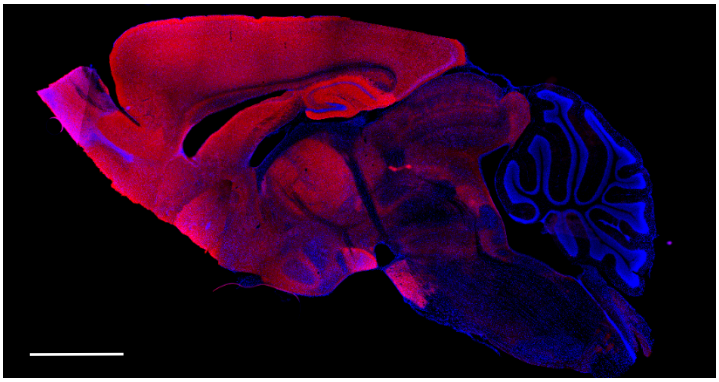
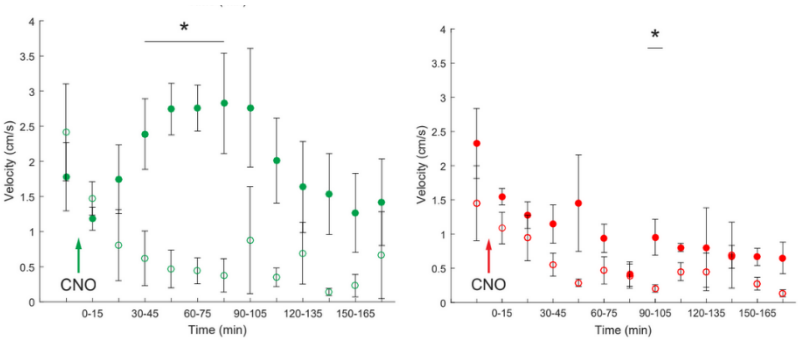
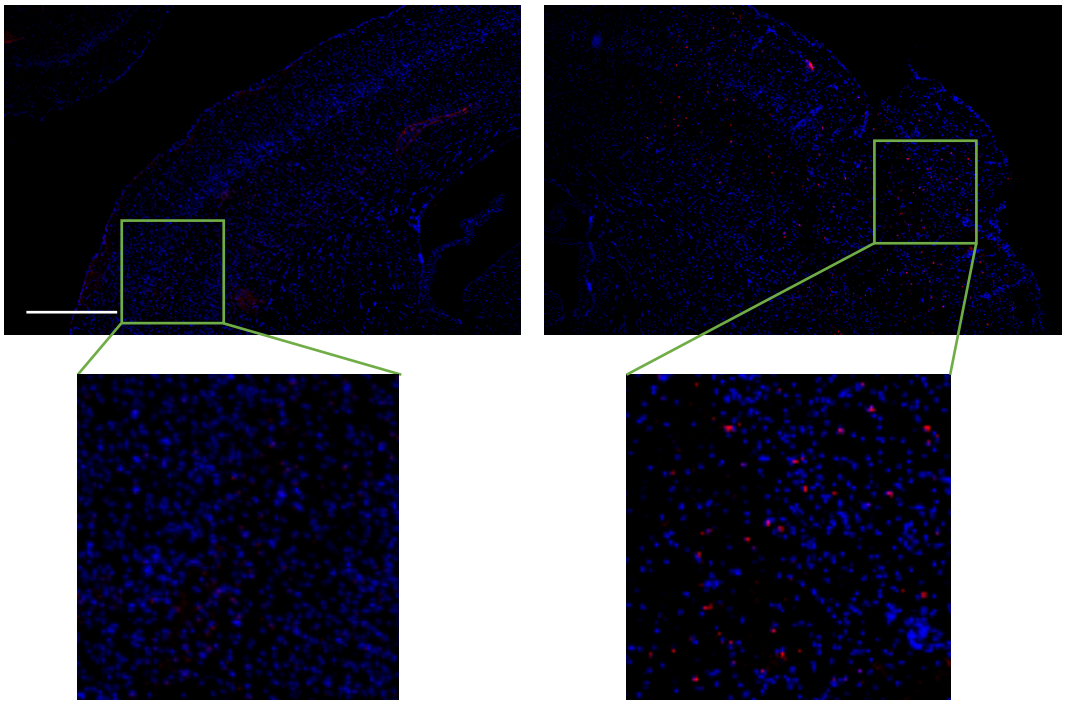
A


HA/DAPI

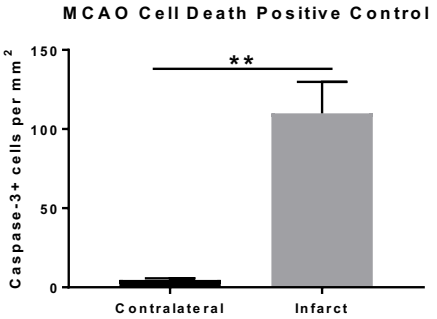
B


Velocity (cm/s)
CNO
0-15
30-45
60-75
90-105
120-135
150-165
Time (min)
*
Velocity (cm/s)
CNO
0-15
30-45
60-75
90-105
120-135
150-165
Time (min)
*

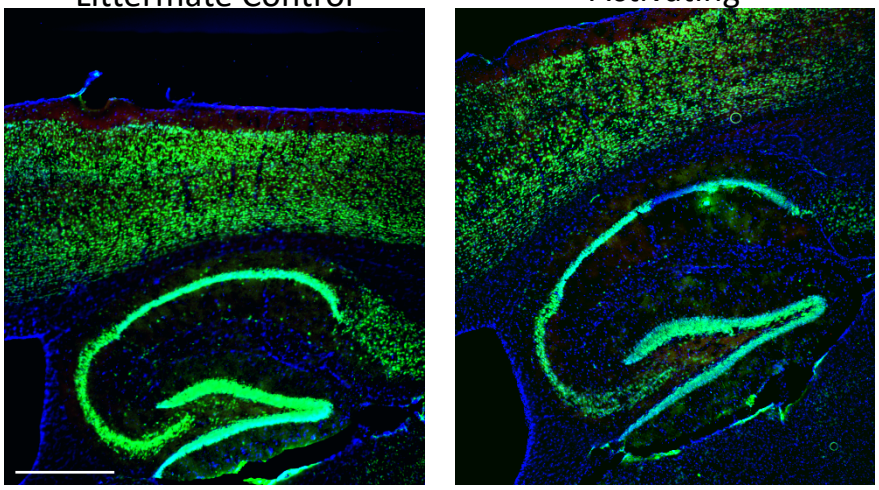
C


Contralateral Control
MCAO Infarct
Caspase-3/DAPI

D


MCAO Cell Death Positive Control
Caspase-3+ cells per mm 2
150
100
50
0
**
Contralateral
Infarct

E


Littermate Control
Activating
NeuN/Caspase-3/DAPI

F

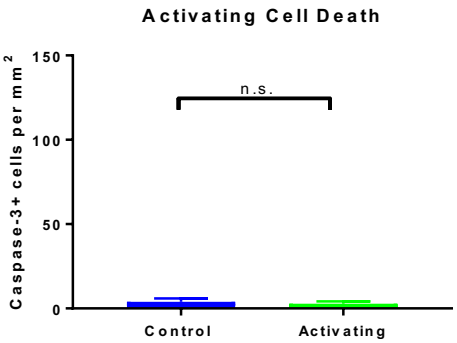

Activating Cell Death
Caspase-3+ cells per mm 2
150
100
50
0
n.s.
Control
Activating

Figure S1. Further Validation of DREADDs (Related to Figure 1)

(A) Photomerge of a representative sagittal section of Silencing DREADDs mouse brain stained for rabbit-anti-HA (red) and cell nuclei with DAPI (blue). Color-matched boxes were added to the edges to make a rectangular image. Scale bar represents 2 mm.

(B) Average velocity of Activating mice vs. paired littermate controls after i.p. injection of 0.5 mg/kg CNO (left) and Silencing mice vs. paired littermate controls after i.p. injection of 1.0 mg/kg of CNO (right) over 3 hour recording sessions. Open circles represent control animals and closed circles represent Activating/Silencing animals. Data represent mean ± SEM (error bars). n=3 per group, *p<0.05 by unpaired Student's t-test.

(C) Representative coronal sections immunostained for rabbit-anti-Cleaved Caspase-3 (red) and DAPI (blue) of MCAO infarct (right) and contralateral control area (left) of the same section from the same mouse. Scale bar represents 500 μm. Inset represents a magnified portion of the main image. The MCAO model of stroke was used as a positive control to identify cell death.

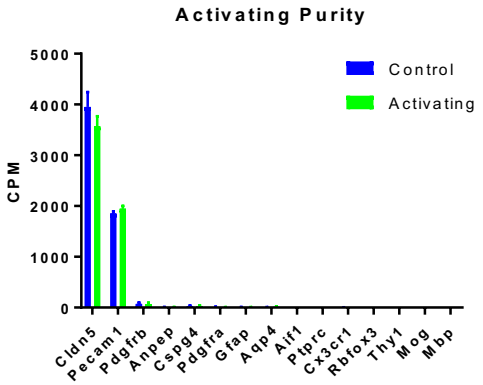
(D) Quantification of Cleaved Caspase-3+ cells per mm^2 in infarct vs contralateral area of the same mice as in (C). Data represent mean ± SEM (error bars). n=4 per group. **p<0.005 by paired Student's t-test.

(E) Representative sagittal cortical/hippocampal sections immunostained for mouse anti-NeuN (green), rabbit anti-Cleaved Caspase-3 (red) and DAPI (blue) of a littermate control mouse (left) and Activating mouse (right) collected 3 hours after injection of 0.5 mg/kg CNO. Scale bar represents 500 μm.

(F) Quantification of Cleaved Caspase-3+ cells per mm^2 in the cortex and hippocampus of Activating mice vs littermate control mice. Data represent mean ± SEM (error bars). n=3 per group. n.s. (not significant) by unpaired Student's t-test.

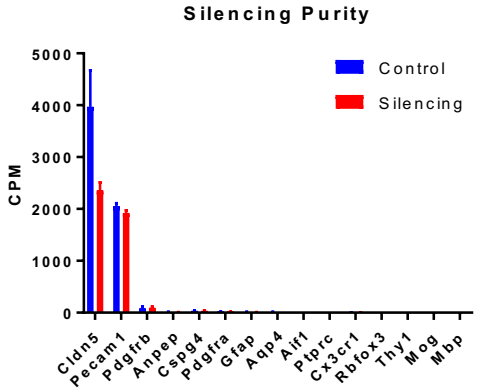
A

Cell Type	Gene	Control CPM	Activating CPM
Endothelial	Cldn5	3950.45	3569.193
	CD31	1852.826	1947.142
Pericyte	Pdgfrb	71.80941	69.28318
	CD13	8.123434	7.389564
Pericyte/OPCs	NG2	29.28712	29.20847
OPCs	Pdgfra	11.84399	10.24598
Astrocytes	GFAP	6.69824	8.634951
	Aqp4	9.345761	14.00008
Microglia	Iba1	0.530904	0.467565
	CD45	0.94533	0.922413
	Cx3cr1	5.016872	5.274231
Neurons	NeuN	0.971562	0.970873
	Thy1	3.092319	3.12039
Oligodendrocytes	Mog	0.107316	0.261564
	Mbp	2.14875	2.286906



B

Cell Type	Gene	Control CPM	Silencing CPM
Endothelial	Cldn5	3970.005	2357.484
	CD31	2052.527	1921.881
Pericyte	Pdgfrb	79.26506	94.81409
	CD13	8.777674	9.974195
Pericyte/OPCs	NG2	33.78414	35.34182
OPCs	Pdgfra	22.6561	21.91366
Astrocytes	GFAP	12.02751	8.4481
	Aqp4	12.09609	10.32857
Microglia	Iba1	0.305715	0.273614
	CD45	0.894348	0.50944
	Cx3cr1	5.068705	4.107045
Neurons	NeuN	1.066674	1.133582
	Thy1	3.061972	3.14312
Oligodendrocytes	Mog	0.189905	0.127891
	Mbp	2.653085	1.981621



C

Cell Type	Gene	- Whisker CPM	+ Whisker CPM
Endothelial	Cldn5	2744.506	2636.557
	CD31	1909.85	2069.65
Pericyte	Pdgfrb	42.30872	29.67534
	CD13	3.328646	3.371701
Pericyte/OPCs	NG2	26.77481	16.53828
OPCs	Pdgfra	12.37082	8.088497
Astrocytes	GFAP	7.464317	3.141213
	Aqp4	18.34414	6.350982
Microglia	Iba1	0.337592	0.571674
	CD45	0.718816	1.186568
	Cx3cr1	6.682205	8.118941
Neurons	NeuN	0.465649	0.194224
	Thy1	1.881724	1.046022
Oligodendrocytes	Mog	0.230766	0.07517
	Mbp	2.825719	0.801201

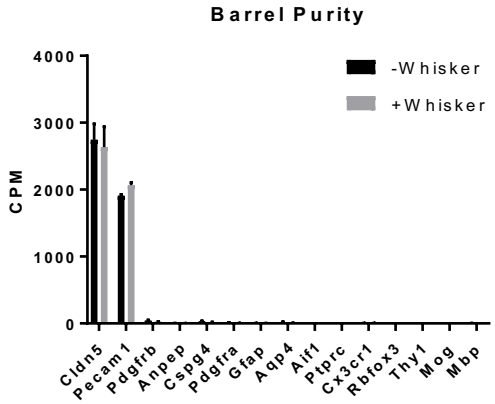


Figure S2. Neuronal Activity-Regulated Brain Endothelial Transcriptome Cell Purity (Related to Figures 2 and 6)

(A-C) The counts per million (CPM) of brain cell-specific markers in the Activating (A), Silencing (B) and Barrel Cortex (C) datasets. Values for each gene are also listed in the tables (left).

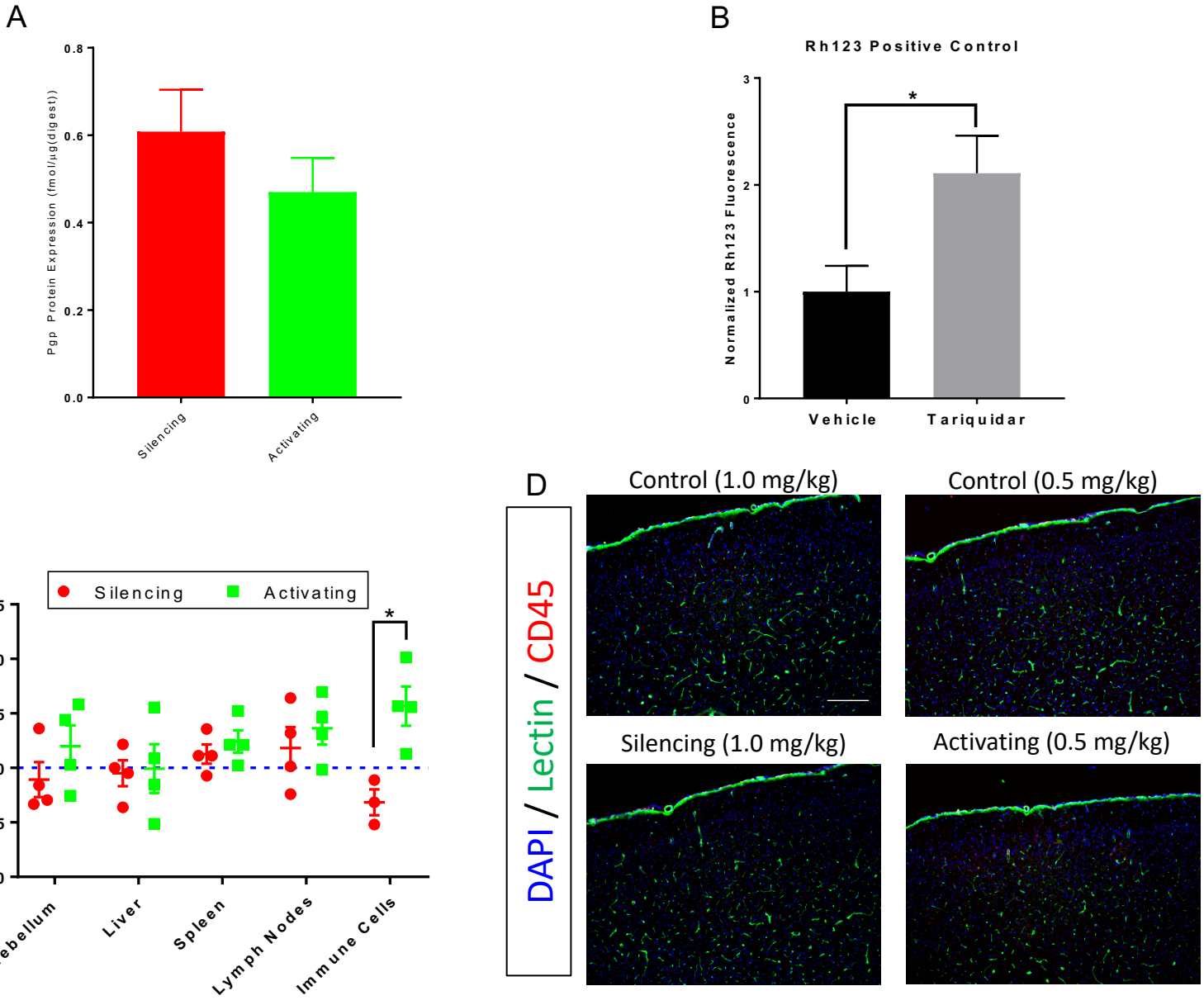
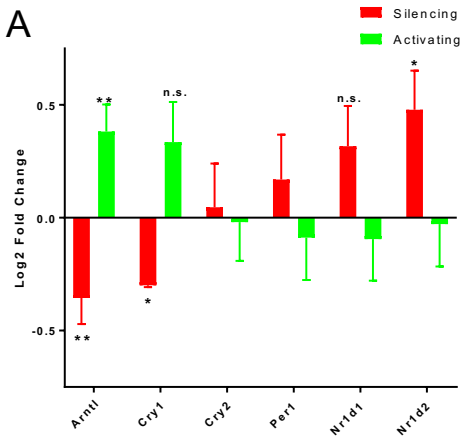
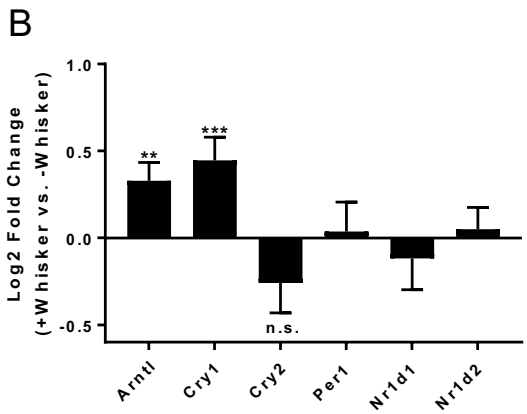
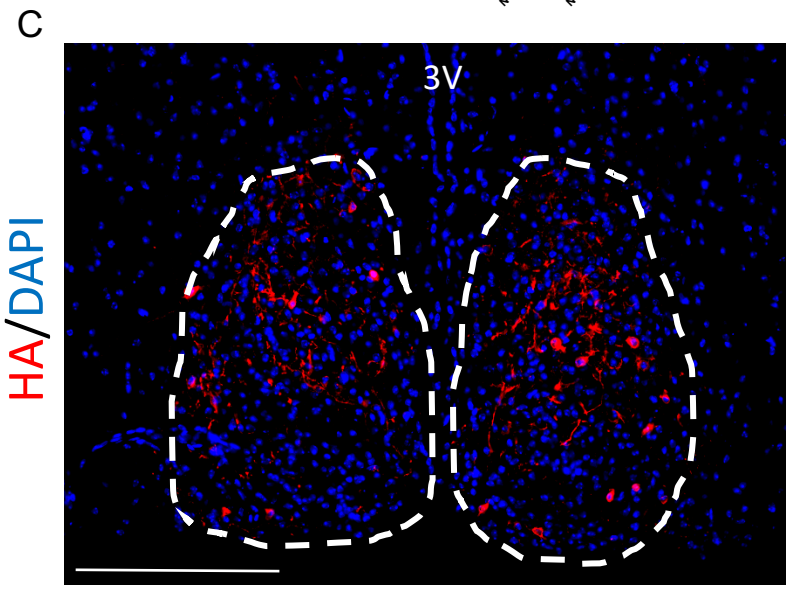

A
Pgp Protein Expression (fmol/µg(digest))
0.8
0.6
0.4
0.2
0.0
Silencing
Activating
B
Rh123 Positive Control
Normalized Rh123 Fluorescence
3
2
1
0
*
Vehicle
Tariquidar
C
Normalized Rh123 Fluorescence
Silencing
Activating
2.5
2.0
1.5
1.0
0.5
0.0
*
Cerebellum
Liver
Spleen
Lymph Nodes
Immune Cells
D
DAPI / Lectin / CD45
Control (1.0 mg/kg)
Control (0.5 mg/kg)
Silencing (1.0 mg/kg)
Activating (0.5 mg/kg)
E
Silencing
Activating
Evan's Blue Fluorescence
200
150
100
50
0
Blood
Brain

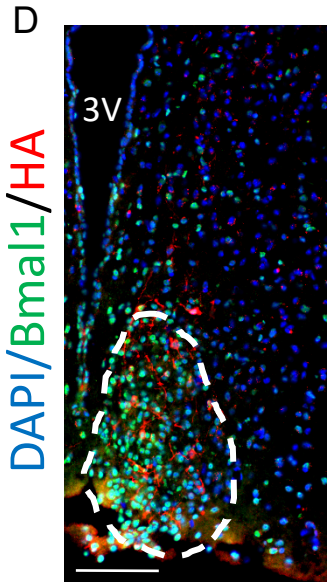
Figure S3. Further Characterization of Neuronal Activity-Regulated BBB Function (Related to Figure 4)

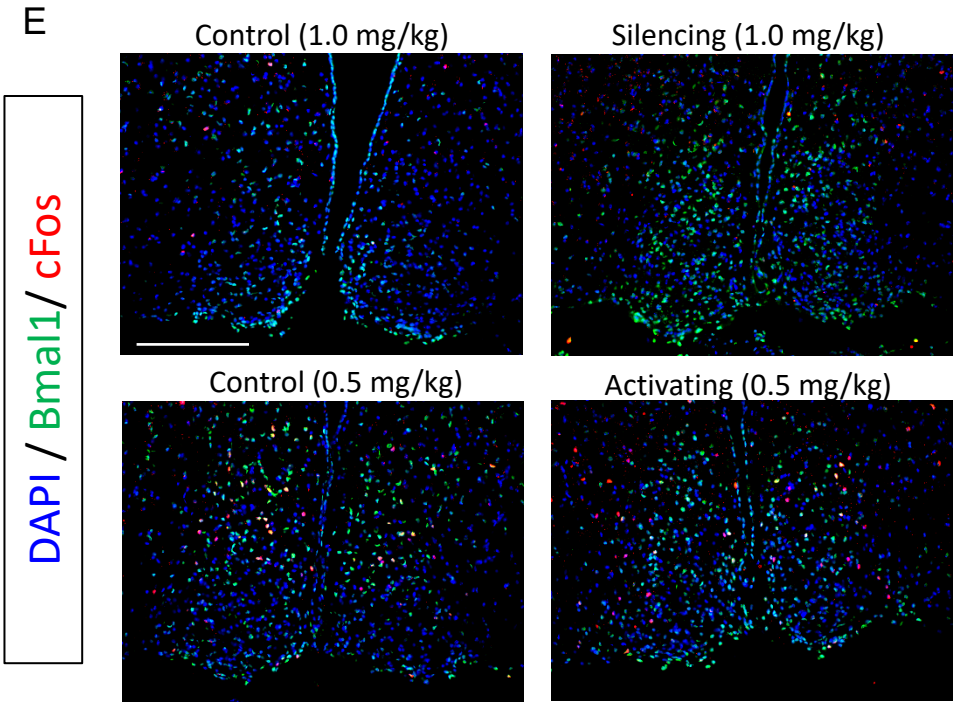
(A) Pgp protein expression of Activating vs. Silencing cortices/hippocampi following CNO administration measured by targeted mass spectrometry. Data represent mean ± SEM (error bars). n=4 per group. p=0.15 by unpaired Student's t-test.
(B) Normalized brain:blood ratios of Rh123 fluorescence in Vehicle-treated vs Tariquidar (Pgp inhibitor)-treated wildtype mice. The rhodamine fluorescence (brain:blood) of each mouse was normalized to the average fluorescence of the vehicle-treated mice (Excitation=505nm, Emission=560nm). n=3 per group. Data represent mean ± SEM (error bars). *p=0.034018 by unpaired Student's t-test.
(C) Normalized Rhodamine123 (Rh123) fluorescence in non-activated brain regions and organs of Activating vs. Silencing mice following CNO administration (~ZT3-ZT4). Mutants were paired with littermate controls. The rhodamine fluorescence (brain:blood) of each mutant was normalized to the fluorescence of its littermate control (Excitation=505nm, Emission=560nm). Data represent mean ± SEM (error bars). Individual data points are shown. *p<0.05 by unpaired Student's t-test.
(D) Representative sagittal sections of the cortex immunostained for lectin (green), rat anti-CD45 (red) and DAPI (blue) of littermate control mice (top), a Silencing mouse (bottom left) and an Activating mouse (bottom right) collected 3 hours after injection of CNO. Dosages are noted. There were no alterations in CD45+ cells due to neuronal modulation. n=3 per group. Scale bar represents 200 μm
(E) Evan's Blue raw fluorescence of the plasma and corresponding brains of Activating mice (green) and respective littermate controls (blue) (left) and Silencing mice (red) and respective littermate controls (blue) (right) following CNO administration. The dotted lines represent the autofluorescence of a control mouse in the given batch that was not injected with Evan's Blue (Excitation=620nm, Emission=680nm). Note that plasma was diluted an extra 40X.

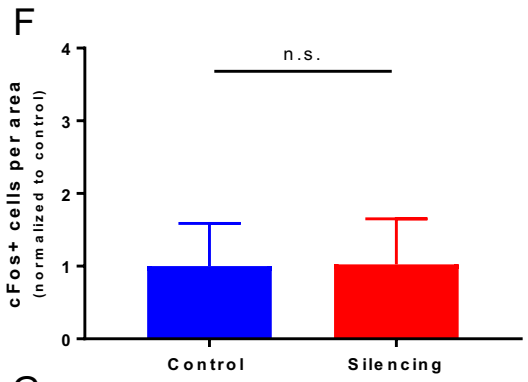

A
Silencing
Activating
Log2 Fold Change
0.5
0.0
-0.5
**
n.s.
*
**
n.s.
*
Arntl
Cry1
Cry2
Per1
Nr1d1
Nr1d2


B
Log2 Fold Change
(+Whisker vs. -Whisker)
1.0
0.5
0.0
-0.5
**
***
n.s.
Arntl
Cry1
Cry2
Per1
Nr1d1
Nr1d2


C
HA/DAPI
3V


D
DAPI/Bmal1/HA
3V


E
DAPI / Bmal1/ cFos
Control (1.0 mg/kg)
Silencing (1.0 mg/kg)
Control (0.5 mg/kg)
Activating (0.5 mg/kg)


F
cFos+ cells per area
(normalized to control)
4
3
2
1
0
n.s.
Control
Silencing

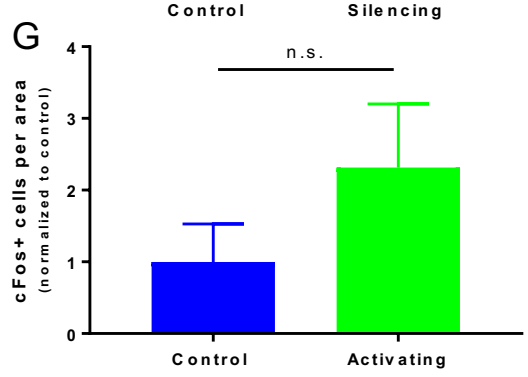

G
cFos+ cells per area
(normalized to control)
4
3
2
1
0
n.s.
Control
Activating

Figure S4. Neuronal Activity-Dependent Effect on Core Circadian Clock (Related to Figures 5 and 6)

(A) Log2 fold change of mRNA expression in Activating or Silencing groups relative to respective littermate controls of core circadian clock genes in brain endothelial cells after DREADDs-mediated manipulation of glutamatergic activity. Data represent mean ± SEM (error bars). n=4 mice per group. *p<0.05, **p<0.005, n.s. (not significant) by Wald Test.

(B) Log2 fold change of mRNA expression in +Whisker group relative to –Whisker group of core circadian clock genes in brain endothelial cells after behaviorally motivated changed in barrel cortex neurons. Data represent mean ± SEM (error bars). n=3 mice per group. **p<0.005, ***p<0.001, n.s. (not significant) by Wald Test.

(C) Representative coronal section of an Activating mouse SCN stained for rabbit anti-HA (red) and DAPI (blue). 3V represents the third ventricle and the dotted area represents the SCN. Scale bar represents 200 μm.

(D) Representative coronal section of an Activating mouse SCN stained for rabbit anti-Bmal1 (green), rat anti-HA (red) and DAPI (blue). 3V represents the third ventricle and the dotted area represents the SCN. Scale bar represents 100 μm.

(E) Representative coronal sections of the SCN immunostained for rabbit anti-Bmal1 (green),goat anti-cFos (red) and DAPI (blue) of littermate control mice (top), a Silencing mouse (bottom left) and an Activating mouse (bottom right) collected 3 hours after injection of CNO. Dosages are noted. Scale bar represents 200 μm.

(F) Quantification of cFos+ cells per mm^2 in the SCN of Activating mice vs paired littermate control mice. Data represent mean ± SEM (error bars). n=6 mice per group. n.s.=not significant (p=0.119) by Unpaired Student's t-test.

(G) Quantification of cFos+ cells per mm^2 in the SCN of Silencing mice vs paired littermate control mice. Data represent mean ± SEM (error bars). n=5 mice per group. n.s.=not significant (p=0.489) by Unpaired Student's t-test.

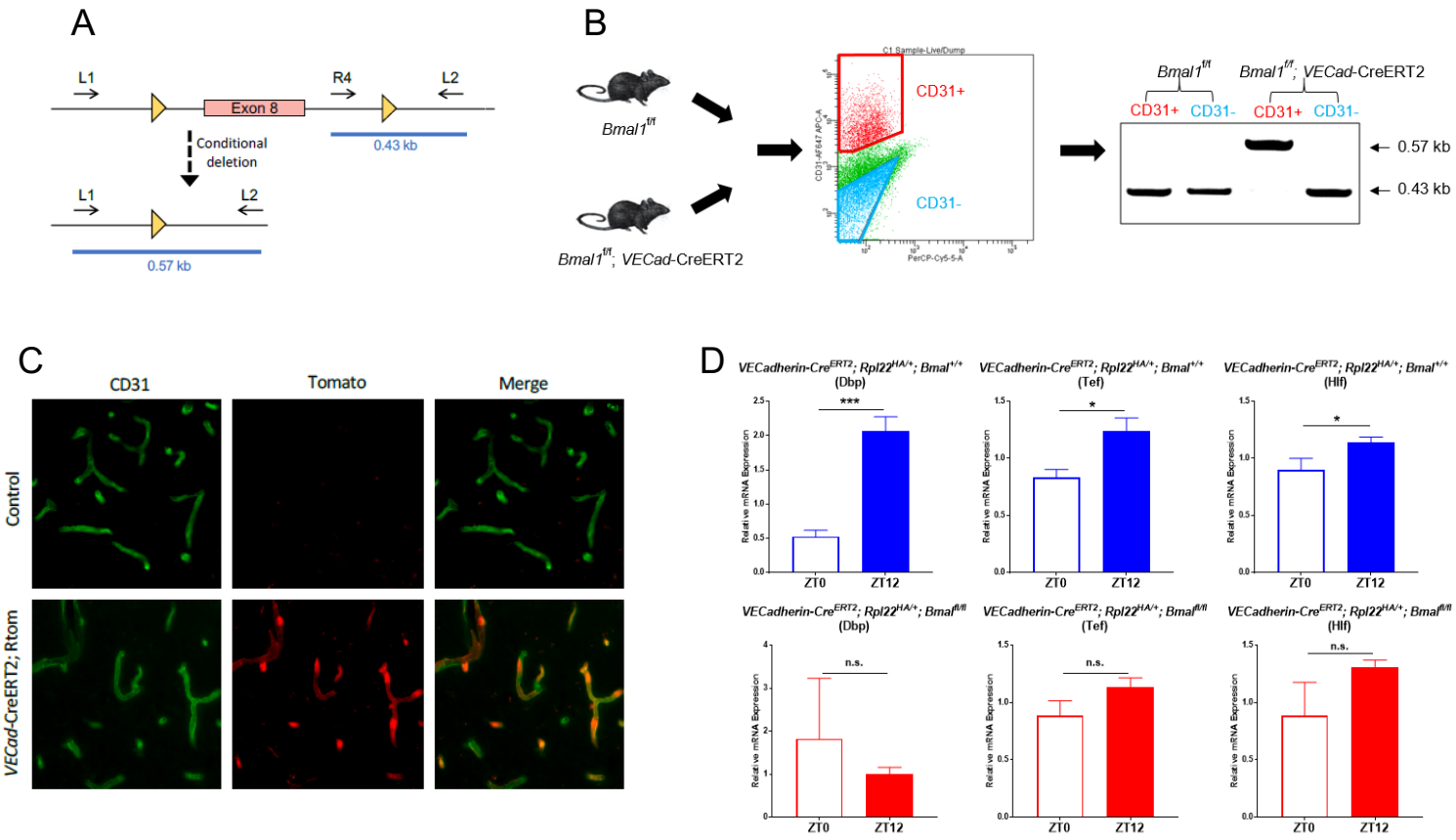

A
L1
Exon 8
R4
L2
Conditional deletion
0.43 kb
L1
L2
0.57 kb
B
Bmal1f/f
Bmal1f/f; VECad-CreERT2
CD31+
CD31-
Bmal1f/f
Bmal1f/f; VECad-CreERT2
CD31+ CD31-
CD31+ CD31-
0.57 kb
0.43 kb
C
CD31
Tomato
Merge
Control
VECad-CreERT2; Rtom
D
VECadherin-CreERT2; Rpl22HA/+; Bmal+/+ (Dbp)
VECadherin-CreERT2; Rpl22HA/+; Bmal+/+ (Tef)
VECadherin-CreERT2; Rpl22HA/+; Bmal+/+ (Hlf)
VECadherin-CreERT2; Rpl22HA/+; Bmalfl/fl (Dbp)
VECadherin-CreERT2; Rpl22HA/+; Bmalfl/fl (Tef)
VECadherin-CreERT2; Rpl22HA/+; Bmalfl/fl (Hlf)
Relative mRNA Expression
***
*
*
n.s.
n.s.
n.s.
ZT0
ZT12
E
Bmal1f/f
Bmal1f/f; VECad-CreERT2
Water Consumption (cm)
Zeitgeber Time
F
Bmal1f/f
Bmal1f/f; VECad-CreERT2
Food Consumption (grams)
Zeitgeber Time
G
BICW=0.68
Bmalf/f
Bmalf/f; VECad-CreERT2
Relative Abcb1a mRNA expression
Zeitgeber Time (h)

Figure S5. Validation of Endothelial-specific *Bmal1* knockout and diurnal behavior (Related to Figure 5)

(A) Schematic of conditional disruption of *Bmal1* and expected PCR product sizes. Yellow triangles represent loxP sites. L1, R4, and L2 represent primers. Adapted from Figure 5A of (Storch *et al.*, 2007).

(B) Schematic of strategy to purify CD31+ (endothelial) cells and CD31- (non-endothelial) cells to determine if *Bmal1* was disrupted from the cells' genomes of endothelial-specific *Bmal1* knockout mice and littermate controls by PCR and gel electrophoresis.

(C) Representative image of section stained with rat anti-CD31 (green) and endogenous tdTomato fluorescence (red) in VECadherin-Cre^{ERT2}; Rosa-lsl-tdTomato mice and wildtype controls in the cortex.

(D) Relative mRNA expression of endothelial PAR bZip genes at ZT0 vs. ZT12 normalized to *GAPDH* in RiboTag-purified brain endothelial cells from littermate control mice (top) and Ribotag-purified brain endothelial cells from endothelial-*Bmal1* conditional knockout mice (bottom). Expression levels represent $2^{-\Delta\Delta ct}$. Data represent mean ± SEM (error bars). n=5. *p<0.05, ***p<0.001, n.s. (not significant) by unpaired Student's t-test.

(E) Water intake at the end of the dark and light periods across 4 days in endothelial-specific *Bmal1* knockout mice and littermate controls. n=8-9 per group.

(F) Chow intake at the end of the dark and light periods across 4 days in endothelial-specific *Bmal1* knockout mice and littermate controls. n=8-9 per group.

(G) Relative mRNA expression of *Abcb1a* normalized to *GAPDH* across a 24 hour day (12:12 hour dark:light) in littermate controls (left) and endothelial-*Bmal1* knockout mice (right). Expression levels represent $2^{-\Delta\Delta ct}$. Data represent mean ± SEM (error bars). n=4 mice per group. Rhythmicity was assessed by linear regression. Results are represented as solid lines if the statistical model indicates rhythmicity. Non-rhythmic fits are represented by dashed lines. The statistical model was only considered if the BICW > 0.4.

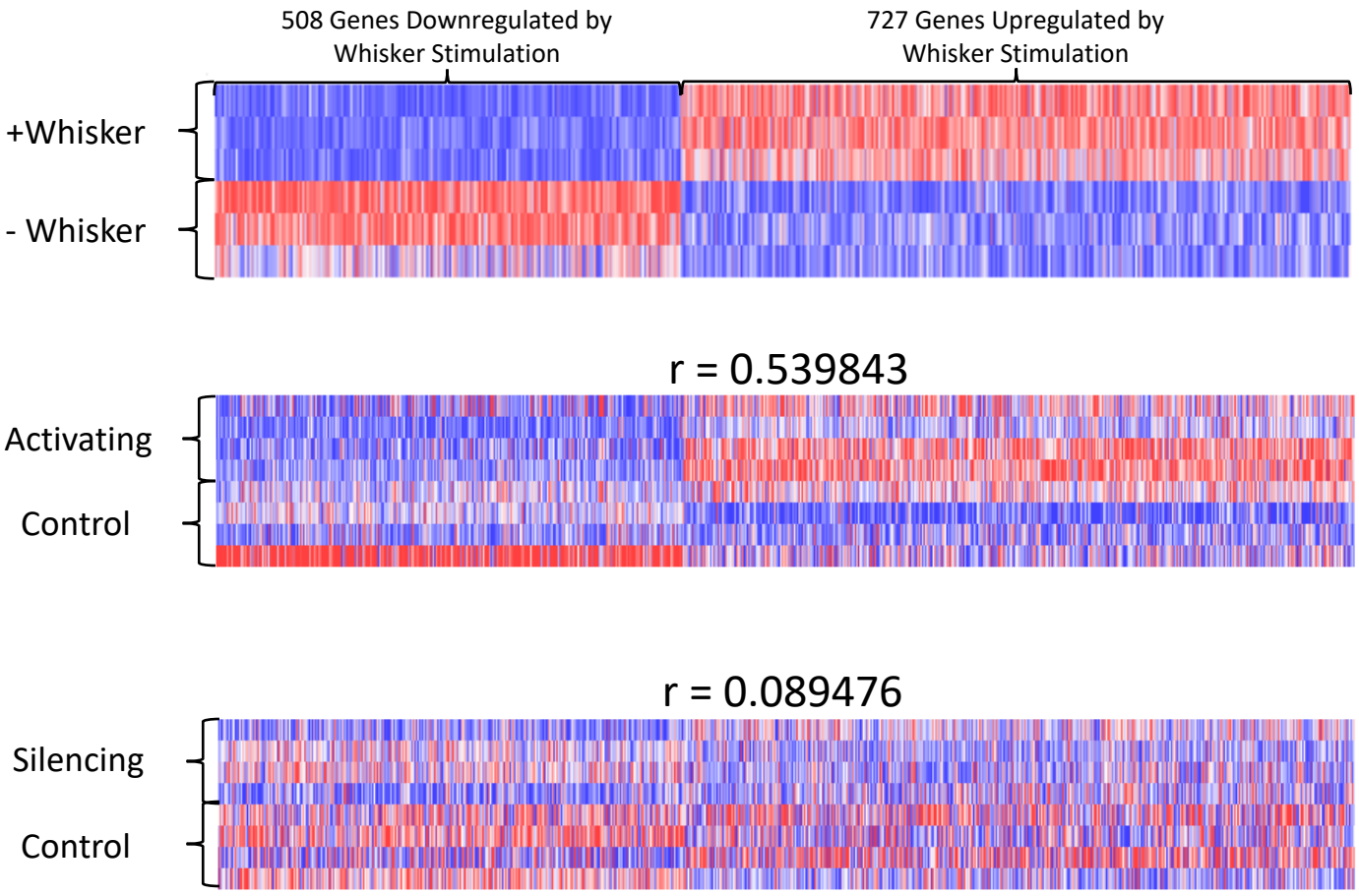
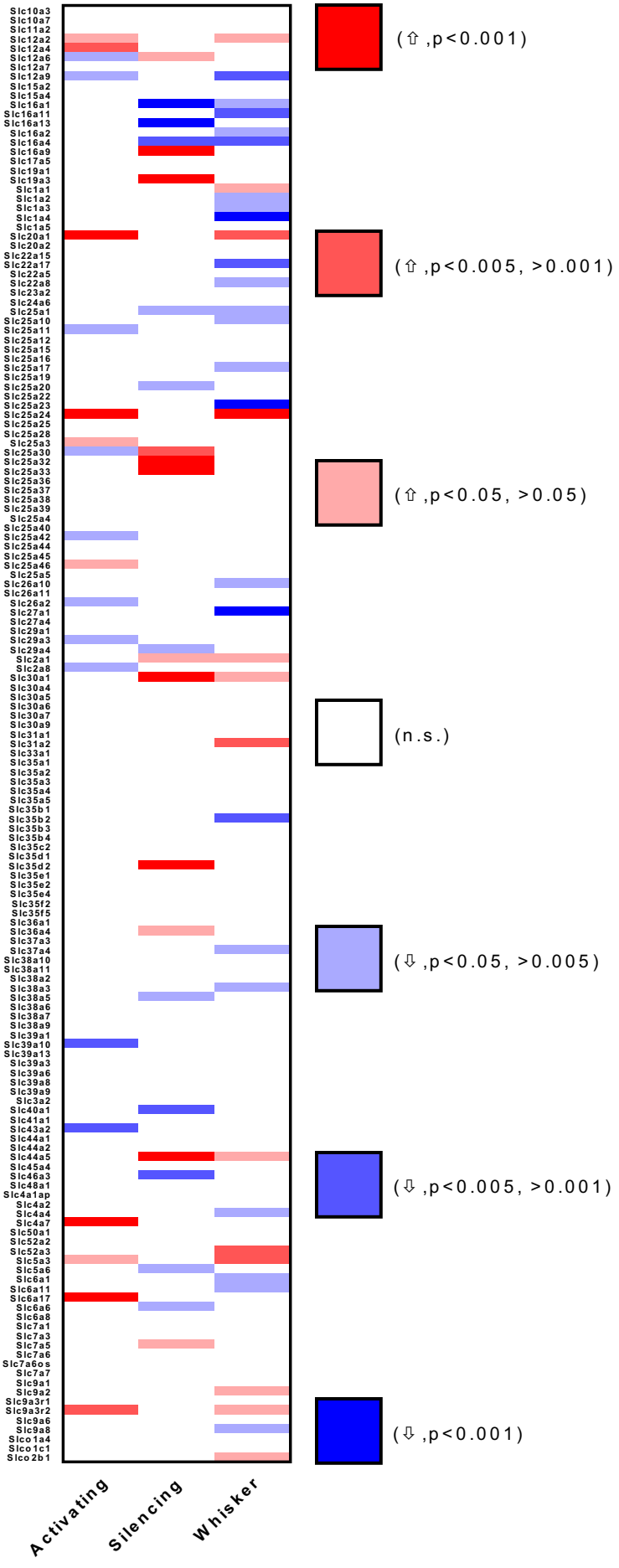


Figure S6. Comparison of Behaviorally Motivated vs. DREADDs-Mediated, Neuronal Activity-Regulated Brain Endothelial Transcriptomes (Related to Figure 6)

Heat maps of genes statistically significantly (by Wald Test) regulated by whisker stimulation in the +Whisker and –Whisker replicates (top) and the same genes viewed in the Activating replicates and paired littermate control replicates (middle) and the Silencing replicates and paired littermate control replicates (bottom). Color scale represents arbitrary units of expression. Blue represents lower expression and red represents higher expression. Pearson Correlation Coefficients shown above respective heat maps.


Slc10a3
Slc10a7
Slc11a2
Slc12a2
Slc12a4
Slc12a6
Slc12a7
Slc12a9
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Slc15a4
Slc16a1
Slc16a11
Slc16a13
Slc16a2
Slc16a4
Slc16a9
Slc17a5
Slc19a1
Slc19a3
Slc1a1
Slc1a2
Slc1a3
Slc1a4
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Slc20a1
Slc20a2
Slc22a15
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Slc26a10
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Slc26a2
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Slc27a4
Slc29a1
Slc29a3
Slc29a4
Slc2a1
Slc2a8
Slc30a1
Slc30a4
Slc30a5
Slc30a6
Slc30a7
Slc30a9
Slc31a1
Slc31a2
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Slc39a3
Slc39a6
Slc39a8
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Slc3a2
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Slc41a1
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Slc4a4
Slc4a7
Slc50a1
Slc52a2
Slc52a3
Slc5a3
Slc5a6
Slc6a1
Slc6a11
Slc6a17
Slc6a6
Slc6a8
Slc7a1
Slc7a3
Slc7a5
Slc7a6
Slc7a6os
Slc7a7
Slc9a1
Slc9a2
Slc9a3r1
Slc9a3r2
Slc9a6
Slc9a8
Slco1a4
Slco1c1
Slco2b1
Activating
Silencing
Whisker
(⇧,p<0.001)
(⇧,p<0.005, >0.001)
(⇧,p<0.05, >0.05)
(n.s.)
(⇩,p<0.05, >0.005)
(⇩,p<0.005, >0.001)
(⇩,p<0.001)

Figure S7. Neuronal Activity-Regulated Slc Transporter Transcriptome (Related to Figures 3 and 6)

Heat map for binned p-values and activity-regulated directionality of Slc transporters (>10 average CPM) in Activating vs. Control (left), Silencing vs. Control (middle) and +Whisker vs. –Whisker (right). Color scale denotes if a given gene was upregulated (↑) (red) or downregulated (↓) (blue) and whether the change was statistically significant by Wald Test (intensity of color).

Table S1. DAVID Pathway Analysis for 748 genes *downregulated* by glutamatergic *activation*, Related to Figure 2

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Oxidoreductase Activity	5.09
2	Endoplasmic Reticulum	4.51
3	Cilium Biogenesis/Degradation	4.12
4	Protein Transport	3.85
5	WD40 repeat-containing domain	3.27
6	Valine, Leucine and Isoleucine Degradation	2.81
7	Peroxisome	2.68
8	Cell projection	2.62
9	Biotin Carboxylation	2.55
10	PIK-related kinase	2.52
11	Lipid Metabolism	2.41
12	Cell Cycle	2.27
13	Protein Kinase Activity	2.2
14	Ciliary Basal Body	2.13
15	Tetratricopeptide repeat	1.93

Table S2. DAVID Pathway Analysis for 625 genes *upregulated* by glutamatergic *activation*, Related to Figure 2

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Cell-cell Adherens Junction	18.31
2	Actin Filament Binding	10.51
3	Nucleotide Binding	5.82
4	GTP Binding	5.37
5	RNA-binding	4.98
6	Translational Initiation	4.42
7	Protein Transport	3.76
8	Protein Folding	3.58
9	snoRNA Binding	3.43
10	Zinc finger, LIM-type	3.03
11	mRNA splicing	3.02
12	Endosome	2.65
13	Actin Filament Bundle Assembly	2.63
14	Actin Filament Capping	2.62
15	Tubulin	2.51

Table S3. DAVID Pathway Analysis for 603 genes *downregulated* by glutamatergic *silencing*, Related to Figure 2

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Mitochondrion	5.73
2	Cell-cell Adherens Junction	5.68
3	snoRNA Binding	4.28
4	Lipid Metabolism	3.28
5	WD40 repeat-containing domain	3
6	Endoplasmic Reticulum	2.93
7	Box H/ACA snoRNA Binding	2.77
8	Small-Subunit Processome	2.26
9	Ribonucleoprotein	2.23
10	Glycolysis	2.06
11	Heme Biosynthesis	1.86
12	Oxidoreductase	1.84
13	PDZ Domain	1.81
14	Steroid Metabolism	1.68
15	Zinc Finger, LIM Type	1.67

Table S4. DAVID Pathway Analysis for 718 genes *upregulated* by glutamatergic *silencing*, Related to Figure 2

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Pleckstrin Homology Domain	9.02
2	Zinc Ion Binding	7.39
3	Transcriptional Regulation, DNA-binding	6.94
4	GTPase Activation	6.35
5	Guanyl-Nucleotide Exchange Factor Activity	3.95
6	Zinc Finger, PHD type	3.9
7	Src Homology-3 Domain	3.23
8	Phosphotyrosine Interaction Domain	3.17
9	Spectrin Repeat	3.02
10	PDZ Domain	3.01
11	Cell Junction	2.72
12	C2 calcium-dependent membrane targeting	2.53
13	Cell Cycle	2.41
14	Biological Rhythms	2.35
15	SH3	2.17

Table S5. DAVID Pathway Analysis for 138 genes *upregulated* after glutamatergic *silencing* AND *downregulated* after glutamatergic *activation*, Related to Figure 2

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Transcriptional Regulation, DNA-binding	2.93
2	Chromo domain	2.71
3	Cytoskeleton	2.16
4	ABC transporters	1.95
5	Basic-leucine zipper domain, biological rhythms	1.88
6	Chromatin Regulation	1.59
7	C2 calcium-dependent membrane targeting	1.51
8	VEGF Signaling	1.38
9	ATP/Nucleotide Binding	1.38
10	Zinc Finger, PHD type	1.32
11	Phosphatidylinositol signaling	1.2
12	Pleckstrin Homology Domain	1.14
13	Proteoglycans in Cancer	1.13
14	EGF-like Domain	1.1
15	Synaptic Signaling	1.09

Table S6. DAVID Pathway Analysis for 105 genes *upregulated* after glutamatergic *activation* AND *downregulated* after glutamatergic *silencing*, Related to Figure 2

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Cell-cell Adherens Junction	4.95
2	Focal adhesion	4.11
3	RNA-binding	1.89
4	tRNA activity/Protein synthesis	1.24
5	WD40 repeat-containing domain	1.14
6	Ribonucleoprotein	0.99
7	Cell adhesion	0.97
8	Methylation	0.73
9	ATP/Nucleotide Binding	0.7
10	Transcriptional Regulation	0.68
11	Zinc Finger, LIM type	0.58
12	Mitochondrion	0.55
13	Nuclease Activity	0.54
14	Nervous System Development	0.44
15	Endoplasmic Reticulum	0.24

Table S7. DAVID Pathway Analysis for 508 genes *downregulated* by *whisker stimulation*, Related to Figure 6

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Oxidoreductase Activity	5
2	Mitochondrion	4.26
3	Transmembrane	4.1
4	Lysosome	4.1
5	Glycolysis	3.66
6	Endoplasmic Reticulum	3.48
7	Lipid Metabolism	3.41
8	Peroxisome	3.32
9	Cilium Biogenesis/Degradation	3.12
10	Disulfide Bond	2.67
11	Tryptophan Metabolism	2.47
12	Cell Projection	2.47
13	Aldehyde Dehydrogenase Activity	2.47
14	Pyridoxal Phosphate	2.36
15	Biotin Carboxylation	2.29

Table S8. DAVID Pathway Analysis for 727 genes *upregulated* by *whisker stimulation*, Related to Figure 6

Cluster Number	Gene Functional Annotation	Enrichment Score
1	Cell-cell Adherens Junction	15.42
2	Protein Folding	10.03
3	Actin-Binding	6.91
4	Nucleotide-Binding	6.69
5	GTPase Activity	5.25
6	Src Homology-3 Domain	4.76
7	Rap1 Signaling Pathway	3.88
8	SH2 Domain	3.72
9	Endosome	3.63
10	Chaperone Tailless Complex Polypeptide 1	3.2
11	14-3-3 Domain	2.68
12	Endoplasmic Reticulum	2.67
13	Beta Tubulin	2.42
14	Ankyrin Repeat-Containing Domain	2.11
15	Fc gamma R-mediated phagocytosis	2.06