Online supplementary figure legends

Supplementary Figure 1. *Trip8b* germline knockout (KO) mice have increased dentate gyrus neurogenesis and dendritic morphology relative to wild type (WT) mice. (a) Photomicrographs of dentate gyrus subgranular zone Ki67-immunoreactive (+) cells in WT and KO littermates. **(b, c)** Proliferating Ki67+ DG cell number does not differ among groups (**b**, one-way ANOVA, $F_{2,17}$=2.106, p>0.05), but KO mice have more Ki67+ cells in posterior DG (coronal section Bregma -4.12 mm) vs. WT and Het (heterozygous; **c**, two-way ANOVA, genotype [$F_{2,221}$=5.753, p<0.01]; Bregma [$F_{12,221}$=28.39, p<0.0001]; genotype X Bregma [$F_{24,221}$=1.254, p>0.05]; posthoc, WT vs. KO: *a* p<0.05, *a'* p<0.01, KO vs. Het: *b* p<0.05, *b'* p<0.01). **(d)** Photomicrographs of dentate gyrus subgranular zone DCX+ cells in WT and KO littermates. **(e, f)** KO mice have more DCX+ DG cells (**e)** and more DCX+ cells in the posterior DG **(f)** vs. WT and Het (**e**, one-way ANOVA, $F_{2,17}$=11.84, ***p<0.001, posthoc, **p<0.01; **f**, two-way ANOVA, genotype [$F_{2,221}$=10.09, p<0.0001]; Bregma [$F_{12,221}$=20.54, p<0.0001]; genotype X Bregma [$F_{24,221}$=0.9315, p>0.05]; posthoc, WT vs. KO: *a* p<0.05, *a'* p<0.01, KO vs. Het: *b* p<0.05, *b'* p<0.01). Scale bars **(a)**=200 μm, applies **(a, d)**, n=6-7/group. **(g)** Reconstruction of soma/dendritic tree of representative DG DCX+ neurons in WT and KO mice. Scale bar **(g)**=10 um. **(h-j)** DCX+ DG granule cell layer (GCL) neurons in KO mice have longer dendrites **(h)** and more nodes **(i)** and ends **(j)** vs. WT (t-test, ****p<0.0001; **h-j)**. **(k-m)** Many measures of dendritic maturation were greater in the posterior DG of KO vs. WT mice, with only length being greater in the anterior DG. **(k)** Dendritic length analysis by anterior vs. posterior Bregma level (two-way ANOVA, genotype [$F_{1,97}$=35.13, p<0.0001]; Bregma level [$F_{1,97}$=0.2498, p>0.05]; genotype X Bregma level [$F_{1,97}$=5.2, p<0.05]; posthoc, KO Bregma level vs. WT Bregma level: *p<0.05, ****p<0.0001). **(l)** Dendritic node by anterior vs. posterior Bregma level (two-way ANOVA, genotype [$F_{1,97}$=35.01, p<0.0001]; Bregma [$F_{1,97}$=0.2367, p>0.05]; genotype X Bregma [$F_{1,97}$=8.723, p<0.01]; posthoc, KO Bregma level vs. WT Bregma level: ****p<0.0001). **(m)** Dendritic end number by anterior vs. posterior Bregma level (two-way ANOVA, genotype [$F_{1,97}$=35.73, p<0.0001]; Bregma [$F_{1,97}$=0.2048, p>0.05]; genotype X Bregma [$F_{1,97}$=8.475, p<0.01], posthoc, KO Bregma level vs. WT Bregma level: ****p<0.0001). n=18-21

neurons/animal, 3 animals/group in each bar. Mean±SEM shown **(b-c, e-f, h-m)** with data points from individual animals **(b, e)** or cells **(h-m)** overlaid. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 2. Brain protein expression pattern of TRIP8b. (a-h) Photomicrographs of coronal brain sections from WT **(a-d)** and *Trip8b* germline KO littermate mice **(e-h)** processed for TRIP8b immunohistochemistry(red). **(a)** Low magnification view of TRIP8b immunoreactivity in a coronal brain section of WT mice, with dotted squares indicating regions presented in higher magnification in **(b)** and **(d)**. **(b)** In WT mice, TRIP8b is expressed in cell bodies of the cerebral cortex (Ctx), particularly in layer V cell bodies and layers I-IV proximal and distal compartments of apical dendrites. **(c)** In WT mice, TRIP8b is also expressed in cell bodies of the entorhinal cortex (Ent) layers II/III and V, and in Ent terminals in layer VI. **(d)** In WT mice, TRIP8b was also expressed in the hippocampal pyramidal cell layer (SP), stratum lacunosum-moleculare (SLM) and DG molecular layer (Mol). However, TRIP8b+ cell bodies were rarely detected in the DG granular cell layer (GCL). In contrast to the expression of TRIP8b+ cell bodies and processes in WT mice **(a-d)**, TRIP8b-immunoreactivity was not evident in the brains of germline KO mice **(e-h)**. Dotted squares in **(e)** indicate regions presented in higher magnification in **(f)** and **(h)**. **(i)** Ctx, cortex; Ent, entorhinal cortex; DG, dentate gyrus; GCL, granule cell layer; Mol, molecular layer; SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; SLM, stratum lacunosum moleculare. Scale bars **(a)**=1mm applies **(a, e)**; **(b)**=200 μm applies **(b-d, f-h)**. See **Online Methods** and the **Life Sciences Reporting Summary** for detailed experimental information.

Supplementary Figure 3. TRIP8b isoform levels, body weight, and adrenal glad weights in susceptible, resilient, and control groups after chronic social defeat stress (CSDS). See **Fig. 1** in main text for timeline of experiment. **(a-e)** Whole blot images with antibodies against IsoA4 **(a)**,

GAPDH **(b, e)**, IsoA5 **(c)** and total TRIP8b **(d)**. After transferring proteins from gel to nitrocellulose membrane, membranes were horizontally cut to enable immunoblotting for proteins (IsoA4, IsoA5, GAPDH, TRIP8b). Stripping and reprobing was used only for TRIP8b, as the membrane stained for IsoA5 antibody was stripped and the blot was then incubated with TRIP8b antibody. Molecular weight indicators do not transfer from membrane to film, and are hand-drawn post-hoc by laying developed film over membrane. Ladders in **(a-e)** have been added via Adobe Illustrator based on sharpie marks on film. **(f)** Breakdown of social interaction (SI) ratio of control, susceptible, and resilient mice (control: n=10, resilient: n=25, susceptible: n=13). **(g)** Body weight in control, susceptible, and resilient mice before and after CSDS (two-way RM ANOVA, group [$F_{2,46}$=0.1871, p>0.05]; day [$F_{1,46}$=55.84, p<0.0001]; Subjects [matching; $F_{46, 46}$= 5.479, p<0.0001]; group X day [$F_{2,46}$=0.2031, p>0.05]; posthoc, Day 1 vs. Day 11: control p<0.01, susceptible p<0.01, resilient p<0.0001), n=10-26/group. **(h)** Adrenal gland weight in control, susceptible, and resilient mice after CSDS. **(i-q)** Level of TRIP8b isoforms and total TRIP8b in the DG of mice in CSDS experiment. **(i)** IsoA4 in control, susceptible, and resilient mice DG (one-way ANOVA, $F_{2,28}$=2.628 p=0.09). **(j)** Correlation of DG IsoA4 levels in susceptible mice to their SI ratio (linear regression, r2=0.1061, p>0.05, n=15). **(k)** Correlation of DG IsoA4 levels in resilient mice to their SI ratio (linear regression, r2=0.6021, *p<0.05, n=7) **(l)** IsoA5 in control, susceptible, and resilient mice DG (one-way ANOVA, $F_{2,28}$=0.01259, p>0.05). **(m)** Correlation of DG IsoA5 levels in susceptible mice to their SI ratio (linear regression, r2=0.02063, p>0.05, n=15) **(n)** Correlation of DG IsoA5 levels in resilient mice to their SI ratio (linear regression, r2=1.026e-005, p>0.05, n=7). **(o)** Total TRIP8b in control, Trip8b levels in susceptible mice to their SI ratio. **(p)** Correlation of DG TRIP8b levels in susceptible mice to their SI ratio (linear regression, r2=0.003588, p>0.05, n=15). **(q)** Correlation of DG TRIP8b levels in resilient mice to their SI ratio (linear regression, r2=0.308, p>0.05, n=7). **(i-q)** n=7-15/group. Mean±SEM shown **(f-i, l, o)** with data points from individual animals overlaid **(f, h-q)**. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 4. TRIP8b knockdown efficiency *in vitro,* efficacy *ex vivo* in Ent slices, and *in vivo* EEG power analysis in control mice vs. Ent-infused TRIP8b shRNA mice. (a-b) Whole blot images with Iso1a-4 and GAPDH **(a)** and with total protein staining **(b)**. **(c-e)** In *ex vivo* slice electrophysiology experiments, the resting membrane potential (Vrest) was similar in the four Ent cell types sampled: TRIP8b shRNA EGFP-, TRIP8b shRNA EGFP+, SCR mRNA EGFP-, and SCR mRNA EGFP+ cells, as was peak **(d)** and steady-state **(e)** input-output analysis. Calibration **(d)**=200 msec, 10 mV applies **(d, e)**. **(c)** one-way ANOVA, $F_{3, 29}$=0.6732, p>0.05, **(d)** two-way RM ANOVA, Amp [$F_{8, 232}$= 86.1, p<0.0001]; virus [$F_{3, 29}$=1.264, p>0.05]; Amp X virus [$F_{24, 232}$=3.683, p<0.0001], subject [matching; $F_{29,32}$=3.683, p<0.0001], TRIP8b shRNA EGFP- vs. SCR shRNA EGFP+: Amp posthoc *a'''* p<0.0001; TRIP8b shRNA EGFP+ vs. SCR shRNA EGFP+: *b'''* p<0.0001; SCR shRNA EGFP- vs. SCR shRNA EGFP+: *c'''* p<0.0001, **(e)** two-way RM ANOVA, Amp [$F_{8, 232}$=332.7, p<0.0001]; virus [$F_{3, 29}$=1.296, p>0.05]; Amp X virus [$F_{24, 232}$=1.048, p>0.05], subject [matching; $F_{29,32}$=25.87, p<0.0001]; n=11 TRIP8b shRNA EGFP-, 5 TRIP8b shRNA EGFP+, 13 SCR shRNA EGFP-, 4 SCR shRNA EGFP-. **(f-g)** In *in vivo* EEG analysis, power value for all analyzed waves (delta, theta, alpha, beta, gamma) was similar in control (SCR shRNA) and TRIP8b shRNA Ent KD mice both during the day **(f)** and the night **(g). (f)** two-way ANOVA, bands [$F_{4, 30}$=61.95, p<0.0001]; virus [$F_{1,30}$=0.3025, p>0.05]; bands X virus [$F_{4,30}$=0.07033, p>0.05], **(g)** two-way ANOVA, bands [$F_{4, 30}$=42.28, p<0.0001]; virus [$F_{1,30}$=0.08503, p>0.05]; bands X virus [$F_{4,30}$=0.059, p>0.05]; n=4 SCR shRNA, 4 TRIP8b shRNA). Mean±SEM shown **(c-g)** with data points from individual cells **(c)** or animals **(f, g)** overlaid. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 5. Target specificity of viral-mediated gene transfer in Ent-infused shRNA mice. (a-h) Nine weeks after bilateral Ent stereotaxic infusions of AAV-SCR EGFP or AAV-

TRIP8b EGFP, GFP+ cell bodies were detected in the lateral and medial Ent (lEnt, **a**; mEnt, **b**), and GFP+ terminals were detected in the outer molecular layer (Mol) of the DG **(c, g)**, the middle Mol of DG **(d),** or both middle and outer Mol DG **(e)**. GFP staining was not detected in the subiculum (Sub) **(f)**, CA3 **(g)**, or amygdala (Amyg; **h**) in any animal whose cellular or behavior data are presented in the main text. Dotted lines in **(c-e, g)** delineates DG GCL, in **(f)** outlines subiculum, and in **(h)** outlines amygdala**.** Scale bar **(a)**=200 um applies **(a-h)**. **(i-k)** After the termination of each behavioral experiment, a few animals were identified whose bilateral infusions were off target, with terminals evident in other brain or hippocampal regions (e.g. CA1, CA2/3, or CA3). As shown in **(i-k)**, animals with "off target" infusions (either uni or bilateral off targets; red bars) had distinct behavior in the FST, with "on target" mice (terminals evident in Mol of DG but not in other brain or hippocampal regions) showing less total immobile time vs. controls, and "off target" mice performing similar to controls (One-way ANOVA, **(i)** $F_{2,17}$=3.629, p=0.0487:posthoc **p<0.01, ***p<0.001; n= 8 SCR shRNA, 10 TRIP8b shRNA, 2 TRIP8b shRNA off-target, **(j)** $F_{2,19}$=11.7, p=0.0005: posthoc *p<0.05; n= 10 SHAM/SCR shRNA, 8 SHAM/TRIP8b shRNA, 4 SHAM/TRIP8b shRNA off-target, **(k)** $F_{3,24}$=2.631, p=0.0732: posthoc *p<0.05; n= 8 VEH/SCR shRNA, 8 CORT/SCR shRNA, 8 CORT/TRIP8b shRNA, 4 CORT/TRIP8b shRNA off-target). Amygdala, amyg; Ent, entorhinal cortex; GCL, granule cell layer; Mol, molecular layer; SP, stratum pyramidale; SR, stratum radiatum; SLM, stratum lacunosum moleculare; Sub, subiculum. Mean±SEM shown with data points from individual animals **(i-k)** overlaid. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 6. Ent-infused TRIP8b shRNA mice have similar number of dentate gyrus type-1 radial glial-like cells as control mice. (a) Representative image of GFP+ type-1 cells in the DG SGZ. Scale bar **(a)**=25um. **(b, c)** Stereological assessment of type-1 radial glial-like cell number in the total DG SGZ **(b)** or according to distance from Bregma **(c)** 4 weeks after Ent infusion

of SCR vs. TRIP8b shRNA. **(b)** Unpaired t-test, $p>0.05$, **(c)** two-way ANOVA, virus [$F_{1, 195}=0.02218$, $p>0.05$]; Bregma [$F_{14, 195}=34.61$, $p<0.0001$]; virus X Bregma level [$F_{14, 195}=0.3688$, $p>0.05$], SCR shRNA: n=8, TRIP8b shRNA: n=7. Mean±SEM shown **(b-c)** with data points from individual animals **(b)** overlaid. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 7. Image-guided irradiation-induced ablation of dentate gyrus neurogenesis prevents Ent-infused TRIP8b shRNA-induced reduction in forced swim test (FST) immobility time. (a-b) One week post-bilateral Ent AAV-infusion, SCR shRNA and TRIP8b shRNA mice received either sham (SHAM) or image-guided DG-targeted irradiation (IRR) to ablate neurogenesis. Five weeks later, when DCX+ cells were still depleted **(Fig. 3,** main text**)**, groups did not differ in LM activity [**(a)** two-way ANOVA, treatment [$F_{1, 43}=0.464$, $p>0.05$]; virus [$F_{1, 43}=0.06712$, $p>0.05$]; treatment X virus [$F_{1, 43}=0.3056$, $p>0.05$]; n= 20 SHAM/SCR shRNA, 8 SHAM/TRIP8b shRNA, 10 IRR/SCR shRNA, 9 IRR/TRIP8b)]. **(b)** AAV-TRIP8b shRNA Ent infusion decreased FST immobile time in SHAM mice, but not in IRR mice (two-way ANOVA, treatment [$F_{1, 44}=3.29$, $p>0.05$]; virus [$F_{1, 44}=10.33$, $p<0.01$]; treatment X virus [$F_{14, 195}=2.044$, $p>0.05$] ; Fisher's LSD: *$p<0.05$, **$p<0.01$; n= 20 SHAM/SCR shRNA, 8 SHAM/TRIP8b shRNA, 10 IRR/SCR shRNA, 10 IRR/TRIP8b). Mean±SEM shown with data points from individual animals overlaid. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 8. Ent TRIP8b knockdown (KD) promotes antidepressive-like behaviors under conditions that mimic chronic stress. (a,b) Beginning one week post-bilateral Ent AAV-infusion, mice received vehicle (VEH) or corticosterone (CORT) via drinking water. Four weeks post-infusion, mice were tested for locomotion, novelty suppressed feeding (NSF, **a**), and forced swim test (FST, **b**). While Ent TRIP8b shRNA mice that received VEH had similar latency to feed in NSF with

Ent SCR shRNA mice that received VEH, Ent SCR shRNA mice that received CORT have longer latency to feed compared to any group that received VEH. TRIP8b shRNA mice that treated with CORT have shorten latency to feed compared to SCR shRNA mice that treated with CORT (**(a)** two-way ANOVA, treatment [$F_{1, 40}$=2.925, p>0.05]; virus [$F_{1, 40}$=2.925, p>0.05 (p=0.0648)]; treatment X virus [$F_{1, 40}$=1.882, p>0.05]: virus posthoc *p<0.05; n= 18 VEH/SCR shRNA, 7 VEH/TRIP8b shRNA, 8 CORT/SCR shRNA, 11 CORT/TRIP8b). Ent-infused TRIP8b shRNA mice that received VEH have shortest immobility time in FST compared to all the other group. TRIP8b shRNA that received CORT have shorter immobility time SCR shRNA that received CORT not TRIP8b shRNA that received VEH (**(b)** two-way ANOVA, treatment [$F_{1, 63}$=11.14, p<0.01]; virus [$F_{1, 63}$=11.64, p<0.01]; CORT X shRNA [$F_{1, 63}$=0.4073, p>0.05]: virus posthoc *p<0.05, ***p<0.001; n= 25 VEH/SCR shRNA, 7 VEH/TRIP8b shRNA, 16 CORT/SCR shRNA, 19 CORT/TRIP8b). Mean±SEM shown with data points from individual animals overlaid. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 9. Ent TRIP8b knockdown (KD) under conditions that mimic chronic stress does not change performance on other anxiety- or depressive-like behavioral tests. Beginning one week post-bilateral Ent AAV-infusion, mice received vehicle (VEH) or corticosterone (CORT) via drinking water. Mice were tested for elevated plus maze (EPM, **a-d**) five weeks post infusion and for splash test **(e, f)** nine weeks post infusion. **(a-d)** Ent TRIP8b shRNA mice which receive CORT do not show difference in entries or duration in open arms **(a-b)** or closed arms **(c-d)** of EPM test compared to SCR shRNA mice which received either VEH or CORT (**(a)** One-way ANOVA, $F_{2,48}$=1.521, p>0.05, **(b)** One-way ANOVA, $F_{2,48}$=0.4123, p>0.05, **(c)** One-way ANOVA, $F_{2,48}$=0.4673, p>0.05, **(d)** $F_{2,48}$=0.2527, p>0.05; n= 16 SCR/VEH, 16 SCR/CORT, 19 TRIP8b/CORT). **(e-f)** Ent TRIP8b shRNA mice which receive CORT do not show any difference in grooming frequency **(e)** or total duration of grooming **(f)** compared to SCR shRNA mice which received either VEH or CORT (**(e)**

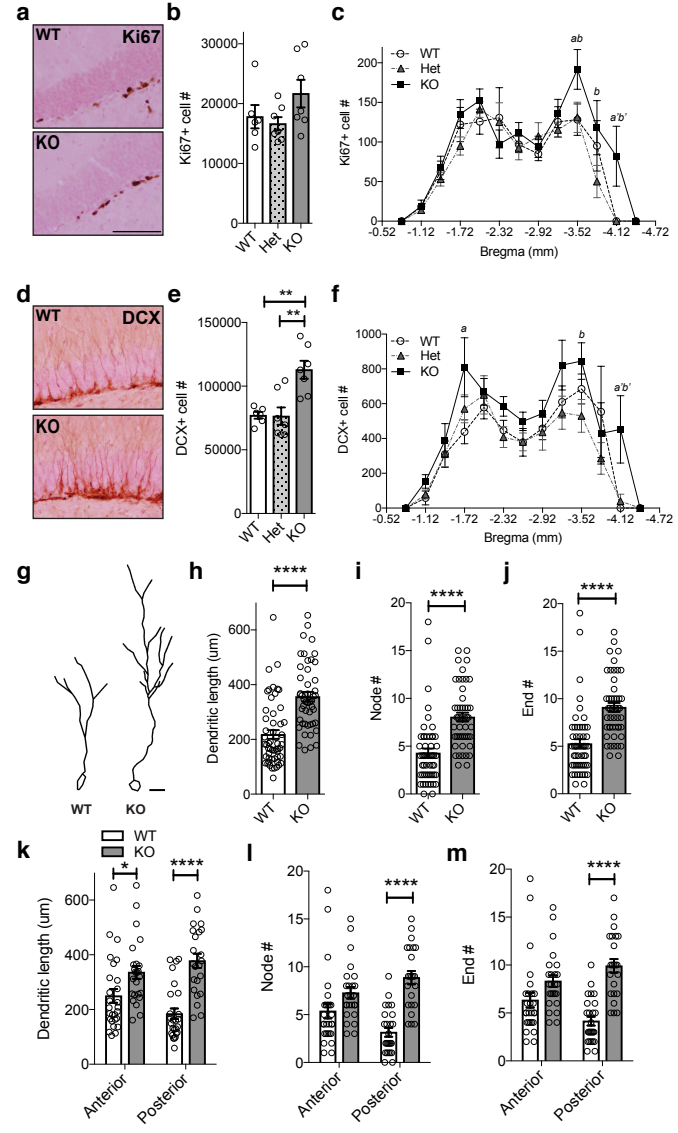
One-way ANOVA, $F_{2,45}$=0.5624, p>0.05, **(f)** One-way ANOVA, $F_{2,45}$=1.474, p>0.05; n=16 SCR/VEH, 14 SCR/CORT, 18 TRIP8b/CORT). Mean±SEM shown with data points from individual animals overlaid. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Figure 10. Target specificity of viral-mediated gene transfer in Ent-infused mCherry and DREADD mice. (a-h) Ten weeks after stereotaxic infusions of AAV-dio-mCherry or AAV-dio-hM3Dq-mCherry bilaterally into Ent, GFP+ cell bodies were evident in the lateral and medial Ent (lEnt, **a, c**; mEnt, **b**), and mCherry+ terminals in the outer molecular layer (Mol) of the DG **(c-f)**, with no terminals evident in CA3 **(f)**, subiculum (Sub, **g**), or amygdala (Amyg, **h**). Dotted lines in **(d-f, g)** delineates DG GCL, in **(g)** outlines subiculum, and in **(h)** outlines amygdala**.** Scale bar **(a)**=200um applies **(a-h)**. **(i)** After CNO injections for 4 weeks, cfos+ cell density was increased in lEnt and mEnt of hM3Dq mice vs. mCherry mice (two-way ANOVA, Ent subregion [$F_{1, 14}$=1.397, p>0.5]; virus [$F_{1, 14}$=23.32, ***p<0.001]; Ent subregion X virus [$F_{1, 14}$=0.2553, p>0.05]: virus posthoc *p<0.05, **p<0.01, n= 5 lEnt/mCherry, 4 lEnt/hM3Dq, 5 mEnt/mCherry, 4 mEnt/hM3Dq). **(j)** cFos+ cell number was also increased along the anterior-posterior axis of the DG (two-way ANOVA, Bregma [$F_{14, 120}$=21.72, ****p<0.0001]; virus [$F_{1, 120}$=53.28, ****p<0.0001]; Bregma X virus [$F_{14, 120}$=2.087, *p<0.05]: virus posthoc **p<0.01, ***p<0.001, ****p<0.0001; n= 5 mCherry, 5 hM3Dq). Amygdala, amyg; Ent, entorhinal cortex; GCL, granule cell layer; Mol, molecular layer; SLM, stratum lacunosum moleculare; Sub, subiculum. Mean±SEM shown **(i-j)** with data points from individual animals overlaid **(i)**. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

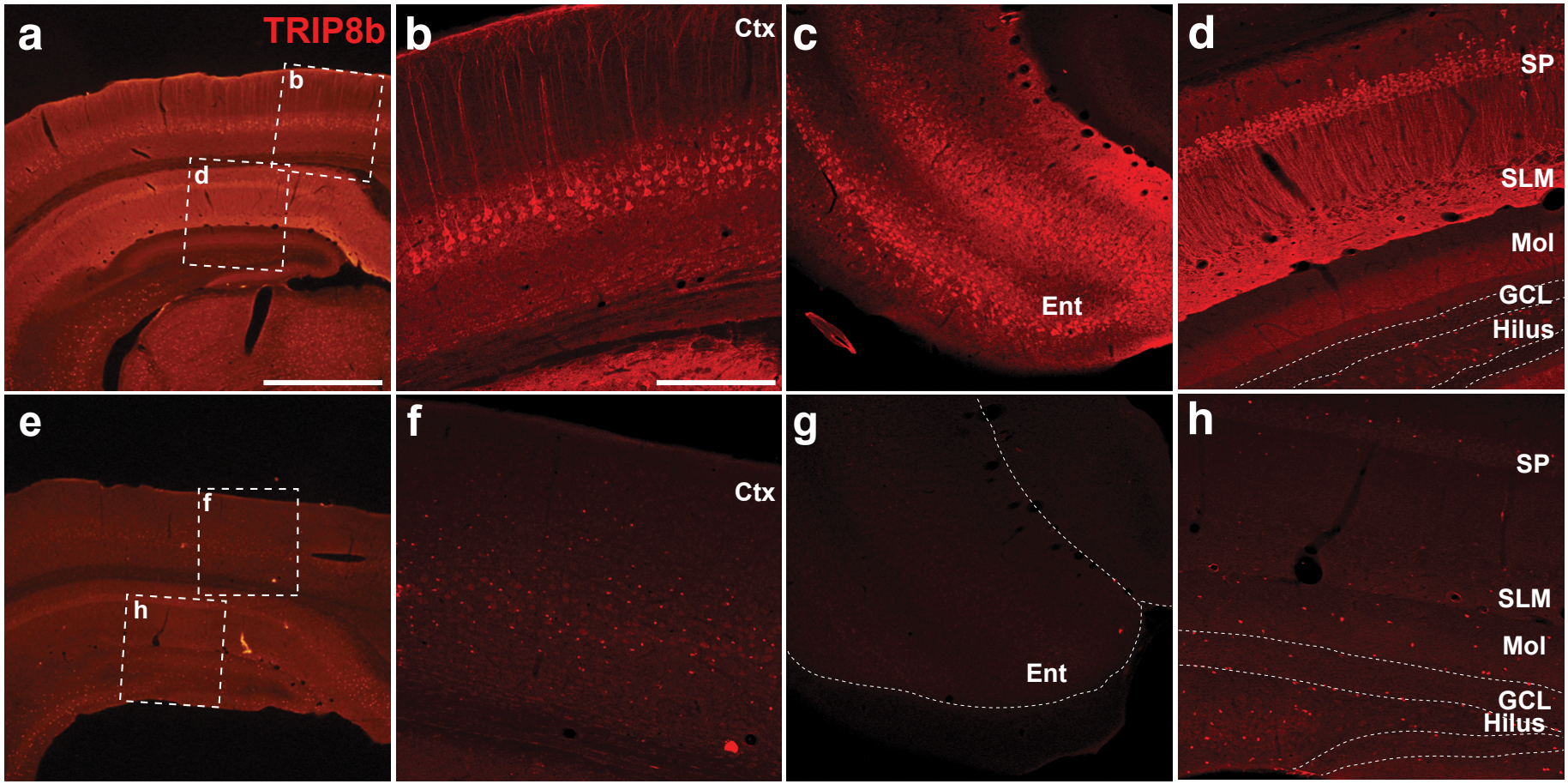
Supplementary Figure 11. *In vivo* EEG analysis reveals similar activity in AAV mCherry-infused vs. AAV-hM3Dq-infused mice. (a) Timeline of *in vivo* awake and behaving EEG

experiments. **(b-d)** Representative hippocampal traces from mice that received bilateral Ent AAV-mCherry **(b)** or AAV-hM3Dq **(c-d)** and CNO at a dose of 1 mg/kg **(b-c)** or 10 mg/kg **(d)**. While the high dose of CNO resulted in epileptiform activity **(d)**, no abnormal activity was detected in either mCherry or hM3Dq mice that received the standard lower dose of CNO. Calibration **(d)**=10 sec, 0.5 mV applies **(b-d)**. **(e-g)** Power value for analyzed waves was similar in control (mCherry) and hM3Dq mice both during the day pre-CNO **(e)**, the day post-CNO **(f)** and the night post-CNO **(g). (e)** two-way ANOVA, bands [$F_{4,30}$=219.2, p<0.0001]; virus [$F_{1,30}$=1.817, p>0.05]; bands X virus [$F_{4,30}$=0.9372, p>0.05], **(f)** two-way ANOVA, bands [$F_{4,30}$=276.6, p<0.0001]; virus [$F_{1,30}$=0.149, p>0.05]; bands X virus [$F_{4,30}$=0.3188, p>0.05], **(g)** two-way ANOVA, bands [$F_{4,30}$=163.6, p<0.0001]; virus [$F_{1,30}$=0.4729, p>0.05]; bands X virus [$F_{4,30}$=0.2888, p>0.05]; n= 4 mCherry, 4 hM3Dq. Mean±SEM shown with data points from individual animals overlaid **(e-g)**. See **Supplementary Table 1** and the **Life Sciences Reporting Summary** for detailed statistical information.

Supplementary Fig 1. Yun et al.



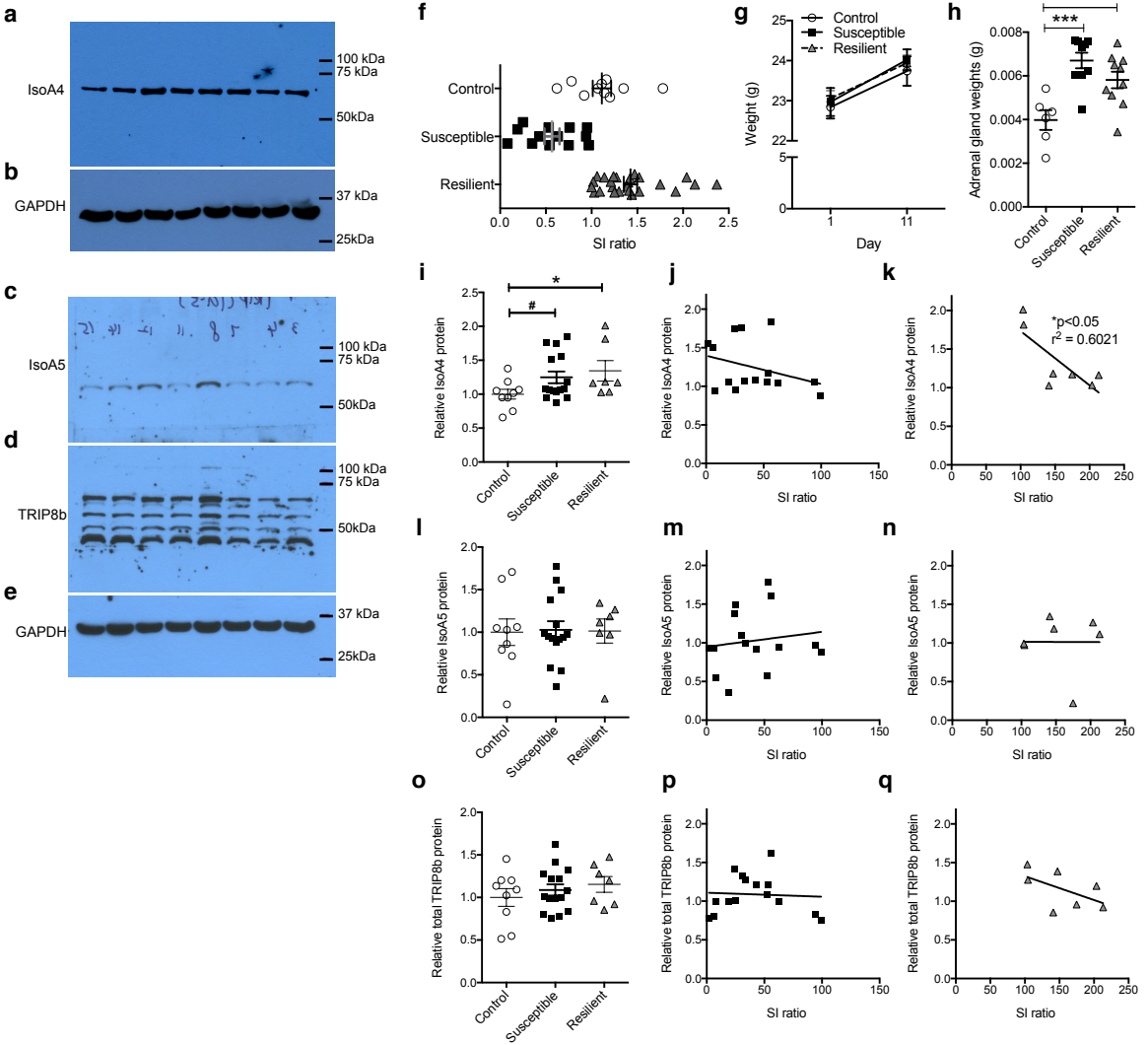
Supplementary Fig 2. Yun et al.

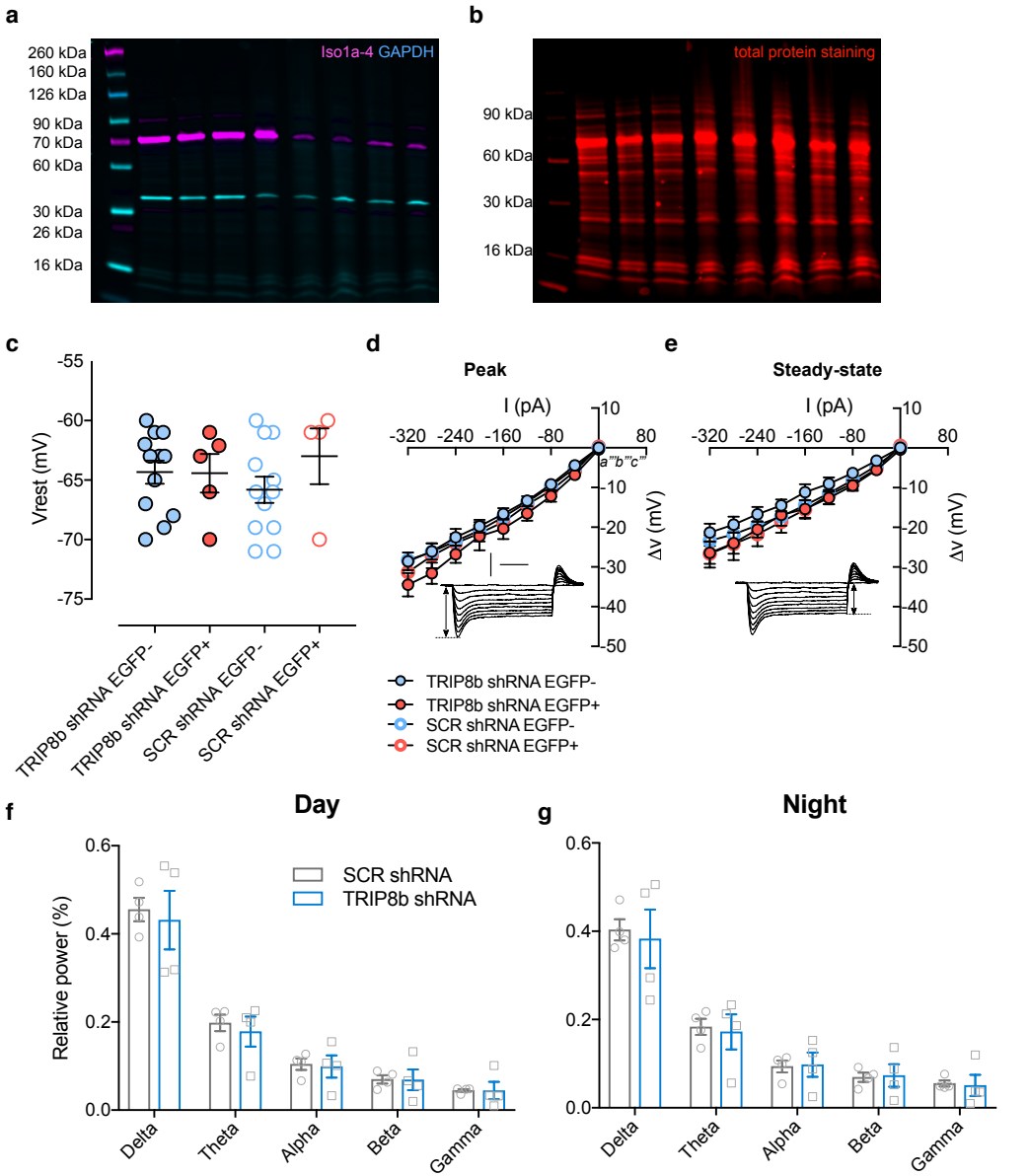


i

Brain region		Expression level	Brain region		Expression level
Ctx	I	+++	CA1	SO	-
	II/III/IV	++		SP	+++
	V/VI	++++		SR	++
Ent	I	-		SLM	++++
	II/III	+++	DG	Mol	+
	IV	-		GCL	-
	V/VI	++++		Hilus	+

Supplementary Fig 3. Yun et al.

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total protein staining
c
Vrest (mV)
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-65
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TRIP8b shRNA EGFP-
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SCR shRNA EGFP-
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SCR shRNA
TRIP8b shRNA
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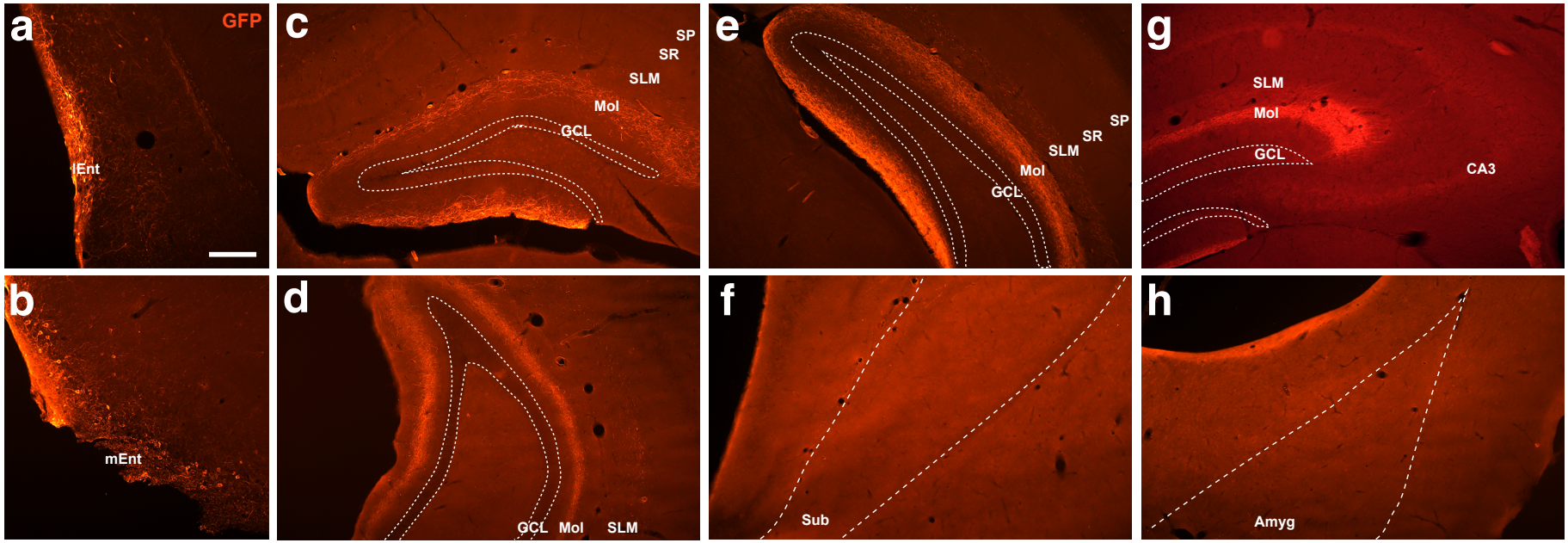
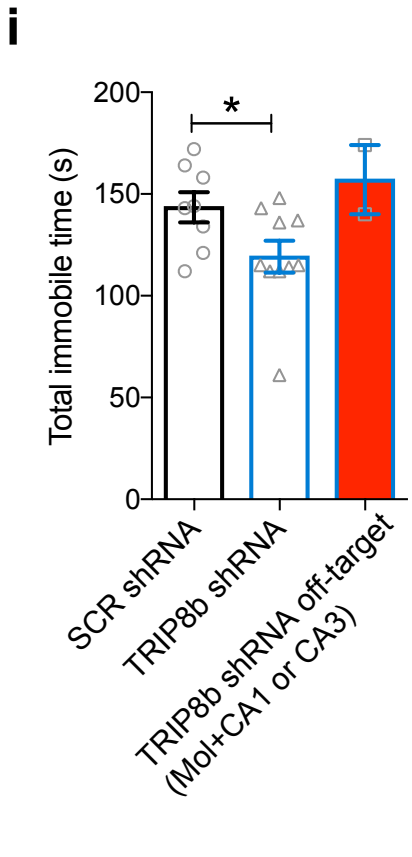
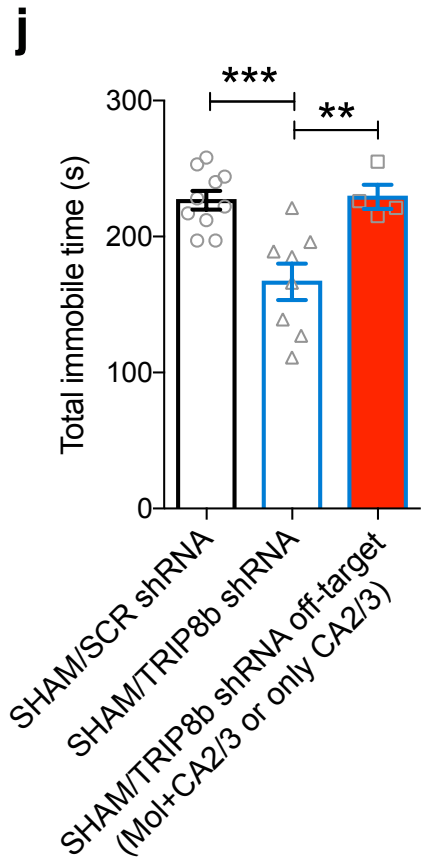
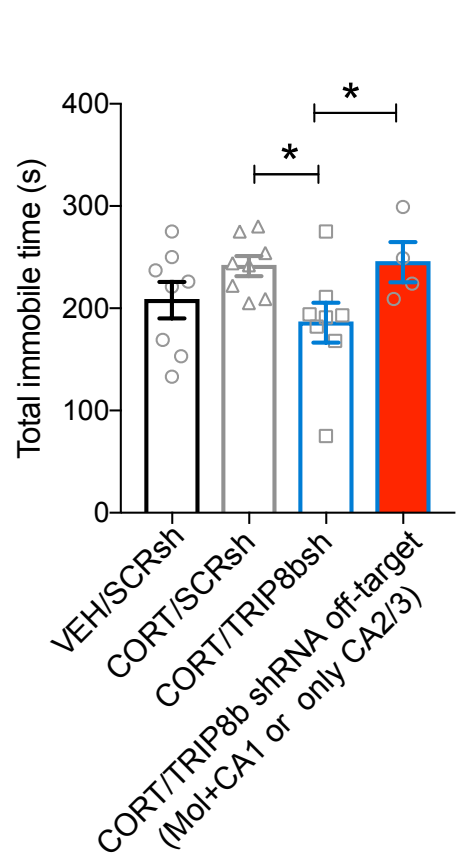
Supplementary Fig 5. Yun et al.

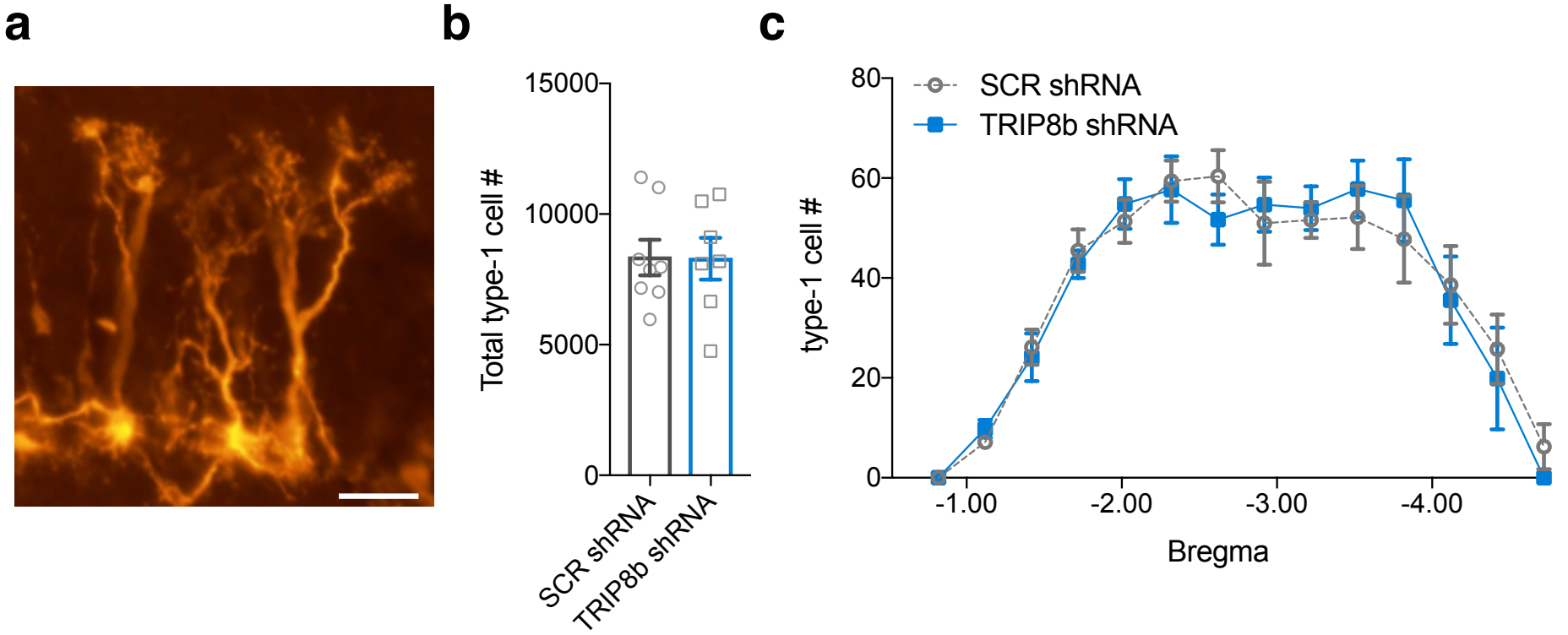




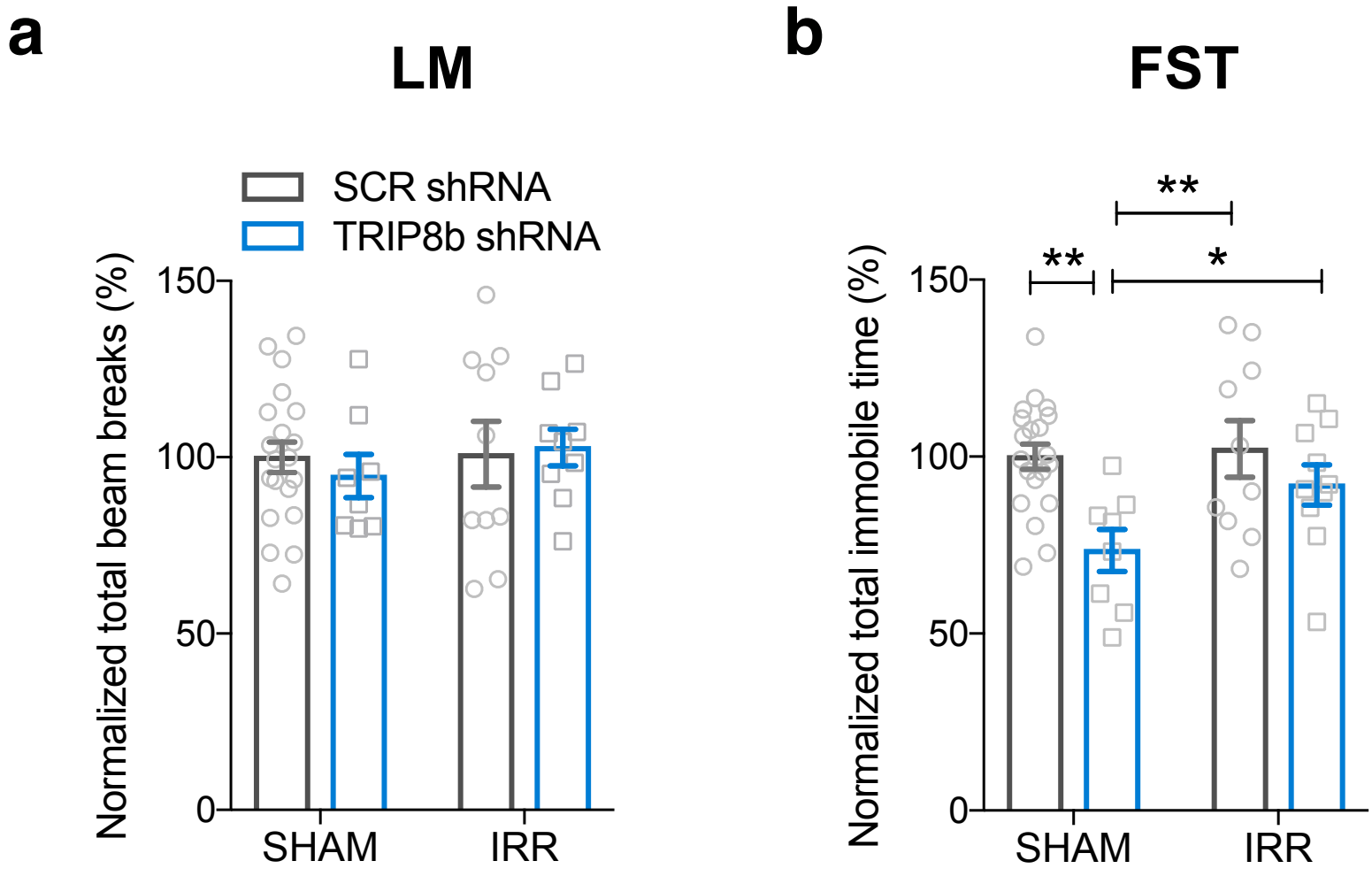




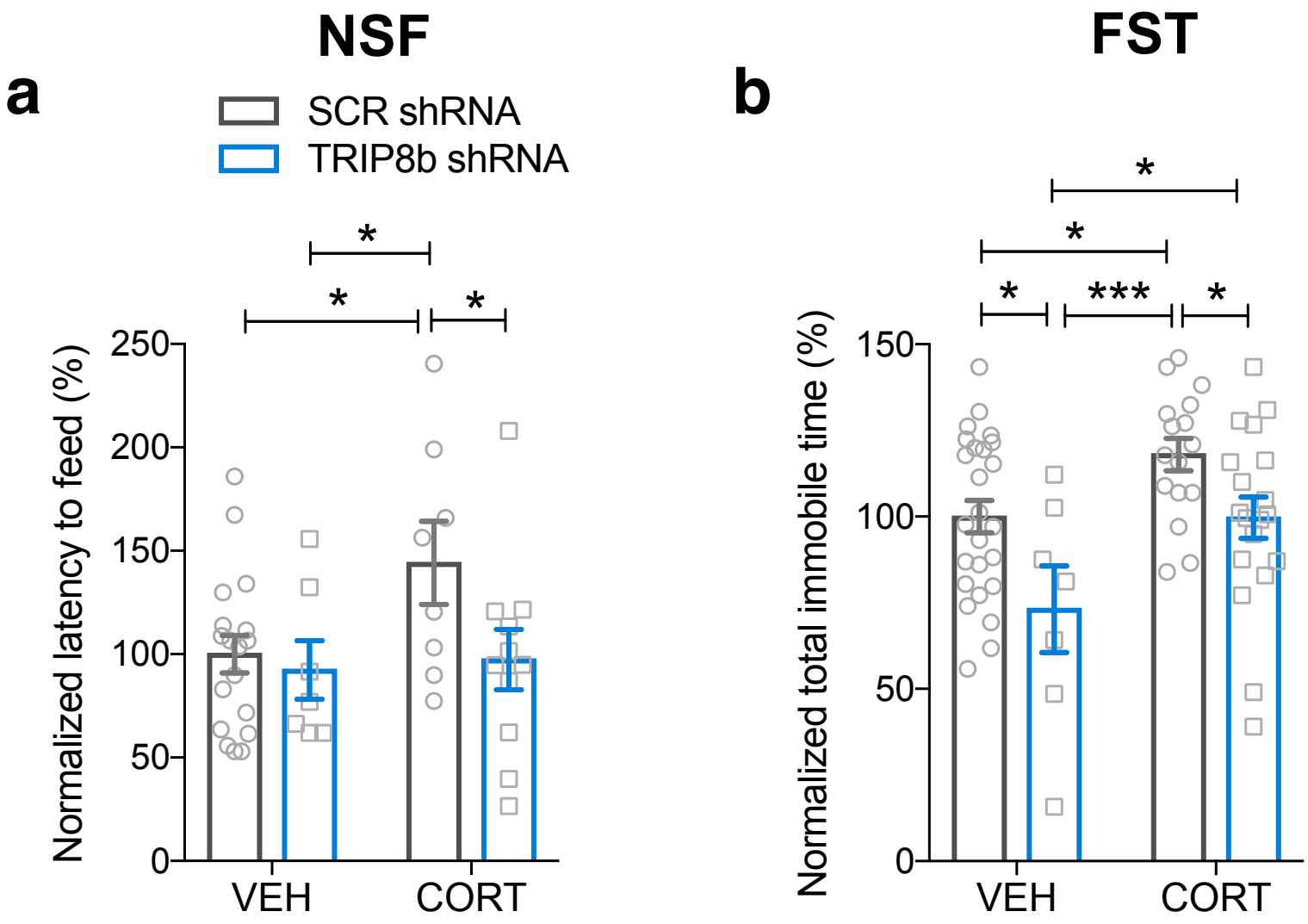
Supplementary Fig 6. Yun et al.



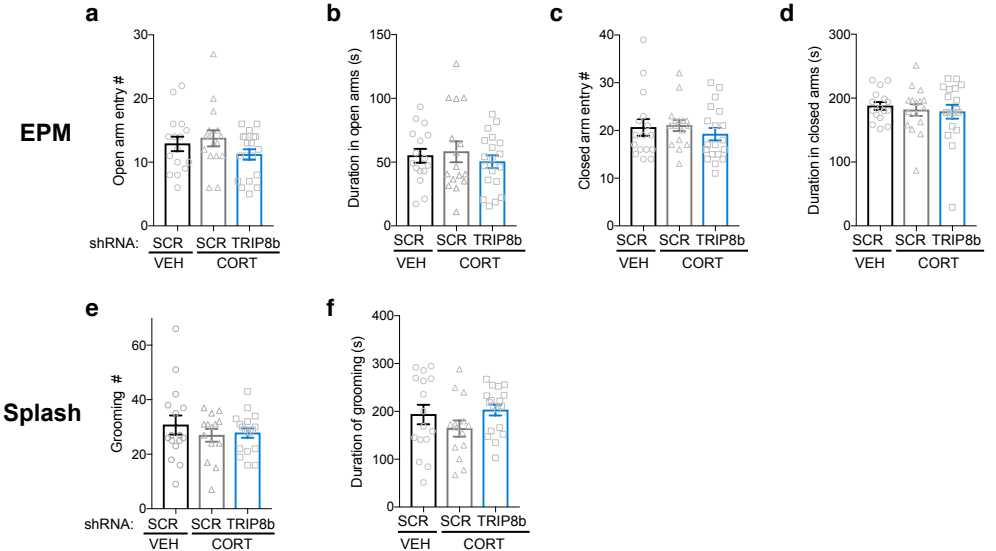
Supplementary Fig 7. Yun et al.



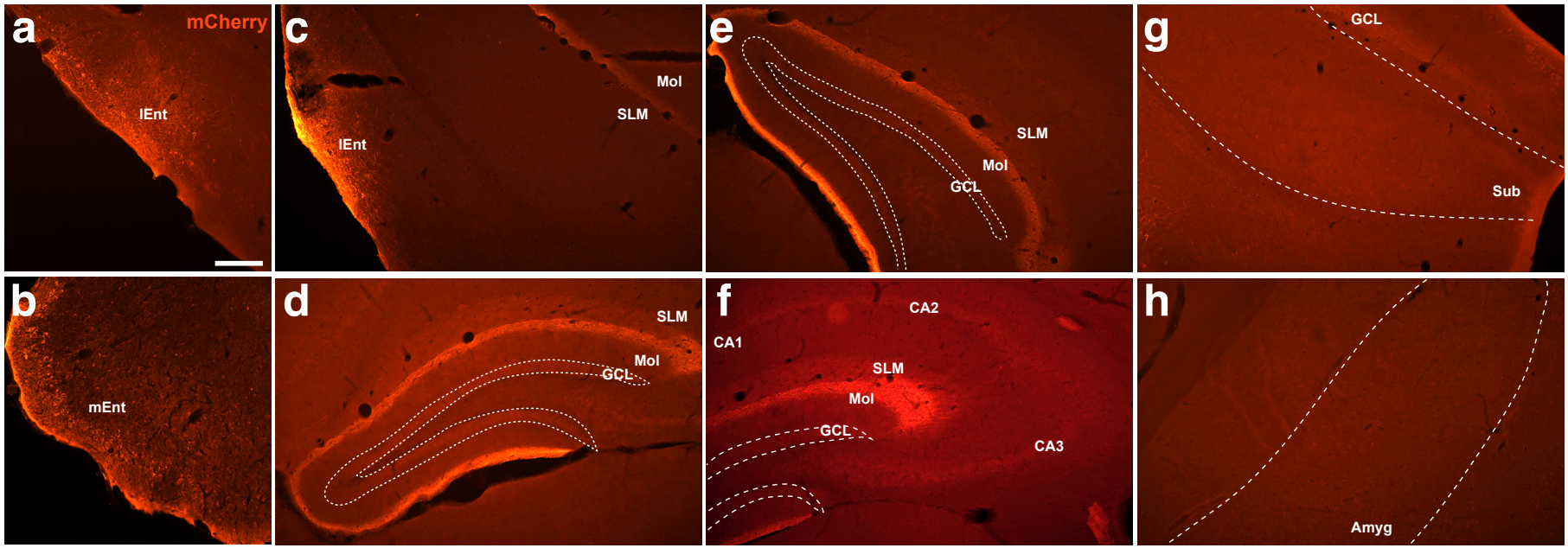
Supplementary Fig 8. Yun et al.

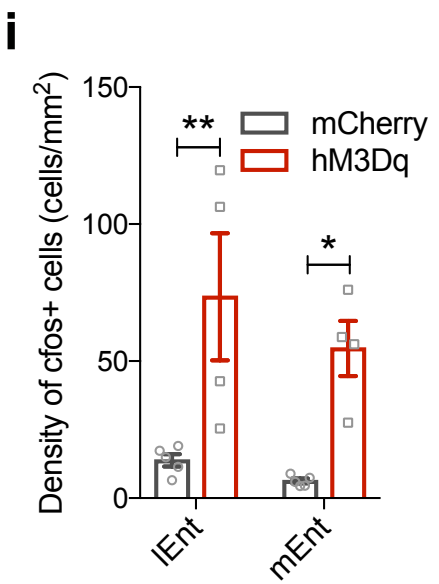


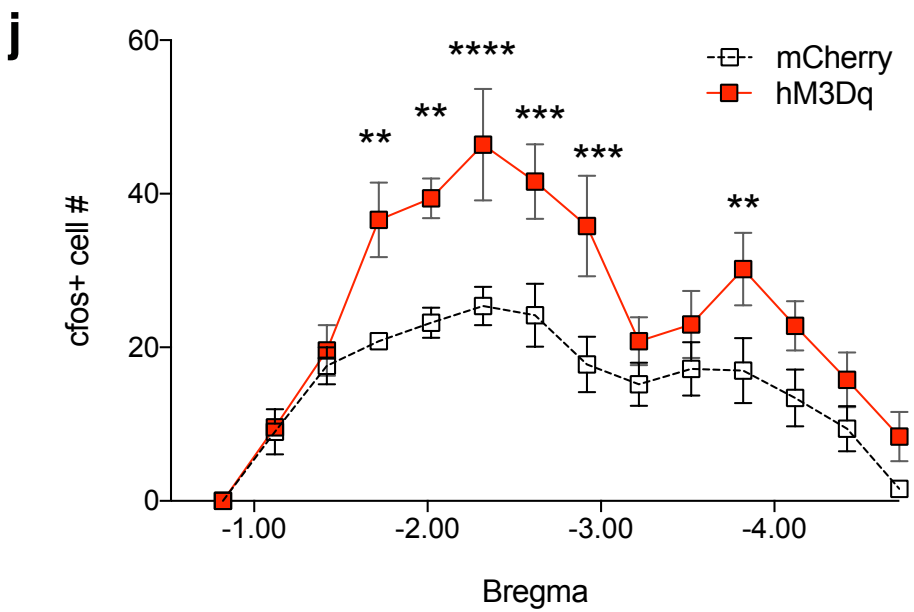
Supplementary Fig 9. Yun et al.



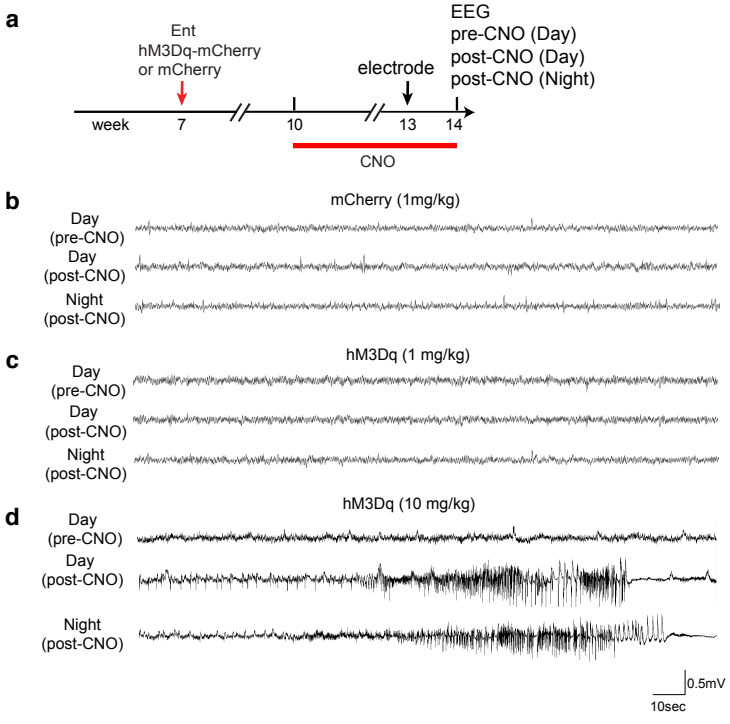
Supplementary Fig 10. Yun et al.

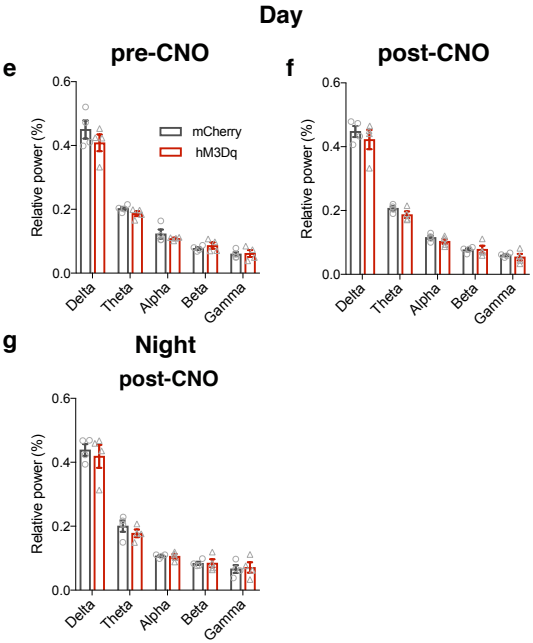






Supplementary Fig 11. Yun et al.





Supplementary Table 1. Reporting statistical results

Subject	Figure	Mean ± SEM	n	Statistics	Interaction	F Value	P value	Post hoc	Was it replicated?
IsoA4 level	1c	1.000 ± 0.07165 1.279 ± 0.07430	Control: 9 Stressed: 22	two-tailed t-test			*p=0.0345		Yes. 2 independent experiments
IsoA5 level	1d	1.000 ± 0.1563 1.023 ± 0.08116	Control: 9 Stressed: 22	two-tailed t-test			p>0.05 (p=0.8872)		Yes. 2 independent experiments
TRIP8b level	1e	1.000 ± 0.1042 1.109 ± 0.05275	Control: 9 Stressed: 22	two-tailed t-test			p>0.05 (p=0.3108)		Yes. 2 independent experiments
TRIP8b level	2c	1 ± 0.1685 0.13 ± 0.01148	SCR shRNA: 4 TRIP8b shRNA: 4	two-tailed t-test			**p=0.0021		Yes. 2 independent experiments
Number of spikes after Ent KD of TRIP8b	2g	0 / 40 / 80 / 120 / 160 / 240 / 280 / 320 0.00 ± 0.00 / 0.524 ± 0.382 / 2.036 ± 0.625 / 4.953 ± 0.712 / 8.024 ± 1.215 / 14.379 ± 1.700 / 17.050 ± 1.683 / 20.264 ± 1.731 0.00 ± 0.00 / 1.334 ± 1.174 / 5.600 ± 2.296 / 10.520 ± 3.120 / 15.260 ± 2.449 / 22.400 ± 2.387 / 25.280 ± 2.379 / 27.800 ± 13.93 0.00 ± 0.00 / 0.00 ± 0.00 / 0.769 ± 0.469 / 3.308 ± 1.273 / 6.846 ± 1.568 / 15.000 ± 2.003 / 18.000 ± 2.022 / 21.000 ± 1.994 0.00 ± 0.00 / 0.00 ± 0.00 / 0.00 ± 0.00 / 0.500 ± 0.500 / 2.500 ± 1.500 / 11.000 ± 2.198 / 14.250 ± 2.287 / 17.000 ± 1.958	TRIP8b shRNA EGFP-: 14 TRIP8b shRNA EGFP+: 5 SCR shRNA EGFP-: 13 SCR shRNA EGFP+: 4	RM two-way	Interaction Input Treatment Subjects (matching)	F (24, 256) = 2.326 F (8, 256) = 188.0 F (3, 32) = 4.143 F (32, 256) = 13.87	p=0.0007 p<0.0001 p=0.0137 p<0.0001	Bonferroni TRIP8b shRNA EGFP+ vs. TRIP8b shRNA EGFP-: a p<0.05, a' p<0.01 TRIP8b shRNA EGFP+ vs. SCR shRNA EGFP-: b p<0.05, b' p<0.01 TRIP8b shRNA EGFP+ vs. SCR shRNA EGFP+: *c* p<0.05, *c'* p<0.01, *c''* p<0.001	No.
DCX+ cell number	2o	68839 ± 2042 76644 ± 2890	SCR shRNA: 6 TRIP8b shRNA: 5	two-tailed t-test			*p=0.0499		No.
BrdU+ cell number	2q	664.0 ± 74.25 1035 ± 145.0	SCR shRNA: 8 TRIP8b shRNA: 7	two-tailed t-test			*p=0.0339		Yes. 2 independent experiments combined.
NeuN/BrdU cell number	2s	350.0 ± 42.74 576.6 ± 88.20	SCR shRNA: 8 TRIP8b shRNA: 7	two-tailed t-test			*p=0.0315		Yes. 2 independent experiments combined.
Dendritic length	2u	189.6 ± 8.300 233.8 ± 10.48	SCR shRNA: 76 TRIP8b shRNA: 95	two-tailed t-test			**p=0.0017		No.
Dendritic nodes	2v	4.434 ± 0.2394 5.547 ± 0.287	SCR shRNA: 76 TRIP8b shRNA: 95	two-tailed t-test			**p=0.0044		No.
Dendritic ends	2w	5.500 ± 0.2410 6.621 ± 0.2918	SCR shRNA: 76 TRIP8b shRNA: 95	two-tailed t-test			**p=0.0047		No.
Activity (LM)	3b	8905 ± 304.0 9734 ± 735.3	SCR shRNA: 16 TRIP8b shRNA: 17	two-tailed t-test			p>0.05 (p=0.3166)		Yes. 2 independent experiments combined.
Forced Swim Test (FST)	3c	143.5 ± 7.358 119.3 ± 7.851	SCR shRNA: 8 SCR shRNA: 10	two-tailed t-test			*p=0.0426		No.
Context, % freezing	3d	33.05 ± 1.664 50.61 ± 4.552	SCR shRNA: 8 TRIP8b shRNA: 7	two-tailed t-test			**p=0.0021		No.
Cue, % freezing	3e	Pre-tone / During-tone 15.714 ± 4.353 / 61.784 ± 6.249 19.999 ± 7.217 / 66.941 ± 2.707	SCR shRNA: 8 TRIP8b shRNA: 7	RM two-way	Interaction Tone (Pre-tone vs. During-tone) shRNA Subjects (matching)	F (1, 13) = 0.004857 F (1, 13) = 55.16 F (1, 13) = 1.117 F (13, 13) = 0.5089	p>0.05 (p=0.09455) p<0.0001 p>0.05 (p=0.3098) p>0.05 (p=0.8817)	Bonferroni *Pre tone vs. During tone SCR shRNA* p<0.01 *Pre tone vs. During tone TRIP8b shRNA* p<0.01	No.
Activity (LM) in IRR experiment	3i	6718 ± 456.9 6361 ± 409.6 6903 ± 349.0	SHAM/SCR shRNA: 10 SHAM/TRIP8b shRNA: 8 IRR/TRIP8b shRNA: 9	One-way		F (2, 24) = 0.4149	p>0.05 (p=0.6651)		Yes. 3 independent experiments combined.
Forced Swim Test (FST) in IRR experiment	3j	226.8 ± 6.868 166.8 ± 13.42 208.7 ± 12.84	SHAM/SCR shRNA:10 SHAM/TRIP8b shRNA: 8 IRR/TRIP8b shRNA:10	One-way		F (2, 25) = 7.070	p=0.0037	Bonferroni *p<0.05 **p<0.01	Yes. 3 independent experiments combined.
Activity (LM) in CORT experiment	4b	10586 ± 698.1 10513 ± 659 10435 ± 762.4	SCR shRNA/VEH: 16 SCR shRNA/CORT: 16 TRIP8b shRNA/CORT: 19	One-way		F (2,48) = 0.01135	p>0.05 (p=0.9887)		Yes. 3 independent experiments combined.
Time spent in light in D/L test	4c	169.3 ± 11.31 162.8 ± 13.7 154.7 ± 13.13	SCR shRNA/VEH: 16 SCR shRNA/CORT: 16 TRIP8b shRNA /CORT:19	One-way		F (2,48) = 0.3328	p>0.05 (p=0.7185)		Yes. 3 independent experiments combined.
Latency to light in /DL test	4d	5.86 ± 0.8118 5.362 ± 0.7654	SCR shRNA/VEH: 16 SCR shRNA/CORT: 16	One-way		F (2,48) = 0.249	p>0.05 (p=0.7806)		Yes. 3 independent experiments combined.

test		5.09 ± 0.7731	TRIP8b shRNA/CORT: 19						combined.
Latency to Feed in NSF test	4e	274.9 ± 17.49 396.1 ± 55.14 267.5 ± 40.07	SCR shRNA/SHAM: 8 SCR shRNA/CORT: 8 TRIP8b shRNA /CORT:11	One-way		F (2,24) = 2.934	p=0.0725	Fisher's LSD *p<0.05	Yes. 3 independent experiments combined.
Food mass in post NSF test	4f	0.1456 ± 0.007076 0.08801 ± 0.01587 0.1006 ± 0.01427	SCR shRNA/SHAM: 8 SCR shRNA/CORT: 8 TRIP8bshRNA/CORT: 11	One-way		F (2,24) = 4.569	p=0.0208	Fisher's LSD *p<0.05 **p<0.01	Yes. 3 independent experiments combined.
FST_CORT experiment	4g	191.8 ± 12.13 226.3 ± 8.986 185.8 ± 10.87	SCR shRNA/SHAM: 16 SCR shRNA/CORT: 16 TRIP8b shRNA/CORT: 19	One-way		F (2,48) = 3.196	p=0.0498	Fisher's LSD *p<0.05	Yes. 3 independent experiments combined.
Total cfos+cells number	5e	DG / CA1 / CA2/CA3 224.8 ± 20.071 / 242.2 ± 31.811 / 191.2 ± 25.60 351 ± 32.278 / 218.4 ± 37.312 / 194.2 ± 6.674	mCherry: 5 hM3Dq: 5	Two-way	Interaction Subregion Treatment (mCherry vs. hM3Dq)	F (2, 24) = 4.221 F (2, 24) = 6.065 F (1, 24) = 2.442	p<0.05 (P=0.0269) p<0.01 (P=0.00740 p>0.05 (P=0.1312)	Bonferroni *p<0.05	No.
Total BrdU+ cell number	5g	1188 ± 50.63 1970 ± 176.1	mCherry: 14 hM3Dq: 14	two-tailed t-test			***p=0.0002		Yes. 2 independent experiments combined.
Bregma BrdU+ cell number post-DREADDs	5h	-0.82 / -1.12 / -1.42 / -1.72 / -2.02 / -2.32 / -2.62 / -2.92 / -3.22 / -3.52 / -3.82 / -4.12 / -4.42 / -4.72 0.000 ± 0.000 / 0.714 ± 0.266 / 3.000 ± 0.611 / 6.071 ± 0.781 / 10.000 ± 1.351 / 9.357 ± 0.723 / 7.071 ± 1.107 / 5.786 ± 0.447 / 4.929 ± 0.774 / 5.286 ± 0.867 / 5.643 ± 0.868 / 6.857 ± 1.073 / 1.357 ± 0.452 / 0.357 ± 0.357 0.000 ± 0.000 / 0.571 ± 0.173 / 4.071 ± 0.880 / 12.714 ± 1.169 / 14.429 ± 1.540 / 12.786 ± 1.704 / 10.714 ± 1.698 / 10.143 ± 1.508 / 10.357 ± 1.532 / 12.286 ± 1.954 / 12.000 ± 2.102 / 8.143 ± 2.019 / 1.214 ± 0.728 / 0.000 ±0.000	mCherry: 14 hM3Dq: 14	Two-way	Interaction Bregma Treatment (mCherry vs. hM3Dq)	F (13, 364) = 2.901 F (13, 364) = 27.90 F (1, 364) = 51.07	p=0.0005 p<0.0001 p<0.0001	Bonferroni *mCherry vs. hM3Dq:* *a* p<0.05 *a'* p<0.01 *a''* p<0.001	Yes. 2 independent experiments combined.
NeuN/BrdU cell number post-DREADDs	5j	706.0 ± 59.11 1618 ± 236.2	mCherry: 5 hM3Dq: 5	two-tailed t-test			**p=0.0057		No.
Activity (LM) post-DREADDs	5l		mCherry: 8 hM3Dq: 7	RM Two-way	Interaction Time Treatment (mCherry vs. hM3Dq) Subjects (matching)	F (79, 1580) = 0.2065 F (79, 1580) = 10.75 F (1, 20) = 0.7316 F (20, 1580) = 3.971	p>0.9999 p<0.0001 p>0.05 (p=0.4025) p<0.0001		Yes. 2 independent experiments combined.
Novelty Suppressed Feeding in NSF test	5m	464.1 ± 70.34 249.6 ± 39.27	mCherry: 8 hM3Dq: 7	two-tailed t-test			*p=0.0239		Yes. 2 independent experiments combined.
Food intake in post NSF test	5n	0.1270 ± 0.01117 0.1557 ± 0.01711	mCherry: 8 hM3Dq: 7	two-tailed t-test			p>0.05 (p=0.1727)		Yes. 2 independent experiments combined.
Activity (LM)	5p		mCherry: 7 hM3Dq: 9	RM Two-way	Interaction Time Treatment (mCherry vs. hM3Dq) Subjects (matching)	F (79, 1106) = 0.7006 F (79, 1106) = 14.82 F (1, 14) = 0.7466 F (14, 1106) = 9.23	p>0.05 (P=0.9775) p<0.0001 p>0.05 (P=0.4021) p<0.0001		Yes. 2 independent experiments combined.
Novelty Suppressed Feeding in NSF test	5q	273.4 ± 50.6 356.8 ± 53.36	mCherry: 7 hM3Dq: 9	two-tailed t-test			p>0.05 (p=0.2870)		Yes. 2 independent experiments combined.
Food intake in post-NSF	5r	0.1277 ± 0.01111 0.1429 ± 0.0206	mCherry: 7 hM3Dq: 9	two-tailed t-test			p>0.05 (p=0.5606)		Yes. 2 independent experiments combined.
Time spent in interaction zone (s) in SI test	5t	mCherry/SHAM / hM3Dq/SHAM / mCherry/CSDS / hM3Dq/CSDS 98.6133333333333 ± 10.0121881280323 / 73.5466666666667 ± 7.27149442075775 / 84.7325 ± 4.71778015419682 / 88.95 ± 4.14630357467146 118.413333333333 ± 6.06184716989063 / 93.12 ± 6.1838240595929 / 80.8225 ± 8.99036074081569 / 102.353333333333 ± 6.1222492070754	mCherry/SHAM: 6 hM3Dq/SHAM: 6 mCherry/CSDS: 16 hM3Dq/CSDS: 12	RM Two-way	Interaction Target Virus Subjects (matching)	F (3, 36) = 2.132 F (1, 36) = 7.494 F (3, 36) = 3.155 F (36, 36) = 2.242	p=0.1132 p=0.0096 p=0.0365 p=0.0088	Fisher's LSD *p<0.05 **p<0.01	Yes. 4 independent experiments combined.
Ki67+ cell number	Supp 1b	17826 ± 1936 16650 ± 1106 21685 ± 2314	WT: 6 Het: 7 KO: 7	One-way		F (2, 17) = 2.106	p>0.05 (p=0.1524)		Yes. 2 independent experiments combined.
		-0.82 / -1.12 / -1.42 / -1.72 / -2.02 / -2.32 / -2.62 / -2.92 / -3.22 / -3.52 / -3.82 / -4.12 / -4.42			Interaction	F (24, 221) = 1.254	p>0.05 (p=0.1989)	Bonferroni	

Ki67+ cell number, Bregma	Supp 1c	0.000 ± 0.000 18.333 ± 8.511 62.667 ± 13.220 122.000 ± 21.736 125.667 ± 15.958 130.667 ± 15.958 97.000 ± 10.383 85.000 ± 8.524 125.500 ± 19.204 128.333 ± 19.792 95.167 ± 31.818 0.000 ± 0.000 0.000 ± 0.000 0.000 ± 0.000 14.143 ± 4.458 53.143 ± 8.727 95.000 ± 11.431 141.000 ± 9.810 125.143 ± 24.407 92.571 ± 15.225 107.286 ± 17.203 115.429 ± 9.661 131.143 ± 19.103 50.143 ± 20.487 0.000 ± 0.000 0.000 ± 0.000 0.000 ± 0.000 19.000 ± 2.488 67.286 ± 14.846 135.429 ± 18.170 152.429 ± 14.633 97.286 ± 17.864 111.571 ± 13.122 93.857 ± 13.500 136.000 ± 17.928 191.714 ± 25.174 118.000 ± 34.317 82.143 ± 37.821 0.000 ± 0.000	WT: 6 Het: 7 KO: 7	Two-way	Bregma Genotype	F (12, 221) = 28.39 F (2, 221) = 5.753	p<0.0001 p=0.0037	*WT vs. KO: a p<0.05, a' p<0.01* *KO vs. Het: b p<0.05, b' p<0.01*	Yes. 2 independent experiments combined.
DCX+ cell number	Supp 1e	77106 ± 2656 76454 ± 6769 112889 ± 7095	WT: 6 Het: 7 KO: 7	One-way		F (2, 17) = 11.84	p=0.0006	Bonferroni ** p<0.01	Yes. 2 independent experiments combined.
DCX+ cell number Bregma	Supp 1f	-0.82 -1.12 -1.42 -1.72 -2.02 -2.32 -2.62 -2.92 -3.22 -3.52 -3.82 -4.12 -4.42 0.000 ± 0.000 58.500 ± 39.855 309.167 ± 75.315 438.167 ± 69.259 579.157 ± 66.473 447.500 ± 64.714 378.167 ± 79.337 457.500 ± 64.714 610.167 ± 91.661 684.667 ± 85.660 553.333 ± 261.645 0.000 ± 0.000 0.000 ± 0.000 0.000 ± 0.000 78.286 ± 25.650 314.571 ± 75.903 570.286 ± 80.769 650.714 ± 110.310 407.857 ± 59.233 380.714 ± 51.385 435.857 ± 102.645 548.429 ± 95.035 530.429 ± 94.826 285.286 ± 91.022 39.857 ± 39.857 0.000 ± 0.000 0.000 ± 0.000 153.286 ±38.833 388.000 ±97.396 809.429 ±169.302 667.857 ± 76.802 584.714 ± 56.350 499.00 ± 52.933 543.286 ± 76.533 821.571 ± 143.471 845.429 ±105.317 429.571 ± 176.325 452.286 ± 193.951 0.000 ± 0.000	WT: 6 Het: 7 KO: 7	Two-way	Interaction Bregma Genotype	F (24, 221) = 0.9315 F (12, 221) = 20.54 F (2, 221) = 10.09	p>0.05 (p=0.5591) p<0.0001 p<0.0001	Bonferroni *WT vs. KO: a p<0.05, a' p<0.01* *KO vs. Het: b p<0.05, b' p<0.01*	Yes. 2 independent experiments combined.
Dendritic length	Supp 1h	218.0 ± 16.10 356.3 ± 17.55	WT: 54 KO: 48	two-tailed t-test			****p<0.0001		No.
Dendritic nodes	Supp 1i	4.283 ± 0.4731 8.042 ± 0.4670	WT: 53 KO: 48	two-tailed t-test			****p<0.0001		No.
Dendritic ends	Supp 1j	5.264 ± 0.4721 9.083 ± 0.4725	WT: 53 KO: 48	two-tailed t-test			****p<0.0001		No.
Anterior vs. posterior Dendritic length	Supp 1k	250.167 ± 25.121 336.204 ± 23.556 184.581 ± 19.294 378.209 ± 25.938	Anterior, WT: 27 Anterior, KO: 25 Posterior, WT: 26 Posterior, KO: 23	Two-way	Interaction Bregma Genotype	F (1, 97) = 5.2 F (1, 97) = 0.2498 F (1, 97) = 35.13	p=0.0248 p=0.6184 p<0.001	Bonferroni * p<0.05 ****p<0.0001	No.
Anterior vs. posterior Dendritic nodes	Supp 1l	5.370 ± 0.770 7.280 ± 0.607 3.154 ± 0.456 8.870 ± 0.690	Anterior, WT: 27 Anterior, KO: 25 Posterior, WT: 26 Posterior, KO: 23	Two-way	Interaction Bregma Genotype	F (1, 97) = 8.723 F (1, 97) = 0.2367 F (1, 97) = 35.01	p=0.0039 p=0.6277 p<0.0001	Bonferroni ****p<0.0001	No.
Anterior vs. posterior Dendritic ends	Supp 1m	6.333 ± 0.770 8.320 ± 0.605 4.154 ± 0.456 9.913 ± 0.708	Anterior, WT: 27 Anterior, KO: 25 Posterior, WT: 26 Posterior, KO: 23	Two-way	Interaction Bregma Genotype	F (1, 97) = 8.475 F (1, 97) = 0.2048 F (1, 97) = 35.73	p= 0.0045 p= 0.6519 p< 0.0001	Bonferroni ****p<0.0001	No.
Body mass	Supp 3g	Day 1 / Day 11 22.840 ± 0.285 / 23.740 ± 0.366 22.969 ± 0.352 / 24.023 ± 0.260 23.058 ± 0.195 / 23.938 ± 0.198	Control: 10 Susceptible: 13 Resilient: 26	RM Two-way	Interaction Day Group Subjects (matching)	F (2,46) = 0.2031 F (1,46) = 55.84 F (2, 46) = 0.1871 F (46, 46) = 5.479	p>0.05 (p=0.8169) p<0.0001 p>0.05 (p=0.8300) p<0.0001	Bonferroni 1 vs 11 days Control p<0.01 1 vs 11 days Susceptible p<0.0001 1 vs 11 days Resilient p<0.0001	Yes. 2 independent experiments combined.
Adrenal gland weights	Supp 3h	0.003987 ± 0.0004542 0.006702 ± 0.0003575 0.005812 ± 0.0003799	Control: 6 Susceptible: 9 Resilient: 10	One-way		F (2, 22) = 10.4	p<0.001 (p=0.0006)	Bonferroni *p<0.05 ***p<0.001	Yes. 2 independent experiments combined.
IsoA4 level	Supp 3i	1.000 ± 0.07165 1.248 ± 0.08603 1.344 ± 0.1506	Control: 9 Susceptible: 15 Resilient: 7	One-way		F (2, 28) = 2.628	p>0.05 (p=0.09)	Fisher's LSD *p<0.05 (p=0.0421) #p>0.05 (p=0.0771)	Yes. 2 independent experiments combined.
Susceptible correlation	Supp 3j		n: 15	linear regression		Y = -0.00368*X + 1.398	p>0.05 (p=0.2362) r2=0.1061		Yes. 2 independent experiments combined.
Resilient correlation	Supp 3k		n: 7	linear regression		Y = -0.007032*X + 2.437	*p<0.05 (p=0.0403) r2=0.6021		Yes. 2 independent experiments combined.
IsoA5 level	Supp 3l	1.000 ± 0.142 1.088 ± 0.06577 1.153 ± 0.09217	Control: 9 Susceptible: 15 Resilient: 7	One-way		F (2, 28) = 0.01259	p>0.05 (p=0.9875)		Yes. 2 independent experiments combined.
Susceptible correlation	Supp 3m		n: 15	linear regression		Y = 0.001931*X + 0.9488	p>0.05 (p=0.6096) r2=0.02063		Yes. 2 independent experiments combined.
Resilient correlation	Supp 3n		n: 7	linear regression		Y = -2.73e-005*X + 1.018	p>0.05 (p=0.9946) r2=1.026e-005		Yes. 2 independent experiments combined.
TRIP8b level	Supp 3o	1.000 ± 0.4689 1.027 ± 0.3964 1.014 ± 0.3747	Control: 9 Susceptible: 15 Resilient: 7	One-way		F (2, 28) = 0.6570	p>0.05 (p=0.5262)		Yes. 2 independent experiments combined.
Susceptible correlation	Supp 3p		n: 15	linear regression		Y = -0.0005175*X + 1.109	p>0.05 (p=0.1960) r2=0.003588		Yes. 2 independent experiments combined.
Resilient correlation	Supp 3q		n: 7	linear regression		Y = -0.003078*X + 1.632	p>0.05 (p=0.1960) r2=0.308		Yes. 2 independent experiments combined.

Resting membrane potential	Supp 4c	-64.33 ± 0.9796 -64.42 ± 1.624 -65.81 ± 1.104 -63 ± 2.345	TRIP8b shRNA EGFP-: 12 TRIP8b shRNA EGFP+: 5 SCR mRNA EGFP-: 12 SCR mRNA EGFP+: 4	One-way		F (3,29) = 0.6732	p>0.05 (p=0.5754)		No.
Peak	Supp 4d	-320 -280 -240 -200 -160 -120 -80 -40 0 TRIP8b shRNA EGFP-: -28.603690 ± 2.222812032; -26.1024727 ± 2.0700056; -22.504154 ± 2.158452; -19.760645 ± 0.5958446; -16.630672 ± 1.465420936; -13.31921 ± 1.116133; -9.17494363 ± 0.9137427; -4.43222663 ± 0.7943111; 0.05176672 ± 0.310016 TRIP8b shRNA EGFP+: -34.4954 ± 2.96119474; -31.58882 ± 2.697815; -26.82276 ± 2.192674; -22.24368 ± 3.5573191; -20.36772 ± 2.60436522; -16.5073 ± 1.8742285; -12.143062 ± 1.4742607; -6.83196 ± 1.117468; -0.438299 ± 0.274198 SCR shRNA EGFP-: -28.2822230 ± 1.2562524; -26.2214230 ± 1.0363664; -23.4689 ± 0.9111424; -20.803707 ± 0.8177314; -17.4395 ± 0.7239544; -13.6902123 ± 0.6083134; -9.5939153 ± 0.47147004; -5.10178615 ± 0.2781783; -0.0645291 ± 0.193732 SCR shRNA EGFP+: -31.2871 ± 2.9058161; -27.194575 ± 3.1127139; -24.05475 ± 2.3575813; -21.554 ± 2.0942703; -18.696775 ± 2.10518323; -14.328472 ± 2.1400216; -10.72582 ± 1.598082; -5.9051425 ± 0.899156; 28.7676637 ± 28.48394	TRIP8b shRNA EGFP-: 11 TRIP8b shRNA EGFP+: 5 SCR shRNA EGFP-: 13 SCR shRNA EGFP+: 4	RM Two-way	Interaction Amp Virus Subjects (matching)	F (24, 232) = 2.811 F (8, 232) = 86.1 F (3, 29) = 1.264 F (29, 232) = 3.683	p<0.0001 p<0.0001 p=0.3052 p<0.0001	Bonferroni TRIP8b shRNA EGFP- vs. SCR shRNA EGFP+: a'''p<0.0001 TRIP8b shRNA EGFP+ vs. SCR shRNA EGFP+: b''' p<0.0001 SCR shRNA EGFP- vs. SCR shRNA EGFP+: c''' p<0.0001	No.
Steady	Supp 4e	-320 -280 -240 -200 -160 -120 -80 -40 0 TRIP8b shRNA EGFP-: -21.2905636 ± 2.2492265; -19.319257 ± 2.0290046; -16.6919590 ± 1.8378067; -14.4450327 ± 1.5412368; -11.12083873 ± 2.02721300; -9.00511809 ± 1.6176172; -6.29795481 ± 1.2022458; -3.21429718 ± 0.7323572; 0.07951218 ± 0.316855 TRIP8b shRNA EGFP+: -26.40746 ± 2.7714972; -23.98112 ± 2.6716100; -20.55528 ± 2.008082; -16.85662 ± 2.7441435; -15.3435 ± 2.2637992; -12.55901 ± 1.5746786; -9.47651 ± 1.3291957; -5.51744 ± 1.0572826; -0.4384188 ± 0.384466 SCR shRNA EGFP-: -23.3665615 ± 1.3151581; -21.7494230 ± 1.2303682; -19.4992923 ± 1.0734836; -17.233161 ± 0.9923560; -14.42766923 ± 0.86823561; -11.4060923 ± 0.6924739; -8.0633353 ± 0.5304270; -4.4703046 ± 0.3512872; -0.0222732 ± 0.142615 SCR shRNA EGFP+: -26.6408 ± 3.4848100; -24.180975 ± 4.0920401; -21.743025 ± 3.0262518; -18.654825 ± 2.739660; -15.522965 ± 2.3088555; -11.8489275 ± 2.3554456; -5.26427 ± 1.147868; -5.9051425 ± 0.8991566; 0.561783 ± 0.647099	TRIP8b shRNA EGFP-: 11 TRIP8b shRNA EGFP+: 5 SCR mRNA EGFP-: 13 SCR mRNA EGFP+: 4	RM Two-way	Interaction Amp Virus Subjects (matching)	F (24, 232) = 1.048 F (8, 232) = 332.7 F (3, 29) = 1.296 F (29, 232) = 25.87	p=0.4057 p<0.0001 p=0.2944 p<0.0001		No.
EEG_Day	Supp 4f	Delta Theta alpha Beta Gamma 0.45523095425 ± 0.0265873535880583; 0.197953318 ± 0.0188213942149131; 0.104157922 ± 0.0130265272820005; 0.0699100225 ± 0.0094522028227181; 0.044854475 ± 0.0031255338423926 0.4312314075 ± 0.0666746722155897; 0.17820712425 ± 0.0340631837778921; 0.09899374325 ± 0.0252030094649347; 0.0686069725 ± 0.0236012113103016; 0.04430875225 ± 0.0197639164246696	SCR sh: 4 TRIP8b sh: 4	Two-way	Interaction bands Virus	F (4, 30) = 0.07033 F (4, 30) = 61.95 F (1, 30) = 0.3025	p=0.9905 p<0.0001 p=0.5864		Yes. 2 independent experiments combined.
EEG_Night	Supp 4g	Delta Theta alpha Beta Gamma 0.403218867 ± 0.0237950869187312; 0.18330743375 ± 0.0182309977269817; 0.093831461 ± 0.0135309551632456; 0.0692423655 ± 0.0103107461261124; 0.05534166375 ± 0.0070680627667643 0.3829223615 ± 0.0664496017857481; 0.1720231145 ± 0.0398459142117736; 0.097820183 ± 0.0275302443953358; 0.07334417525 ± 0.0256392100834831; 0.05082008875 ± 0.0239054372950111	SCR sh: 4 TRIP8b sh: 4	Two-way	Interaction bands Virus	F (4, 30) = 0.059 F (4, 30) = 42.28 F (1, 30) = 0.08503	p=0.9932 p<0.0001 p=0.7726		Yes. 2 independent experiments combined.
FST	Supp 5i	143.5 ± 7.358 119.3 ± 7.851 157 ± 17	SCR shRNA: 8 TRIP8b shRNA:10 TRIP8b Mol+CA1, 2 or 3: 2	One-way		F (2, 17) = 3.629	p=0.0487	Fisher's LSD **p<0.01 (p=0.0019) ***p<0.001 (p=0.0003)	No.
FST	Supp 5j	226.8 ± 6.868 166.8 ± 13.42 229.3 ± 8.873	SHAM/SCR shRNA: 10 SHAM/TRIP8b shRNA: 8 SHAM/TRIP8b shRNA with Mol+CA2/3: 4	One-way		F (2, 19) = 11.7	p=0.0005	Fisher's LSD *p<0.05 (p=0.0421)	Yes. 3 independent experiments combined.
FST	Supp 5k	208 ± 17.81 241.4 ± 9.943 186.1 ± 19.52 245.3 ± 19.72	Veh/SCRsh: 8 CORT/SCRsh: 8 CORT/TRIP8bsh: 8 Mol+CA1 or only CA2/3: 4	One-way		F (3, 24) = 2.631	p=0.0732	Fisher's LSD *p<0.05 (p=0.0421)	Yes. 3 independent experiments combined.
total type-1 cells	Supp 6b	8338 ± 677.6 8297 ± 799.5	SCR shRNA: 8 TRIP8b shRNA: 7	two-tailed t-test			p>0.05 (p=0.9693)		Yes. 2 independent experiments combined.
type-1 cell Bregma	Supp 6c	-0.82 -1.12 -1.42 -1.72 -2.02 -2.32 -2.62 -2.92 -3.22 -3.52 -3.82 -4.12 -4.42 -4.72 -5.02 0.000 ± 0.000; 7.125 ± 0.7891564 21213727; 26.125 ± 3.5729014 8198911; 45.5 ± 4.2510502 9039043; 51.375 ± 4.3091990 4722112; 59.375 ± 4.14874120 323606; 60.375 ± 5.2574352 1120327; 51 ± 8.31521840 6203; 51.625 ± 3.60028520 695633; 52.125 ± 6.3511458 4712307; 47.75 ± 8.69677 690707; 38.625 ± 7.79179 398928; 25.75 ± 6.94557 9272355 29; 6.25 ± 4.50693 9094329 99; 0.000 ± 0.000 0.000 ± 0.000; 9.8571428 5714286 ± 1.7651193 3265244; 24.142857 1428571 ± 4.7780678 0747083; 42.714285 7142857 ± 2.7577966 162991; 54.857142 85714 ± 4.9638146 402049; 57.7142857 142857 ± 6.6608184 392844; 51.714285 7142857 ± 5.0413258 1632992; 54.714285 7142857 ± 5.4585637 6415509; 54 ± 4.3861253 1035027; 57.857142 8571429 ± 5.7421937 546242; 55.5714 2857142 86 ± 8.24868 5733286 89; 35.5714 2857142 86 ± 8.74740 0002441 93; 19.8571 4285714 29 ± 10.2013 7379037 18; 0.000 ± 0.000; 0.000 ± 0.000	SCR shRNA: 8 TRIP8b shRNA: 7	Two-way	Interaction Bregma Virus	F (14, 195) = 0.3688 F (14, 195) = 34.61 F (1, 195) = 0.02218	p=0.9820 p<0.0001 p=0.8818		Yes. 2 independent experiments combined.
LM	Supp 7a	100.000000005 ± 4.365051968644 94.68552288125 ± 6.09726411679324 100.840584738 ± 9.32324686304143 102.76309804 ± 5.19559931146576	SHAM/SCRsh: 20 SHAM/TRIPsh: 8 IRR/SCRsh: 10 IRR/TRIP8bsh: 9	Two-way	Interaction Treatment Virus	F (1, 43) = 0.3056 F (1, 43) = 0.464 F (1, 43) = 0.06712	p=0.5833 p=0.4994 p=0.7968		Yes. 3 independent experiments combined.
FST	Supp 7b	100.000000005 ± 3.52357978378701 73.52292768875 ± 5.91713738878808 102.189311012 ± 7.95613669877523 92.019400351 ± 5.66255757408644	SHAM/SCRsh: 20 SHAM/TRIPsh: 8 IRR/SCRsh: 10 IRR/TRIP8bsh: 10	Two-way	Interaction Treatment Virus	F (1, 44) = 2.044 F (1, 44) = 3.29 F (1, 44) = 10.33	p=0.1598 p=0.0765 p=0.0025	Fisher's LSD *p<0.05 **p<0.01	Yes. 3 independent experiments combined.
NSF	Supp 8a	100.000000005 ± 9.00540967051263 92.4555745285714 ± 14.1281034005357 144.11095952625 ± 20.0586945638211 97.3004258127273 ± 14.5764699801463	VEH/SCRsh: 18 VEH/TRIPsh: 7 CORT/SCRsh: 8 CORT/TRIP8bsh: 11	Two-way	Interaction Treatment Virus	F (1, 40) = 1.882 F (1, 40) = 2.925 F (1, 40) = 3.606	p=0.1778 p=0.0950 p=0.0648	Fisher's LSD *p<0.05	Yes. 3 independent experiments combined.
FST	Supp	100.000000005 ± 4.72342104720483 73.1429010328571 ± 12.5597961778881	VEH/SCRsh: 25 VEH/TRIPsh: 7	Two-way	Interaction Treatment	F (1, 63) = 0.4073 F (1, 63) = 11.14	p=0.5257 p=0.0014	Fisher's LSD *p<0.05	Yes. 3 independent experiments

TST	8b	118.024771841875 ± 4.68605281429836 99.6912097815789 ± 6.02840847953546	CORT/SCRsh: 16 CORT/TRIP8bsh: 19	Two-way	Virus	F (1, 63) = 11.45	p=0.0012	***p<0.001	experiments combined.
EPM Frequency (open arms)	Supp 9a	12.88 ± 1.132 13.75 ± 1.263 11.21 ± 0.8327	VEH/SCRsh: 16 CORT/SCRsh: 16 CORT/TRIP8bsh: 19	One-way		F (2, 48) = 1.521	p=0.2289		Yes. 3 independent experiments combined.
EPM Duration (open arms)	Supp 9b	55.05 ± 5.439 58.14 ± 8.183 50.33 ± 4.991	VEH/SCRsh: 16 CORT/SCRsh: 16 CORT/TRIP8bsh: 19	One-way		F (2, 48) = 0.4123	p=0.6645		Yes. 3 independent experiments combined.
EPM Frequency (closed arms)	Supp 9c	20.63 ± 1.749 21 ± 1.162 19.21 ± 1.292	VEH/SCRsh: 16 CORT/SCRsh: 16 CORT/TRIP8bsh: 19	One-way		F (2, 48) = 0.4673	p=0.6295		Yes. 3 independent experiments combined.
EPM Duration (closed arms)	Supp 9c	187.7 ± 6.049 181.3 ± 9.246 178.7 ± 10.81	VEH/SCRsh: 16 CORT/SCRsh: 16 CORT/TRIP8bsh: 19	One-way		F (2, 48) = 0.2527	p=0.7777		Yes. 3 independent experiments combined.
Splash Frequency	Supp 9e	30.69 ± 3.501 26.93 ± 2.331 27.78 ± 1.706	VEH/SCRsh: 16 CORT/SCRsh: 14 CORT/TRIP8bsh: 18	One-way		F (2, 45) = 0.5624	p=0.5738		Yes. 3 independent experiments combined.
Splash Duration	Supp 9f	193.5 ± 20.24 164.1 ± 17.01 202.8 ± 11.24	VEH/SCRsh: 16 CORT/SCRsh: 14 CORT/TRIP8bsh: 18	One-way		F (2, 45) = 1.474	p=0.2398		Yes. 3 independent experiments combined.
cfos+ cell density (Ent)	Supp 10i	lEnt: 13.8430071398 ± 2.22142353532157; 6.2700885928 ± 0.859287488035335 mEnt: 73.52736983 ± 23.2051956093183; 54.6471281375 ± 10.0646426289692	Both lEnt/mEnt mCherry: 5 hM3Dq: 4	Two-way	Interaction Ent subregions virus	F (1, 14) = 0.2553 F (1, 14) = 1.397 F (1, 14) = 23.32	p=0.6212 p=0.2569 p=0.0003	Bonferroni *p<0.05 **p<0.01	Yes. 2 independent experiments combined.
cfos+ cell Bregma	Supp 10j	-0.82: 0.000 ± 0.000; -1.12: 9 ± 2.96647939483826; -1.42: 17.6 ± 2.4; -1.72: 20.8 ± 0.8602325 26704263; -2.02: 23.2 ± 1.9595917 9422654; -2.32: 25.4 ± 2.50199920 63936; -2.62: 24.2 ± 4.1036569 0573664; -2.92: 17.8 ± 3.6110940 1705356; -3.22: 15.2 ± 2.8178005 6072107; -3.52: 17.2 ± 3.4842502 7803687; -3.82: 17 ± 4.26614 5801540 31; -4.12: 13.4 ± 3.70944 7398198 28; -4.42: 9.4 ± 2.94278 7793912 43; -4.72: 1.6 ± 0.67823 2998312 527; -5.02: 0.000 ± 0.000 -0.82: 0.000 ± 0.000; -1.12: 9.6 ± 0.8717797 88708135; -1.42: 19.6 ± 3.2954514 1065682; -1.72: 36.6 ± 4.8435524 1532493; -2.02: 39.4 ± 2.6; -2.32: 46.4 ± 7.25672102 261069; -2.62: 41.6 ± 4.8744230 4278158; -2.92: 35.8 ± 6.5681047 4946921; -3.22: 20.8 ± 3.1208973 0686545; -3.52: 23 ± 4.3931765 2729776; -3.82: 30.2 ± 4.73708 7712930 8; -4.12: 22.8 ± 3.21558 7038162 71; -4.42: 15.8 ± 3.56931 3659514 95; -4.72: 8.4 ± 3.20312 3475609 39; -5.02: 1 ± 1	mCherry: 5 hM3Dq: 5	Two-way	Interaction Bregma Virus	F (14, 120) = 2.087 F (14, 120) = 21.72 F (1, 120) = 53.28	p=0.0170 p<0.0001 p<0.0001	Fisher's LSD **p<0.01 ***p<0.001 ****p<0.0001	Yes. 2 independent experiments combined.
EEG_Day (Pre-CNO)	Supp 11e	Delta: 0.450414002 ± 0.028473716743004; 0.40848298925 ± 0.026302873243249 Theta: 0.20231102075 ± 0.00526809576757308; 0.18664270725 ± 0.00778074330018127 Alpha: 0.1228955395 ± 0.0140295713226281; 0.108499074 ± 0.00250330049328292 Beta: 0.0774707285 ± 0.00410525744148152; 0.086444102 ± 0.00958501151240765 Gamma: 0.05970658775 ± 0.0066806686416066 3; 0.06152485725 ± 0.0106857366907932	mCherry: 4 hM3Dq: 4	Two-way	Interaction bands Virus	F (4, 30) = 0.9372 F (4, 30) = 219.2 F (1, 30) = 1.817	p=0.4559 p<0.0001 p=0.1878		Yes. 2 independent experiments combined.
EEG_Day (Post-CNO)	Supp 11f	Delta: 0.44766052675 ± 0.0172764015393249; 0.42238062375 ± 0.0302678080681449 Theta: 0.20650387275 ± 0.00630667359840694; 0.186902698 ± 0.0103924927192682 Alpha: 0.1153227695 ± 0.00600830092292557; 0.1034664675 ± 0.00796345034071587 Beta: 0.07692092975 ± 0.0045286886593444; 0.07803589475 ± 0.0114663691852645 Gamma: 0.06005650225 ± 0.0030738092910463; 0.05405130725 ± 0.0104057283895814	mCherry: 4 hM3Dq: 4	Two-way	Interaction bands Virus	F (4, 30) = 0.3188 F (4, 30) = 276.6 F (1, 30) = 2.193	p=0.8632 p<0.0001 p=0.1490		Yes. 2 independent experiments combined.
EEG_Night (Post-CNO)	Supp 11g	Delta: 0.43833400275 ± 0.0182029488709943; 0.41890417575 ± 0.0359184886734102 Theta: 0.200400754 ± 0.0174702499159458; 0.17775036075 ± 0.0118276713159797 Alpha: 0.10664645725 ± 0.00285277670003575; 0.1057029185 ± 0.00681036689734467 Beta: 0.083813766 ± 0.00517257836826144; 0.08411452 ± 0.0123975463569172 Gamma: 0.06603167075 ± 0.0122055309981947; 0.07086175275 ± 0.0163131603933876	mCherry: 4 hM3Dq: 4	Two-way	Interaction bands Virus	F (4, 30) = 0.2888 F (4, 30) = 163.6 F (1, 30) = 0.5285	p=0.8829 p<0.0001 P=0.4729		Yes. 2 independent experiments combined.