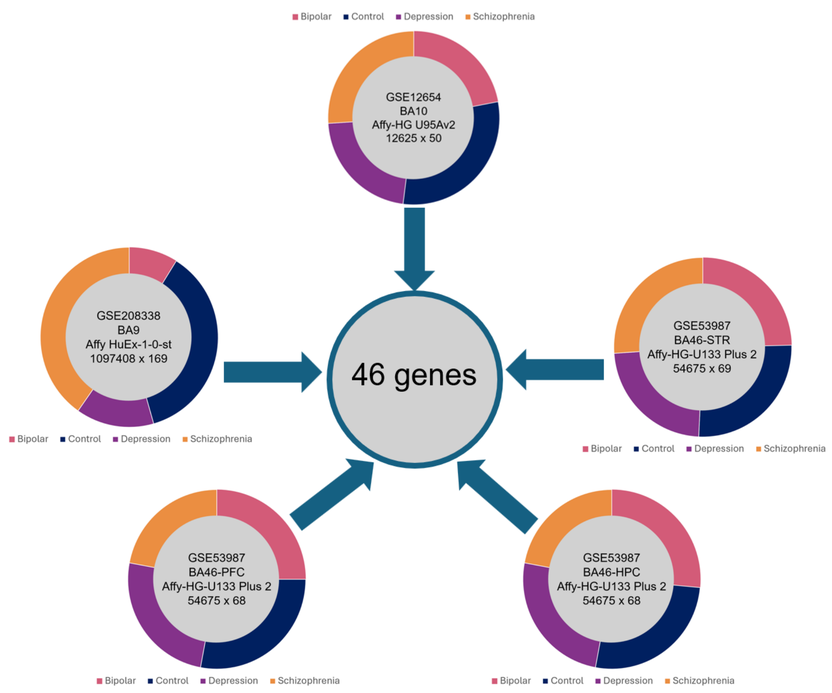
Differential gene expression analysis across several brain regions in subjects affected by mental disorders: bipolar disorder, depression and schizophrenia

Rayan Slatni, Mario Lauria

Department of Cellular, Computational and Integrative Biology, University of trento

Contacts: rayan.slatni@studenti.unitn.it

Datasets from GEO Omnibus



BA 10: risk and decision making, odor evaluation, reward and conflict, pain, and working memory

BA 9: motor planning, organization, and regulation, and sustaining attention and working memory

DLPFC: sustaining attention and managing working memory, and regulate self-control

HPC: integrates memories formed in temporal proximity

STR: integrates memories formed in the same space

Pipeline in R

Datasets retrieved from GEO Omnibus

↓

Log2 transformation and normalization by housekeeping gene GAPDH

↓

Row pairwise T-test to look at differences in gene expression across 4 groups ($p < 0.001$)

↓

Split data into trainining (80%) and validation set (20%) to apply supervised learning (LDA, RF)

↓

Model evaluation and selection of first 200 genes for each group according to model importance

↓

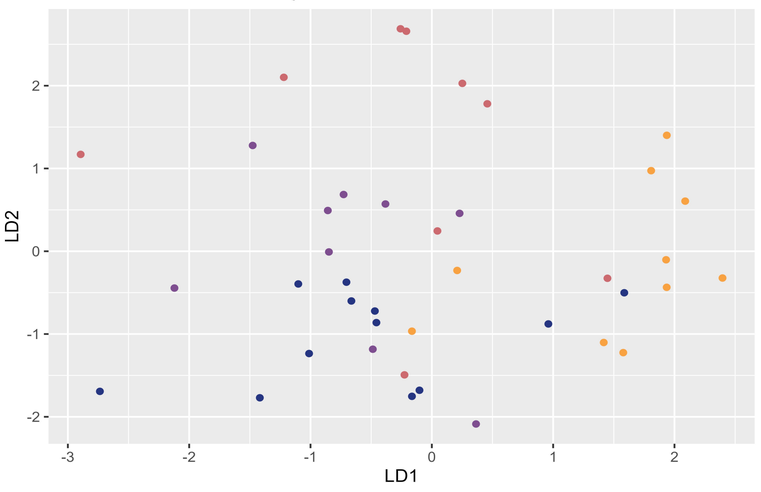
Selection of genes up or downregulated (logFC =1) in at least 3 groups comparison

↓

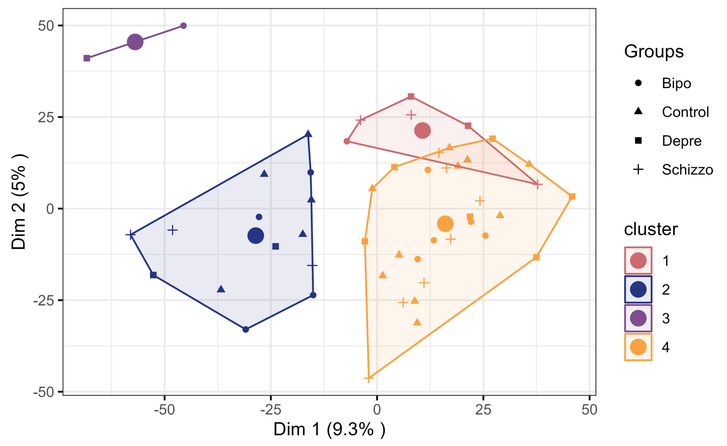
Enrichment pathway analysis using g:profiler (Bonferroni correction)

Method selection

Linear Discriminant Analysis



K-mean



Supervised learing like LDA gives better results respect to unsupervised methods.

Pathways results

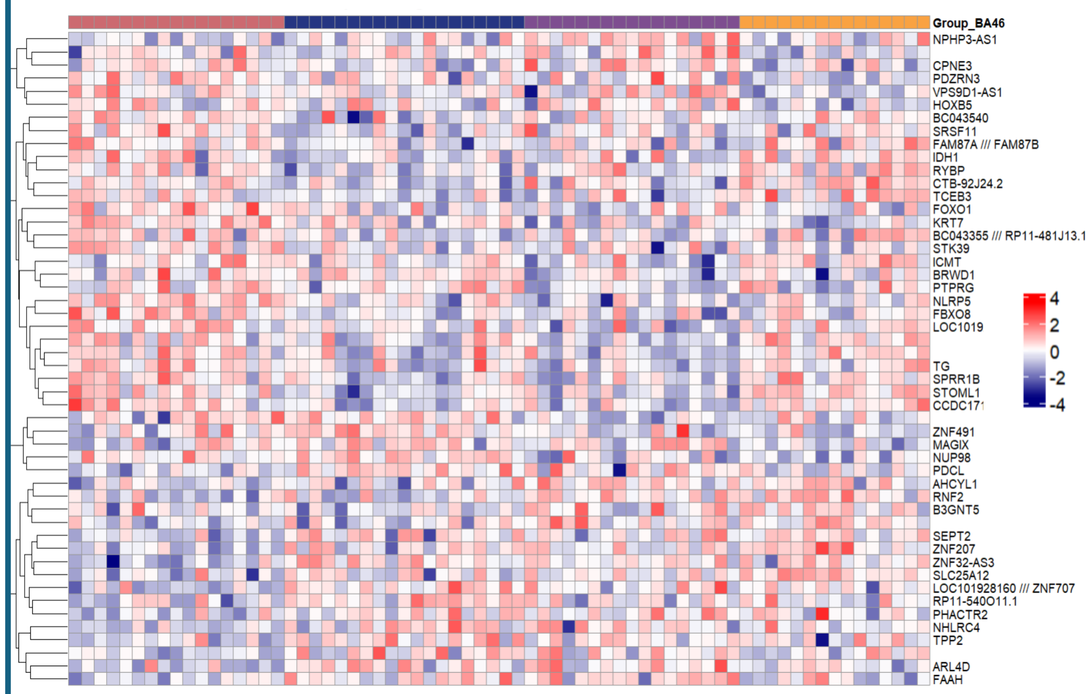
Pathway GO:BP	P Value	Genes Driving Pathway
Intracellular signal transduction	2.000×10^{-5}	RALGAPA2, DDIT4, MARVELD3, RAB21, ETAA1, PPP2R5C, NUCB2, TP53BP1, DDKA, MAST4, PARK2, FZR1
Response to stress	1.885×10^{-4}	IL4, SCL2A1, SNAP23, DDIT4, MARVELD3, ANKFN1, ETAA1, PPP2R5C, TP53BP1, FZR1, STAT5B
Positive regulation of B cell activation	6.167×10^{-4}	IL4, SLC39A10, SLC36A1, PPP2R5C
Cell death	1.024×10^{-3}	IL4, SLC39A10, HINT2, DDIT4, C6orf120, PPP2R5C, NUCB2, PARK2, STAT5B, TIMM50
DNA damage checkpoint signaling	3.490×10^{-3}	ETAA1, PPP2R5C, TP53BP1, FZR1
Intrinsic apoptotic signaling pathway by p53 class mediated	4.879×10^{-2}	DDIT4, PPP2R5C, PARK2

Table 1: GO:BP pathways considering all the most significant DEGs across all 5 datasets

The pathways related to stress, DNA damage and cell death result to be alterated in mental disorders. For example the gene **ANKFN1** plays a role in Mek1-2/Erk signalling, and is linked to mania symptoms in BD. **DDIT4** influence many pathways and is responsible to negative regulation of mTOR signalling and result to be up regulated in SCZ.

Differentially expressed genes

Heatmap of DEGs in BA46 prefrontal cortex



HINT2-3 are already linked to SCZ, in fact down-regulation disturb the post-pre dopaminergic synapse at the level of striatum and nucleus accumbes. **HINT1** is not linked to SCZ, but is over expressed in the thalamus and lower expressed in the DLPFC.

ANKFN1 is linked to mania symptoms in BD, cannabis addiction (DRD2), memory, hyperactivity. In hepato-carcinoma induce the transition G1/S by activating Mek1-2/Erk signalling, leading to proliferation/apoptosis.

List of DEGs for SCZ compared to BD and MDD

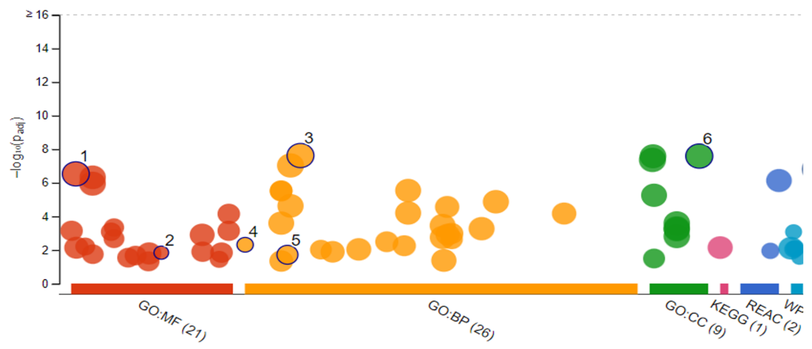
Brain area	Gene symbol	Gene name	BS	CS	SD
BA10	CDX2	Caudal-Type Homeobox Protein 2	↑	↑	↓
	PTPN9	Protein Tyrosine Phosphatase Non-Receptor Type 9	↓	↓	↑
Striatum	ANKFN1	Ankyrin Repeat And Fibronectin Type III Domain Containing 1	↓	↓	↑
	C6orf120	Chromosome 6 Open Reading Frame 120	↑	↑	↓
	FOXN3-AS1	FOXN3 Antisense RNA 1	↓	↓	↑
	ZNF788	Zinc Finger Family Member 788, Pseudogene	↓	↓	↑
Hippocampus	C21orf59	Cilia And Flagella Associated Protein 298	↑	↑	↓
	SLC39A10	Solute Carrier Family 39 Member 10	↓	↑	↓
	RALGAPA2	Ral GTPase Activating Protein Catalytic Subunit Alpha 2	↑	↓	↓
	HINT2	Histidine Triad Nucleotide Binding Protein 2	↑	↑	↓
	DDIT4	DNA Damage Inducible Transcript 4	↓	↓	↑

Table 1: Log2 Foldchange represented with up or down arrows of the most significant genes with three comparison: BS bipolar vs schizophrenia, CS control vs schizophrenia, SD schizophrenia vs depression

The gene **C1orf59** is a methyl tranferase, might be linked to SCZ but no evidence. DNA metilation (e.g. BDNF) is already linked to depression. **PTPN9** promotes cell proliferation in KO mice model, the family member PTPN3 is linked to SCZ, but PTPTN9 not yet. KO mice for **C6orf120** present high level of Treg, but no evidence in mental disease.

FOXN3-AS1 if over-expressed inhibit the activation of Akt/ MDM2/p53, this gene is down-regulated in glioma and there are evidence of less susceptibility to glioma for SCZ.

Highlight the pathways involved in DEGs comparing BD and SCZ



ID	Source	Term ID	Term Name	p_{adj} (query_1)
3	GO:BP	GO:0009987	cellular process	2.388×10^{-8}
6	GO:CC	GO:0110165	cellular anatomical entity	2.576×10^{-8}
1	GO:MF	GO:0003674	molecular_function	2.957×10^{-7}
4	GO:BP	GO:0000041	transition metal ion transport	4.939×10^{-3}
2	GO:MF	GO:0046915	transition metal ion transmembrane transporter ac...	1.456×10^{-2}
5	GO:BP	GO:0007417	central nervous system development	1.941×10^{-2}

Among the genes DE in the pathway between BD and SCZ are relevant the genes of solute carrier family. For example **SLC39A10** is known to be up-regulated in DLPFC in SCZ, but in the HPC is down-regulated.