Fig. S1. Monitoring of freezing behavior in CFD under different optogenetic and behavioral manipulations. Related to Figure 1.
(**A**) Contextual fear discrimination (CFD) task with optogenetic activation of the LC-DG projection. Animals received a shock in context A (red), but not in context B (yellow) for nine days (left). Pattern of laser stimulation (both contexts) and electrical foot shock (only in context A) during a CFD session (right). (**B**) Analysis of progressive days of training in CFD. Acute activation of LC-DG projection impairs behavioral pattern separation in mice expressing ChR2 in LC-DG projections (Th-Cre$^{LC\text{-}DG}$::ChR2, n = 10; Context: $F_{(1,18)} = 19.430$, $p < 0.001$; Days: $F_{(1,144)} = 10.940$, $p < 0.001$; Days × Context: $F_{(8,144)} = 0.892$, $p = 0.525$), but not in wild-type controls (ChR2(-), n = 10; ChR2(-): Context: $F_{(1,18)} = 2.685$, $p = 0.119$; Days: $F_{(1,144)} = 14.568$, $p < 0.001$; Days × Context: $F_{(8,144)} = 1.386$, $p = 0.206$). (**C**) CFD task with optogenetic inhibition of the LC-DG projection. Animals received a shock in context A (red), but not in context B (yellow) for nine days (left). Pattern of laser stimulation and electrical foot shock (only in context A) during a CFD session (right). (**D**) Analysis of progressive days of training in CFD. Acute inhibition of LC-DG projection resulted in enhancement of behavioral pattern separation in mice expressing ArchT in LC-DG projections (Th-Cre$^{LC\text{-}DG}$::ArchT, n = 8; Context: $F_{(1,12)} = 5.743$, $p = 0.034$; Days: $F_{(8,96)} = 2.470$, $p = 0.018$; Days × Context: $F_{(8,96)} = 2.085$, $p = 0.045$), but not in wild-type controls (ArchT(-), n = 8; $F_{(1,14)} = 0.681$, $p = 0.423$; Days: $F_{(8,112)} = 1.865$, $p < 0.073$; Days × Context: $F_{(8,112)} = 1.251$, $p = 0.276$). (**E**) CFD task with optogenetic stimulation. Animals received a shock in context A (red), but not in context B (yellow) for nine days (left). Pattern of laser stimulation and shock (only in context A) during CFD (right). (**F**) Schematic of experimental approach depicts infection of LC-NE cells using Th-Cre mouse line with fluorescent reporter virus. (**G**) Mice expressing the reporter (Th-Cre$^{LC\text{-}DG}$::eYFP) were able to discriminate between the two contexts in a similar fashion to wild-type controls (Day 1: Group: $F_{(1,15)} = 0.533$, $p = 0.477$; Context: $F_{(1,15)} = 5.75$, $p = 0.0299$; Group × Context: $F_{(1,15)} = 1.34$, $p = 0.266$; Day 9: Group: $F_{(1,15)} = 2.26$, $p = 0.154$; Context: $F_{(1,15)} = 44.94$, $p < 0.0001$; Group × Context: $F_{(1,15)} = 0.0292$, $p = 0.867$). Both groups received optogenetic light during trial, shaded bar denotes successful stimulation of opsin. (**H**) Th-Cre$^{LC\text{-}DG}$::ArchT mice were subjected to one-shock contextual fear conditioning before contextual fear discrimination task (right). Pattern of laser stimulation and electrical foot shock during a CFD session (right). (**I**) Th-cre$^{LC\text{-}DG}$::ArchT mice (n = 7) did not differ from ArchT(-) controls (n = 8) even with LC-DG optogenetic inhibition during both the acquisition and retrieval stage ($t_{(14)} = 2.075$; $p = 0.1737$). Both groups received optogenetic light during trial, shaded bar denotes successful stimulation of opsin. (**J**) CFD task with restraint stress administration replacing optogenetic activation. (**K**) Restraint stress did not affect shock reactivity (indirect measure of pain sensitivity; Group × Days: $F_{(3,18)} = 1.264$, $p = 0.317$). (**L**) Acute restraint stress impairs performance in CFD (n = 7; Stress: $F_{(1,12)} = 1.823$, $p = 0.201$; Days: $F_{(7,84)} = 3.169$, $p = 0.005$; Days × Context: $F_{(7,84)} = 0.640$, $p = 0.721$), while naïve animals successfully discriminated between the two contexts (n = 7; Naïve: Context: $F_{(1,7.86)} = 2.790$, $p = 0.134$; Days: $F_{(7,87.88)} = 2.712$, $p = 0.014$; Days × Context: $F_{(7,87.88)} = 4.449$, $p < 0.001$). (**M**) Contextual fear discrimination (CFD) task with optogenetic activation of the LC-DG projection, with a dissimilar context C (green) replacing context B. Animals received a shock in context A (red), but not in context C, for three days (left). Pattern of laser stimulation (both contexts) and electrical foot shock (only in context A) during a CFD session (right). (**N**) Acute activation of LC-DG projection still impairs behavioral pattern separation in mice expressing ChR2 (Th-Cre$^{LC\text{-}DG}$::ChR2, n = 5; Context: $F_{(1,4)} = 3.32$, $p < 0.142$; Days: $F_{(2,8)} = 75.08$, $p < 0.001$; Days × Context: $F_{(2,8)} = 0.905$, $p = 0.442$), but not in wild-type controls (ChR2(-), n = 6; Context: $F_{(1,5)} = 68.1$, $p < 0.001$; Days: $F_{(2,10)} = 3.071$, $p < 0.091$; Days × Context: $F_{(2,10)} = 2.433$, $p = 0.137$). (**O**) Although both groups successfully discriminated on the first day of training, Th-Cre$^{LC\text{-}DG}$::ChR2 mice failed to discriminate between contexts in later training sessions (Day 1: Group: $F_{(1,9)} = 2.661$, $p = 0.137$; Context: $F_{(1,9)} = 12.79$, $p = 0.006$; Group × Context: $F_{(1,9)} = 0.055$, $p = 0.82$; Day 3: Group: $F_{(1,9)} = 6.645$, $p = 0.0298$; Context: $F_{(1,9)} = 48.84$, $p < 0.0001$; Group ×

Context: $F_{(1,9)}$ = 8.509, p = 0.017). Both groups received optogenetic light during trial, shaded bar denotes successful stimulation of opsin. (**P**) Contextual fear discrimination (CFD) task with optogenetic activation of the LC-DG projection, with a dissimilar context C (green) replacing context B, and alternating order of presentation of contexts during training. Animals received a shock in context A (red), but not in context C, for nine days (left). Pattern of laser stimulation (both contexts) and electrical foot shock (only in context A) during a CFD session (right). (**Q**) Acute activation of LC-DG projection impairs behavior in mice expressing ChR2 (n = 7) but not in wild-type controls (n = 11; Day 1: Group: $F_{(1,16)}$ = 0.611, p = 0.446; Context: $F_{(1,16)}$ = 0.363, p = 0.555; Group × Context: $F_{(1,16)}$ = 0.114, p = 0.740; Day 5: Group: $F_{(1,16)}$ = 2.51, p = 0.132; Context: $F_{(1,16)}$ = 9.80, p = 0.0065; Group × Context: $F_{(1,16)}$ = 5.62, p = 0.0307; Day 9: Group: $F_{(1,16)}$ = 6.43, p = 0.0221; Context: $F_{(1,16)}$ = 18.1, p = 0.0006; Group × Context: $F_{(1,16)}$ = 4.97, p = 0.0406). Both groups received optogenetic light during trial, shaded bar denotes successful stimulation of opsin. All data are mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.005.

Fig. S2. Validation of injection and implant sites and unmodulated behavior. Related to Figures 1, 2, 3, 4

(**A**) Reconstruction of approximate locations of fiber-optic implant tips for Th-Cre^{LC-DG}::ChR2, Th-Cre^{LC-DG}::ArchT. vGlut1-Cre^{DG}::Opto-β_2 mice and vGAT-Cre^{DG}::Opto-β_2 mice. (**B**) Distance traveled in center of open field assay by Th-Cre and wild-type control animals without any circuit manipulations ($t_{(18)}$ = -0.5002; p = 0.6230). (**C**) Distance traveled in perimeter of open field assay by Th-Cre and wild-type control animals without any circuit manipulations ($t_{(18)}$ = -0.6720; p = 0.5101). (**D**) Time spent in center of open field assay by Th-Cre and wild-type controls without any circuit manipulations ($t_{(18)}$ = 0.2176; p = 0.8301). (**E**) Speed in center of open field assay by Th-Cre and wild-type control animals without any circuit manipulations ($t_{(18)}$ = -1.3705; p = 0.1874). No significant differences in terms of motor control and behavior were detected between Th-Cre (n = 11) and wild-type controls (*n* = 9). All data are mean ± SEM. *ns.*

Fig. S3. Timeline of imaging technique and supplementary imaging analysis. Related to Figures 2, 3.

(**A**) Schematic depicting procedural timeline for *in vivo* imaging of DG neuronal ensemble in contextual fear conditioning (CFD). Th-Cre mice and wild-type controls were injected with HM3Dq in LC to enable increased modulation of LC-NE cells chemogenetically (Th-Cre$^{LC\text{-}DG}$::HM3Dq), and Ca^{2+} indicator (GCaMP6f) in the DG to enable imaging of the neural ensemble. Microendoscopic GRIN lenses were implanted above the DG in the same mice 2 weeks post-injection. 2 weeks post-implant, mice were trained in CFD. Following 10 days of training, mice were sacrificed for immunohistochemistry. (**B**) Schematic depicts placement of GCaMP6f injection and GRIN lens implant, as well as mini-microscope used during imaging. (**C**) Schematic of experimental approach depicts infection of LC-NE cells using Th-Cre mouse line with HM3Dq. (D) CFD with saline or CNO injection in Th-Cre$^{LC\text{-}DG}$::HM3Dq mice 30 minutes prior to task. (**F**E Th-Cre$^{LC\text{-}DG}$::HM3Dq mice injected with saline (n = 8) prior to CFD task are able to discriminate between the two contexts on day 9 of training, while Th-Cre$^{LC\text{-}DG}$::HM3Dq mice injected with CNO (n = 9) prior to CFD task are not. (**F**) Average response amplitude of neurons responding selectively to context A or context B in both wild-type controls and Th-Cre$^{LC\text{-}DG}$::HM3Dq mice, at the beginning and end of training (Day 1: Group: $F_{(1,15)} = 0.390$, $p = 0.541$; Context: $F_{(1,15)} = 0.21.34$, $p = 0.0003$; Group × Context: $F_{(1,15)} = 0.553$, $p = 0.469$; Day 5: Group: $F_{(1,15)} = 1.44$, $p = 0.249$; Context: $F_{(1,15)} = 4.47$, $p = 0.052$; Group × Context: $F_{(1,15)} = 0.0181$, $p = 0.895$; Day 9: Group: $F_{(1,15)} = 12.49$, $p = 0.003$; Context: $F_{(1,15)} = 25.57$, $p = 0.0001$; Group × Context: $F_{(1,15)} = 4.68$, $p = 0.0471$). (**G**) Averaged cell activity traces for cells imaged from Th-Cre$^{LC\text{-}DG}$::HM3Dq mice during day 1 of CFD task for neurons responding selectively to context A or context B. (**H**) Representative neurons responding selectively to context A (unsafe, top), context B (safe, bottom), or responding nonselectively (middle). For each neuron the binarized calcium event trace is plotted below, and the raw calcium trace is plotted above (Context Selectivity: $F_{(3,1126)} = 73.6$, $p < 0.0001$; Group: $F_{(1,1126)} = 0.513$, $p = 0.474$; Group x Selectivity: $F_{(3,1126)} = 0.452$, $p = 0.716$). (**I**) Reconstruction of approximate locations of GRIN lens implants in both wild-type controls and Th-Cre$^{LC\text{-}DG}$::HM3Dq mice Scale bar = 300 µm. All data are mean ± SEM. *$p < 0.05$, ***$p < 0.005$.

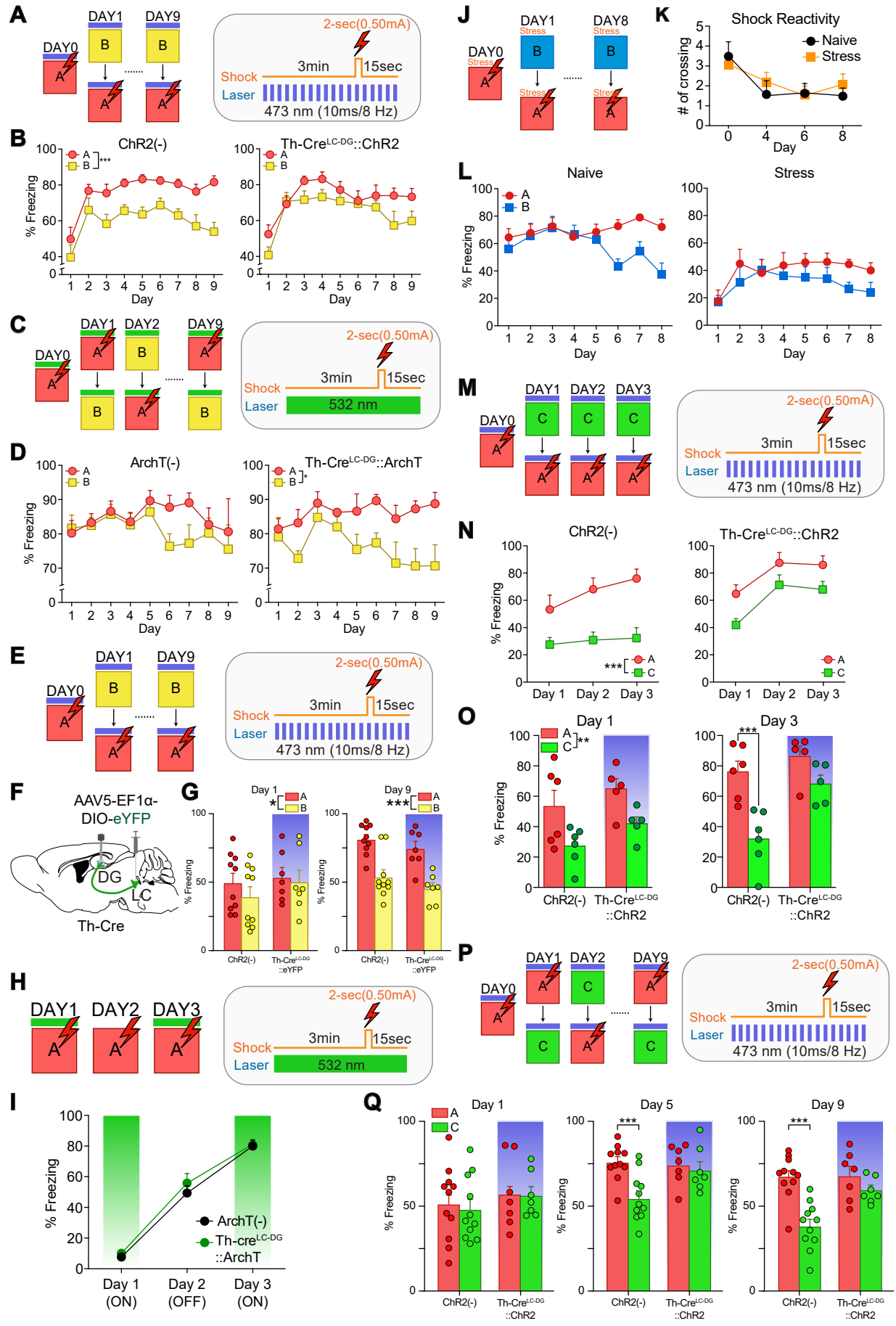
Fig. S4. In situ hybridization and control experiment proving specific effect of Opto-β_2 in CFD and quantification of Opto-β_2 transfection. Related to Figure 4.

(**A**) *In-situ* hybridization depicting coronal images of colocalization of the following: Left column: DAPI (blue), *Adrb2* (white), *Vgat* (red), *Vglut2* (green) within the dentate gyrus of wild-type mice; Right column: DAPI (blue), *Adrb2* (white), *Vgat* (red), *Vglut3* (green) within the dentate gyrus of wild-type mice. (**B**) Quantification of colocalization percentage of *Vgat*, *Vglut2*, and *Vglut3* with *Adrb2* showed high colocalization of *Adrb2* with *Vgat*, and *Vglut3*, but not *Vglut2.* (**C**) Schematic of experimental approach depicts infection of DG interneurons using vGAT-Cre mouse line with channelrhodopsin (vGAT-Cre^{DG}::ChR2). (**D**) Contextual fear discrimination (CFD) task with optogenetic activation of the DG interneurons. Animals received a shock in context A (red), but not in context B, for nine days (left). Pattern of laser stimulation (both contexts) and electrical foot shock (only in context A) during a CFD session (right). (**E**) Mice expressing channelrhodopsin (vGAT-Cre^{DG}::ChR2, n = 9) were able to discriminate between the two contexts in a similar fashion to wild-type controls (n = 8; Day 1: Group: $F_{(1,15)}$ = 0.467, p = 0.505; Context: $F_{(1,15)}$ = 0.0248, p = 0.877; Group × Context: $F_{(1,15)}$ = 3.72e-5, p = 0.995; Day 5: Group: $F_{(1,15)}$ = 0.0017, p = 0.968; Context: $F_{(1,15)}$ = 5.77, p = 0.0297; Group × Context: $F_{(1,15)}$ = 1.648, p = 0.219; Day 9: Group: $F_{(1,15)}$ = 0.438, p = 0.518; Context: $F_{(1,15)}$ = 18.2, p = 0.0007; Group × Context: $F_{(1,15)}$ = 0.117, p = 0.737). Both groups received optogenetic light during trial, shaded bar denotes successful stimulation of opsin. (**F**) Representative image depicting expression of Opto-β_2 in DG hilus and GCL in vGlut1-Cre mice and vGAT-Cre mice. Scale bar = 100 µm. (**G**) Quantification of overlap between DAPI and Opto-β_2 shows higher infection of GCL in vGlut1-Cre mice, and higher infection of hilus in vGAT-Cre mice. Representative from 17 mice in two cohorts. All data are mean ± SEM. *$p < 0.05$, ***$p < 0.005$.

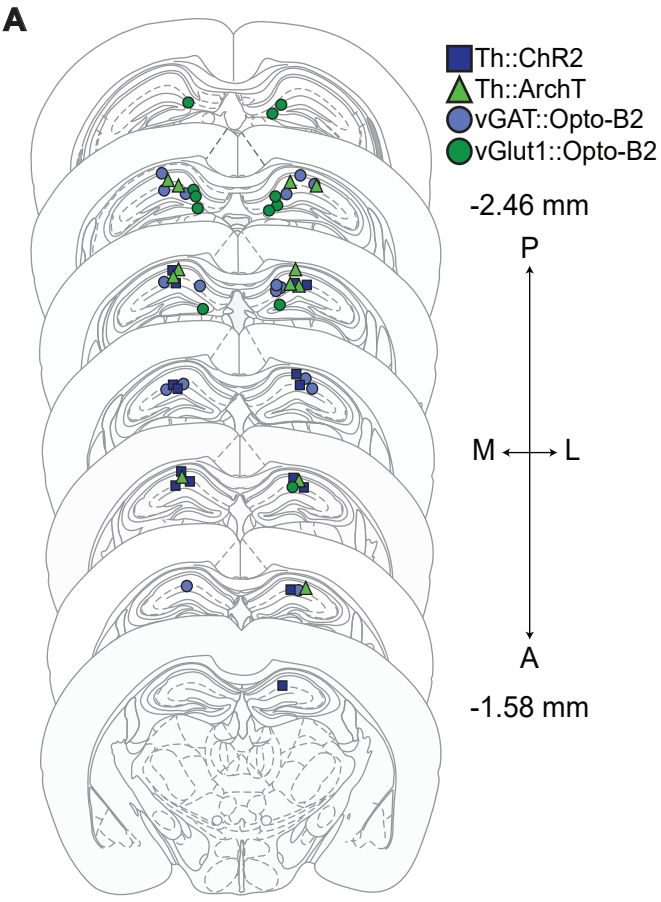
Table S1. Quantification and Statistical Analysis. Related to Figures 1, 2, 3, and 4.

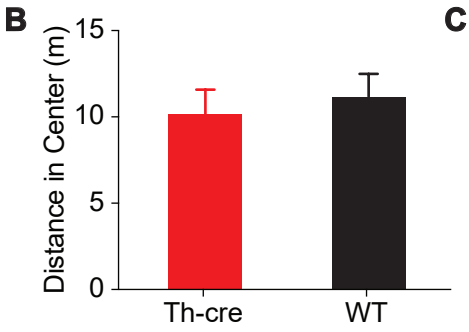
Table S2. List of Neurons Recorded From During *In Vivo* Calcium Imaging. Related to Figures 2 and 3.

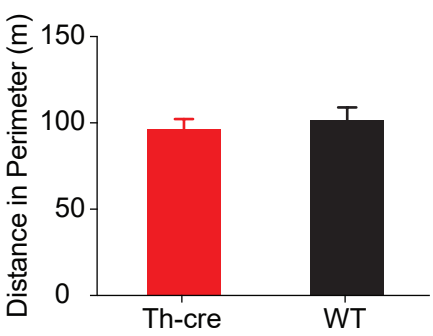
SUPPLEMENTAL FIGURE 1

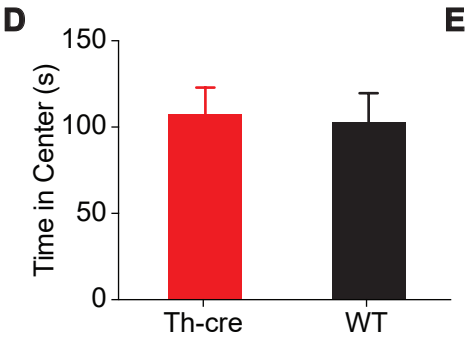


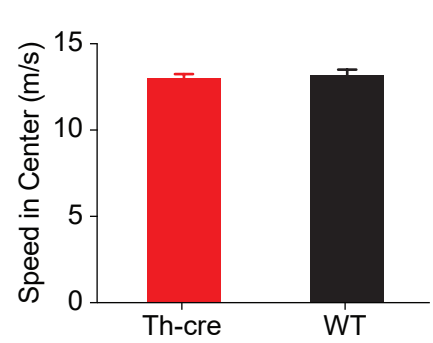
SUPPLEMENTAL FIGURE 2



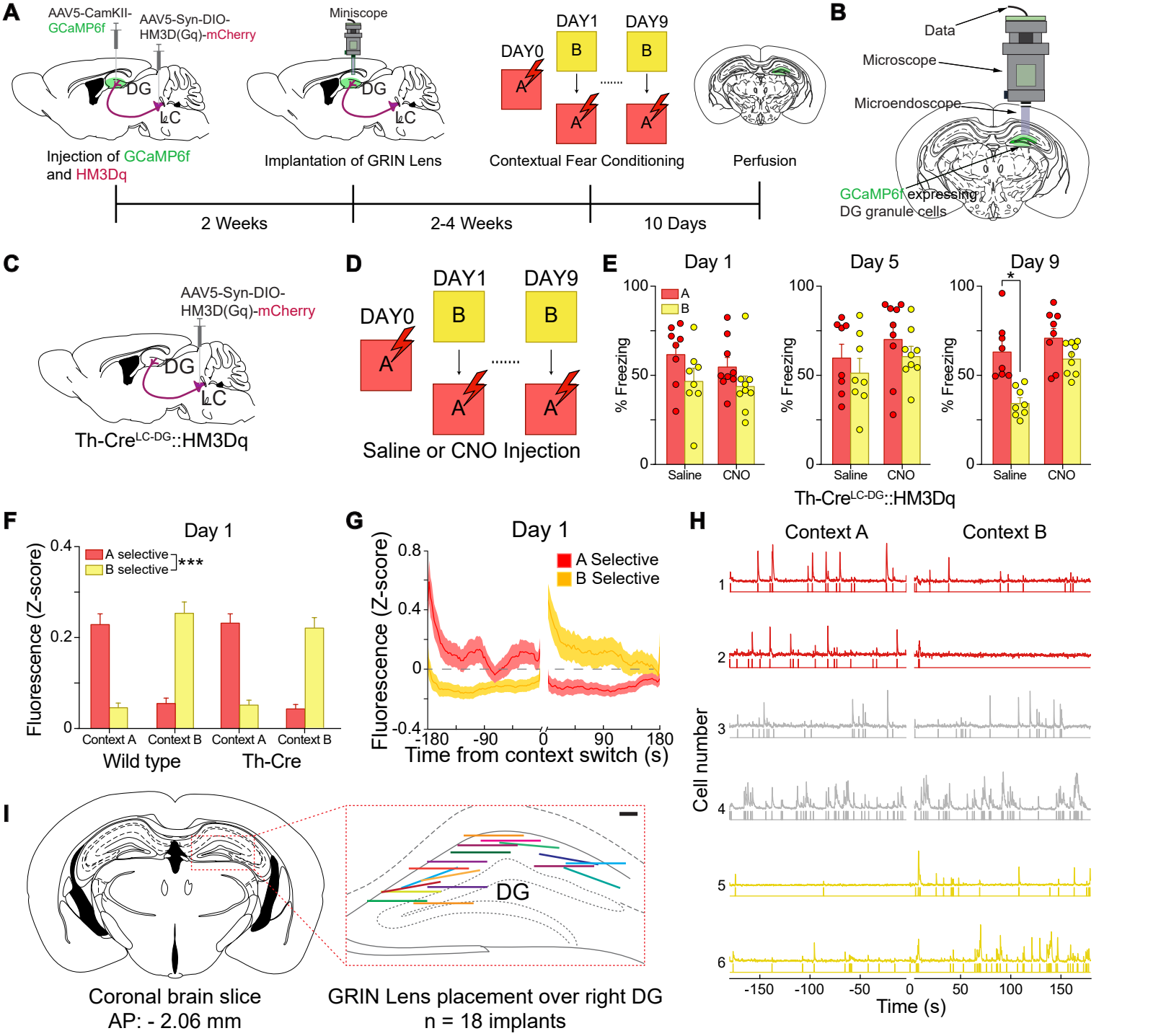








SUPPLEMENTAL FIGURE 3



SUPPLEMENTAL FIGURE 4

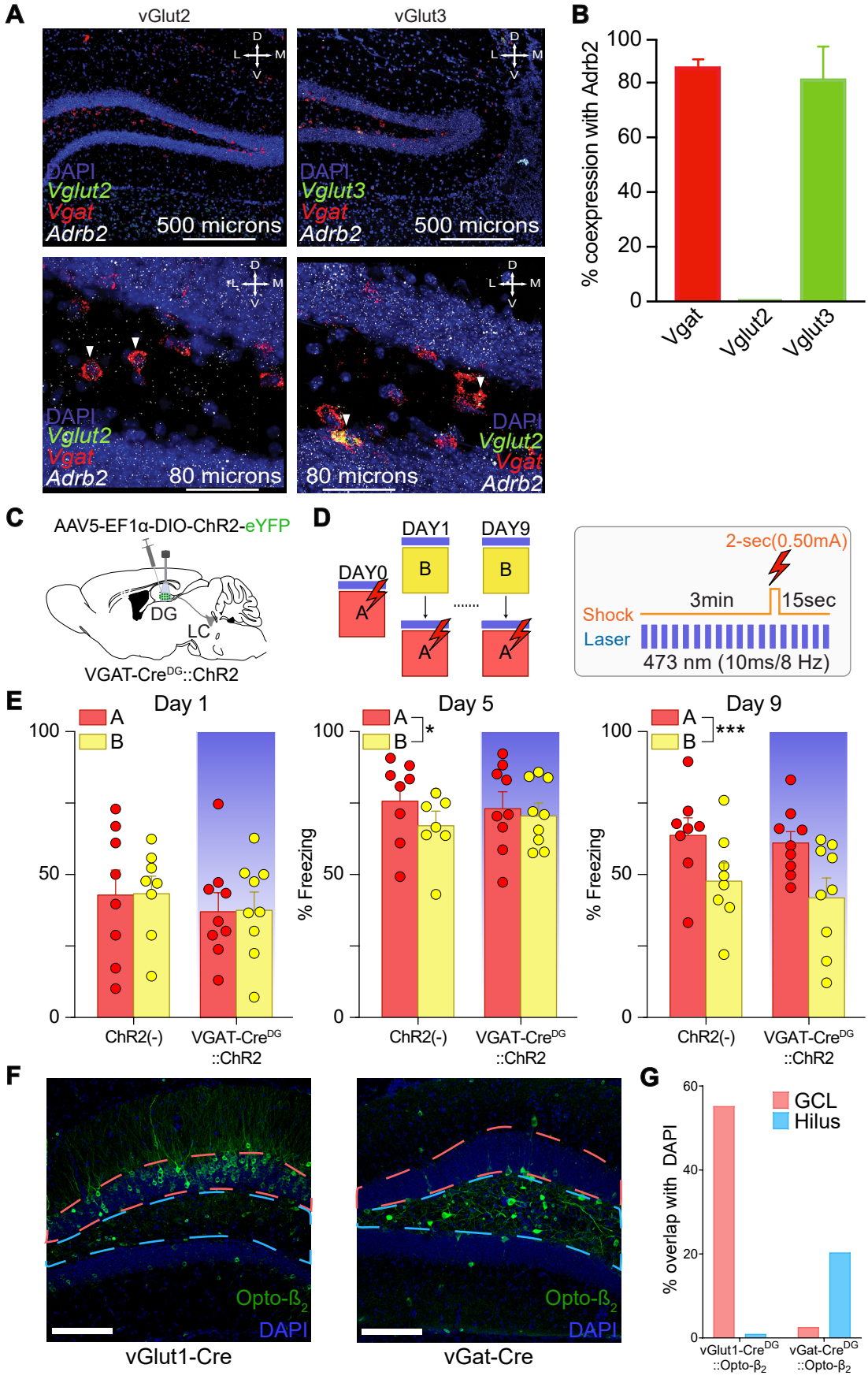


TABLE S1

Figure		Experimental Variables	Statistical Test	Results	Results (post-hoc)
1	E	Optogenetic Stimulation (ChR2)	REML	Day 1: Group: $F_{(1,18)} = 0.055$, p = 0.818; Context: $F_{(1,18)} = 16.885$, p < 0.001; Days × Context: $F_{(1,18)} = 0.076$, p = 0.786	N/A
				Day 5: Group: $F_{(1,18)} = 0.012$, p = 0.913; Context: $F_{(1,18)} = 30.608$, p < 0.001; Days × Context: $F_{(1,18)} = 8.034$, p = 0.011	ChR2(-), A vs B, p < 0.001; Context A, ChR2(-) vs. Th-Cre$^{LC\text{-}DG-}$::ChR2, p = 0.709
				Day 9: Group: $F_{(1,18)} = 0.040$, p = 0.843; Context: $F_{(1,18)} = 36.016$, p < 0.001; Group × Context: $F_{(1,18)} = 4.463$, p = 0.049	ChR2(-), A vs B, p < 0.001; Context A, ChR2(-) vs. Th-Cre$^{LC\text{-}DG-}$::ChR2, p = 0.608
	H	Optogenetic Stimulation (ArchT)	REML	Day 1: Group: $F_{(1, 13)} = 0.025$, p = 0.878; Context: $F_{(1,13)} = 0.014$, p = 0.907; Group × Context: $F_{(1,13)} = 0.256$, p = 0.621	N/A
				Day 5: Group: $F_{(1, 13)} = 2.464$, p = 0.141; Context: $F_{(1,13)} = 4.804$, p = 0.047; Group × Context: $F_{(1,13)} = 1.435$, p = 0.252	N/A
				Day 9: Group: $F_{(1,13)} = 0.027$, p = 0.871; Context: $F_{(1,13)} = 17.03$, p = 0.001; Group × Context: $F_{(1,13)} = 5.39$, p = 0.037	Th-Cre$^{LC\text{-}DG-}$::ArchT, A vs B, p < 0.005
2	L	Context Selectivity	Chi-squared	Context A: Chi-square = 0.168, Bonferonni adj. p-value (p < 0.008) = 0.682	N/A
				Context B: Chi-square = 27.3, Bonferonni adj. p-value (p < 0.008) < 0.001	N/A
				Nonselective: Chi-square = 18.1575, Bonferonni adj. p-value (p < 0.008) < 0.001	N/A
			Unpaired t-test	Context A: $t_{(16)} = 0.396$, p = 0.697	N/A
				Context B: $t_{(16)} = 2.01$, p = 0.0618	N/A
	M	Cell Response-Freezing Response Correlation	Pearson correlation	Day 1: r = -0.132, $r^2 = 0.0173$, p = 0.737	N/A
				Day 9: r = 0.749, $r^2 = 0.561$, p = 0.0202	N/A
	O	Context Selectivity	Chi-squared	Context A: Chi-square = 0, Bonferonni adj. p-value (p < 0.008) = 1	N/A
				Context B: Chi-square = 13.9, Bonferonni adj. p-value (p < 0.008) < 0.001	N/A
				Nonselective: Chi-square = 7.54, Bonferonni adj. p-value (p < 0.008) = 0.006	N/A
3	D	Treatment (CNO)	REML	Day 1: Group: $F_{(1,16)} = 2.15$, p = 0.162; Context: $F_{(1,16)} = 0.0566$, p = 0.815; Group × Context: $F_{(1,16)} = 5.20$, p = 0.0366	HM3Dq(-), A vs B, p = 0.308; Th-Cre$^{LC\text{-}DG-}$::HM3Dq, A vs B, p = 0.179
				Day 5: Group: $F_{(1,16)} = 0.207$, p = 0.655; Context: $F_{(1,16)} = 5.06$, p = 0.0389; Group × Context: $F_{(1,16)} = 0.0392$, p = 0.846	N/A
				Day 9: Group: $F_{(1,16)} = 3.46$, p = 0.0811; Context: $F_{(1,16)} = 23.82$, p = 0.0002; Group × Context: $F_{(1,16)} = 4.497$, p = 0.0499	HM3Dq(-), A vs B, p < 0.001
	H	Context Selectivity	Chi-squared	Context A: Chi-square = 2.35, Bonferonni adj. p-value (p < 0.008) = 0.125	N/A
				Context B: Chi-square = 6.16, Bonferonni adj. p-value (p < 0.008) = 0.0131	N/A
				Nonselective: Chi-square = 0.683, Bonferonni adj. p-value (p < 0.008) = 0.006	N/A
			Unpaired t-test	Context A: $t_{(16)} = 0.747$, p = 0.466	N/A
				Context B: $t_{(16)} = 1.37$, p = 0.191	N/A
	I	Cell Response-Freezing Response Correlation	Pearson correlation	Day 1: r = 0.375, $r^2 = 0.141$, p = 0.32	N/A
				Day 9: r = -0.109, $r^2 = 0.0001$, p = 0.98	N/A
	L	Context Selectivity	Chi-squared	Context A: Chi-square = 8.82, Bonferonni adj. p-value (p < 0.008) = 0.003	N/A
				Context B: Chi-square = 6.98, Bonferonni adj. p-value (p < 0.008) = 0.0082	N/A
				Nonselective: Chi-square = 0.307, Bonferonni adj. p-value (p < 0.008) = 0.580	N/A
	M	Context Selectivity	Kolmogorov–Smirnov test	HM3Dq(-): K-stat = 0.171, p < 0.001	N/A
				Th-Cre$^{LC\text{-}DG-}$::HM3Dq: K-stat = 0.0724, p = 0.0533	N/A
4	D	Treatment (Propranolol)	REML	Day 1: Group: $F_{(1,12)} = 0.665$, p = 0.431; Context: $F_{(1,12)} = 0.361$, p = 0.559; Group × Context: $F_{(1,12)} = 3.29$, p = 0.0947	N/A
				Day 5: Group: $F_{(1,12)} = 1.31$, p = 0.274; Context: $F_{(1,12)} = 1.15$, p = 0.305; Group × Context: $F_{(1,12)} = 1.39$, p = 0.261	N/A
				Day 9: Group: $F_{(1,12)} = 0.109$, p = 0.747; Context: $F_{(1,12)} = 6.34$, p = 0.0271; Group × Context: $F_{(1,12)} = 4.78$, p = 0.0494	Propranolol, A vs B, p = 0.0121
	L	Optogenetic Stimulation (Opto-β2)	REML	Day 1: Group: $F_{(1, 12)} = 0.0468$, p = 0.832; Context: $F_{(1,12)} = 1.49$, p = 0.246; Group × Context: $F_{(1,12)} = 0.398$, p = 0.540	N/A
				Day 5: Group: $F_{(1, 12)} = 0.0913$, p = 0.768; Context: $F_{(1,12)} = 5.20$, p = 0.0417; Group × Context: $F_{(1,12)} = 0.0151$, p = 0.904	N/A
				Day 9: Group: $F_{(1, 12)} = 0.101$, p = 0.757; Context: $F_{(1,12)} = 16.14$, p = 0.0017; Group × Context: $F_{(1,12)} = 0.310$, p = 0.588	N/A
	M	Action Potentials	REML	Depolarization Step: $F_{(15,288)} = 9.303$, p<0.0001; Drug: $F_{(2,288)} = 59.84$, p<0.0001; Depolarization Step x Drug: $F_{(30,288)} = 2.207$, p = 0.0005	Veh vs Prop: p<0.0001; Veh vs Iso: p<0.0001; Prop vs Iso: p<0.0001
	N			Statistics derived from Two-way ANOVA of the data specified in Figure 4I. Veh vs Prop: p=0.1411. Veh vs Iso: p=0.0385. Prop vs Iso: p=0.0005.	N/A
	O			Statistics derived from Two-way ANOVA of the data specified in Figure 4I. Veh vs Prop: p=0.0007. Veh vs Iso: p=0.2752. Prop vs Iso: p<0.0001	N/A
	R	Optogenetic Stimulation (Opto-β2)	REML	Day 1: Group: $F_{(1, 17)} = 0.862$, p = 0.366; Context: $F_{(1,17)} = 0.352$, p = 0.561; Group × Context: $F_{(1,17)} = 7.167$, p = 0.016	Opto-β2(-), A vs B, p = 0.275; vGAT-Cre^{DG-}::Opto-β2, A vs B, p = 0.074; Context A, Opto-β2(-) vs. vGAT1-Cre^{DG-}::Opto-β2, p = 0.270
				Day 5: Group: $F_{(1, 17)} = 0.196$, p = 0.664; Context: $F_{(1,17)} = 2.175$, p = 0.159; Group × Context: $F_{(1,17)} = 3.281$, p = 0.088	Context A, Opto-β2(-) vs. vGAT1-Cre^{DG-}::Opto-β2, p = 0.596
				Day 9: Group: $F_{(1,17)} = 0.407$, p = 0.532; Context: $F_{(1,17)} = 44.286$, p < 0.001; Group × Context: $F_{(1,17)} = 12.026$, p = 0.003	Opto-β2(-), A vs B, p < 0.001; Context A, Opto-β2(-) vs. vGlut1-Cre^{DG-}::Opto-β2, p = 0.257
	U	Stress/Naive	REML	Day 3: Group: $F_{(1,9.76)} = 6.137$, p = 0.033	N/A
				Day 6: Group: $F_{(1,9.46)} = 4.044$, p = 0.073; Context: $F_{(1,13.8)} = 21.429$, p < 0.001; Days × Context: $F_{(1, 13.8)} = 3.824$, p = 0.071	N/A
				Day 8: Group: $F_{(1,10.39)} = 7.109$, p = 0.023; Context: $F_{(1,14.87)} = 24.6072$, p < 0.001; Days × Context: $F_{(1, 14.87)} = 3.322$, p = 0.085	N/A
S1	B	Optogenetic Stimulation (ChR2)	REML	ChR2(-): Context: $F_{(1,18)} = 2.685$, p = 0.119; Days: $F_{(1,144)} = 14.568$, p < 0.001; Days × Context: $F_{(8,144)} = 1.386$, p = 0.206	N/A
				Th-Cre$^{LC\text{-}DG-}$::ChR2: Context: $F_{(1,18)} = 19.430$, p < 0.001; Days: $F_{(1,144)} = 10.940$, p < 0.001; Days × Context: $F_{(8,144)} = 0.892$, p = 0.525	N/A
	D	Optogenetic Stimulation (ArchT)	REML	ArchT(-): Context: $F_{(1,14)} = 0.681$, p = 0.423; Days: $F_{(8,112)} = 1.865$, p < 0.073; Days × Context: $F_{(8,112)} = 1.251$, p = 0.276	N/A
				Th-Cre$^{LC\text{-}DG-}$::ArchT: Context: $F_{(1,12)} = 5.743$, p = 0.034; Days: $F_{(8,96)} = 2.470$, p = 0.018; Days × Context: $F_{(8,96)} = 2.085$, p = 0.045	N/A
	G	Transgenic Background (Th-Cre)	REML	Day 1: Group: $F_{(1,15)} = 0.533$, p = 0.477; Context: $F_{(1,15)} = 5.75$, p = 0.0299 ; Group × Context: $F_{(1,15)} = 1.34$, p = 0.266	N/A
				Day 9: Group: $F_{(1,15)} = 2.26$, p = 0.154; Context: $F_{(1,15)} = 44.94$, p < 0.0001 ; Group × Context: $F_{(1,15)} = 0.0292$, p = 0.867	N/A
	I	Optogenetic Stimulation (ArchT)	Paired t-test	$t_{(14)} = 2.075$; p = 0.1737	N/A
	K	Stress/Naive	REML	Group × Days: $F_{(3,18)} = 1.264$, p = 0.317	N/A
	L	Stress/Naive	REML	Naïve: Context: $F_{(1,7.86)} = 2.790$, p = 0.134; Days: $F_{(7,87.88)} = 2.712$, p = 0.014; Days × Context: $F_{(7,87.88)} = 4.449$, p < 0.001	N/A
				Stress: Context: $F_{(1,12)} = 1.823$, p = 0.201; Days: $F_{(7,84)} = 3.169$, p = 0.005; Days × Context: $F_{(7,84)} = 0.640$, p = 0.721	N/A
	N	Optogenetic Stimulation (ChR2)	REML	ChR2(-): Context: $F_{(1,5)} = 68.1$, p < 0.001; Days: $F_{(2,10)} = 3.071$, p < 0.091; Days × Context: $F_{(2,10)} = 2.433$, p = 0.137	N/A
				Th-Cre$^{LC\text{-}DG-}$::ChR2: Context: $F_{(1,4)} = 3.32$, p < 0.142; Days: $F_{(2,8)} = 75.08$, p < 0.001; Days × Context: $F_{(2,8)} = 0.905$, p = 0.442	N/A
	O	Optogenetic Stimulation (ChR2)	REML	Day 1: Group: $F_{(1,9)} = 2.661$, p = 0.137; Context: $F_{(1,9)} = 12.79$, p = 0.006 ; Group × Context: $F_{(1,9)} = 0.055$, p = 0.82	N/A
				Day 3: Group: $F_{(1,9)} = 6.645$, p = 0.0298; Context: $F_{(1,9)} = 48.84$, p < 0.0001 ; Group × Context: $F_{(1,9)} = 8.509$, p = 0.017	ChR2(-), A vs C, p < 0.001
	Q	Optogenetic Stimulation (ChR2)	REML	Day 1: Group: $F_{(3,16)} = 0.611$, p = 0.446; Context: $F_{(1,16)} = 0.363$, p = 0.555; Group × Context: $F_{(3,16)} = 0.114$, p = 0.740	N/A
				Day 5: Group: $F_{(1,16)} = 2.51$, p = 0.132; Context: $F_{(1,16)} = 9.80$, p = 0.0065; Group × Context: $F_{(1,16)} = 5.62$, p = 0.0307	ChR2(-), A vs C, p < 0.001
				Day 9: Group: $F_{(3,16)} = 6.43$, p = 0.0221; Context: $F_{(1,16)} = 18.1$, p = 0.0006; Group × Context: $F_{(3,16)} = 4.97$, p = 0.0406	ChR2(-), A vs C, p < 0.001
S2	B	Th-cre/WT	Paired t-test	$t_{(18)} = -0.5002$; p = 0.6230	N/A
	C	Th-cre/WT	Paired t-test	$t_{(18)} = -0.6720$; p = 0.5101	N/A
	D	Th-cre/WT	Paired t-test	$t_{(18)} = 0.2176$; p = 0.8301	N/A
	E	Th-cre/WT	Paired t-test	$t_{(18)} = -1.3705$; p = 0.1874	N/A
S3	F	Transgenic Background (Th-Cre)	REML	Day 1: Group: $F_{(1,15)} = 0.390$, p = 0.541; Context: $F_{(1,15)} = 0.21.34$, p = 0.0003; Group × Context: $F_{(1,15)} = 0.553$, p = 0.469	N/A
				Day 5: Group: $F_{(1,15)} = 1.44$, p = 0.249; Context: $F_{(1,15)} = 4.47$, p = 0.052; Group × Context: $F_{(1,15)} = 0.0181$, p = 0.895	N/A
				Day 9: Group: $F_{(1,15)} = 12.49$, p = 0.003; Context: $F_{(1,15)} = 25.57$, p = 0.0001; Group × Context: $F_{(1,15)} = 4.68$, p = 0.0471	Saline Treatment, A vs B, p < 0.001
	H	Cell Selective Activity	REML	Context Selectivity: $F_{(3,1126)} = 73.6$, p < 0.0001; Group: $F_{(1,1126)} = 0.513$, p = 0.474; Group x Selectivity: $F_{(3,1126)} = 0.452$, p = 0.716	N/A
S4	E	Optogenetic Stimulation (ChR2)	REML	Day 1: Group: $F_{(1,15)} = 0.467$, p = 0.505; Context: $F_{(1,15)} = 0.0248$, p = 0.877; Group × Context: $F_{(1,15)} = 3.72e\text{-}5$, p = 0.995	N/A
				Day 5: Group: $F_{(1,15)} = 0.0017$, p = 0.968; Context: $F_{(1,15)} = 5.77$, p = 0.0297; Group × Context: $F_{(1,15)} = 1.648$, p = 0.219	N/A
				Day 9: Group: $F_{(1,15)} = 0.438$, p = 0.518; Context: $F_{(1,15)} = 18.2$, p = 0.0007; Group × Context: $F_{(1,15)} = 0.117$, p = 0.737	N/A

Table S2							
Mouse	**Day 1 Total**	**Day 1 A Selective**	**Day 1 B Selective**	**Day 9 Total**	**Day 9 A Selective**	**Day 9 B Selective**	**Matched Cells**
Th-cre 2-1	43	5	15	50	7	19	9
Th-cre 2-2	105	50	13	137	37	15	80
Th-cre 2-3	78	29	17	98	24	35	58
Th-cre 348-1	32	15	1	25	8	9	5
Th-cre 349-2	355	90	85	221	59	68	28
Th-cre 386-2	45	8	12	10	0	3	0
Th-cre 387-4	31	5	12	31	5	21	8
Th-cre 396-1	37	5	8	38	10	6	26
Th-cre 396-3	63	1	14	67	5	14	21
WT 122-1	16	6	3	32	20	6	9
WT 122-2	36	10	5	43	6	9	19
WT 122-3	43	14	12	60	6	30	18
WT 124-2	11	4	2	9	4	3	0
WT 1055-1	46	6	7	49	12	6	24
WT 1055-2	165	4	4	142	3	27	55
WT 1055-3	122	10	29	111	12	23	64
WT 1055-4	93	13	34	107	21	47	51
WT 14-0	39	19	0	45	1	27	17