Dissociable control of depression and visceral pain by the pIC^{Glu}–avBNST circuit in male mice with chronic colitis

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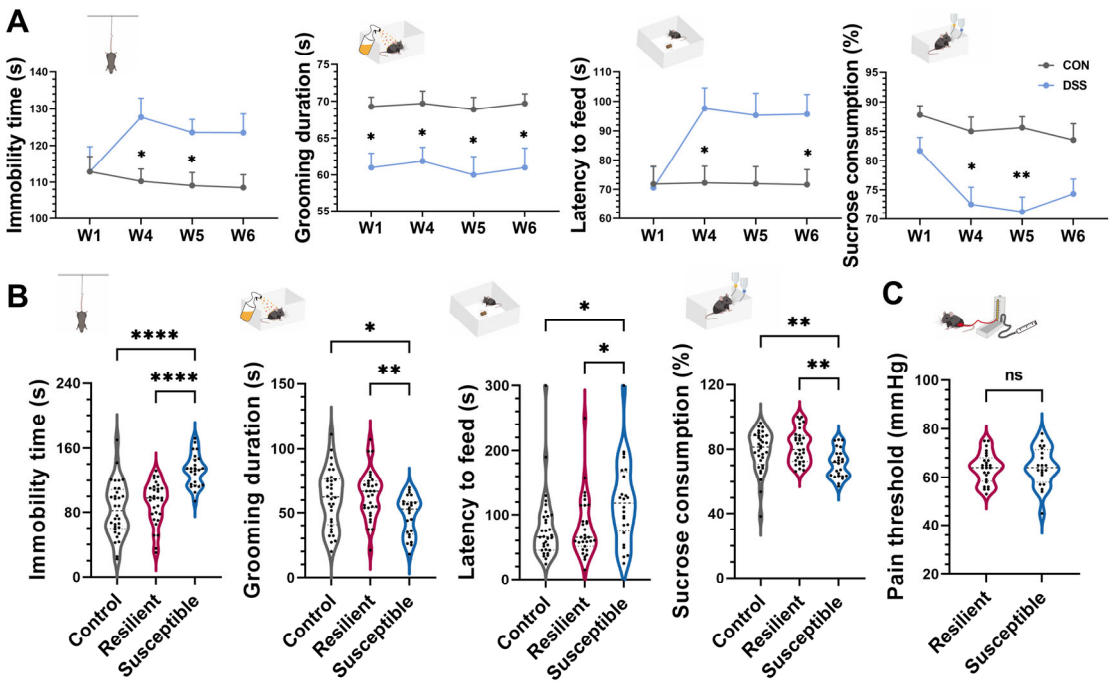


Fig. S1 Depression-like behaviors and the visceral pain in mice with IBD. (A) Depression-like behavioral outcomes at weeks 1, 4, 5, and 6 after IBD modeling (n = 10; two-way ANOVA with Bonferroni's post-hoc analysis). (B) Depression-like behavior after assigning TST, ST, NSFT, and SPT test results to different groups using a K-means classifier in female mice (n = 32, 31, and 24 mice in control, resilient, and susceptible groups, respectively; one-way ANOVA with Tukey's post-hoc analysis). (C) The visceral pain threshold of female mice 4 weeks after IBD modeling (n=25 and 20 mice in resilient groups and susceptible groups, respectively; unpaired t-test). *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. Statistical details are provided in Table S3.

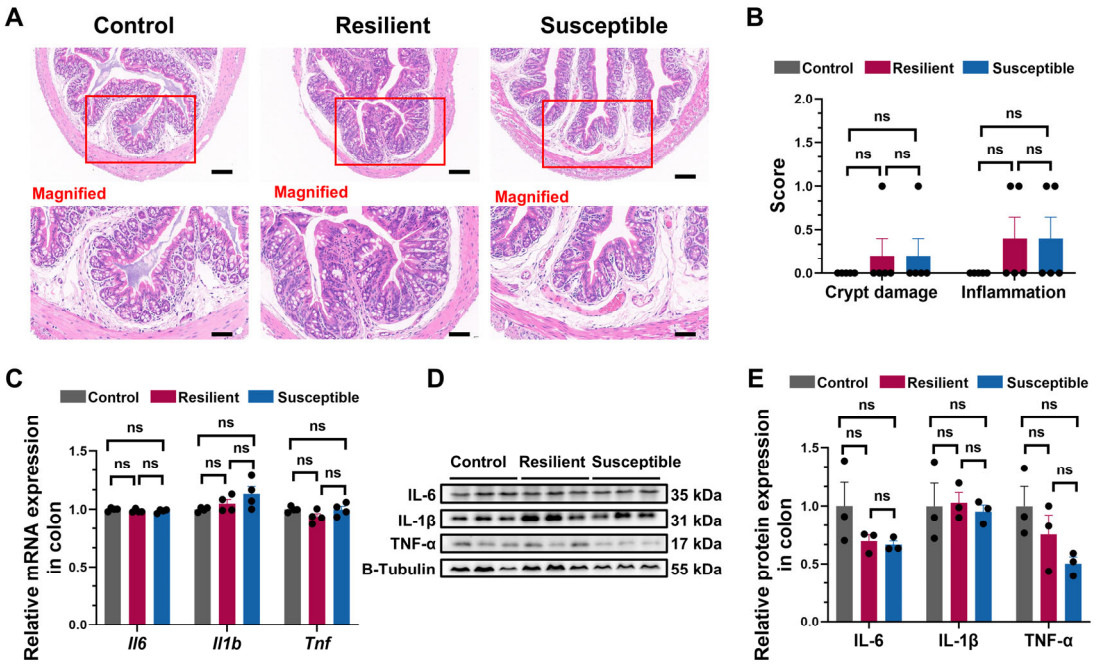


Fig. S2 Histological and inflammatory analyses in resilient and susceptible mice. (A) Representative light microscopy images of colon sections stained with H&E from control and DSS-treated mice. Scale bars = 100 μm (top); Scale bars = 50 μm (bottom). (B) The crypt damage score and inflammation score of colon section (n = 5; one-way ANOVA with Tukey's post-hoc analysis). (C) *Il6*, *Il1b* and *Tnf* expression in distal colon sections detected by qPCR (n = 4; one-way ANOVA with Tukey's post-hoc analysis). (D-E) IL-6, IL-1β and TNF-α expression in distal colon sections detected by Western blot (n = 3; one-way ANOVA with Tukey's post-hoc analysis). *$P < 0.05$, **$P < 0.01$. Statistical details are provided in Table S3.

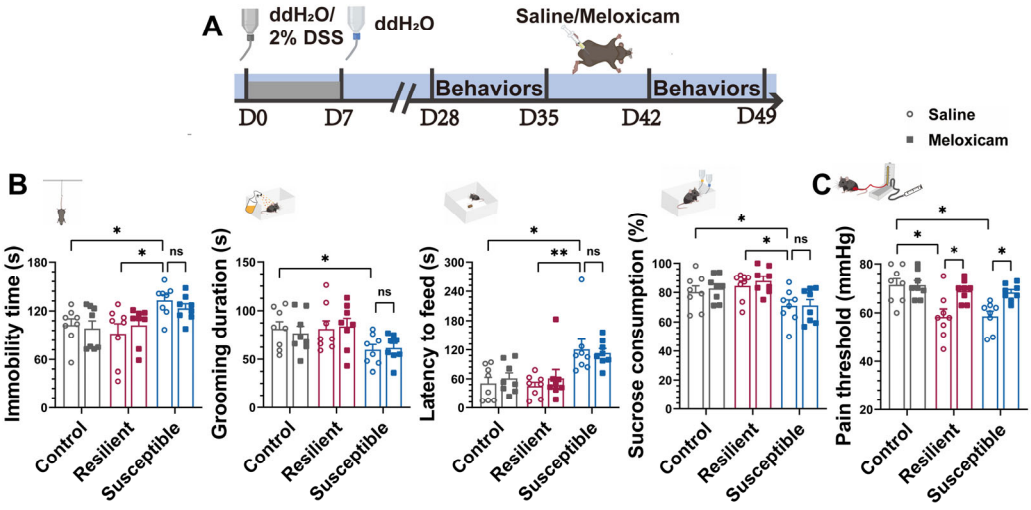


Fig. S3 Behavioral responses to analgesics in colitic mice. (A) Time course of mice intraperitoneal injection and behavioral testing. (B) Behavioral tests showed the effect of relief of visceral pain on depression-like behavior (n = 8 per group; two-way ANOVA with Šídák's post-hoc analysis). (C). Visceral pain threshold results showed the effect of relief of visceral pain on visceral pain threshold in mice (n = 8 per group; two-way ANOVA with Šídák's post-hoc analysis). *$P < 0.05$, **$P < 0.01$. Statistical details are provided in Table S3.

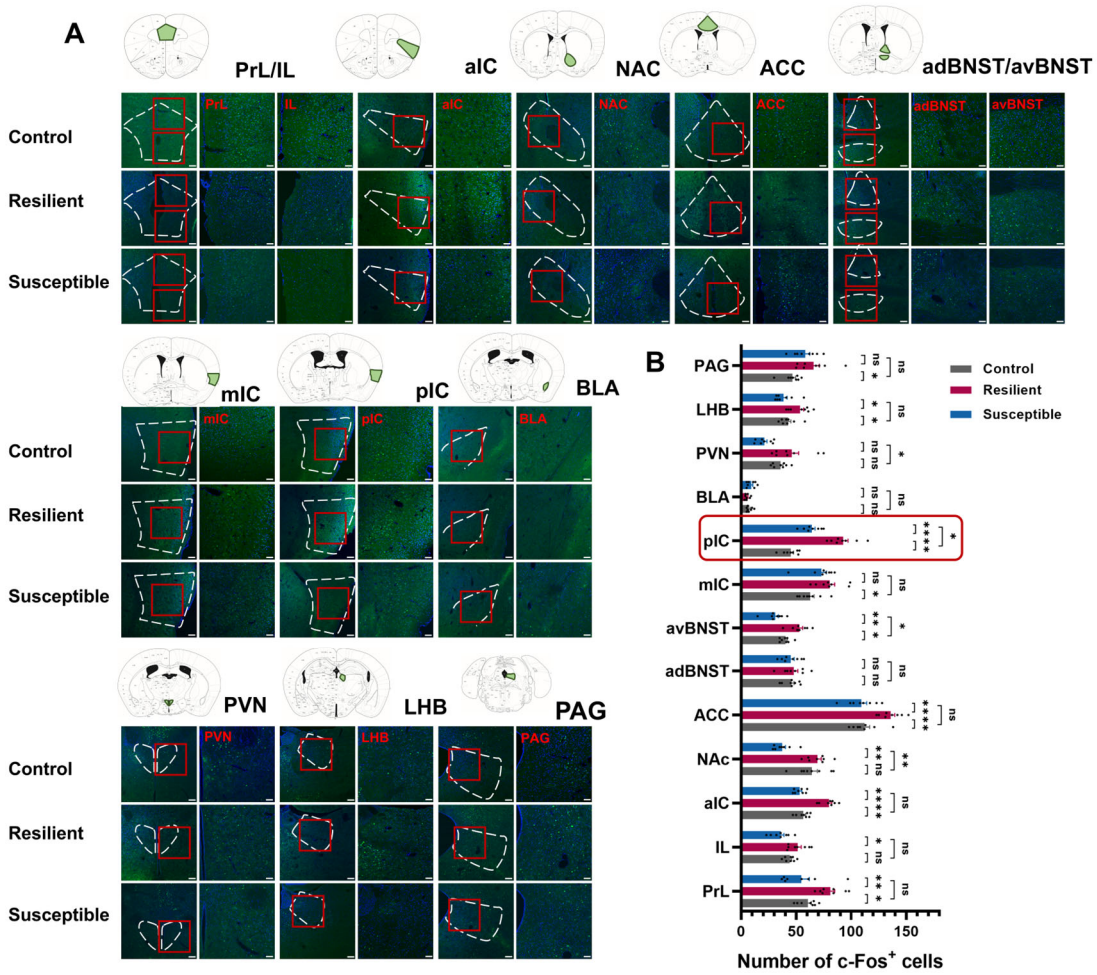


Fig. S4 Immunofluorescence of whole brain in mice with IBD. (A) c-Fos expression in different brain regions of control, resilient and susceptible: PrL/IL, prelimbic and infralimbic subareas in the medial prefrontal cortex (mPFC); aIC, anterior insular cortex; NAC, nucleus accumbens; ACC, anterior cingulate cortex; adBNST/avBNST, anterior dorsal/ventral bed nucleus of the stria terminalis; mIC, middle insular cortex; pIC , posterior insular cortex; BLA, basolateral amygdala; PVN, paraventricular nucleus; LHB, lateral habenula; PAG, periaqueductal grey region. Scale bars = 100 μm (left); Scale bars = 50 μm (right). (B) Quantification of c-Fos protein expression in different brain regions (n = 8 in per group; one-way ANOVA with Tukey's post-hoc analysis). *$P < 0.05$, **$P < 0.01$. Statistical details are provided in Table S3.

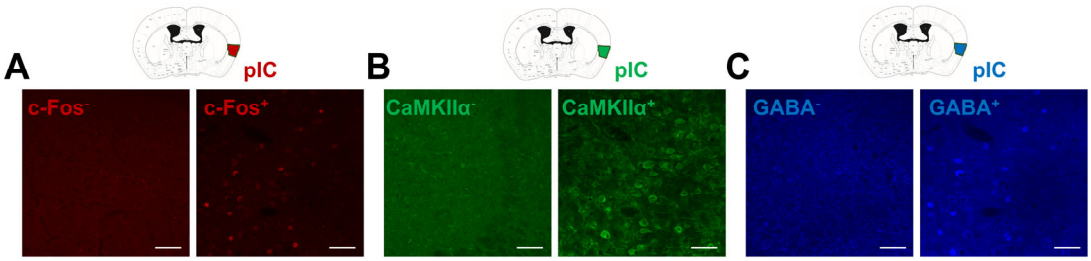
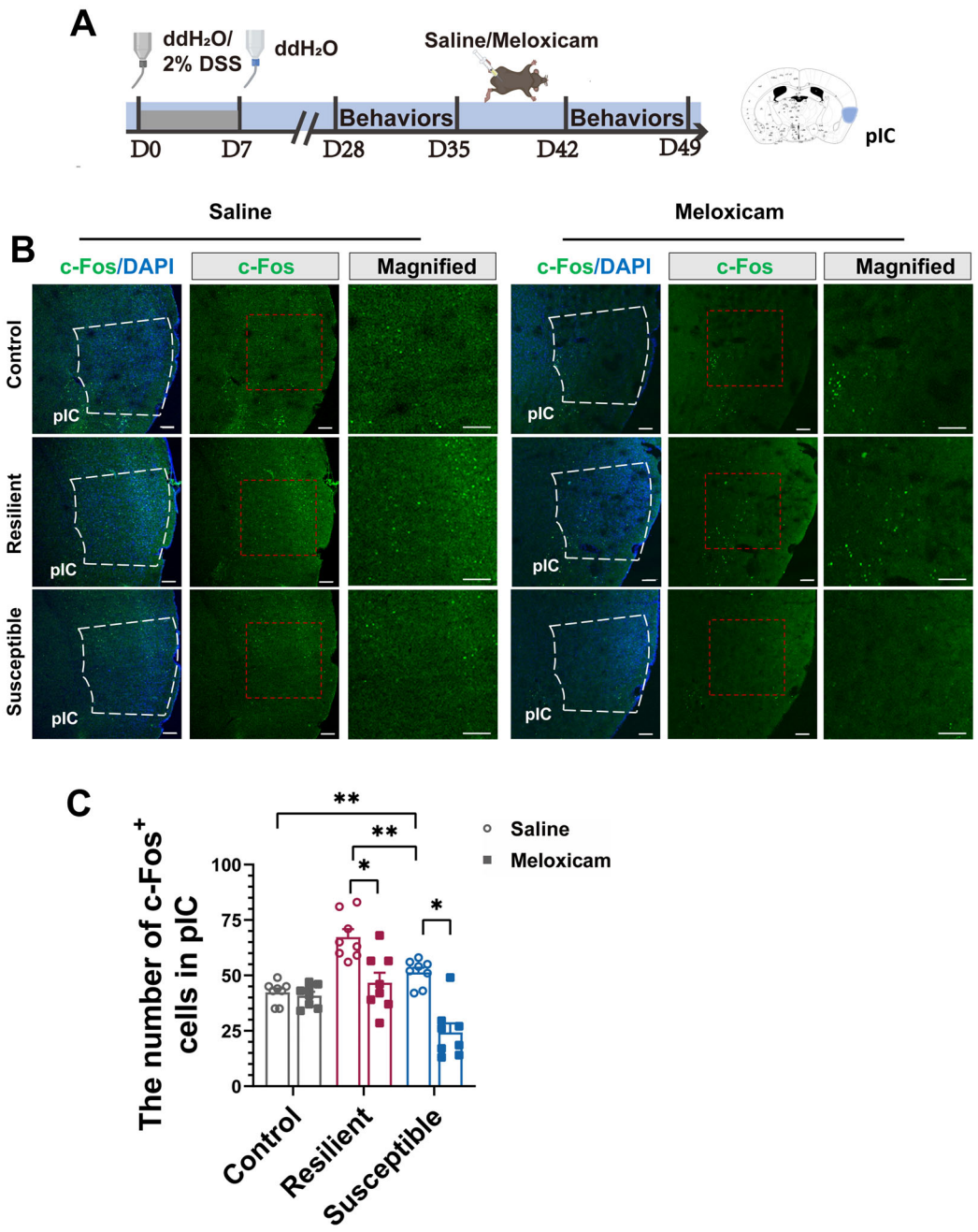


Fig. S5 No-primary-antibody control immunofluorescence staining for c-Fos CaMKIIα, and GABA in the mouse pIC. (A) Representative images showing no-primary-antibody control (left) and c-Fos immunostaining (right) using Alexa Fluor 594–conjugated secondary antibody. (B) Representative images showing no-primary-antibody control (left) and CaMKIIα immunostaining (right) using Alexa Fluor 488–conjugated secondary antibody. (C) Representative images showing no-primary-antibody control (left) and GABA immunostaining (right) using Alexa Fluor 405–conjugated secondary antibody. Scale bar = 50 μm.



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74 **Fig. S6 Impact of visceral analgesia on pIC function.** (A) Time course of mice
75 intraperitoneal injection and behavioral testing. (B) c-Fos expression in pIC of control,
76 resilient and susceptible after intraperitoneal injection of saline and meloxicam. Scale
77 bars = 100 μm (all panels). (C) Quantification of c-Fos$^+$ cells in pIC (n = 8 in per group;
78 one-way ANOVA with Tukey's post-hoc analysis). *P < 0.05, **P < 0.01. Statistical
79 details are provided in Table S3.

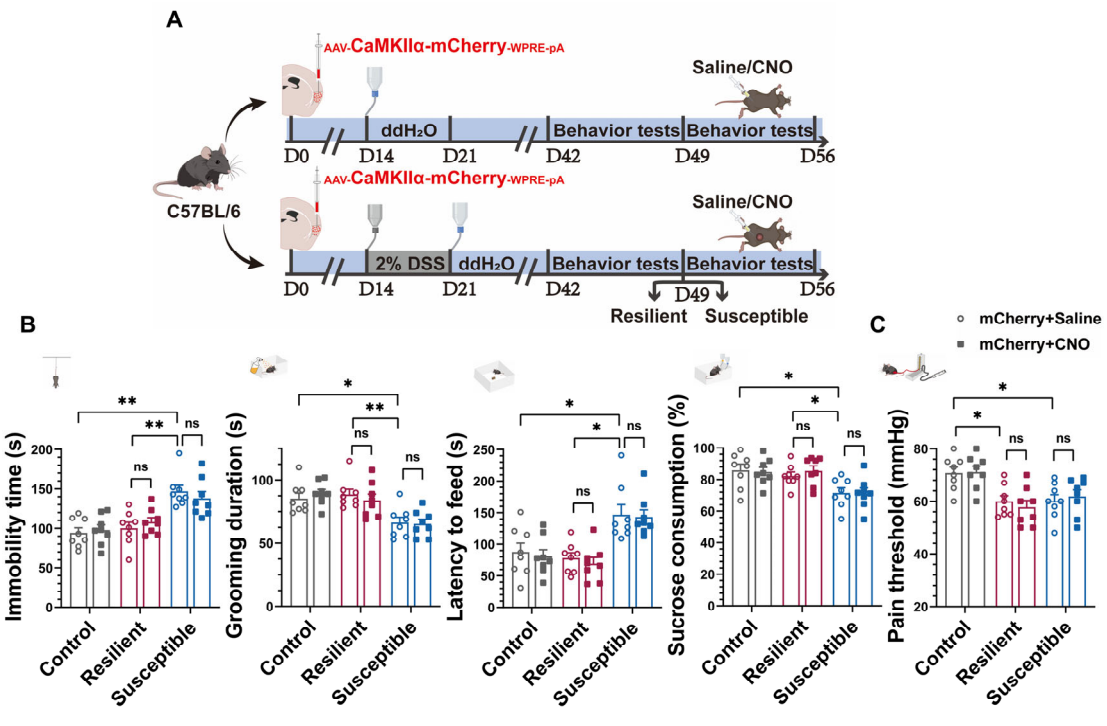

Fig. S7 CNO has no effect on mouse behaviors without the expression of hM4Di/hM3Dq. (A) Time course of mice virus injection and behavioral testing. (B) Behavioral tests showed the effect of CNO on depression-like behavior (n = 8 in per group; two-way ANOVA with Šídák's post-hoc analysis). (C) Visceral pain threshold results showed the effect of CNO on visceral pain threshold in mice (n = 8 in per group; two-way ANOVA with Šídák's post-hoc analysis). *$P < 0.05$, **$P < 0.01$. Statistical details are provided in Table S3.

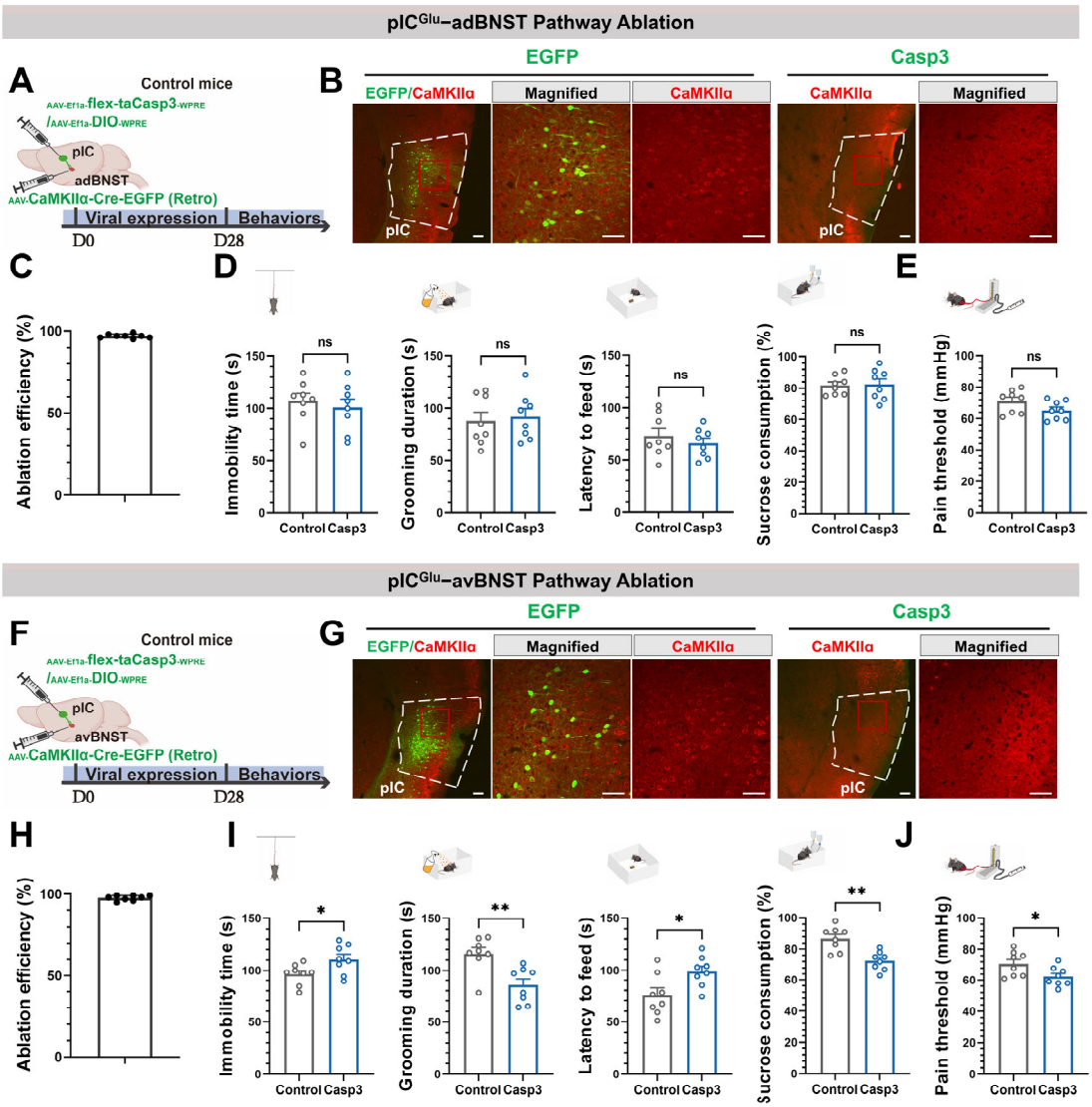

Fig. S8 pIC^{Glu}–avBNST neural circuitry mediates depressive-like behavior and visceral pain sensitization in mice. (A) Time course of mice virus injection and behavioral testing. (B) The representative images verified the expression of EGFP and taCasp3 in pIC^{Glu}–adBNST (Scale bars = 100 μm (left); Scale bars = 50 μm (right)). (C) The ablation efficiency in Casp3 mice (n = 8). (D) Behavioral tests showed the effect of pIC^{Glu}–adBNST depletion on depression-like behavior (n = 8; unpaired t-test). (E). Visceral pain threshold results showed the effect of damaged pIC^{Glu}–adBNST on visceral pain threshold in mice (n = 8; unpaired t-test). (F) Time course of mice virus injection and behavioral testing. (G) The representative images verified the expression of EGFP and taCasp3 in pIC^{Glu}–avBNST (Scale bars = 100 μm (left); Scale bars = 50 μm (right)). (H) The ablation efficiency in Casp3 mice (n = 8). (I)

Behavioral tests showed the effect of pIC^{Glu}–avBNST depletion on depression-like behavior (n = 8; unpaired t-test). (J). Visceral pain threshold results showed the effect of damaged pIC^{Glu}–avBNST on visceral pain threshold in mice (n = 8; unpaired t-test). *P < 0.05, **P < 0.01. Statistical details are provided in Table S3.

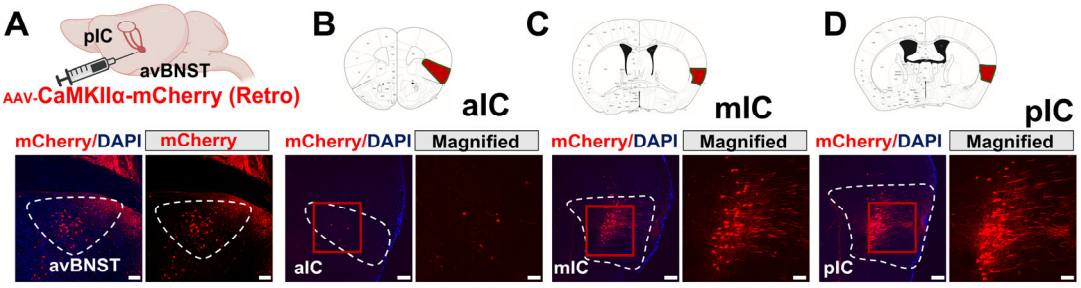

Fig. S9 Retrograde tracing of avBNST projecting neurons. (A) Virus injection diagram. (B-D) Representative images verifying mCherry expression in aIC, mIC and pIC glutamatergic neurons. Scale bars = 100 μm (left); Scale bar = 50 μm (right).

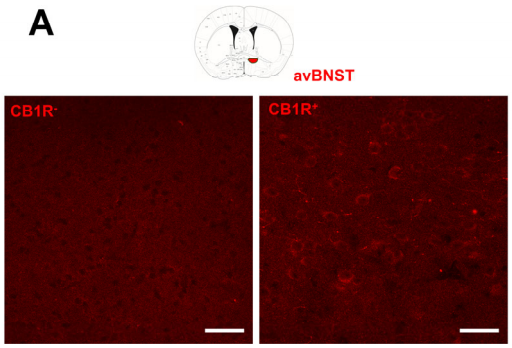

Fig. S10 No-primary-antibody control immunofluorescence staining for CB1R in the mouse avBNST. (A) Representative images showing no-primary-antibody control (left) and CB1R immunostaining (right) using Alexa Fluor 594–conjugated secondary antibody. Scale bar = 50 μm.

Table S1 Antibodies, drugs and other reagents

Reagent	Source	Dilution	Identifier
Rabbit anti-c-Fos	Cell Signaling technology	1:1000(IF)	Cat#2250S; RRID: AB_2247211
Mouse anti-CaMKIIα	Thermo Fisher Scientific	1:300(IF)	Cat# MA1-048, RRID: AB_325403
Guinea pig anti-c-Fos	Synaptic Systems	1:500(IF)	Cat#226004; RRID: AB_2619946
Rabbit anti-GABA	Sigma-Aldrich	1:400(IF)	Cat#A2052
Rabbit anti-CB1R	Proteintech	1:200(IF) 1:1000(WB)	Cat# 17978-1-AP, RRID: AB_10859098
Rabbit anti-GAPDH	Proteintech	1:3000(WB)	Cat# 10494-1-AP, RRID: AB_2263076
Rabbit anti-Tubulin	Affinity	1:3000(WB)	Cat# DF7967
Alexa Fluor 488 donkey anti-Mouse IgG (H + L)	Thermo Fisher Scientific	1:400(IF)	Cat#A-21202 RRID: AB_141607
Alexa Fluor 594 donkey anti-Mouse IgG (H + L)	Thermo Fisher Scientific	1:400(IF)	Cat#A-21203 RRID: AB_2535789
Alexa Fluor 488 donkey anti-Rabbit IgG (H + L)	Thermo Fisher Scientific	1:400(IF)	Cat#A32790 RRID: AB_2762833
Alexa Fluor 405 donkey anti-Rabbit IgG (H + L)	Thermo Fisher Scientific	1:400(IF)	Cat#A48258 RRID: AB_2890547
Alexa Fluor 594 goat anti-guinea pig IgG (H + L)	Thermo Fisher Scientific	1:400(IF)	Cat#A-11076; RRID: AB 2534120
Alexa Fluor 594 donkey anti-Rabbit IgG (H +L)	Thermo Fisher Scientific	1:400(IF)	Cat#A32754; RRID: AB 2762827
Dextran sulfate sodium (DSS)	Sigma-Aldrich	-	Cat#D0564-1MG
CNO	MCE	-	Cat#HY-17366
BCA protein assay kit	Beyotime	-	Cat#P0012
AM251	Tocris	-	Cat#1117/1
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Table S2 Virus

Reagent	Source	Concentration	Identifier
rAAV-CaMKIIα-GCaMP6s-WPRE-hGH polyA, AAV2/9	BrainVTA	5.00×10^{12} vg/ml	Cat#PT-0110
rAAV-CaMKIIα-hM3D(Gq)-mCherry-WPRE-hGH pA, AAV2/9	BrainVTA	4.98×10^{12} vg/ml	Cat#PT-1144
rAAV-CaMKIIα-hM4D(Gi)-mCherry-WPRE-hGH polyA, AAV2/9	BrainVTA	5.12×10^{12} vg/ml	Cat#PT-0017
rAAV-CaMKIIα-mCherry-WPRE-hGH polyA, AAV2/9	BrainVTA	2.26×10^{12} vg/ml	Cat#PT-0108
rAAV-CaMKIIα-hChR2(H134R)-mCherry-WPRE-hGH pA, AAV2/9	BrainVTA	6.62×10^{12} vg/ml	Cat#PT-0297
rAAV- CaMKIIα -eNpHR3.0-mCherry-WPRE-hGH polyA, AAV2/9	BrainVTA	6.12×10^{12} vg/ml	Cat#PT-0011
rAAV-CaMKIIα-EGFP-WPRE-hGH polyA, AAV2/9	BrainVTA	5.22×10^{12} vg/ml	Cat#PT-8218
rAAV-CaMKIIα-mCherry-WPRE-hGH polyA, (Retro)	BrainVTA	5.0×10^{12} vg/ml	Cat# PT-0108-R
rAAV-Ef1α-fDIO-EGFP-WPRE-hGH-pA, AAV2/9	BrainVTA	5.12×10^{12} vg/ml	Cat#PT-1047
rAAV-CAG-DIO-WGA-FLP-WPRE-hGH-PA, AAV2/9	BrainVTA	5.26×10^{12} vg/ml	Cat#PT-0557
rAAV-EF1a-flex-taCasp3-TEVp-WPRE-hGH pA, AAV2/9	BrainVTA	5.12×10^{12} vg/ml	Cat# PT-0206
AAV-CaMKIIα-Cre-EGFP-WPRE-hGH-pA, (Retro)	BrainVTA	5.0×10^{12} vg/ml	Cat#PT-8218-R
pAAV-CaMKIIα-mCherry-3xFLAG-miR30s-hRNA (Cnr1)-WPRE	OBIO	4.21×10^{12} vg/ml	Cat#RC1203
pAAV-CaMKIIα-mCherry-3xFLAG-miR30s-hRNA (NC2)-WPRE	OBIO	4.23×10^{12} vg/ml	Cat# OP0913

128 **Table S3** Statistical analysis

Figure	Statistical methods	Statistics	*P* value
Fig. 1B	Two-way repeated-measures ANOVA with Geisser-Greenhouse correction, followed by Bonferroni post-hoc analysis; n = 10 per group	F (1, 18) = 110.2 D0: t = 0.2335 D7: t = 5.882 D14: t = 6.606 D21: t = 4.704 D28: t = 3.723 D35: t = 3.590 D42: t = 3.414 D49: t = 3.230 D56: t = 3.397	$P < 0.0001$ $P > 0.9999$ $P = 0.0001$ $P < 0.0001$ $P = 0.0023$ $P = 0.0202$ $P = 0.0205$ $P = 0.0281$ $P = 0.0414$ $P = 0.0285$
Fig. 1C	TST: Unpaired t-test with Welch's correction; CON n = 54, DSS n = 110	t (150.9) = 2.460	$P = 0.0150$
	ST: Unpaired t-test; CON n = 54, DSS n = 110	t (162) = 2.263	$P = 0.0249$
	NSFT: Unpaired t-test with Welch's correction; CON n = 54, DSS n = 110	t (147.0) = 3.742	$P = 0.0013$
	SPT: Unpaired t-test with Welch's correction; CON n = 54, DSS n = 110	t (149.9) = 2.325	$P = 0.0214$
Fig. 1E	TST: Kruskal-Wallis test with Dunn's post hoc test; Control n = 54, Resilient n = 70, Susceptible n = 40	KW = 27.06 Control vs. Resilient Control vs. Susceptible	$P < 0.0001$ $P = 0.7184$ $P < 0.0001$

Figure	Statistical methods	Statistics	*P* value
		Resilient vs. Susceptible	$P < 0.0001$
	ST: Ordinary one-way ANOVA with Tukey's post-hoc analysis; Control n = 54, Resilient n = 70, Susceptible n = 40	F (2, 161) = 12.41 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P < 0.0001$ $P = 0.8947$ $P < 0.0001$ $P < 0.0001$
	NSFT: Kruskal-Wallis test with Dunn's post-hoc analysis; Control n = 54, Resilient n = 70, Susceptible n = 40	KW = 28.67 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P < 0.0001$ $P = 0.1976$ $P < 0.0001$ $P = 0.0001$
	SPT: Kruskal-Wallis test with Dunn's post-hoc analysis; Control n = 54, Resilient n = 70, Susceptible n = 40	KW = 51.66 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P < 0.0001$ $P = 0.5824$ $P < 0.0001$ $P < 0.0001$
Fig. 1F	Unpaired t-test; Resilient n = 25, Susceptible n = 18	t (41) = 0.1170	$P = 0.9075$
Fig. 2B	One-way ANOVA with Tukey's post-hoc analysis; n = 4 per group	F (2,9) = 37.20 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P < 0.001$ $P < 0.001$ $P = 0.0454$ $P = 0.0008$
Fig. 2C	One-way ANOVA with Tukey's post-hoc analysis; n = 4 per group	F (2, 9) = 20.75 Control vs. Resilient Control vs. Susceptible	$P = 0.0004$ $P = 0.0006$ $P = 0.0016$

Figure	Statistical methods	Statistics	*P* value
		Resilient vs. Susceptible	$P = 0.6933$
Fig. 2F	Linear mixed-effects model (nested random effects: mouse/cell) with Bonferroni's post-hoc analysis; Control n = 4 mice (13 cells), Resilient n = 4 mice (13 cells), Susceptible n = 4 mice (13 cells)	F (2, 9) = 12.47 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.0024$ $P = 0.0019$ $P = 0.0311$ $P = 0.0041$
Fig. 2G	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Control n = 4 mice (13 cells), Resilient n = 4 mice (13 cells), Susceptible n = 4 mice (13 cells)	F (2, 9) = 59.24 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P < 0.0001$ $P < 0.0001$ $P < 0.0001$ $P < 0.0001$
Fig. 2H	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Control n = 4 mice (13 cells), Resilient n = 4 mice (13 cells), Susceptible n = 4 mice (13 cells)	F (2, 9) = 0.134 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.616$ $P = 0.996$ $P = 0.871$ $P = 0.909$
Fig. 2L	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Control n = 4 mice (21 trails), Resilient n = 4 mice (21 trails), Susceptible n = 4 mice (17 trails)	F (2, 9) = 0.134 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.013$ $P = 0.309$ $P = 0.001$ $P < 0.001$
Fig. 2O	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Control n = 4 mice (20 trails), Resilient n = 4 mice (22 trails), Susceptible n = 4 mice (19 trails)	F (2, 9) = 4.61 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.037$ $P = 0.958$ $P = 0.022$ $P = 0.009$

Figure	Statistical methods	Statistics	*P* value
Fig. 2R	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Control n = 4 mice (20 trails), Resilient n = 4 mice (21 trails), Susceptible n = 4 mice (21 trails)	F (2, 9) = 14.35 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P < 0.0001$ $P < 0.0001$ $P < 0.0001$ $P = 0.456$
Fig. 2U	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Control n = 4 mice (22 trails), Resilient n = 4 mice (20 trails), Susceptible n = 4 mice (18 trails)	F (2, 9) = 4.61 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.036$ $P = 0.028$ $P = 0.134$ $P = 0.637$
Fig. 3D	TST: Unpaired t-test; n = 9 per group	t (16) = 2.941	$P = 0.0096$
	ST: Unpaired t-test; n = 9 per group	t (16) = 2.249	$P = 0.0390$
	NSFT: Unpaired t-test; n = 9 per group	t (16) = 4.004	$P = 0.0010$
	SPT: Unpaired t-test; n = 9 per group	t (16) = 3.498	$P = 0.0030$
Fig. 3E	Unpaired t-test with Welch's correction; n = 9 per group	t (8.383) = 2.711	$P = 0.0255$
Fig. 3I	TST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 5.179 Control vs. Resilient: t (42) = 0.1252 Control vs. Susceptible: t (42) = 4.240 Resilient vs. Susceptible: t (42) = 4.366	$P = 0.0098$ $P = 0.9990$ $P = 0.0004$ $P = 0.0002$

Figure	Statistical methods	Statistics	*P* value
	Saline vs. CNO	Control: t (42) = 0.2863 Resilient: t (42) = 0.6083 Susceptible: t (42) = 3.704	*P* = 0.9888 *P* = 0.9066 *P* = 0.0018
	Control: Saline vs. Susceptible: CNO	t (42) = 0.5368	*P* > 0.9999
	ST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 2.247 Control vs. Resilient: t (42) = 0.3651 Control vs. Susceptible: t (42) = 3.476 Resilient vs. Susceptible: t (42) = 3.111	*P* = 0.2282 *P* = 0.9773 *P* = 0.0036 *P* = 0.0100
	Saline vs. CNO	Control: t (42) = 0.4089 Resilient: t (42) = 0.6864 Susceptible: t (42) = 2.556	*P* = 0.9686 *P* = 0.8721 *P* = 0.0423
	Control: Saline vs. Susceptible: CNO	t (42) = 9201	*P* = 0.9988
	NSFT: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 2.988 Control vs. Resilient: t (42) = 1.283 Control vs. Susceptible: t (42) = 4.611 Resilient vs. Susceptible: t (42) = 3.327	*P* = 0.0612 *P* = 0.5002 *P* = 0.0001 *P* = 0.0055
	Saline vs. CNO	Control: t (42) = 0.0183 Resilient: t (42) = 0.3758 Susceptible: t (42) = 2.796	*P* > 0.9999 *P* = 0.9753 *P* = 0.0231
	Control: Saline vs. Susceptible:	t (42) = 1.815	*P* = 0.6978

Figure	Statistical methods	Statistics	*P* value
	CNO		
	SPT: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 3.288 Control vs. Resilient: t (42) = 0.03828 Control vs. Susceptible: t (42) = 2.912 Resilient vs. Susceptible: t (42) = 2.950	*P* = 0.0471 *P* > 0.9999 *P* = 0.0171 *P* = 0.0155
	Saline vs. CNO	Control: t (42) = 0.3918 Resilient: t (42) = 0.5427 Susceptible: t (42) = 2.671	*P* = 0.9722 *P* = 0.9312 *P* = 0.0318
	Control: Saline vs. Susceptible: CNO	t (42) = 0.2490	*P* > 0.9999
Fig. 3J	Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 1.835 Control vs. Resilient: t (42) = 2.664 Control vs. Susceptible: t (42) = 2.415 Resilient vs. Susceptible: t (42) = 0.2493	*P* = 0.1721 *P* = 0.0324 *P* = 0.0594 *P* = 0.9925
	Saline vs. CNO	Control: t (42) = 0.0422 Resilient: t (42) = 0.9889 Susceptible: t (42) = 0.9986	*P* = 2.557 *P* = 0.2849 *P* = 0.1424
	Control: Saline vs. Susceptible: CNO	t (42) = 2.557	*P* = 0.1938
Fig. 3N	TST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 1.204 Control vs. Resilient: t (42) = 0.4002 Control vs. Susceptible: t (42) = 3.716	*P* = 0.3101 *P* = 0.9705 *P* = 0.0018

Figure	Statistical methods	Statistics	*P* value
		Resilient vs. Susceptible: t (42) = 3.316	*P* = 0.0057
	Saline vs. CNO	Control: t (42) = 2.773 Resilient: t (42) = 2.587 Susceptible: t (42) = 0.7862	*P* = 0.0245 *P* = 0.0392 *P* = 0.8208
	Control: Saline vs. Resilient: CNO	t (42) = 2.987	*P* = 0.0680
	ST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 4.527 Control vs. Resilient: t (42) = 1.911 Control vs. Susceptible: t (42) = 5.569 Resilient vs. Susceptible: t (42) = 3.659	*P* = 0.016 *P* = 0.1770 *P* = 0.0010 *P* = 0.0021
	Saline vs. CNO	Control: t (42) = 2.400 Resilient: t (42) = 3.309 Susceptible: t (42) = 0.7457	*P* = 0.0614 *P* = 0.0058 *P* = 0.8425
	Control: Saline vs. Resilient: CNO	t (42) = 5.220	*P* = 0.0001
	NSFT: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 2.436 Control vs. Resilient: t (42) = 0.6131 Control vs. Susceptible: t (42) = 5.529 Resilient vs. Susceptible: t (42) = 4.916	*P* = 0.0997 *P* = 0.9046 *P* = 0.0001 *P* = 0.0001
	Saline vs. CNO	Control: t (42) = 3.584 Resilient: t (42) = 3.721 Susceptible: t (42) = 0.9514	*P* = 0.0026 *P* = 0.0017 *P* = 0.7213
	Control: Saline vs. Resilient: CNO	t (42) = 4.334	*P* = 0.0013

Figure	Statistical methods	Statistics	*P* value
	SPT: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 1.861 Control vs. Resilient: t (42) = 0.1451 Control vs. Susceptible: t (42) = 3.013 Resilient vs. Susceptible: t (42) = 2.868	*P* = 0.1681 *P* = 0.9985 *P* = 0.0130 *P* = 0.0192
	Saline vs. CNO	Control: t (42) = 2.763 Resilient: t (42) = 2.811 Susceptible: t (42) = 0.4248	*P* = 0.0252 *P* = 0.0222 *P* = 0.9651
	Control: Saline vs. Resilient: CNO	t (42) = 2.957	*P* = 0.0736
Fig. 3O	Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.9610 Control vs. Resilient: t (42) = 3.616 Control vs. Susceptible: t (42) = 3.078 Resilient vs. Susceptible: t (42) = 0.5379	*P* = 0.3908 *P* = 0.0024 *P* = 0.0110 *P* = 0.9328
	Saline vs. CNO	Control: t (42) = 1.165 Resilient: t (42) = 2.958 Susceptible: t (42) = 2.749	*P* = 0.5789 *P* = 0.0151 *P* = 0.0261
	Control: Saline vs. Resilient: CNO	t (42) = 0.6574	*P* > 0.9999
Fig. 4J	TST: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 4.264 Control vs. Resilient: t (42) = 0.2297 Control vs. Susceptible: t (42) = 2.556 Resilient vs. Susceptible: t (42) = 2.786	*P* = 0.0206 *P* = 0.9941 *P* = 0.0423 *P* = 0.0238
	Light off vs. Light on	Control: t (42) = 0.9764	*P* = 0.7052

Figure	Statistical methods	Statistics	*P* value
		Resilient: t (42) = 1.321 Susceptible: t (42) = 2.800	*P* = 0.4757 *P* = 0.0229
	Control: Light off vs. Susceptible: Light on	t (42) = 0.2411	*P* > 0.9999
	ST: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 3.320 Control vs. Resilient: t (42) = 1.400 Control vs. Susceptible: t (42) = 2.651 Resilient vs. Susceptible: t (42) = 4.050	*P* = 0.0458 *P* = 0.4261 *P* = 0.0335 *P* = 0.0006
	Light off vs. Light on	Control: t (42) = 0.9166 Resilient: t (42) = 0.7803 Susceptible: t (42) = 2.861	*P* = 0.07435 *P* = 0.8340 *P* = 0.0195
	Control: Light off vs. Susceptible: Light on	t (42) = 0.2106	*P* > 0.9999
	NSFT: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 2.641 Control vs. Resilient: t (42) = 0.2640 Control vs. Susceptible: t (42) = 4.816 Resilient vs. Susceptible: t (42) = 4.552	*P* = 0.083 *P* = 0.991 *P* = 0.001 *P* = 0.001
	Light off vs. Light on	Control: t (42) = 0.7393 Resilient: t (42) = 0.3591 Susceptible: t (42) = 2.587	*P* = 0.9998 *P* = 0.9784 *P* = 0.0391
	Control: Light off vs. Susceptible: Light on	t (42) = 2.228	*P* = 0.3790

Figure	Statistical methods	Statistics	*P* value
	SPT: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 1.777 Control vs. Resilient: t (42) = 0.4610 Control vs. Susceptible: t (42) = 4.827 Resilient vs. Susceptible: t (42) = 4.366	*P* = 0.1817 *P* = 0.9561 *P* = 0.0001 *P* = 0.0002
	Light off vs. Light on	Control: t (42) = 0.6479 Resilient: t (42) = 0.2049 Susceptible: t (42) = 2.703	*P* = 0.8898 *P* = 0.9958 *P* = 0.0293
	Control: Light off vs. Susceptible: Light on	t (42) = 2.124	*P* = 0.4542
Fig. 4K	Two-way ANOVA with Šídák's post hoc test (Light off); n = 8 per group	F (2, 42) = 2.170 Control vs. Resilient: t (42) = 2.501 Control vs. Susceptible: t (42) = 2.533 Resilient vs. Susceptible: t (42) = 0.03207	*P* = 0.1268 *P* = 0.0483 *P* = 0.0447 *P* > 0.9999
	Light off vs. Light on	Control: t (42) = 2.982 Resilient: t (42) = 1.026 Susceptible: t (42) = 0.09620	*P* = 0.0142 *P* = 0.6725 *P* = 0.996
	Control: Light off vs. Susceptible: Light on	t (42) = 2.629	*P* = 0.1644
Fig. 4O	TST: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 1.772 Control vs. Resilient: t (42) = 0.6136 Control vs. Susceptible: t (42) = 2.873 Resilient vs. Susceptible: t (42) = 3.487	*P* = 0.1825 *P* = 0.9044 *P* = 0.0189 *P* = 0.0035

Figure	Statistical methods	Statistics	*P* value
	Light off vs. Light on	Control: t (42) = 2.524 Resilient: t (42) = 2.859 Susceptible: t (42) = 0.4044	*P* = 0.0457 *P* = 0.0196 *P* = 0.9696
	Control: Light off vs. Resilient: Light on	t (42) = 2.245	*P* = 0.3674
	ST: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 0.7467 Control vs. Resilient: t (42) = 0.3301 Control vs. Susceptible: t (42) = 3.796 Resilient vs. Susceptible: t (42) = 3.466	*P* = 0.4801 *P* = 0.9830 *P* = 0.0014 *P* = 0.0037
	Light off vs. Light on	Control: t (42) = 2.678 Resilient: t (42) = 2.769 Susceptible: t (42) = 1.229	*P* = 0.0313 *P* = 0.0248 *P* = 0.5363
	Control: Light off vs. Resilient: Light on	t (42) = 3.099	*P* = 0.0506
	NSFT: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 3.584 Control vs. Resilient: t (42) = 0.5219 Control vs. Susceptible: t (42) = 4.460 Resilient vs. Susceptible: t (42) = 3.938	*P* = 0.0365 *P* = 0.9381 *P* = 0.0002 *P* = 0.0009
	Light off vs. Light on	Control: t (42) = 2.242 Resilient: t (42) = 3.297 Susceptible: t (42) = 0.3796	*P* = 0.0882 *P* = 0.0060 *P* = 0.9746
	Control: Light off vs. Resilient:	t (42) = 3.819	*P* = 0.0065

Figure	Statistical methods	Statistics	*P* value
	Light on		
	SPT: Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 1.927 Control vs. Resilient: t (42) = 0.5765 Control vs. Susceptible: t (42) = 3.467 Resilient vs. Susceptible: t (42) = 2.891	*P* = 0.1583 *P* = 0.9190 *P* = 0.0037 *P* = 0.0181
	Light off vs. Light on	Control: t (42) = 2.512 Resilient: t (42) = 2.999 Susceptible: t (42) = 0.3888	*P* = 0.0470 *P* = 0.0136 *P* = 0.9728
	Control: Light off vs. Resilient: Light on	t (42) = 3.576	*P* = 0.0133
Fig. 4P	Two-way ANOVA with Šídák's post-hoc analysis (Light off); n = 8 per group	F (2, 42) = 2.156 Control vs. Resilient: t (42) = 4.199 Control vs. Susceptible: t (42) = 4.364 Resilient vs. Susceptible: t (42) = 0.1653	*P* = 0.1284 *P* = 0.0004 *P* = 0.0002 *P* = 0.9978
	Light off vs. Light on	Control: t (42) = 0.4629 Resilient: t (42) = 2.678 Susceptible: t (42) = 3.240	*P* = 0.9556 *P* = 0.0312 *P* = 0.0070
	Control: Light off vs. Resilient: Light on	t (42) = 1.521	*P* = 0.8880
Fig. 5B	One-way ANOVA with Tukey's post-hoc analysis; n = 6 per group	F (2, 15) = 42.75 Control vs. Resilient Control vs. Susceptible	*P* < 0.0001 *P* = 0.0016 *P* = 0.0001

Figure	Statistical methods	Statistics	*P* value
		Resilient vs. Susceptible	*P* = 0.0005
Fig. 5C	One-way ANOVA with Tukey's post-hoc analysis; n = 6 per group	F (2, 5) = 14.28 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0003 *P* = 0.0486 *P* = 0.0002 *P* = 0.0388
Fig. 5E	Unpaired t-test; n = 6 per group	t (10) = 4.362	*P* = 0.0014
Fig. 5F	Unpaired t-test; n = 4 per group	t (6) = 4.313	*P* = 0.0050
Fig. 5G	TST: Ordinary one-way ANOVA with Tukey's post-hoc analysis; Scramble+H_2O n = 7, Scramble+DSS n = 13, CB1R-shRNA+H_2O n = 7, CB1R-shRNA+DSS n = 13	F (3, 36) = 4.286 Scramble+H_2O vs. Scramble+DSS Scramble+H_2O vs. CB1R-shRNA+H_2O Scramble+DSS vs. CB1R-shRNA+DSS	*P* = 0.0110 *P* = 0.0494 *P* = 0.9999 *P* = 0.0277
	ST: Ordinary one-way ANOVA with Tukey's post-hoc analysis; Scramble+H_2O n = 7, Scramble+DSS n = 13, CB1R-shRNA+H_2O n = 7, CB1R-shRNA+DSS n = 13	F (3, 36) = 3.902 Scramble+H_2O vs. Scramble+DSS Scramble+H_2O vs. CB1R-shRNA+H_2O Scramble+DSS vs. CB1R-shRNA+DSS	*P* = 0.0164 *P* = 0.0139 *P* = 0.7723 *P* = 0.1832
	NSFT: Ordinary one-way ANOVA with Tukey's post-hoc analysis; Scramble+H_2O n = 7, Scramble+DSS n = 13, CB1R-shRNA+H_2O n = 7, CB1R-shRNA+DSS n = 13	F (3, 36) = 5.460 Scramble+H_2O vs. Scramble+DSS Scramble+H_2O vs. CB1R-shRNA+H_2O Scramble+DSS vs. CB1R-shRNA+DSS	*P* = 0.0034 *P* = 0.0121 *P* = 0.9981 *P* = 0.0243
	SPT: Ordinary one-way ANOVA with Tukey's post-hoc analysis;	F (3, 36) = 4.949	*P* = 0.0056

Figure	Statistical methods	Statistics	*P* value
	Scramble+H_2O n = 7, Scramble+DSS n = 13, CB1R-shRNA+H_2O n = 7, CB1R-shRNA+DSS n = 13	Scramble+H_2O vs. Scramble+DSS Scramble+H_2O vs. CB1R-shRNA+H_2O Scramble+DSS vs. CB1R-shRNA+DSS	*P* = 0.0138 *P* = 0.9700 *P* = 0.0283
Fig. 5H	Ordinary one-way ANOVA with Tukey's post-hoc analysis; Scramble+H_2O n = 7, Scramble+DSS n = 13, CB1R-shRNA+H_2O n = 7, CB1R-shRNA+DSS n = 13	F (3, 36) = 8.526 Scramble+H_2O vs. Scramble+DSS Scramble+H_2O vs. CB1R-shRNA+H_2O Scramble+DSS vs. CB1R-shRNA+DSS CB1R-shRNA+H2O vs. CB1R-shRNA+DSS	*P* = 0.0002 *P* = 0.0047 *P* = 0.6417 *P* = 0.7154 *P* = 0.0159
Fig. 5L	Linear mixed-effects model (nested random effects: mouse/cell) with Bonferroni's post-hoc analysis; Vehicle n = 4 mice (13 cells), AM251 n = 4 mice (13 cells)	F (1, 6) = 7.82	*P* = 0.031
Fig. 5M	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Vehicle n = 4 mice (13 cells), AM251 n = 4 mice (13 cells)	F (1, 6) = 13.76 t = -3.71	*P* = 0.010 *P* = 0.010
Fig. 5N	Linear mixed-effects model (nested random effects: mouse/cell) with Tukey's post-hoc analysis; Vehicle n = 4 mice (13 cells), AM251 n = 4 mice (13 cells)	F (1, 6) = 0.01 t = 0.154	*P* = 0.917 *P* = 0.917
Fig. 5P	TST: Two-way ANOVA with Šídák's post-hoc analysis (Vehicle); n = 8 per group	F (2, 42) = 7.057 Control vs. Resilient: t (42) = 0.7763 Control vs. Susceptible: t (42) = 3.319	*P* = 0.0023 *P* = 0.8262 *P* = 0.0056

Figure	Statistical methods	Statistics	*P* value
		Resilient vs. Susceptible: t (42) = 4.095	*P* = 0.0006
	Vehicle vs. AM251	Control: t (42) = 1.921 Resilient: t (42) = 1.999 Susceptible: t (42) = 3.067	*P* = 0.1733 *P* = 0.1483 *P* = 0.0113
	Control: Vehicle vs. Susceptible: AM251	t (42) = 0.2523	*P* > 0.9999
	ST: Two-way ANOVA with Šídák's post-hoc analysis (Vehicle); n = 8 per group	F (2, 42) = 3.273 Control vs. Resilient: t (42) = 2.081 Control vs. Susceptible: t (42) = 1.835 Resilient vs. Susceptible: t (42) = 3.916	*P* = 0.0478 *P* = 0.1251 *P* = 0.2048 *P* = 0.0010
	Vehicle vs. AM251	Control: t (42) = 1.771 Resilient: t (42) = 0.8660 Susceptible: t (42) = 2.598	*P* = 0.2311 *P* = 0.7746 *P* = 0.0381
	Control: Vehicle vs. Susceptible: AM251	t (42) = 0.7626	*P* = 0.9999
	NSFT: Two-way ANOVA with Šídák's post-hoc analysis (Vehicle); n = 8 per group	F (2, 42) = 1.955 Control vs. Resilient: t (42) = 0.7577 Control vs. Susceptible: t (42) = 3.919 Resilient vs. Susceptible: t (42) = 4.677	*P* = 0.1543 *P* = 0.8362 *P* = 0.0010 *P* = 0.0001
	Vehicle vs. AM251	Control: t (42) = 1.314 Resilient: t (42) = 0.1776 Susceptible: t (42) = 2.617	*P* = 0.4801 *P* = 0.9972 *P* = 0.0364

Figure	Statistical methods	Statistics	*P* value
	Control: Vehicle vs. Susceptible: AM251	t (42) = 1.302	*P* = 0.9647
	SPT: Two-way ANOVA with Šídák's post-hoc analysis (Vehicle); n = 8 per group	F (2, 42) = 1.758 Control vs. Resilient: t (42) = 0.04825 Control vs. Susceptible: t (42) = 3.721 Resilient vs. Susceptible: t (42) = 3.673	*P* = 0.1848 *P* = 0.9999 *P* = 0.0017 *P* = 0.0020
	Vehicle vs. AM251	Control: t (42) = 1.568 Resilient: t (42) = 0.1260 Susceptible: t (42) = 2.775	*P* = 0.3285 *P* = 0.9990 *P* = 0.0244
	Control: Vehicle vs. Susceptible: AM251	t (42) = 0.9463	*P* = 0.9984
Fig. 5Q	Two-way ANOVA with Šídák's post-hoc analysis (Vehicle); n = 8 per group	F (2, 42) = 8.650 Control vs. Resilient: t (42) = 4.168 Control vs. Susceptible: t (42) = 4.168 Resilient vs. Susceptible: t (42) = 0.001	*P* = 0.0007 *P* = 0.0005 *P* = 0.0005 *P* = 0.9999
	Vehicle vs. AM251	Control: t (42) = 3.615 Resilient: t (42) = 1.734 Susceptible: t (42) = 1.180	*P* = 0.0024 *P* = 0.2473 *P* = 0.5688
	Control: Vehicle vs. Susceptible: AM251	t (42) = 2.988	*P* = 0.0680
Supplementary. Fig.1 A	TST: Two-way ANOVA followed by Bonferroni's post-hoc analysis; n =10 per group per time	F (1, 72) = 15.65 W1: t = 0.00	*P* = 0.0009 *P* > 0.9999

Figure	Statistical methods	Statistics	*P* value
	point	W4: t = 2.834 W5: t = 2.889 W6: t = 2.397	*P* = 0.0480 *P* = 0.0385 *P* = 0.1109
	ST: Two-way ANOVA followed by Bonferroni's post-hoc analysis; n =10 per group per time point	F (1, 72) = 26.35 W1: t = 3.594 W4: t = 3.130 W5: t = 2.987 W6: t = 2.959	*P* < 0.0001 *P* = 0.0102 *P* = 0.0231 *P* = 0.0354 *P* = 0.0430
	NSFT: Two-way ANOVA followed by Bonferroni's post-hoc analysis; n =10 per group per time point	F (1, 72) = 10.44 W1: t = 0.1377 W4: t = 2.820 W5: t = 2.454 W6: t = 2.856	*P* = 0.0046 *P* = 0.9999 *P* = 0.0457 *P* = 0.0968 *P* = 0.0431
	SPT: Two-way ANOVA followed by Bonferroni's post hoc test; n =10 per group per time point	F (1, 72) = 35.88 W1: t = 2.247 W4: t = 3.275 W5: t = 4.591 W6: t = 2.432	*P* < 0.0001 *P* = 0.1479 *P* = 0.0174 *P* = 0.0011 *P* = 0.0992
	TST: Brown-Forsythe and Welch ANOVA with Dunnett's T3 post-hoc analysis; Control n = 32,	F (2, 78.20) = 24.64 Control vs. Resilient	*P* < 0.0001 *P* = 0.6064

Figure	Statistical methods	Statistics	*P* value
Supplementary. Fig.1 B	Resilient n = 31, Susceptible n = 24	Control vs. Susceptible Resilient vs. Susceptible	$P < 0.0001$ $P < 0.0001$
	ST: Ordinary one-way ANOVA with Tukey's post-hoc analysis; Control n = 32, Resilient n = 31, Susceptible n = 24	F (2, 84) = 5.101 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.0081$ $P = 0.8156$ $P = 0.0373$ $P = 0.0084$
	NSFT: Kruskal-Wallis test with Dunn's post-hoc analysis; Control n = 32, Resilient n = 31, Susceptible n = 24	KW = 8.667 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.0131$ $P = 0.9999$ $P = 0.0200$ $P = 0.0393$
	SPT: Kruskal-Wallis test with Dunn's post-hoc analysis; Control n = 32, Resilient n = 31, Susceptible n = 24	KW = 13.64 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	$P = 0.0011$ $P = 0.9999$ $P = 0.0069$ $P = 0.0017$
Supplementary. Fig.1 C	Unpaired t-test; Resilient n = 25, Susceptible n = 20	t (43) = 0.1491	$P = 0.8821$
Supplementary. Fig.2 B	Crypt damage: One-way ANOVA with Tukey's post-hoc analysis; n = 5 per group	F (2, 12) = 0.500 Control vs. Resilient	$P = 0.6186$ $P = 0.6709$

Figure	Statistical methods	Statistics	*P* value
		Control vs. Susceptible	*P* = 0.6709
		Resilient vs. Susceptible	*P* = 0.9999
	Inflammation: One-way ANOVA with Tukey's post-hoc analysis; n = 5 per group	F (2, 12) = 1.333	*P* = 0.300
		Control vs. Resilient	*P* = 0.3648
		Control vs. Susceptible	*P* = 0.3648
		Resilient vs. Susceptible	*P* = 0.9999
Supplementary. Fig.2 C	*Il6*: One-way ANOVA with Tukey's post-hoc analysis; n = 4 per group	F (2, 9) = 1.101	*P* = 0.3734
		Control vs. Resilient	*P* = 0.4331
		Control vs. Susceptible	*P* = 0.4419
		Resilient vs. Susceptible	*P* = 0.9998
	Il1b: One-way ANOVA with Tukey's post-hoc analysis; n = 4 per group	F (2, 9) = 2.572	*P* = 0.1308
		Control vs. Resilient	*P* = 0.6799
		Control vs. Susceptible	*P* = 0.1160
		Resilient vs. Susceptible	*P* = 0.3851
	Tnf: One-way ANOVA with Tukey's post-hoc analysis; n = 4 per group	F (2, 9) = 2.527	*P* = 0.1346
		Control vs. Resilient	*P* = 0.1752
		Control vs. Susceptible	*P* = 0.9987
		Resilient vs. Susceptible	*P* = 0.1879
Supplementary. Fig.2 E	IL-6: One-way ANOVA with Tukey's post-hoc analysis; n = 3 per group	F (2, 6) = 2.270	*P* = 0.1845
		Control vs. Resilient	*P* = 0.2647
		Control vs. Susceptible	*P* = 0.2106
		Resilient vs. Susceptible	*P* = 0.9816

Figure	Statistical methods	Statistics	*P* value
	IL-1β: One-way ANOVA with Tukey's post-hoc analysis; n = 3 per group	F (2, 6) = 0.09017 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.9150 *P* = 0.9859 *P* = 0.9636 *P* = 0.9085
	TNF-α: One-way ANOVA with Tukey's post-hoc analysis; n = 3 per group	F (2, 6) = 3.148 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.1162 *P* = 0.4765 *P* = 0.1009 *P* = 0.4590
Supplementary. Fig.3 B	TST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.7378 Control vs. Resilient: t (42) = 0.8877 Control vs. Susceptible: t (42) = 2.488 Resilient vs. Susceptible: t (42) = 3.375	*P* = 0.4843 *P* = 0.7614 *P* = 0.0499 *P* = 0.0048
	Saline vs. Meloxicam	Control: t (42) = 0.3406 Resilient: t (42) = 0.8671 Susceptible: t (42) = 0.7948	*P* = 0.9814 *P* = 0.7739 *P* = 0.8160
	Control: Saline vs. Susceptible: Meloxicam	t (42) = 1.693	*P* = 0.7867
	ST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.1590 Control vs. Resilient: t (42) = 0.0125 Control vs. Susceptible: t (42) = 2.175 Resilient vs. Susceptible: t (42) = 2.163	*P* = 0.8535 *P* = 0.999 *P* = 0.1022 *P* = 0.1050
	Saline vs. Meloxicam	Control: t (42) = 0.4626	*P* = 0.9557

Figure	Statistical methods	Statistics	*P* value
		Resilient: t (42) = 0.2625 Susceptible: t (42) = 0.1875	*P* = 0.9913 *P* = 0.9968
	Control: Saline vs. Susceptible: Meloxicam	t (42) = 1.988	*P* = 0.5609
	NSFT: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.3811 Control vs. Resilient: t (42) = 0.2798 Control vs. Susceptible: t (42) = 3.488 Resilient vs. Susceptible: t (42) = 3.768	*P* = 0.6855 *P* = 0.9895 *P* = 0.0035 *P* = 0.0015
	Saline vs. Meloxicam	Control: t (42) = 0.5223 Resilient: t (42) = 0.8020 Susceptible: t (42) = 0.3793	*P* = 0.9380 *P* = 0.8119 *P* = 0.9747
	Control: Saline vs. Susceptible: Meloxicam	t (42) = 3.109	*P* = 0.0493
	SPT: Two-way ANOVA with Šídák's post-hoc analysist (Saline); n = 8 per group	F (2, 42) = 0.1065 Control vs. Resilient: t (42) = 0.8018 Control vs. Susceptible: t (42) = 1.838 Resilient vs. Susceptible: t (42) = 2.639	*P* = 0.8992 *P* = 0.8120 *P* = 0.2039 *P* = 0.0344
	Saline vs. Meloxicam	Control: t (42) = 0.4655 Resilient: t (42) = 0.6921 Susceptible: t (42) = 0.04874	*P* = 0.9549 *P* = 0.8694 *P* = 0.9999
	Control: Saline vs. Susceptible: Meloxicam	t (42) = 1.789	*P* = 0.7177

Figure	Statistical methods	Statistics	*P* value
Supplementary. Fig.3 C	Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 3.591 Control vs. Resilient: t (42) = 4.177 Control vs. Susceptible: t (42) = 4.096 Resilient vs. Susceptible: t (42) = 0.08032	*P* = 0.0363 *P* = 0.0004 *P* = 0.0006 *P* = 0.9997
	Saline vs. Meloxicam	Control: t (42) = 0.04016 Resilient: t (42) = 3.374 Susceptible: t (42) = 3.092	*P* = 0.9999 *P* = 0.0048 *P* = 0.0105
	Control: Saline vs. Susceptible: Meloxicam	t (42) = 1.004	*P* = 0.9970
Supplementary. Fig.4 B	PrL: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 7.524 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0034 *P* = 0.024 *P* = 0.682 *P* = 0.004
	IL: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 8.500 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0020 *P* = 0.160 *P* = 0.093 *P* = 0.001
	aIC: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 48.745 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0001 *P* = 0.001 *P* = 0.495 *P* = 0.001
	NAc: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per	F (2, 21) = 19.153	*P* = 0.0001

Figure	Statistical methods	Statistics	*P* value
	group	Control vs. Resilient	$P = 0.632$
		Control vs. Susceptible	$P = 0.001$
		Resilient vs. Susceptible	$P = 0.001$
	ACC: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 11.620	$P = 0.0004$
		Control vs. Resilient	$P = 0.002$
		Control vs. Susceptible	$P = 0.884$
		Resilient vs. Susceptible	$P = 0.001$
	adBNST: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 0.195	$P = 0.8244$
		Control vs. Resilient	$P = 0.883$
		Control vs. Susceptible	$P = 0.993$
		Resilient vs. Susceptible	$P = 0.828$
	avBNST: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 18.850	$P = 0.0001$
		Control vs. Resilient	$P = 0.005$
		Control vs. Susceptible	$P = 0.045$
		Resilient vs. Susceptible	$P = 0.001$
	mIC: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 4.280	$P = 0.0276$
		Control vs. Resilient	$P = 0.022$
		Control vs. Susceptible	$P = 0.242$
		Resilient vs. Susceptible	$P = 0.437$
	pIC: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 51.439	$P = 0.0001$
		Control vs. Resilient	$P = 0.001$
		Control vs. Susceptible	$P = 0.002$
		Resilient vs. Susceptible	$P = 0.001$

Figure	Statistical methods	Statistics	*P* value
	BLA: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 3.189 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0618 *P* = 0.386 *P* = 0.479 *P* = 0.050
	PVN: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 9.309 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0013 *P* = 0.204 *P* = 0.050 *P* = 0.001
	LHB: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 6.425 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0067 *P* = 0.048 *P* = 0.632 *P* = 0.006
	PAG: One-way ANOVA with Tukey's post-hoc analysis; n = 8 per group	F (2, 21) = 6.667 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0057 *P* = 0.004 *P* = 0.136 *P* = 0.251
Supplementary. Fig.6 C	One-way ANOVA with Tukey's post-hoc analysis (Saline); n = 8 per group	F (2, 21) = 30.482 Control vs. Resilient Control vs. Susceptible Resilient vs. Susceptible	*P* = 0.0001 *P* = 0.0001 *P* = 0.041 *P* = 0.002
	Unpaired t-test (Saline vs. Meloxicam); n = 8 per group	Control: t (14) = 1.189 Resilient: t (14) = 2.596 Susceptible: t (14) = 4.712	*P* = 0.2542 *P* = 0.0211 *P* = 0.0003

Figure	Statistical methods	Statistics	*P* value
Supplementary. Fig.7 B	TST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.7401 Control vs. Resilient: t (42) = 0.5963 Control vs. Susceptible: t (42) = 5.230 Resilient vs. Susceptible: t (42) = 4.634	*P* = 0.4832 *P* = 0.9114 *P* = 0.001 *P* = 0.001
	Saline vs. CNO	Control: t (42) = 0.3602 Resilient: t (42) = 0.7702 Susceptible: t (42) = 0.8820	*P* = 0.9782 *P* = 0.8295 *P* = 0.7649
	ST: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.5589 Control vs. Resilient: t (42) = 0.5610 Control vs. Susceptible: t (42) = 3.280 Resilient vs. Susceptible: t (42) = 3.841	*P* = 0.5760 *P* = 0.9247 *P* = 0.0063 *P* = 0.0012
	Saline vs. CNO	Control: t (42) = 0.6905 Resilient: t (42) = 0.7984 Susceptible: t (42) = 0.1726	*P* = 0.8702 *P* = 0.8140 *P* = 0.9975
	NSFT: Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.02676 Control vs. Resilient: t (42) = 0.5786 Control vs. Susceptible: t (42) = 3.494 Resilient vs. Susceptible: t (42) = 4.072	*P* = 0.9736 *P* = 0.9182 *P* = 0.0034 *P* = 0.0006
	Saline vs. CNO	Control: t (42) = 0.4302 Resilient: t (42) = 0.5267 Susceptible: t (42) = 0.2077	*P* = 0.9638 *P* = 0.9366 *P* = 0.9956
	SPT: Two-way ANOVA with Šídák's post-hoc analysis (Saline);	F (2, 42) = 0.2467	*P* = 0.7852

Figure	Statistical methods	Statistics	*P* value
	n = 8 per group	Control vs. Resilient: t (42) = 0.7832 Control vs. Susceptible: t (42) = 3.144 Resilient vs. Susceptible: t (42) = 2.361	*P* = 0.8224 *P* = 0.0091 *P* = 0.0673
	Saline vs. CNO	Control: t (42) = 0.2336 Resilient: t (42) = 0.6953 Susceptible: t (42) = 0.07420	*P* = 0.9938 *P* = 0.8679 *P* = 0.9998
Supplementary. Fig.7 C	Two-way ANOVA with Šídák's post-hoc analysis (Saline); n = 8 per group	F (2, 42) = 0.3743 Control vs. Resilient: t (42) = 3.236 Control vs. Susceptible: t (42) =3.199 Resilient vs. Susceptible: t (42) = 0.03763	*P* = 0.6900 *P* = 0.0071 *P* = 0.0079 *P* = 0.9999
	Saline vs. CNO	Control: t (42) = 0.1129 Resilient: t (42) = 0.6774 Susceptible: t (42) = 0.5268	*P* = 0.9993 *P* = 0.8764 *P* = 0.9365
Supplementary. Fig.8 D	TST: Unpaired t-test; n = 8 per group	t (14) = 0.5734	*P* = 0.5755
	ST: Unpaired t-test; n = 8 per group	t (14) = 0.3397	*P* = 0.7392
	NSFT: Unpaired t-test; n = 8 per group	t (14) = 0.8053	*P* = 0.4341
	SPT: Unpaired t-test; n = 8 per group	t (14) = 0.1544	*P* = 0.8795
	Unpaired t-test; n = 8 per group	t (14) = 1.739	*P* = 0.1039

Figure	Statistical methods	Statistics	*P* value
Supplementary. Fig.8 E			
Supplementary. Fig.8 I	TST: Unpaired t-test; n = 8 per group	t (14) = 2.313	*P* = 0.0364
	ST: Unpaired t-test; n = 8 per group	t (14) = 3.593	*P* = 0.0029
	NSFT: Unpaired t-test; n = 8 per group	t (14) = 2.660	*P* = 0.0186
	SPT: Unpaired t-test; n = 8 per group	t (14) = 4.140	*P* = 0.0010
Supplementary. Fig.8 J	Unpaired t-test; n = 8 per group	t (14) = 2.327	*P* = 0.0355

129