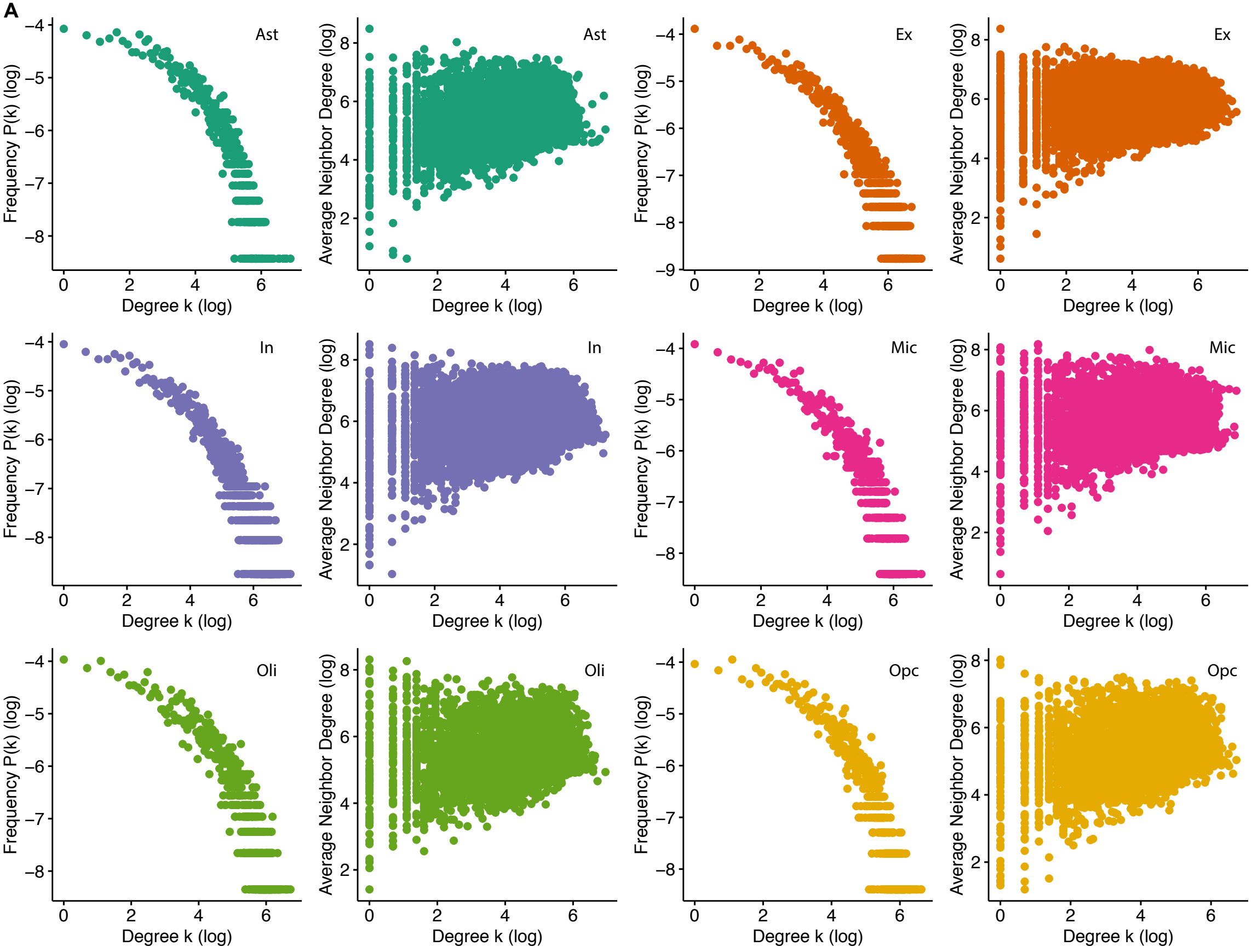
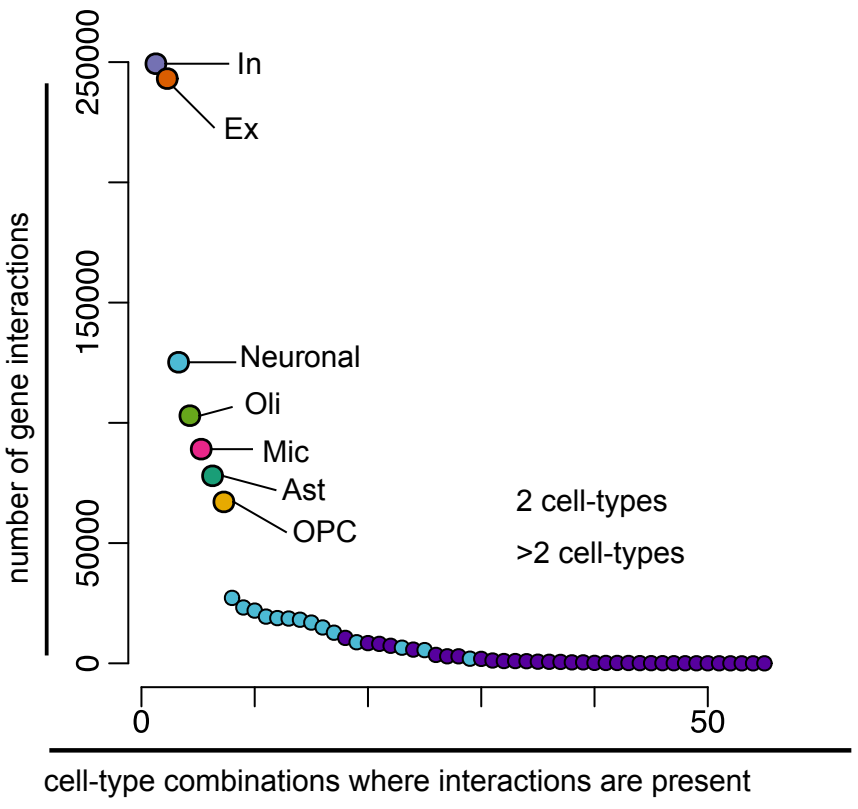
Supplementary Data

Data S1. Disease-associated Gene Set Lists. Related to Figure 3, Figure 4, and Figure 5. Includes a collection of spreadsheets presenting the gene sets used for disease network association analyses, including genes from DisGeNET, SZDB2, and from GWAS studies.

A


Ast
Ex
In
Mic
Oli
Opc
Frequency P(k) (log)
Average Neighbor Degree (log)
Degree k (log)

B


Patterns of shared and private interactions
number of gene interactions
250000
150000
50000
0
In
Ex
Neuronal
Oli
Mic
Ast
OPC
2 cell-types
>2 cell-types
0
50
cell-type combinations where interactions are present

C

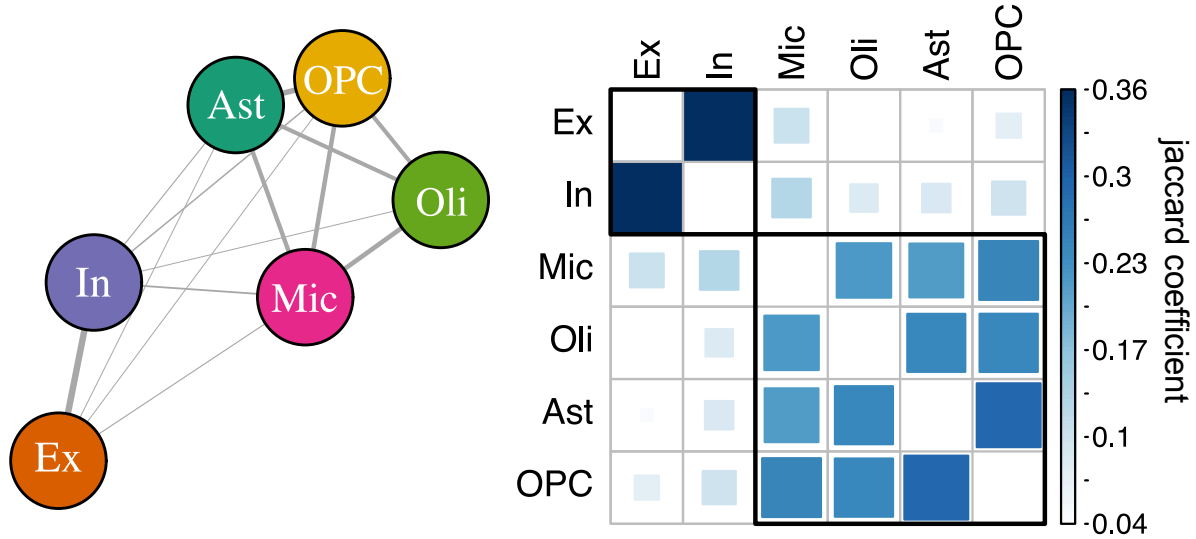

Interaction overlap-based similarity
Ast
OPC
Oli
In
Mic
Ex
Ex
In
Mic
Oli
Ast
OPC
0.36
0.3
0.23
0.17
0.1
0.04
jaccard coefficient

Figure S1. Gene connectivity and partner preference distributions across cell-type specific interactomes, Related to Figure 2. A, Degree (total number of interactions of a given gene) distributions are displayed in log scale (left). Patterns of gene neighbors' connectivity as a function of a gene's degree are displayed in log scale (right). Overall, connected genes show a slight preference to interact with genes. **B,** number of gene interactions that are observed in only one cell-type (cell-type colors), only two different cell-types (light blue), or more than two different cell-types (purple). Cell-type combinations refers to any combination of one of more cell-types in which a gene interactions occurs. **C**, Network representation linking cell-types based on the degree of overlap in shared gene interactions (left). Cell-types that share more interactions appear positioned close together. Edge weight is proportional to the degree of overlap. Degree of overlap in interactions is quantified using the pairwise jaccard coefficient. Corresponding Jaccard coefficients are shown in matrix form (right).

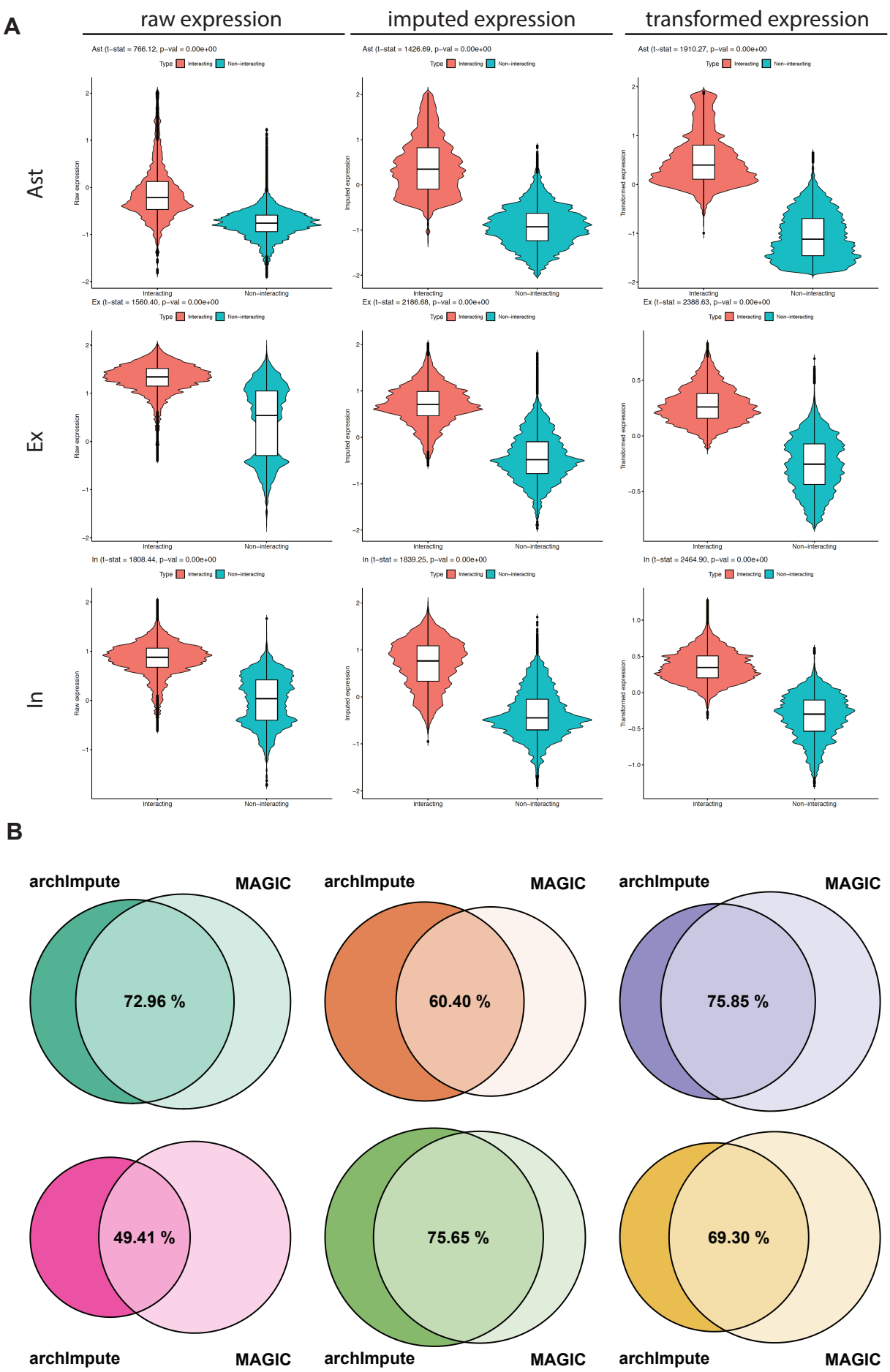

A
raw expression
imputed expression
transformed expression
Ast
Ex
In
Ast (t−stat = 766.12, p−val = 0.00e+00
Ast (t−stat = 1426.69, p−val = 0.00e+00
Ast (t−stat = 1910.27, p−val = 0.00e+00
Ex (t−stat = 1560.40, p−val = 0.00e+00
Ex (t−stat = 2186.68, p−val = 0.00e+00
Ex (t−stat = 2388.63, p−val = 0.00e+00
In (t−stat = 1808.44, p−val = 0.00e+00
In (t−stat = 1839.25, p−val = 0.00e+00
In (t−stat = 2464.90, p−val = 0.00e+00
Type Interacting Non−interacting
Raw expression
Imputed expression
Transformed expression
Interacting
Non−interacting
B
archImpute
MAGIC
72.96 %
60.40 %
75.85 %
49.41 %
75.65 %
69.30 %

Figure S2. SCINET robustness to data transformation and imputation, Related to STAR Methods. A, Plots show raw (input) expression values, as well as imputed (archimpute) and transformed after imputed expression values for genes predicted as interacting in the given cell-type (row) vs. genes predicted as non-interacting. Expression values at three different levels of processing: raw expression values, imputed expression values (archimpute), and transformed after imputed expression values. For each gene pair, the minimum value of expression of the two genes is shown. Three representative cell types are presented due to space constraints. **B,** Each panel shows the overlap of identified edges, after thresholding *p*-values (0.05), across different cell types. Except in microglia, the majority of predicted edges overlap with each other, with the strongest overlap observed in inhibitory neuron and oligodendrocyte-specific networks. Expression values for genes were imputed, independently, using either ACTION-based archetype imputation (archImpute, see Methods) or MAGIC method. Imputed profiles were used to infer cell-type specificity of edges.

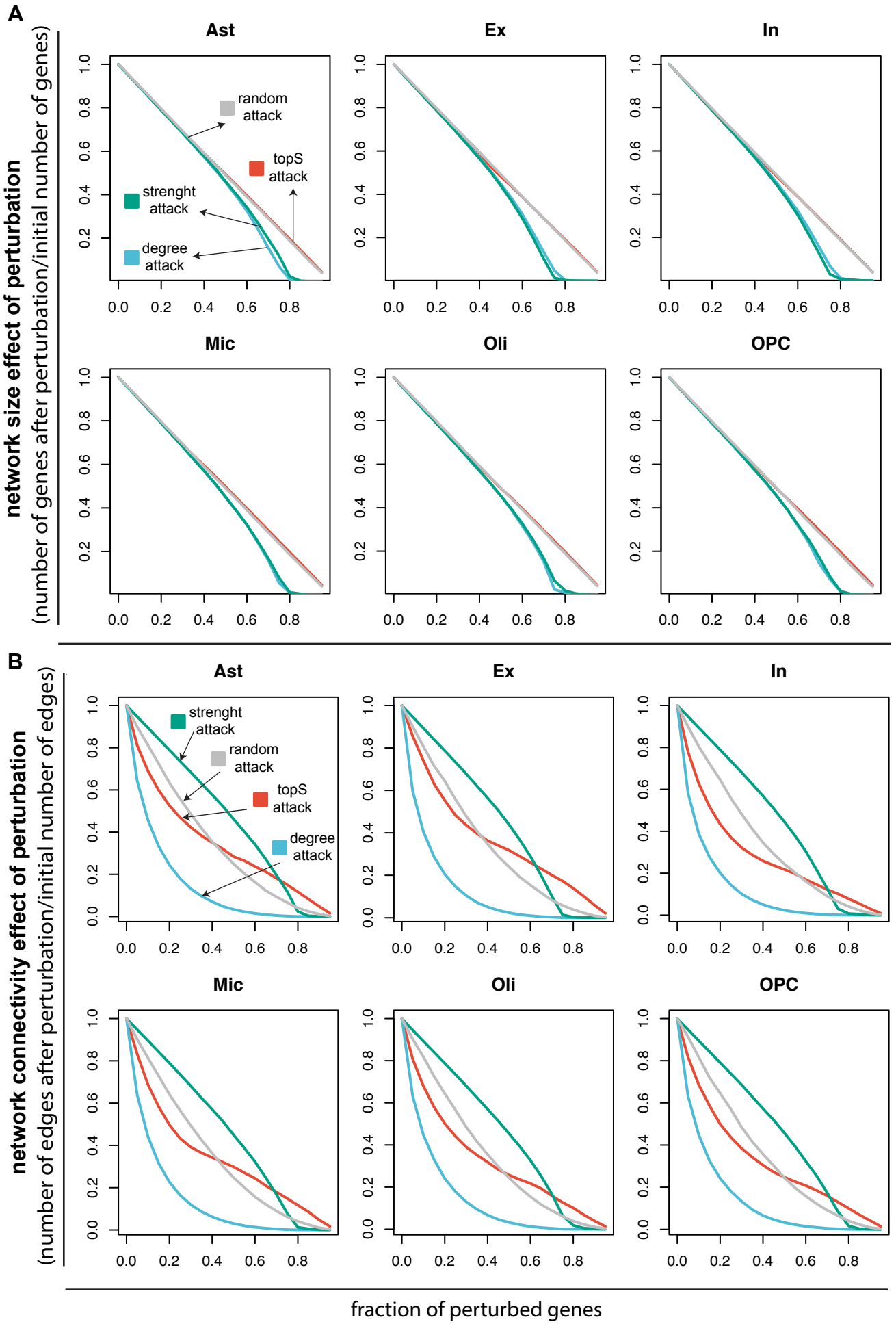
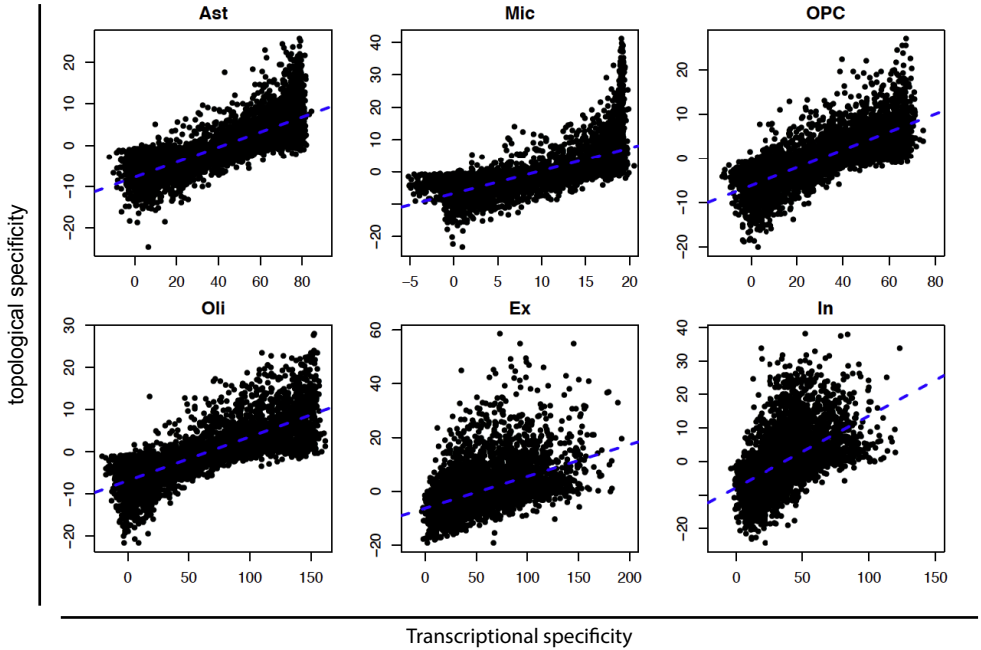

A
network size effect of perturbation
(number of genes after perturbation/initial number of genes)
Ast
Ex
In
Mic
Oli
OPC
random attack
topS attack
strenght attack
degree attack
B
network connectivity effect of perturbation
(number of edges after perturbation/initial number of edges)
fraction of perturbed genes

Figure S3. Simulated perturbation experiments, Related to Figure 2. A, Decrease in the size (number of genes) of the largest connected component as a function of incremental node removal perturbations. **B,** Decrease in the total connectivity (number of edges) of the largest connected component as a function of incremental node removal perturbations. The type of attack (strength, random, topS, or degree) determines the decreasing order in which genes are removed -- i.e., starting with genes with the highest value of the metric.

A



B

Topologically specificity genes with unspecific transcription

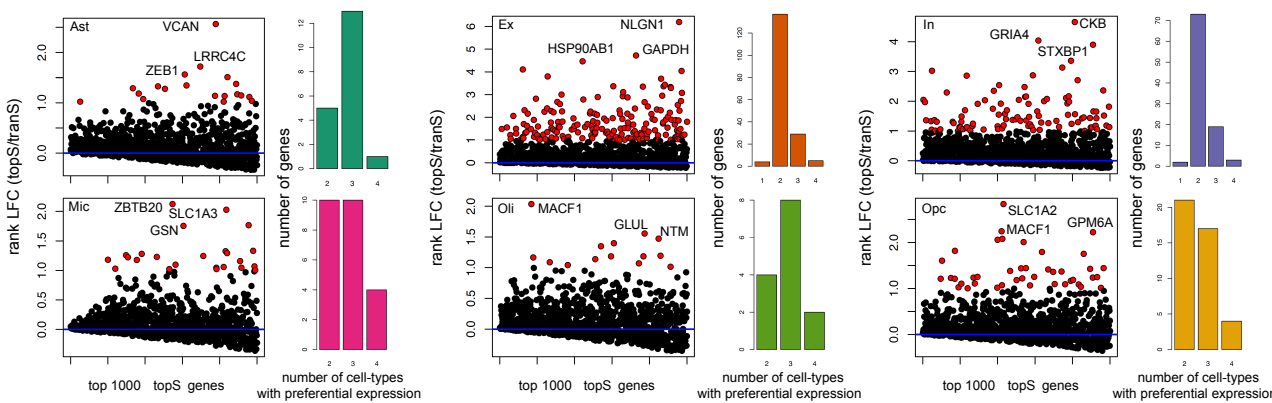


Figure S4. Consistency of topological and transcriptional specificity, Related to Figure 2. A Plots show corresponding topological and transcriptional specificity values across genes of each cell-type specific network. Blue line represents the best linear regression fit. **B,** Topologically specific genes that show promiscuous expression across cell-types.

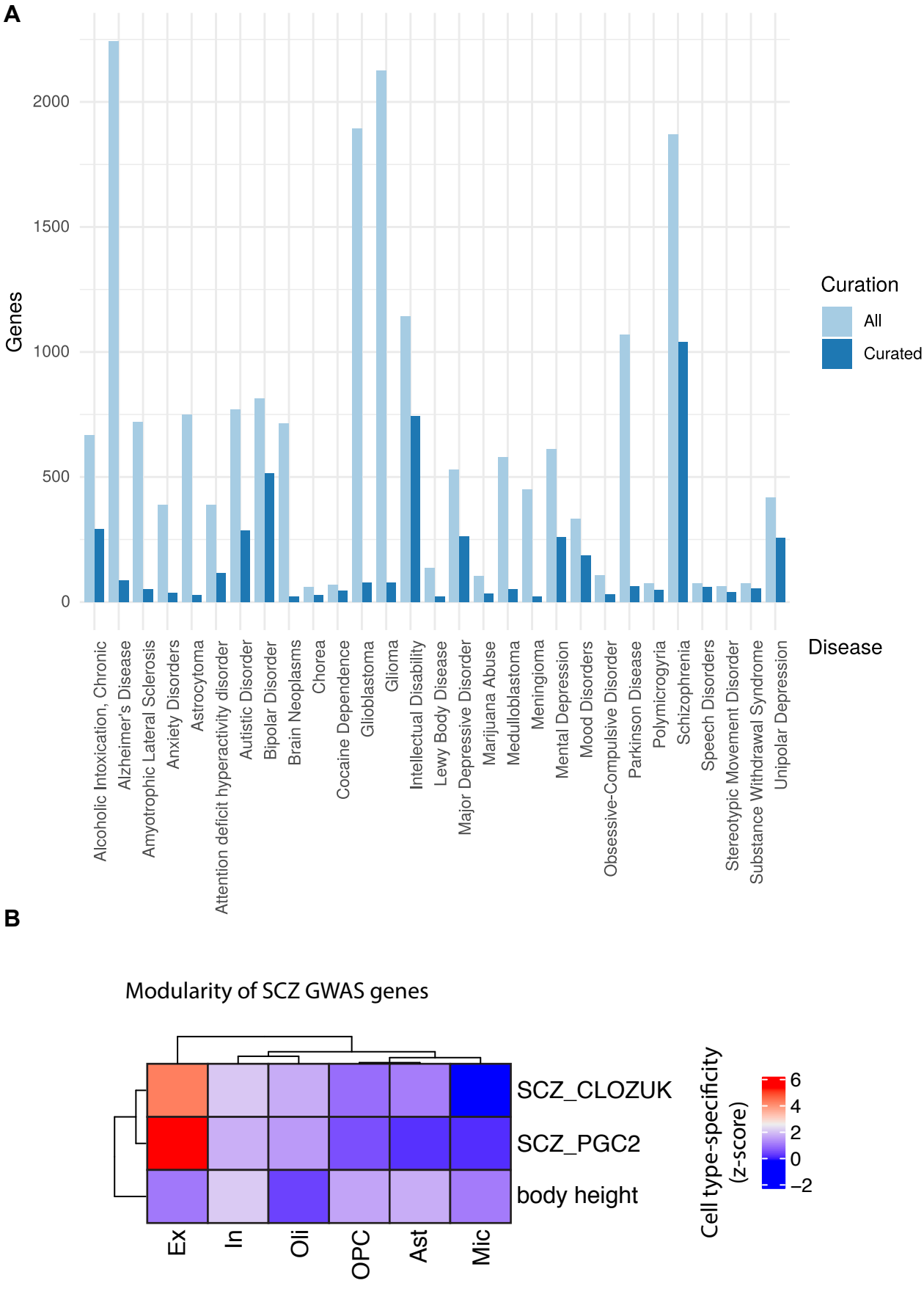

A
Genes
2000
1500
1000
500
0
Curation
All
Curated
Disease
Alcoholic Intoxication, Chronic
Alzheimer's Disease
Amyotrophic Lateral Sclerosis
Anxiety Disorders
Astrocytoma
Attention deficit hyperactivity disorder
Autistic Disorder
Bipolar Disorder
Brain Neoplasms
Chorea
Cocaine Dependence
Glioblastoma
Glioma
Intellectual Disability
Lewy Body Disease
Major Depressive Disorder
Marijuana Abuse
Medulloblastoma
Meningioma
Mental Depression
Mood Disorders
Obsessive-Compulsive Disorder
Parkinson Disease
Polymicrogyria
Schizophrenia
Speech Disorders
Stereotypic Movement Disorder
Substance Withdrawal Syndrome
Unipolar Depression
B
Modularity of SCZ GWAS genes
SCZ_CLOZUK
SCZ_PGC2
body height
Ex
In
Oli
OPC
Ast
Mic
Cell type-specificity
(z-score)
6
4
2
0
−2

Figure S5. Disease associated genes, Related to Figure 4. A, Bars show the number of genes reported to be associated with a given disease in DisGeNET (http://www.disgenet.org/**).** Only genes reported as "curated" in the database (dark blue) were considered in this study. Only brain-related disorders included in this study are shown. **B**, The heatmap shows compactness scores (similar to Figure 4C) for genes identified in major GWAS studies for schizophrenia.

Table S1. Top 10 proteins topologically specific genes. Related to Figure 2.

Ast	**Ex**	**In**	**Mic**	**Oli**	**OPC**
SLC1A2	SNAP25	GRIA1	PTPRC	MOG	PDGFRA
EGFR	SYT1	GAD2	LAPTM5	PLP1	ITGAV
GJA1	CAMK2A	GRIK1	SYK	TMEM144	FGFR1
PRKCA	RGS7	SLC6A1	FLI1	TF	VCAN
FYN	GRIN2A	GAD1	LY86	MBP	NRXN1
ATP1A2	STXBP1	ERBB4	INPP5D	FRYL	FYN
TIMP3	GRIA2	HSP90AB1	CSF1R	FGFR2	BCAN
PLSCR4	NRXN1	HSP90AA1	ARHGAP25	PICALM	OLIG2
NTRK2	SLC17A7	GRIN2B	CD53	ZBTB20	ZBTB20
CPE	CAMK2B	SYT1	TLR1	ZNF638	CNTN1
B	**CD4**	**CD8**	**mDC**	**Mono**	**NK**
DDX21	EIF3E	CCL5	CTSS	SRGN	NKG7
PRMT1	EEF1B2	NKG7	CASP1	PLAUR	GNLY
RAN	EIF3H	GNLY	TYROBP	S100A11	CCL5
MS4A1	NPM1	CD8A	FCER1G	SOD2	GZMA
ODC1	NACA	CST7	HCK	CTSS	IRF1
NHP2	BTF3	TNFAIP3	AIF1	ANXA5	RAC2
SET	LDHB	PTPRC	SRGN	CD44	GZMB
NME1	EIF4B	IRF1	LYN	TIMP1	CD247
EBNA1BP2	HINT1	RUNX3	MYD88	CTSB	CST7
MYC	NSA2	JUN	LST1	FCER1G	PRF1