# Multi-modal analysis of psychiatric disorders in the human cortex on a cell-type level

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## 1 Research Goals

The project aims to identify **key genes and regulatory elements** that drive **psychiatric disorders** in cortical cell types of the human brain. We are analyzing and integrating cell type specific **differential expression and chromatin accessibility** patterns between cases and controls. Furthermore, we are interested in dysregulations related to the **genetic risk for psychiatric disorders**.

## 2 Data

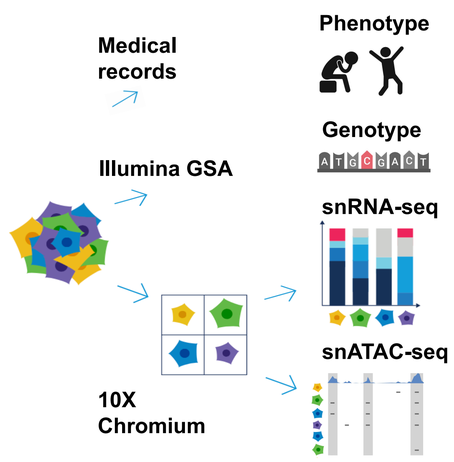



***Figure 1:*** *Overview of data modalities*

***Table 1:*** *Overview of cohort*

| | Controls (n=35) | Cases (n=57) |
|---|---|---|
| Diagnoses | - | SCZ (38), SCA (7), MDD (7), BIP (5) |
| Sex | 13f/22m | 22f/35m |
| Age (mean ± s.e.m) | 55.8 ± 2.3 | 53.3 ± 1.8 |
| PMI (h) (mean ± s.e.m) | 31.8 ± 1.9 | 35.2 ± 2.2 |
| pH (mean ± s.e.m) | 6.66 ± 0.04 | 6.57 ± 0.03 |
| Cause of death | Accident (1), Natural (33), Unknown (1) | Accident (3), Natural (36), Suicide (16), Unknown (2) |

The dataset contains **phenotype**, **genotype**, single nuclei transcriptomic (**snRNA-seq**) and open chromatin (**snATAC-seq**) data from the **postmortem orbitofrontal cortex** tissue of **92 donors**.

## 3 Methods

- Calculation of **polygenic risk scores (PRS)** with PRS-CS[1] for multiple psychiatric and stress-related disorders
- Demultiplexing and **alignment** with *CellRanger*[2]
- **Downsampling** of reads with *DropletUtils*[3]
- **Processing of snRNA-seq** data with *Scanpy*[4], *DoubletDetection*[5], *sctransform*[6] and *scArches*[7]
- **Processing of snATAC-seq** data with *ArchR*[8]
- Cell-type label transfer with data from *Allen Brain Atlas*[9] as **reference data** and manual refinement
- **Differential analysis** with *DESeq2*[10] on pseudobulk data
- **Enrichment analysis** with *clusterProfiler*[11]

## 4 Gene expression and chromatin accessibility at the resolution of single cells

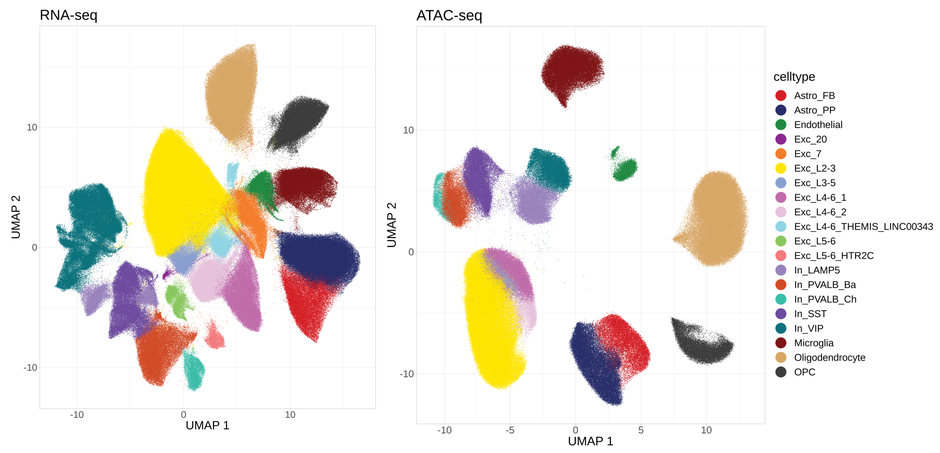



***Figure 2:*** *UMAP representation of snRNA-seq and snATAC-seq data.*

The **snRNA-seq data** consists of gene expression values for **26.195 genes** across **813.095 cells** originating from 87 individuals. Cells were assigned to **18 distinct cell types** that cover the major cell types of the prefrontal cortex and the different neuronal layers.

The **snATAC-seq data** consists of fragments from accessible chromatin across **399.439 cells** originating from 90 donors. Cells were assigned to **15 distinct cell types** - neuronal subtypes present in the RNA-seq data are missing.

## 5 Differential gene expression between cases and controls

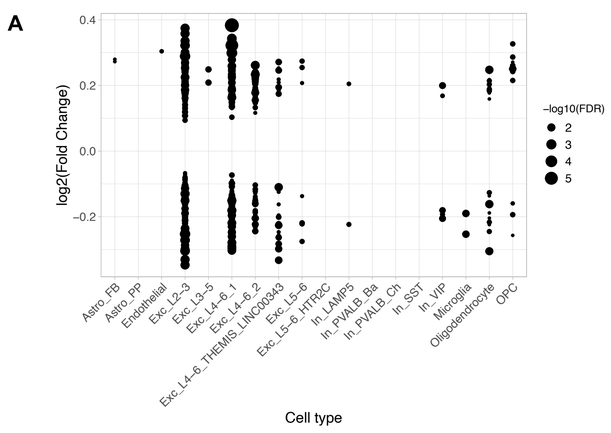
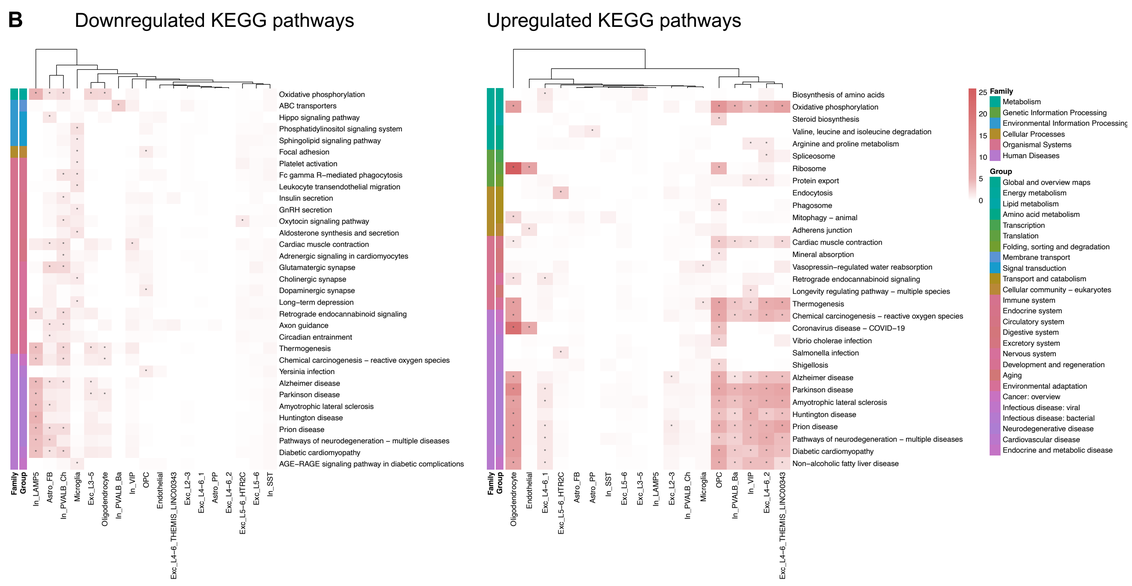


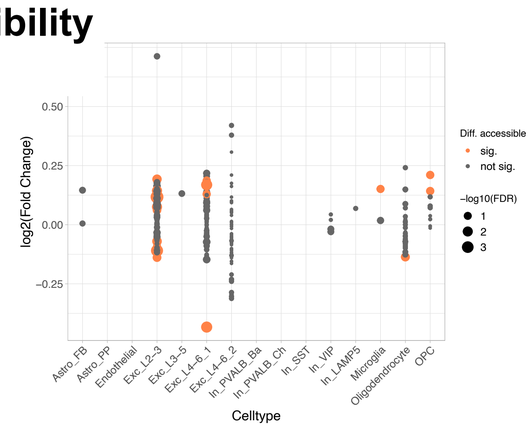

***Figure 3:*** *Differentially expressed (DE) genes across cortical cell types. A. DE genes plotted with fold change on y-axis and p-value indicated by dot size. B. KEGG pathways enriched for up- and downregulated genes in different cell types. Color scale represents the –log10-transformed FDR values. Annotation colors represent a grouping of pathways.*



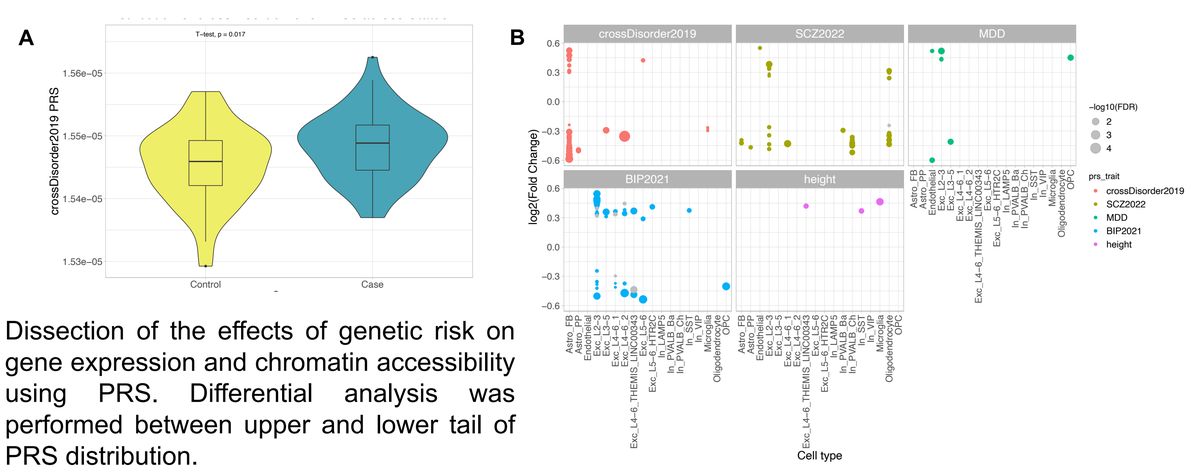

## 6 Differential chromatin accessibility between cases and controls

Analysis of differential accessibility (DA) was performed on gene scores[8] combining the chromatin accessibility of regulatory elements in the gene region.

***Figure 4:*** *Results of a DA analysis for genes identified as DE in cortical cell types. DA genes plotted with fold change on y-axis and p-value indicated by dot size. Color indicates the significance of DA in the respective cell type.*




## 7 Differential analysis between individuals with high and low polygenic risk




Dissection of the effects of genetic risk on gene expression and chromatin accessibility using PRS. Differential analysis was performed between upper and lower tail of PRS distribution.

***Figure 5:*** *Polygenic risk-modulated differential gene regulation. A. PRS based on Cross-Disorder GWAS study[12] for cases and controls. B. DE genes for PRS based on different GWAS studies[12,13,14,15,16]. C. Genome track visualizing the ATAC-seq signal in the region of INO80E – a DE and DA gene for schizophrenia PRS. Signal is shown separately for high and low PRS.*


## 8 Conclusion

- High number of DE genes between cases and controls in excitatory neurons across multiple layers and oligodendrocytes. DA detectable for only few of these genes.
- Upregulation of genes encoding ribosomal proteins in oligodendrocytes.
- Dysregulation of genes encoding key proteins for neurodegeneration.

## References

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