Cell type-specific NRBF2 orchestrates autophagic flux and adult hippocampal neurogenesis in chronic stress-induced depression

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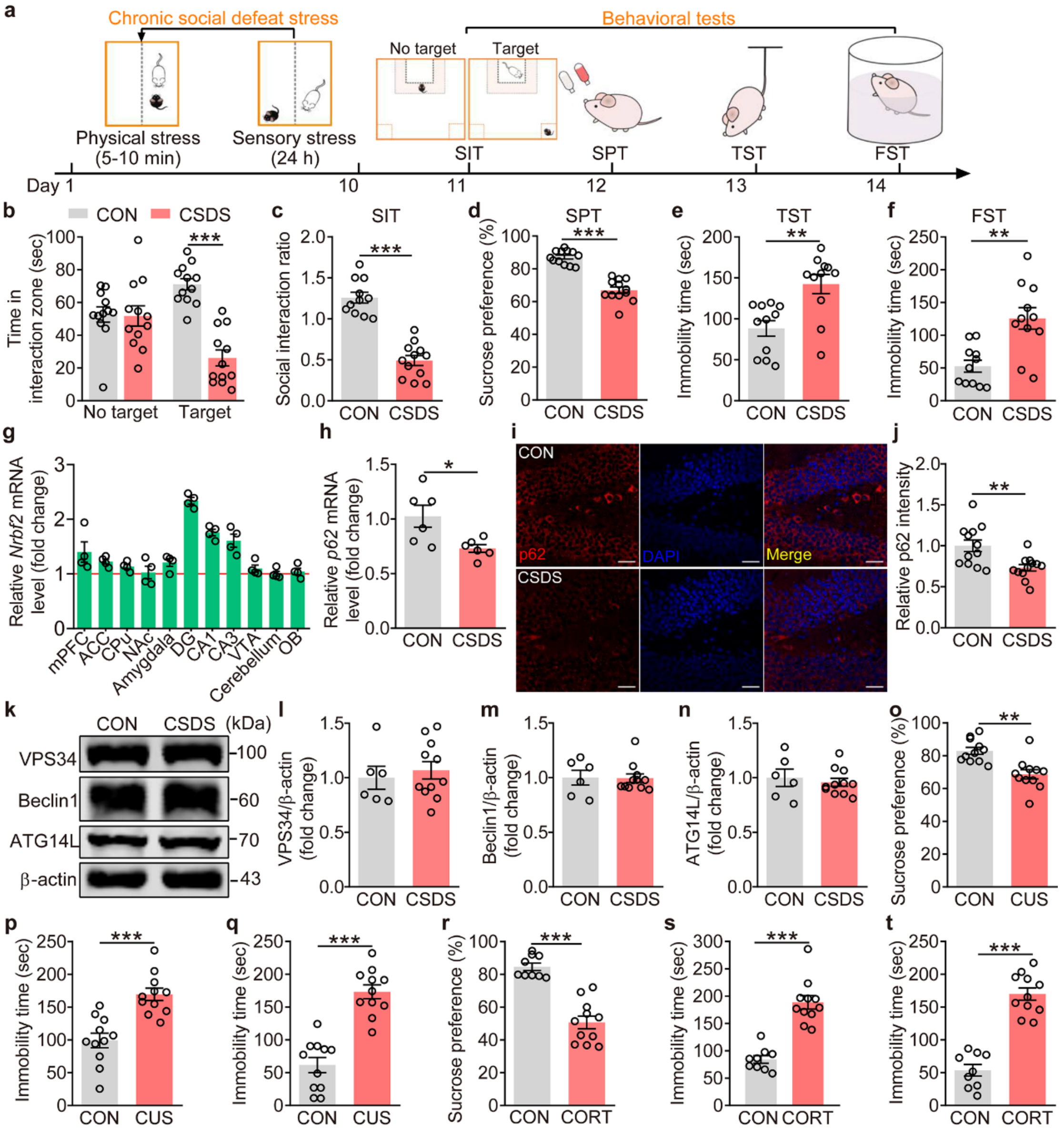
Running title: aNSCs-specific NRBF2 regulates depression-like behavior

Supplementary figures



Supplementary Fig. S1. Chronic stress induces depression-like behavior in mice.

a Experimental paradigms for CSDS and behavioral tests.

b-f Depression-like behavior in CSDS-exposed mice, as measured by the social interaction time (**b**) and social interaction ratio (**c**) in SIT, the sucrose preference in SPT (**d**), and the immobility time in TST (**e**) and FST (**f**) (*n* = 11-12 mice per group).

g *Nrbf2* mRNA level in different brain areas of adult naive mice (*n* = 4 mice per group). mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; CPu, caudate putamen; NAc, nucleus accumbens; DG, dentate gyrus, CA1, cornu ammonis 1; CA3, cornu ammonis 3; VTA, ventral tegmental area; OB, olfactory bulb.

h Quantitative real-time PCR result showing the *p62* mRNA level in the DG (*n* = 6 mice per group).

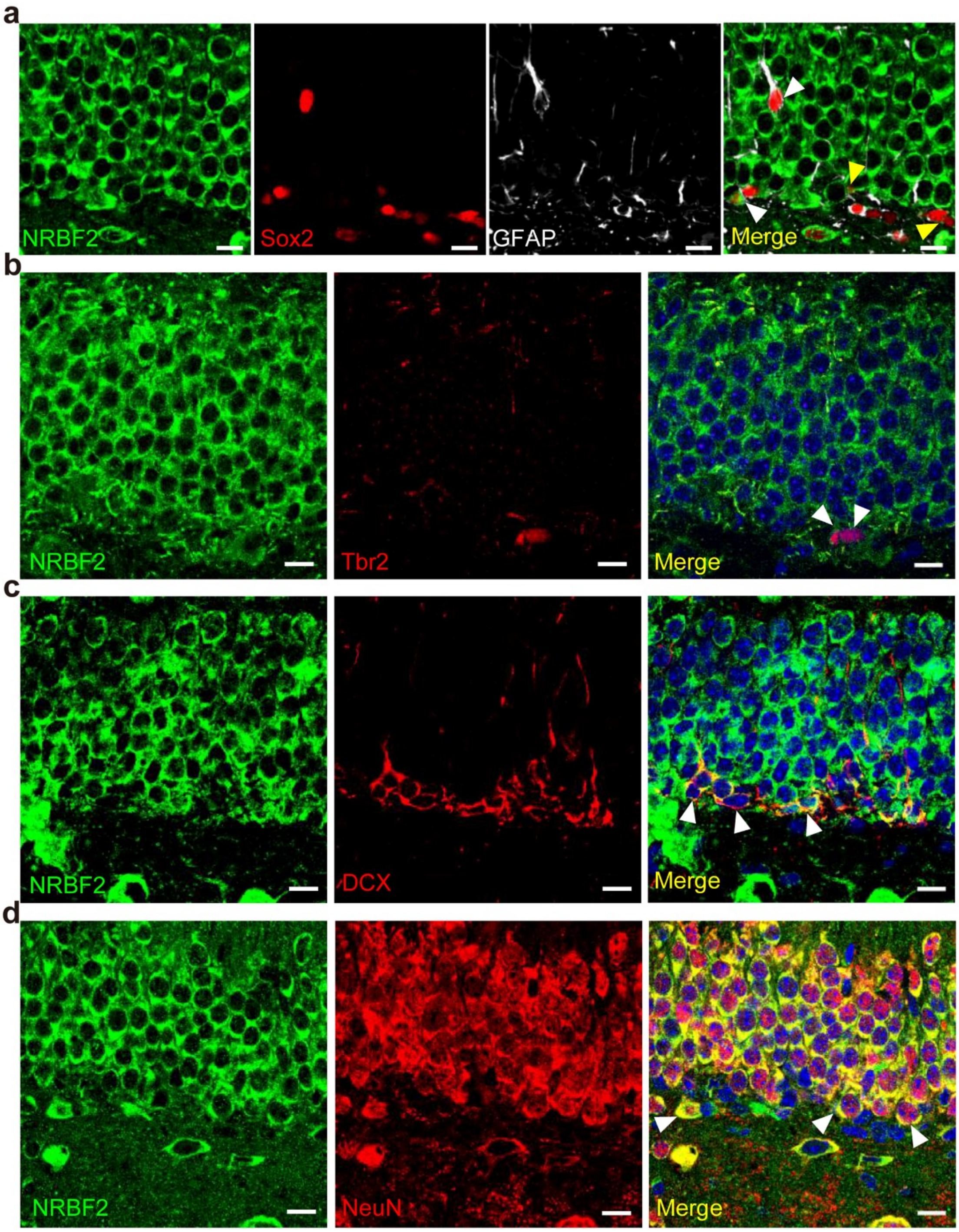
i, j Representative images (**i**) and quantification (**j**) of p62 intensity in the DG (*n* = 12 slices per group). Scale bars, 30 μm.

k-n Representative images (**k**) and quantification of the protein expressions of VPS34 (**l**), Beclin1 (**m**), and ATG14L (**n**) in the DG (*n* = 6-11 mice per group).

o-q Behavioral tests of SPT (**o**), TST (**p**), and FST (**q**) in control and CUS-treated mice (*n* = 11 mice per group).

r-t Behavioral tests of SPT (**r**), TST (**s**) and FST (**t**) in control and CORT-treated mice (*n* = 9-11 mice per group).

Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**c-f**, **h**, **j**, **l-t**) or two-way ANOVA following by Bonferroni's post hoc test (**b**). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

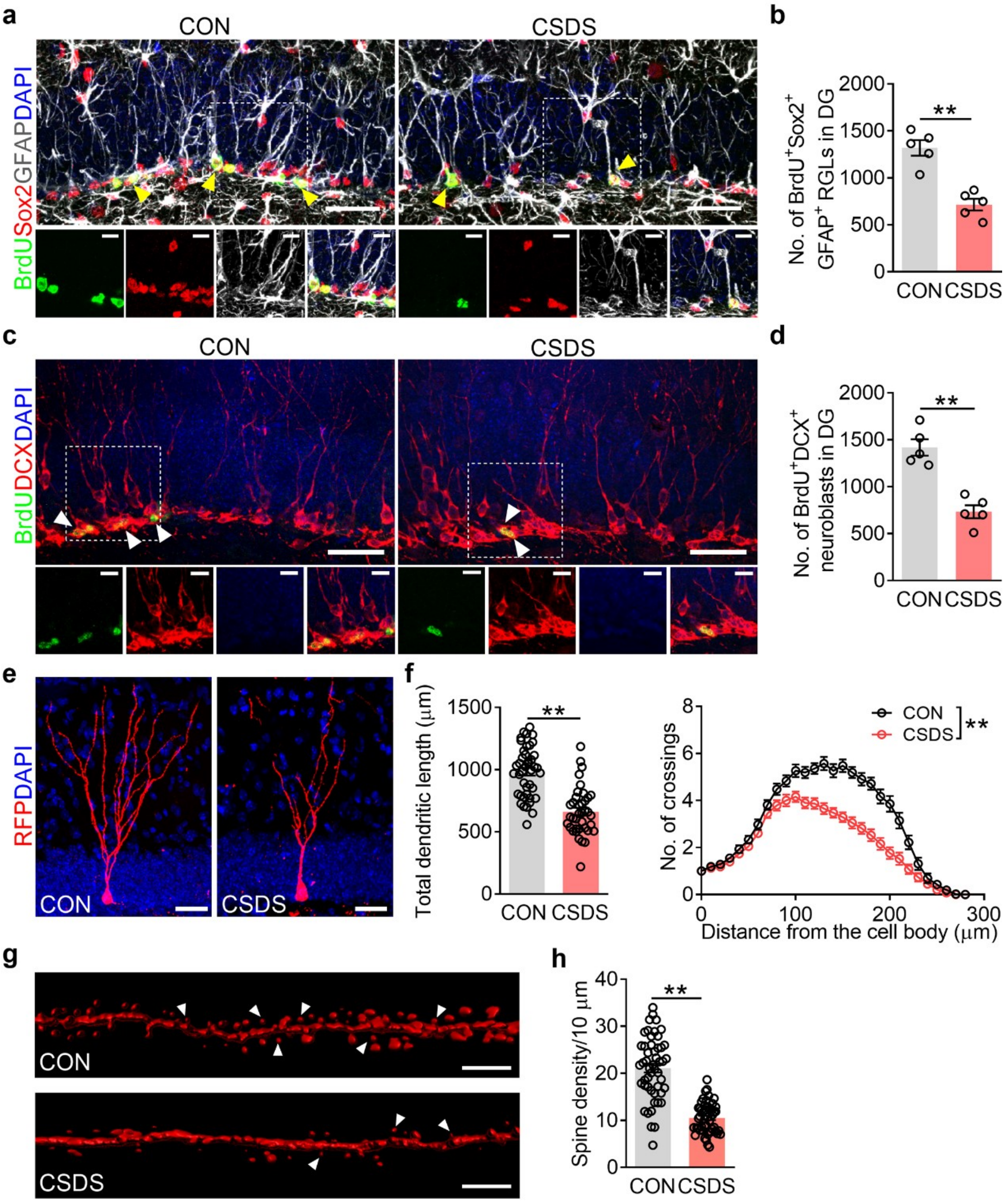


Supplementary Fig. S2 The NRBF2 expression in dentate gyrus of adult mice.

a Immunofluorescent analysis of NRBF2 expression in Sox2$^+$GFAP$^+$ type 1 NSCs and Sox2$^+$GFAP$^-$ type 2 NSCs. White arrows indicating NRBF2$^+$Sox2$^+$GFAP$^+$ type 1 NSCs and yellow arrows indicating NRBF2$^+$Sox2$^+$GFAP$^-$ type 2 NSCs. Scale bars, 10 µm.

b Immunofluorescent analysis of NRBF2 expression in Tbr2$^+$ IPCs. White arrow indicating NRBF2$^+$Tbr2$^+$ IPCs. Scale bars, 10 µm.

c, d Immunofluorescent analysis of NRBF2 expression in DCX$^+$ neuroblasts (**c**) and NeuN$^+$ neurons (**d**) in the DG. White arrows indicating NRBF2$^+$DCX$^+$ neuroblasts or NRBF2$^+$NeuN$^+$ neurons. Scale bars, 10 µm.



Supplementary Fig. S3 CSDS impairs AHN and the development of newborn neuron in the DG of mice.

a Representative confocal image of BrdU$^+$Sox2$^+$GFAP$^+$ RGLs in the DG of control and CSDS-exposed mice. Bottom panels: higher magnification views of selected regions (white square), BrdU (green), Sox2 (red), GFAP (white), and DAPI (blue). Yellow arrows indicating BrdU$^+$Sox2$^+$GFAP$^+$ RGLs. Scale bars, 30 μm (overview) and 10 μm (zoom).

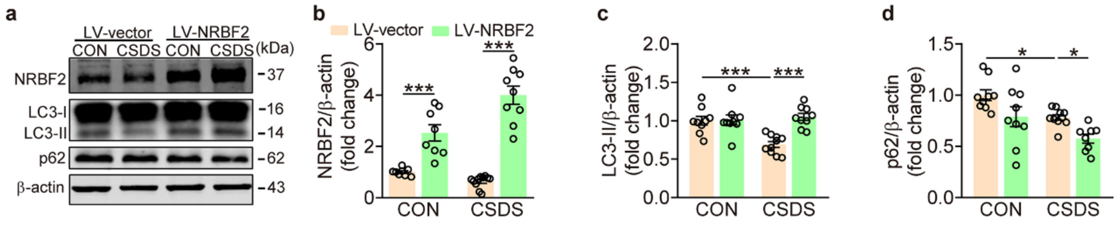
b Quantifications showing the number of BrdU$^+$Sox2$^+$GFAP$^+$ RGLs in the DG (*n* = 5 mice per group).

c, d Representative images (**c**) and quantifications (**d**) showing the number of BrdU$^+$DCX$^+$ neuroblasts in the DG (*n* = 5 mice per group). BrdU (green), DCX (red), and DAPI (blue). White arrows indicating BrdU$^+$DCX$^+$ neuroblasts. Scale bars, 30 μm (overview) and 10 μm (zoom).

e, f Representative confocal images (**e**) and quantifications of the dendritic length (**f**, left) and dendritic complexity (**f**, right) in RFP$^+$ newborn neurons ($n = 38$-42 cells per group). Scale bars, 30 μm.

g, h Representative images (**g**) and quantifications (**h**) of dendritic spines density of RFP$^+$ newborn neurons ($n = 50$ segments per group). White arrows indicating spines. Scale bars, 5 μm.

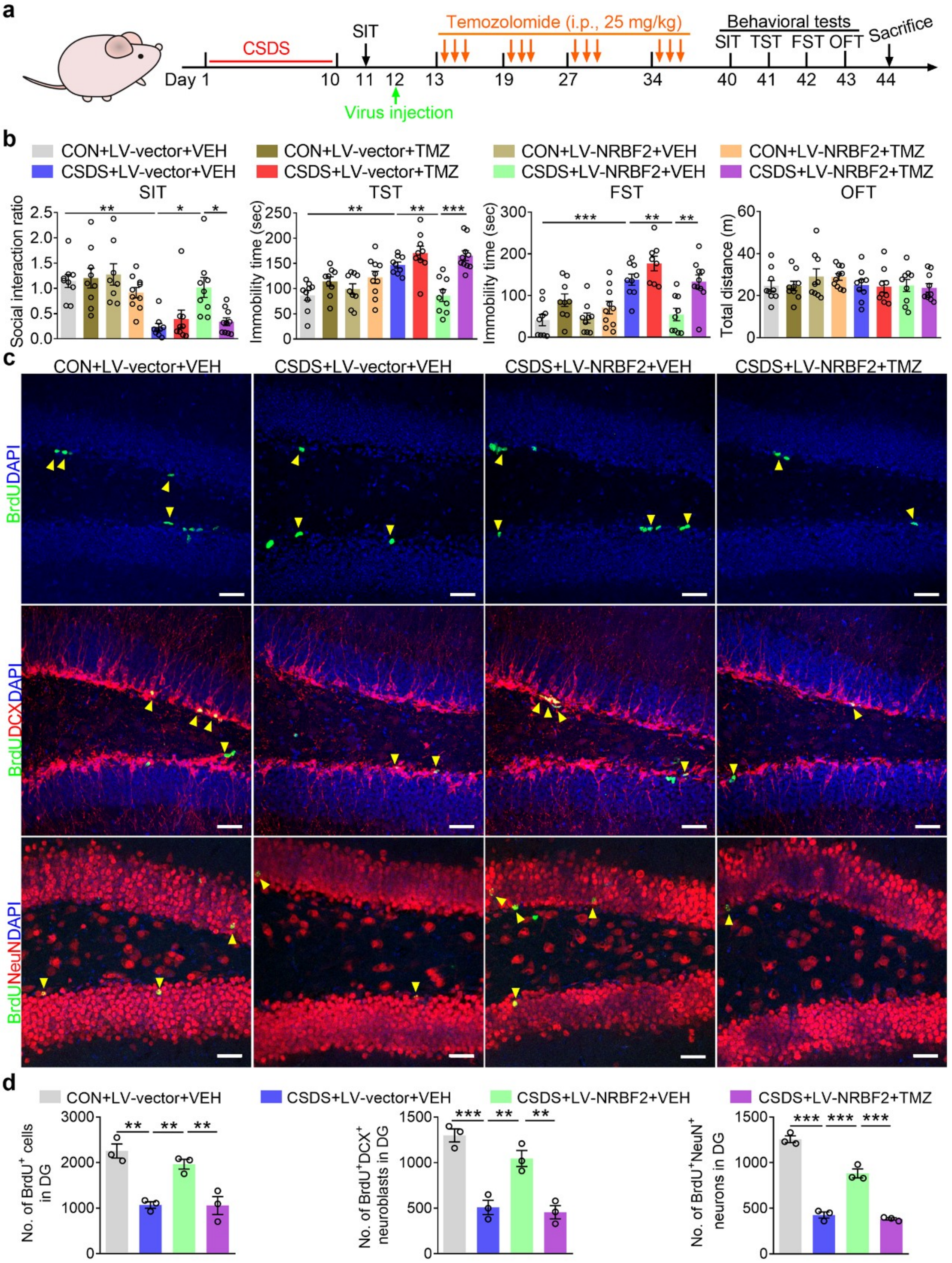
Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**b**, **d**, **f**, **h**) or repeated measures ANOVA (**f**, right). $^{**}P < 0.01$ and $^{***}P < 0.001$.



Supplementary Fig. S4 Overexpression of NRBF2 ameliorates CSDS-induced autophagic deficiency in the DG.

a-d Representative images (**a**) and quantifications of NRBF2 (**b**), LC3-II (**c**) and p62 (**d**) protein expression in the DG upon control and CSDS-exposed mice treated with LV-vector or LV-NRBF2 (*n* = 8-11 mice per group).

Data are presented as mean ± SEM and analyzed by two-way ANOVA following by Bonferroni's post hoc test (**b-d**). *$P < 0.05$ and ***$P < 0.001$.



Supplementary Fig. S5 Chronic temozolomide treatment abolishes the antidepressant and proneurogenic effects of NRBF2 overexpression.

a Timeline of experiments.

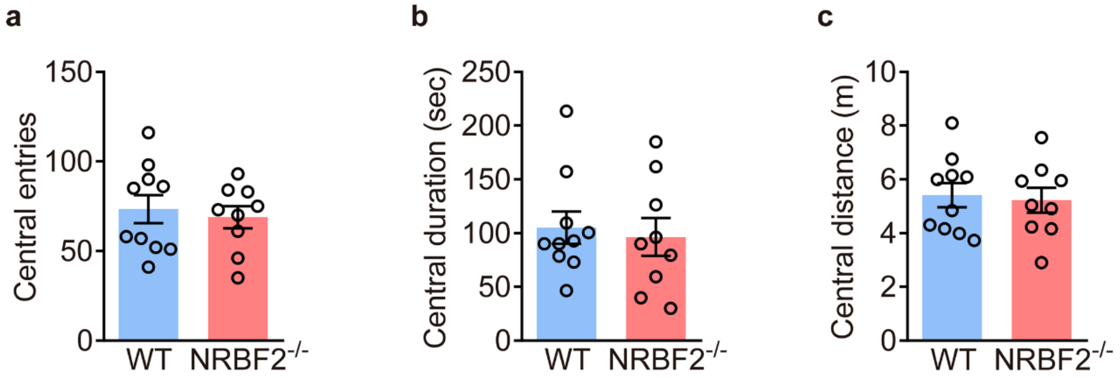
b Behavioral tests of SIT, TST, FST, and OFT in control and CSDS-exposed mice expressing LV-vector or LV-NRBF2, and following by treatment with temozolomide (TMZ) for 4 weeks (*n* = 8-10 mice per group).

c Representative images of BrdU$^+$ cells, BrdU$^+$DCX$^+$ neuroblasts, and BrdU$^+$NeuN$^+$ neurons in the

DG of CON + LV-vector + VEH, CSDS + LV-vector + VEH, CSDS + LV-NRBF2 + VEH, and CSDS + LV-NRBF2 + TMZ group. Yellow arrows indicating BrdU$^+$ and marker$^+$ cells. Scale bars, 30 μm.

d Quantification of BrdU$^+$ cells, BrdU$^+$DCX$^+$ neuroblasts, and BrdU$^+$NeuN$^+$ neurons in the DG ($n = 3$ mice per group).

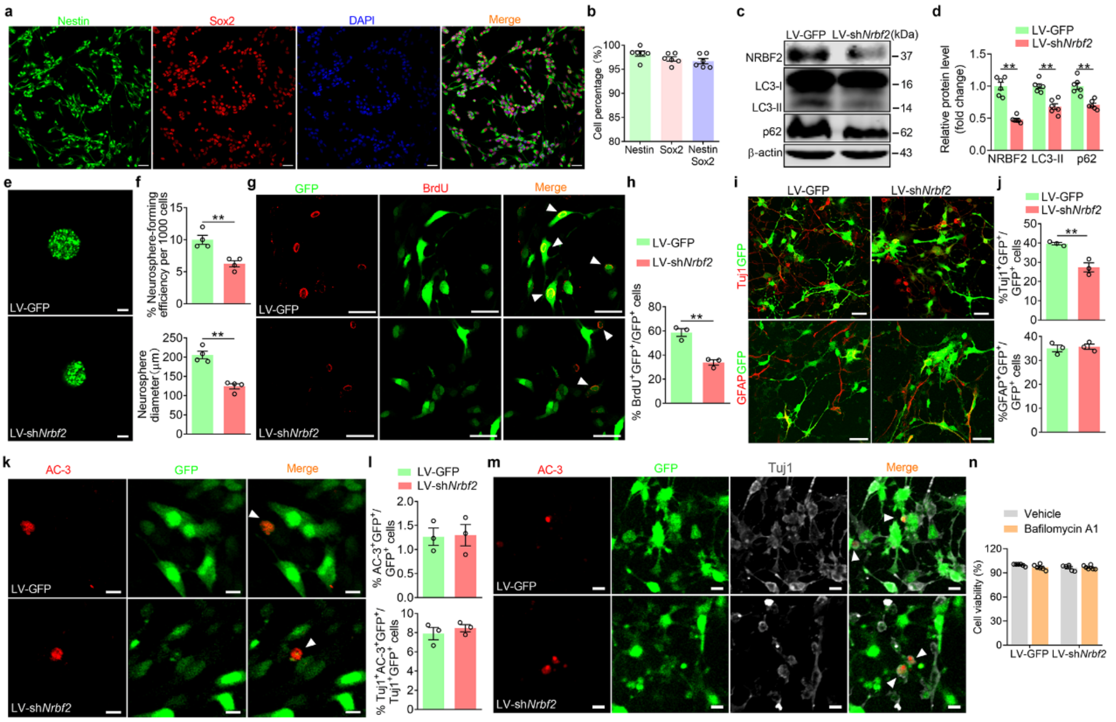
Data are presented as mean ± SEM and analyzed by one-way ANOVA following by Tukey’s post hoc test (**b**, **d**). $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.



Supplementary Fig. S6 NRBF2 deletion does not lead to anxiety-like behavior of mice.

a-c Behavioral tests of OFT, such as central entries, central duration and central distance, in WT and NRBF2$^{-/-}$ mice (n = 9-10 mice per group).

Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**a-c**).



Supplementary Fig. S7 Deficiency of NRBF2 impairs proliferation and neural differentiation, but not apoptosis in adult neural stem cells.

a, b Representative images (**a**) and quantifications (**b**) of Nestin$^+$Sox2$^+$ aNSCs, Nestin (green), Sox2 (red), DAPI (blue). Scale bars, 50 μm. The majority of aNSCs (96.69%) expressed both neural stem cell markers Nestin and Sox2 (*n* = 6 independent experiments per group).

c, d Representative images (**c**) and quantifications (**d**) of NRBF2, LC3-II and p62 protein expression in aNSCs treated with LV-sh*Nrbf2* or LV-GFP (*n* = 6 independent experiments per group).

e Representative images of neurospheres. Scale bars, 50 μm.

f Quantification of the neurosphere-forming efficiency and the diameter of neurospheres (*n* = 4 independent experiments per group).

g, h Representative images (**g**) and quantifications (**h**) of proliferating aNSCs, followed by BrdU pulse labeling and immunofluorescent analysis (*n* = 3 independent experiments per group). White arrows indicating BrdU$^+$GFP$^+$ cells. Scale bars, 30 μm.

i Representative images of differentiated aNSCs, followed by immunostaining with the neuronal marker, Tuj1, and the astrocytic marker, GFAP. Scale bars, 30 μm.

j Quantification of the percentage of differentiated Tuj1$^+$GFP$^+$ neurons and GFAP$^+$GFP$^+$ astrocytes (*n* = 3 independent experiments per group).

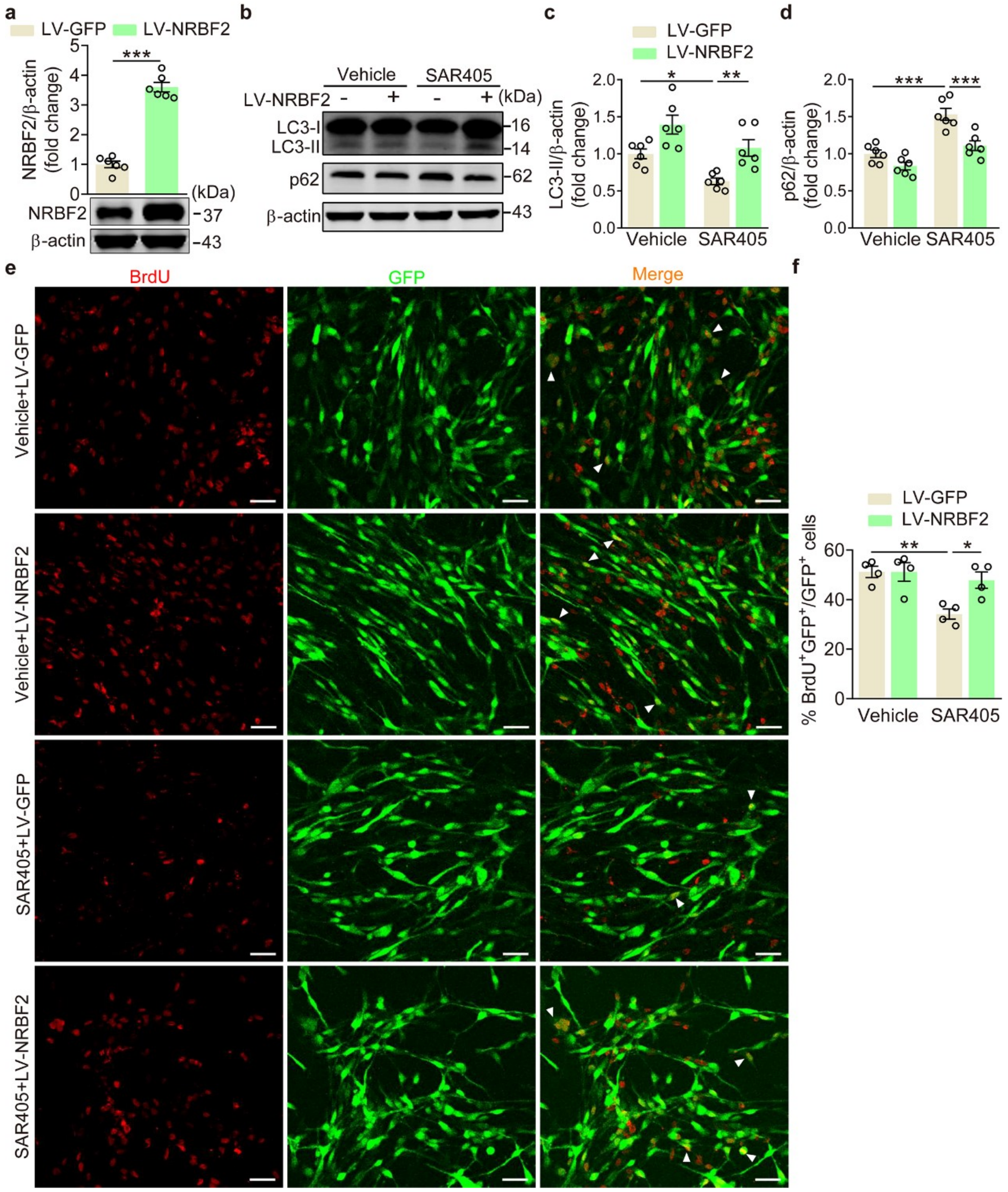
k Representative images of proliferating aNSCs, followed by immunostaining with activated caspase-3 (AC-3). White arrows indicating AC-3$^+$GFP$^+$ cells. Scale bars, 10 μm.

l Quantification of the percentage of AC-3$^+$GFP$^+$ proliferating aNSCs or Tuj1$^+$AC-3$^+$GFP$^+$ differentiated aNSCs (*n* = 3 independent experiments per group).

m Representative images of differentiated aNSCs, followed by immunostaining with Tuj1 and AC-3. White arrows indicating Tuj1$^+$AC-3$^+$GFP$^+$ cells. Scale bars, 10 μm.

n Quantification of the cell viability in control and NRBF2-deficient aNSCs treated with vehicle (0.1% DMSO) or bafilomycin A1 (*n* = 6 independent experiments per group).

Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**d**, **f**, **h**, **j, l**) or two-way ANOVA following by Bonferroni's post hoc test (**n**). **$P < 0.01$.



Supplementary Fig. S8 NRBF2 overexpression ameliorates SAR405-induced inhibition of autophagy and proliferated deficiency of aNSCs *in vitro*.

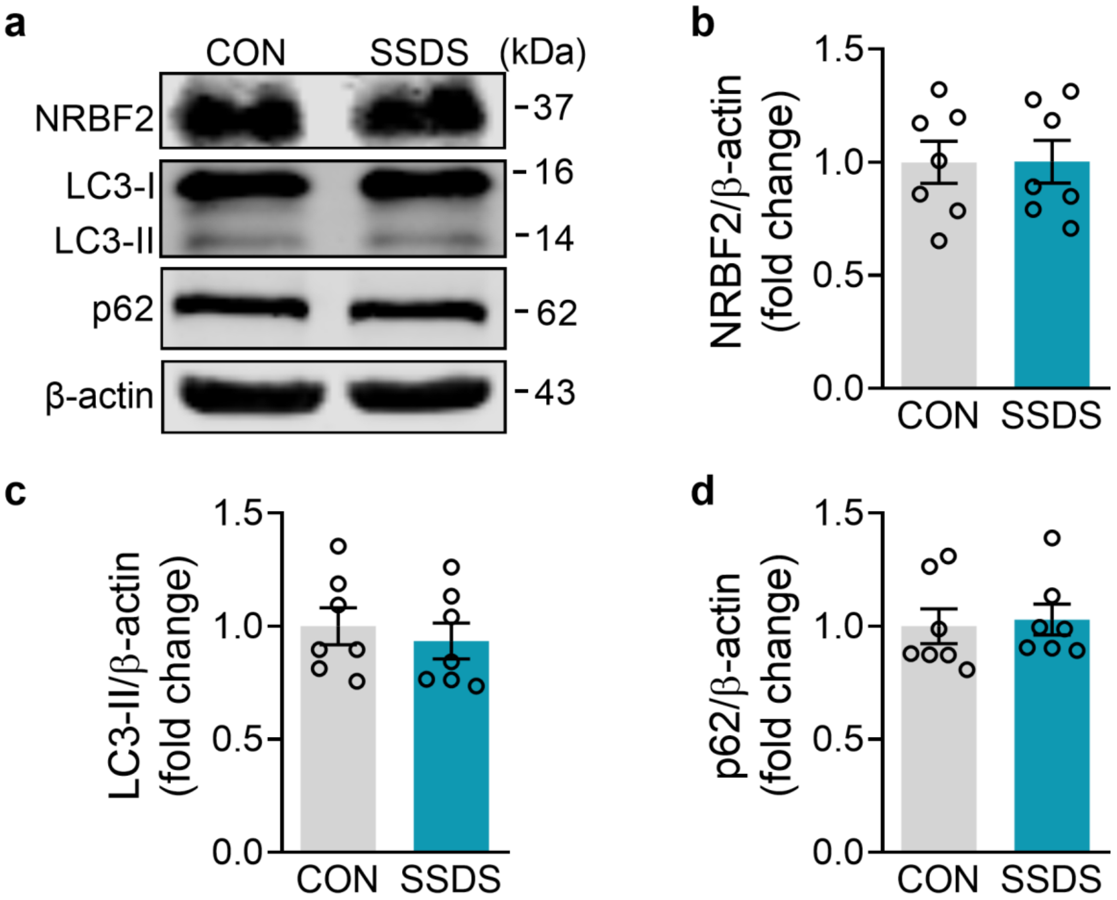
a Representative western blotting images and quantification of NRBF2 protein expression in aNSCs transfected with LV-GFP or LV-NRBF2 (*n* = 6 independent experiments per group).

b-d Representative western blotting images (**b**) and quantification of LC3-II (**c**) and p62 (**d**) protein expression in vehicle (0.1% DMSO) and SAR405-treated aNSCs transfected with LV-GFP or LV-NRBF2 (*n* = 6 independent experiments per group).

e, **f** Representative images (**e**) and quantifications (**f**) of proliferating aNSCs transfected with LV-GFP or LV-NRBF2, followed by SAR405 treatment and BrdU pulse labeling (*n* = 4 independent experiments per group). White arrows indicating BrdU$^+$GFP$^+$ cells. Scale bars, 30 μm.

Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**a**) or two-way

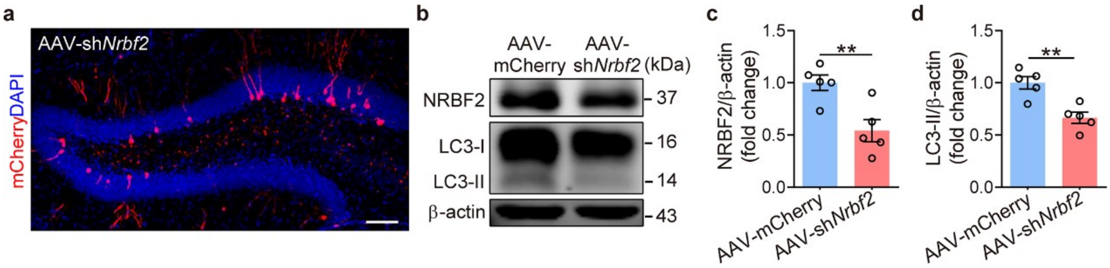
ANOVA following by Bonferroni's post hoc test (**c**, **d, f**). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.



Supplementary Fig. S9 Subthreshold social defeat stress does not affect the expression of NRBF2 in the DG.

a-d Representative western blotting images (**a**) and quantification of NRBF2 (**b**), LC3-II (**c**) and p62 (**d**) protein expression in control and subthreshold social defeat stress (SSDS)-treated mice (*n* = 7 mice per group).

Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**b-d**).

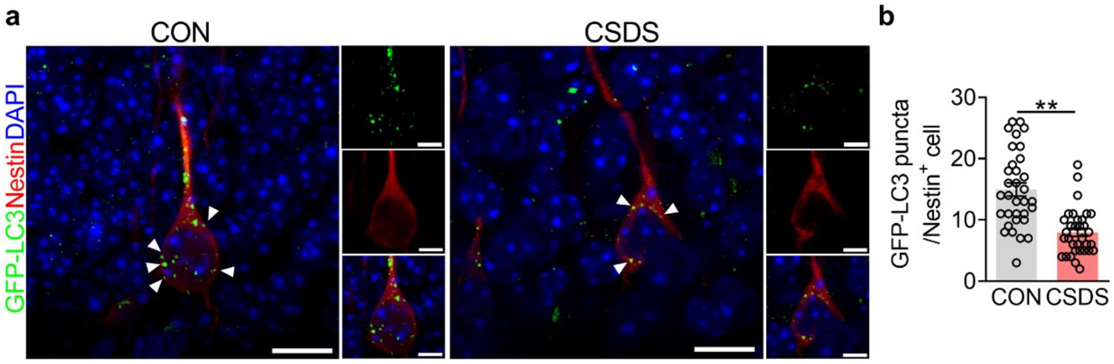


Supplementary Fig. S10 Conditional knockdown of NRBF2 in the DG of Nestin-CreER^{T2} mice.

a Representative image of mCherry^{+} cells in the DG of Nestin-CreER^{T2} mice that treated with AAV-sh*Nrbf2*. Scale bars, 100 µm.

b-d Western blotting analysis (**b**) and quantifications of NRBF2 (**c**) and LC3-II (**d**) protein expression in the DG (*n* = 5 mice per group).

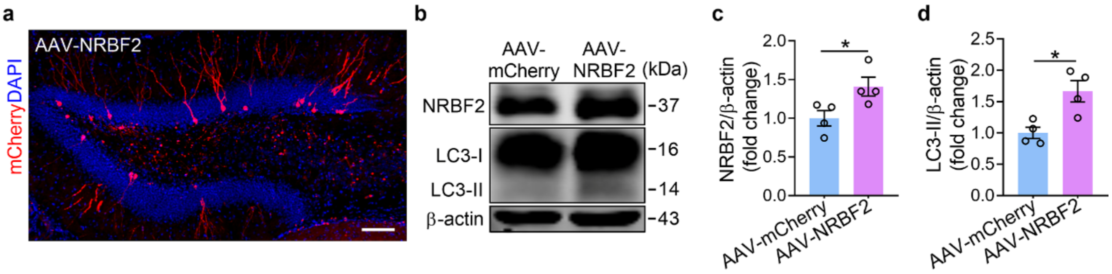
Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**c**, **d**). $^{**}P < 0.01$.



Supplementary Fig. S11 Chronic stress leads to the autophagy deficiency of aNSCs in the DG of CSDS-exposed mice.

a, b Representative images of (**a**) and quantifications of GFP-LC3 puncta within the soma of Nestin$^+$ cells in the DG (*n* = 33 cells per group). Nestin (red) and DAPI (blue). Scale bars, 10 μm (overview) and 5 μm (zoom).

Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**b**). $^{**}P < 0.01$.

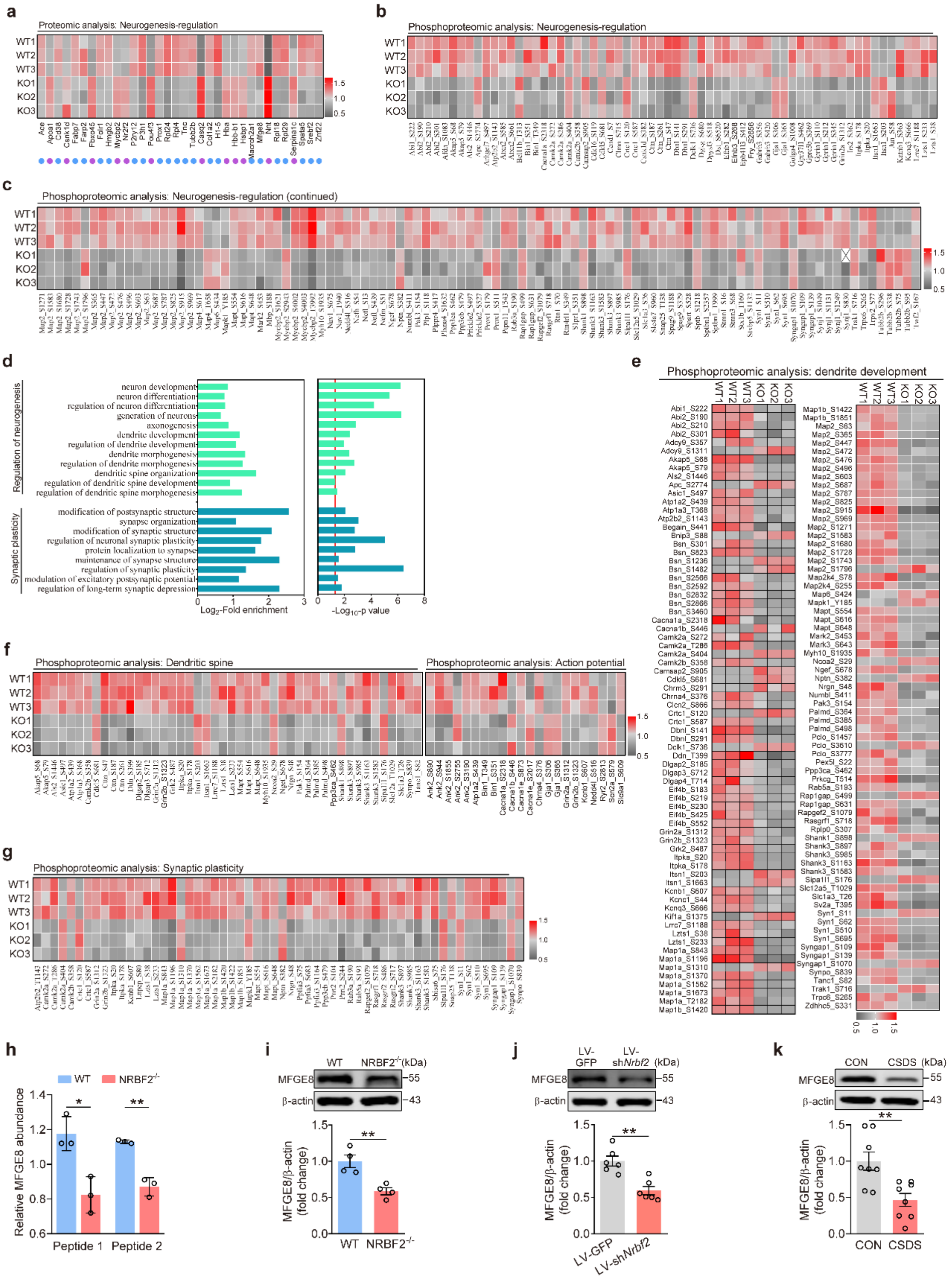


Supplementary Fig. S12 Conditional overexpression of NRBF2 in the DG of Nestin-CreER^{T2} mice.

a Representative image of mCherry^{+} cells in the DG of mice that treated with AAV-NRBF2. Scale bars, 100 μm.

b-d Western blotting analysis (**b**) and quantifications of NRBF2 (**c**) and LC3-II (**d**) protein expression in the DG (*n* = 4 mice per group).

Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**c**, **d**). *$P < 0.05$.



Supplementary Fig. S13 Deletion of NRBF2 in the DG alters the expression or phosphorylation of proteins involved in different biological processes.

a Knockout (KO) of NRBF2 altered the expression of several proteins in the DG involved in the biological processes of neurogenesis in proteomic analysis (*n* = 3 mice per group).

b, c NRBF2 deletion altered the phosphorylation of some proteins involved in the biological process of neurogenesis in phosphoproteomic analysis (*n* = 3 mice per group).

d In bioinformatics analysis, the closely related biological processes were combined to better indicate the alteration of biological processes by NRBF2 deletion, especially, the regulation of neurogenesis or synapse plasticity. **e** NRBF2 deletion altered the phosphorylation of many proteins involved in biological processes of dendritic development (*n* = 3 mice per group).

f, g NRBF2 deletion altered the phosphorylation of many proteins involved in biological processes of dendritic spine (**f**, left), action potential (**f**, right) and synaptic plasticity (**g**) (*n* = 3 mice per group).

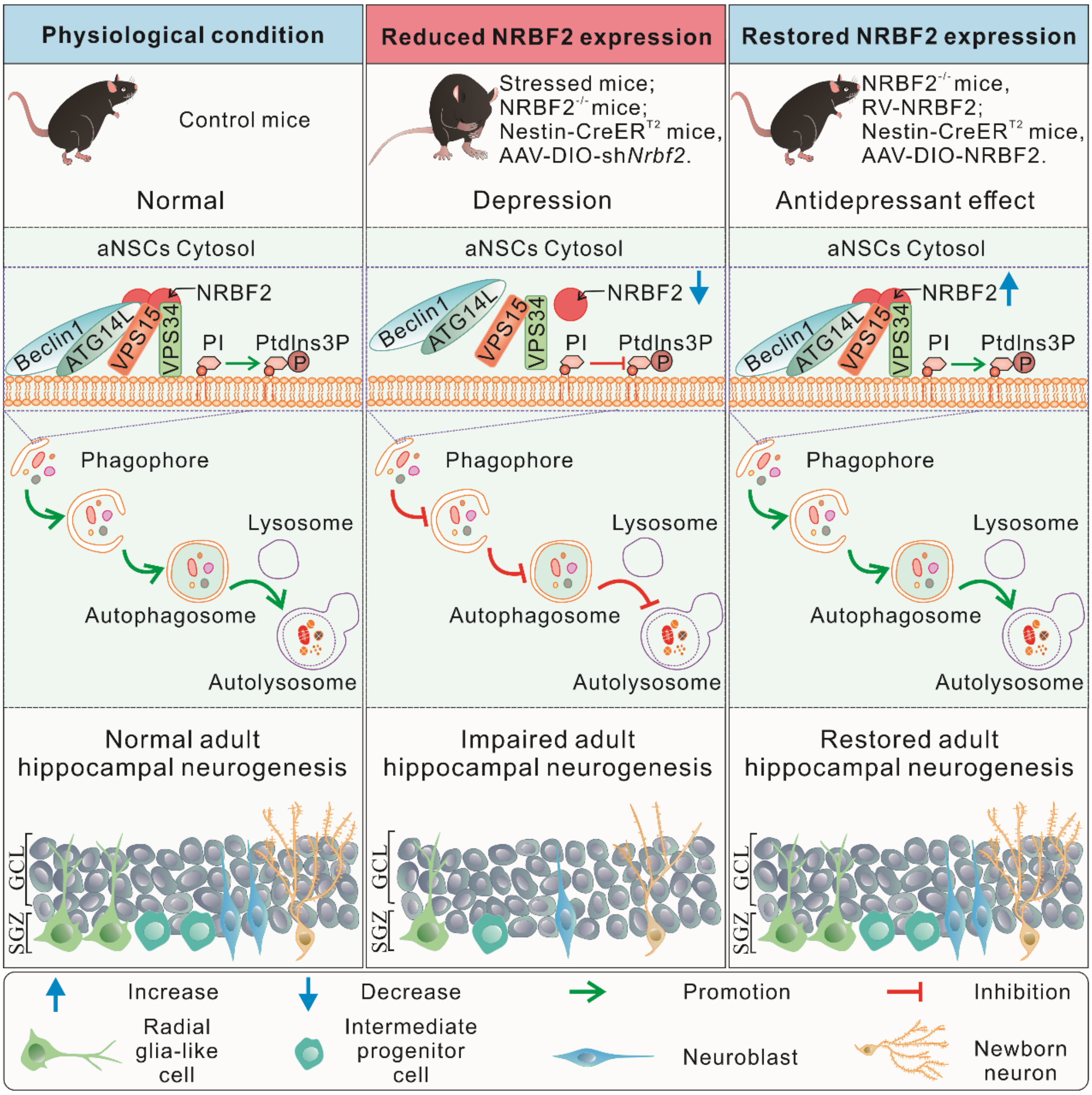
h Parallel reaction monitoring proteomics verified the reduce abundance of MFGE8, including peptide 1 and peptide 2, in the DG of NRBF2$^{-/-}$ mice (*n* = 3 mice per group). Peptide 1: FELLGCELHGCSEPLGLK; Peptide 2: QVTGIITQGAR.

i Western blotting analysis and quantification of MFGE8 protein expression in the DG of WT and NRBF2$^{-/-}$ mice (*n* = 4 mice per group).

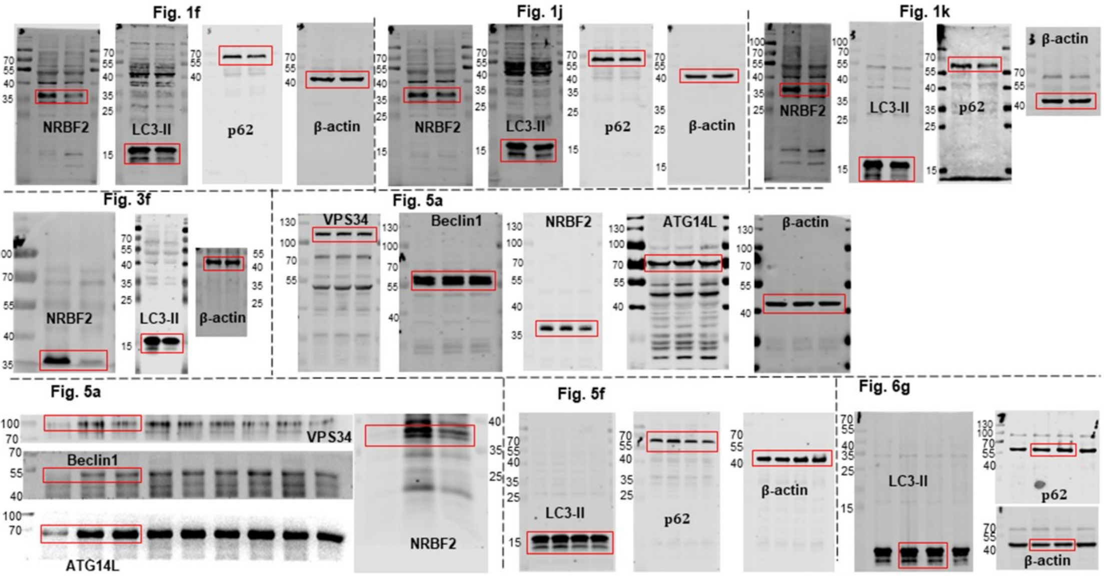
j Western blotting analysis and quantification of MFGE8 protein expression in control and NRBF2-deficient aNSCs (*n* = 6 independent experiments per group).

k Western blotting analysis and quantification of MFGE8 protein expression in the DG of control and CSDS-exposed mice (*n* = 8 mice per group).

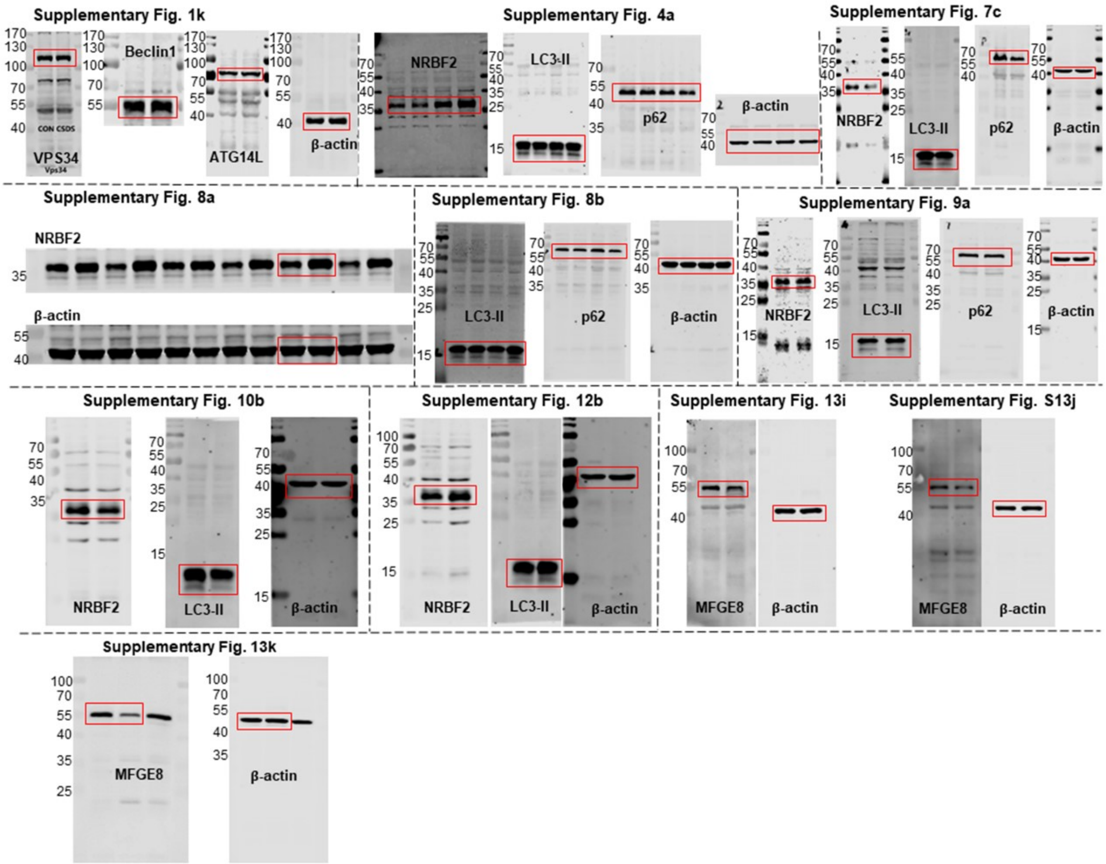
Data are presented as mean ± SEM and analyzed by two-sided unpaired t test (**h**-**k**). $^*P < 0.05$ and $^{**}P < 0.01$.



Supplementary Fig. S14 Schematic representation of the aNSCs-specific mechanism of NRBF2 in mediating the impairment of AHN in chronic stress-induced depression.
The expression of NRBF2 is enriched in the aNSCs and their progeny of dentate gyrus, a hippocampal neurogenic niche. Under normal condition, NRBF2-ATG14L interaction mediates the binding with other components in the cytosol and consequent assembly of activated Ptdlns3K complex at the phagophore, synthesizing Ptdlns3P by using phosphatidylinositol (PI), resulting in autophagy induction. Chronic stress induces the decrease of NRBF2 in the dentate gyrus. The deficiency of NRBF2 suppresses the Ptdlns3K complex activity and autophagosome information in aNSCs, disrupts the neurogenesis-related protein network, and finally leads to the exhaustion of the aNSCs pool and developmental defects of newborn neurons, which induces depression-like behavior in mice. Importantly, restoring NRBF2 expression in DG aNSCs increases autophagic flux and rescues AHN deficits of NRBF2$^{-/-}$ mice and CSDS-exposed mice.



Supplementary Fig. S15 Original blots for Fig. 1f, 1j, 1k, 3f, 5a, 5f, and 6g.



Supplementary Fig. S16. Original blots for Fig. S1k, S4a, S7c, S8a, S8b, S9a, S10b, S12b, S13i, S13j, and S13k.

Supplementary Table

Supplementary Table S1. Primers for qPCR analyses.

Gene	Primer sequences	
	Forward	**Reverse**
Nrbf2	AAGGACCCCTCAACCTTGCT	CAGTTCCAGTGATAAGTGAGCC
p62	AGGATGGGGACTTGGTTGC	TCACAGATCACATTGGGGTGC
Hbb-b1	GCACCTGACTGATGCTGAGAA	TTCATCGGCGTTCACCTTTCC
Nnt	CTCAGGCTTGTGCTGTGTTG	CTCGGCCATGCAGGTAAGAA
Pou4f3	ATGCGCCGAGTTTGTCTCC	GGGCTTGAACGGATGGTTCT
Apoa1	GGCACGTATGGCAGCAAGAT	CCAAGGAGGAGGATTCAAACTG
Mfge8	AGATGCGGGTATCAGGTGTGA	GGGGCTCAGAACATCCGTG
Fabp7	GGACACAATGCACATTCAAGAAC	CCGAACCACAGACTTACAGTTT
Farp2	GTTATTTGACATCGAGCCGAAGT	GAACTCCAGACCAAAGTAGTCAC
P3h1	ACACAAGCTATTGAATGTGCCA	TTCCCGTTCAGACTTCTGTTTC
Gapdh	AACGACCCCTTCATTGAC	TCCACGACATACTCAGCAC

Supplementary Table S2. List of antibodies

Antibodies	**Species**	**dilution**	**Supplier**
Anti-ATG14L	Rabbit	1:1000 (WB)	MBL, Cat# PD026
Anti-β-actin	Mouse	1:3000 (WB)	Santa Cruz, Cat# sc-517582
Anti-Beclin1	Rabbit	1:1000 (WB)	Novus, Cat# NB110-87318SS
Anti-BrdU	Rat	1:1000 (WB)	Abcam, Cat# ab6126
Anti-cleaved Caspase3	Rabbit	1:500 (IF)	Cell Signaling, Cat# 9661
Anti-DCX	Rabbit	1:400 (IF)	Cell Signaling, Cat# 4604
Anti-GFAP	Mouse	1:400 (IF)	Cell Signaling, Cat# 3670
Anti-GFAP	Rabbit	1:200 (IF)	Proteintech, Cat# 16825-1-AP
Anti-LC3B	Rabbit	1:1000 (WB)	Cell Signaling, Cat# 2775
Anti-LC3	Rabbit	1:200 (IF)	MBL, Cat# PM036
Anti-MFGE8	Mouse	1:1000 (WB)	Santa Cruz, Cat# sc-33546
Anti-Nestin	Chicken	1:500 (JF)	Aves Labs, Cat# AB_2314882
Anti-NeuN	Rabbit	1:500 (IF)	Abcam, Cat# ab177487
Anti-NRBF2	Rabbit	1:1000 (WB)	Cell Signaling, Cat# 8066
Anti-NRBF2	Mouse	1:200 (IF)	Santa Cruz, Cat# sc-365213
Anti-RFP	Rabbit	1:200 (IF)	Abcam, Cat# ab62341
Anti-Sox2	Goat	1:200 (IF)	R&D Systems. Cat# AF2018
Anti-SQSTM1/p62	Mouse	1:1000 (WB)	Abcam, Cat# ab56416
Anti-SQSTM1/p62	Mouse	1:200 (IF)	Abcam, Cat# ab56416
Anti-Tbr2	Rabbit	1:200 (IF)	Abcam, Cat# ab23345
Anti-Tuj1	Mouse	1:500 (IF)	Proteintech, Cat# 66375-1-Ig
Anti-VPS34	Rabbit	1:1000 (WB)	Proteintech, Cat# 12452-1-AP
Alexa fluor-405-anti-Rat secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat# A48261
Alexa fluor-488-anti-Rat secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat#A21208
Alexa fluor-488-anti-Rabbit secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat#A21206
Alexa fluor-647-anti-Rabbit secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat#A31573
Alexa fluor-594-anti-Chicken secondary antibody	Donkey	1:1000 (IF)	Jackson ImmunoResearch, Cat# 703-585-155
Alexa fluor-594-anti-Rabbit secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat# A21207
Alexa fluor-594-anti-Goat secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat# A-11058
Alexa fluor-594-anti-Mouse secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat# A21203
Alexa fluor-647-anti-Mouse secondary antibody	Donkey	1:1000 (IF)	Invitrogen, Cat#A31571

IRDye® LI-COR 800CW anti-Mouse IgG (H + L)	Goat	1:20000 (WB)	LI-COR Biosciences, Cat# 926-32352
IRDye® 800CW anti-Rabbit IgG (H + L)	Goat	1:20000 (WB)	LI-COR Biosciences, Cat# 925-32211

Supplementary Table S3. The statistical information about this study.

Figures and numbers of animals or cells	**Statistical analysis**	**Post hoc tests**	**mean ± SEM**
1b: Number of AVs in DG in CSDS model CON ($n = 22$) CSDS ($n = 18$)	Unpaired t test t = 4.612, $P < 0.001$		CON 2.727 ± 0.256 CSDS 1.333 ± 0.114
1d: LC3 puncta in DG in CSDS model CON ($n = 35$) CSDS ($n = 38$)	Unpaired t test t = 7.744, $P < 0.001$		CON 12.486 ± 0.850 CSDS 5.316 ± 0.420
1e: *Nrbf2* mRNA level in DG in CSDS model CON ($n = 11$) CSDS ($n = 13$)	Unpaired t test t = 4.761, $P < 0.001$		CON 1.014 ± 0.054 CSDS 0.708 ± 0.038
1g: NRBF2 protein expression in DG in CSDS model CON ($n = 14$) CSDS ($n = 14$)	Unpaired t test t = 4.991, $P < 0.001$		CON 1.000 ± 0.065 CSDS 0.594 ± 0.049
1h: LC3-II protein expression in DG in CSDS model CON ($n = 14$) CSDS ($n = 14$)	Unpaired t test t = 5.180, $P < 0.001$		CON 1.000 ± 0.046 CSDS 0.599 ± 0.062
1i: p62 protein expression in DG in CSDS model CON ($n = 14$) CSDS ($n = 14$)	Unpaired t test t = 3.288, $P = 0.003$		CON 1.000 ± 0.061 CSDS 0.743 ± 0.049
1j: protein expression in DG in CUS model CON ($n = 13$) CUS ($n = 13$)	NRBF2: Unpaired t test, t = 6.710, $P < 0.001$		CON 1.000 ± 0.045 CUS 0.654 ± 0.031
	LC3-II: Unpaired t test, t = 3.560, $P = 0.002$		CON 1.000 ± 0.090 CUS 0.643 ± 0.045
	p62: Unpaired t test, t = 3.343, $P = 0.003$		CON 1.000 ± 0.042 CUS 0.776 ± 0.052

1k: protein expression in DG in CORT model CON ($n = 9$) CORT ($n = 11$)	NRBF2: Unpaired t test, t = 3.554, $P = 0.003$ LC3-II: Unpaired t test, t = 3.116, $P = 0.006$ p62: Unpaired t test, t = 2.298, $P = 0.034$		CON 1.000 ± 0.090 CORT 0.646 ± 0.052 CON 1.000 ± 0.113 CORT 0.625 ± 0.058 CON 1.000 ± 0.135 CUS 0.687 ± 0.056
2b. BrdU$^+$Sox2$^+$GFAP$^+$ RGLs after virus injection CON + LV-vector ($n = 3$) CON + LV-NRBF2 ($n = 3$) CSDS + LV-vector ($n = 3$) CSDS + LV-NRBF2 ($n = 3$)	Two-way ANOVA: Stress: F (1, 8) = 6.819, $P = 0.031$ Virus: F (1, 8) = 48.820, $P < 0.001$ Stress × Virus: F (1, 8) = 4.483, $P = 0.067$	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, $P < 0.001$; CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.018$; CON + LV-vector vs CON + LV-NRBF2, $P > 0.999$; CSDS + LV-vector vs CSDS + LV-NRBF2, $P = 0.020$	CON + LV-vector 1495.0 ± 72.111 CON + LV-NRBF2 1530.0 ± 73.993 CSDS + LV-vector 850.0 ± 49.244 CSDS + LV-NRBF2 1185.0 ±83.516
BrdU$^+$DCX$^+$ neuroblasts after virus injection CON + LV-vector ($n = 4$) CON + LV-NRBF2 ($n = 4$) CSDS + LV-vector ($n = 5$) CSDS + LV-NRBF2 ($n = 5$)	Two-way ANOVA: Stress: F (1, 14) = 19.220, $P = 0.001$ Virus: F (1, 14) = 37.860, $P < 0.001$ Stress × Virus: F (1, 14) = 12.150, $P = 0.004$	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, $P < 0.001$; CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.160$; CON + LV-vector vs CON + LV-NRBF2, $P = 0.803$; CSDS + LV-vector vs CSDS + LV-NRBF2, $P < 0.001$	CON + LV-vector 1102.5 ± 73.072 CON + LV-NRBF2 1152.5 ± 41.105 CSDS + LV-vector 566.0 ± 25.612 CSDS + LV-NRBF2 1004.0 ± 69.036
BrdU$^+$NeuN$^+$ neurons after virus injection CON + LV-vector ($n = 3$)	Two-way ANOVA: Stress: F (1, 8) = 16.000, $P = 0.004$ Virus: F (1, 8) =	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-	CON + LV-vector 1135.0 ± 39.051 CON + LV-NRBF2 1125.0 ± 31.225

CON + LV-NRBF2 ($n = 3$) CSDS + LV-vector ($n = 3$) CSDS + LV-NRBF2 ($n = 3$)	172.800, $P < 0.001$ Stress × Virus: F (1, 8) = 18.100, $P = 0.003$	vector, $P < 0.001$; CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.001$; CON + LV-vector vs CON + LV-NRBF2, $P > 0.999$; CSDS + LV-vector vs CSDS + LV-NRBF2, $P = 0.001$	CSDS + LV-vector 450.0 ± 52.678 CSDS + LV-NRBF2 775.0 ± 30.414
2d: RFP-LC3 puncta in the DG after NRBF2 overexpression CON + LV-vector ($n = 36$) CON + LV-NRBF2 ($n = 35$) CSDS + LV-vector ($n = 35$) CSDS + LV-NRBF2 ($n = 32$)	Two-way ANOVA Stress: F (1, 134) = 11.030, $P = 0.001$ Virus: F (1, 134) = 9.814, $P = 0.002$ Stress × virus: F (1, 134) = 0.631, $P = 0.428$	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, $P = 0.011$; CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.211$; CON + LV-vector vs CON + LV-NRBF2, $P = 0.144$; CSDS + LV-vector vs CSDS + LV-NRBF2, $P = 0.010$	CON + LV-vector 14.944 ± 1.051 CON + LV-NRBF2 17.371 ± 0.918 CSDS + LV-vector 11.171 ± 0.709 CSDS + LV-NRBF2 15.125 ± 1.129
2g. Total dendritic length after virus injection CON + LV-vector ($n = 29$) CON + LV-NRBF2 ($n = 29$) CSDS + LV-vector ($n = 33$) CSDS + LV-NRBF2 ($n = 30$)	Two-way ANOVA: Stress: F (1, 117) = 22.970, $P < 0.001$ Virus: F (1, 117) = 53.260, $P < 0.001$ Stress × virus: F (1, 117) = 16.070, $P < 0.001$	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, $P < 0.001$; CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.047$; CON + LV-vector vs CON + LV-NRBF2, $P > 0.999$; CSDS + LV-vector vs CSDS + LV-NRBF2, $P < 0.001$	CON + LV-vector 1078.330 ± 35.059 CON + LV-NRBF2 1107.072 ± 39.224 CSDS + LV-vector 663.663 ± 31.497 CSDS + LV-NRBF2 986.461 ± 40.846
2h. Number of crossings after virus injection CON + LV-vector ($n = 29$) CON + LV-NRBF2	Repeated measures ANOVA: Stress: F (1, 60) = 72.700, $P < 0.001$ LV-NRBF2: F (1, 61) =		

($n = 29$) CSDS + LV-vector ($n = 33$) CSDS + LV-NRBF2 ($n = 30$)	40.610, $P < 0.001$		
2i. Spine density after virus injection CON + LV-vector ($n = 33$) CON + LV-NRBF2 ($n = 35$) CSDS + LV-vector ($n = 37$) CSDS + LV-NRBF2 ($n = 37$)	Two-way ANOVA: Stress: F (1, 138) = 2.410, $P = 0.123$ Virus: F (1, 138) = 83.130, $P < 0.001$ Stress × virus: F (1, 138) = 14.510, $P < 0.001$	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, $P < 0.001$; CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.001$; CON + LV-vector vs CON + LV-NRBF2, $P = 0.241$; CSDS + LV-vector vs CSDS + LV-NRBF2, $P < 0.001$	CON + LV-vector 22.299 ± 1.455 CON + LV-NRBF2 19.869 ± 1.187 CSDS + LV-vector 8.382 ± 0.686 CSDS + LV-NRBF2 14.154 ± 0.920
2j. SIT after virus injection CON + LV-vector ($n = 9$) CON + LV-NRBF2 ($n = 8$) CSDS + LV-vector ($n = 10$) CSDS + LV-NRBF2 ($n = 14$)	Two-way ANOVA: Stress: F (1, 37) = 7.532, $P = 0.009$ Virus: F (1, 37) = 28.210, $P < 0.001$ Stress × virus: F (1, 37) = 4.582, $P = 0.039$	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, $P < 0.001$; CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.057$; CON + LV-vector vs CON + LV-NRBF2, $P > 0.999$; CSDS + LV-vector vs CSDS + LV-NRBF2, $P = 0.001$	CON + LV-vector 1.165 ± 0.048 CON + LV-NRBF2 1.226 ± 0.077 CSDS + LV-vector 0.419 ± 0.061 CSDS + LV-NRBF2 0.908 ± 0.124
2k. TST after virus injection CON + LV-vector ($n = 14$) CON + LV-NRBF2 ($n = 14$) CSDS + LV-vector ($n = 11$) CSDS + LV-NRBF2 ($n = 13$)	Two-way ANOVA: Stress: F (1, 48) = 6.600, $P = 0.013$ Virus: F (1, 48) = 2.964, $P = 0.092$ Stress × virus: F (1, 39) = 11.550, $P = 0.001$	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, $P = 0.002$ CON + LV-NRBF2 vs CSDS + LV-NRBF2, $P = 0.462$ CON + LV-vector vs CON + LV-	CON + LV-vector 86.737 ± 10. 724 CON + LV-NRBF2 95.172 ± 8.137 CSDS + LV-vector 138.788 ± 12.381 CSDS + LV-NRBF2 78.121 ± 9.478

		NRBF2, *P* > 0.999 CSDS + LV-vector vs CSDS + LV-NRBF2, *P* < 0.001	
2l. FST after virus injection CON + LV-vector (*n* = 15) CON + LV-NRBF2 (*n* = 15) CSDS + LV-vector (*n* = 12) CSDS + LV-NRBF2 (*n* = 13)	Two-way ANOVA: Stress: F (1, 51) = 6.435, *P* = 0.014 Virus: F (1, 51) = 11.04, *P* = 0.002 Stress × virus: F (1, 51) = 6.224, *P* = 0.016	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, *P* < 0.001; CON + LV-NRBF2 vs CSDS + LV-NRBF2, *P* > 0.999; CON + LV-vector vs CON + LV-NRBF2, *P* > 0.999; CSDS + LV-vector vs CSDS + LV-NRBF2, *P* = 0.003	CON + LV-vector 54.337 ± 8.414 CON + LV-NRBF2 53.885 ± 10.399 CSDS + LV-vector 117.291 ± 13.438 CSDS + LV-NRBF2 62.842 ± 11. 310
3b: NRBF2$^{-/-}$ mice-SPT WT (*n* = 10) NRBF2$^{-/-}$ (*n* = 9)	Unpaired t test t = 4.268, *P* = 0.001		WT 89.434 ± 1.972 NRBF2$^{-/-}$ 54.874 ± 8.274
3c: NRBF2$^{-/-}$ mice-TST WT (*n* = 10) NRBF2$^{-/-}$ (*n* = 8)	Unpaired t test t = 2.830, *P* = 0.012		WT 105.676 ± 11.290 NRBF2$^{-/-}$ 162.248 ± 17.395
3d: NRBF2$^{-/-}$ mice-FST WT (*n* = 10) NRBF2$^{-/-}$ (*n* = 9)	Unpaired t test t = 3.789, *P* = 0.002		WT 89.083 ± 14.431 NRBF2$^{-/-}$ 161.964 ± 12.388
3e: NRBF2$^{-/-}$ mice-OFT: total distance WT (*n* = 10) NRBF2$^{-/-}$ (*n* = 9)	Unpaired t test t = 0.561, *P* = 0.582		WT 19.774 ± 1.030 NRBF2$^{-/-}$ 18.939 ± 1.074
3g: protein expression in DG of NRBF2$^{-/-}$ mice WT (*n* = 4) NRBF2$^{-/-}$ (*n* = 4)	NRBF2: unpaired t test t = 14.140, *P* < 0.001 LC3-II: unpaired t test t = 6.202, *P* = 0.001		WT 1.000 ± 0.067 NRBF2$^{-/-}$ 0.053 ± 0.007 WT 1.000 ± 0.063 NRBF2$^{-/-}$ 0.512 ± 0.047
3i: LC3 puncta within Nestin^{+} cells in DG of NRBF2$^{-/-}$ mice WT (*n* = 25) NRBF2$^{-/-}$ (*n* = 29)	Unpaired t test t = 5.295, *P* < 0.001		WT 12.840 ± 0.984 NRBF2$^{-/-}$ 7.069 ± 0.552

3l: BrdU$^+$Sox2$^+$GFAP$^+$ RGLs of NRBF2$^{-/-}$ mice WT (*n* = 5) NRBF2$^{-/-}$ (*n* = 5)	Unpaired t test t = 6.305, *P* = 0.001		WT 1398.0 ± 82.89 NRBF2$^{-/-}$ 783.0 ± 51.40
BrdU$^+$Tbr2$^+$ IPCs of NRBF2$^{-/-}$ mice WT (*n* = 5) NRBF2$^{-/-}$ (*n* = 5)	Unpaired t test t = 5.972, *P* = 0.001		WT 1326.0 ± 98.32 NRBF2$^{-/-}$ 672.0 ± 48.23
BrdU$^+$DCX$^+$ neuroblasts of NRBF2$^{-/-}$ mice WT (*n* = 5) NRBF2$^{-/-}$ (*n* = 5)	Unpaired t test t = 6.511, *P* = 0.001		WT 1190.0 ± 86.96 NRBF2$^{-/-}$ 513.0 ± 57.00
3o: BrdU$^+$NeuN$^+$ neurons of NRBF2$^{-/-}$ mice WT (*n* = 5) NRBF2$^{-/-}$ (*n* = 5)	Unpaired t test t = 13.220, *P* < 0.001		WT 1023.0 ± 45.349 NRBF2$^{-/-}$ 336.0 ± 25.367
4b: cOE-SPT WT + RV-mCherry (*n* = 10) WT + RV-NRBF2 (*n* = 10) NRBF2$^{-/-}$ + RV-mCherry (*n* = 10) NRBF2$^{-/-}$ + RV-NRBF2 (*n* = 10)	Two-way ANOVA NRBF2$^{-/-}$: F (1, 36) = 8.806, *P* = 0.005 RV-NRBF2: F (1, 36) = 15.520, *P* < 0.001 NRBF2$^{-/-}$ × RV-NRBF2: F (1, 36) = 13.210, *P* = 0.001	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-mCherry, *P* < 0.001; WT + RV-NRBF2 vs NRBF2$^{-/-}$ + RV-NRBF2, *P* > 0.999; WT + RV-mCherry vs WT + RV-NRBF2, *P* > 0.999; NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, *P* < 0.001	WT + RV-mCherry 91.497 ± 0.757 WT + RV-NRBF2 88.593 ± 2.070 NRBF2$^{-/-}$ + RV-mCherry 58.549 ± 7.865 NRBF2$^{-/-}$ + RV-NRBF2 87.268 ± 2.994
cOE-TST: WT + RV-mCherry (*n* = 10) WT + RV-NRBF2 (*n* = 10) NRBF2$^{-/-}$ + RV-mCherry (*n* = 10) NRBF2$^{-/-}$ + RV-NRBF2	Two-way ANOVA NRBF2$^{-/-}$: F (1, 36) = 15.090, *P* = 0.001 RV-NRBF2: F (1, 36) = 1.886, *P* = 0.178 NRBF2$^{-/-}$ × RV-NRBF2: F (1, 36) = 20.700, *P* < 0.001	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-mCherry, *P* = 0.001; WT + RV-NRBF2 vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.062;	WT + RV-mCherry 91.461 ± 17.229 WT + RV-NRBF2 99.368 ± 10.070 NRBF2$^{-/-}$ + RV-mCherry 161.772 ± 10.889 NRBF2$^{-/-}$ + RV-NRBF2

(*n* = 10)		WT + RV-mCherry vs WT + RV-NRBF2, *P* > 0.999; NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, *P* < 0.001	61.662 ± 6.834
cOE-FST: WT + RV-mCherry (*n* = 10) WT + RV-NRBF2 (*n* = 10) NRBF2$^{-/-}$ + RV-mCherry (*n* = 10) NRBF2$^{-/-}$ + RV-NRBF2 (*n* = 10)	Two-way ANOVA NRBF2$^{-/-}$: F (1, 36) = 9.499, *P* = 0.004 RV-NRBF2: F (1, 36) = 50.340, *P* < 0.001 NRBF2$^{-/-}$ × RV-NRBF2: F (1, 36) = 2.404, *P* = 0.130	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-mCherry, *P* < 0.001; WT + RV-NRBF2 vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.001; WT + RV-mCherry vs WT + RV-NRBF2, *P* = 0.572; NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.005	WT + RV-mCherry 57.802 ± 13.554 WT + RV-NRBF2 35.587 ± 9.896 NRBF2$^{-/-}$ + RV-mCherry 183.198 ± 15.399 NRBF2$^{-/-}$ + RV-NRBF2 116.006 ± 17.967
4d: BrdU^{+}Sox2^{+}GFAP^{+} RGLs of NRBF2$^{-/-}$ mice WT + RV-mCherry (*n* = 4) WT + RV-NRBF2 (*n* = 4) NRBF2$^{-/-}$ + RV-mCherry (*n* = 4) NRBF2$^{-/-}$ + RV-NRBF2 (*n* = 4)	Two-way ANOVA NRBF2$^{-/-}$: F (1, 12) = 12.690, *P* = 0.004 RV-NRBF2: F (1, 12) = 50.760, *P* < 0.001 NRBF2$^{-/-}$ × RV-NRBF2: F (1, 12) = 23.310, *P* < 0.001	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-mCherry, *P* < 0.001; WT + RV-NRBF2 vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.261; WT + RV-mCherry vs WT + RV-NRBF2, *P* = 0.777; NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, *P* < 0.001	WT + RV-mCherry 1522.500 ± 102.926 WT + RV-NRBF2 1421.250 ± 58.537 NRBF2$^{-/-}$ + RV-mCherry 566.250 ± 63.159 NRBF2$^{-/-}$ + RV-NRBF2 1237.500 ± 87.142
BrdU^{+}DCX^{+} neuroblasts of NRBF2$^{-/-}$ mice WT + RV-mCherry (*n* = 4)	Two-way ANOVA NRBF2$^{-/-}$: F (1, 12) = 13.430, *P* = 0.003 RV-NRBF2: F (1, 12) =	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-	WT + RV-mCherry 1327.500 ± 67.222 WT + RV-NRBF2 1380.000 ± 125.946

NRBF2$^{-/-}$ + RV-mCherry (*n* = 4) WT + RV-NRBF2 (*n* = 4) NRBF2$^{-/-}$ + RV-NRBF2 (*n* = 4)	17.330, *P* = 0.001 NRBF2$^{-/-}$ × RV-NRBF2: F (1, 12) = 9.779, *P* = 0.009	mCherry, *P* = 0.001 WT + RV-NRBF2 vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.956 WT + RV-mCherry vs WT + RV-NRBF2, *P* > 0.999 NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.001	NRBF2$^{-/-}$ + RV-mCherry 615.000 ± 50.867 NRBF2$^{-/-}$ + RV-NRBF2 1278.750 ± 123.447
BrdU^{+}NeuN^{+} neurons of NRBF2$^{-/-}$ mice WT + RV-mCherry (*n* = 4) NRBF2$^{-/-}$ + RV-mCherry (*n* = 4) WT + RV-NRBF2 (*n* = 4) NRBF2$^{-/-}$ + RV-NRBF2 (*n* = 4)	Two-way ANOVA NRBF2$^{-/-}$: F (1, 12) = 6.216, *P* = 0.028 RV-NRBF2: F (1, 12) = 41.250, *P* < 0.001 NRBF2$^{-/-}$ × RV-NRBF2: F (1, 12) = 6.381, *P* = 0.027	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-mCherry, *P* < 0.001; WT + RV-NRBF2 vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.035; WT + RV-mCherry vs WT + RV-NRBF2, *P* > 0.999; NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, *P* = 0.008	WT + RV-mCherry 1065.000 ± 67.639 WT + RV-NRBF2 1062.500 ± 61.695 NRBF2$^{-/-}$ + RV-mCherry 387.500 ± 56.771 NRBF2$^{-/-}$ + RV-NRBF2 767.500 ± 106.409
4g: Dendritic length of newborn neurons WT + RV-mCherry (*n* = 49) WT + RV-NRBF2 (*n* = 44) NRBF2$^{-/-}$ + RV-mCherry (*n* = 41) NRBF2$^{-/-}$ + RV-NRBF2 (*n* = 45)	Two-way ANOVA NRBF2$^{-/-}$: F (1, 175) = 127.700, *P* < 0.001 RV-NRBF2: F (1, 175) = 103.700, *P* < 0.001 NRBF2$^{-/-}$ × RV-NRBF2: F (1, 175) = 11.640, *P* = 0.001	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-mCherry, *P* < 0.001; NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, *P* < 0.001	WT + RV-mCherry 968.827 ± 24.809 WT + RV-NRBF2 1192.521 ± 24.809 NRBF2$^{-/-}$ + RV-mCherry 632.262 ± 24.104 NRBF2$^{-/-}$ + RV-NRBF2 1015.899 ± 29.630
4h: Number of crossings WT + RV-mCherry (*n* = 49) WT + RV-NRBF2 (*n* = 44) NRBF2$^{-/-}$ + RV-mCherry	Repeated measures ANOVA NRBF2$^{-/-}$: F (1, 88) = 100.800, *P* < 0.001 RV-NRBF2: F (1, 84) = 89.760, *P* < 0.001		

($n = 41$) NRBF2$^{-/-}$ + RV-NRBF2 ($n = 45$)			
4i: Spine density of newborn neurons WT + RV-mCherry ($n = 46$) WT + RV-NRBF2 ($n = 45$) NRBF2$^{-/-}$ + RV-mCherry ($n = 44$) NRBF2$^{-/-}$ + RV-NRBF2 ($n = 48$)	Two-way ANOVA NRBF2$^{-/-}$: F (1, 179) = 11.210, $P = 0.001$ RV-NRBF2: F (1, 179) = 66.080, $P < 0.001$ NRBF2$^{-/-}$ × RV-NRBF2: F (1, 179) = 2.282, $P = 0.133$	Bonferroni's post hoc test WT + RV-mCherry vs NRBF2$^{-/-}$ + RV-mCherry, $P < 0.001$; WT + RV-NRBF2 vs NRBF2$^{-/-}$ + RV-NRBF2, $P < 0.001$; WT + RV-mCherry vs WT + RV-NRBF2, $P = 0.393$; NRBF2$^{-/-}$ + RV-mCherry vs NRBF2$^{-/-}$ + RV-NRBF2, $P = 0.001$	WT + RV-mCherry 17.403 ± 0.833 WT + RV-NRBF2 18.802 ± 0.913 NRBF2$^{-/-}$ + RV-mCherry 10.063 ± 0.584 NRBF2$^{-/-}$ + RV-NRBF2 13.762 ± 0.670
5b: NRBF2: ATG14L LV-GFP ($n = 7$) LV-sh*Nrbf*2 ($n = 7$)	Unpaired t test t = 6.302, $P < 0.001$		LV-GFP 1.000 ± 0.050 LV-sh*Nrbf2* 0.599 ± 0.039
5c: VPS34: ATG14L LV-GFP ($n = 7$) LV-sh*Nrbf2* ($n = 7$)	Unpaired t test t = 2.971, $P = 0.012$		LV-GFP 1.000 ± 0.117 LV-sh*Nrbf2* 0.582 ± 0.077
5d: Beclin1: ATG14L LV-GFP ($n = 7$) LV-sh*Nrbf2* ($n = 7$)	Unpaired t test t = 1.133, $P = 0.280$		LV-GFP 1.000 ± 0.041 LV-sh*Nrbf2* 0.939 ± 0.035
5e: Ptdlns3P level in NRBF2-deficient aNSCs LV-GFP ($n = 8$) LV-sh*Nrbf2* ($n = 8$)	Unpaired t test t = 4.800, $P < 0.001$		LV-GFP 1.182 ± 0.105 LV-sh*Nrbf*2 0.504 ± 0.094
5g: LC3-II protein expression in NRBF2-deficient aNSCs LV-GFP + Vehicle ($n = 9$) LV-GFP + BafA1 ($n = 9$) LV-sh*Nrbf2* + Vehicle ($n = 9$) LV-sh*Nrbf2* + BafA1 ($n = 9$)	Two-way ANOVA LV-sh*Nrbf2*: F (1, 32) = 19.610, $P < 0.001$ BafA1: F (1, 32) = 59.740, $P < 0.001$ LV-sh*Nrbf2* × BafA1: F (1, 32) = 12.500, $P = 0.001$	Bonferroni's post hoc test LV-GFP + Vehicle vs LV-sh*Nrbf2* + Vehicle, $P = 0.011$; LV-GFP + BafA1 vs LV-sh*Nrbf2* + BafA1, $P < 0.001$; LV-GFP + Vehicle vs LV-GFP + BafA1, $P < 0.001$; LV-sh*Nrbf2* +	LV-GFP + Vehicle 1.000 ± 0.029 LV-GFP + BafA1 1.554 ± 0.122 LV-sh*Nrbf2* + Vehicle 0.708 ± 0.035 LV-sh*Nrbf2* + BafA1 0.770 ± 0.049

		Vehicle vs LV-sh*Nrbf2* + BafA1, $P > 0.999$	
5h: p62 protein expression in NRBF2-deficient aNSCs LV-GFP + Vehicle ($n = 9$) LV-GFP + BafA1 ($n = 9$) LV-sh*Nrbf2* + Vehicle ($n = 9$) LV-sh*Nrbf2* + BafA1 ($n = 9$)	Two-way ANOVA LV-sh*Nrbf2*: F (1, 32) = 12.670, $P = 0.001$ BafA1: F (1, 32) = 59.310, $P < 0.001$ LV-sh*Nrbf2* × BafA1: F (1, 32) = 5.008, $P = 0.032$	Bonferroni's post hoc test LV-GFP + Vehicle vs LV-sh*Nrbf2* + Vehicle, $P = 0.001$; LV-GFP + BafA1 vs LV-sh*Nrbf2* + BafA1, $P < 0.001$; LV-GFP + Vehicle vs LV-GFP + BafA1, $P < 0.001$; LV-sh*Nrbf2* + Vehicle vs LV-sh*Nrbf2* + BafA1, $P = 0.714$	LV-GFP + Vehicle 1.000 ± 0.037 LV-GFP + BafA1 1.268 ± 0.063 LV-sh*Nrbf2* + Vehicle 0.747 ± 0.037 LV-sh*Nrbf2* + BafA1 0.808 ± 0.042
5j: GFP-RFP-LC3 puncta in NRBF2 KD aNSCs CON + Vehicle ($n = 25$) CON + BafA1 ($n = 21$) NRBF2 KD + Vehicle ($n = 25$) NRBF2 KD + BafA1 ($n = 25$)	Two-way ANOVA NRBF2 KD: F (1, 92) = 20.330, $P < 0.001$ BafA1: F (1, 92) = 78.080, $P < 0.001$ NRBF2 KD × BafA1: F (1, 92) = 14.920, $P < 0.001$	Bonferroni's post hoc test CON + Vehicle vs NRBF2 KD + Vehicle, $P = 0.001$; CON + BafA1 vs NRBF2 KD + BafA1, $P < 0.001$; CON + Vehicle vs CON + BafA1, $P < 0.001$; NRBF2 KD + Vehicle vs NRBF2 KD + BafA1, $P > 0.999$	CON + Vehicle 32.320 ± 2.153 CON + BafA1 55.143 ± 4.809 NRBF2 KD + Vehicle 18.760 ± 1.740 NRBF2 KD + BafA1 20.520 ± 1.829
5k: RFP-LC3 puncta in NRBF2 KD aNSCs CON + Vehicle ($n = 25$) CON + BafA1 ($n = 21$) NRBF2 KD + Vehicle ($n = 25$) NRBF2 KD + BafA1 ($n = 25$)	Two-way ANOVA NRBF2 KD: F (1, 92) = 6.010, $P = 0.016$ BafA1: F (1, 92) = 104.600, $P < 0.001$ NRBF2 KD × BafA1: F (1, 92) = 6.824, $P = 0.011$	Bonferroni's post hoc test CON + Vehicle vs NRBF2 KD + Vehicle, $P < 0.001$; CON + BafA1 vs NRBF2 KD + BafA1, $P < 0.001$; CON + Vehicle vs CON + BafA1,	CON + Vehicle 48.760 ± 2.727 CON + BafA1 65.143 ± 5.647 NRBF2 KD + Vehicle 24.120 ± 2.001 NRBF2 KD + BafA1 23.600 ± 2.129

		$P = 0.001$; NRBF2 KD + Vehicle vs NRBF2 KD + BafA1, $P > 0.999$	
6b: SAR405-SIT Vehicle + CON ($n = 10$) SAR405 + CON ($n = 10$) Vehicle + SSDS ($n = 9$) SAR405 + SSDS ($n = 12$)	Two-way ANOVA SSDS: F (1, 37) = 13.830, $P = 0.001$ SAR405: F (1, 37) = 12.880, $P = 0.001$ SSDS × SAR405: F (1, 37) = 7.686, $P = 0.009$	Bonferroni's post hoc test CON + Vehicle vs SSDS + Vehicle, $P > 0.999$; CON + SAR405 vs SSDS + SAR405, $P < 0.001$; Vehicle + CON vs SAR405 + CON, $P > 0.999$; Vehicle + SSDS vs SAR405 + SSDS, $P < 0.001$	Vehicle + CON 1.282 ± 0.110 SAR405 + CON 1.180 ± 0.128 Vehicle + SSDS 1.194 ± 0.094 SAR405 + SSDS 0.496 ± 0.093
6c: SAR405-SPT Vehicle + CON ($n = 10$) SAR405 + CON ($n = 10$) Vehicle + SSDS ($n = 10$) SAR405 + SSDS ($n = 12$)	Two-way ANOVA SSDS: F (1, 38) = 10.480, $P = 0.003$ SAR405: F (1, 38) = 6.361, $P = 0.016$ SSDS × SAR405: F (1, 38) = 7.100, $P = 0.011$	Bonferroni's post hoc test CON + Vehicle vs SSDS + Vehicle, $P > 0.999$; CON + SAR405 vs SSDS + SAR405, $P = 0.001$; Vehicle + CON vs SAR405 + CON, $P > 0.999$; Vehicle + SSDS vs SAR405 + SSDS, $P < 0.001$	Vehicle + CON 85.043 ± 1.446 SAR405 + CON 83.168 ± 2.141 Vehicle + SSDS 85.510 ± 1.832 SAR405 + SSDS 66.210 ± 5.028
6d: SAR405-TST Vehicle + CON ($n = 10$) SAR405 + CON ($n = 10$) Vehicle + SSDS ($n = 10$) SAR405 + SSDS ($n = 12$)	Two-way ANOVA SSDS: F (1, 38) = 6.871, $P = 0.013$ SAR405: F (1, 38) = 7.541, $P = 0.009$ SSDS × SAR405: F (1, 38) = 3.228, $P = 0.080$	Bonferroni's post hoc test CON + Vehicle vs SSDS + Vehicle, $P > 0.999$; CON + SAR405 vs SSDS + SAR405, $P = 0.004$; Vehicle + CON vs SAR405 + CON,	Vehicle + CON 98.007 ± 9.866 SAR405 + CON 111.748 ± 10.494 Vehicle + SSDS 113.827 ± 22.075 SAR405 + SSDS 187.446 ± 18.985

		$P > 0.999$; Vehicle + SSDS vs SAR405 + SSDS, $P = 0.006$	
6e: SAR405-FST Vehicle + CON ($n = 10$) SAR405 + CON ($n = 10$) Vehicle + SSDS ($n = 9$) SAR405 + SSDS ($n = 12$)	Two-way ANOVA SSDS: F (1, 37) = 11.350, $P = 0.002$ SAR405: F (1, 37) = 7.692, $P = 0.009$ SSDS × SAR405: F (1, 37) = 1.728, $P = 0.197$	Bonferroni's post hoc test CON + Vehicle vs SSDS + Vehicle, $P = 0.545$; CON + SAR405 vs SSDS + SAR405, $P = 0.010$; Vehicle + CON vs SAR405 + CON, $P = 0.315$; Vehicle + SSDS vs SAR405 + SSDS, $P = 0.004$	Vehicle + CON 83.174 ± 12.726 SAR405 + CON 105.786 ± 11.063 Vehicle + SSDS 99.228 ± 13.168 SAR405 + SSDS 150.763 ± 7.459
6f: SAR405-OFT Vehicle + CON ($n = 10$) SAR405 + CON ($n = 10$) Vehicle + SSDS ($n = 9$) SAR405 + SSDS ($n = 12$)	Two-way ANOVA SSDS: F (1, 37) = 0.272, $P = 0.605$ SAR405: F (1, 37) = 0.683, $P = 0.414$ SSDS × SAR405: F (1, 37) = 0.224, $P = 0.639$	Bonferroni's post hoc test CON + Vehicle vs SSDS + Vehicle, $P > 0.999$; CON + SAR405 vs SSDS + SAR405, $P = 0.694$; Vehicle + CON vs SAR405 + CON, $P = 0.979$; Vehicle + SSDS vs SAR405 + SSDS, $P > 0.999$	Vehicle + CON 34.494 ± 2.123 SAR405 + CON 32.295 ± 2.338 Vehicle + SSDS 35.276 ± 2.714 SAR405 + SSDS 35.168 ± 1.754
6h: LC3-II expression in the DG of SAR405-treated mice Vehicle + SSDS ($n = 7$) SAR405 + SSDS ($n = 7$)	Unpaired t test t = 2.440, $P = 0.031$		Vehicle + SSDS 1.000 ± 0.116 SAR405 + SSDS 0.675 ± 0.066
6i: p62 expression in the DG of SAR405-treated mice Vehicle + SSDS ($n = 7$) SAR405 + SSDS ($n = 7$)	Unpaired t test t = 2.453, $P = 0.030$		Vehicle + SSDS 1.000 ± 0.077 SAR405 + SSDS 1.386 ± 0.138
6l: BrdU$^+$Sox2$^+$GFAP$^+$	Unpaired t test		Vehicle + SSDS

RGLs in the DG of SAR405-treated mice Vehicle + SSDS ($n = 4$) SAR405 + SSDS ($n = 4$) BrdU$^+$DCX$^+$ neuroblasts in DG of SAR405-treated mice Vehicle + SSDS ($n = 6$) SAR405 + SSDS ($n = 6$)	t = 3.720, $P = 0.010$ Unpaired t test t = 3.938, $P = 0.003$		1380.000 ± 50. 867 SAR405 + SSDS 776.250 ± 154.115 Vehicle + SSDS 1168.333 ± 61.936 SAR405 + SSDS 825.000 ± 61.360
7b: cKD-SPT CON ($n = 8$) cKD ($n = 10$)	Unpaired t test t = 3.505, $P = 0.003$		CON 88.712 ± 2.643 cKD 72.238 ± 3.621
7c: cKD-TST CON ($n = 8$) cKD ($n = 10$)	Unpaired t test t = 2.595, $P = 0.020$		CON 98.053 ± 19.978 cKD 151.101 ± 9.050
7d: cKD-FST CON ($n = 8$) cKD ($n = 10$)	Unpaired t test t = 3.890, $P = 0.001$		CON 50.743 ± 13.892 cKD 134.207 ± 15.610
7e: cKD-OFT: total distance CON ($n = 8$) cKD ($n = 10$)	Unpaired t test t = 0.661, $P = 0.518$		CON 39.939 ± 2.223 cKD 37.470 ± 2.819
7h: BrdU$^+$Sox2$^+$ GFAP$^+$ RGLs of NRBF2 cKD mice CON ($n = 4$) cKD ($n = 4$) BrdU$^+$DCX$^+$ neuroblasts of NRBF2 cKD mice CON ($n = 4$) cKD ($n = 4$) BrdU$^+$NeuN$^+$ neurons of NRBF2 cKD mice CON ($n = 4$) cKD ($n = 4$)	Unpaired t test t = 5.966, $P = 0.001$ Unpaired t test t = 5.832, $P = 0.001$ Unpaired t test t = 4.681, $P = 0.003$		CON 1380.00 ± 113.80 cKD 615.00 ± 59.09 CON 1412.50 ± 140.26 cKD 590.00 ± 14.72 CON 1267.50 ± 108.94 cKD 723.75 ± 40.33
7i: Membrane potential CON ($n = 26$) cKD ($n = 22$)	Unpaired t test t = 0.105, $P = 0.917$		CON -63.148 ± 1.358 cKD -63.329 ± 0.934

7j: Membrane resistance CON (n = 26) cKD (n = 22)	Unpaired t test t = 1.576, P = 0.122		CON 238.513 ± 20.959 cKD 189.985 ± 22.531
7l: AP frequency CON (n = 26) cKD (n = 22)	Two-way ANOVA Current injection: F (5, 276) = 39.680, P < 0.001 cKD: F (1, 276) = 41.910, P < 0.001 Current injection × cKD: F (5, 276) = 1.725, P < 0.128	Bonferroni's post hoc test 0 pA: CON vs cKD, P > 0.999 30 pA: CON vs cKD, P = 0.632 60 pA: CON vs cKD, P = 0.042 90 pA: CON vs cKD, P = 0.002 120 pA: CON vs cKD, P = 0.001 150 pA: CON vs cKD, P = 0.002	0 pA: CON 0.654 ± 0.277 cKD 0.000 ± 0.000 30 pA: CON 2.462 ± 0.633 cKD 0.682 ± 0.363 60 pA: CON 4.885 ± 0.860 cKD 1.909 ± 0.714 90 pA: CON 7.423 ± 0.933 cKD 3.500 ± 0.930 120 pA: CON 9.808 ± 0.925 cKD 5.591 ± 1.023 150 pA: CON 11.115 ± 0.982 cKD 7.091 ± 0.835
7m: AP threshold CON (n = 26) cKD (n = 22)	Unpaired t test t = 3.110, P = 0.003		CON -45.126 ± 0.717 cKD -42.201 ± 0.572
8b: cOE-SIT CON + AAV-mCherry (n = 11) CON + AAV-NRBF2 (n = 11) CSDS + AAV-mCherry (n = 13) CSDS + AAV-NRBF2 (n = 12)	Two-way ANOVA Stress: F (1, 43) = 19.340, P < 0.001 AAV-NRBF2: F (1, 43) = 80.630, P < 0.001 Stress × AAV-NRBF2: F (1, 43) = 18.320, P < 0.001	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, P < 0.001; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, P = 0.004; CON + AAV-mCherry vs CON + AAV-NRBF2, P > 0.999; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, P < 0.001	CON + AAV-mCherry 1.143 ± 0.074 CON + AAV-NRBF2 1.151 ± 0.060 CSDS + AAV-mCherry 0.200 ± 0.056 CSDS + AAV-NRBF2 0.817 ± 0.089

cOE-TST CON + AAV-mCherry ($n = 12$) CON + AAV-NRBF2 ($n = 12$) CSDS + AAV-mCherry ($n = 13$) CSDS + AAV-NRBF2 ($n = 13$)	Two-way ANOVA Stress: F (1, 46) = 13.130, $P = 0.001$ AAV-NRBF2: F (1, 46) = 11.680, $P = 0.001$ Stress × AAV-NRBF2: F (1, 46) = 2.530, $P = 0.119$	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, $P = 0.002$; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, $P = 0.406$; CON + AAV-mCherry vs CON + AAV-NRBF2, $P = 0.331$; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, $P = 0.001$	CON + AAV-mCherry 103.526 ± 11.920 CON + AAV-NRBF2 80.170 ± 14.517 CSDS + RV-mCherry 161.060 ± 8.434 CSDS + AAV-NRBF2 101.159 ± 10.771
cOE-FST CON + AAV-mCherry ($n = 12$) CON + AAV-NRBF2 ($n = 12$) CSDS + AAV-mCherry ($n = 12$) CSDS + AAV-NRBF2 ($n = 12$)	Two-way ANOVA Stress: F (1, 44) = 13.330, $P = 0.001$ AAV-NRBF2: F (1, 44) = 13.080, $P = 0.001$ Stress ×AAV-NRBF2: F (1, 46) = 4.659, $P = 0.036$	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, $P < 0.001$; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, $P = 0.616$; CON + AAV-mCherry vs CON + AAV-NRBF2, $P = 0.594$; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, $P < 0.001$	CON + AAV-mCherry 64.657 ± 13.441 CON + AAV-NRBF2 45.852 ± 11.272 CSDS + AAV-mCherry 135.372 ± 14.175 CSDS + AAV-NRBF2 62.230 ± 11.212
8d: BrdU$^+$Sox2$^+$GFAP$^+$ RGLs of CSDS-exposed Nestin-CreER^{T2} mice CON + AAV-mCherry ($n = 4$) CON + AAV-NRBF2	Two-way ANOVA Stress: F (1, 12) = 2.633, $P = 0.131$ AAV-NRBF2: F (1, 12) = 22.940, $P < 0.001$	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, $P = 0.001$;	CON + AAV-mCherry 1327.5 ± 61.695 CON + AAV-NRBF2 1290.0 ± 147.097

($n = 4$) CSDS + AAV-mCherry ($n = 4$) CSDS + AAV-NRBF2 ($n = 4$)	Stress × AAV-NRBF2: F (1, 12) = 4.075, $P = 0.067$	CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, $P = 0.148$; CON + AAV-mCherry vs CON + AAV-NRBF2, $P > 0.999$; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, $P = 0.049$	CSDS + AAV-mCherry 682.5 ± 49.181 CSDS + AAV-NRBF2 1027.5 ± 89.687
BrdU$^+$DCX$^+$ neuroblasts of CSDS-exposed Nestin-CreER^{T2} mice CON + AAV-mCherry ($n = 4$) CON + AAV-NRBF2 ($n = 4$) CSDS + AAV-mCherry ($n = 4$) CSDS + AAV-NRBF2 ($n = 4$)	Two-way ANOVA Stress: F (1, 12) = 4.796, $P = 0.049$ AAV-NRBF2: F (1, 12) = 32.910, $P < 0.001$ Stress × AAV-NRBF2: F (1, 12) = 3.657, $P = 0.080$	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, $P < 0.001$; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, $P = 0.038$ CON + AAV-mCherry vs CON + AAV-NRBF2, $P > 0.999$; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, $P = 0.027$	CON + AAV-mCherry 1481.25 ± 133.094 CON + AAV-NRBF2 1515.00 ± 126.541 CSDS + AAV-mCherry 551.25 ± 58.216 CSDS + AAV-NRBF2 1050.00 ± 148.366
BrdU$^+$NeuN$^+$ neurons of CSDS-exposed Nestin-CreER^{T2} mice CON + AAV-mCherry ($n = 5$) CON + AAV-NRBF2 ($n = 5$) CSDS + AAV-mCherry ($n = 5$) CSDS + AAV-NRBF2	Two-way ANOVA Stress: F (1, 15) = 6.116, $P = 0.026$ AAV-NRBF2: F (1, 15) = 11.860, $P = 0.004$ Stress × AAV-NRBF2: F (1, 15) = 5.464, $P = 0.034$	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, $P = 0.002$; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, $P = 0.918$; CON + AAV-	CON + AAV-mCherry 942.00 ± 68.476 CON + AAV-NRBF2 951.00 ± 51.439 CSDS + AAV-mCherry 558.00 ± 56.405 CSDS + AAV-NRBF2 877.50 ± 91.754

($n = 4$)		mCherry vs CON + AAV-NRBF2, $P > 0.999$; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, $P = 0.010$	
8h. Relative mRNA level in the DG of CSDS-exposed mice			
Hbb-b1 CON ($n = 6$) CSDS ($n = 8$)	Unpaired t test t = 3.810, $P = 0.003$		CON 1.013 ± 0.070 CSDS 3.086 ± 0.464
Nnt CON ($n = 5$) CSDS ($n = 8$)	Unpaired t test t = 3.237, $P = 0.008$		CON 0.905 ± 0.124 CSDS 1.273 ± 0.048
Pou4f3 CON ($n = 6$) CSDS ($n = 6$)	Unpaired t test t = 2.335, $P = 0.042$		CON 1.083 ± 0.169 CSDS 2.148 ± 0.424
Apoa1 CON ($n = 6$) CSDS ($n = 6$)	Unpaired t test t = 2.904, $P = 0.016$		CON 1.008 ± 0.054 CSDS 1.832 ± 0.278
Mfge8 CON ($n = 6$) CSDS ($n = 7$)	Unpaired t test t = 3.369, $P = 0.006$		CON 1.006 ± 0.047 CSDS 0.813 ± 0.034
Fabp7 CON ($n = 6$) CSDS ($n = 7$)	Unpaired t test t = 3.865, $P = 0.003$		CON 1.012 ± 0.073 CSDS 0.536 ± 0.095
Farp2 CON ($n = 6$) CSDS ($n = 7$)	Unpaired t test t = 3.621, $P = 0.004$		CON 1.005 ± 0.043 CSDS 0.767 ± 0.048
P3h1 CON ($n = 6$) CSDS ($n = 8$)	Unpaired t test t = 2.282, $P = 0.042$		CON 1.014 ± 0.080 CSDS 0.807 ± 0.051
8i: *Mfge8* mRNA level in DG of CSDS-exposed	Two-way ANOVA Stress: F (1, 20) =	Bonferroni's post hoc test	CON + AAV-mCherry 1.007 ± 0.053

mice CON + AAV-mCherry (*n* = 6) CON + AAV-NRBF2 (*n* = 6) CSDS + AAV-mCherry (*n* = 6) CSDS + AAV-NRBF2 (*n* = 6)	52.090, *P* < 0.001 AAV-NRBF2: F (1, 20) = 2.427, *P* = 0.135 Stress × AAV-NRBF2: F (1, 20) = 19.980, *P* < 0.001	CON + AAV-mCherry vs CSDS + AAV-mCherry, *P* = 0.001; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, *P* = 0.105; CON + AAV-mCherry vs CON + AAV-NRBF2, *P* = 0.133; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, *P* < 0.001	CON + AAV-NRBF2 1.157 ± 0.047 CSDS + AAV-mCherry 0.676 ± 0.032 CSDS + AAV-NRBF2 1.317 ± 0.077
8j: *Fabp7* mRNA level in DG of CSDS-exposed mice CON + AAV-mCherry (*n* = 5) CON + AAV-NRBF2 (*n* = 5) CSDS + AAV-mCherry (*n* = 6) CSDS + AAV-NRBF2 (*n* = 6)	Two-way ANOVA Stress: F (1, 18) = 33.070, *P* < 0.001 Virus: F (1, 18) = 1.441, *P* = 0.246 Stress × virus: F (1, 18) = 8.044, *P* = 0.011	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, *P* = 0.021; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, *P* = 0.525; CON + AAV-mCherry vs CON + AAV-NRBF2, *P* = 0.128; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, *P* < 0.001	CON + AAV-mCherry 1.042 ± 0.036 CON + AAV-NRBF2 1.217 ± 0.056 CSDS + AAV-mCherry 0.798 ± 0.046 CSDS + AAV-NRBF2 1.316 ± 0.082
8k: *Hbb-b1* mRNA level in DG of CSDS-exposed mice CON + AAV-mCherry (*n* = 6) CON + AAV-NRBF2 (*n* = 6) CSDS + AAV-mCherry (*n* = 6)	Two-way ANOVA Stress: F (1, 20) = 84.790, *P* < 0.001 AAV-NRBF2: F (1, 20) = 12.140, *P* = 0.002 Stress × AAV-NRBF2: F (1, 20) = 28.930, *P* < 0.001	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, *P* < 0.001; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2,	CON + AAV-mCherry 1.005 ± 0.047 CON + AAV-NRBF2 0.814 ± 0.031 CSDS + AAV-mCherry 1.448 ± 0.075 CSDS + AAV-NRBF2 0.720 ± 0.034

CSDS + AAV-NRBF2 (*n* = 6)		*P* = 0.391; CON + AAV-mCherry vs CON + AAV-NRBF2, *P* = 0.027; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, *P* < 0.001	
8l: *Nnt* mRNA level in DG of CSDS-exposed mice CON + AAV-mCherry (*n* = 6) CSDS + AAV-mCherry (*n* = 5) CON + AAV-NRBF2 (*n* = 6) CSDS + AAV-NRBF2 (*n* = 6)	Two-way ANOVA Stress: F (1, 19) = 25.980, *P* < 0.001 AAV-NRBF2: F (1, 19) = 17.300, *P* = 0.001 Stress × AAV-NRBF2: F (1, 19) = 5.051, *P* = 0.037	Bonferroni's post hoc test CON + AAV-mCherry vs CSDS + AAV-mCherry, *P* = 0.001; CON + AAV-NRBF2 vs CSDS + AAV-NRBF2, *P* = 0.364; CON + AAV-mCherry vs CON + AAV-NRBF2, *P* = 0.106; CSDS + AAV-mCherry vs CSDS + AAV-NRBF2, *P* < 0.001	CON + AAV-mCherry 1.014 ± 0.072 CON + AAV-NRBF2 0.888 ± 0.024 CSDS + AAV-mCherry 1.297 ± 0.023 CSDS + AAV-NRBF2 0.973 ± 0.031
S1b: CSDS-social interaction time CON (*n* = 12) CSDS (*n* = 12)	Two-way ANOVA Stress: F (1, 44) = 21.950, *P* < 0.001	Bonferroni's post hoc test Target: CON vs CSDS, *P* < 0.001	No target: CON 52.658 ± 4.705 CSDS 51.783 ± 6.150 Target: CON 71.075 ± 3.474 CSDS 26.158 ± 4.849
S1c: CSDS-SIT CON (*n* = 11) CSDS (*n* = 12)	Unpaired t test t = 8.607, *P* < 0.001		CON 1.258 ± 0.065 CSDS 0.492 ± 0.061
S1d: CSDS-SPT CON (*n* = 12) CSDS (*n* = 12)	Unpaired t test t = 8.726, *P* < 0.001		CON 87.131 ± 1.214 CSDS 66.962 ± 1.967
S1e: CSDS-TST CON (*n* = 11) CSDS (*n* = 11)	Unpaired t test t = 3.597, *P* = 0.002		CON 88.378 ± 9.392 CSDS 142.492 ± 11.755

S1f: CSDS-FST CON ($n = 11$) CSDS ($n = 11$)	Unpaired t test t = 3.900, $P = 0.001$		CON 52.640 ± 9.075 CSDS 125.800 ± 16.410
S1g: N*rbf2* mRNA level in the brain ($n = 4$)			mPFC 1.401 ± 0.185 ACC 1.226 ± 0.046 CPu 1.136 ± 0.044 NAc 1.026 ± 0.115 Amygdala 1.210 ± 0.072 DG 2.338 ± 0.061 CA1 1.757 ± 0.060 CA3 1.609 ± 0.118 VTA 1. 098 ± 0.063 Cerebellum 1.003 ± 0.045 OB 1.045 ± 0.059
1h: *p62* mRNA level in DG in CSDS model CON ($n = 6$) CSDS ($n = 6$)	Unpaired t test t = 2.765, $P = 0.020$		CON 1.025 ± 0.100 CSDS 0.731 ± 0.035
1j: p62 intensity in DG in CSDS model CON ($n = 12$) CSDS ($n = 12$)	Unpaired t test t = 3.274, $P = 0.004$		CON 1.000 ± 0.071 CSDS 0.732 ± 0.040
S1l: VPS34 expression CON ($n = 6$) CSDS ($n = 11$)	Unpaired t test t = 0.521, $P = 0.610$		CON 1.000 ± 0.105 CSDS 1.069 ± 0.079
S1m: Beclin1 expression CON ($n = 6$) CSDS ($n = 11$)	Unpaired t test t = 0.063, $P = 0.951$		CON 1.000 ± 0.067 CSDS 0.995 ± 0.039
S1n: ATG14L expression CON ($n = 6$) CSDS ($n = 11$)	Unpaired t test t = 0.543, $P = 0.595$		CON 1.000 ± 0.080 CSDS 0.959 ± 0.037
S1o: CUS-SPT CON ($n = 11$) CUS ($n = 11$)	Unpaired t test t = 4.009, $P = 0.001$		CON 82.984 ± 2.129 CUS 68.701 ± 2.857
S1p: CUS-TST CON ($n = 11$) CUS ($n = 11$)	Unpaired t test t = 4.812, $P < 0.001$		CON 99.167 ± 11.126 CUS 169.569 ± 9.498
S1q: CUS-FST CON ($n = 11$) CUS ($n = 11$)	Unpaired t test t = 7.143, $P < 0.001$		CON 61.667 ± 11.525 CUS 173.271 ± 10.549

S1r: CORT-SPT CON ($n = 9$) CORT ($n = 11$)	Unpaired t test t = 7.142, $P < 0.001$		CON 84.613 ± 2.227 CORT 50.687 ± 3.877
S1s: CORT-TST CON ($n = 9$) CORT ($n = 11$)	Unpaired t test t = 7.022, $P < 0.001$		CON 84.233 ± 6.947 CORT 188.642 ± 12.145
S1t: CORT-FST CON ($n = 9$) CORT ($n = 11$)	Unpaired t test t = 8.921, $P < 0.001$		CON 53.811 ± 8.842 CORT 169.851 ± 9.266
S3b: BrdU$^+$Sox2$^+$GFAP$^+$ RGLs CON ($n = 5$) CSDS ($n = 5$)	Unpaired t test t = 5.837, $P = 0.001$		CON 1320.0 ± 82.432 CSDS 717.0 ± 62.282
S3d: BrdU$^+$DCX$^+$ neuroblasts CON ($n = 5$) CSDS ($n = 5$)	Unpaired t test t = 6.113, $P = 0.001$		CON 1418.0 ± 87.943 CSDS 734.0 ± 69.181
S3f: Dendritic length of newborn neurons CON ($n = 42$) CSDS ($n = 38$)	Unpaired t test t = 7.228, $P < 0.001$		CON 982.5 ± 31.151 CSDS 662.2 ± 31.378
S3f: Number of crossings CON ($n = 42$) CSDS ($n = 38$)	Repeated measures ANOVA Stress: F (1, 78) = 43.980, $P < 0.001$		
S4h: Spine density of newborn neurons CON ($n = 50$) CSDS ($n = 50$)	Unpaired t test t = 10.090, $P < 0.001$		CON 21.121 ± 0.947 CSDS 10.505 ± 0.459
S4b. NRBF2 protein expression after virus injection CON + LV-vector ($n = 8$) CON + LV-NRBF2 ($n = 8$) CSDS + LV-vector ($n = 11$) CSDS + LV-NRBF2 ($n = 9$)	Two-way ANOVA Stress: F (1, 32) = 109.800, $P < 0.001$ Virus: F (1, 32) = 5.581, $P = 0.024$ Stress × Virus: F (1, 32) = 15.510, $P < 0.001$	Bonferroni's post hoc test CON + AAV-mCherry vs CON + AAV-NRBF2, $P < 0.001$; CSDS + AAV-VECTOR vs CSDS + AAV-NRBF2, $P < 0.001$	CON + LV-vector 1.000 ± 0.050 CON + LV-NRBF2 2.528 ± 0.321 CSDS + LV-vector 0.632 ± 0.072 CSDS + LV-NRBF2 4.001 ± 0.354
S4c. LC3-II protein expression after virus injection	Two-way ANOVA Stress: F (1, 33) = 12.710, $P = 0.001$	Bonferroni's post hoc test CON + LV-vector	CON + LV-vector 1.000 ± 0.056 CON + LV-NRBF2

CON + LV-vector (*n* = 9) CON + LV-NRBF2 (*n* = 9) CSDS + LV-vector (*n* = 10) CSDS + LV-NRBF2 (*n* = 9)	Virus: F (1, 33) = 6.777, *P* = 0.014 Stress × Virus: F (1, 33) =11.300, *P* = 0.002	vs CSDS + LV-vector, *P* < 0.001; CON + LV-NRBF2 vs CSDS + LV-NRBF2, *P* > 0.999; CON + LV-vector vs CON + LV-NRBF2, *P* = 0.999; CSDS + LV-vector vs CSDS + LV-NRBF2, *P* < 0.001	1.010 ± 0.065 CSDS + LV-vector 0.691 ± 0.039 CSDS + LV-NRBF2 1.050 ± 0.046
S4d. p62 protein expression after virus injection CON + LV-vector (*n* = 9) CON + LV-NRBF2 (*n* = 9) CSDS + LV-vector (*n* = 10) CSDS + LV-NRBF2 (*n* = 8)	Two-way ANOVA Stress: F (1, 32) = 11.730, *P* = 0.002 Virus: F (1, 32) = 12.610, *P* = 0.001 Stress × Virus: F (1, 32) =0.001, *P* = 0.980	Bonferroni's post hoc test CON + LV-vector vs CSDS + LV-vector, *P* = 0.028; CON + LV-NRBF2 vs CSDS + LV-NRBF2, *P* = 0.042; CON + LV-vector vs CON + LV-NRBF2, *P* = 0.040; CSDS + LV-vector vs CSDS + LV-NRBF2, *P* = 0.045	CON + LV-vector 1.000 ± 0.052 CON + LV-NRBF2 0.790 ± 0.098 CSDS + LV-vector 0.782 ± 0.027 CSDS + LV-NRBF2 0.576 ± 0.044
S5b: TMZ-SIT CON + LV-vector + VEH (*n* = 9) CON + LV-vector + TMZ (*n* = 9) CON + LV-NRBF2 + VEH (*n* = 8) CON + LV-NRBF2 + TMZ (*n* = 10) CSDS + LV-vector + VEH (*n* = 9) CSDS + LV-vector + TMZ (*n* = 9) CSDS + LV-NRBF2 + VEH (*n* = 9) CSDS + LV-NRBF2 + TMZ (*n* = 10)	One-way ANOVA F (7, 65) = 7.949, *P* < 0.001	Tukey's post hoc test CON + LV-vector+ VEH vs CSDS + LV-vector + VEH, *P* = 0.002; CSDS + LV-vector + VEH vs CSDS + LV-NRBF2 + VEH, *P* = 0.011 CSDS + LV-NRBF2 + TMZ vs CSDS + LV-NRBF2 + VEH, *P* = 0.035	CON + LV-vector + VEH 1.145 ± 0.128 CON + LV-vector + TMZ 1.203 ± 0.196 CON + LV-NRBF2 + VEH 1.277 ± 0.211 CON + LV-NRBF2 + TMZ 0.914 ± 0.102 CSDS + LV-vector + VEH 0.234 ± 0.071 CSDS + LV-vector + TMZ 0.397 ± 0.174 CSDS + LV-NRBF2 + VEH 1.017 ± 0.199 CSDS + LV-NRBF2 + TMZ 0.341 ± 0.076
S5b: TMZ-TST	One-way ANOVA	Tukey's post hoc	CON + LV-vector +

CON + LV-vector + VEH ($n = 9$) CON + LV-vector + TMZ ($n = 9$) CON + LV-NRBF2 + VEH ($n = 9$) CON + LV-NRBF2 + TMZ ($n = 10$) CSDS + LV-vector + VEH ($n = 9$) CSDS + LV-vector + TMZ ($n = 9$) CSDS + LV-NRBF2 + VEH ($n = 9$) CSDS + LV-NRBF2 + TMZ ($n = 10$)	F (7, 66) = 10.110, $P < 0.001$	test CON + LV-vector+ VEH vs CSDS + LV-vector + VEH, $P = 0.004$ CSDS + LV-vector + VEH vs CSDS + LV-NRBF2 + VEH, $P = 0.004$ CSDS + LV-NRBF2 + TMZ vs CSDS + LV-NRBF2 + VEH, $P < 0.001$	VEH 86.624 ± 9.765 CON + LV-vector + TMZ 114.208 ± 9.246 CON + LV-NRBF2 + VEH 99.155 ± 10.552 CON + LV-NRBF2 + TMZ 122.171 ± 12.034 CSDS + LV-vector + VEH 146.749 ± 5.884 CSDS + LV-vector + TMZ 170.467 ± 13.602 CSDS + LV-NRBF2 + VEH 86.151 ± 11.704 CSDS + LV-NRBF2 + TMZ 165.383 ± 9.699
S5b: TMZ-FST CON + LV-vector + VEH ($n = 9$) CON + LV-vector + TMZ ($n = 9$) CON + LV-NRBF2 + VEH ($n = 9$) CON + LV-NRBF2 + TMZ ($n = 10$) CSDS + LV-vector + VEH ($n = 9$) CSDS + LV-vector + TMZ ($n = 8$) CSDS + LV-NRBF2 + VEH ($n = 9$) CSDS + LV-NRBF2 + TMZ ($n = 10$)	One-way ANOVA F (7, 65) = 10.840, $P < 0.001$	Tukey's post hoc test CON + LV-vector + VEH vs CSDS + LV-vector + VEH, $P = 0.001$ CSDS + LV-vector + VEH vs CSDS + LV-NRBF2 + VEH, $P = 0.005$ CSDS + LV-NRBF2 + TMZ vs CSDS + LV-NRBF2 + VEH, $P = 0.007$	CON + LV-vector + VEH 41.333 ± 13.430 CON + LV-vector + TMZ 89.972 ± 15.272 CON + LV-NRBF2 + VEH 46.064 ± 12.011 CON + LV-NRBF2 + TMZ 71.342 ± 15.044 CSDS + LV-vector + VEH 138.239 ± 13.509 CSDS + LV-vector + TMZ 177.154 ± 17.354 CSDS + LV-NRBF2 + VEH 54.624 ± 15.071 CSDS + LV-NRBF2 + TMZ 133.287 ± 16.479
S5b: TMZ-OFT CON + LV-vector + VEH ($n = 9$) CON + LV-vector + TMZ ($n = 9$) CON + LV-NRBF2 + VEH ($n = 9$) CON + LV-NRBF2 + TMZ ($n = 10$) CSDS + LV-vector +	One-way ANOVA F (7, 66) = 0.698, $P = 0.674$	Tukey's post hoc test CON + LV-vector + VEH vs CSDS + LV-vector + VEH, $P > 0.999$ CSDS + LV-vector + VEH vs CSDS + LV-NRBF2 + VEH, $P > 0.999$	CON + LV-vector + VEH 24.707 ± 2.566 CON + LV-vector + TMZ 24.642 ± 2.224 CON + LV-NRBF2 + VEH 29.094 ± 3.654 CON + LV-NRBF2 + TMZ 28.915 ± 1.577 CSDS + LV-vector + VEH 25.036 ± 2.496

VEH ($n = 9$) CSDS + LV-vector + TMZ ($n = 9$) CSDS + LV-NRBF2 + VEH ($n = 9$) CSDS + LV-NRBF2 + TMZ ($n = 10$)		CSDS + LV-NRBF2 + TMZ vs CSDS + LV-NRBF2 + VEH, $P > 0.999$	CSDS + LV-vector + TMZ 24.319 ± 2.717 CSDS + LV-NRBF2 + VEH 24.859 ± 2.857 CSDS + LV-NRBF2 + TMZ 23.720 ± 2.029
S5d: TMZ-BrdU$^+$ cells CON + LV-vector + VEH ($n = 3$) CSDS + LV-vector + VEH ($n = 3$) CSDS + LV-NRBF2 + VEH ($n = 3$) CSDS + LV-NRBF2 + TMZ ($n = 3$)	One-way ANOVA F (3, 8) = 19.420, $P = 0.001$	Tukey's post hoc test CON + LV-vector + VEH vs CSDS + LV-vector + VEH, $P = 0.001$ CSDS + LV-NRBF2 + VEH vs CSDS + LV-NRBF2 + TMZ, $P = 0.008$ CSDS + LV-NRBF2 + TMZ vs CSDS + LV-NRBF2 + VEH, $P = 0.007$	CON + LV-vector + VEH 2255.0 ± 152.56 CSDS + LV-vector + VEH 1070.0 ± 72.11 CSDS + LV-NRBF2 + VEH 1965.0 ± 105.36 CSDS + LV-NRBF2 + TMZ 1060.0 ± 195.64
S5d: TMZ-BrdU$^+$DCX$^+$ neuroblasts CON + LV-vector + VEH ($n = 3$) CSDS + LV-vector + VEH ($n = 3$) CSDS + LV-NRBF2 + VEH ($n = 3$) CSDS + LV-NRBF2 + TMZ ($n = 3$)	One-way ANOVA F (3, 8) = 28.090, $P < 0.001$	Tukey's post hoc test CON + LV-vector + VEH vs CSDS + LV-vector + VEH, $P < 0.001$ CSDS + LV-vector + VEH vs CSDS + LV-NRBF2 + VEH, $P = 0.005$ CSDS + LV-NRBF2 + TMZ vs CSDS + LV-NRBF2 + VEH, $P = 0.003$	CON + LV-vector + VEH 1300.0 ± 72.110 CSDS + LV-vector + VEH 510.0 ± 78.100 CSDS + LV-NRBF2 + VEH 1047.0 ± 87.620 CSDS + LV-NRBF2 + TMZ 456.7 ± 72.190
S5d: TMZ- BrdU$^+$NeuN$^+$ neuron CON + LV-vector + VEH ($n = 3$) CSDS + LV-vector + VEH ($n = 3$) CSDS + LV-NRBF2 + VEH ($n = 3$)	One-way ANOVA F (3, 8) = 136.500, $P < 0.001$	Tukey's post hoc test CON + LV-vector + VEH vs CSDS + LV-vector + VEH, $P < 0.001$ CSDS + LV-vector + VEH vs CSDS +	CON + LV-vector + VEH 1256.7 ± 37.118 CSDS + LV-vector + VEH 426.7 ± 33.830 CSDS + LV-NRBF2 + VEH 883.3 ± 48.419 CSDS + LV-NRBF2 + TMZ 383.3 ± 12.019

CSDS + LV-NRBF2 + TMZ (*n* = 3)		LV-NRBF2 + VEH, *P* < 0.001 CSDS + LV-NRBF2 + TMZ vs CSDS + LV-NRBF2 + VEH, *P* < 0.001	
S6a: NRBF2$^{-/-}$ mice-OFT: central entries WT (*n* = 10) NRBF2$^{-/-}$ (*n* = 9)	Unpaired t test t = 0.444, *P* = 0.663		WT 73.400 ± 7.820 NRBF2$^{-/-}$ 68.889 ± 6.235
S6b: NRBF2$^{-/-}$ mice-OFT: central duration WT (*n* = 10) NRBF2$^{-/-}$ (*n* = 9)	Unpaired t test t = 0.380, *P* = 0.709		WT 105.180 ± 14.991 NRBF2$^{-/-}$ 96.444 ± 17.591
S6c: NRBF2$^{-/-}$ mice-OFT: central distance WT (*n* = 10) NRBF2$^{-/-}$ (*n* = 9)	Unpaired t test t = 0.286, *P* = 0.779		WT 5.412 ± 0.451 NRBF2$^{-/-}$ 5.227 ± 0.462
S7b: Identification of aNSCs in vitro aNSCs (*n* = 6)	Unpaired t test t = 8.157, *P* < 0.001		Nestin 98.250 ± 0.540 Sox2 97.170 ± 0.453 NestinSox2 96.690 ± 0.556
S7d: NRBF2 protein expression in NRBF2-deficient aNSCs LV-GFP (*n* = 6) LV-sh*Nrbf2* (*n* = 6)	Unpaired t test t = 8.157, *P* < 0.001		LV-GFP 1.000 ± 0.058 LV-shNrbf2 0.479 ± 0.020
S7d: LC3-II protein expression in NRBF2-deficient aNSCs LV-GFP (*n* = 6) LV-sh*Nrbf2* (*n* = 6)	Unpaired t test t = 5.532, *P* < 0.001		LV-GFP 1.000 ± 0.036 LV-sh*Nrbf2* 0.681 ± 0.045
S7d: p62 protein expression in NRBF2-deficient aNSCs LV-GFP (*n* = 6) LV-sh*Nrbf2* (*n* = 6)	Unpaired t test t = 4.917, *P* = 0.001		LV-GFP 1.000 ± 0.052 LV-sh*Nrbf2* 0.708 ± 0.029
S7f: neurospheres in NRBF2-deficient aNSCs Number LV-GFP (n = 4) LV-sh*Nrbf2* (n = 4)	Unpaired t test t = 4.392, *P* = 0.005		LV-GFP 10.000 ± 0.707 LV-sh*Nrbf2* 6.250 ± 0.479

Diameter LV-GFP (*n* = 4) LV-sh*Nrbf2* (*n* = 4)	Unpaired t test t = 6.847, *P* = 0.001		LV-GFP 205.684 ± 9.796 LV-sh*Nrbf2* 124.240 ± 6.747
S7h: the percent of BrdU$^+$GFP$^+$ cell in NRBF2-deficient aNSCs LV-GFP (*n* = 3) LV-sh*Nrbf2* (*n* = 3)	Unpaired t test t = 6.327, *P* = 0.003		LV-GFP 58.660 ± 3.237 LV-sh*Nrbf2* 33.805 ± 2.225
S7j: the percent of Tuj1$^+$GFP$^+$ cell in NRBF2-deficient aNSCs LV-GFP (*n* = 3) LV-sh*Nrbf2* (*n* = 3)	Unpaired t test t = 5.064, *P* = 0.007		LV-GFP 39.653 ± 0.629 LV-sh*Nrbf2* 27.338 ± 2.349
the percent of GFAP$^+$GFP$^+$ cell in NRBF2-deficient aNSCs LV-GFP (*n* = 3) LV-sh*Nrbf2* (*n* = 3)	Unpaired t test t = 0.390, *P* = 0.717		LV-GFP 35.047 ± 1.393 LV-sh*Nrbf2* 35.737 ± 1.094
S7l: the percent of AC3$^+$GFP$^+$ cell in NRBF2-deficient aNSCs LV-GFP (*n* = 3) LV-sh*Nrbf2* (*n* = 3)	Unpaired t test t = 0.108, *P* = 0.920		LV-GFP 1.268 ± 0.180 LV-sh*Nrbf2* 1.299 ± 0.223
the percent of Tuj1$^+$AC3$^+$GFP$^+$ cells in NRBF2-deficient aNSCs LV-GFP (*n* = 3) LV-sh*Nrbf2* (*n* = 3)	Unpaired t test t = 0.765, *P* = 0.487		LV-GFP 7.902 ± 0.641 LV-sh*Nrbf2* 8.468 ± 0.368
S7n: Cell viability in NRBF2- deficient aNSCs LV-GFP + Vehicle (*n* = 6) LV-GFP + BafA1 (*n* = 6) LV-sh*Nrbf2* + Vehicle (*n* = 6) LV-sh*Nrbf2* + BafA1 (*n* = 6)	Two-way ANOVA LV-sh*Nrbf2*: F (1, 20) = 1.547, *P* = 0.228 BafA1: F (1, 20) = 2.855, *P* = 0.107 LV-sh*Nrbf2* × BafA1: F (1, 20) = 2.352, *P* = 0.141	Bonferroni's post hoc test LV-GFP + Vehicle vs LV-sh*Nrbf2* + Vehicle, *P* = 0.068; LV-GFP + BafA1 vs LV-sh*Nrbf2* + BafA1, *P* > 0.999; LV-GFP + Vehicle vs LV-GFP + BafA1, *P* = 0.127; LV-sh*Nrbf2* +	LV-GFP + Vehicle 100.000 ± 0.567 LV-GFP + BafA1 96.953 ± 1.336 LV-sh*Nrbf2* + Vehicle 96.465 ± 1.299 LV-sh*Nrbf2* + BafA1 96.782 ± 1.009

		Vehicle vs LV-sh*Nrbf2* + BafA1, $P > 0.999$	
S8a: NRBF2 expression in aNSCs treated with LV-GFP or LV-NRBF2 LV-GFP ($n = 6$) LV-NRBF2 ($n = 6$)	Unpaired t test t = 13.360, $P < 0.001$		LV-GFP 1.000 ± 0.109 LV-NRBF2 3.600 ± 0.161
S8c: LC3-II expression in SAR405-treated aNSCs Vehicle + LV-GFP ($n = 6$) Vehicle + LV-NRBF2 ($n = 6$) SAR405 + LV-GFP ($n = 6$) SAR405 + LV-NRBF2 ($n = 6$)	Two-way ANOVA SAR405: F (1, 20) = 19.740, $P < 0.001$ Virus: F (1, 20) = 11.080, $P = 0.003$ SAR405 × Virus: F (1, 20) = 3.428, $P = 0.079$	Bonferroni's post hoc test Vehicle + LV-GFP vs SAR405 + LV-GFP, $P = 0.003$ Vehicle + LV-NRBF2 vs SAR405 + LV-NRBF2, $P = 0.617$ Vehicle + LV-GFP vs Vehicle + LV-NRBF2, $P = 0.164$ SAR405 + LV-GFP vs SAR405 + LV-NRBF2, $P = 0.001$	Vehicle + LV-GFP 1.000 ± 0.067 Vehicle + LV-NRBF2 1.395 ± 0.128 SAR405 + LV-GFP 0.630 ± 0.044 SAR405 + LV-NRBF2 1.080 ± 0.113
S8d: p62 expression in SAR405-treated aNSCs Vehicle + LV-GFP ($n = 6$) Vehicle + LV-NRBF2 ($n = 6$) SAR405 + LV-GFP ($n = 6$) SAR405 + LV-NRBF2 ($n = 6$)	Two-way ANOVA SAR405: F (1, 20) = 22.060, $P < 0.001$ Virus: F (1, 20) = 41.430, $P < 0.001$ SAR405 × Virus: F (1, 20) = 4.173, $P = 0.055$	Bonferroni's post hoc test Vehicle + LV-GFP vs SAR405 + LV-GFP, $P < 0.001$ Vehicle + LV-NRBF2 vs SAR405 + LV-NRBF2, $P = 0.011$ Vehicle + LV-GFP vs Vehicle + LV-NRBF2, $P = 0.151$ SAR405 + LV-GFP vs SAR405 + LV-NRBF2, $P < 0.001$	Vehicle + LV-GFP 1.000 ± 0.050 Vehicle + LV-NRBF2 0.834 ± 0.052 SAR405 + LV-GFP 1.531 ± 0.079 SAR405 + LV-NRBF2 1.109 ± 0.065
S8f: the precent of BrdU^{+}GFP^{+} cells in SAR405-treated aNSCs Vehicle + LV-GFP ($n = 4$)	Two-way ANOVA SAR405: F (1, 12) = 5.473, $P = 0.037$ Virus: F (1, 12) = 12.100, $P = 0.005$	Bonferroni's post hoc test Vehicle + LV-GFP vs SAR405 + LV-GFP, $P = 0.003$	Vehicle + LV-GFP 51.231 ± 2.290 Vehicle + LV-NRBF2 51.181 ± 3.728 SAR405 + LV-GFP

Vehicle + LV-NRBF2 ($n = 4$) SAR405 + LV-GFP ($n = 4$) SAR405 + LV-NRBF2 ($n = 4$)	SAR405 × Virus: F (1, 12) = 5.553, $P = 0.036$	Vehicle + LV-NRBF2 vs SAR405 + LV-NRBF2, $P = 0.886$ Vehicle + LV-GFP vs Vehicle + LV-NRBF2, $P > 0.999$ SAR405 + LV-GFP vs SAR405 + LV-NRBF2, $P = 0.012$	34.166 ± 2.059 SAR405 + LV-NRBF2 47.899 ± 3.290
S9b: NRBF2 expression in SSDS-treated mice CON ($n = 7$) SSDS ($n = 7$)	Unpaired t test t = 0.020, $P = 0.985$		CON 1.000 ± 0.093 SSDS 1.003 ± 0.094
S9c: LC3-II expression in SSDS-treated mice CON ($n = 7$) SSDS ($n = 7$)	Unpaired t test t = 0.572, $P = 0.578$		CON 1.000 ± 0.082 SSDS 0.935 ± 0.079
S9d: p62 expression in SSDS-treated mice CON ($n = 7$) SSDS ($n = 7$)	Unpaired t test t = 0.291, $P = 0.776$		CON 1.000 ± 0.077 SSDS 1.030 ± 0.068
S10c: NRBF2 expression in NRBF2 cKD mice AAV-mCherry ($n = 5$) AAV-sh*Nrbf2* ($n = 5$)	Unpaired t test t = 3.521, $P = 0.008$		AAV-mCherry 1.000 ± 0.075 AAV-sh*Nrbf2* 0.541 ± 0.107
S10d: LC3-II expression in NRBF2 cKD mice AAV-mCherry ($n = 5$) AAV-sh*Nrbf2* ($n = 5$)	Unpaired t test t = 4.197, $P = 0.003$		AAV-mCherry 1.000 ± 0.059 AAV-sh*Nrbf2* 0.665 ± 0.053
S11b: LC3 puncta within Nestin^{+} cells in DG of CSDS-exposed mice CON ($n = 33$) CSDS ($n = 33$)	Unpaired t test t = 5.530, $P < 0.001$		CON 14.970 ± 1.079 CSDS 7.970 ± 0.662
S12c: NRBF2 expression AAV-mCherry ($n = 4$) AAV-NRBF2 ($n = 4$)	Unpaired t test t = 2.593, $P = 0.041$		AAV-mCherry 1.000 ± 0.099 AAV-sh*Nrbf2* 1.409 ± 0.123
S12d: LC3-II expression AAV-mCherry ($n = 4$) AAV-NRBF2 ($n = 4$)	Unpaired t test t = 3.449, $P = 0.014$		AAV-mCherry 1.000 ± 0.091 AAV-NRBF2 1.665 ± 0.170

S13h: MFGE8 peptides in NRBF2$^{-/-}$ mice WT ($n = 3$) NRBF2$^{-/-}$ ($n = 3$)	Peptide 1: Unpaired t test, t = 4.257, $P = 0.013$ Peptide 2: Unpaired t test, t = 8.362, $P = 0.001$		Peptides 1: WT 1.177 ± 0.058 NRBF2$^{-/-}$ 0.825 ± 0.060 Peptides 2: WT 1.130 ± 0.007 NRBF2$^{-/-}$ 0.870 ± 0.028
S13i: MFGE8 expression in DG of NRBF2$^{-/-}$ mice WT ($n = 4$) NRBF2$^{-/-}$ ($n = 4$)	Unpaired t test t = 4.134, $P = 0.006$		WT 1.000 ± 0.087 NRBF2$^{-/-}$ 0.587 ± 0.048
S13j: MFGE8 expression in NRBF2-deficient aNSCs LV-GFP ($n = 6$) LV-sh*Nrbf2* ($n = 6$)	Unpaired t test t = 4.552, $P = 0.001$		LV-GFP 1.000 ± 0.068 LV-sh*Nrbf2* 0.593 ± 0.058
S13k: MFGE8 expression in DG after CSDS CON ($n = 8$) CSDS ($n = 8$)	Unpaired t test t = 3.468, $P = 0.004$		CON 1.000 ± 0.126 CSDS 0.465 ± 0.089