

A decorative scatter plot in the top left corner showing various colored dots (black, green, orange, purple, blue, pink, etc.) arranged in a pattern that resembles a stylized brain or neural network.

Brain cell type analysis and why it matters for disease

A decorative scatter plot in the middle left area showing a cluster of red dots, with some green and blue dots nearby.

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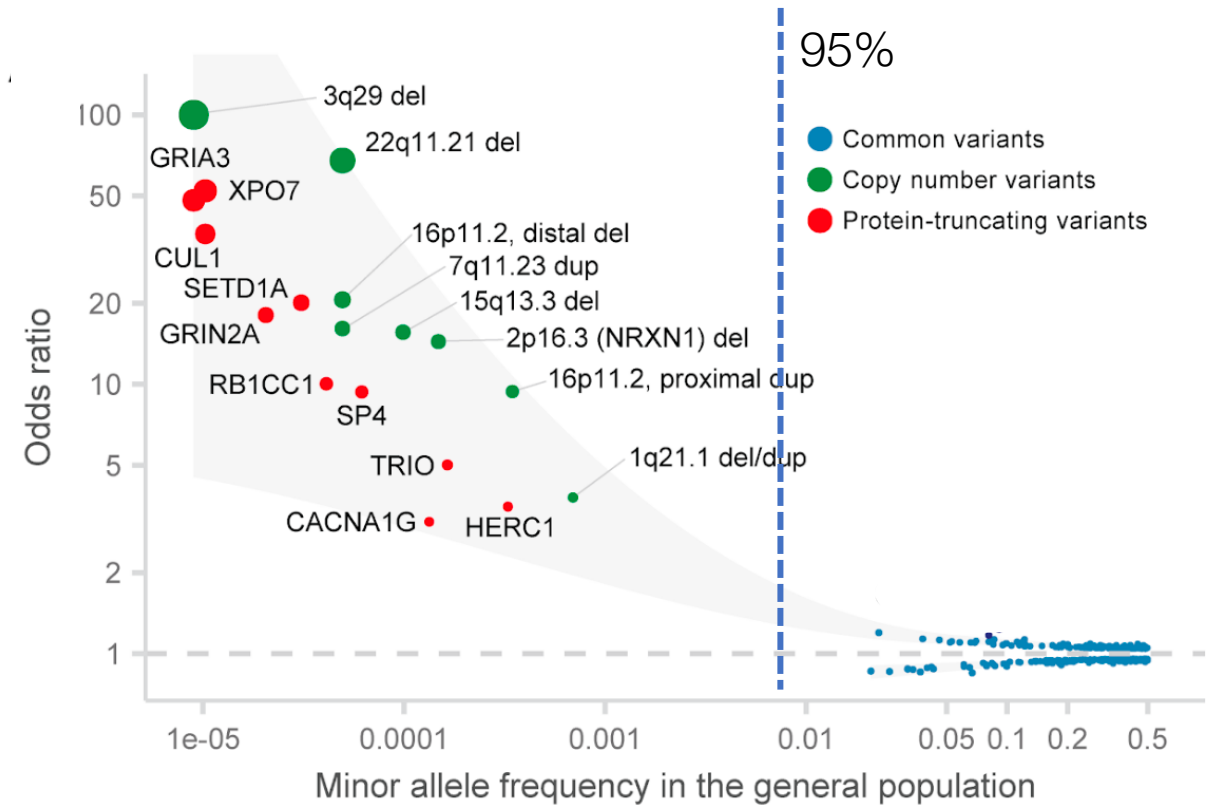
A large orange circle is positioned on the left side of the slide, partially cut off by the edge.

Conflicts of
interest:

JHL is a co-founder and shareholder of
~ Oscellaria AB



Psychiatric disorders are genetically complex

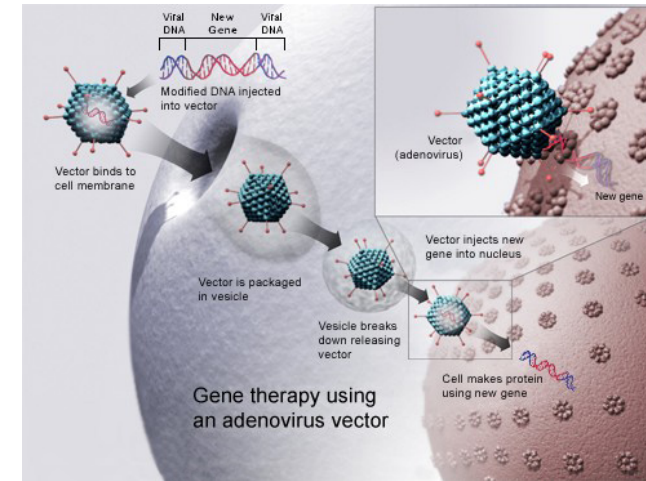
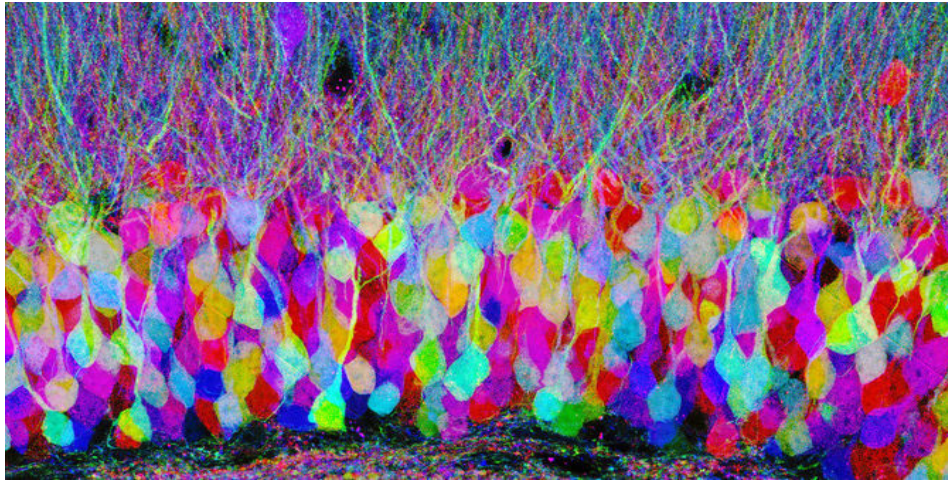


Genetics has revealed the structure of disorders

How can we begin to sort this complexity out?

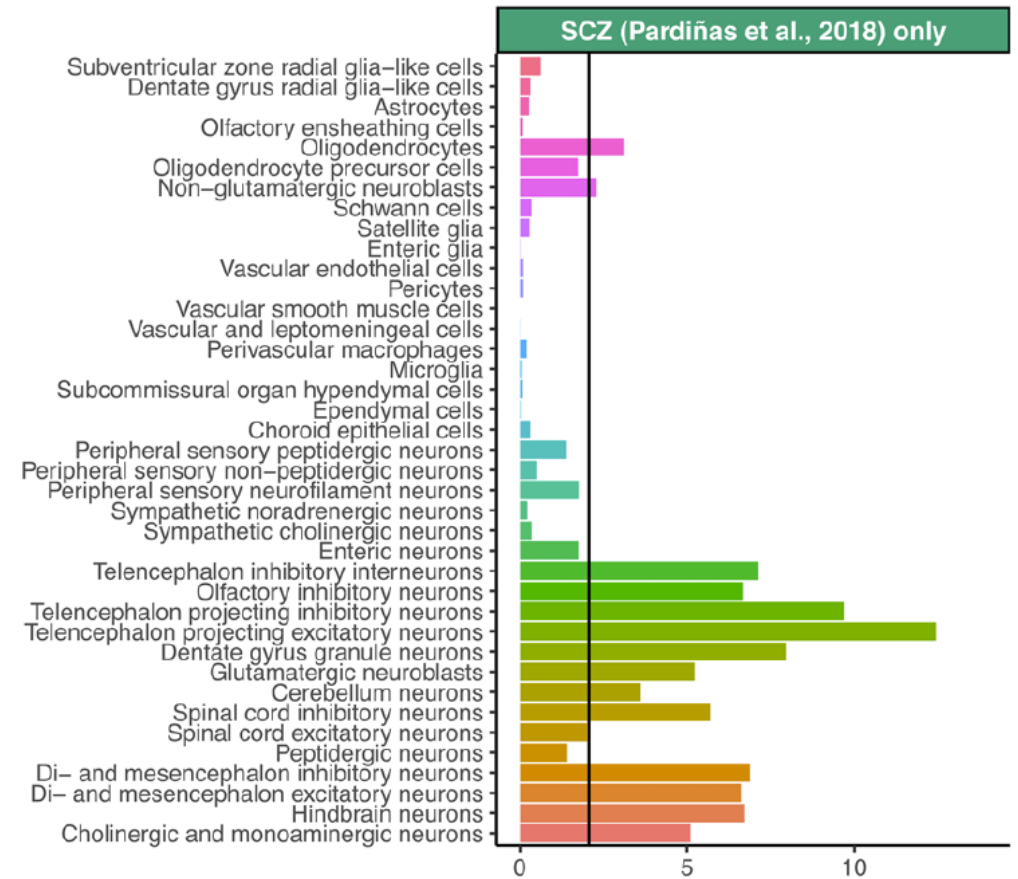
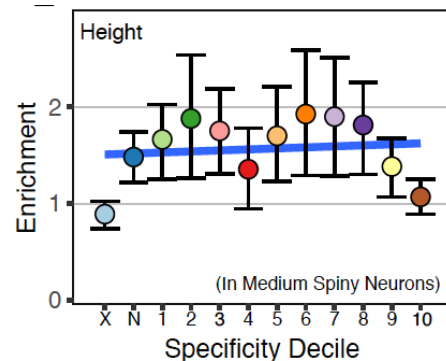
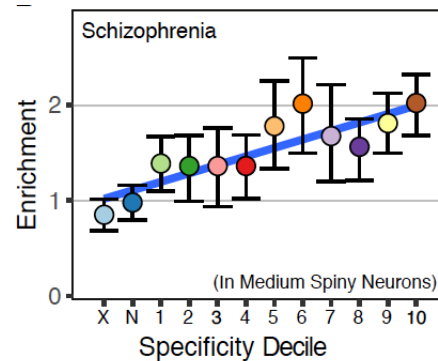
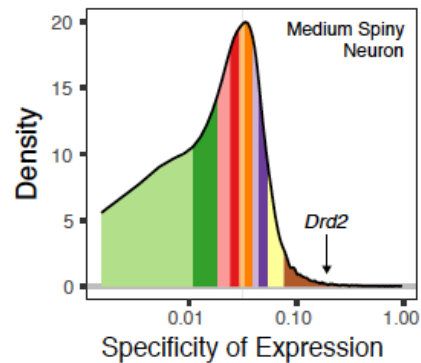
Common biological mechanisms? – if so, where/when?

Partitioning the brain – cell types



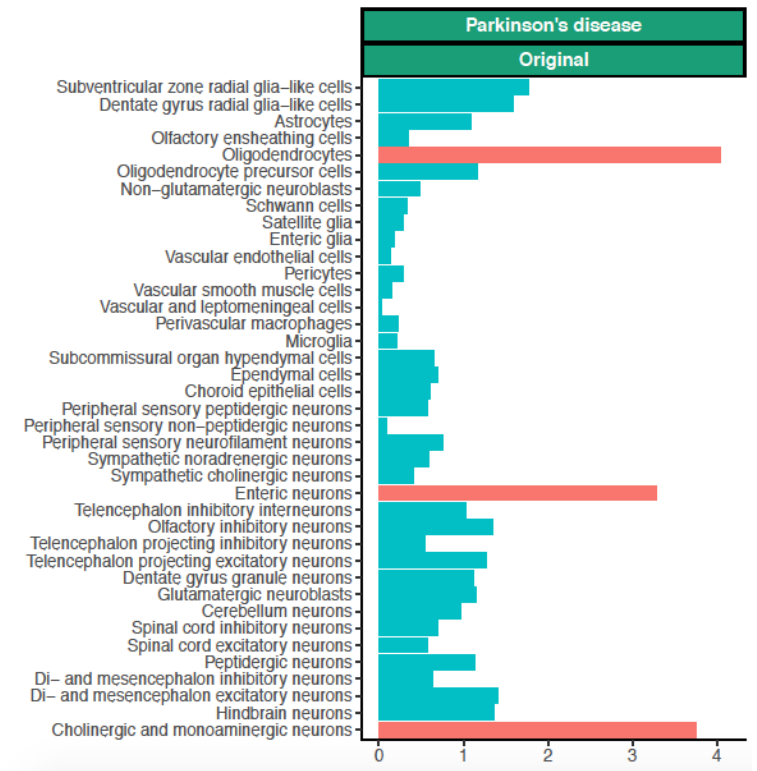
- Fundamental unit of the brain – smallest unit for evolution.
- Classification has been central to Neuroscience since 19th century
- Single-cell Resolution transcriptomics has reached “CAP”-criteria
- Quantitative measures of diversity
- Therapeutic access increasing for gene-therapy

Integrating GWAS and Transcriptomics allows for prioritization

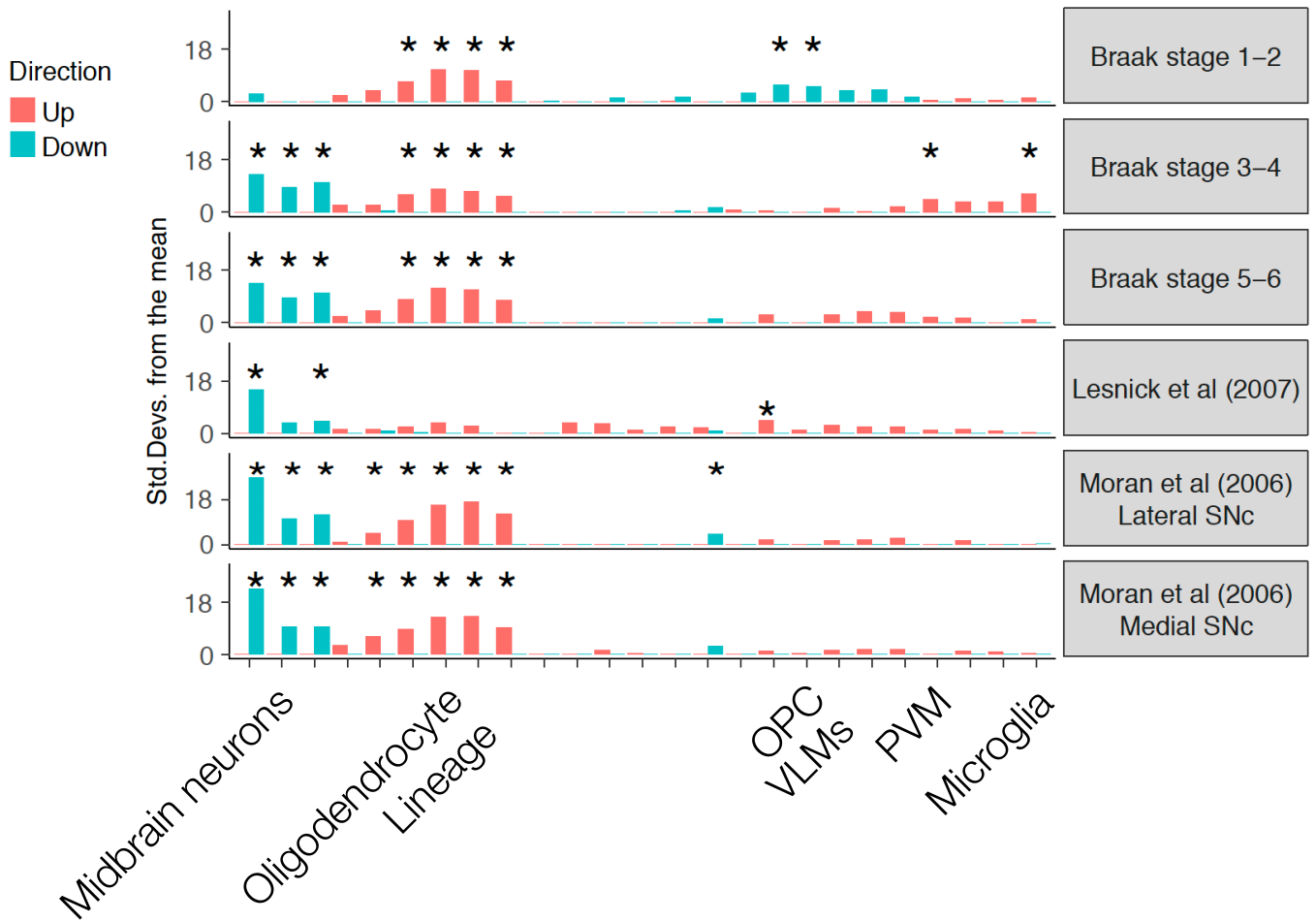


Integrating GWAS and Transcriptomics allows for prioritization

GWAS+scRNAseq prediction

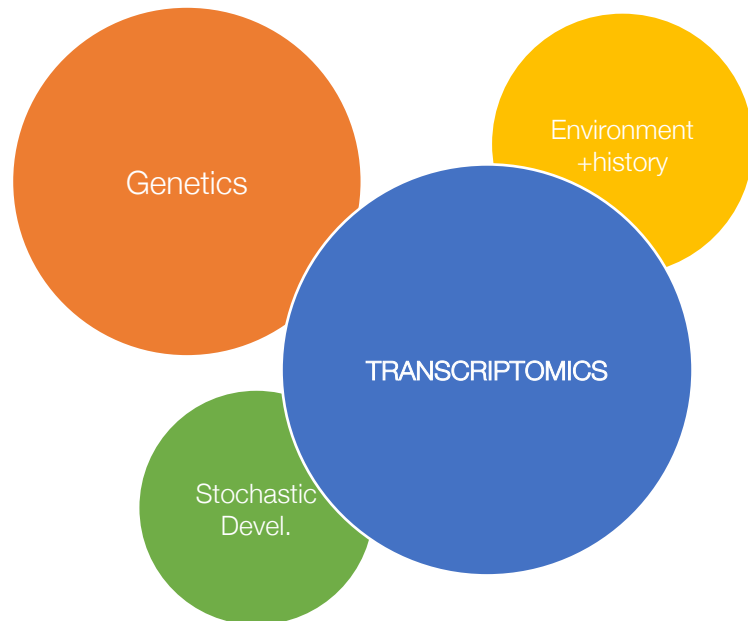


Confirmation in patient samples

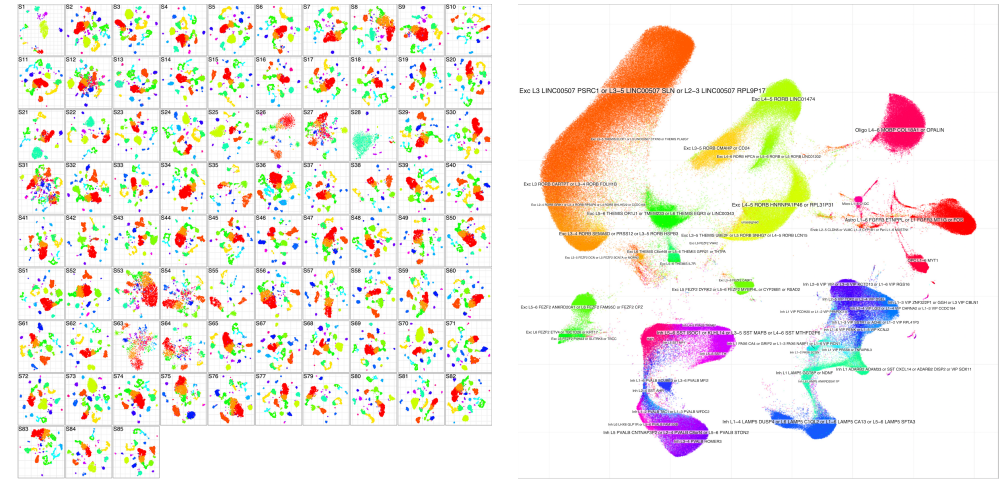


Direct measurements of changes: case/control single cell transcriptomics

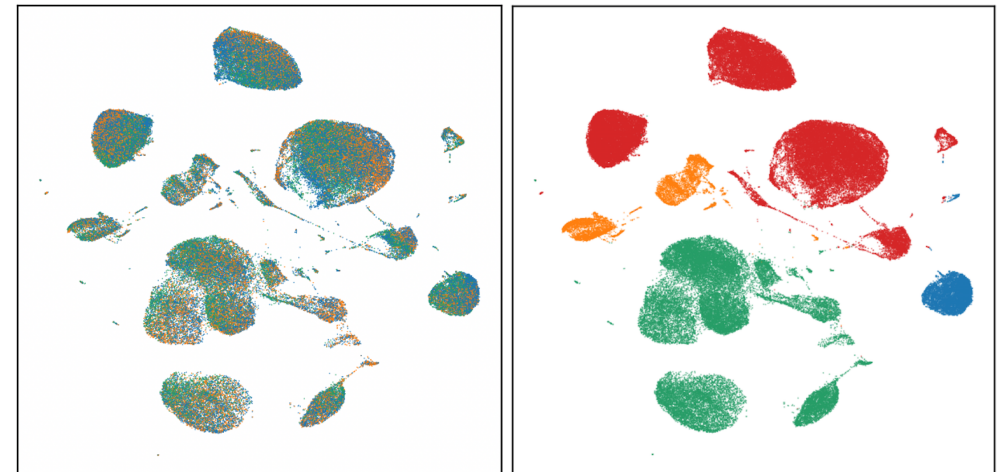
- Cellular resolution
- Multidimensional read-out
- Measuring endpoint –integrative approach
- Etiology?



Human Case/Control

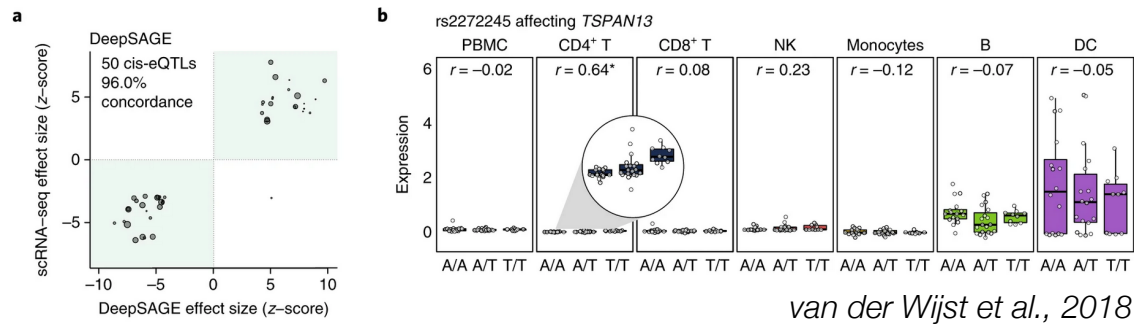


Mouse models

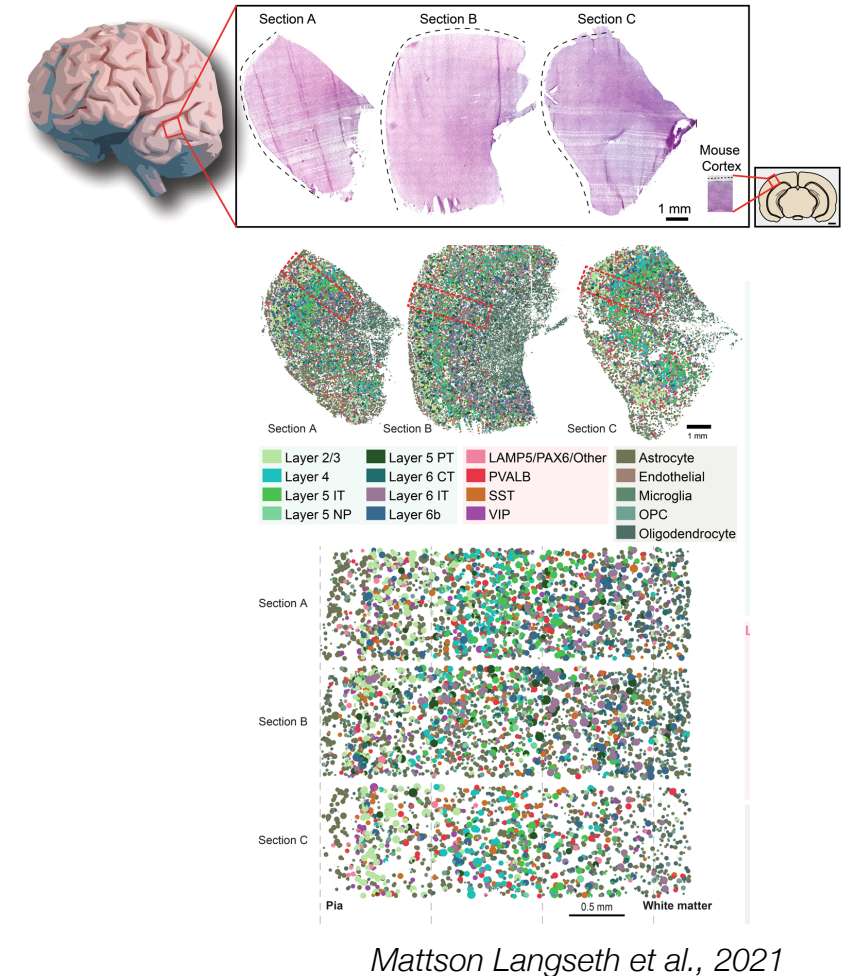


Single cell transcriptomics informs genetics and pathology

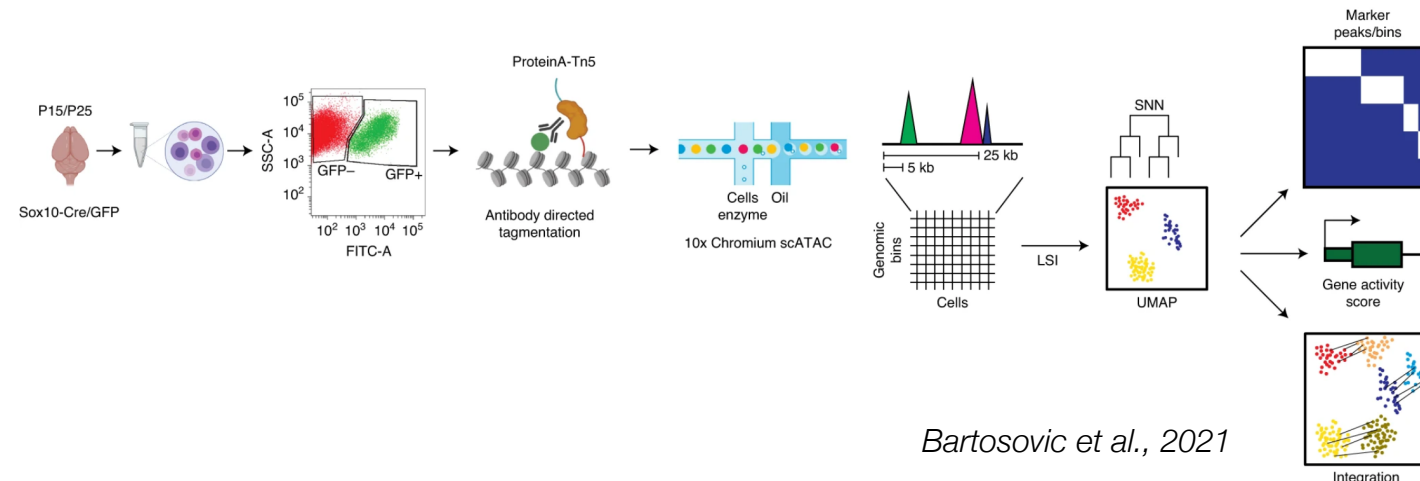
Cell type-specific eQTLs reveal hidden elements



Spatial transcriptomics links to cellular pathology

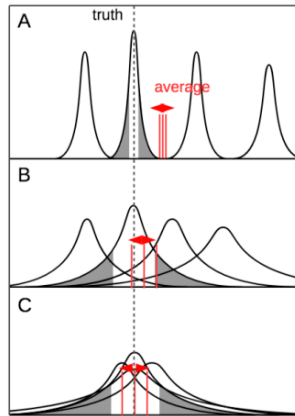
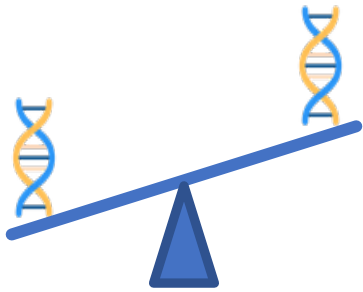


Cell type-specific CUT&Tag identifies binding sites and gene regulation



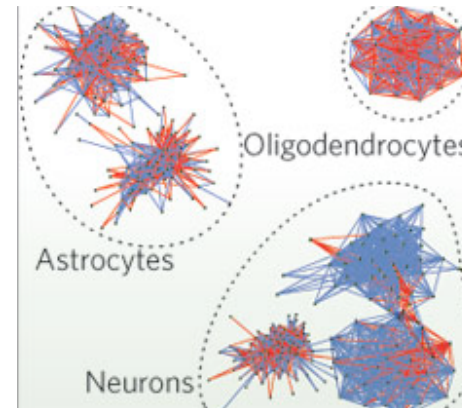
Overcoming or leveraging biological variability

Differential expression



Overcoming technical and biological variability
(size and similarity)

Network biology



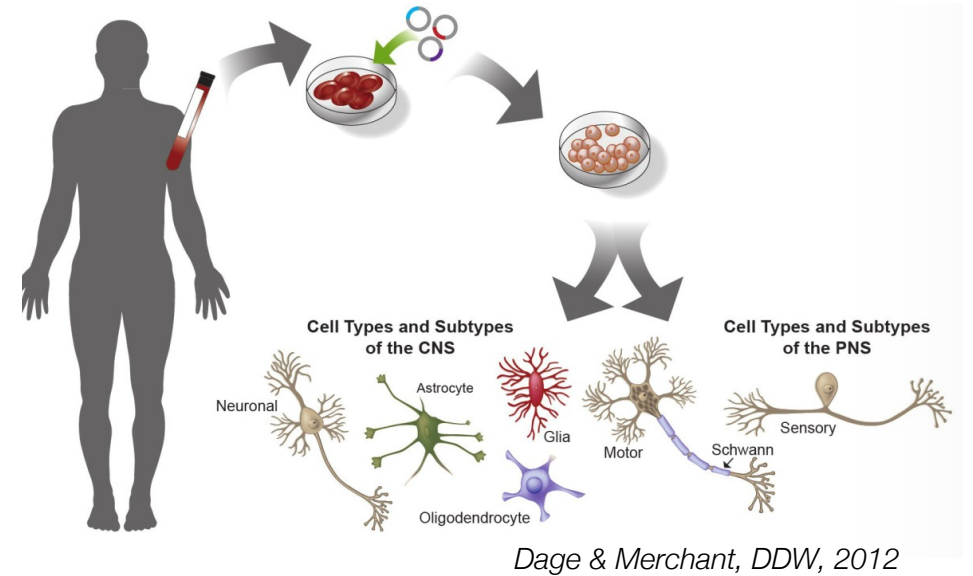
Geschwind and Konopka 2009



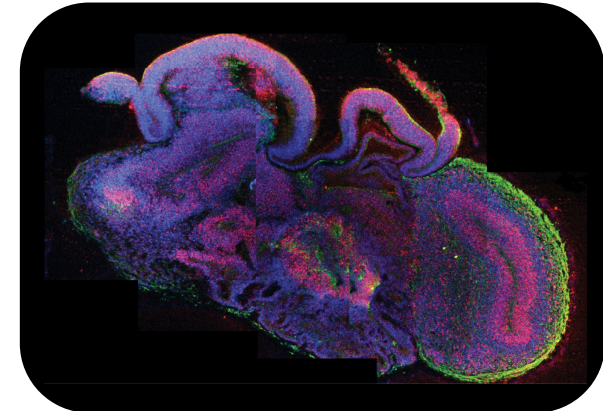
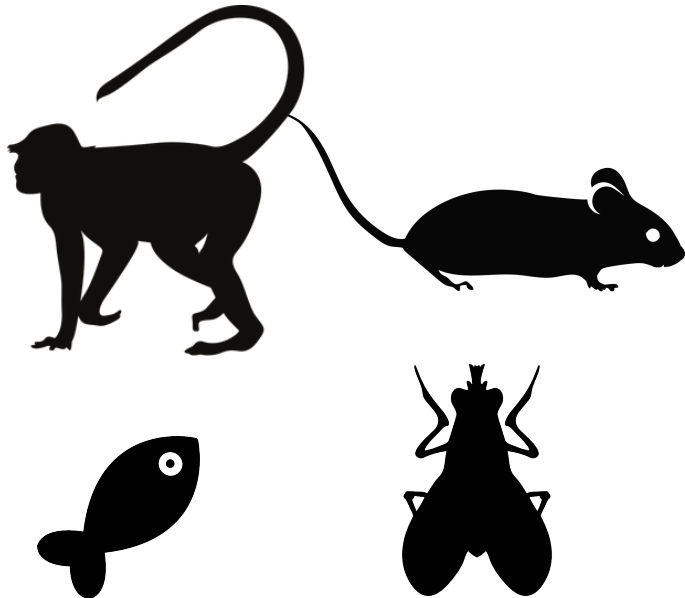
Leveraging biological variability

Observation -> experimentation

Human-specific aspects:
IPSCs – cell culture – 3D organoids



Mechanistic animal models



The search of biological mechanisms:

- Larger data sets needed - unknown effect size.
- Maximize controlled biological variability (genetic diversity)
 - Key to understand this diversity
- Minimizing or measuring other variability
 - Detailed clinical and life history measurements
 - Decreasing technical variability (multiplexing and measuring)
- Mechanistic animal/cell models

