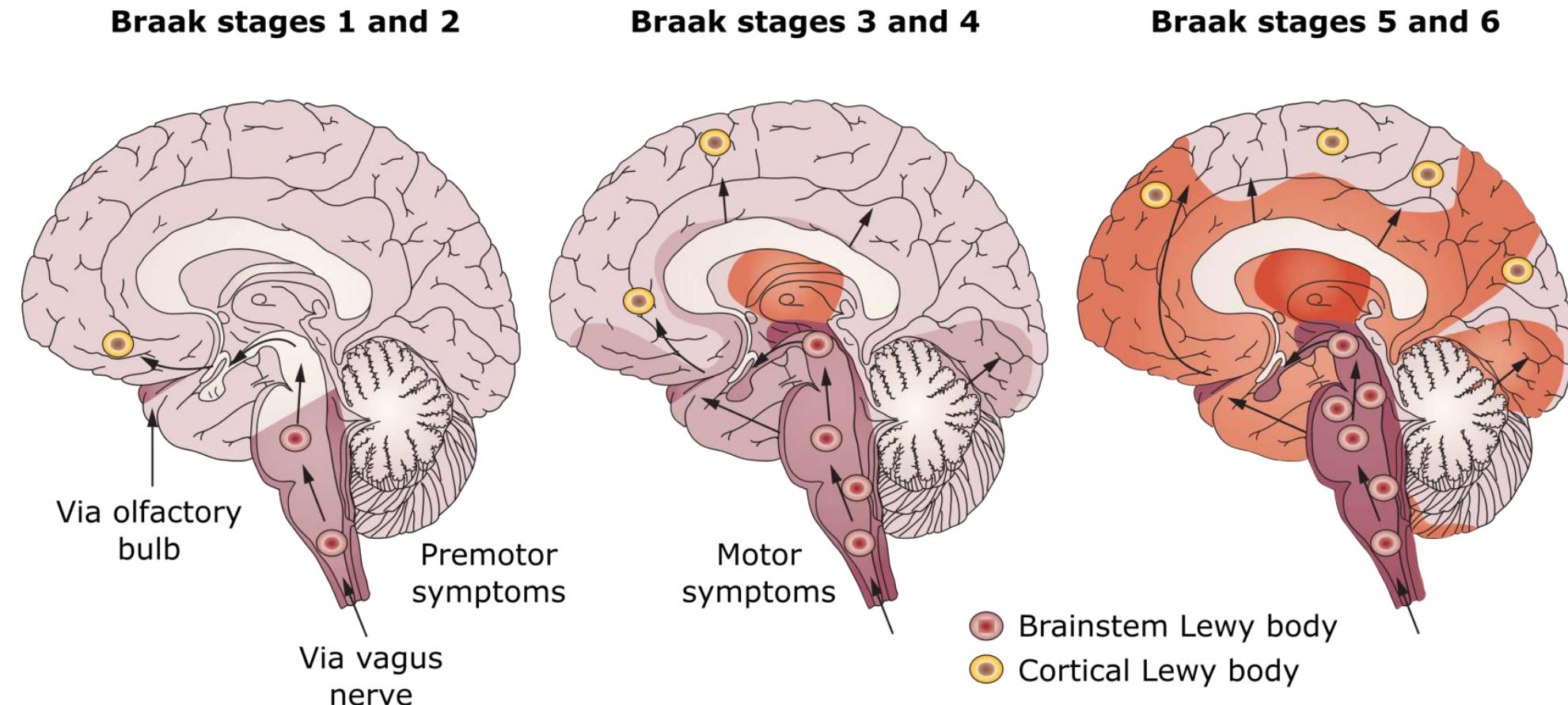


Loss of smell  
Little or no facial expression  
Tremor

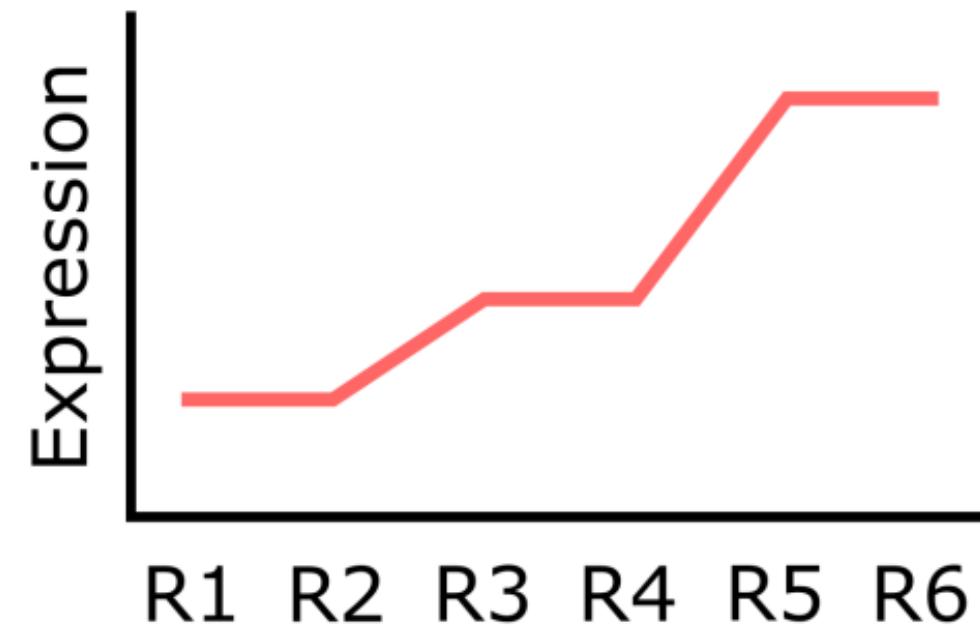
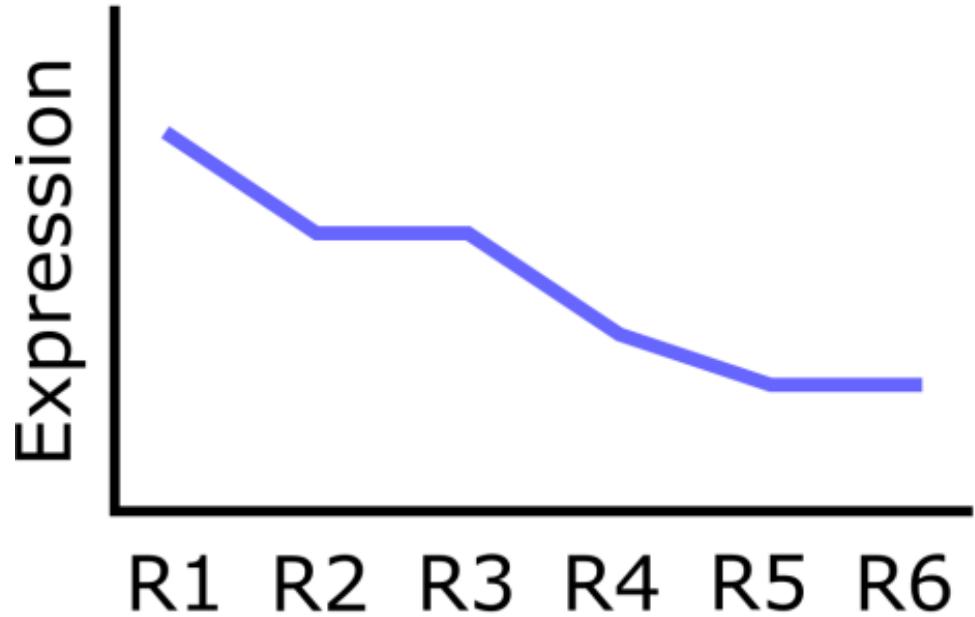


Cognitive impairment  
Dementia

# Progressive pathology described by Braak

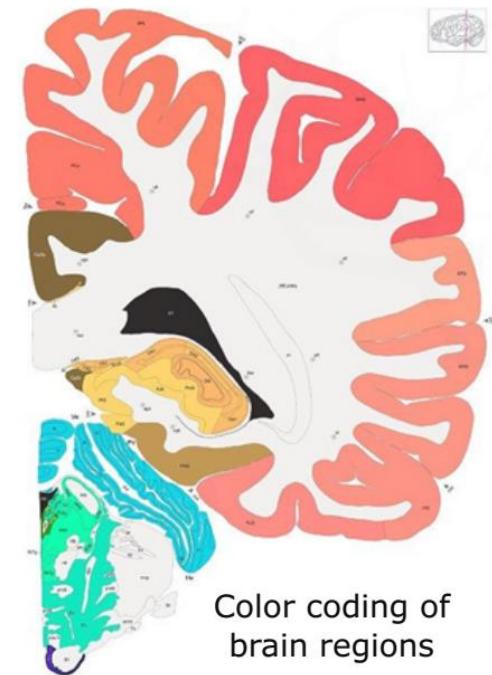
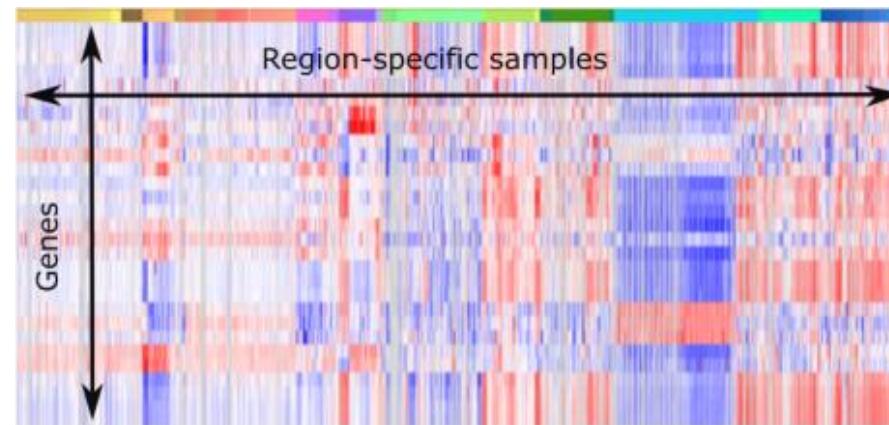
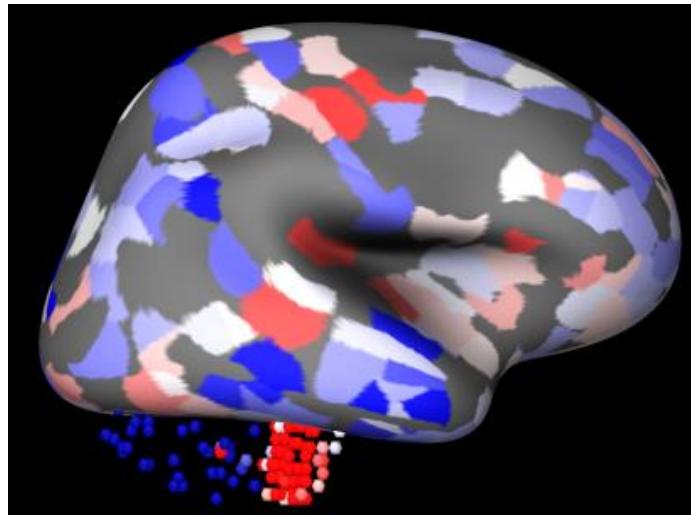


# Region-specific expression patterns underly selective regional vulnerability in PD



# Allen Human Brain Atlas (AHBA)

- Genome-wide microarray data of the healthy brain (20,017 genes)
- 6 Adult donors (5 males & 1 female, mean age 42, range 24-57 years)
- 3,702 Samples (363-946 per donor)
- Samples: MNI coordinates, anatomical annotation



# Brain regions involved in Braak stages

Myelencephalon (**R1**, N=279)

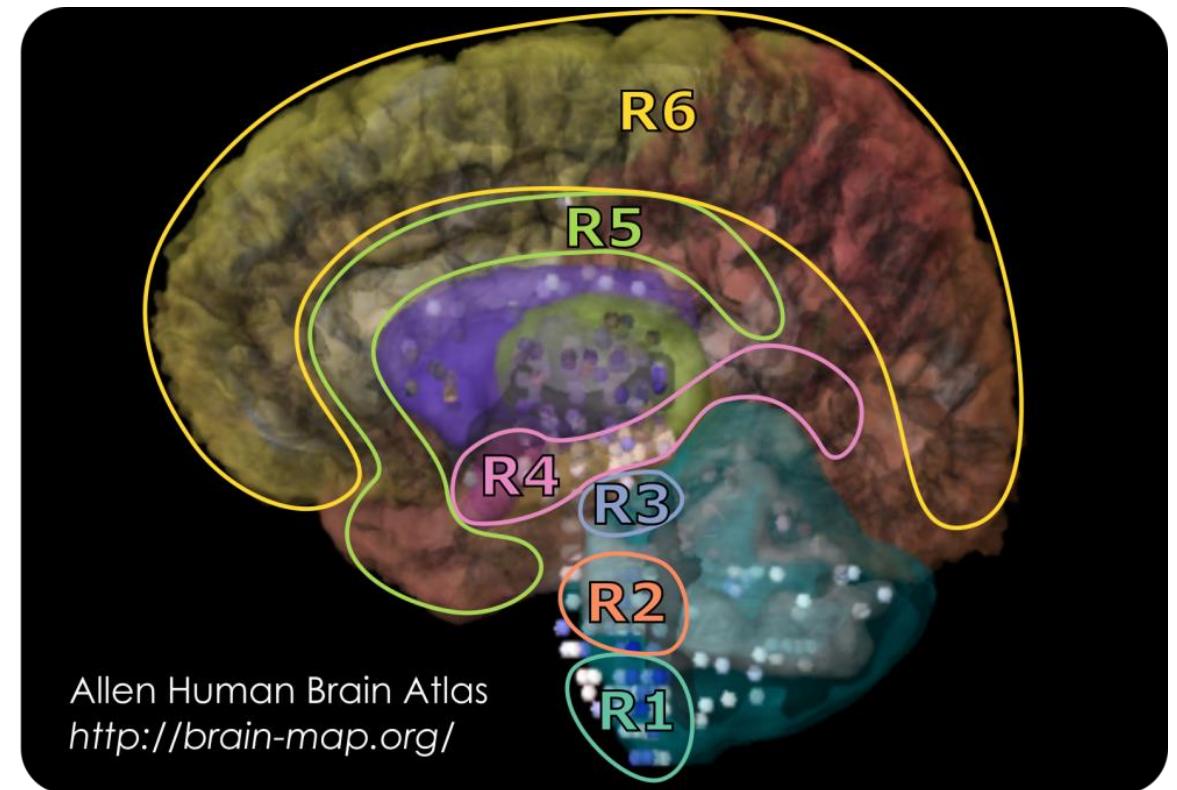
Pontine tegmentum (**R2**, N=414)

Substantia nigra, basal nucleus of Meynert,  
CA2 field (**R3**, N=89)

Amygdala, occipito-temporal gyrus (**R4**, N=107)

Cingulate gyrus, temporal lobe (**R5**, N=618)

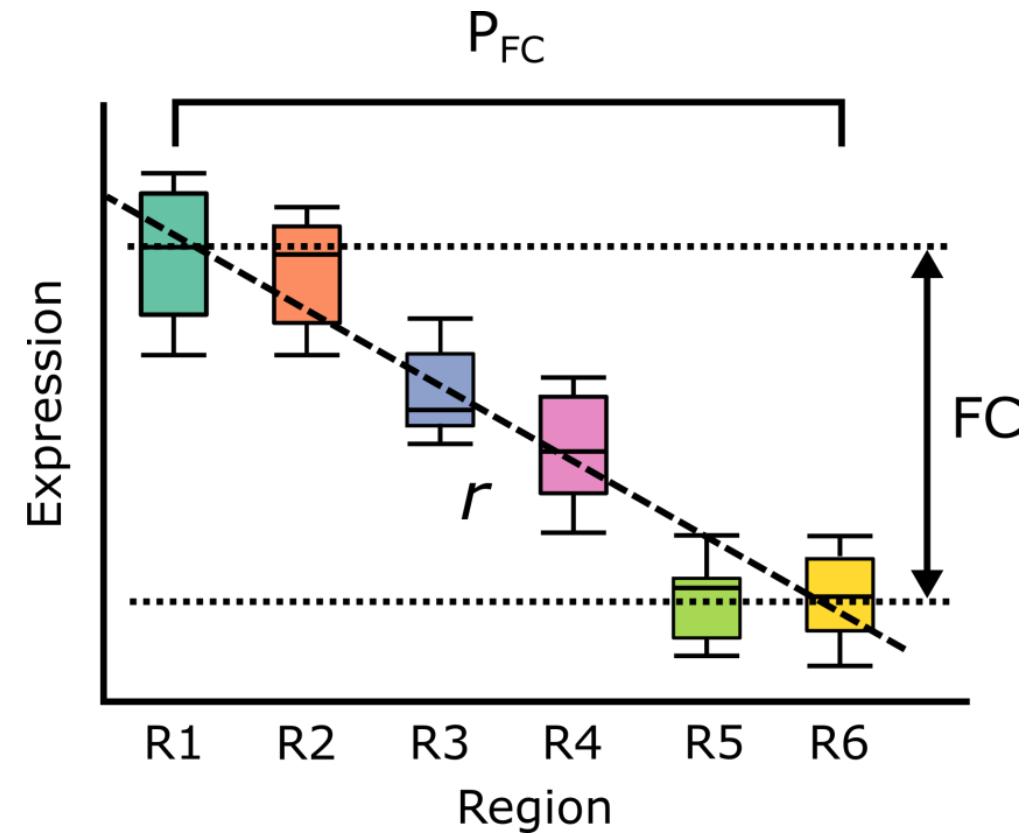
Frontal lobe, parietal lobe (**R6**, N=827)



# Braak stage-related genes (BRGs)

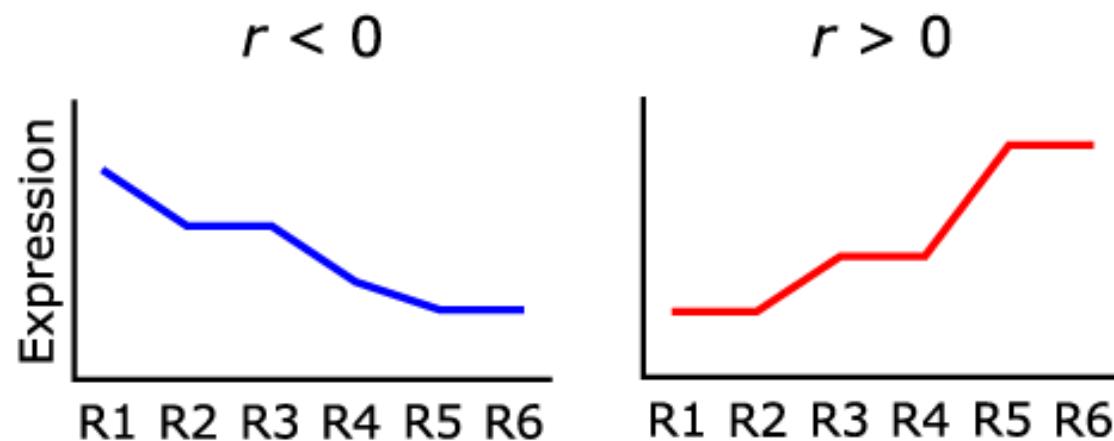
Criteria for BRGs selection:

1. Correlation between gene expression and Braak stage labels
2. Differential expression between R1 & R6

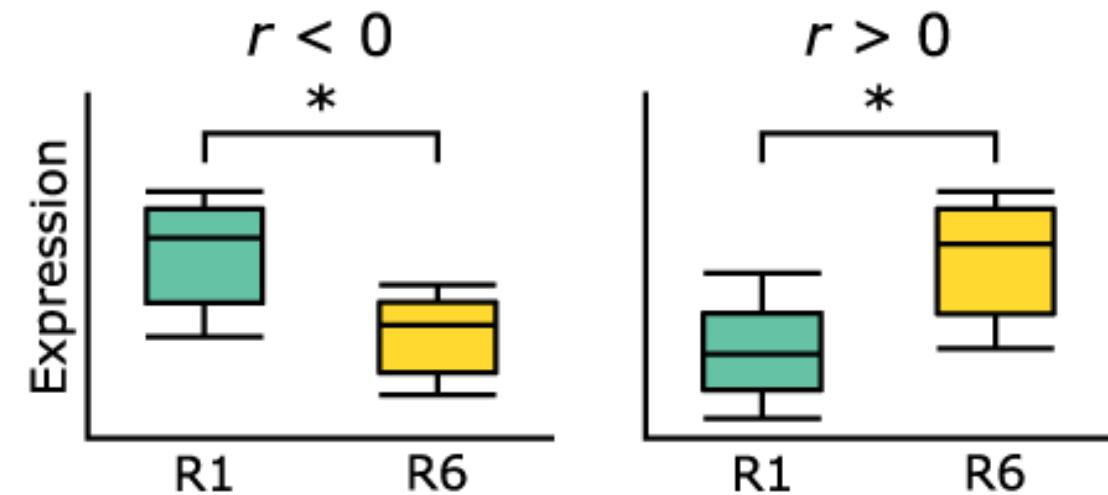


# Braak stage-related genes (BRGs)

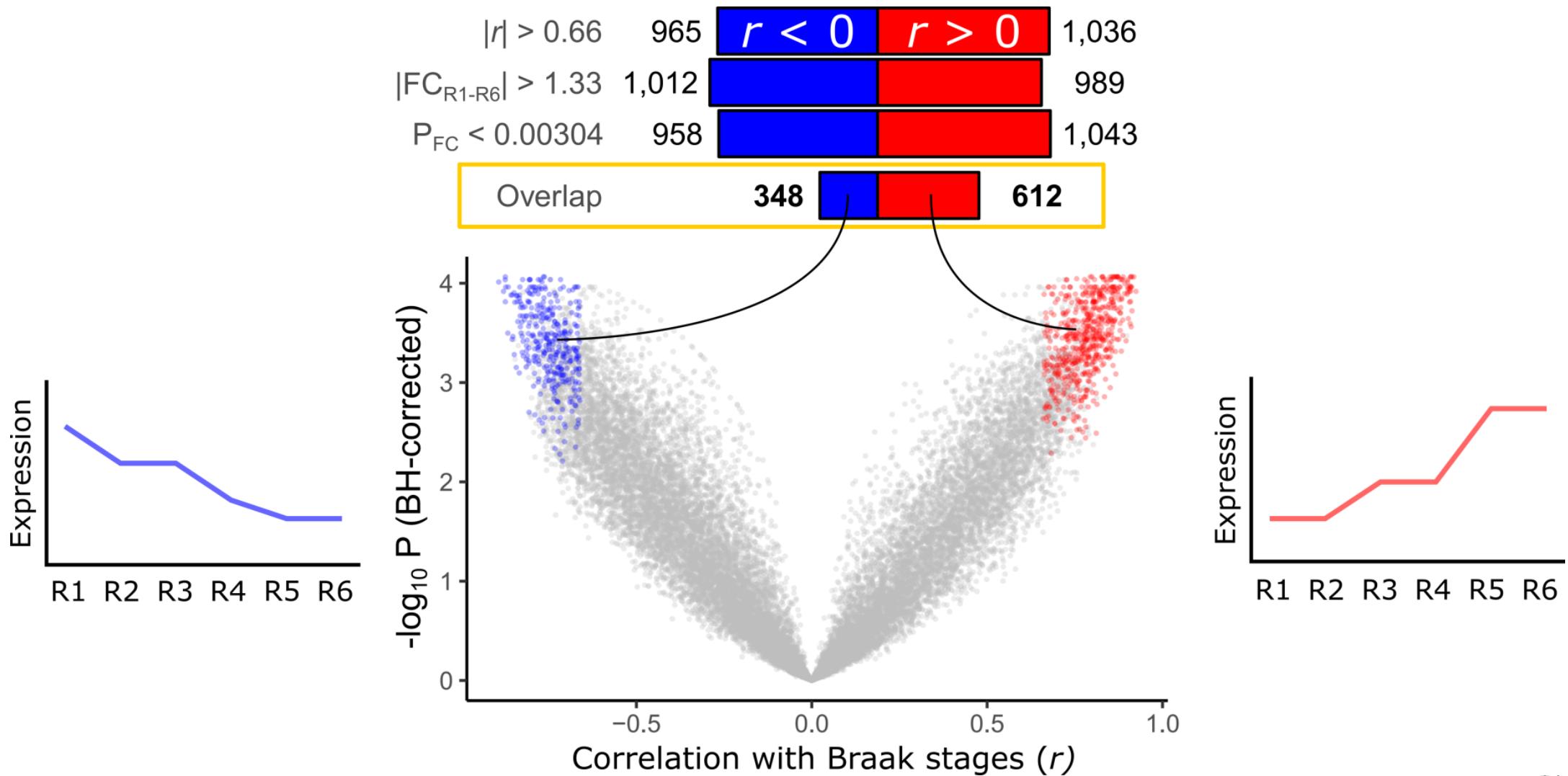
Gene-Braak correlation



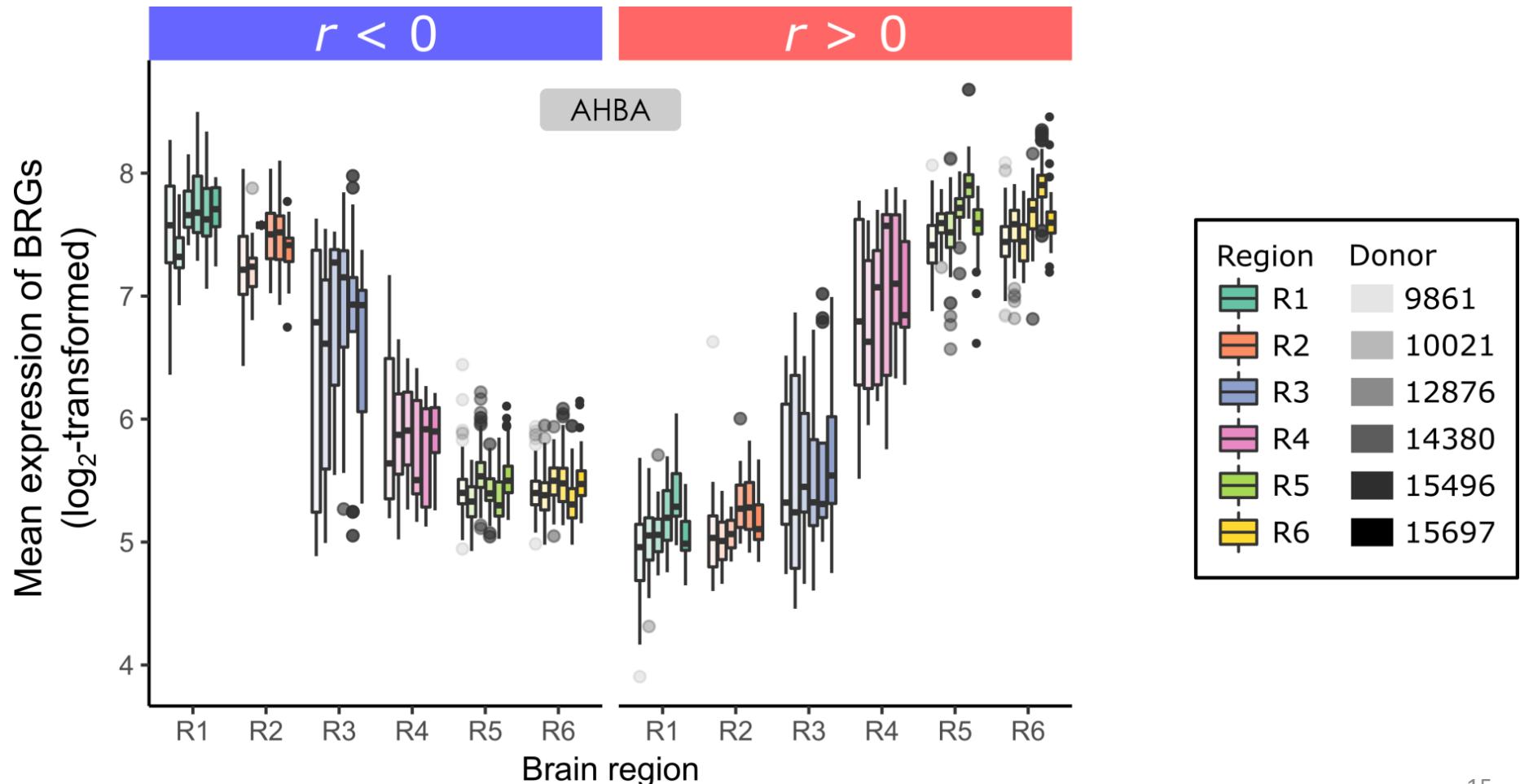
Differential expression



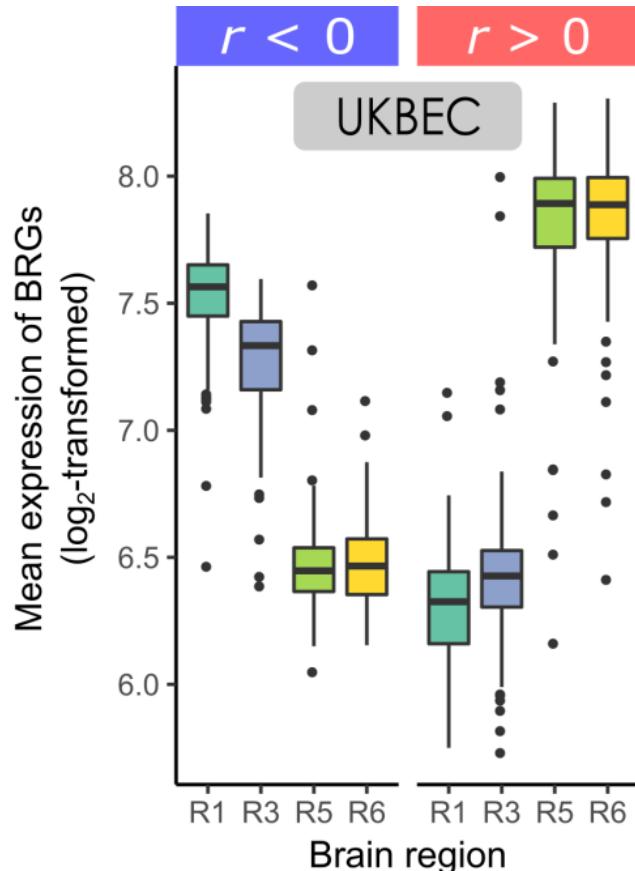
# Braak stage-related genes (BRGs)



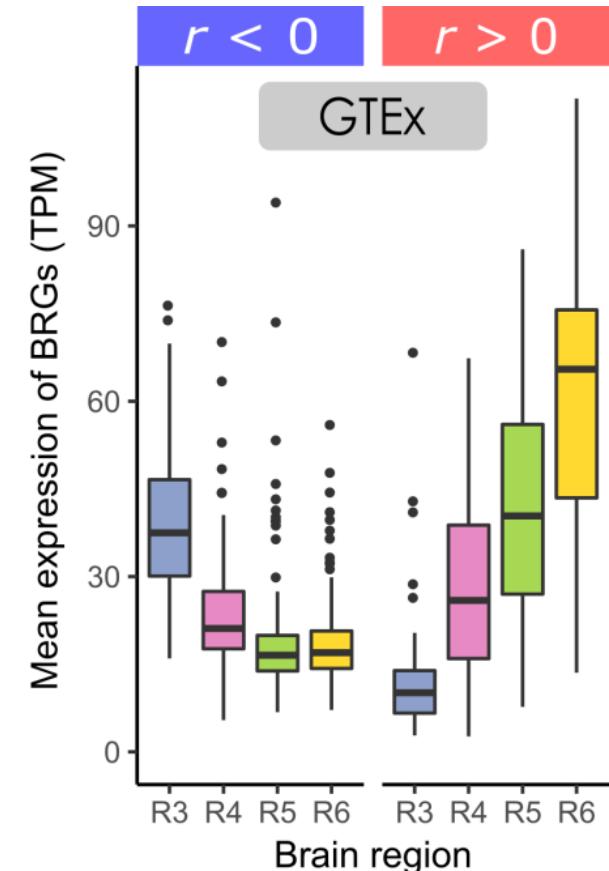
# Expression of BRGs for one donor across AHBA donors



# Validation in larger (healthy) cohorts

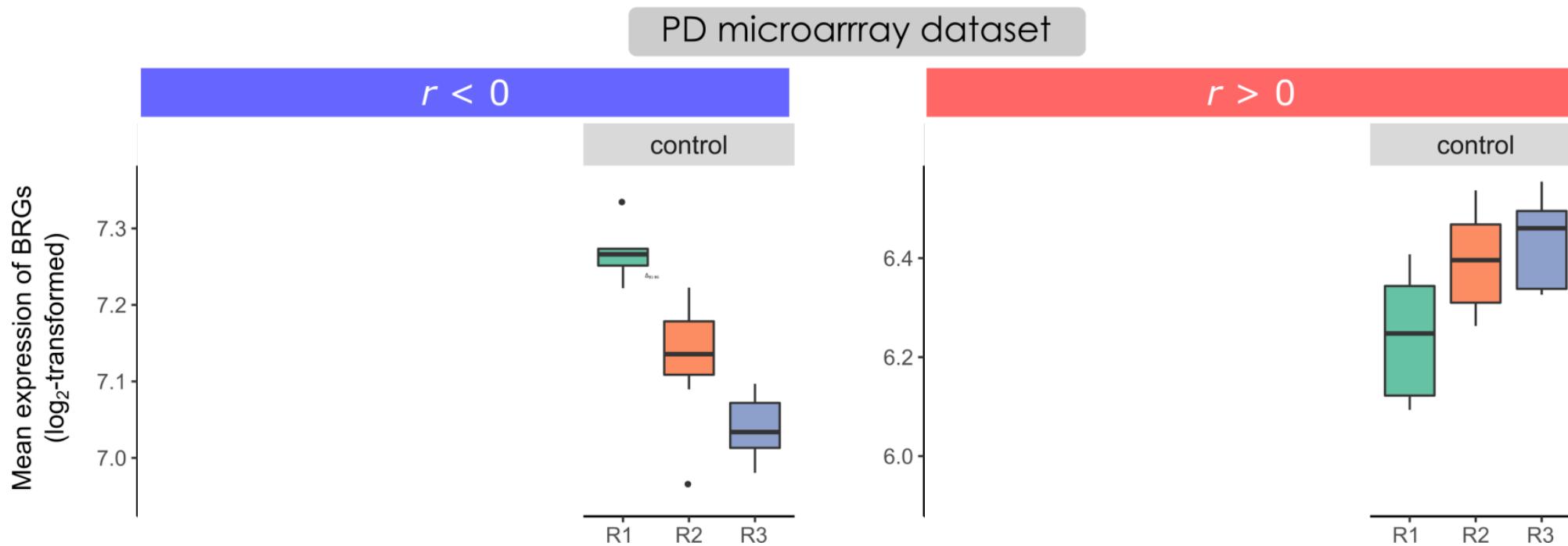


134 Brain donors



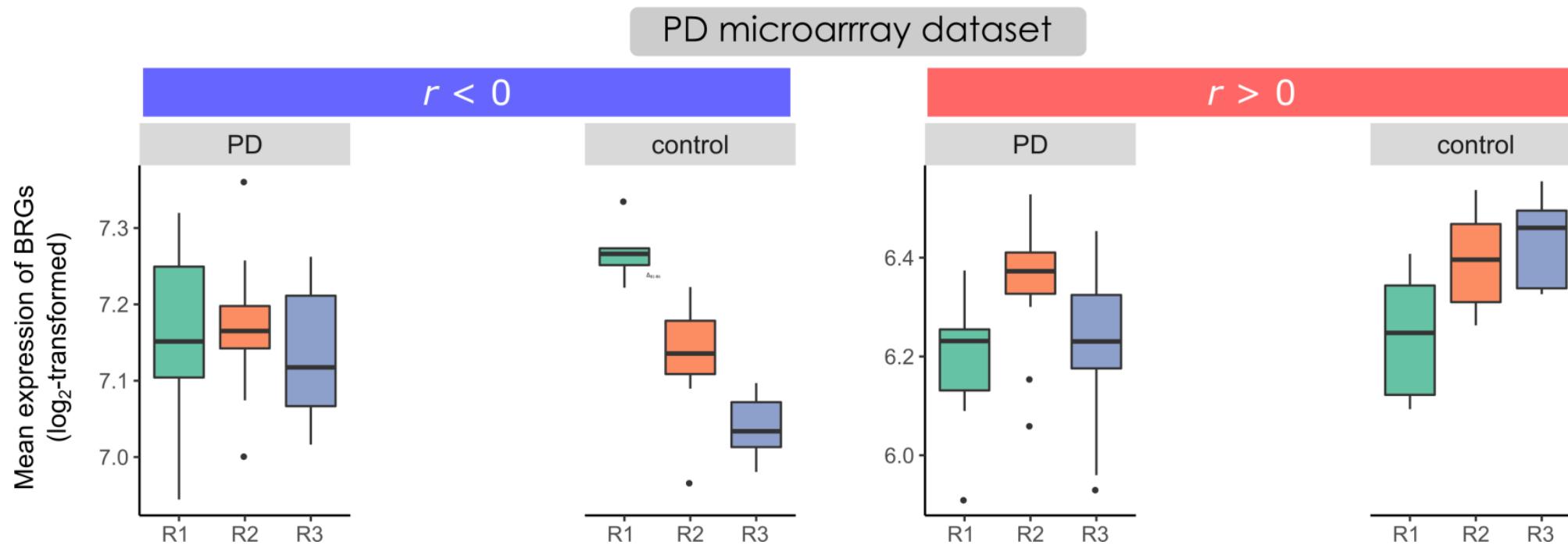
751 Brain donors

# Validation in PD brains



medulla oblongata (R1), locus ceruleus (R2), and substantia nigra (R3)

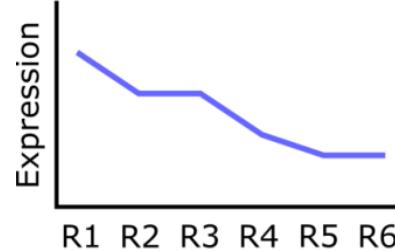
# Validation in PD brains



medulla oblongata (R1), locus ceruleus (R2), and substantia nigra (R3)

# Expression of PD-implicated genes is related to Braak staging

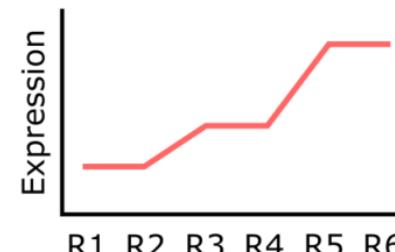
## Negative correlated BRGs



Gene	Braak correlation	Fold-change	P-value (BH-corrected)	Reference
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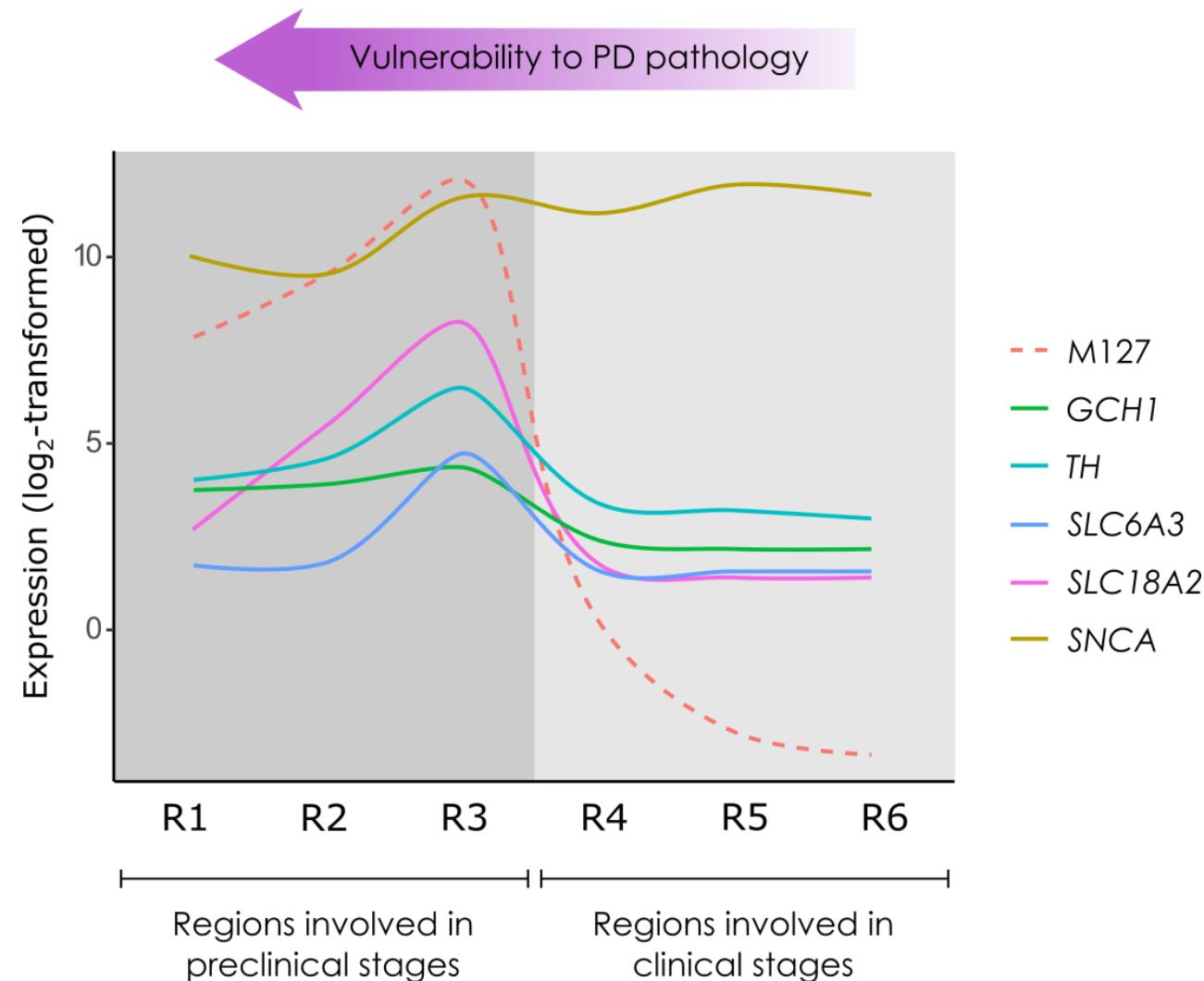
<i>SCARB2</i>	-0.78	-1.44	1.7E-03	Nalls et al. 2014
<i>ELOVL7</i>	-0.67	-1.35	1.4 E-03	Chang et al. 2017

## Positive correlated BRGs

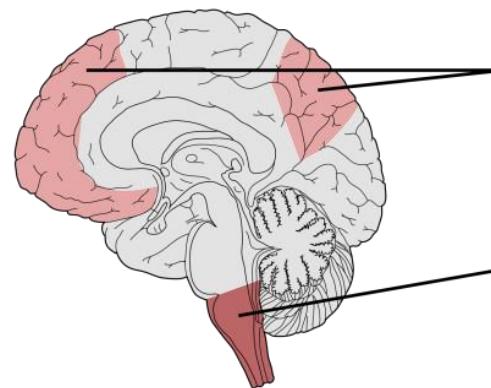
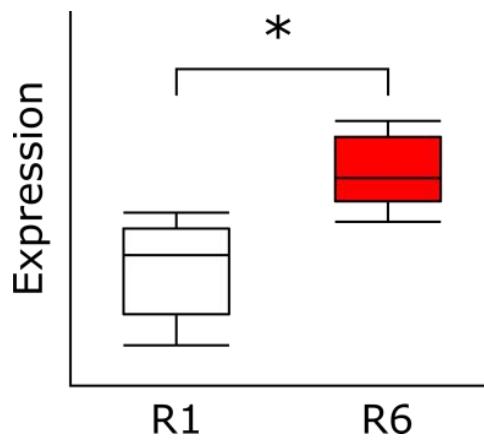


<i>SH3GL2</i>	0.70	1.40	2.3E-03	Chang et al. 2017
<i>SNCA</i>	0.70	1.75	4.3E-04	Bonifati et al. 2014, Chang et al. 2017, Nalls et al. 2014
<i>BAP1</i>	0.77	1.99	1.6E-03	Chang et al. 2017
<i>ZNF184</i>	0.81	2.34	2.9E-03	Chang et al. 2017

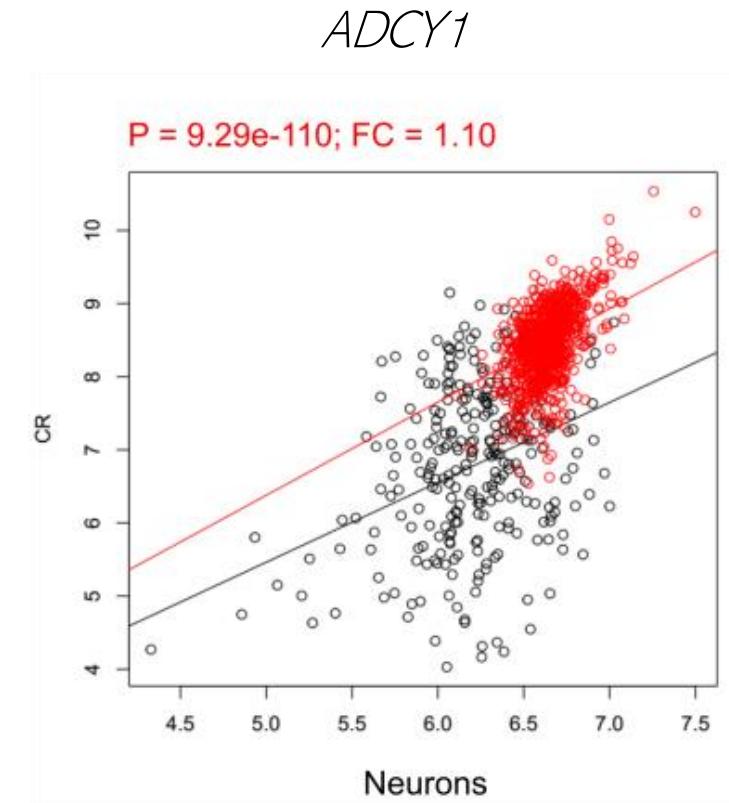
# Dopamine pathways across Braak stages



# Do we mainly capture cell type composition differences?

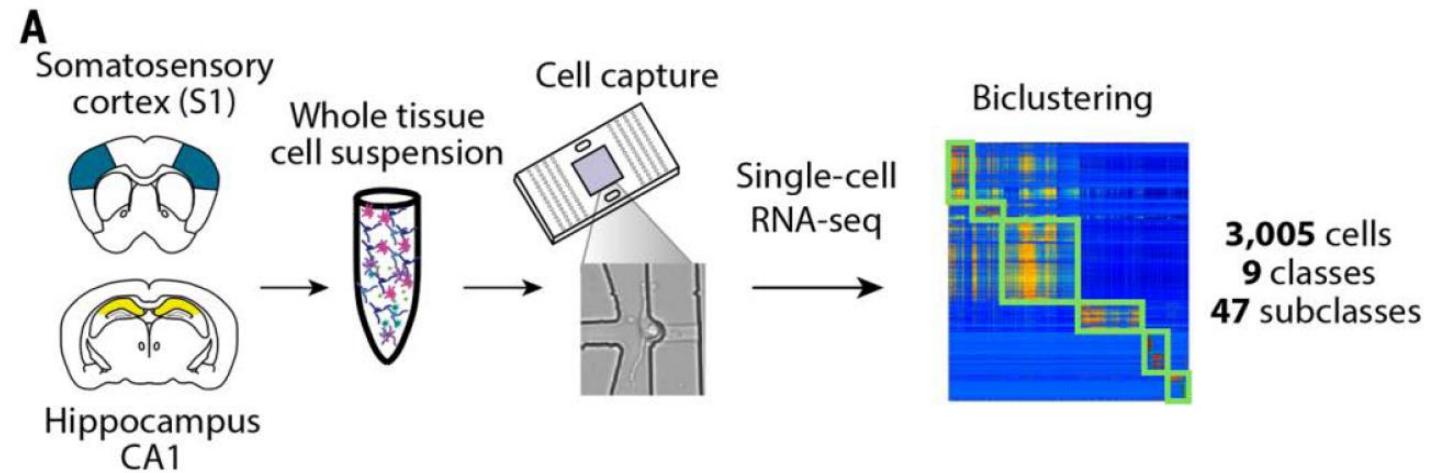


Expression in R6  
vs.  
Expression in R1

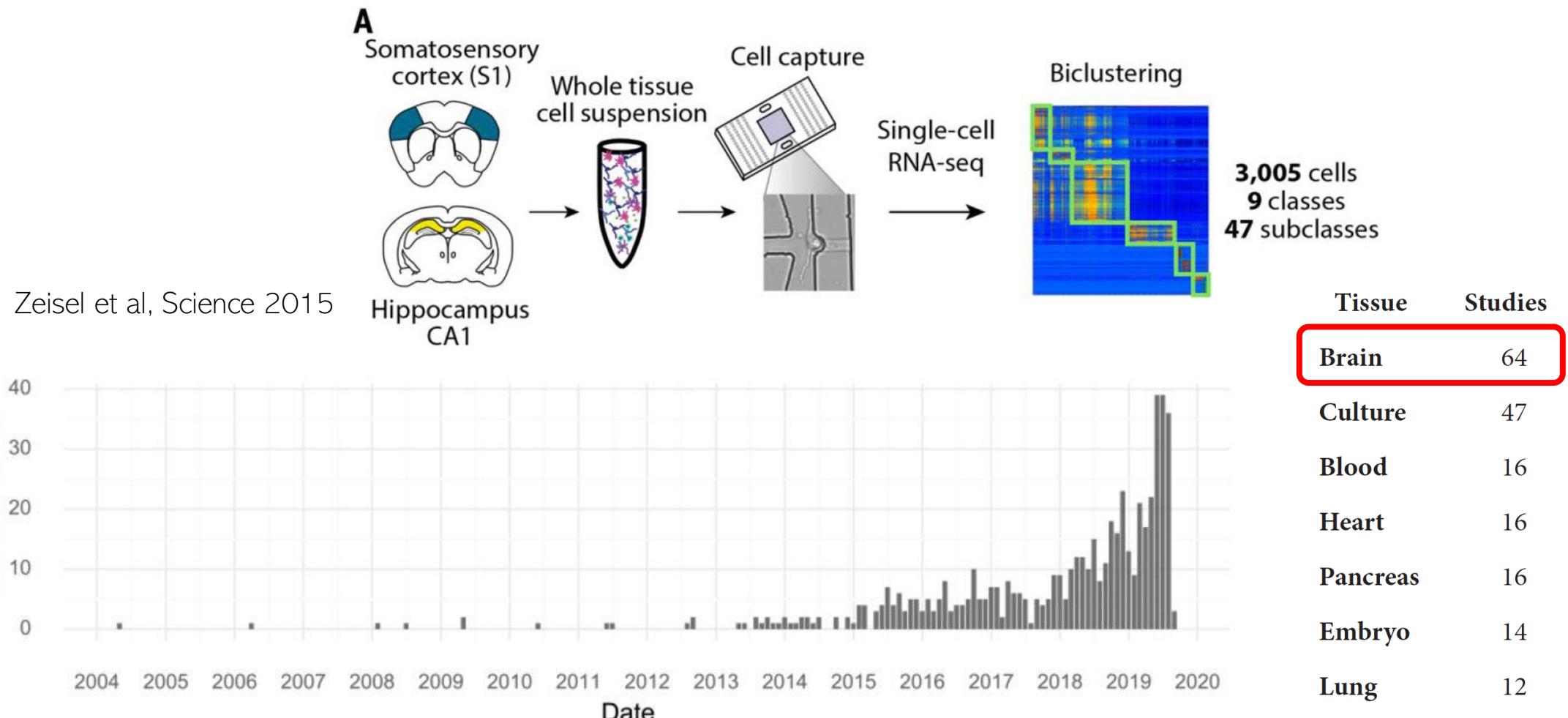


# From bulk to single-cell transcriptomics

Zeisel et al, Science 2015

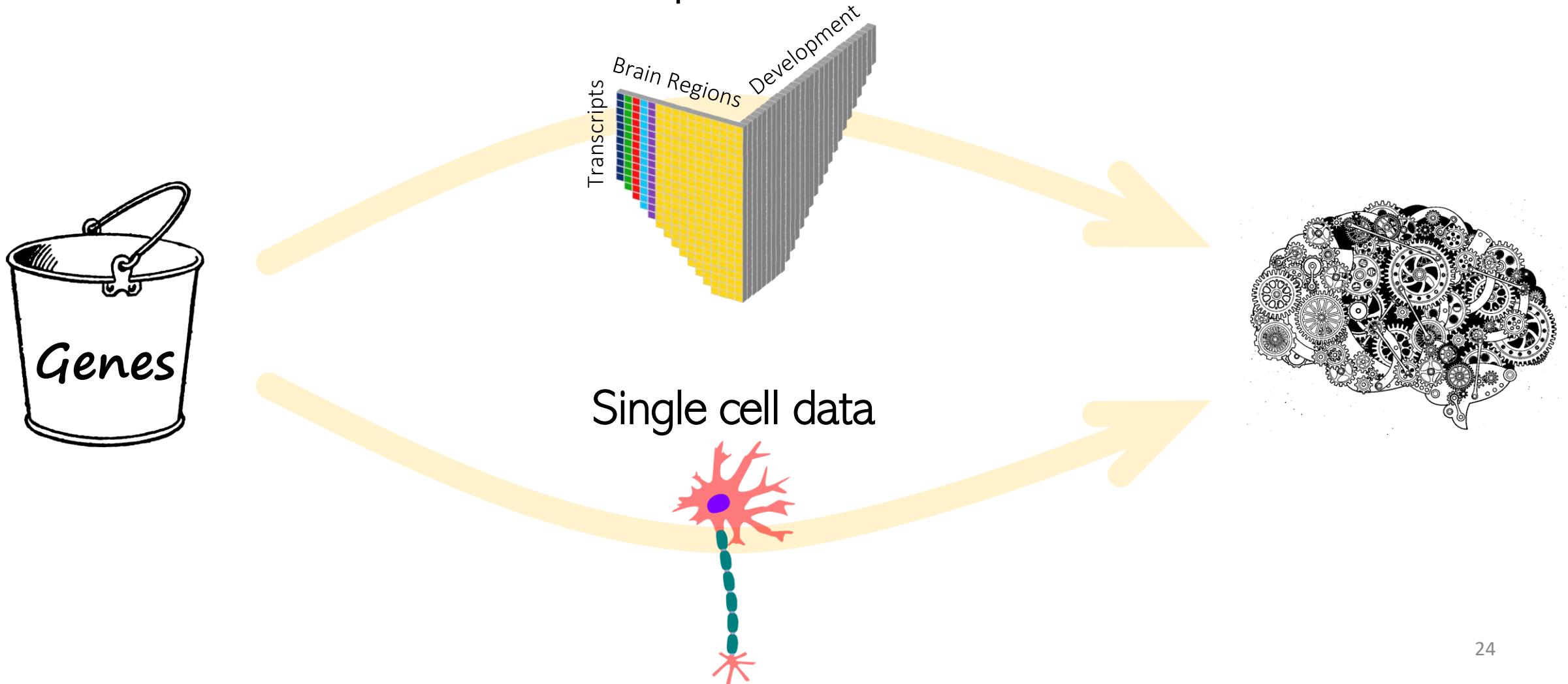


# From bulk to single-cell transcriptomics

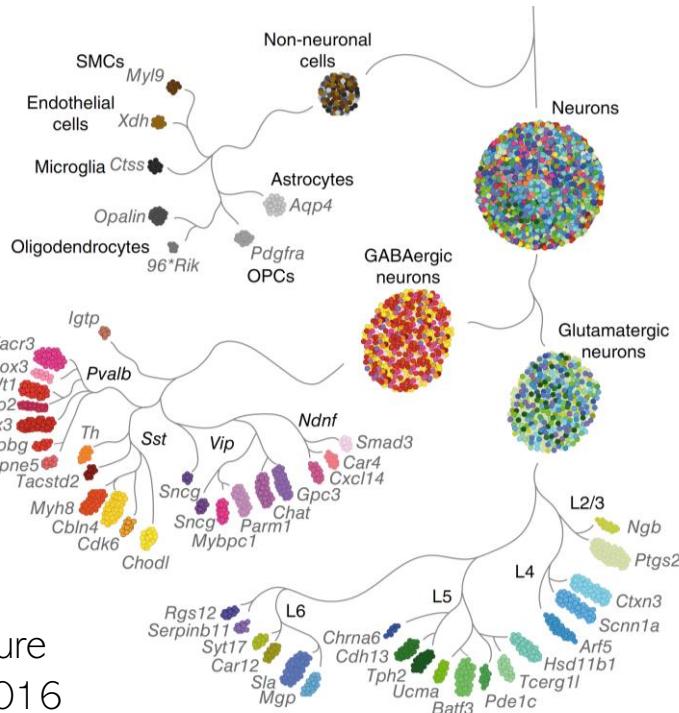


# A functional genomics approach

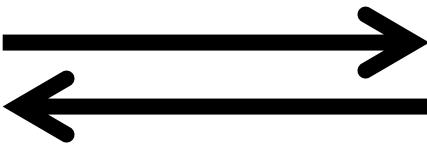
## Transcriptome atlases



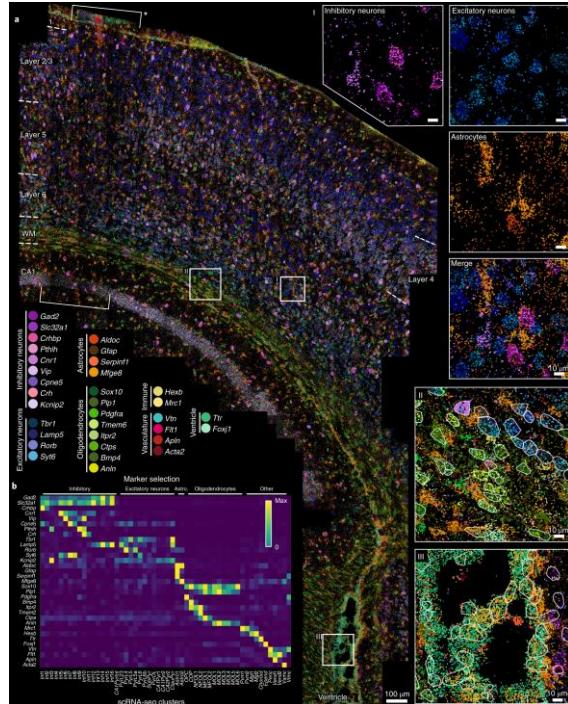
# A good understanding of biological functions requires data integration technologies



scRNA-seq  
Whole transcriptome  
Loss of spatial information



Codeluppi et al, Nature methods 2018



Spatial transcriptomics  
Retain spatial information  
Limited in the number of genes



Tamim Abdelaal

## SpaGE: Spatial Gene Enhancement using scRNA-seq

**Tamim Abdelaal**<sup>1,2</sup>, **Soufiane Mourragui**<sup>1,3</sup>, **Ahmed Mahfouz**<sup>1,2,4,†</sup> and  
**Marcel J.T. Reinders**<sup>1,2,4,\*†</sup>

<sup>1</sup>Delft Bioinformatics Lab, Delft University of Technology, Delft 2628XE, The Netherlands, <sup>2</sup>Leiden Computational Biology Center, Leiden University Medical Center, Leiden 2333ZC, The Netherlands, <sup>3</sup>Computational Cancer Biology, Division of Molecular Carcinogenesis, Oncode Institute, the Netherlands Cancer Institute, Amsterdam 1066 CX, The Netherlands and <sup>4</sup>Department of Human Genetics, Leiden University Medical Center, Leiden 2333ZC, The Netherlands

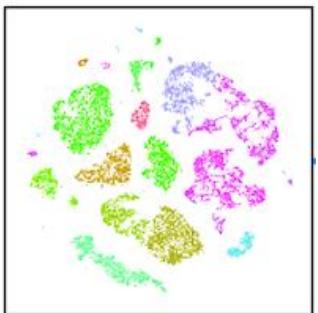
Received May 16, 2020; Revised July 30, 2020; Editorial Decision August 24, 2020; Accepted August 25, 2020

Abdelaal et al. *Nucleic Acids Research* 2020

# SpaGE

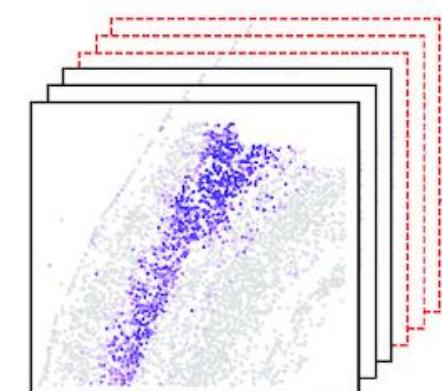
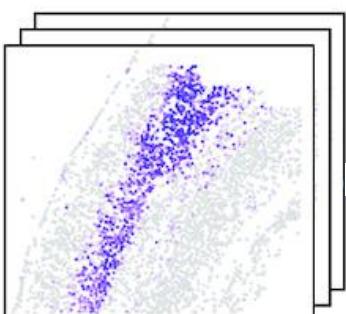
## *Spatial Gene Expression Enhancement*

scRNA-seq (reference)  
(~25,000 genes)



+

Spatial transcriptomics (query)  
(~ 10-1,000 genes)



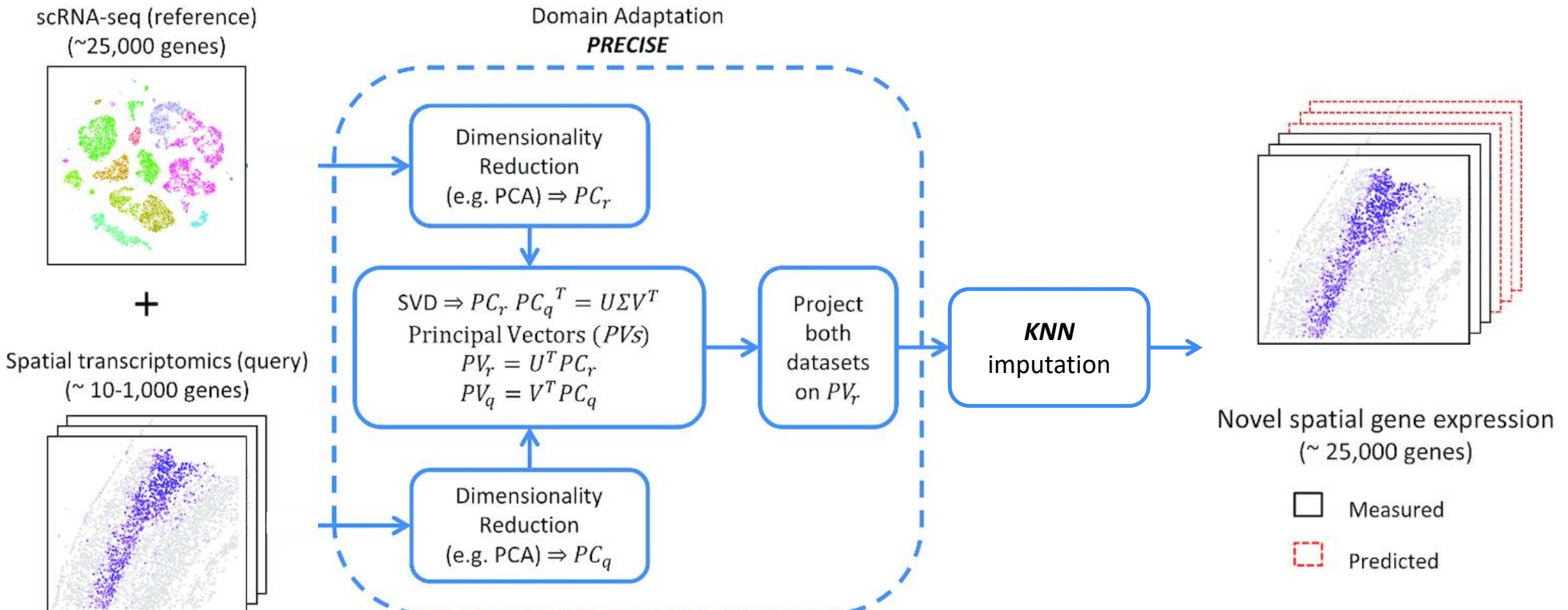
Novel spatial gene expression  
(~ 25,000 genes)

□ Measured

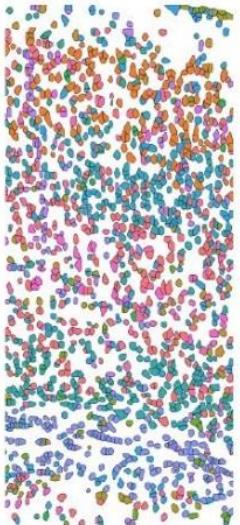
□ Predicted

# SpaGE

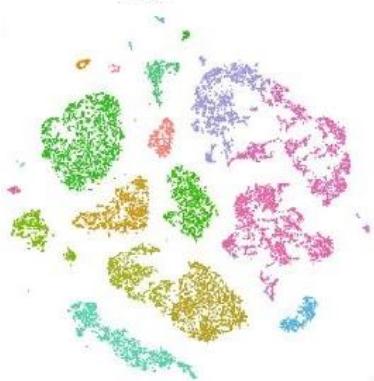
## *Spatial Gene Expression Enhancement*



# SpaGE on primary visual cortex (V1Sp)

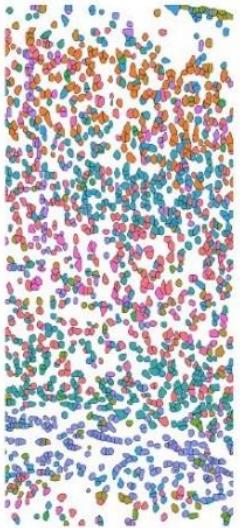


**STARmap**  
1,549 cells  
1,020 genes  
Wang et al. Science 2018

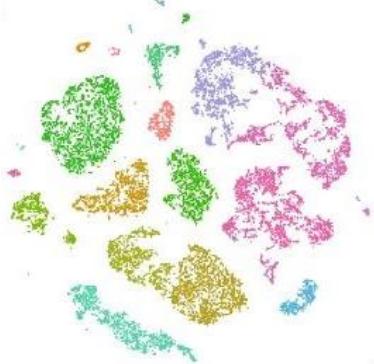


**scRNA-seq**  
14,249 cells  
34,617 transcripts  
Tasic et al. Nature 2018

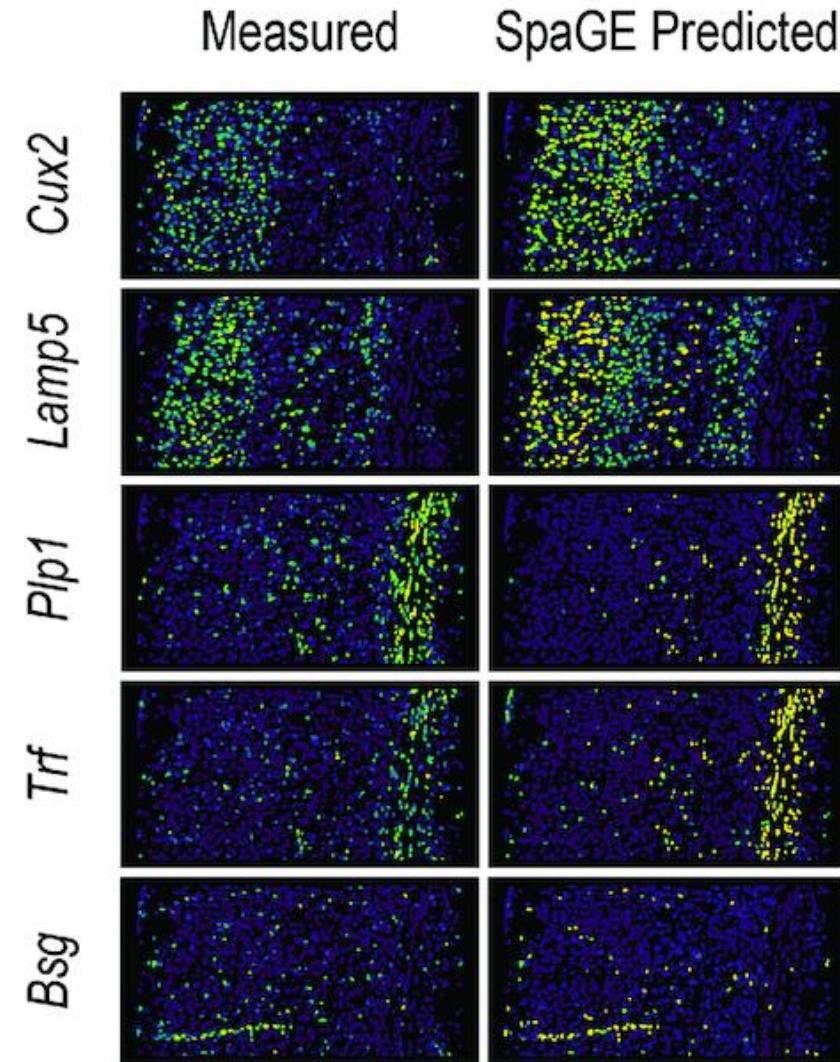
# SpaGE on primary visual cortex (V1Sp)



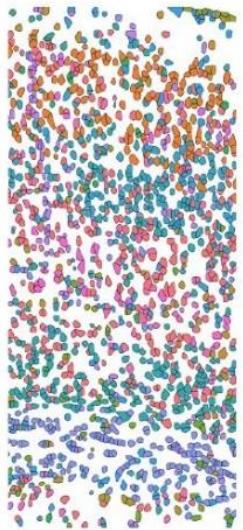
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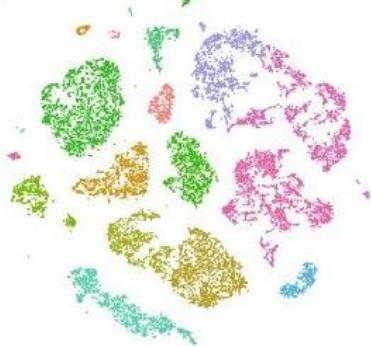
scRNA-seq  
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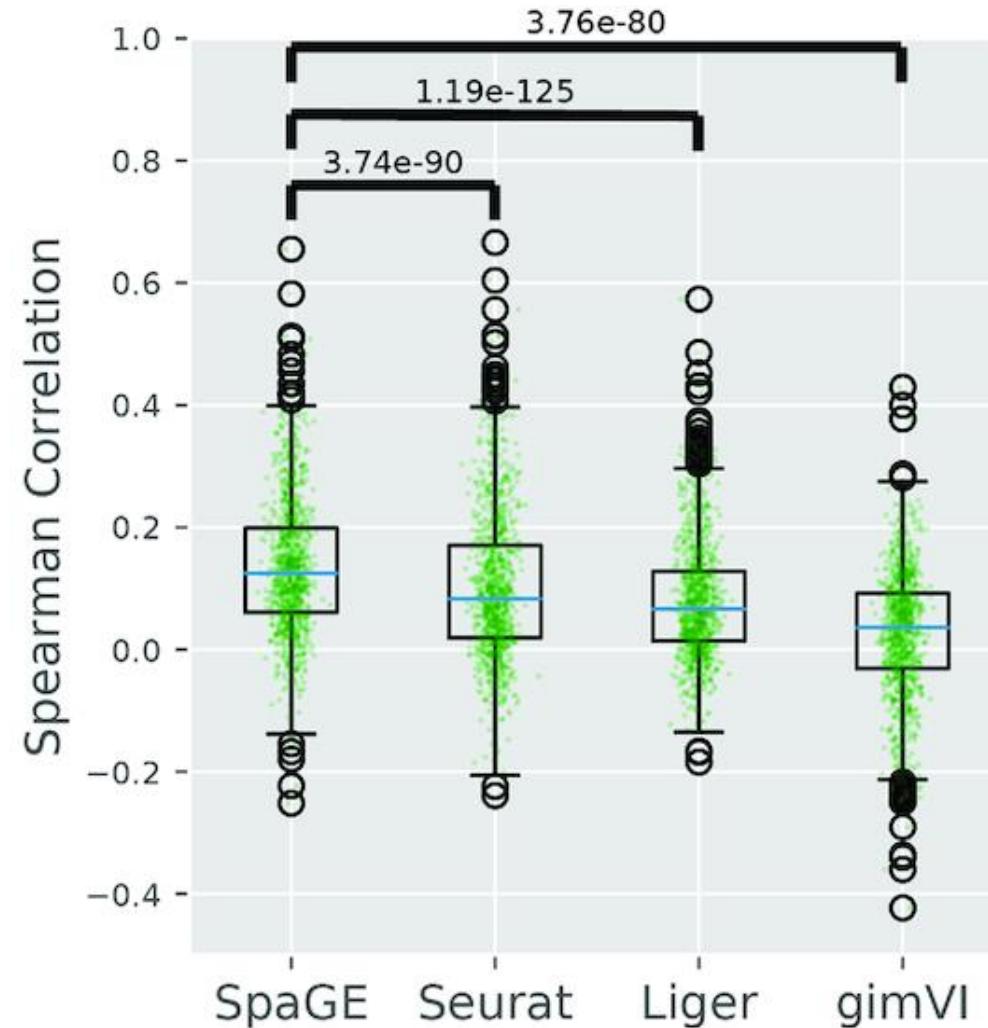
# SpaGE outperforms Seurat, Liger and gimVI



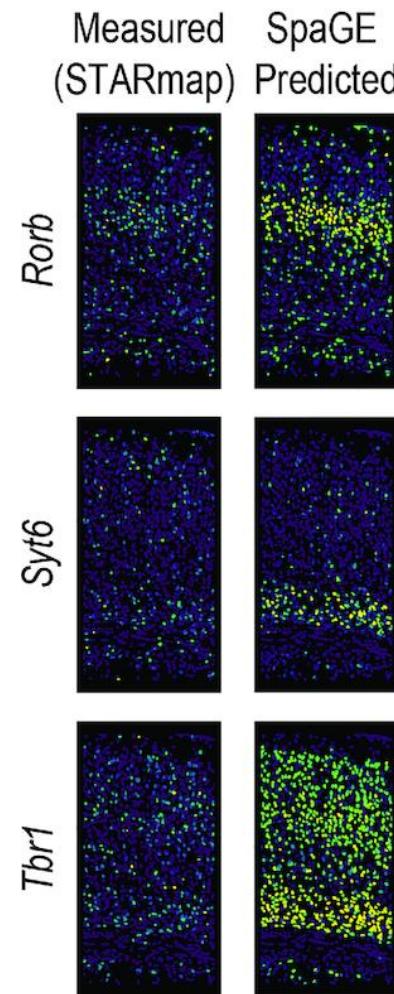
STARmap  
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Wang et al. Science 2018



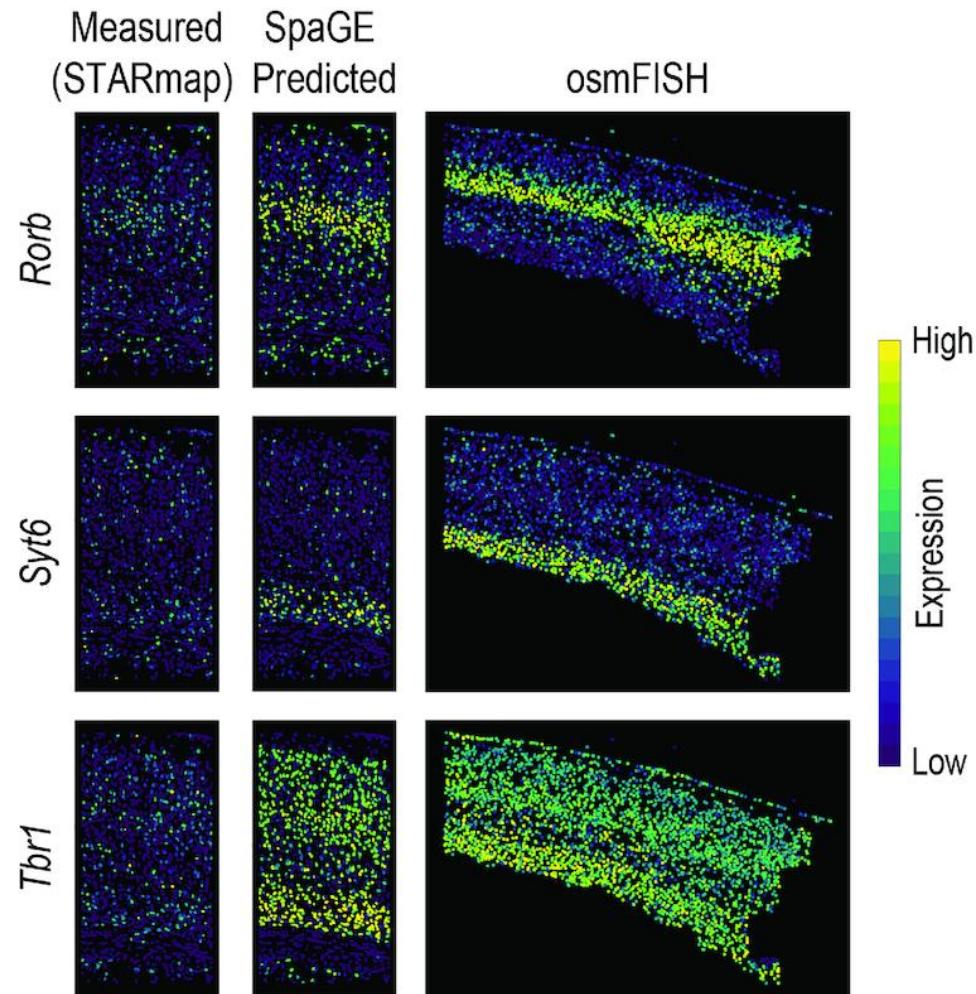
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# Wrongly measured, correctly predicted



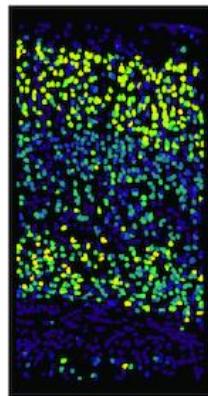
# Wrongly measured, correctly predicted



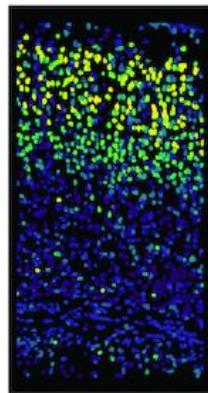
# Predicting unmeasured genes

SpaGE Predicted

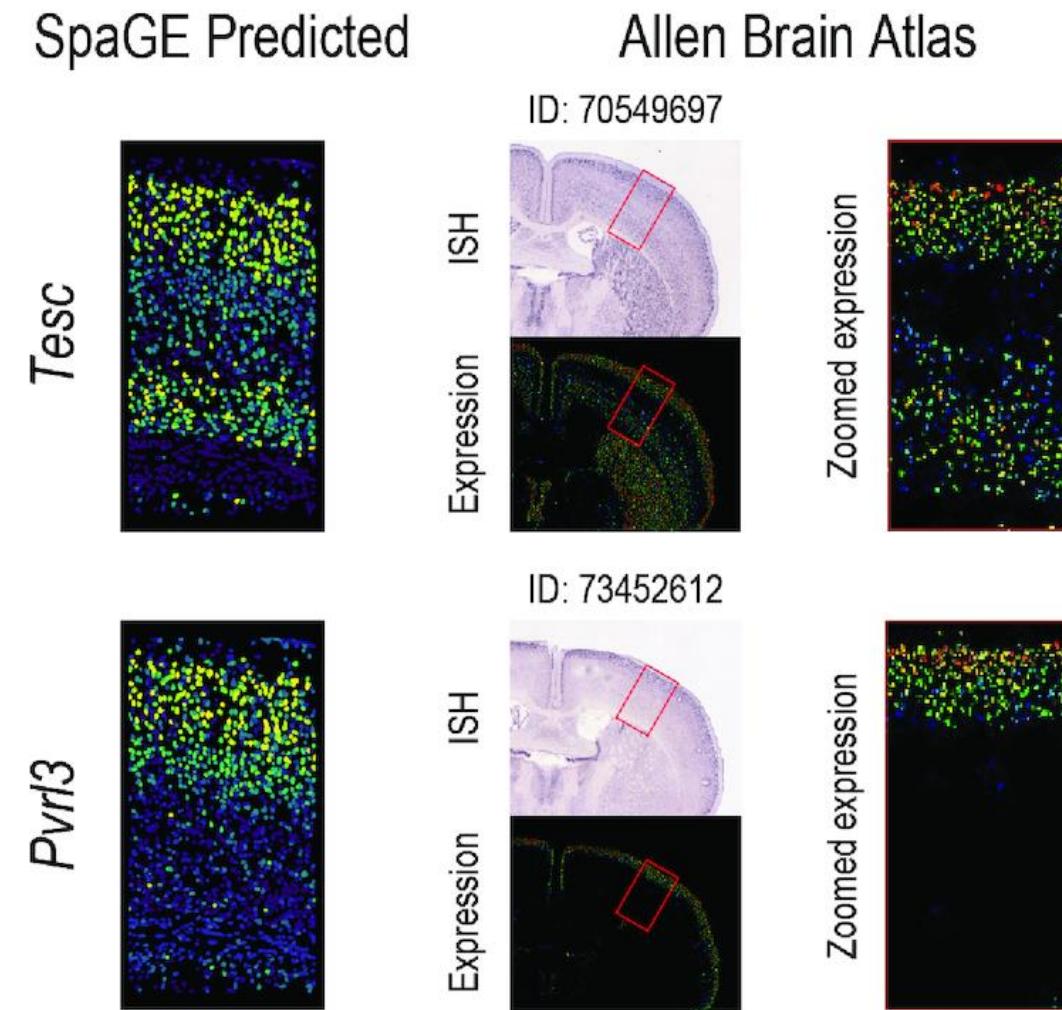
*Tesc*



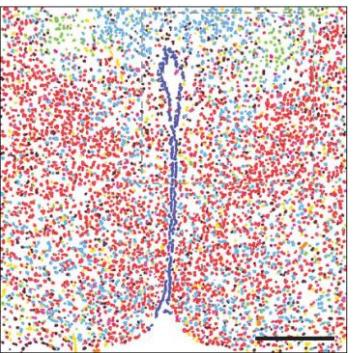
*Pvrl3*



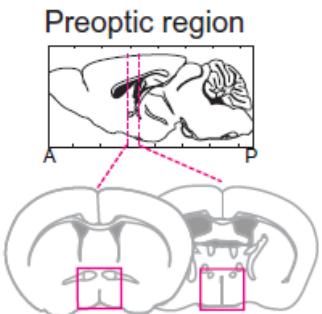
# Predicting unmeasured genes



# SpaGE scales to large spatial datasets

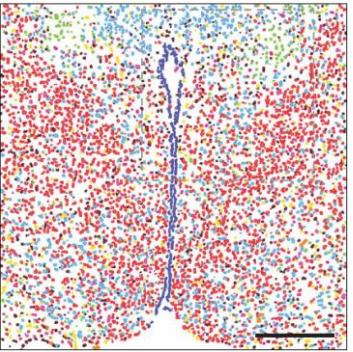


MERFISH  
64,373 cells  
155 genes  
Moffit et al. Science 2018

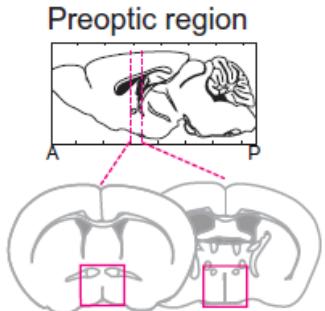


scRNA-seq  
31,299 cells  
18,646 transcripts  
Moffit et al. Nature 2018

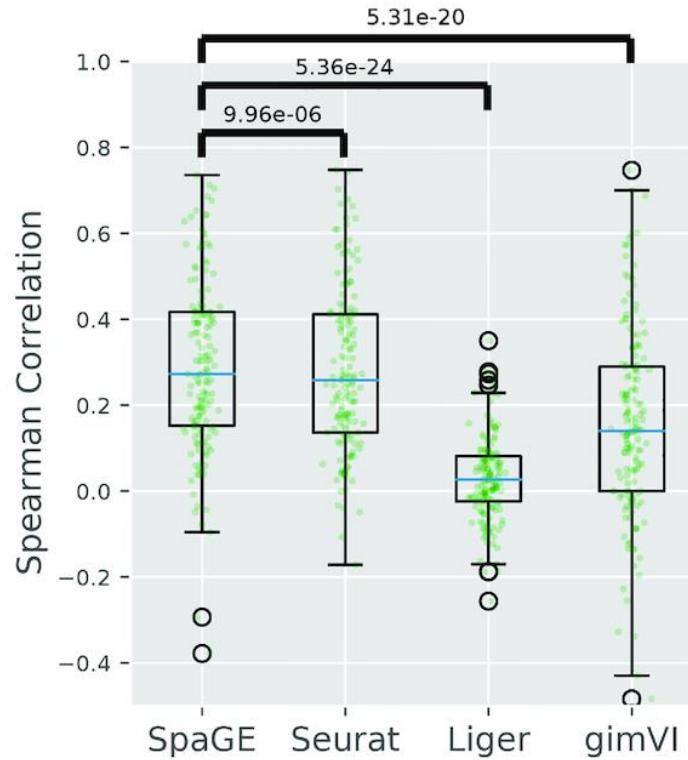
# SpaGE scales to large spatial datasets



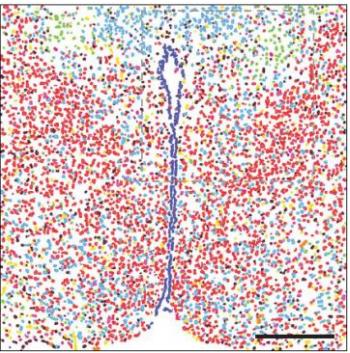
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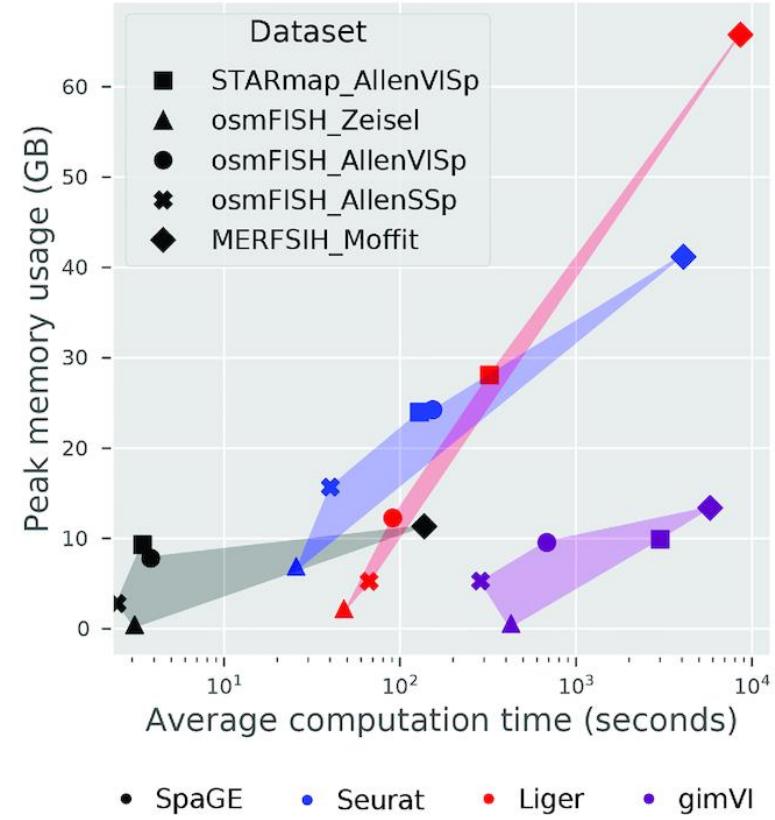
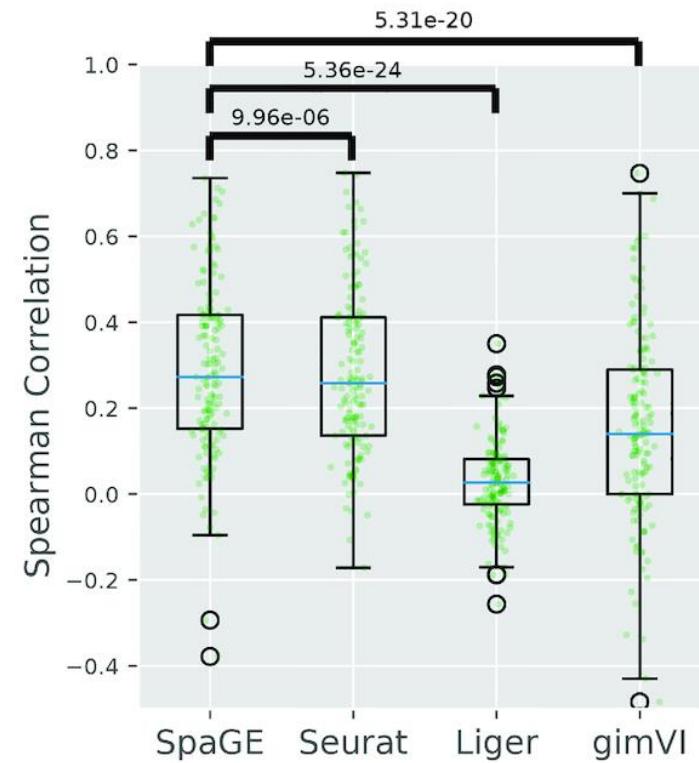
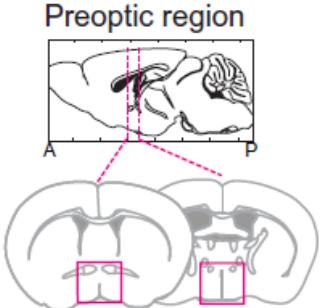


# SpaGE scales to large spatial datasets



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Moffit et al. Science 2018

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# Summary

- We take a functional genomics approach to better understand the role of genetic variation in brain function and disease
- Using the AHBA, we identified several genes and pathways associated with the PD progression in the brain
- SpaGE predicts spatial expression of unmeasured genes at the single cell level
- SpaGE outperforms state-of-the-art methods using is simpler, scalable and more flexible approach.

# Thank You!



Arlin Keo



Tamim Abdelaal



Laura Heezen



Gerard Bouland



Mostafa Eltager



Mohammed Charrout



Dongxu Zheng



Lieke Michielsen



Mikhael Manurung



a.mahfouz@lumc.nl



<https://www.lcbc.nl/>



@ahmedElkoussy

TU Delft

Soufiane Mourragui  
Marcel Reinders

LUMC

Bob J. van Hilt

Amsterdam UMC

Wilma D.J. van de Berg

Université de Lille

Marie-Christine Chartier-Harlin

Erasmus MC

Vincenzo Bonifati



CHAN  
ZUCKERBERG  
INITIATIVE



IMID



Single-cell eQTL  
Consortium