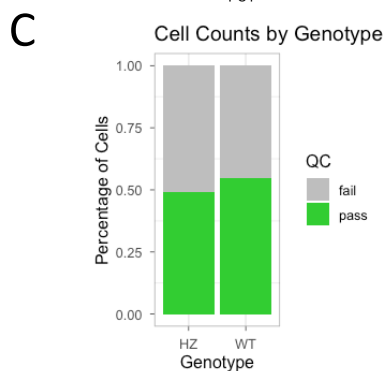
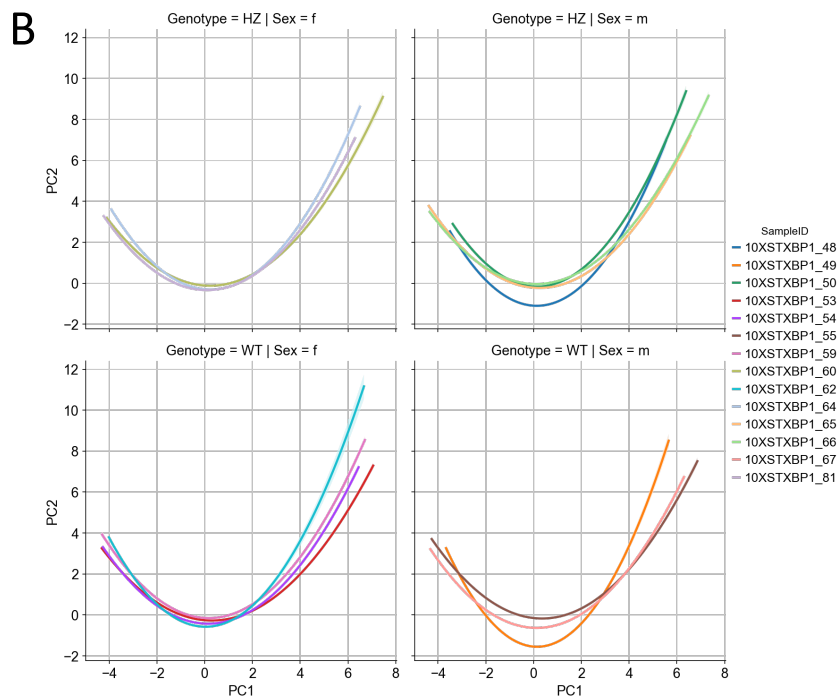
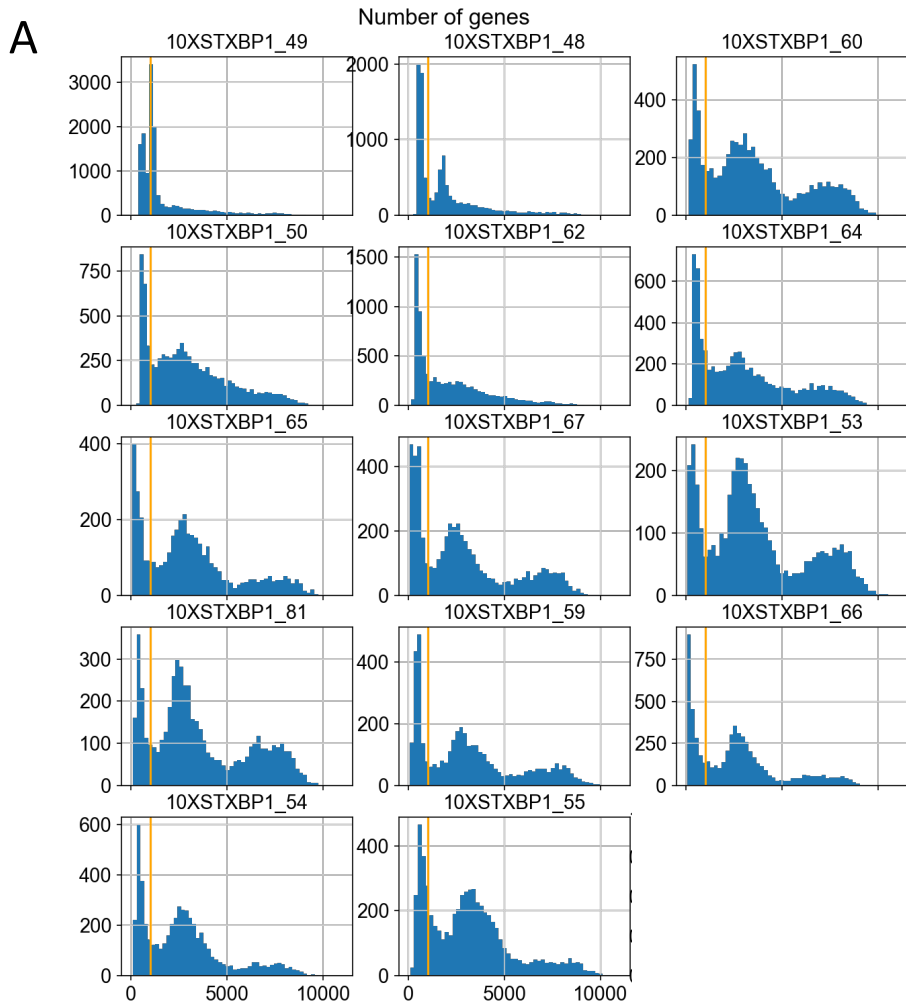
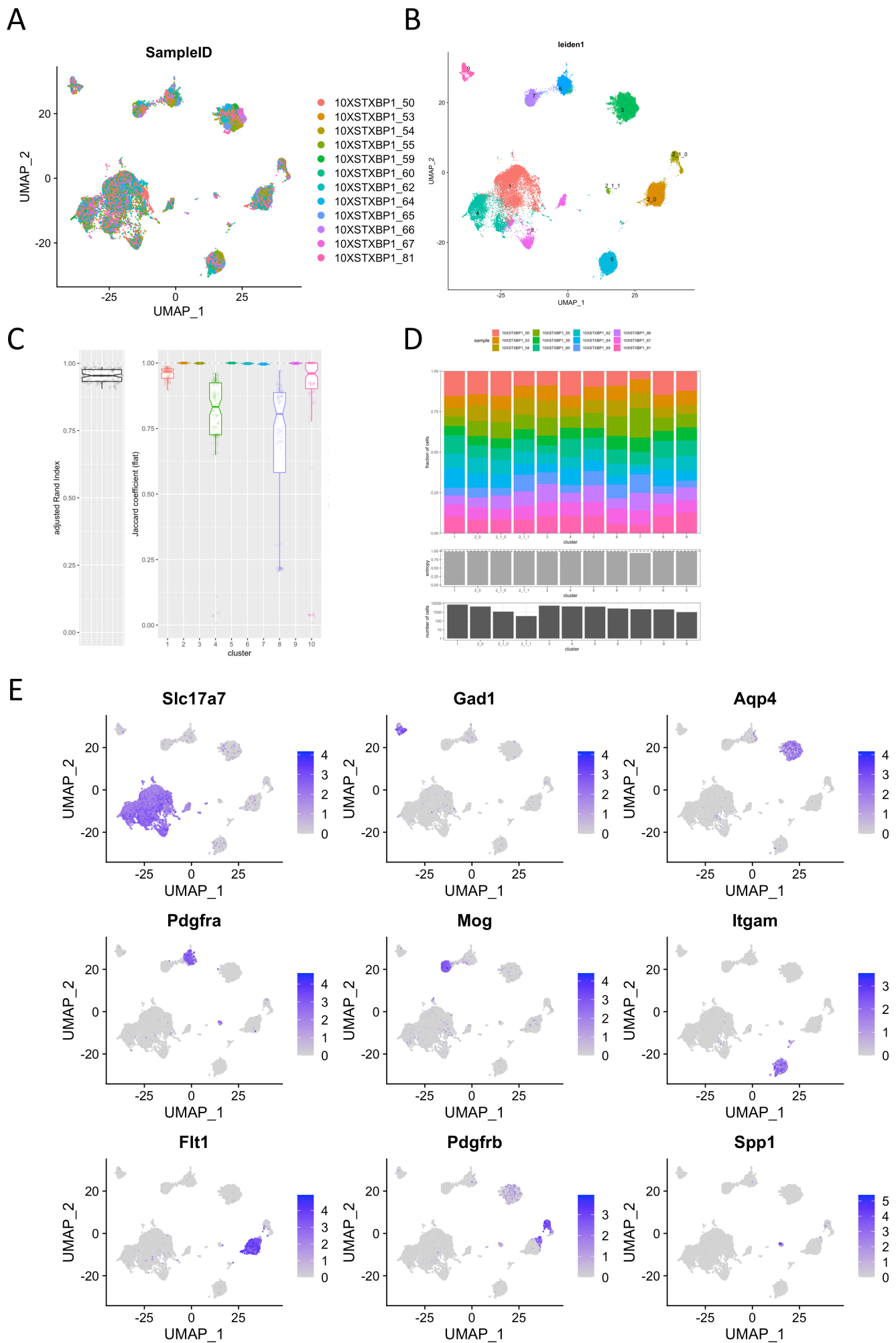


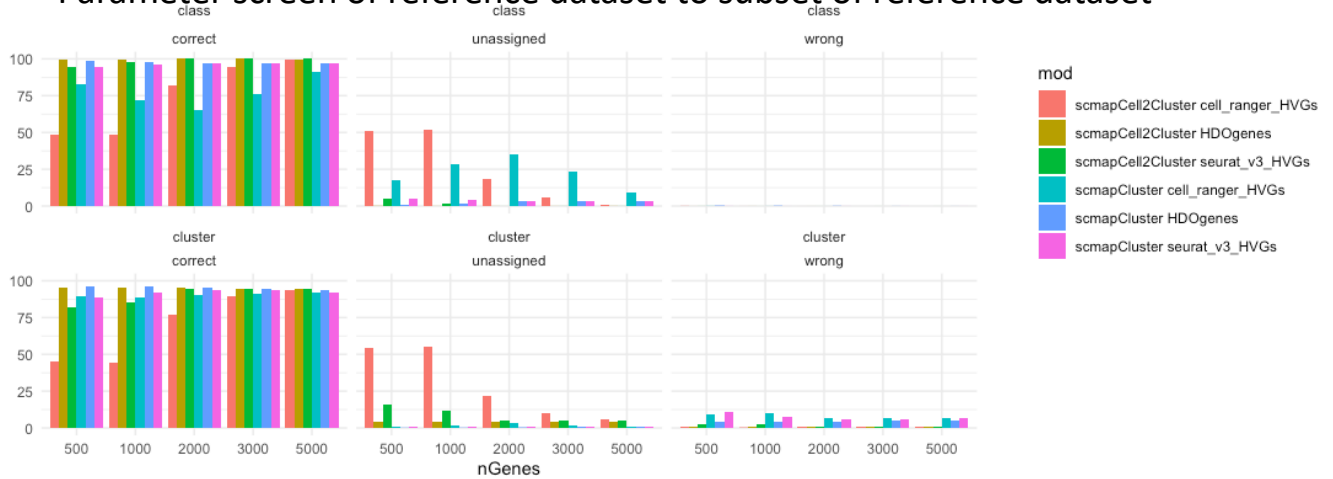


Supplementary Figure 1. Quality control metrics. (A) Histogram of the number of genes detected by cell per sample. (B) PCA of all quality metrics per sample showing two samples overall deviating from the group. (C) Percentage of cells passing QC filters per genotype.

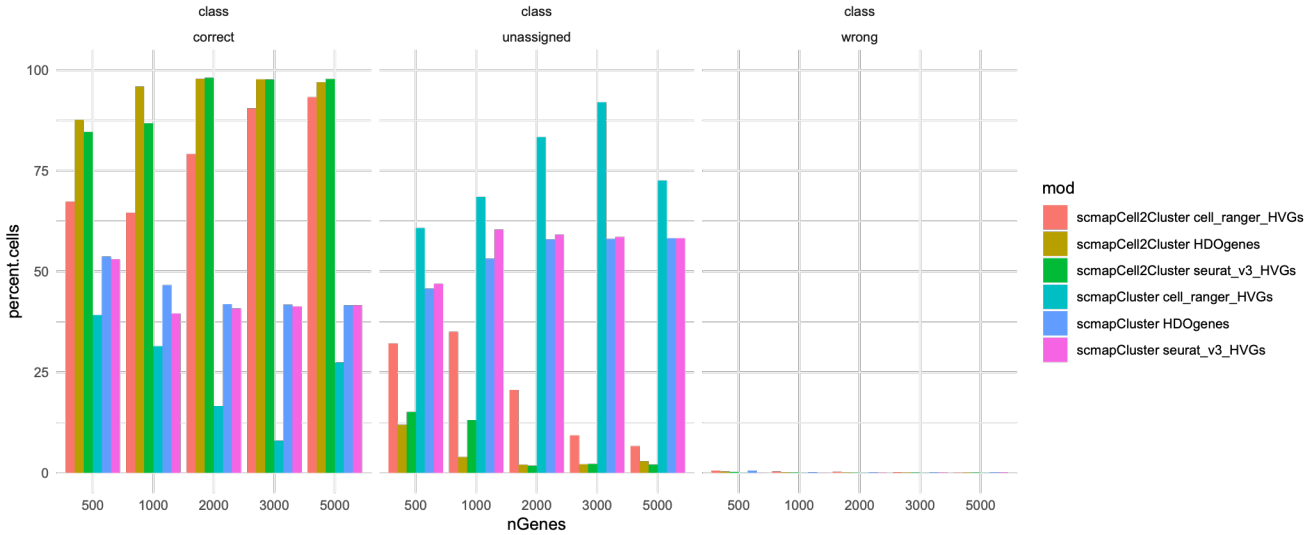


Supplementary Figure 2. Cell class clustering and annotation. (A) UMAP of cell class clustering color-coded by Sample ID. (B) UMAP of cell class clustering color-coded by conos clusters. (C) Stability metrics of defined clusters. (D) Fraction of cells per sample in each cluster. (E) Canonical gene markers to determine cluster annotations.

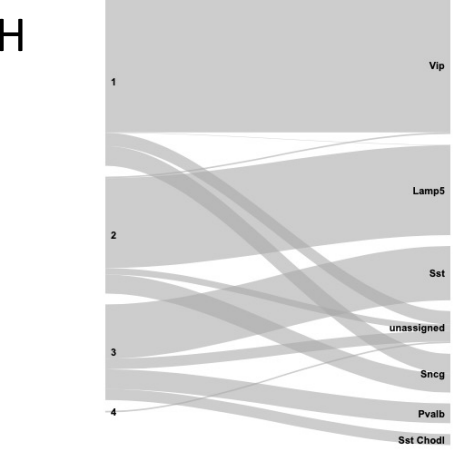
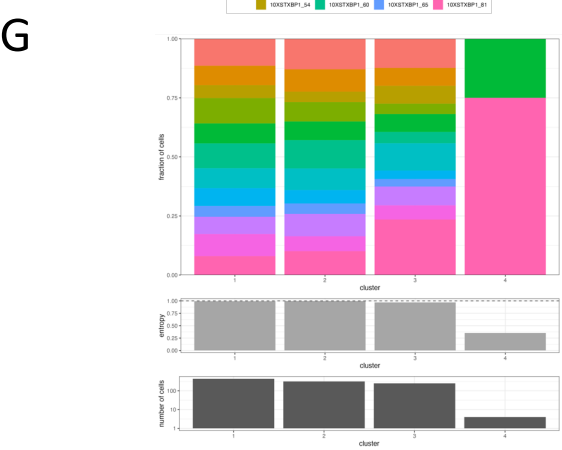
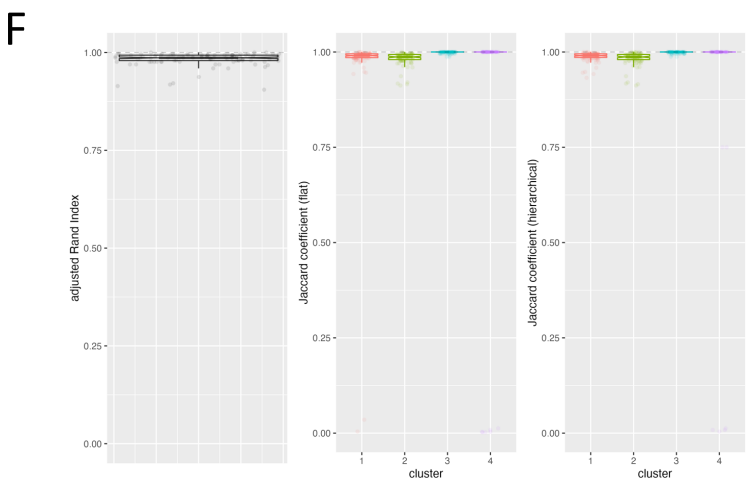
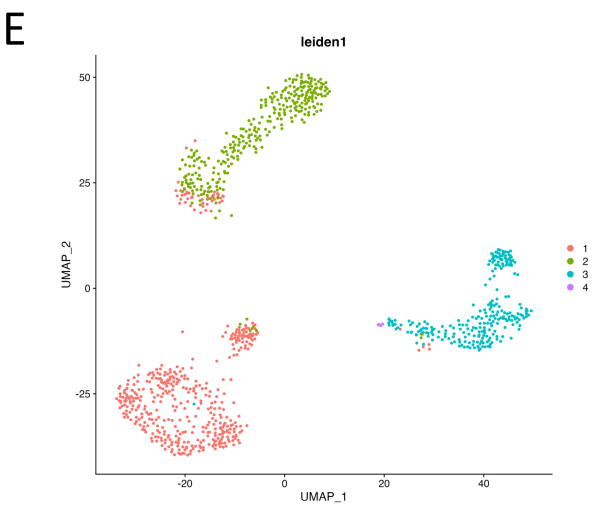
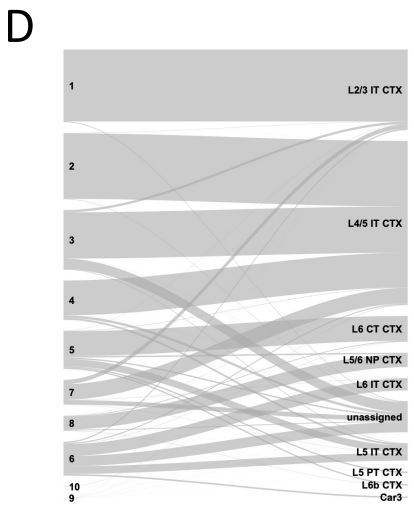
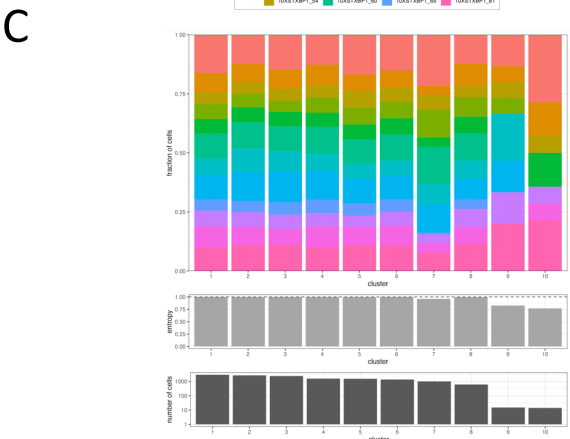
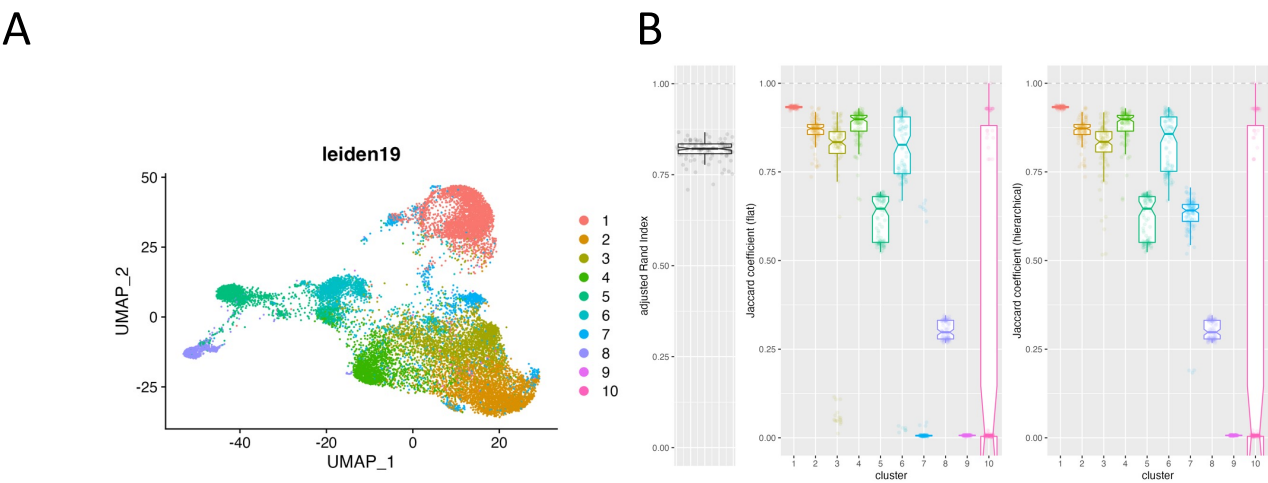
A Parameter screen of reference dataset to subset of reference dataset

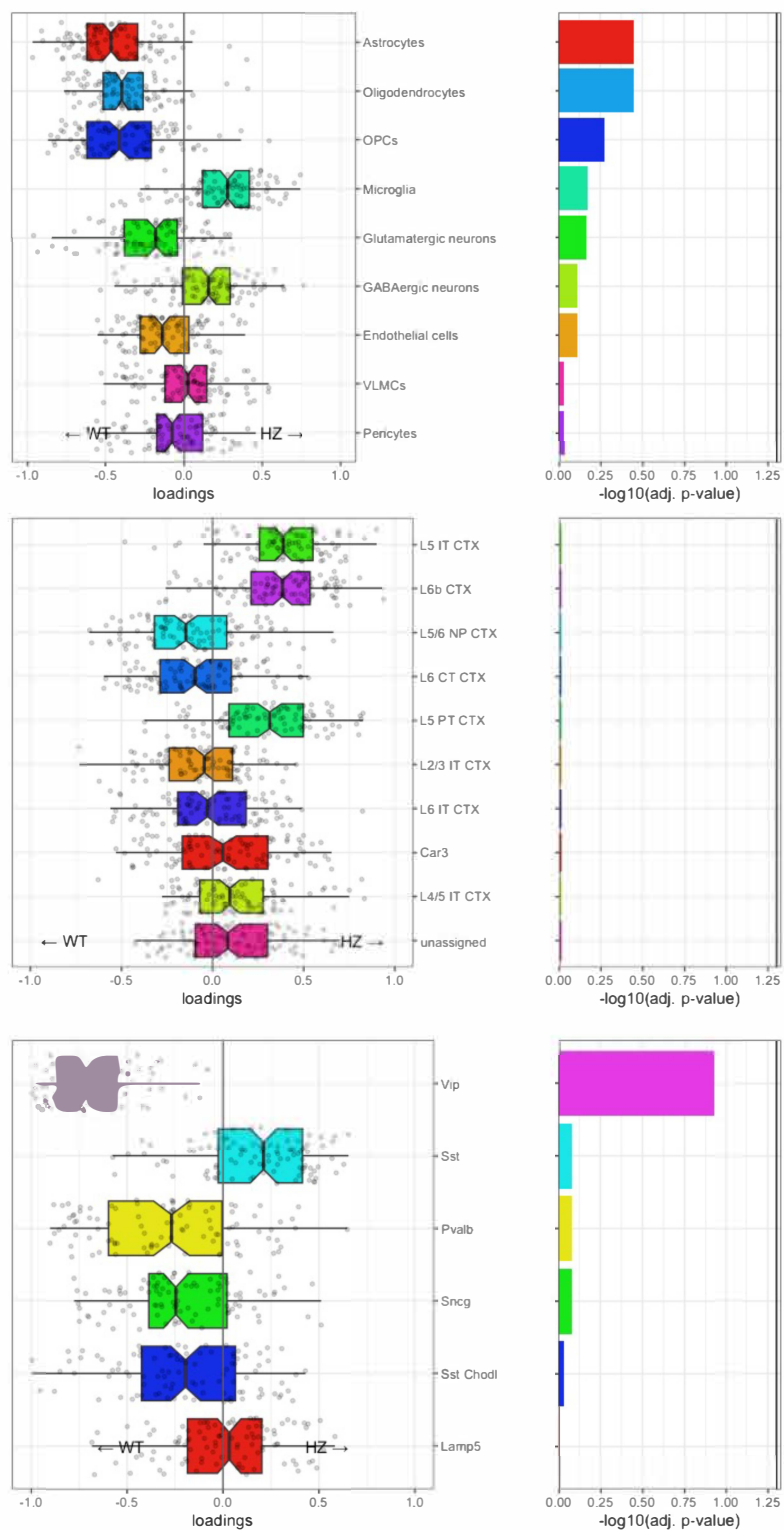


B Parameter screen of our dataset cell classes with reference dataset

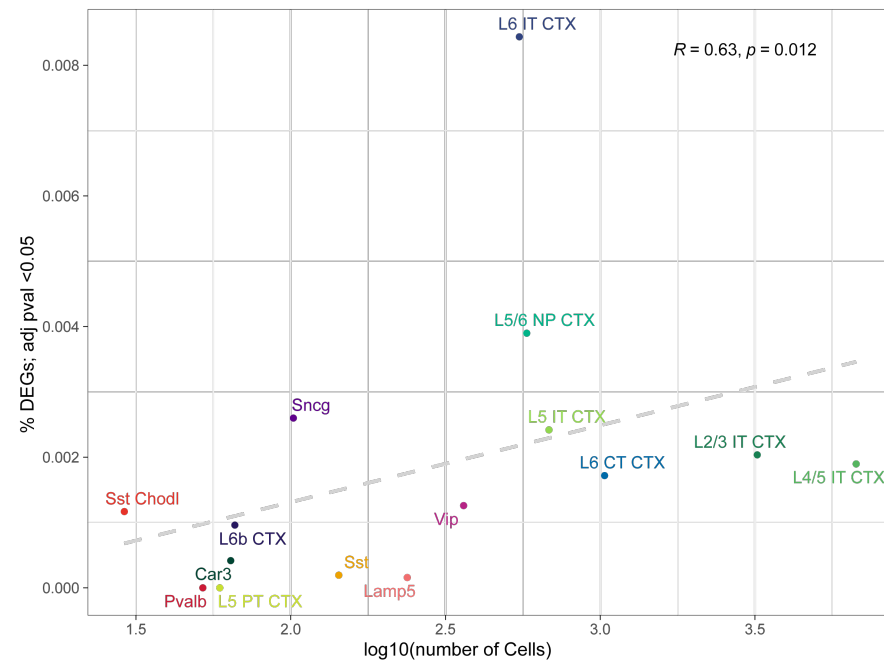
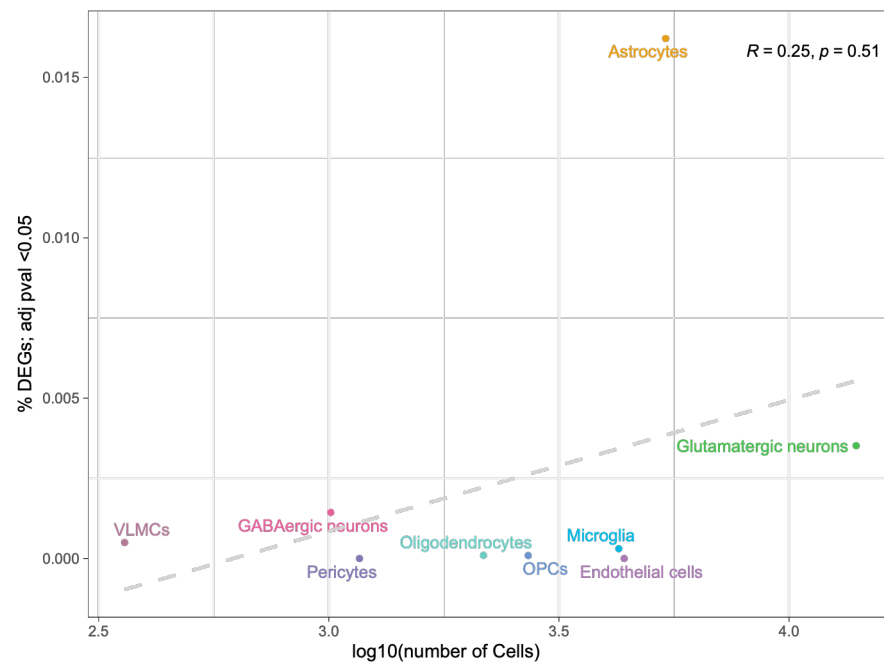


Supplementary Figure 3. Scmap parameter screen for neuronal type annotation to reference. (A) Parameter screen of reference dataset to annotate a subset of the same dataset. (B) Parameter screen of our dataset annotating cell classes to the reference Allen Mouse Brain dataset.

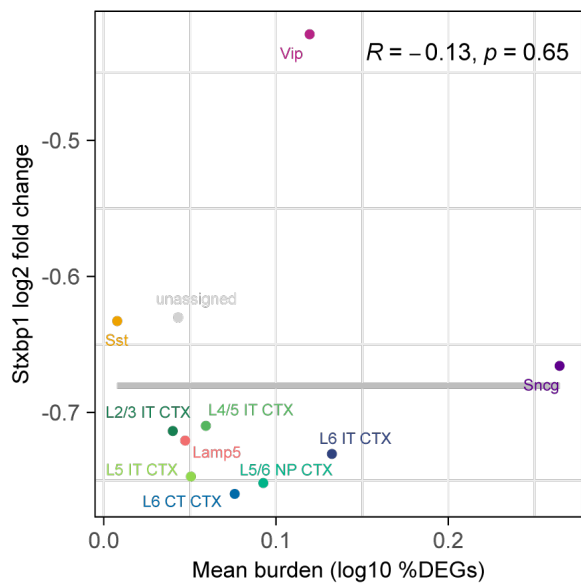
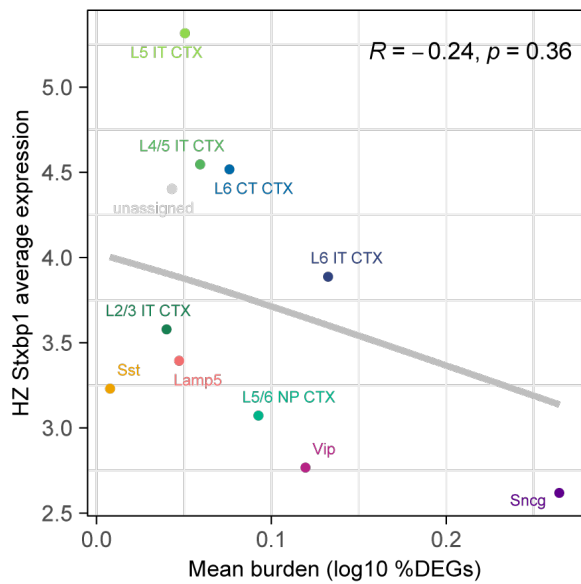
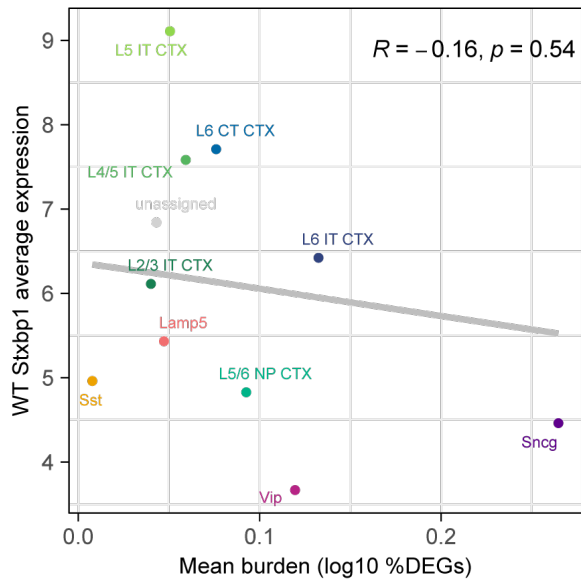




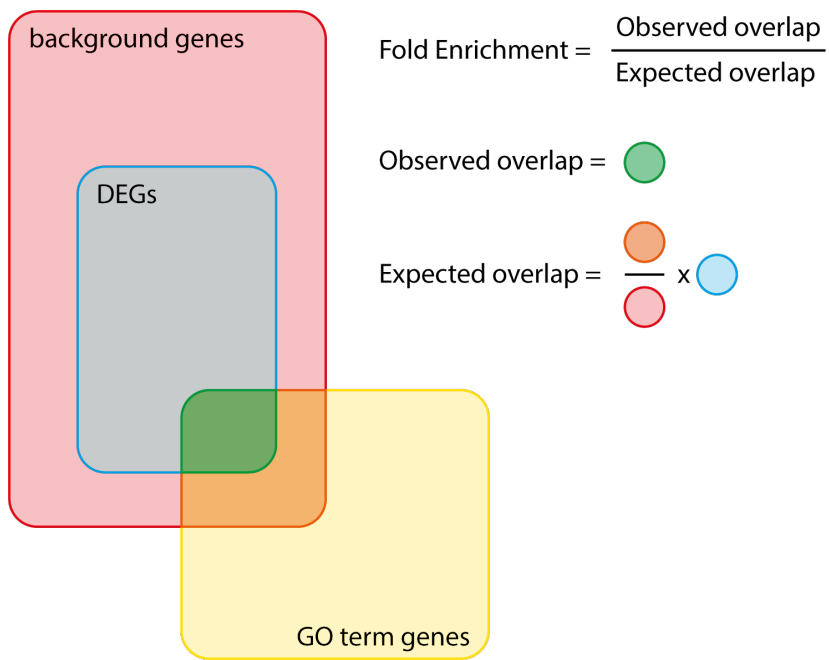
Supplementary Figure 5. Cacao cell type abundance test. Cell type abundance shifts between *Stxbp1*^{+/+} and *Stxbp1*^{+/-} mice (left) and significance values (right) as calculated with the cacao algorithm.



Supplementary Figure 6. Number of cells correlates to percentage of DEGs detected per cell class (top) and neuronal type (bottom).

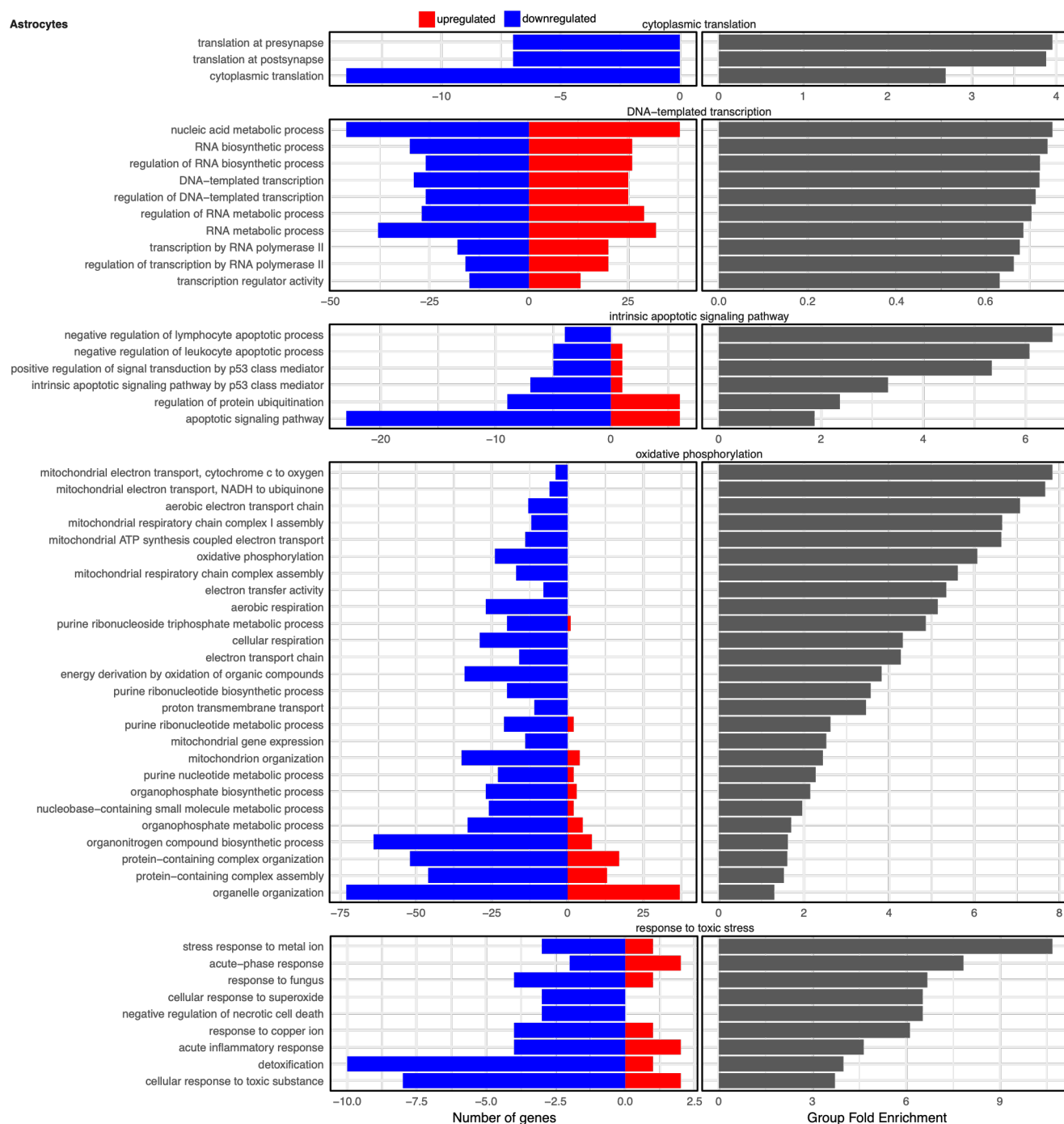


Supplementary Figure 7. Burden analysis does not correlate to Stxbp1 expression of fold change between wild type and Stxbp1^{+/-} conditions.

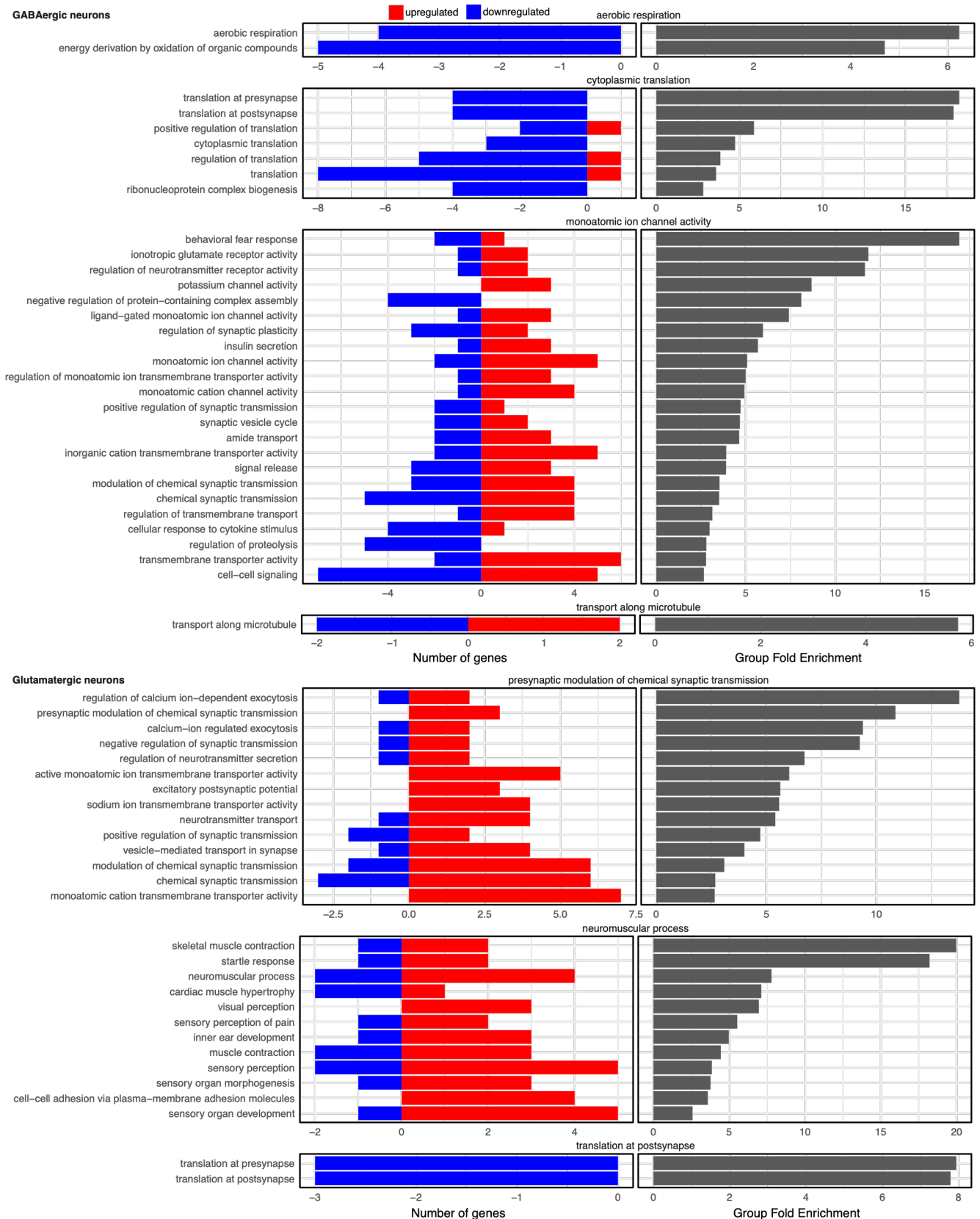


Supplementary Figure 8. Schematic of fold enrichment calculation

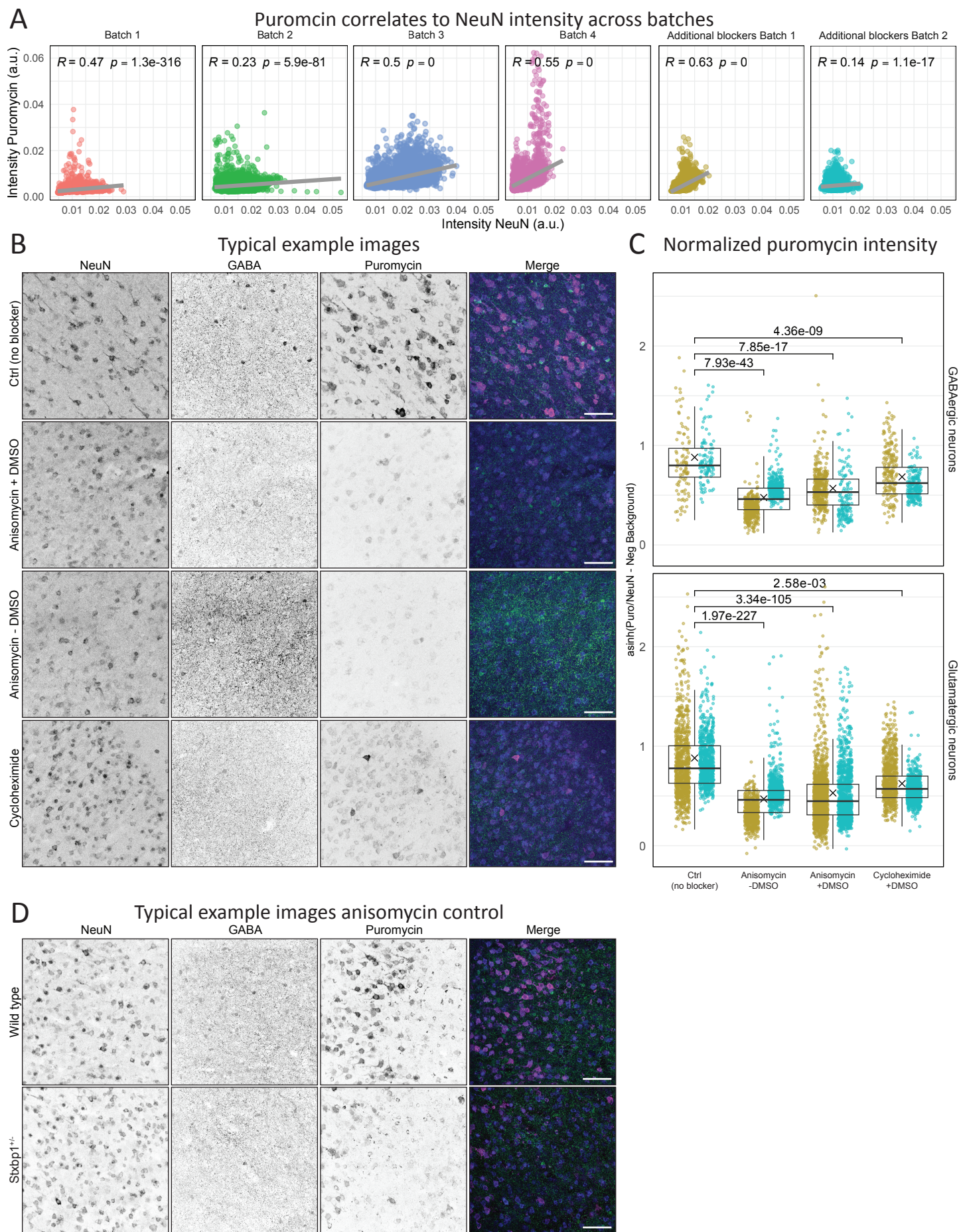
Astrocytes



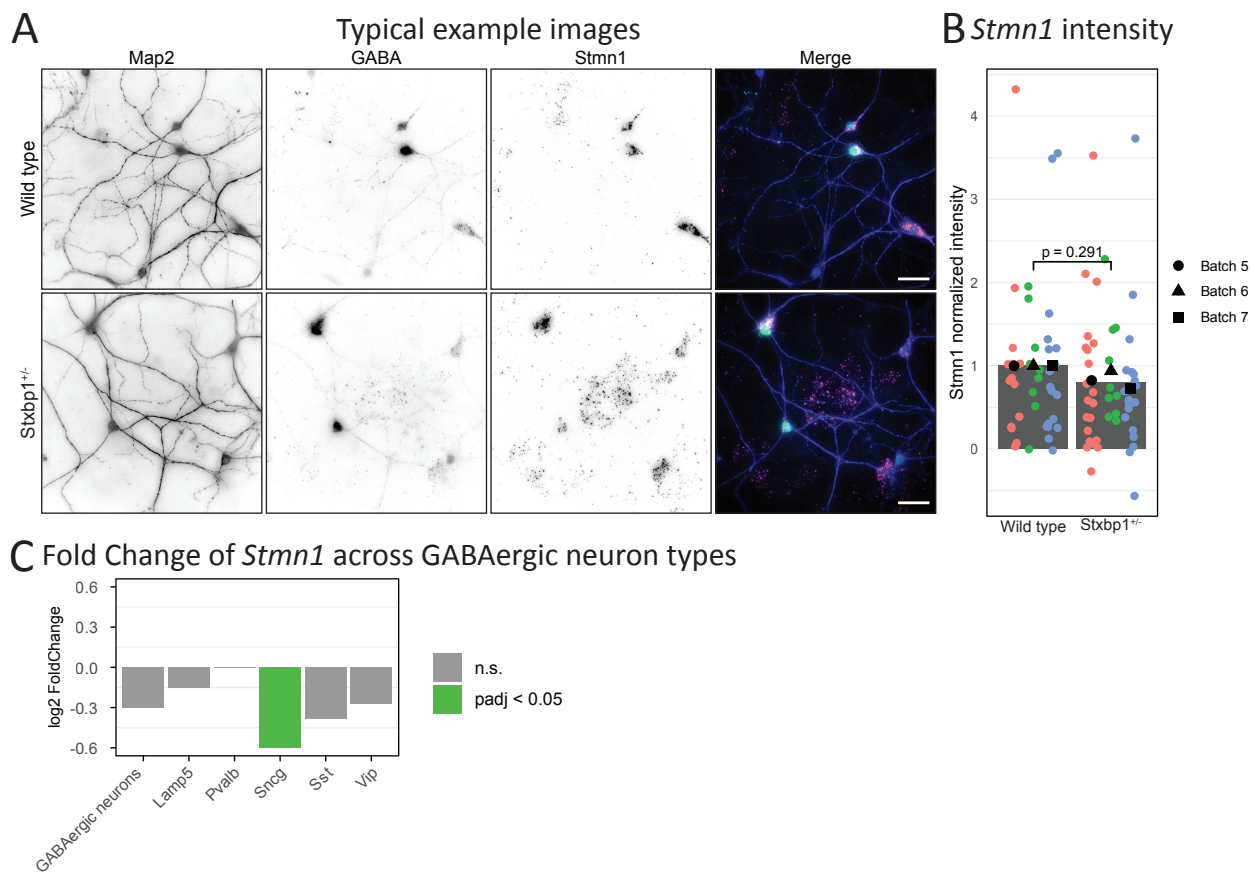
Supplementary Figure 9. Astrocytes GO terms gene count (left) and fold enrichment (right)



Supplementary Figure 10. Neuronal class GO terms gene count (left) and fold enrichment (right)



Supplementary Figure 11. SUNSET puromycin assay. (A) Scatter plot showing correlation between NeuN and Puromycin intensity across batches. (B) Typical example images from additional translation blocker combinations. (C) Representative images of SSp from wild type mice brain slices stained for NeuN (blue), GABA (green) and Puromycin (magenta). Scale bar = 200 μ m. (D) Quantification of puromycin intensity per condition. Normalized to the wild type



Supplementary Figure 12. *Stmn1* smFISH in cultured cortical neurons. (A) Representative images of cortical neurons from wild type and *Stxbp1*^{+/-} mice stained for Map2 (blue), GABA (green) and *Stmn1* mRNA smFISH (magenta). Scale bar = 100 μ m. (B) Quantification of *Stmn1* intensity per cell normalized to the corresponding batch wild type. (C) Log2 Fold Change of *Stmn1* mRNA as measured in the scRNA-seq dataset in all GABAergic neurons and corresponding GABAergic cell types.

L 2/3 IT CTX

upregulated
downregulated

cellular response to cytokine stimulus

inner ear development

cellular response to cytokines

inner ear development

synaptic transmission

response to cocaine

presynaptic modulation of chemical synaptic transmission

acidic amino acid transport

negative regulation of synaptic transmission

regulation of neurotransmitter secretion

dicarboxylic acid transport

regulation of amine transport

neurotransmitter transport

active monoatomic ion transmembrane transporter activity

regulated exocytosis

sodium ion transmembrane transporter activity

calcium ion homeostasis

calcium-mediated signaling

sodium ion transport

regulation of exocytosis

organic anion transport

vesicle-mediated transport in synapse

modulation of chemical synaptic transmission

calcium ion transmembrane transport

monoatomic cation channel activity

monoatomic cation homeostasis

signal release

learning or memory

metal ion transmembrane transporter activity

monoatomic cation transmembrane transporter activity

synaptic signaling

chemical synaptic transmission

protein secretion

regulation of synaptic plasticity

regulation of secretion by cell

secretion by cell

salt transmembrane transporter activity

cellular response to organic cyclic compound

regulation of monoatomic cation transmembrane transport

inorganic cation transmembrane transport

positive regulation of immune response

response to organic cyclic compound

regulation of vesicle-mediated transport

cell surface receptor signaling pathway involved in cell-cell signaling

monoatomic ion transport

regulation of monoatomic ion transport

transmembrane transporter activity

response to organonitrogen compound

cellular response to nitrogen compound

cell-cell signaling

positive regulation of cell projection organization

positive regulation of transport

response to other organism

regulation of transport

positive regulation of MAPK cascade

positive regulation of intracellular signal transduction

protein glycosylation

protein homooligomerization

calcium ion homeostasis

calcium ion transmembrane transport

monoatomic cation homeostasis

signal release

synaptic signaling

protein secretion

regulation of secretion by cell

secretion by cell

regulation of neuron death

monoatomic ion transport

regulation of monoatomic ion transport

transmembrane transporter activity

positive regulation of cell projection organization

positive regulation of cell death

L4/5 IT CTX

synaptic vesicle exocytosis

translation at presynapse

translation at postsynapse

ribosomal large subunit biogenesis

cytoplasmic translation

ribonucleoprotein complex assembly

ribonucleoprotein complex biogenesis

ribosome biogenesis

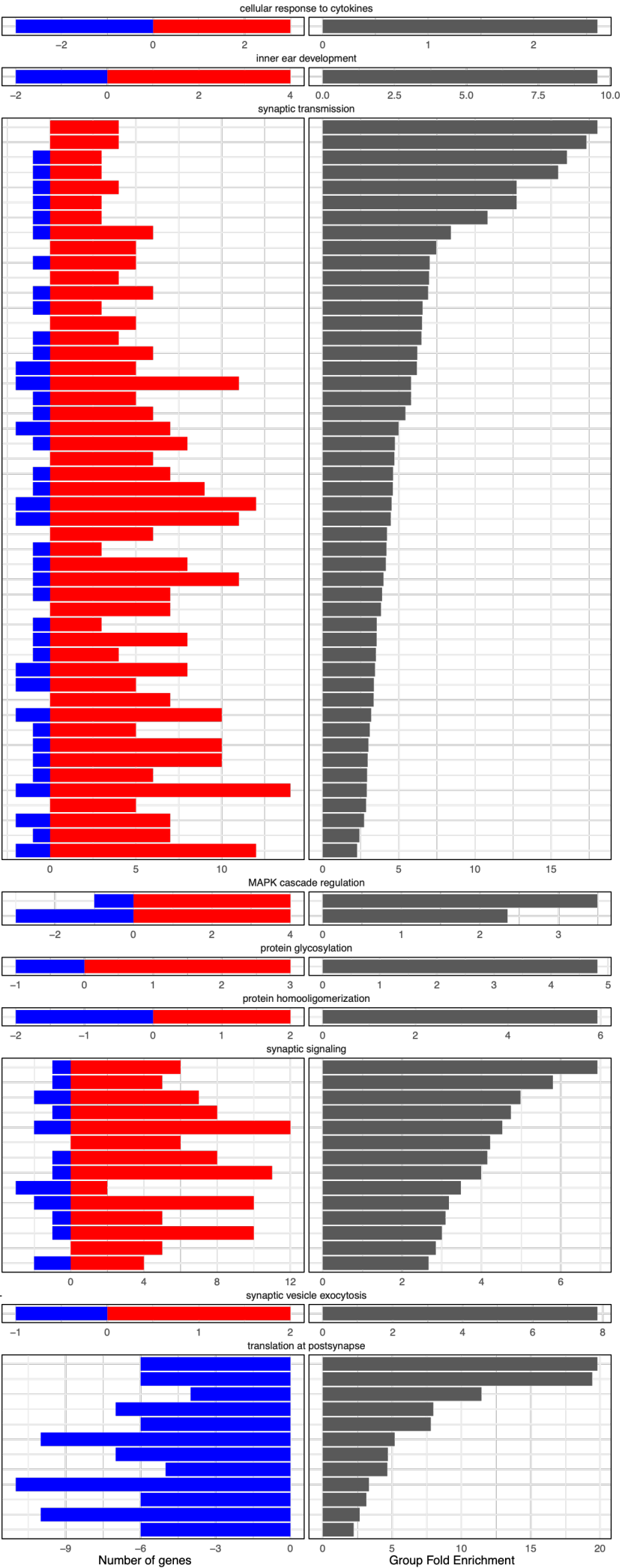
rRNA processing

translation

regulation of translation

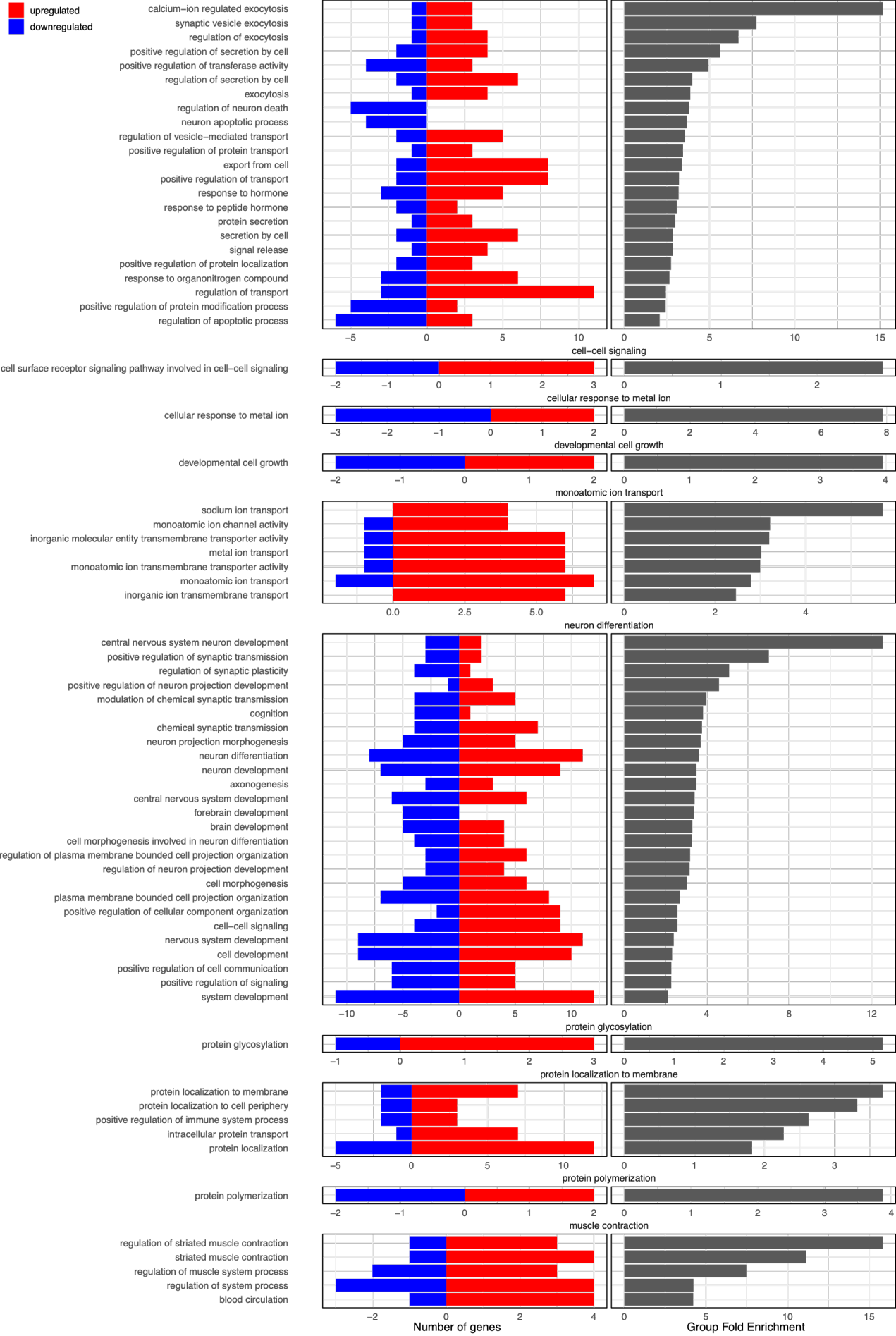
RNA processing

mRNA metabolic process

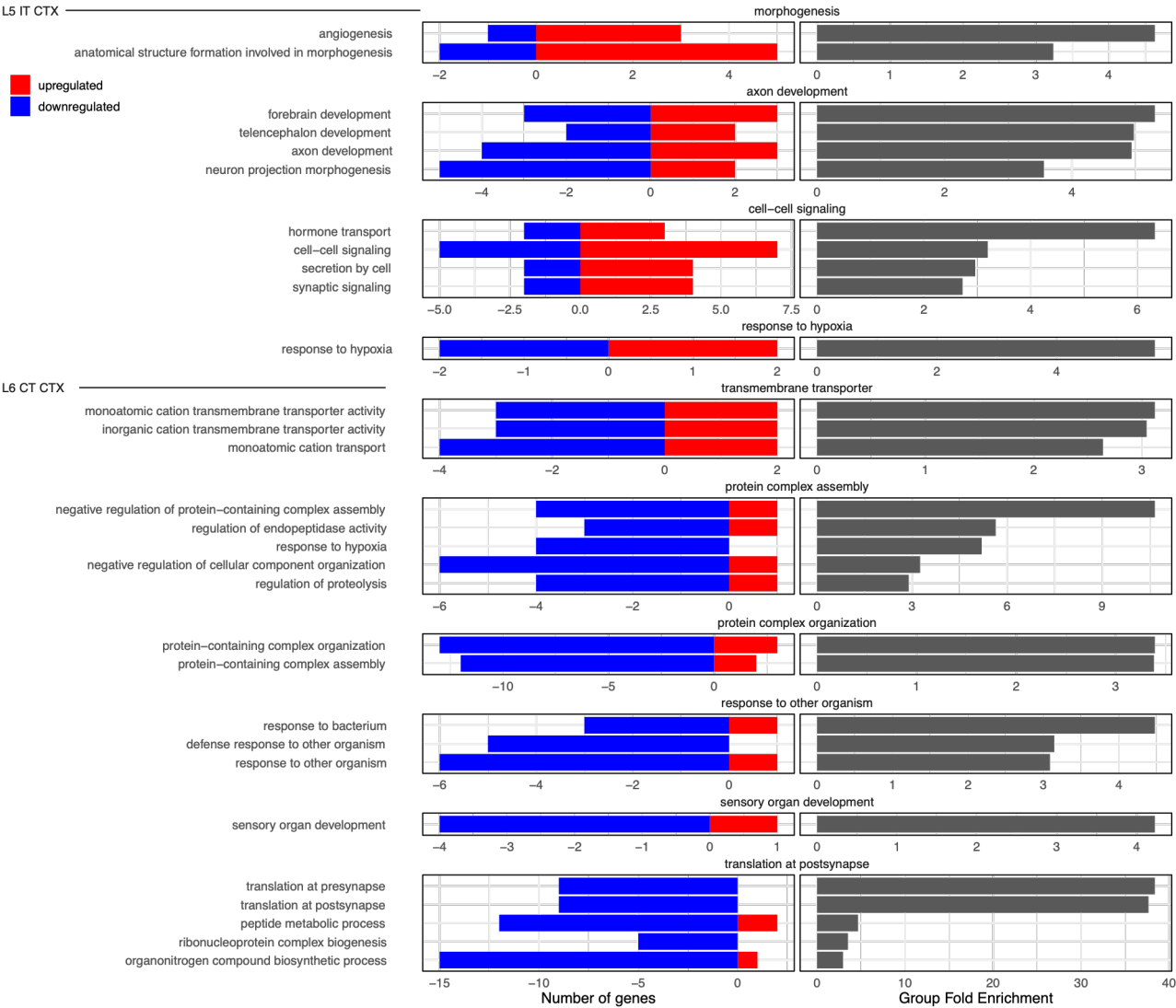


Supplementary Figure 13. Neuronal types GO terms gene count (left) and fold enrichment (right)

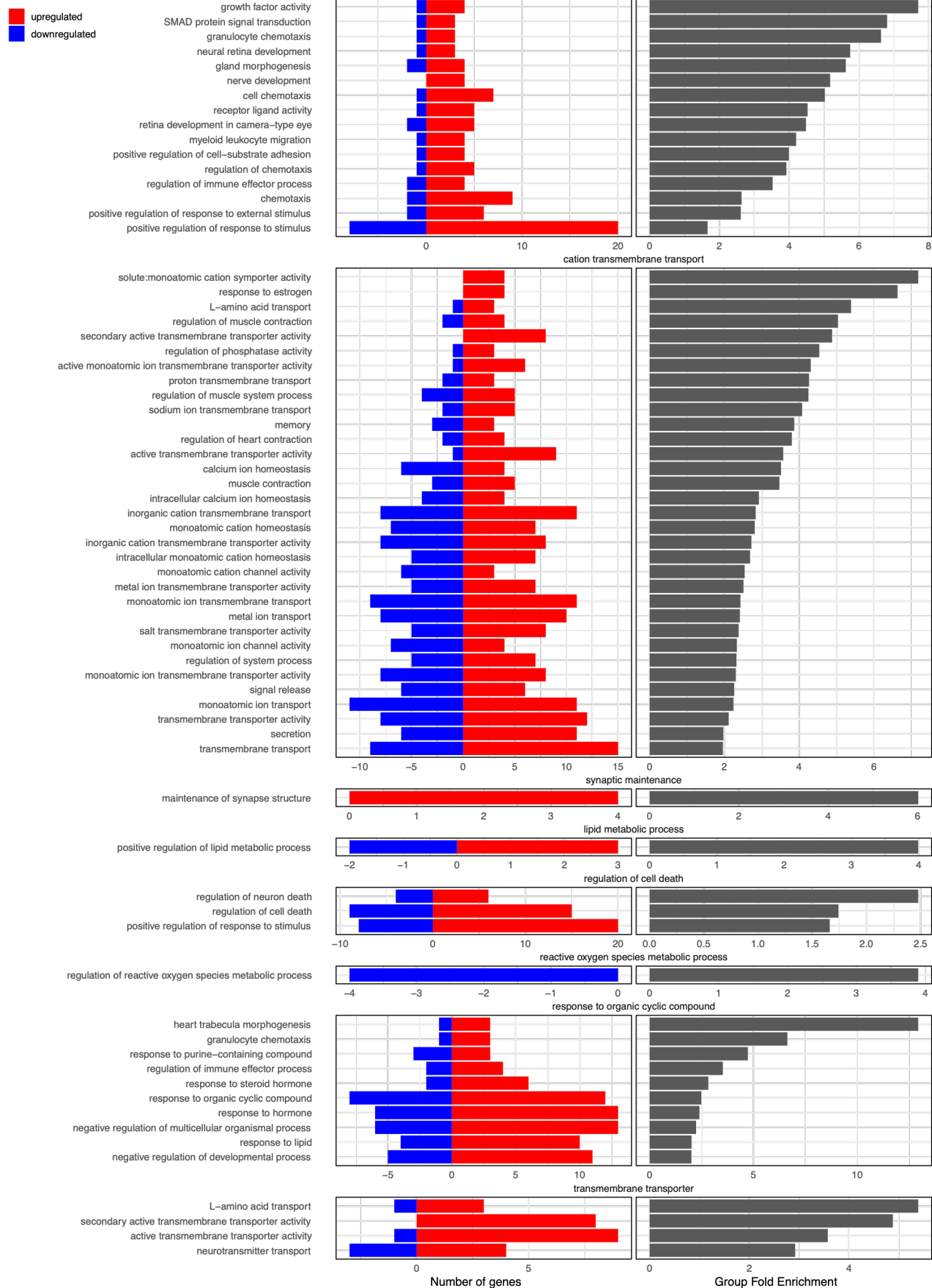
upregulated
downregulated



Supplementary Figure 14. Neuronal types GO terms gene count (left) and fold enrichment (right)



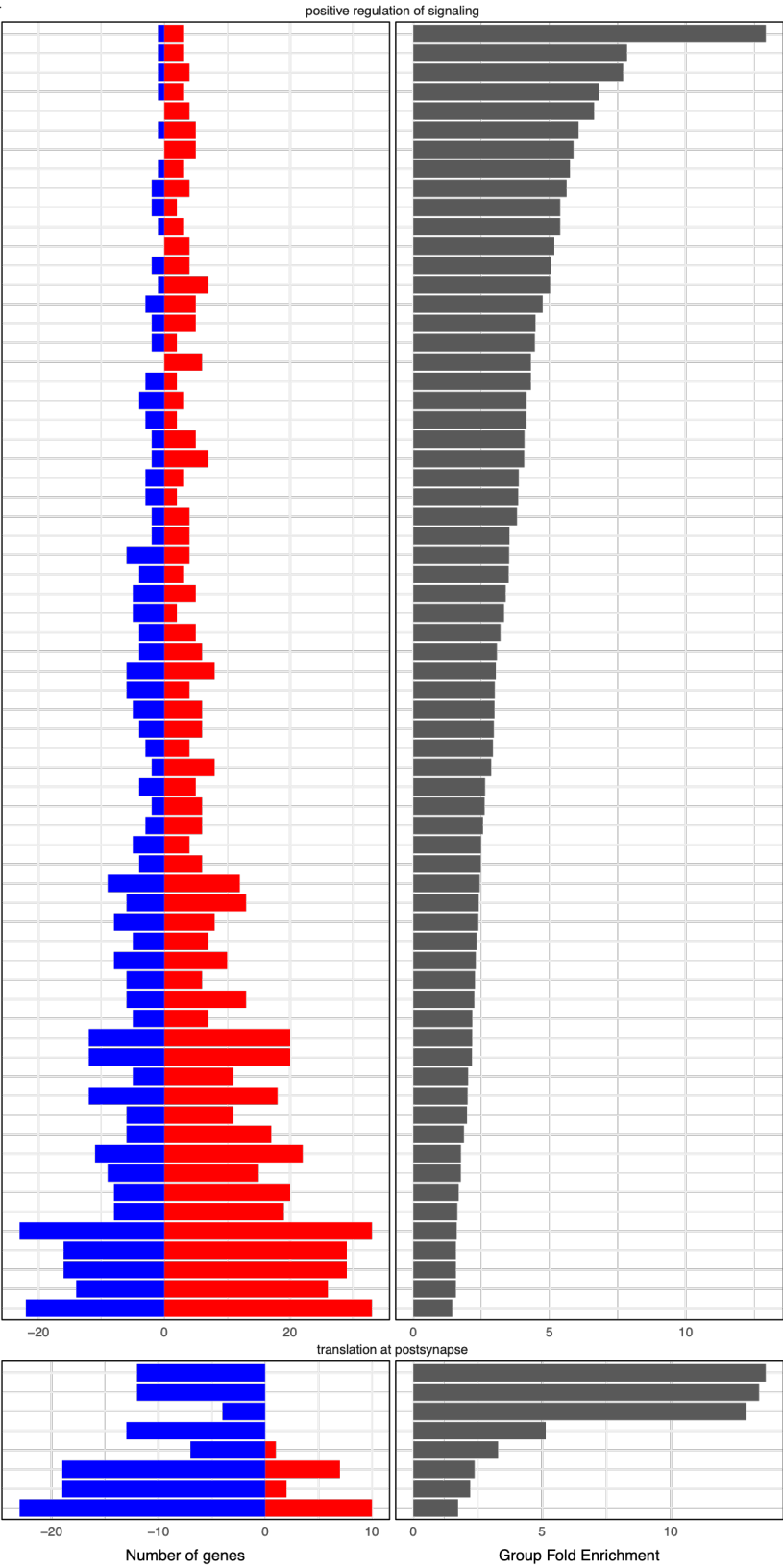
Supplementary Figure 15. Neuronal types GO terms gene count (left) and fold enrichment (right)



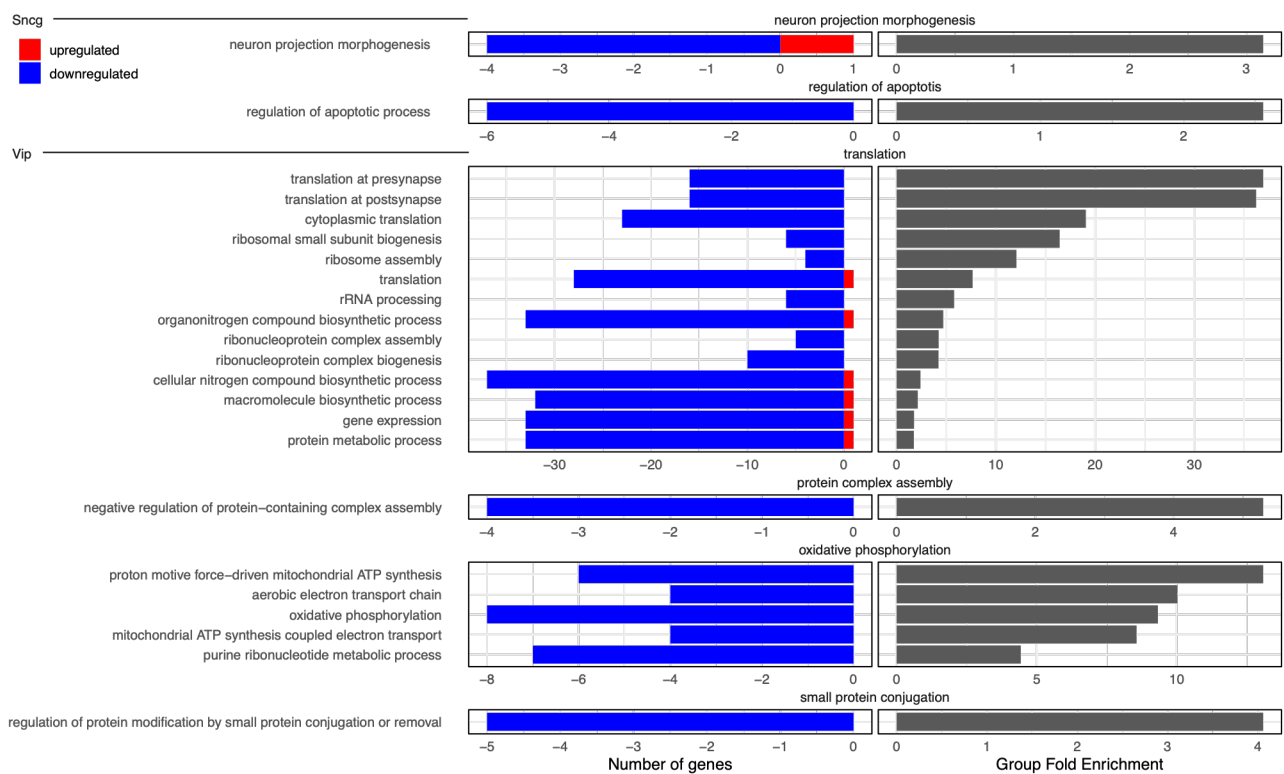
upregulated
downregulated

heart trabecula morphogenesis
cardiac ventricle morphogenesis
growth factor activity
SMAD protein signal transduction
response to estrogen
cardiac chamber morphogenesis
embryonic skeletal system development
neural retina development
gland morphogenesis
defense response to bacterium
L-amino acid transport
nerve development
regulation of muscle contraction
cell chemotaxis
negative regulation of nervous system development
retina development in camera-type eye
positive regulation of protein kinase B signaling
cartilage development
synaptic vesicle endocytosis
ear development
regulation of neurotransmitter secretion
sodium ion transmembrane transport
connective tissue development
memory
long-term synaptic potentiation
regulation of heart contraction
regulation of immune effector process
calcium ion homeostasis
learning
regulation of synaptic plasticity
positive regulation of synaptic transmission
peptide hormone secretion
hormone transport
sensory organ development
learning or memory
amide transport
eye development
neurotransmitter transport
skeletal system development
positive regulation of protein transport
positive regulation of response to external stimulus
embryonic organ development
vesicle-mediated transport in synapse
protein secretion
chemical synaptic transmission
response to hormone
modulation of chemical synaptic transmission
regulation of system process
animal organ morphogenesis
signal release
negative regulation of multicellular organismal process
regulation of vesicle-mediated transport
positive regulation of cell communication
positive regulation of signaling
negative regulation of developmental process
cell-cell signaling
secretion
positive regulation of signal transduction
cell surface receptor signaling pathway
regulation of cell death
positive regulation of response to stimulus
generation of neurons
system development
regulation of cell communication
regulation of signaling
nervous system development
signal transduction

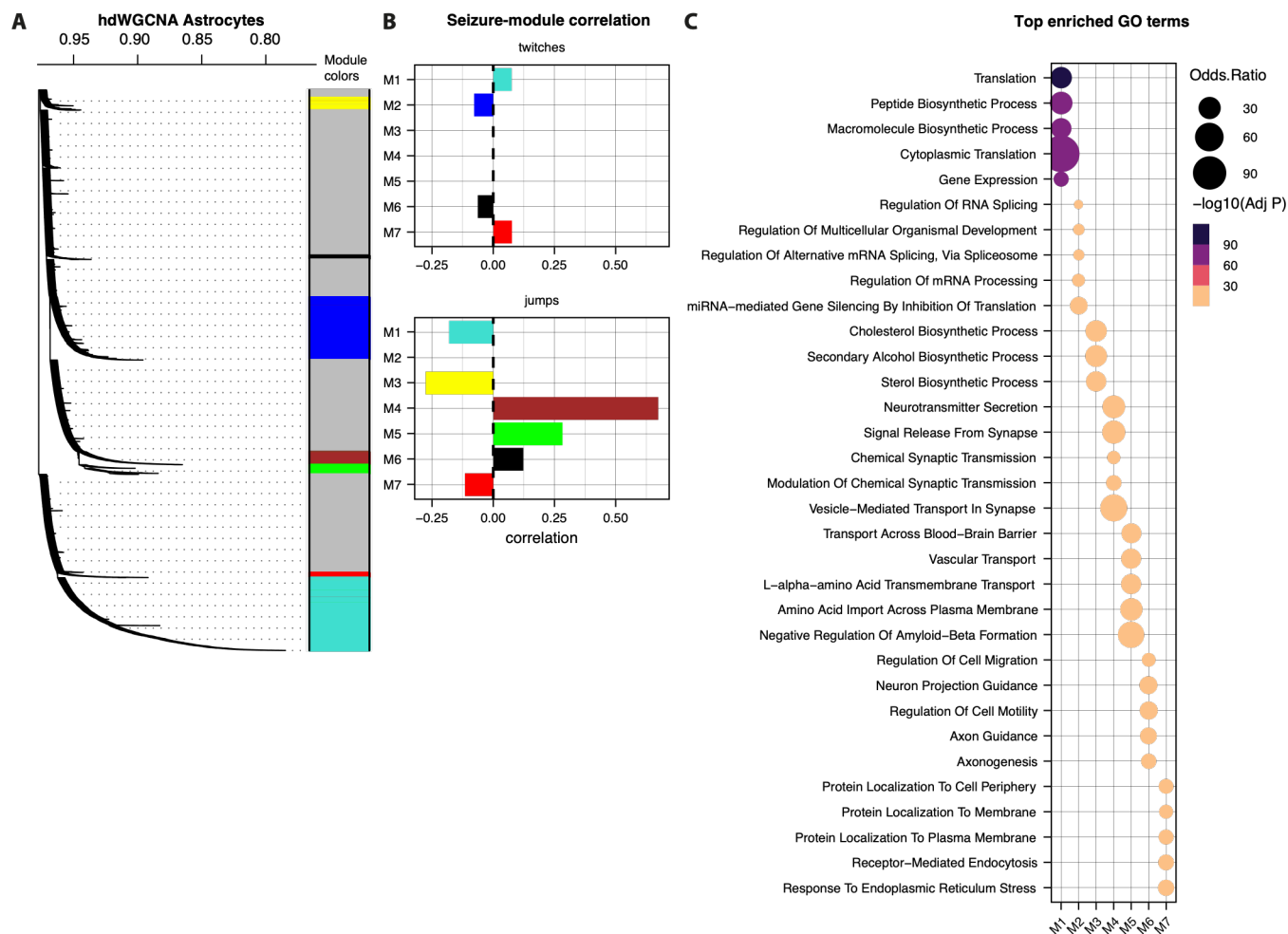
translation at presynapse
translation at postsynapse
ribosomal small subunit assembly
cytoplasmic translation
ribonucleoprotein complex assembly
peptide metabolic process
translation
organonitrogen compound biosynthetic process



Supplementary Figure 17. Neuronal types GO terms gene count (left) and fold enrichment (right)



Supplementary Figure 18. Neuronal types GO terms gene count (left) and fold enrichment (right)



Supplementary Figure 20. Modules of co-expressed genes in astrocytes correlate to seizure-like events in *Stxbp1*^{+/-} mice. (A) Clustering of genes into co-expression modules using hdWGCNA in *Stxbp1*^{+/-} astrocytes. (B) Pearson correlation of module eigengene in astrocytes and seizure-like events in *Stxbp1*^{+/-} mice (only significantly correlated modules shown; FDR-adjusted $p < 0.05$) color-coded by module identity. (C) Dot plot showing the top GO terms enriched in modules correlated to seizure-like events in astrocytes (maximum 5 terms shown, adjusted $p < 0.05$, odds ratio > 5). Dot size corresponds to the odds ratio and color code to the adjusted p -value.