Multi-modal analysis of psychiatric disorders in the human cortex

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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 going to analyze and integrate cell type specific **differential expression and chromatin accessibility** patterns between cases and controls as well as between donors with high and low genetic risk for psychiatric disorders. Furthermore, we are interested in **allele-specific** regulatory and transcriptional effects and cell-type specific **gene regulatory networks**.

2 Data

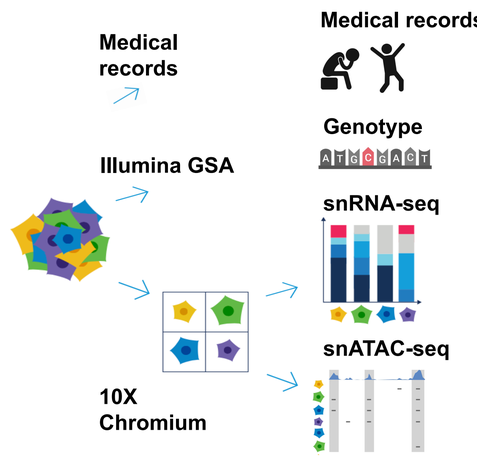


Figure 1: *Overview of data modalities*

Table 1: *Overview of cohort*

	Controls (n=35)	Cases (n=57)
Diagnoses	-	SCZ (38), SCA (7), MDD (7), BIP (5)
Sex	13 Female	22 Female
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] on multiple diseases and stress-related traits
- 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

4 Genetic risk for psychiatric diseases

Polygenic risk scores (PRS) calculated for multiple diseases and stress-related traits are **not always correlated with diagnoses** for psychiatric disorders. It is therefore important to not only **identify molecular differences** between cases and controls, but also individuals with **high and low genetic risk**.

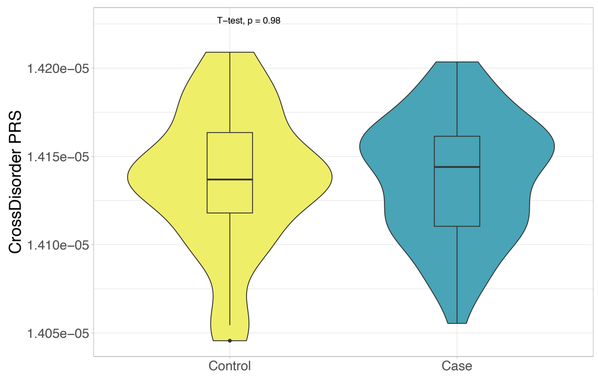


Figure 2: *Distribution of PRS based on cross disorder GWAS[11] for groups of controls and cases.*

5 Gene expression and chromatin accessibility at the resolution of single cells

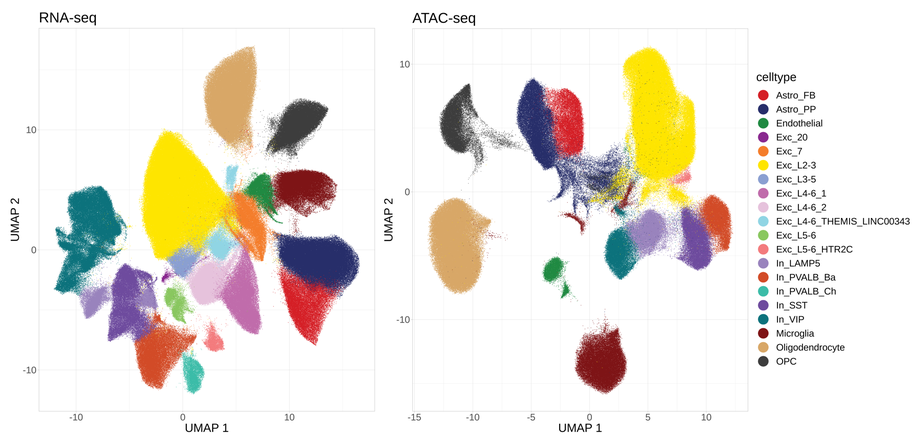


Figure 3: *UMAP representation of snRNA-seq and snATAC-seq data.*

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 **20 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 **459.678 cells** originating from 91. Cells were assigned to **12 distinct cell types** - neuronal subtypes present in the RNA-seq data are missing.

6 Differential gene expression between cases and controls

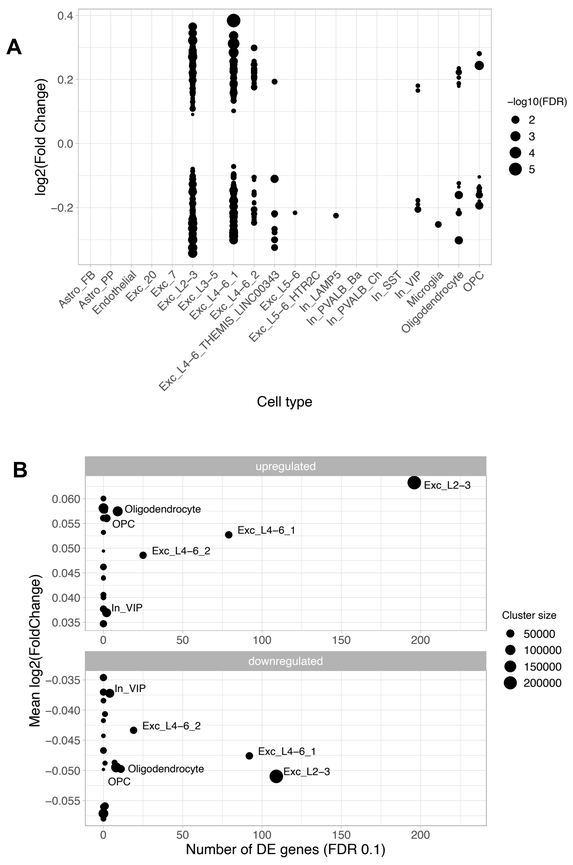
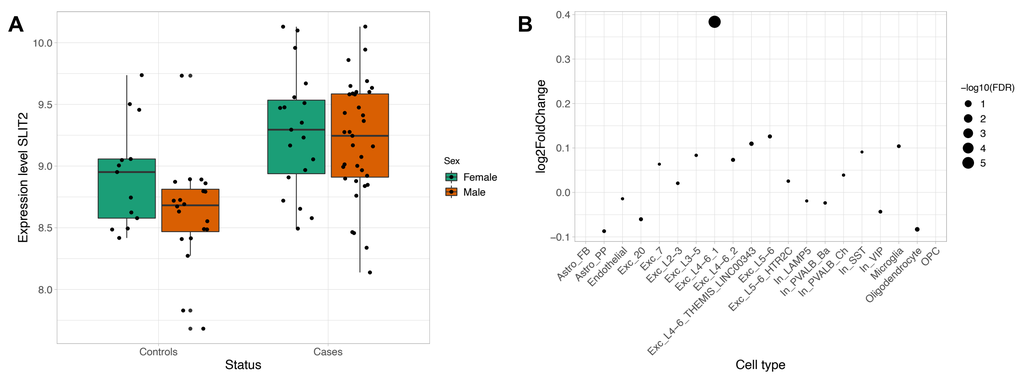


Figure 4: *Differentially expressed (DE) genes across cortical cell types. A. DE genes plotted with fold change on y-axis and p-value indicated by dot size. B. Mean fold change of all genes plotted against the number of DE genes per cell cluster. Dot size indicates cluster size.*

7 Upregulation of *Slit2* in deep layer excitatory neuron cluster



Slit2 is a glycoprotein of the Slit family that plays a highly conserved role in axon guidance and neuronal migration. It was previously shown that *Slit2* overexpression causes depression-/anxiety-like behaviour in adult mice[12]. *Slit2* is one of the genes with the strongest differential expression in the Exc_L4-6_1 cluster.

Figure 5: *Upregulation of Slit2 gene in deep layer excitatory neuron cluster. A. Expression levels of Slit2 in cases and controls. Colour indicates sex of donor. B. Fold Change of Slit2 per cell type.*

8 Outlook

The analyses plan include the **differential analysis of gene expression and chromatin accessibility** between cases and controls and genetic risk exposures. We are planning to analyze allele specific effects in the different cell types. **Gene regulatory networks** will be inferred for the different cortical cell types.

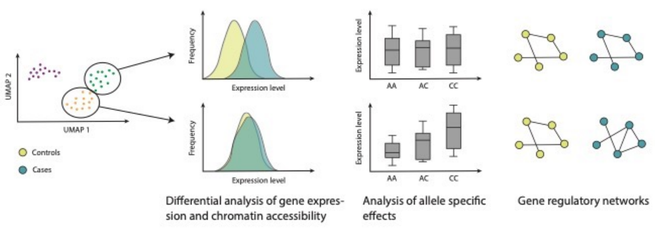


Figure 6: *Analyses steps planned to perform.*

References

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