Supplementary Methods

Linear mixed model analysis

For most of the statistical analysis, we utilized linear mixed model (LMM) analysis. This approach estimates the effect size of each factor while accounting for intra- and inter-animal variability. LMMs were fitted with random intercepts to assess for the correlation between repeated measurements on the same mouse, and experiment-specific effects were analyzed for statistical significance. t values > 1.96 and < −1.96 were considered to be statistically significant and corresponded to 95% confidence intervals that did not cross zero. Each LMM examined both main fixed effects and interactions between the effects.

Experiments with a traditional 2 X 2 factorial design (including those for Figures 3-5) used LMM to examine fixed effects of CCI, 2-DG treatment, and the interaction between these two effects. To compare input-output curves in Figure 1, the fixed effects were current injection, 2-DG treatment, and the interaction between the two effects. LMM was also utilized to compare excitatory and inhibitory neurons in Figure 1, by examining cell type as the fixed effect.

In Figure 2, the statistical approach also paralleled the experimental design. The primary experimental question was whether synaptic activity onto interneurons was altered acutely after CCI (as this had not been shown previously); thus “Stage 1” of the statistical approach was to examine CCI as the solitary fixed effect. Then, in “Stage 2” of the experiment and statistical analysis, we examined the effects of in vitro 2-DG wash-on to slices taken from either CCI or sham animals (and thus used both CCI and 2-DG as fixed effects).

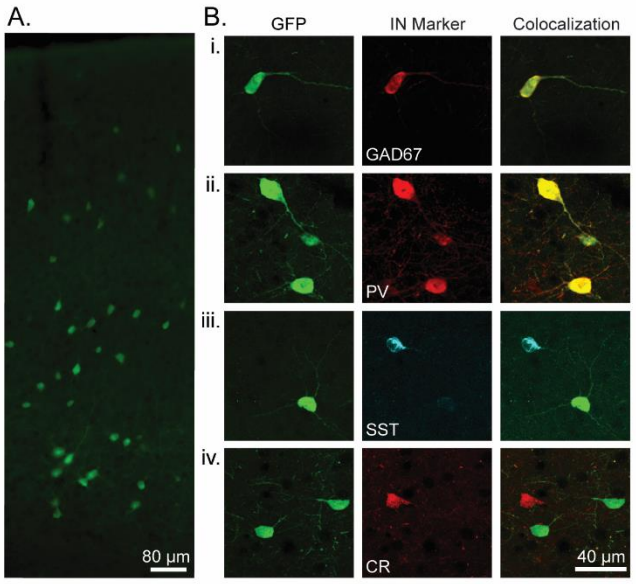
In Figure 6, there was another fixed effect (ROI), introduced as a categorical variable. We performed LMM with fixed effects of CCI, 2-DG, ROI, and interactions between each of these.

Comparisons were made with ROI5 (the furthest region from the CCI lesion) as the reference point. To further interpret these complex results, we utilized LMM with the Type III analysis of variance (ANOVA) test with Satterthwaite's method to assess the global significance of "ROI" as a single factor instead of each ROI as an independent factor relative to ROI5. Thus, the Type III ANOVA reports global effects across all ROIs (Table S2).

Cumulative distribution generation

Cumulative distributions were generated by randomly selecting 100 events from each recording to ensure that data from more active cells were not more heavily weighted than data from cells with fewer events. Random event selection was accomplished using a custom-written MATLAB script. Within each treatment group, randomly selected events from each cell were pooled to generate a single cumulative distribution, and distributions were compared using a 2-sample Kolmogorov-Smirnov (K-S) test. To account for the large degrees of freedom associated with comparing distributions and to prevent false positives, we decreased α to 0.001. We further corrected for repeated comparisons when doing multiple 2-sample K-S tests on the same data set by dividing α by 6 possible comparisons across the four treatment groups (final α = 1.67E-4).

Supplementary Figures



C.

Interneuron Marker	# GFP+ Cells Counted	# GFP+ Cells Co-labeled with IN Marker	Colocalization
GAD67	158	122	77.30%
Parvalbumin (PV)	318	233	73.30%
Somatostatin (SST)	318	0	0.00%
Calretinin (CR)	276	0	0.00%

Figure S1: Characterization of *G42* mouse line. A. Immunohistochemical labeling of genetically-encoded GFP (green) in the somatosensory cortex (SSC) of adult *G42* mice. **B.** Co-labeling of GFP in *G42* mice with markers of inhibitory interneurons in layers V-VI of SSC (**i.** GAD67, **ii.** Parvalbumin (PV), **iii.** Somatostatin (SST), **iv.** Calretinin (CR)). **C.** Table showing abundant co-labeling of GFP+ cells with PV and GAD67. (n=4 mice)

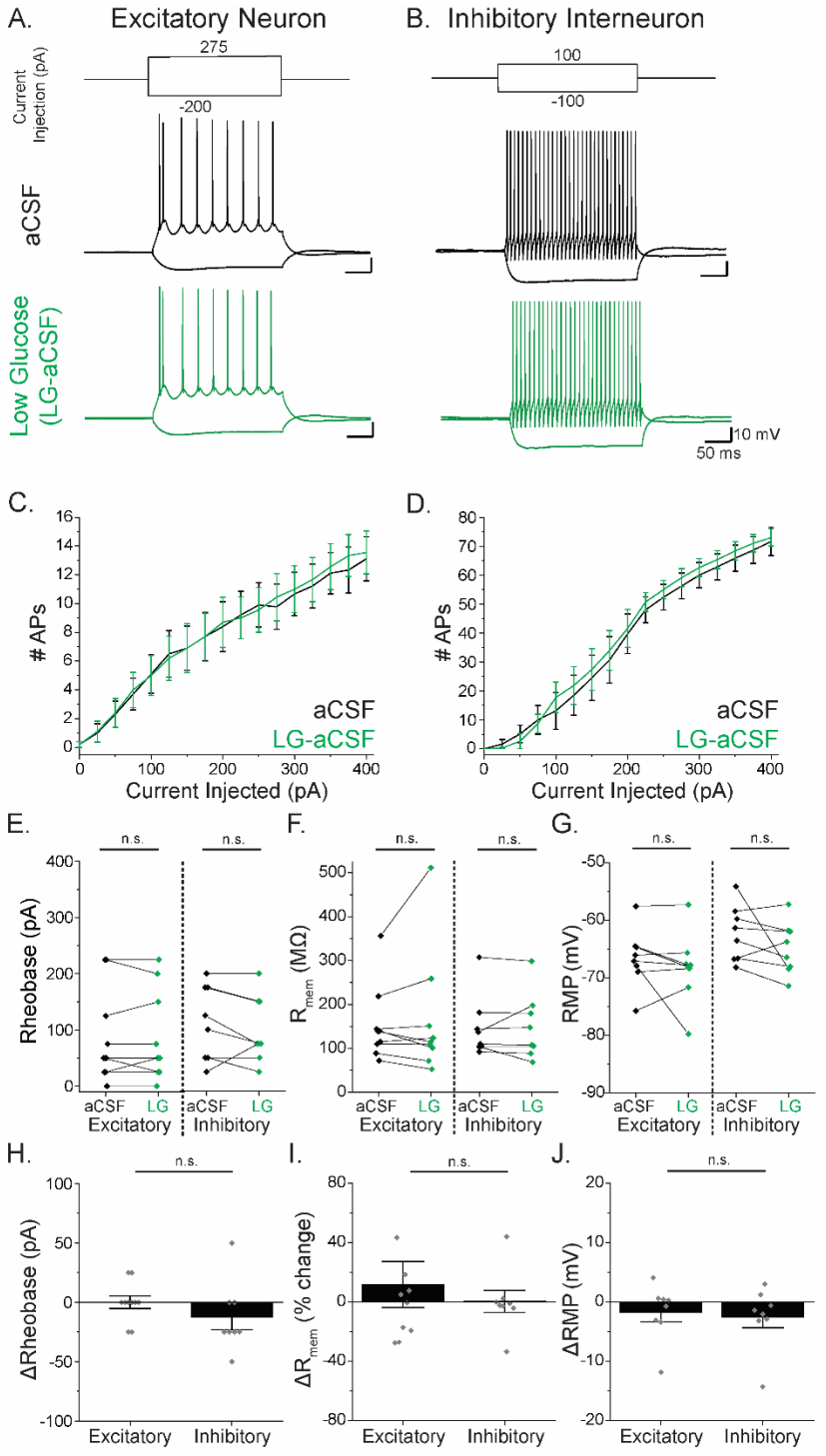


Figure S2: Treatment with Low Glucose (LG)-aCSF did not affect the excitability of excitatory or inhibitory neurons. A-B. Representative traces following current injection into layer V cortical excitatory pyramidal neurons (A) or interneurons (B) before (black) or after (green) treating the cortical slice with LG-aCSF for 10 minutes. **C-D.** Input-output curves in excitatory (C) or inhibitory (D) neurons. **E.** Rheobase (current injection required to fire the first action potential) before (black) and after (green) LG-aCSF treatment in each cell type. **F.**

Membrane resistance before and after LG-aCSF in each cell type. **G.** Resting membrane potential (RMP) before and after LG-aCSF treatment in each cell type. **H.** ΔRheobase (rheobase in LG-aCSF versus baseline) in excitatory neurons and interneurons. **I.** % change in membrane resistance of excitatory neurons and interneurons following LG-aCSF treatment. **J.** Change in resting membrane potential (RMP) in excitatory neurons and interneurons in LG-aCSF. (Error bar = SEM. n=10 excitatory neurons from 5 animals, 8 inhibitory neurons from 5 animals. n.s. not significant.)

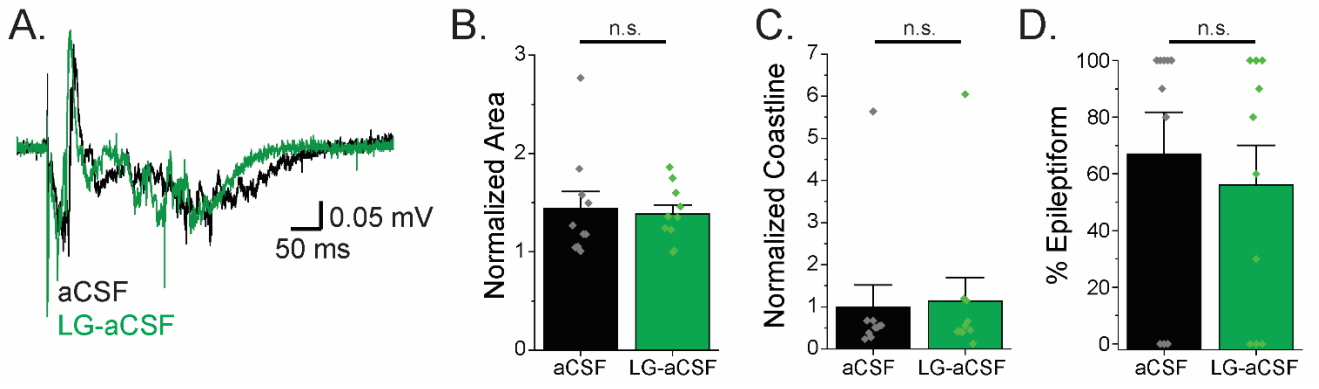


Figure S3: Low glucose (LG) conditions do not attenuate epileptiform activity following CCI. **A.** Representative stimulus-evoked field potentials in an acute cortical slice 3-5 weeks following CCI surgery. **B-C.** Area (B) and coastline (C) measurements from fEPSPs from CCI-injured animals with or without 30 minutes of LG-aCSF. **D.** The percentage of sweeps exhibiting epileptiform activity in slices from CCI animals with or without LG-aCSF treatment. (Error bar = SEM. n=10 slices from 4 animals. n.s. not significant.)

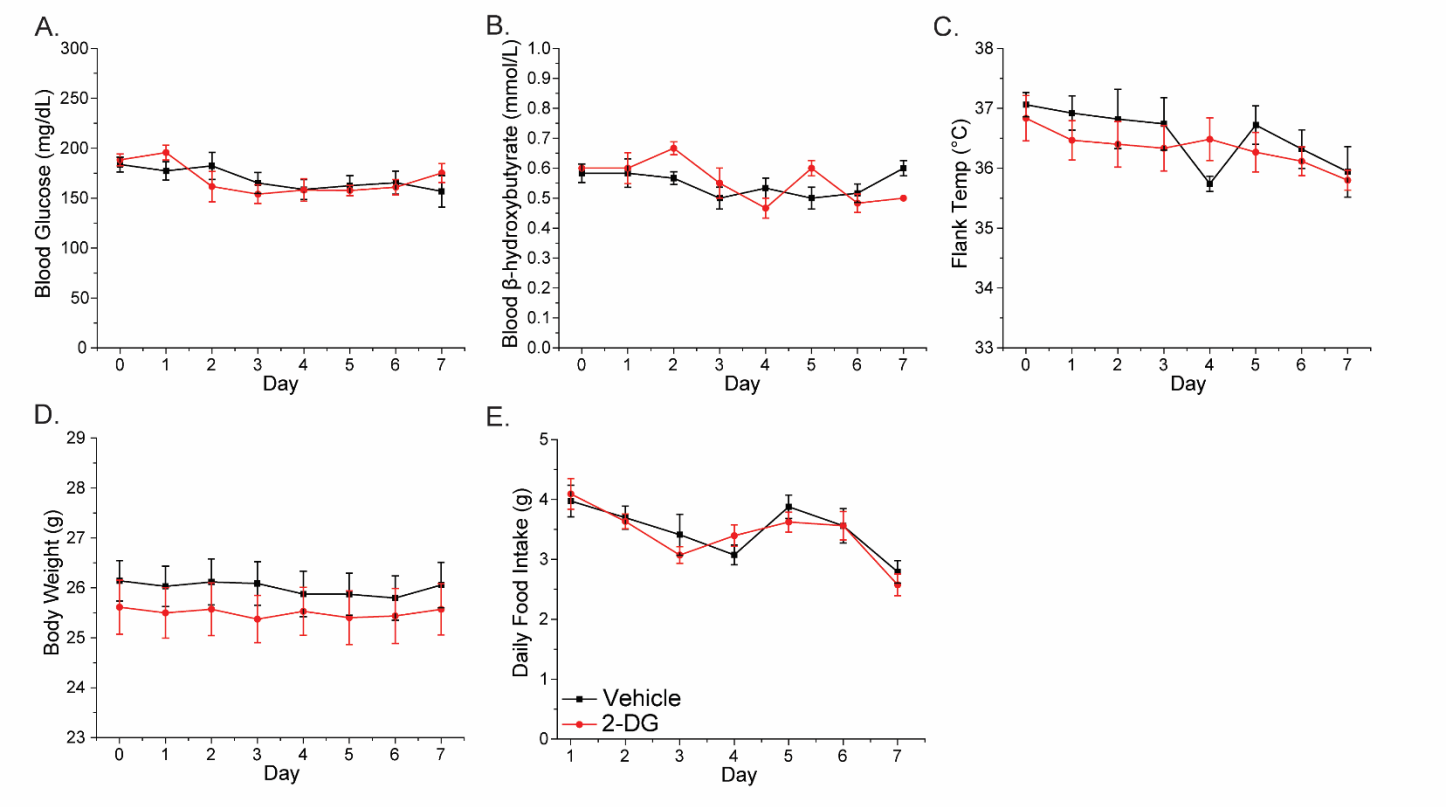
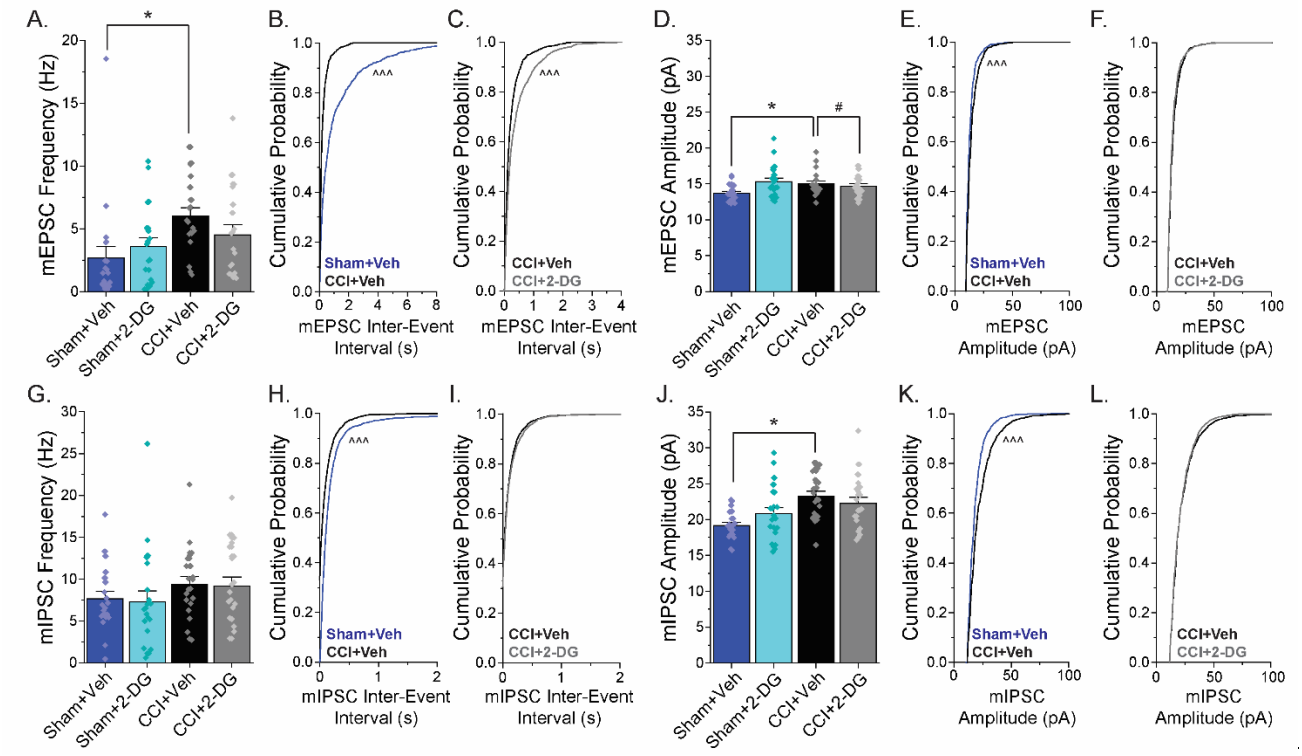


Figure S4: 2-DG has no effect on daily blood glucose, blood β-hydroxybutyrate, temperature, body weight, or food intake during a week-long dosing regimen. Animals were injected daily with 2-DG or vehicle. Shown are blood glucose (**A**), β-hydroxybutyrate (**B**), flank temperature (**C**), body weight (**D**), and daily food intake (**E**) measured immediately prior to each daily injection. (Error bar = SEM. n=6 animals/group.)



~~**Figure S5: CCI and in vivo 2-DG treatment have complex effects on miniature synaptic activity. A.** Mean mEPSC frequency. **B-C.** Cumulative distributions of mEPSC inter-event interval. **D.** Mean mEPSC amplitude. **E-F.** mEPSC amplitude cumulative distributions. **G.** Mean mIPSC frequency. **H-I.** Cumulative distributions of mIPSC inter-event interval. **J.** Mean mIPSC amplitude. **K-L.** Cumulative distributions of mIPSC amplitude. (Error bar = SEM. n = 19-21 cells from 5 animals/group. LMM: *t > ±1.96, effect: CCI; #t > ±1.96, effect: interaction between CCI and 2-DG. 2-sample K-S test corrected for multiple comparisons: ^^^p < 1E-5)~~

Linear Mixed Model Effects											
Figure	**N**	**Fixed effect**	**Coefficient**	**SE**	**t value**	**Significant**	**Fixed effect**	**Coefficient**	**SE**	**t value**	**Significant**
1	**Excitatory:** n=14 cells from 9 animals **Inhibitory:** n=13 cells from 10 animals	**Excitatory Neuron Input/Output** Units: # APs					**Inhibitory Interneuron Input/Output** Units: # APs				
		Current Injection	0.03133	0.001336	23.451	*	Current Injection	0.14475	0.008215	17.62	*
		2-DG *(in vitro)*	0.273077	0.456739	0.598		2-DG *(in vitro)*	2.522917	2.808498	0.898	
		Interaction Current/2-DG	-0.007801	0.001889	-4.129	*	Interaction Current/2-DG	-0.005598	0.011618	-0.482	
		ΔRheobase (excitatory versus inhibitory) Units: pA					**%ΔR$_{mem}$ (excitatory versus inhibitory)** Units: % change				
		Cell Type	75.687	26.982	2.805	*	Cell Type	-38.62%	11.14%	-3.468	*
		ΔRMP (excitatory versus inhibitory) Units: mV									
		Cell Type	1.827	1.542	1.184						
2	**Sham+aCSF:** n=17 cells **Sham+2-DG:** n=11 cells **CCI+aCSF:** n=20 cells **CCI+2-DG:** n=15 cells **4 animals/group**	**Frequency - sEPSCs onto INs (PID3)** Units: Hz					**Amplitude - sEPSCs onto INs (PID3)** Units: pA				
		Stage 1: CCI only	2.559	1.0263	2.493	*	*Stage 1: CCI only*	3.144	1.773	1.773	
		Stage 2: CCI + 2-DG Effects					*Stage 2: CCI + 2-DG Effects*				
		CCI	2.559	1.619	1.581		CCI	2.653	2.251	1.178	
		2-DG *(in vitro)*	2.387	1.272	1.877		2-DG *(in vitro)*	-1.709	1.619	-1.056	
		Interaction CCI/2-DG	-5.148	1.696	-3.036	*	Interaction CCI/2-DG	-2.815	2.158	-1.304	
3	**Sham:** n=6 slices from 3 animals **CCI:** n=10 slices from 6 animals	**fEPSP % Epileptiform - *In vitro* 2-DG treatment** Units: % sweeps					**fEPSP Area - *In vitro* 2-DG treatment** Units: mV*ms				
		CCI	90.20%	7.27%	12.412	*	CCI	3.1432	1.4637	2.147	*
		2-DG *(in vitro)*	-2.36E-16	6.45%	0		2-DG *(in vitro)*	0.8189	1.2192	0.672	
		Interaction CCI/2-DG	-72.00%	8.16%	-8.825	*	Interaction CCI/2-DG	-4.6187	1.5157	-3.047	*
		fEPSP Coastline - *In vitro* 2-DG treatment Units: ΔmV/ms									
		CCI	1.23E-05	4.05E-06	3.034	*					
		2-DG *(in vitro)*	5.36E-06	3.48E-06	1.542						
		Interaction CCI/2-DG	-1.67E-05	4.32E-06	-3.859	*					
4	**Sham+Veh:** n=15 slices **Sham+2-DG:** n=12 slices **CCI+Veh:** n=10 slices **CCI+2-DG:** n=9 slices **3 animals/group**	**fEPSP % Epileptiform - *In vivo* 2-DG treatment** Units: % sweeps					**fEPSP Area - *In vivo* 2-DG treatment** Units: mV*ms				
		CCI	67.50%	12.13%	5.566	*	CCI	6.0403	1.3315	4.537	*
		2-DG *(in vivo)*	-5.83%	11.83%	-0.493		2-DG *(in vivo)*	0.6882	1.2991	0.53	
		Interaction CCI/2-DG	-59.72%	18.26%	-3.27	*	Interaction CCI/2-DG	-6.2079	1.9901	-3.119	*
		fEPSP Coastline - *In vivo* 2-DG treatment Units: ΔmV/ms					**fEPSP Input/Output - *In vivo* 2-DG treatment** Units: ratio				
		CCI	2.05E-05	7.58E-06	2.701	*	CCI	-0.81373	0.23292	-3.494	*
		2-DG *(in vivo)*	-1.97E-06	7.65E-06	-0.258		2-DG *(in vivo)*	-0.01304	0.23067	-0.057	
		Interaction CCI/2-DG	-2.39E-05	1.14E-05	-2.102	*	Interaction CCI/2-DG	0.5443	0.34703	1.568	
	Vehicle: n=4 animals **2-DG:** n=6 animals	**Blood Glucose - single 2-DG injection** Units: mg/dL					**Blood β-hydroxybutyrate - single 2-DG injection** Units: mmol/L				
		Interaction (Hour 1)/2-DG	78.083	26.131	2.988	*	Interaction (Hour 1)/2-DG	-0.20833	0.08598	-2.423	*
		Interaction (Hour 2)/2-DG	86.5	26.131	3.31	*	Interaction (Hour 2)/2-DG	-0.30833	0.08598	-3.586	*
		Interaction (Hour 4)/2-DG	0.25	26.131	0.01		Interaction (Hour 4)/2-DG	-0.06667	0.08598	-0.775	
		Flank Temperature - single 2-DG injection Units: °C									
		Interaction (Hour 1)/2-DG	0.75	0.50827	1.476						
		Interaction (Hour 2)/2-DG	0.675	0.50827	1.328						
		Interaction (Hour 4)/2-DG	-0.09167	0.50827	-0.18						
5	**sEPSCs:** n=22-26 cells/group from 5 animals/group **sIPSCs:** n=21-25 cells/group from 5 animals/group	**Frequency - sEPSCs onto pyramidal neurons (PID21-35)** Units: Hz					**Amplitude - sEPSCs onto pyramidal neurons (PID21-35)** Units: pA				
		CCI	3.0884	1.0952	2.82	*	CCI	1.151	1.551	0.742	
		2-DG *(in vivo)*	0.654	1.1057	0.591		2-DG *(in vivo)*	3.066	1.555	1.972	*
		Interaction CCI/2-DG	-3.1991	1.5744	-2.032	*	Interaction CCI/2-DG	-3.902	2.215	-1.762	
		Frequency - sIPSCs onto pyramidal neurons (PID21-35) Units: Hz					**Amplitude - sIPSCs onto pyramidal neurons (PID21-35)** Units: pA				
		CCI	-2.9437	1.4551	-2.023	*	CCI	5.504	1.56	3.528	*
		2-DG *(in vivo)*	-0.258	1.4203	-0.182		2-DG *(in vivo)*	2.97	1.533	1.938	
		Interaction CCI/2-DG	2.8493	2.0781	1.371		Interaction CCI/2-DG	-5.487	2.21	-2.483	*
6	3 slices analyzed to generate 1 average value per animal **Sham+Veh:** 5 animals **Sham+2-DG:** 5 animals **CCI+Veh:** 7 animals **CCI+2-DG:** 6 animals	**PV+ Density** Units: cells/10,000 μm^2					**tdT+ Density** Units: cells/10,000 μm^2				
		Interaction CCI/ROI1	-1.771	0.2083	-8.501	*	Interaction CCI/ROI1	-1.665	0.2567	-6.487	*
		Interaction CCI/ROI2	-1.148	0.2083	-5.513	*	Interaction CCI/ROI2	-1.027	0.2567	-4	*
		Interaction CCI/ROI3	-0.6815	0.2083	-3.271	*	Interaction CCI/ROI3	-0.4762	0.2567	-1.855	
		Interaction CCI/ROI4	-0.4185	0.2083	-2.009	*	Interaction CCI/ROI4	-0.2377	0.2567	-0.926	
		Interaction CCI/2-DG/ROI1	1.111	0.2997	3.707	*	Interaction CCI/2-DG/ROI1	0.8247	0.3693	2.233	*
		Interaction CCI/2-DG/ROI2	0.9103	0.2997	3.037	*	Interaction CCI/2-DG/ROI2	0.532	0.3693	1.44	
		Interaction CCI/2-DG/ROI3	0.7652	0.2997	2.553	*	Interaction CCI/2-DG/ROI3	0.6053	0.3693	1.639	
		Interaction CCI/2-DG/ROI4	0.4751	0.2997	1.585		Interaction CCI/2-DG/ROI4	0.5779	0.3693	0.156	
		PV+ tdT+ Colocalized Density Units: cells/10,000 μm^2					**Ratio of tdT+ Cells Lacking PV+** Units: ratio				
		Interaction CCI/ROI1	-1.393	0.1829	-7.614	*	Interaction CCI/ROI1	0.364877	0.05684	6.419	*
		Interaction CCI/ROI2	-0.9167	0.1829	-5.011	*	Interaction CCI/ROI2	0.191243	0.05684	3.365	*
		Interaction CCI/ROI3	-0.5225	0.1829	-2.856	*	Interaction CCI/ROI3	0.091818	0.05684	1.615	
		Interaction CCI/ROI4	-0.248	0.1829	-1.356		Interaction CCI/ROI4	0.027345	0.05684	0.481	
		Interaction CCI/2-DG/ROI1	0.761	0.2632	2.892	*	Interaction CCI/2-DG/ROI1	-0.336425	0.081767	-4.114	*
		Interaction CCI/2-DG/ROI2	0.5429	0.2632	2.063	*	Interaction CCI/2-DG/ROI2	-0.157418	0.081767	-1.925	
		Interaction CCI/2-DG/ROI3	0.6884	0.2632	2.616	*	Interaction CCI/2-DG/ROI3	-0.139133	0.081767	-1.702	
		Interaction CCI/2-DG/ROI4	0.2361	0.2632	0.897		Interaction CCI/2-DG/ROI4	-0.087048	0.081767	-1.065	

Table S1. Linear mixed model results, organized by figure.

Type III Analysis of Variance with Satterthwaite's Method			
Data	**Effect/Interaction**	**p value**	**Signficant**
PV+ Density	CCI	1.83E-04	*
	2-DG	0.074809	
	ROI	1.27E-11	*
	CCI/ROI	5.83E-15	*
	2-DG/ROI	1.21E-04	*
	CCI/2-DG	0.058903	
	CCI/2-DG/ROI	0.002792	*
tdT+ Density	CCI	6.07E-09	*
	2-DG	0.35164	
	ROI	1.02E-06	*
	CCI/ROI	1.48E-11	*
	2-DG/ROI	0.09617	
	CCI/2-DG	0.10985	
	CCI/2-DG/ROI	0.11161	
PV+ tdT+ Colocalized Density	CCI	0.0037177	*
	2-DG	0.0729436	
	ROI	9.72E-09	*
	CCI/ROI	7.91E-15	*
	2-DG/ROI	2.34E-04	*
	CCI/2-DG	0.101366	
	CCI/2-DG/ROI	0.0202878	*
Ratio of tdT+ Lacking PV+	CCI	0.307487	
	2-DG	0.067198	
	ROI	1.58E-06	*
	CCI/ROI	2.78E-06	*
	2-DG/ROI	1.34E-06	*
	CCI/2-DG	0.127384	
	CCI/2-DG/ROI	0.001373	*

Table S2. Type III ANOVA results.