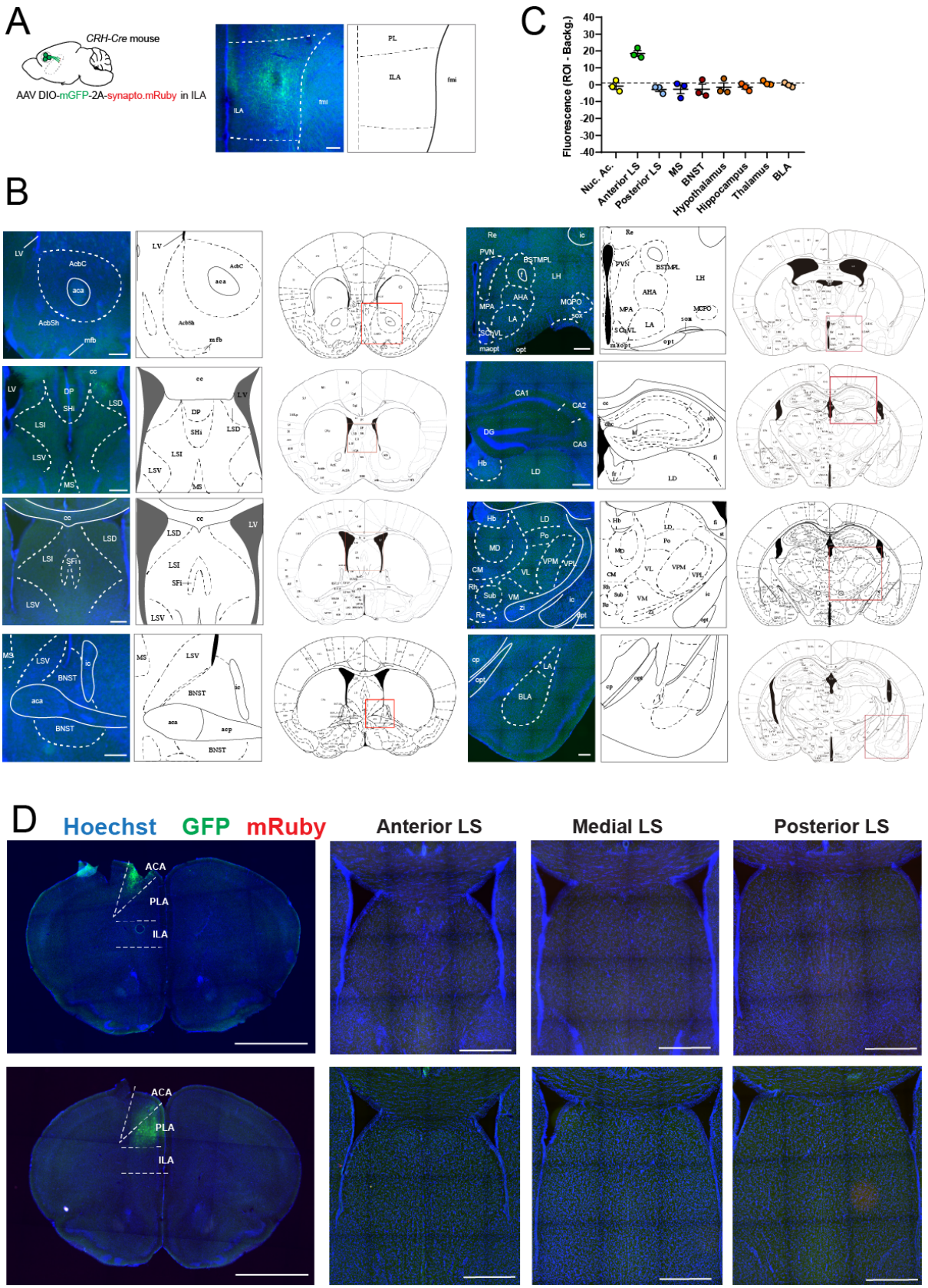
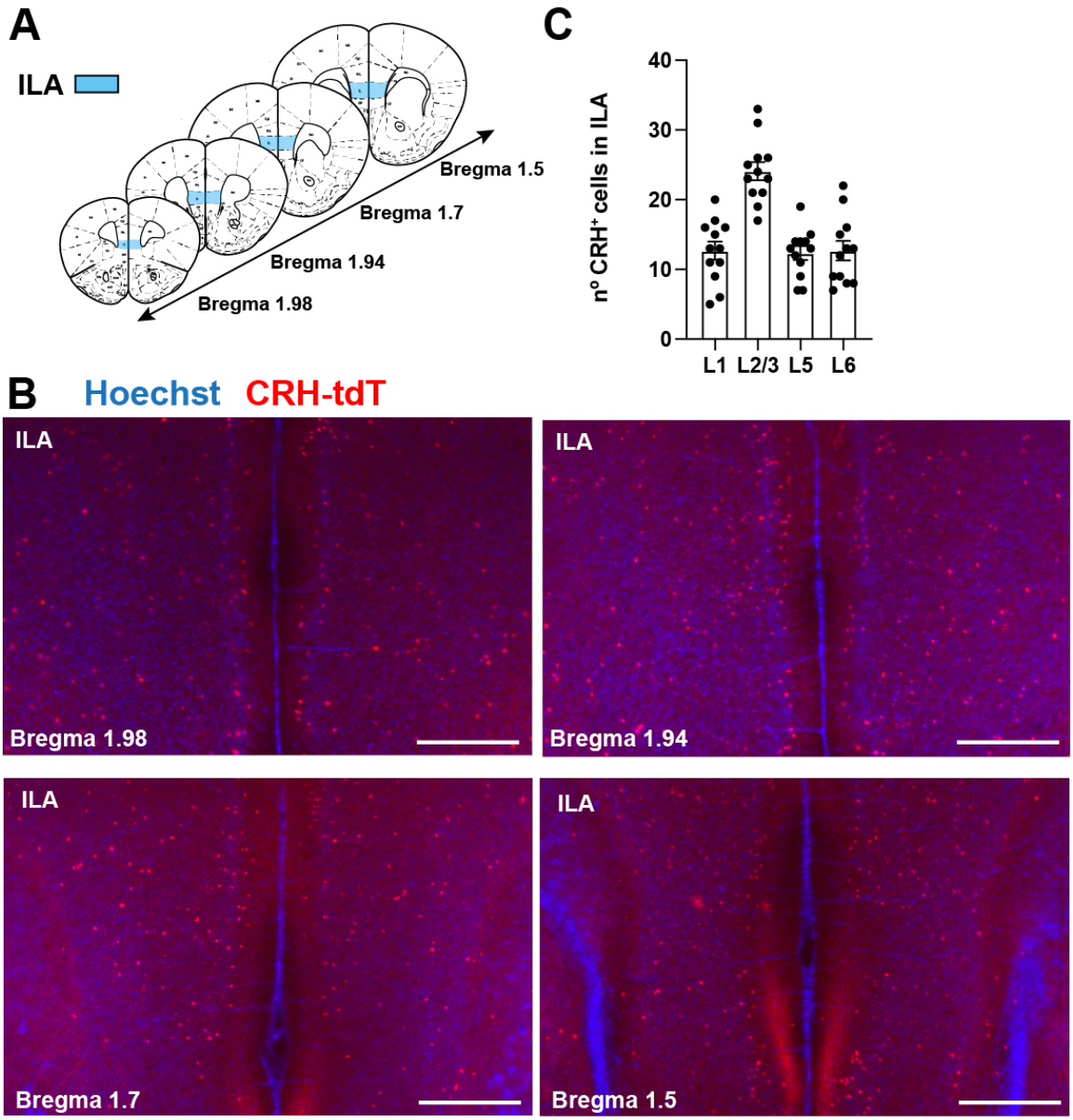
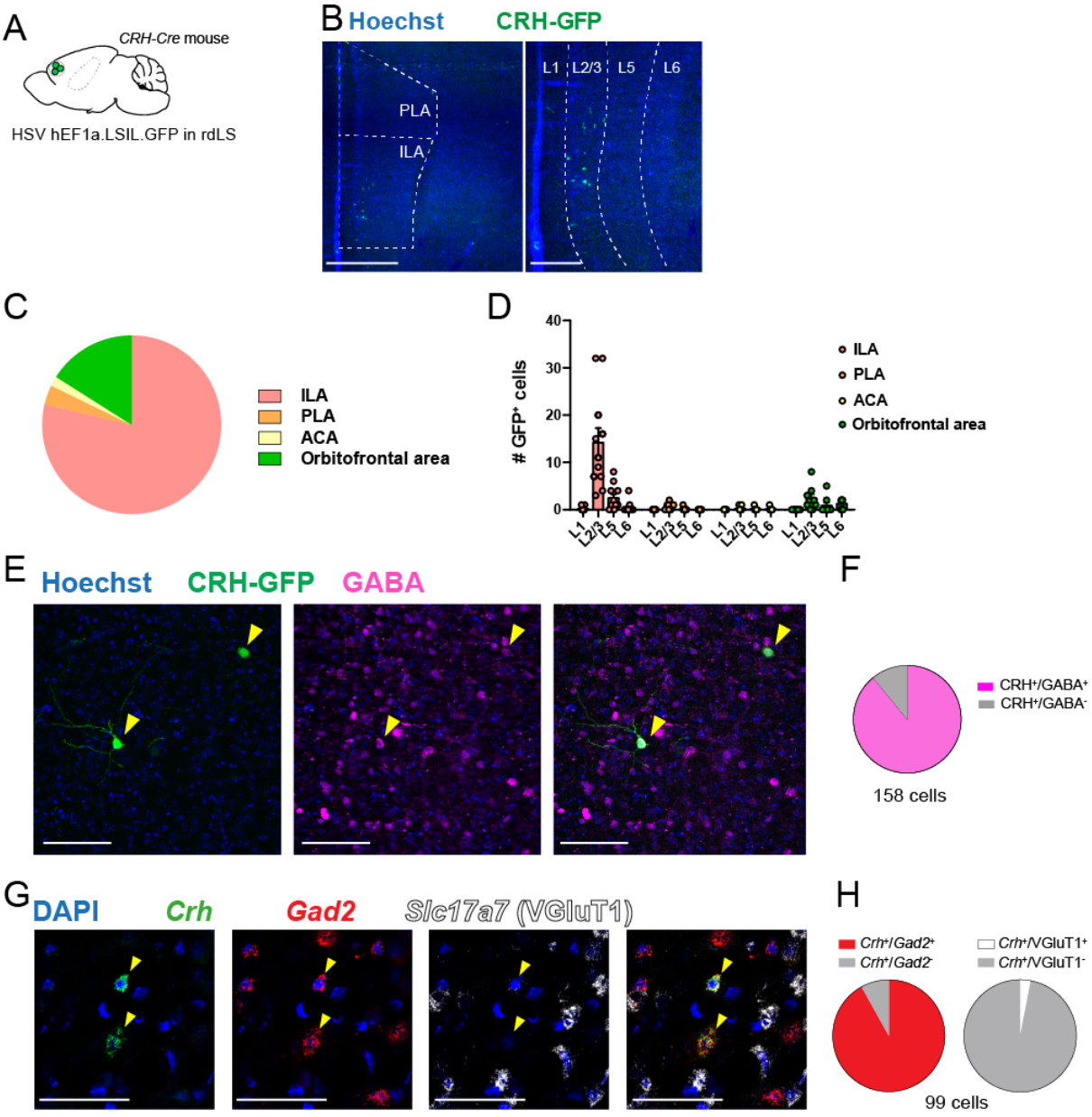


Supplementary Figure 1 related to Figure 1: A. *CRH-Cre* mice injected in ILA with AAV2/DJ hSyn.FLEX.mGFP.2A.Synatophysin-mRuby (left) and Immunohistochemistry image of the injection site (right). Scale bar: 200 µm. **B.** Immunohistochemistry images of several know

target regions of the mPFC. Scale bars: 200 µm **C.** Quantification of the GFP signal in each region. Each dot is a different mouse. **D.** *CRH-Cre* mice injected in ACA or PLA with AAV2/DJ hSyn.FLEX.mGFP.2A.Synatophysin-mRuby. Immunohistochemistry images of mPFC and LS section showing injection site on the right and lack of projection in LS on the left. Scale bars: 2 mm (mPFC) and 500 µm (LS).



Supplementary Figure 2 related to Figure 1: CRH-tdTomato cells in ILA across the rostro-caudal axis. Scale bars 400 µm.



Supplementary Figure 3 related to Figure 1: Molecular identity of ILA^{CRH} cells. A. *CRH-Cre* mice injected with HSV hEF1a.LSIL.GFP in rdLS. 3 mice. **B.** Images of the mPFC and ILA showing CRH/GFP$^+$ cells retrogradely labeled. Scale bars: 500 µm (left) and 200 µm (right). **C.** Distribution of GFP$^+$ cells per regions. **D.** Number of GFP$^+$ cells per region and layers. (C-D) 3 sections/mice. N = 3 mice. **E.** Immunohistochemistry images of the ILA labeled for GABA. Scale bars: 100 µm. **F.** Associated distribution of GFP$^+$ cells. N = 3 mice. **G.** In situ hybridization images of the ILA labeled for *Crh*, *Gad2* and *Slc17a7* (VGluT1). N = 3 mice. Scale bars: 50 µm. **H.** Associated distribution of *Crh*$^+$ cells.

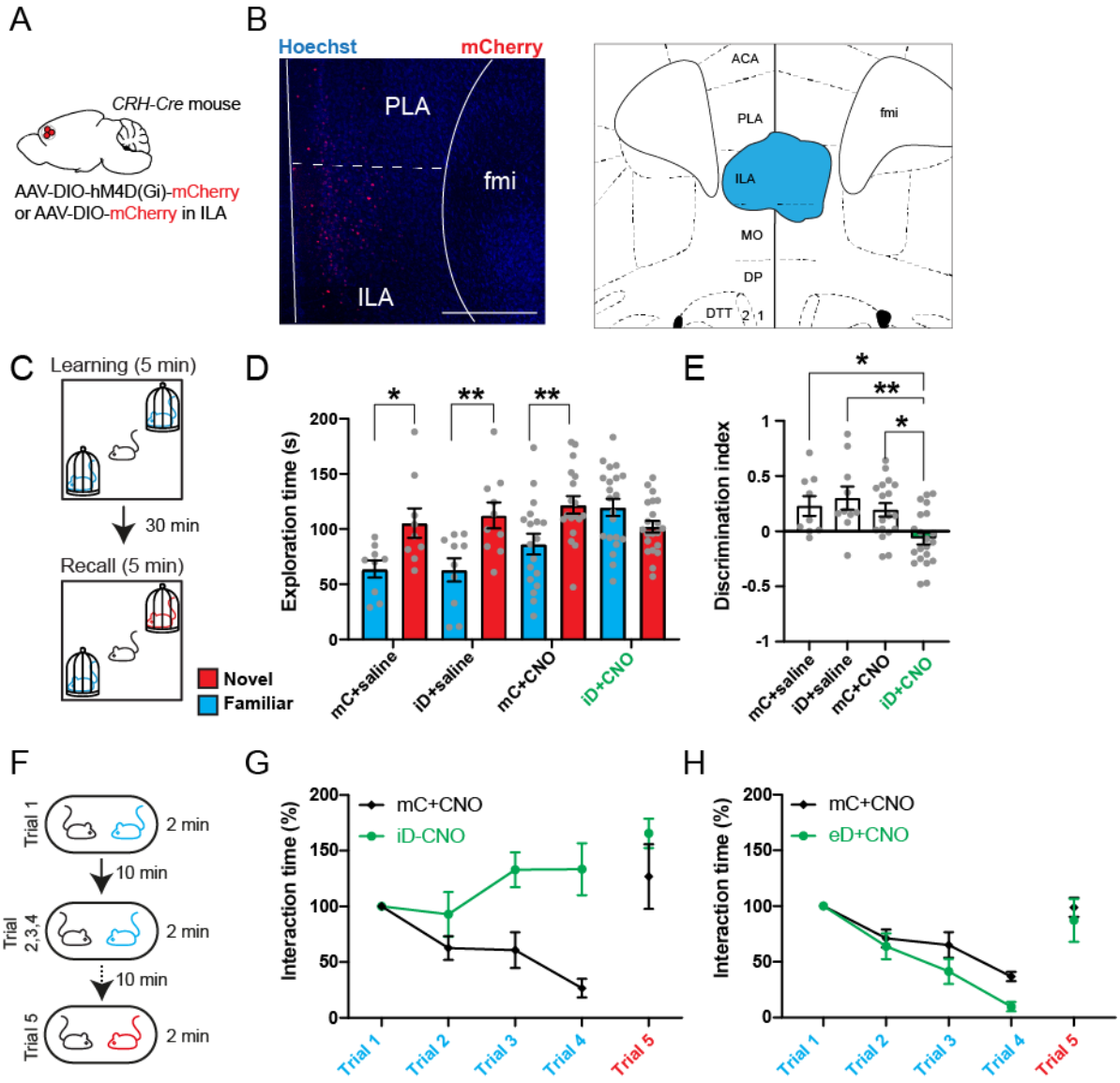
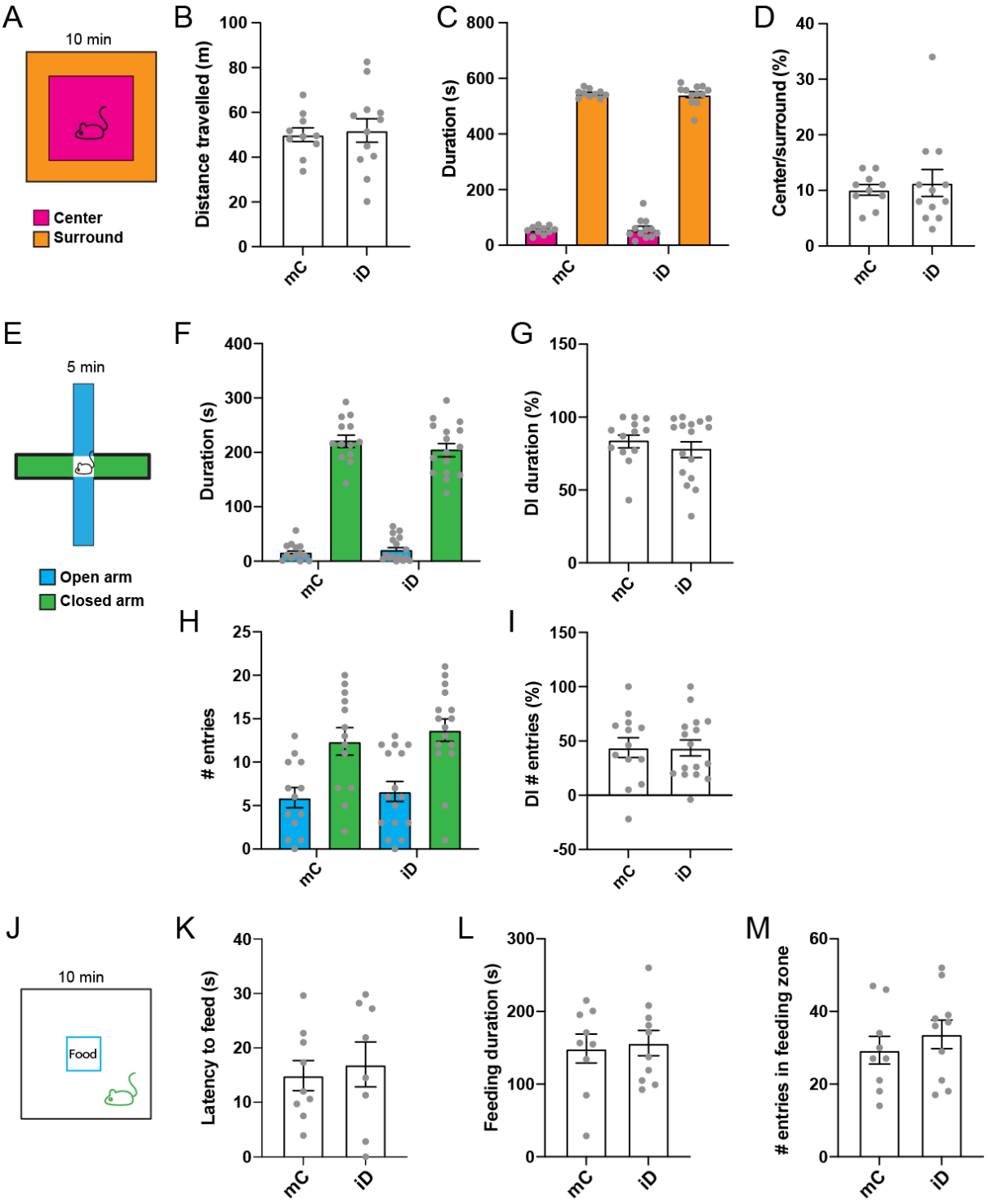


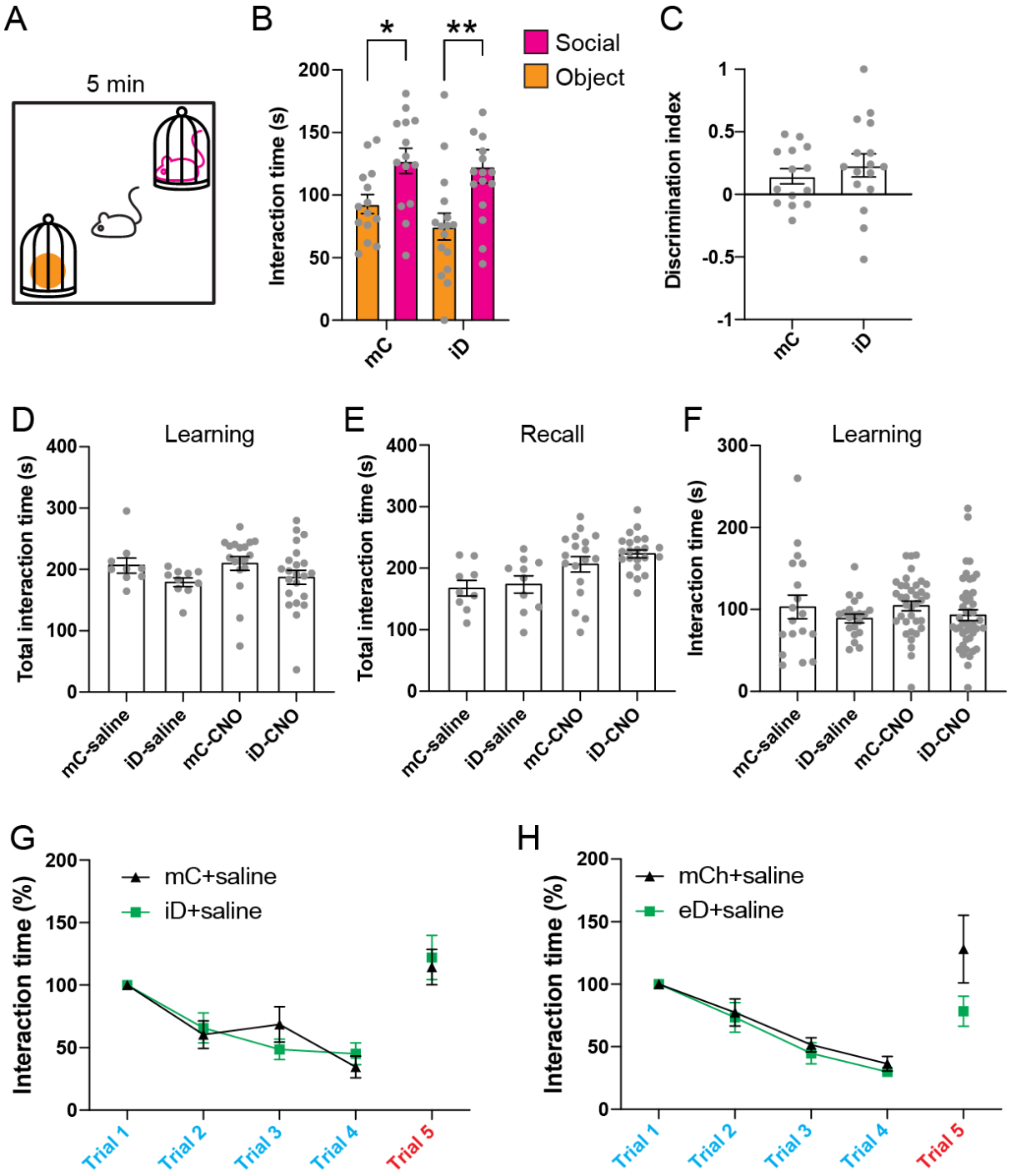
Figure 2: ILA^{CRH} cells support social novelty preference and familiarization. A. *CRH-Cre* mice injected in ILA with AAV2/8 hSyn.DIO.hM4D(Gi)-mCherry (iDREADD) or AAV2/8 hSyn.DIO.mCherry. **B.** Left: immunohistochemistry image showing the extent of iDREADD expression. Scale bar: 500 µm. Right: maximal extent of iDREADD expression across several mPFC sections. **C.** Schematic of the social novelty preference test. **D.** Interaction time with novel (red) or familiar (blue) mouse during recall in mice expressing mCherry (mC) or hM4Di (iD). Both groups were injected with saline (left groups) or 5 mg/kg of the DREADD agonist CNO (right groups). Grey dots are different mice. 3-way ANOVA F(novelty x injection x virus)$_{1,108}$ = 3.471, p = 0.02. Sidak's multiple comparison tests novel vs. familiar: mC + saline, p = 0.04; iD + saline, p = 0.006; mC + CNO, p = 0.008; iD + CNO, p = 0.3. **E.** Discrimination indexes for social novelty preference of the four groups during recall trial. One-sample t tests compared to 0: mC + saline, p = 0.04; iD + saline, p = 0.02; mC + CNO, p = 0.006; iD + CNO, p =

0.2. 2-way ANOVA: $F(\text{virus x injection})_{1, 54} = 4.7$, $p = 0.03$; $F(\text{virus})_{1, 54} = 7.1$, $p = 0.01$; $F(\text{injection})_{1, 54} = 1.5$, $p = 0.2$. Tukey's multiple comparison tests compared to the iD + CNO group: mC + saline, $p = 0.04$; iD + saline, $p = 0.004$; mC + CNO, $p = 0.02$. **F.** Schematic of the repetitive social presentation test. **G.** Normalized interaction times during social presentations (inhibitory DREADD-expressing mice and controls injected with CNO). 8 mice per group. Two-way ANOVA, $F(\text{trial}_{1\text{-}4} \text{ x virus})_{3,55} = 5.44$, $p = 0.002$; $F(\text{trial})_{3,55} = 1.28$, $p = 0.2$; $F(\text{virus})_{3,55} = 26.82$, $p < 0.0001$. Post-hoc Sidak's multiple comparison tests between mC and iD groups, trial 2 $p = 0.4$, trial 3 $p = 0.004$ and trial 4 $p < 0.0001$. **H.** Normalized interaction times during repetitive social presentation test in *CRH-Cre* mice injected in ILA with AAV5 hSyn.DIO.hM3D(Gq)-mCherry (excitatory DREADD) or with AAV5 hSyn.DIO.mCherry as a control. 8 mice per group. Two-way ANOVA: $F(\text{trial}_{1\text{-}4} \text{ x virus})_{3,56} = 1.36$, $p = 0.26$; $F(\text{trial})_{3,56} = 33.05$, $p < 0.0001$; $F(\text{virus})_{3,56} = 6.765$, $p = 0.012$.



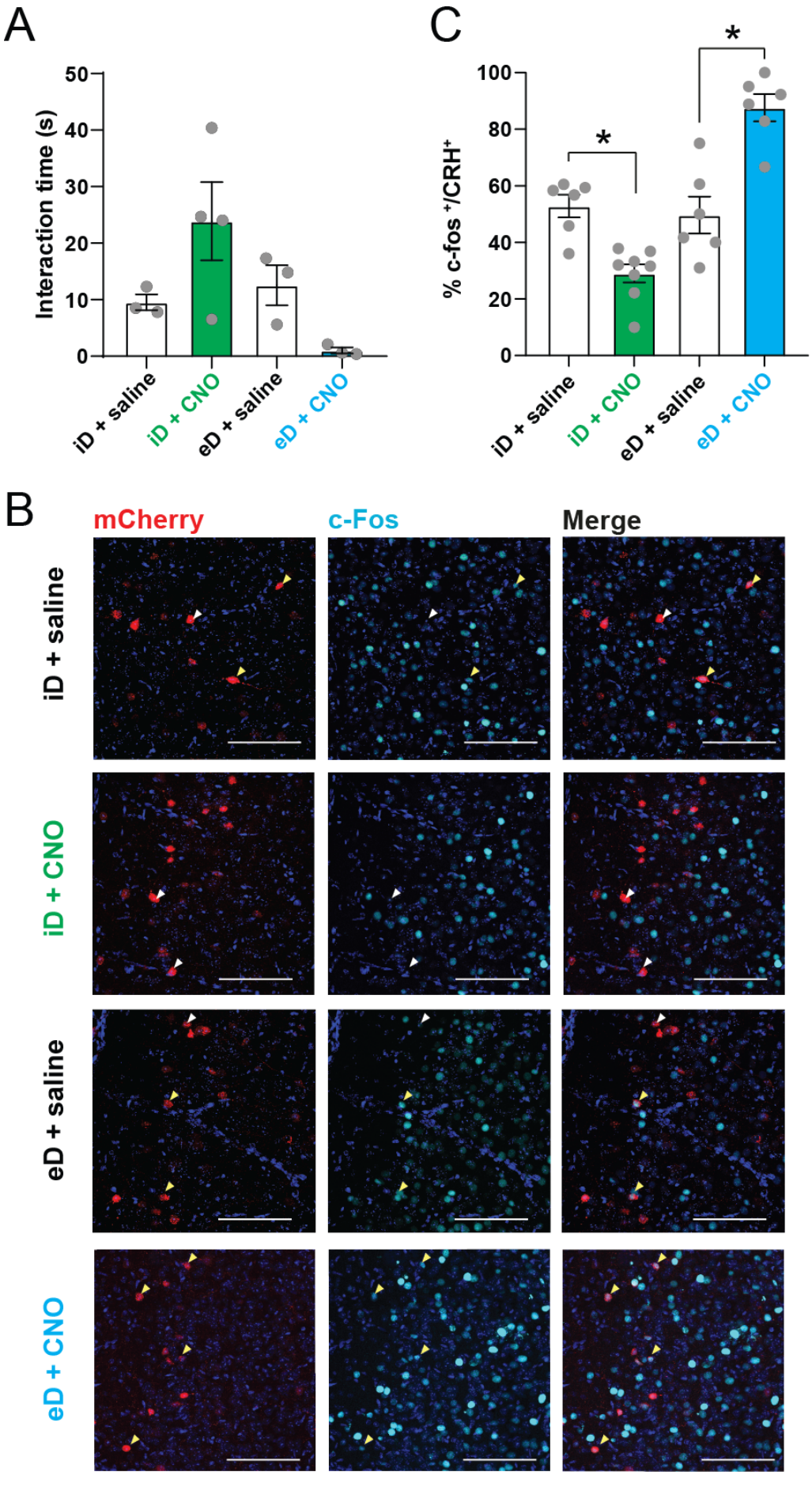
Supplementary Figure 4 related to Figure 2: Locomotion, anxiety and feeding behavior are not affected by chemogenetic silencing of ILACH neurons. *CRH-Cre* mice injected in ILA with AAV2/8 hSyn.DIO.hM4D(Gi)-mCherry (iD) or AAV2/8 hSyn.DIO.mCherry (mC). **A.** Schematic of the open-field test. **B.** Total distance travelled during open-field test. **C.** Time spent in the center or surround of the open-field. **D.** Ratio of the time spent in the center/surround. **E.** Schematic of the elevated-plus maze test. **F.** Time spent in the open or closed arms. **G.**

Discrimination indexes for closed arm preference using the time spent in the arms. **H.** Number of entries in the open or closed arms. **I.** Discrimination indexes for closed arm preference using the number of arm entries. **J.** Schematic of the novelty suppressed feeding test. **K.** Latency to feed. **L.** Feeding duration. **M.** Number of entries in the feeding zone. For the entire figure, bar graphs represent mean ± S.E.M. Grey dots are different mice.

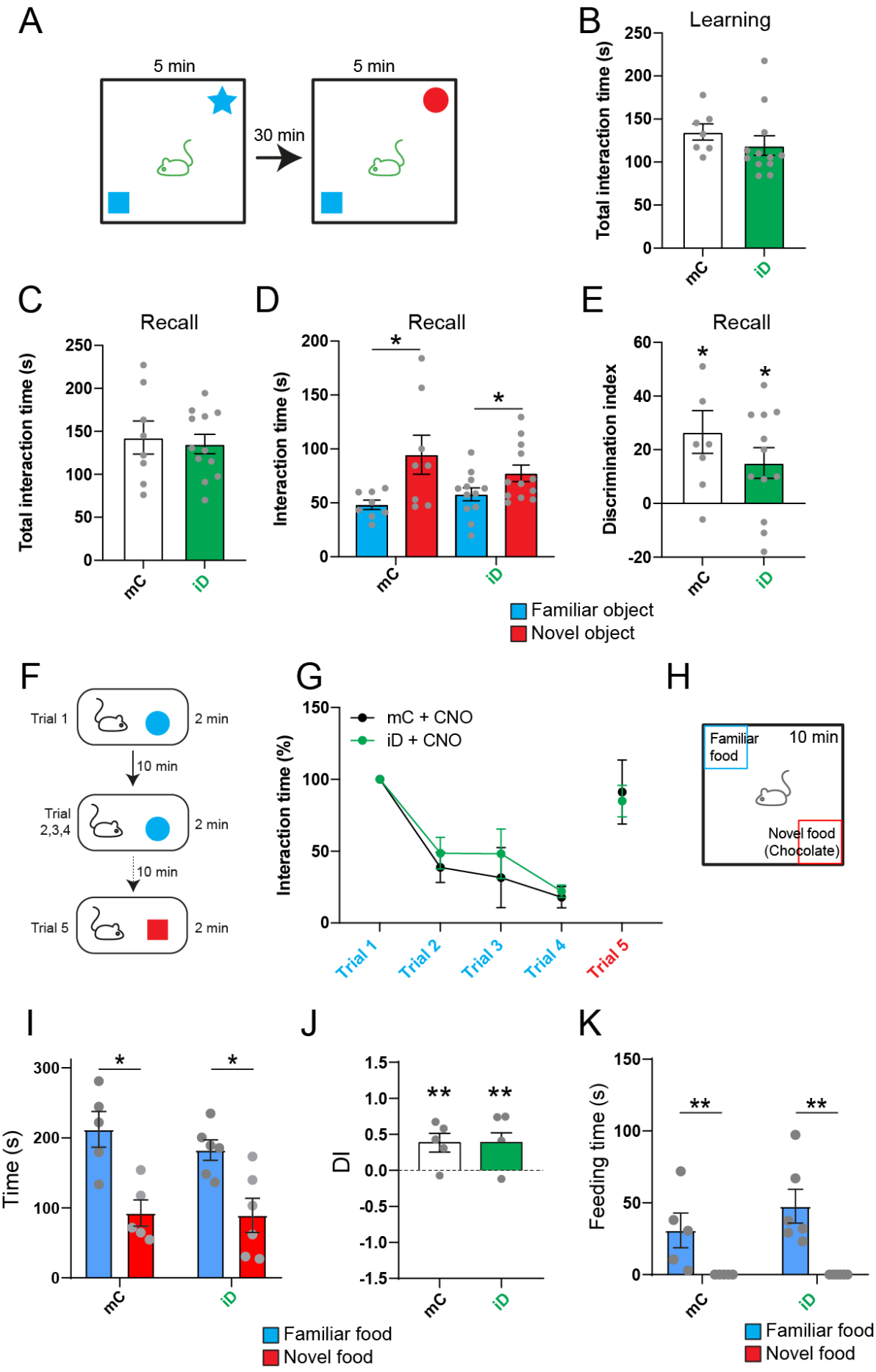


Supplementary Figure 5 related to Figure 2: Social behavior controls for chemogenetic silencing of ILA^{CRH} cells. *CRH-Cre* mice injected in ILA with AAV2/8 hSyn.DIO.hM4D(Gi)-

mCherry (iD) or AAV2/8 hSyn.DIO.mCherry (mC). **A.** Schematic of the sociability test. **B.** Interaction times with mouse (purple) or object (orange). Paired *t* tests: $p = 0.01$, $p = 0.009$. **C.** Discrimination indexes for social preference. One-sample *t* tests compared to 0: $p = 0.03$ and $p = 0.02$. Unpaired *t* test: $p = 0.4$. **D-E.** Total interaction times during learning (D) or recall trial of the social novelty preference test (E). Two-way ANOVAs $F(\text{CNO vs. saline})_{1,55} = 0.19$, $p = 0.7$ and $F(\text{CNO vs. saline})_{1,55} = 14.51$, $p = 0.0004$ respectively. **F.** Interaction time with each novel mouse during the learning trial of the social novelty preference test. One-way ANOVA, $F(\text{CNO vs. saline})_{1,114} = 0.1109$, $p = 0.7$. **G.** Normalized interaction times during social presentations (inhibitory DREADD-expressing mice and controls injected with saline). 8 mice per group. Two-way ANOVA: $F(\text{trial}_{1\text{-}4} \text{ x virus})_{3,56} = 1.03$, $p = 0.39$; $F(\text{trial})_{3,56} = 14.72$, $p < 0.0001$; $F(\text{virus})_{1,56} = 0.003$, $p = 0.9$. **H.** Normalized interaction times during social presentations (excitatory DREADD-expressing mice and controls injected with saline). 8 mice per group. Two-way ANOVA: $F(\text{trial}_{1\text{-}4} \text{ x virus})_{3,56} = 0.09$, $p = 0.96$; $F(\text{trial})_{3,56} = 33.86$, $p < 0.0001$; $F(\text{virus})_{1,56} = 0.72$, $p = 0.4$. For the entire figure, bar graphs represent mean ± S.E.M. Grey dots are from different mice except for (F) where two observations per mice were made since the mice interacted with two novel mice during the learning trial.


A
Interaction time (s)
50
40
30
20
10
0
iD + saline
iD + CNO
eD + saline
eD + CNO
C
% c-fos +/CRH+
100
80
60
40
20
0
*
*
iD + saline
iD + CNO
eD + saline
eD + CNO
B
mCherry
c-Fos
Merge
iD + saline
iD + CNO
eD + saline
eD + CNO

Supplementary Figure 6 related to Figure 2: DREADDs modulate ILA^{CRH} cells activity. *CRH-Cre* mice injected in ILA with AAV2/8 hSyn.DIO.hM4D(Gi)-mCherry (iD) or AAV5 hSyn.DIO.hM3D(Gq)-mCherry (excitatory DREADD). Mice received CNO or saline i.p. injection 30 min before being presented to a familiar animal for 2 min. Mice were thereafter perfused and processed for c-fos labelling. **A.** Interaction times. Each point is one mouse. **B.** Immunohistochemistry images of the ILA labelled for c-fos. Scale bars: 100 µm. **C.** Percentage of mCherry^{+} cells in ILA expressing c-fos. Minimum of 3 mice per group. 2 observations per mice. Nested *t* tests: $p = 0.01$ and $p = 0.02$.


A
5 min
30 min
5 min
B
Learning
Total interaction time (s)
250
200
150
100
50
0
mC
iD
C
Recall
Total interaction time (s)
D
Recall
Interaction time (s)
*
*
E
Recall
Discrimination index
60
40
20
0
-20
Familiar object
Novel object
F
Trial 1
2 min
10 min
Trial 2,3,4
2 min
10 min
Trial 5
2 min
G
mC + CNO
iD + CNO
Interaction time (%)
150
100
50
0
Trial 1
Trial 2
Trial 3
Trial 4
Trial 5
H
Familiar food
10 min
Novel food (Chocolate)
I
Time (s)
300
200
100
0
*
*
J
DI
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
**
**
K
Feeding time (s)
150
100
50
0
**
**
Familiar food
Novel food

Supplementary Figure 7 related to Figure 2: Object recognition memory and familiar food preference are unchanged following chemogenetic silencing of ILA^{CRH} cells. A. Schematic of the object recognition memory test in *CRH-Cre* mice injected in ILA with AAV2/8 hSyn.DIO.hM4D(Gi)-mCherry (iD) or AAV2/8 hSyn.DIO.mCherry (mC). **B-C.** Total interaction times during learning (B) or recall (C) trial of the novel object memory test. Grey dots are different mice. **D.** Interaction times with familiar (blue) or novel object (red). Grey dots are different mice. Paired *t* tests: $p = 0.04$ and $p = 0.03$. **E.** Discrimination indexes for novel object preference. Grey dots are different mice. One-sample *t* tests compared to 0: $p = 0.01$ and $p = 0.02$. Unpaired *t* test between groups: $p = 0.2$. **F.** Schematic of the repetitive object presentation test. **G.** Normalized interaction times during the repetitive object presentation test (inhibitory DREADD-expressing mice and control mice injected with 5 mg/kg CNO). 4 mice per group, 8 mice total. Two-way ANOVA: $F(\text{trial}_{1\text{-}4} \times \text{virus})_{3,24} = 0.198$, $p = 0.9$; $F(\text{trial})_{3,24} = 18.15$, $p < 0.0001$; $F(\text{virus})_{1,24} = 0.895$, $p = 0.4$. For the entire figure, bar graphs represent mean ± S.E.M. **H.** Schematic of the food preference test. **I.** Time spent in each feeding zone. Paired *t* tests: $p = 0.04$ and 0.03. **J.** Discrimination index between feeding zones. One-sample *t* tests compared to 0: mC, $p = 0.01$ and iD, $p = 0.01$. Unpaired *t* test between groups: $p = 0.98$ **K.** Time spent feeding. Paired *t* tests: $p = 0.001$ and 0.01.

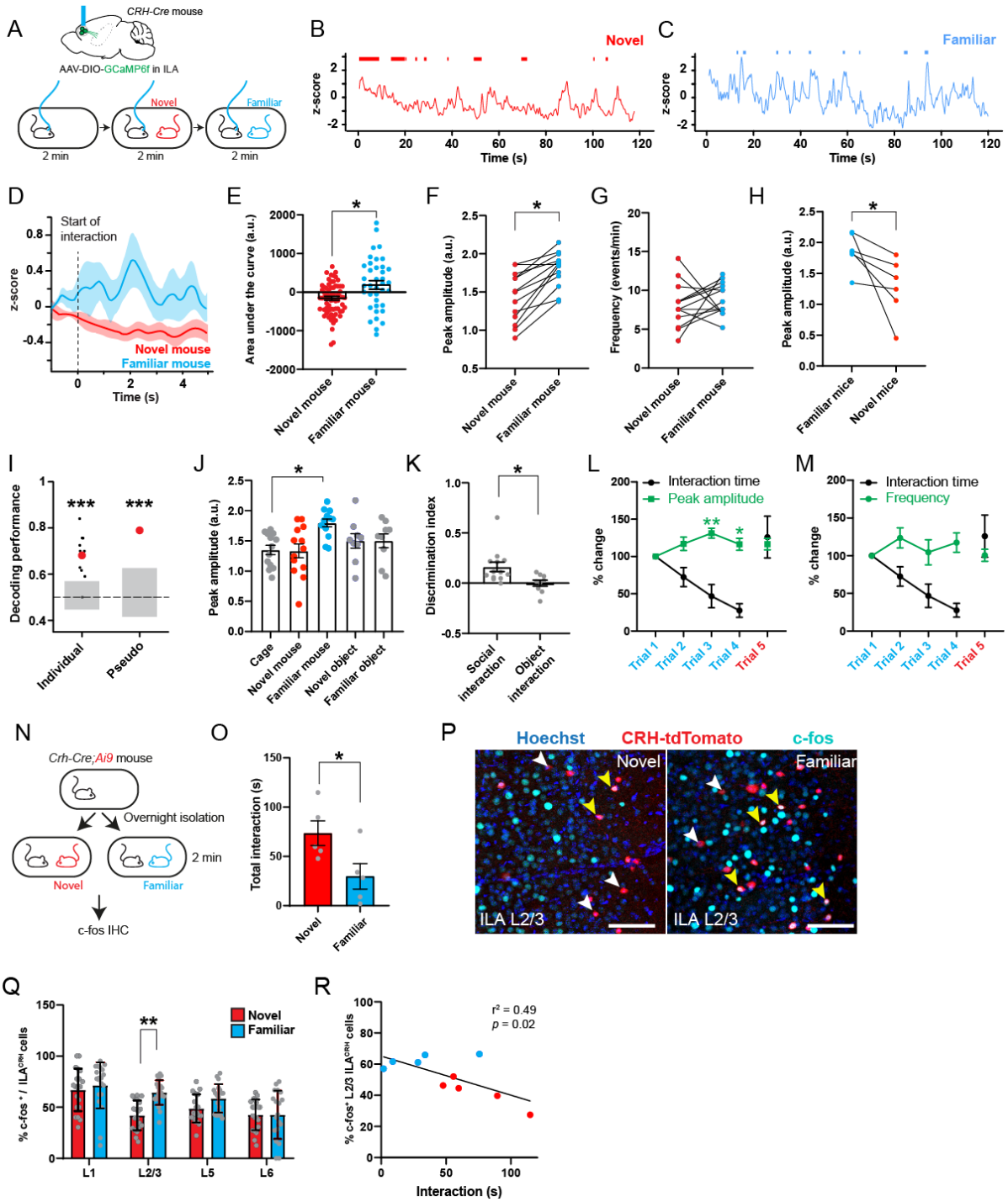
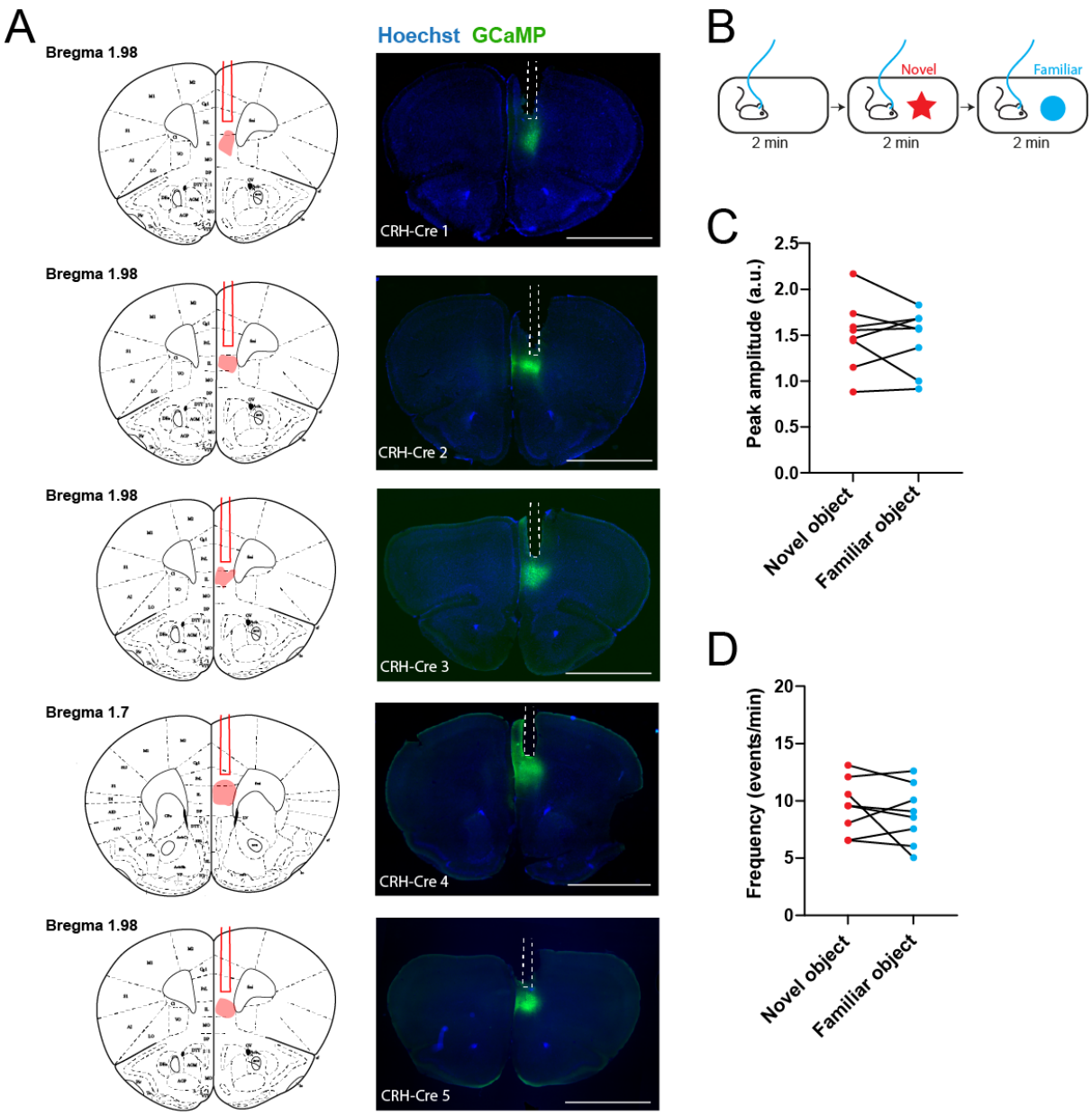


Figure 3. ILA^{CRH} cells respond preferentially to familiar mouse presentation. A. *CRH-Cre* mice injected in ILA with AAV2/1 syn.FLEX.GCaMP6f and implanted with an optical ferrule over ILA (top). Schematic of the fiber-photometry recording experiment (bottom). **B-C.** Example traces of recording during presentation of a novel (B) or familiar (C) mouse to the same test mouse. Interaction bouts intervals are shown above each trace. **D.** Peri-stimulus time histogram during social interaction with novel or familiar mouse, 5 mice. **E.** Area under the curve during familiar and novel mouse interaction. Each point is an interaction, 5 mice. One-sample nested

t tests: Familiar response vs. 0, $p = 0.003$, Novel responses vs. 0, $p = 0.005$. Nested *t* test between groups: $p = 0.01$. **F.** Average peak amplitude of the z-score during social presentations of a novel then familiar mouse. For panels F, G and J, each dot is a different recording session using 5 mice. Nested *t* test between groups: $p = 0.02$. **G.** Frequency of calcium events during presentation of a novel then familiar mouse. Nested *t* test: $p = 0.4$. **H.** Average peak amplitude of the z-score during inverted presentation of a familiar then a novel mouse. 3 mice per groups. 2 observations per mice. Nested *t* test, $p = 0.03$. **I.** Decoding performance for familiarity versus novelty from individual recordings or pseudo-simultaneous data. Small black dots on the left are the results from individual recording sessions (N = 5 mice), using 20 cross-validation iterations, large red dot is the average. Red dot on the right is the result of pseudo-population analysis from 100 cross-validation iterations. Grey areas denote chance level computed using permutation tests (2.5 – 97.5 percentiles in distribution of shuffled decoding performances). In both cases, statistical significance is determined by the probability of drawing the observed decoding performance from the distribution of shuffled decoding performances (null-hypothesis). $p < 0.001$ (two-tailed permutation test, see *Methods*). **J.** Average peak amplitude during each type of presentation (novel then familiar experiments only). Nested One-way ANOVA $F_{4,16} = 24.20$ followed by Tukey's multiple comparison test: cage vs. novel mouse $p = 0.9$; cage vs. familiar mouse $p = 0.03$; cage vs. novel object $p = 0.7$; cage vs. familiar object $p = 0.7$. **K.** Discrimination indexes for familiarity preference calculated from z-scores during mouse or object presentation. Each point is one recording session. N = 5 mice. One-sample *t* tests compared to 0: $p = 0.001$ and $p = 0.3$ respectively. Unpaired *t* test between groups taking the average value per mice: $p = 0.03$. **L.** Fiber-photometry recording during repetitive social presentation test (10 sessions in 5 mice). One-sample *t* tests compared to: trial 1 $p = 0.06$; trial 3 $p = 0.002$ and trial 4 $p = 0.04$. **M.** Frequency of calcium events during repetitive social presentation test (10 sessions in 5 mice). **N.** *CRH-Cre;Ai9* mice were presented with novel or familiar mice after overnight isolation before being processed for immunohistochemistry. **O.** Interaction times following 2 min social presentation. Unpaired *t* test novel vs. familiar interaction time, $p = 0.04$. **P.** Immunohistochemistry images of c-fos labelling in ILA layer 2/3. Yellow arrowheads: c-fos$^+$ / tdTomato$^+$ cells. White arrowheads: c-fos$^-$ / tdTomato$^+$ cells. Scale bars: 100 µm. **Q.** Percentage of ILA^{CRH} cells positive for c-fos per layer. Each point corresponds to each side of 2 sections. 5 mice per group. Nested *t* test, $p = 0.003$. **R.** Percentage of layer 2/3 ILA^{CRH} cells

positive for c-fos vs. interaction time during social interaction with novel (red) or familiar (blue) mouse. Each point represents one mouse. For the entire figure, bar graphs represent mean ± S.E.M.



Supplementary Figure 8 related to Figure 3: Fiber-photometry recordings of ILA^{CRH} cells. A. Immunohistochemistry images of GCaMP expression and lens implant in the ILA of recorded *CRH-Cre* mice. Scale bars: 2 mm. **B.** Schematic of the object presentation experiment. **C.** Average peak amplitude of the z-score during presentation of a novel or familiar object. Dots are different sessions using 3 mice. Nested *t* test between groups, $p = 0.9$. **D.** Frequency of calcium events during presentation of a novel or familiar object. Dots are different sessions using 3 mice. Nested *t* test between groups, $p = 0.4$.

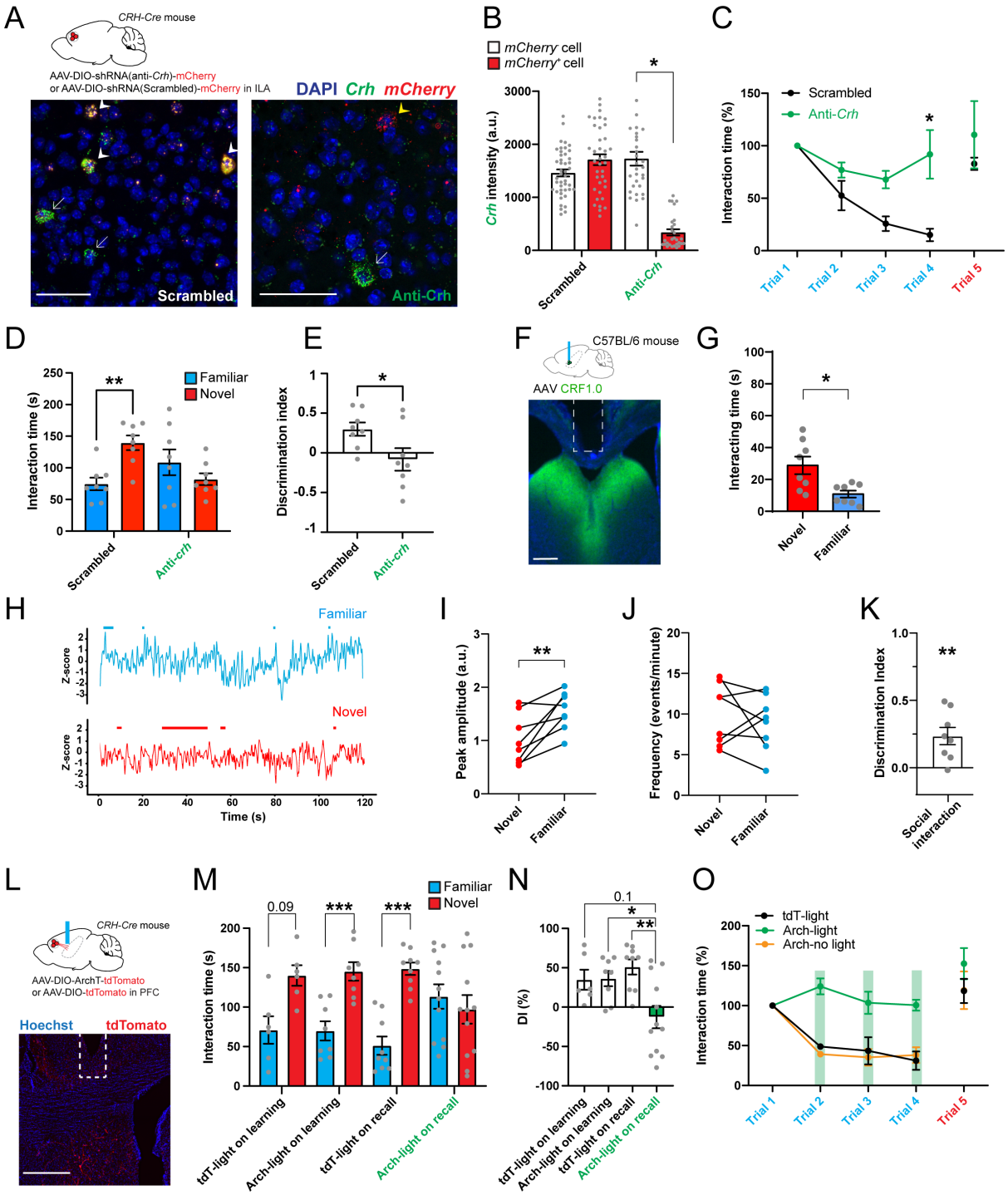
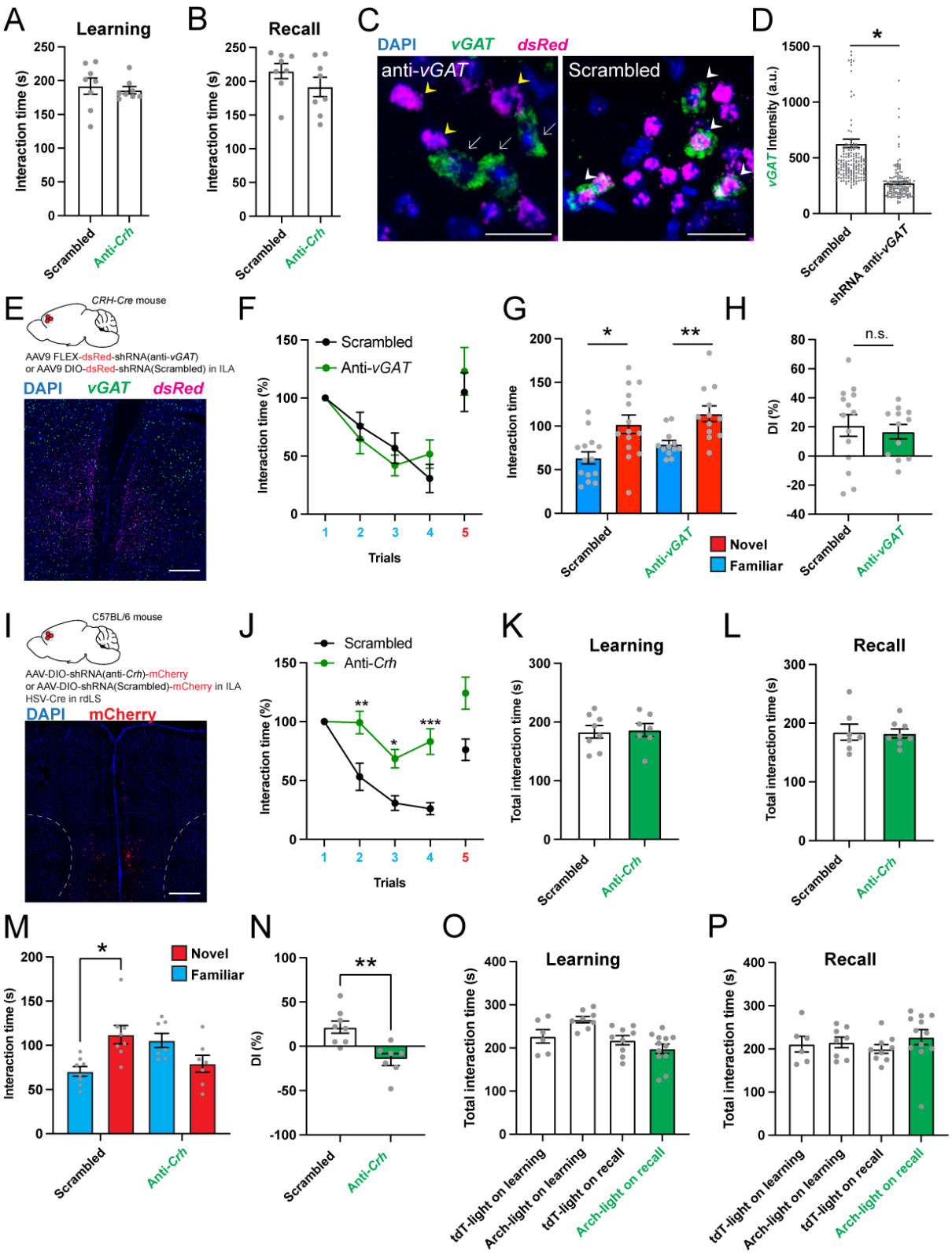


Figure 4: CRH release from ILA in rdLS suppresses social interactions with familiar mice and supports social novelty preference. A. *CRH-Cre* mice injected in ILA with AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(anti-*Crh*) to downregulate *Crh* or control AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(scrambled) (top). In situ hybridization images of ILA slices expressing the scrambled shRNA (right) or the shRNA against *Crh* (left) labelled for *mCherry* and *Crh*. White arrows denote CRH$^+$ neurons that do not express the virus. Yellow arrowhead denotes CRH$^+$ cells expressing the anti-*Crh* shRNA, with reduced level of *Crh*. White arrowheads denote CRH$^+$

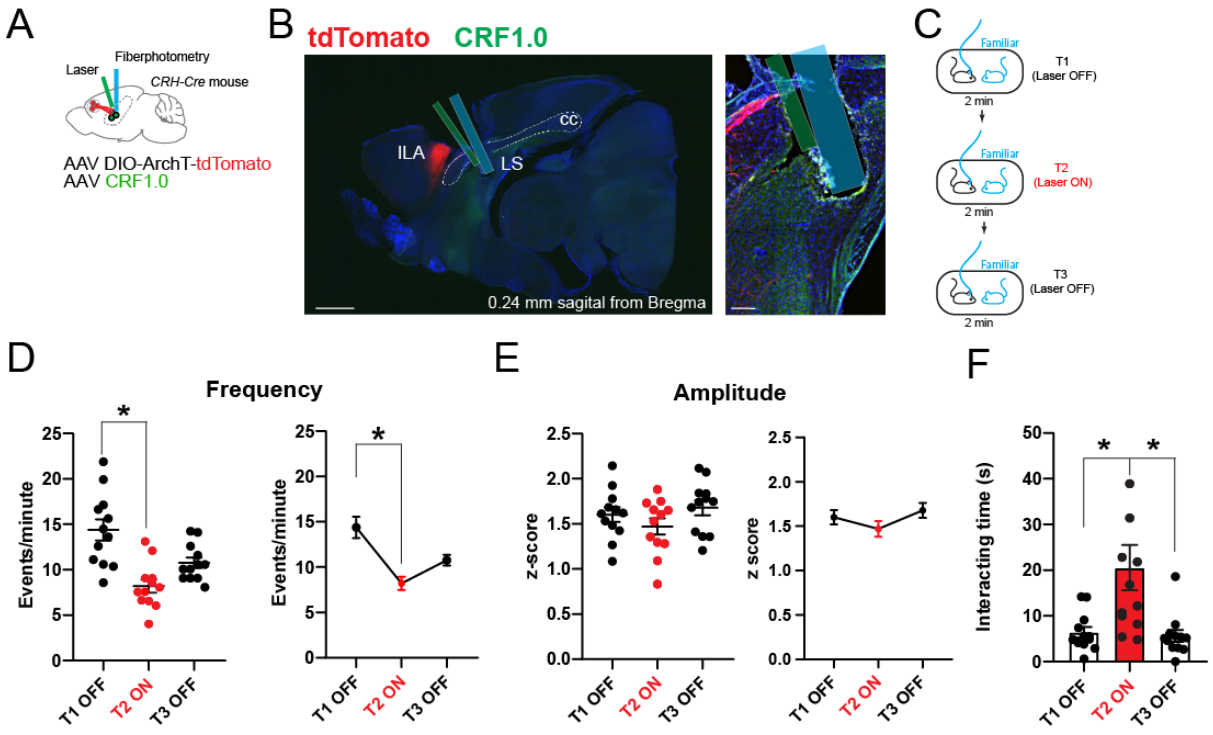
neurons expressing the scrambled shRNA, with intact *Crh* level. Scale bars: 50 µm. **B.** Quantification of *Crh* expression. In each slice neurons were classified as to whether they were uninfected or infected with virus based on *mCherry* expression (3 mice per group; each point is a different neuron). Nested one-way ANOVA $F_{3,8} = 6.41$, $p = 0.016$ followed by Tukey's multiple comparison test, anti-*Crh* + mCherry$^+$ vs. anti-*Crh* + mCherry$^-$, $p = 0.03$. **C.** Normalized interaction time during the repetitive social presentation test in mice expressing scrambled or anti-*Crh* shRNAs. 4 mice per group. Two-way ANOVA; $F(\text{trial}_{1\text{-}4} \times \text{virus})_{3,24} = 4.4$ $p = 0.01$; $F(\text{trial})_{3,24} = 9.6$, $p = 0.0002$; $F(\text{virus})_{3,24} = 21.9$, $p < 0.0001$ followed by Tukey's multiple comparison test between scrambled and anti-*Crh* groups: trial 2, $p = 0.8$; trial 3, $p = 0.2$; trial 4, $p = 0.009$. **D.** Interaction time with familiar (blue) or novel (red) mouse during the recall trial of the social novelty preference test in mice expressing scrambled or anti-*Crh* shRNAs. Grey dots are different mice. 2-way ANOVA $F(\text{novelty} \times \text{virus})_{1,28} = 11.53$, $p = 0.002$. Sidak's multiple comparison tests novel vs. familiar: scrambled, $p = 0.004$; anti-*Crh*, $p = 0.3$. Paired *t* test: $p = 0.0095$, $p = 0.6$. **E.** Discrimination indexes for social novelty preference during recall trial. Grey dots are different mice. Unpaired *t* test: $p = 0.03$. **F.** Top: C57BL/6J wild-type mice injected in rdLS with AAV2/9 Syn.CRF1.0 and implanted with an optical ferrule above rdLS. Bottom: immunohistochemistry image showing CRF1.0 expression in rdLS and the optical ferrule implanted above the injection site. Scale bar: 300 µm. **G.** Bar graph showing the interaction time with novel and familiar mice. 8 mice. Paired *t* test, $p = 0.002$. **H.** Trace of a representative fiberphotometry recording during interaction with a familiar mouse or a novel mouse. Interaction bouts are shown above each trace. **I.** Average peak amplitude of the z-score during presentation of a novel or familiar mouse. 8 mice. Paired *t* test: $p = 0.008$. **J.** Frequency of events during presentation of a novel or a familiar mouse. 8 mice. Paired *t* test: $p = 0.5$. **K.** Discrimination index for social familiarity preference calculated from z-scores. 8 mice. One-sample *t* tests compared to 0: $p = 0.008$. **L.** *CRH-Cre* mice injected in ILA with AAV2/2 CAG.FLEX.ArchT-tdTomato or control AAV2/2 CAG.FLEX.tdTomato. Optical ferrule implant is above rdLS. Scale bar: 500 µm. **M.** Interaction time with familiar (blue) or novel (red) mouse during the recall trial of the social novelty preference test in the same mice. Laser was on during the learning or recall trial. Each dot is a mouse. 3-way ANOVA $F(\text{novelty} \times \text{light} \times \text{virus})_{1,62}=14.44$, $p=0.007$. Šidák's multiple comparison tests novel vs. familiar: p=0.03, 0.004, <0.0001 and 0.8. **N.** Discrimination index for social novelty preference during recall trial of the social novelty preference test. One-sample *t*-tests: p=0.04, 0.007, 0.0007 and 0.4. Two-way

ANOVA: $F(\text{virus x light})_{1,31}=6.232$, $p=0.01$. $F(\text{light})_{1,31}=1.578$, $p=0.2$; $F(\text{virus})_{1,31}=5.701$, $p=0.02$. Šidák's multiple comparison tests: $p=0.09$, 0.04 and 0.003.. **O.** Normalized interaction time during the repetitive social presentation test in the same mice. The laser was on during trials 1 to 4 of the Arch-light and mC-light groups (4 mice and 3 mice respectively). Laser was not on for the Arch-no light group (4 mice). Two-way ANOVA: $F(\text{trial}_{1\text{-}4} \text{ x virus})_{6,32} = 5.84$, $p = 0.0003$; $F(\text{trial})_{3,32} = 14.35$, $p < 0.0001$; $F(\text{group})_{2,32} = 49.32$, $p < 0.0001$. For the entire figure, bar graphs represent mean ± S.E.M. Grey dots are different mice.



Supplementary Figure 9, related to Figure 4: Social behavior controls for CRH release from ILA to rdLS. A-B. Total interaction time during the learning (A) and recall (B) phases of the social novelty preference test following *Crh* knock-down in ILA^{CRH} neurons. **C.** In situ hybridization against *vGAT* and *dsRed* in the ILA of *CRH-Cre* mice injected with AAV2/9

hSyn.FLEX.dsRed-shRNA(*vGAT*) or control AAV2/9 hSyn.FLEX.dsRed-shRNA(scrambled). Cells that express the shRNA against *vGAT* (yellow arrowheads) express *dsRed* but no more *vGAT* unlike nearby *vGAT*$^{+}$ cells that did not incorporate the virus (white arrows). Cells expressing the scrambled shRNA express *dsRed* and retain *vGAT* expression (white arrowheads). Scale bars 50 µm. **D.** Quantification of *vGAT* intensity in *dsRed*$^{+}$ neurons in mice injected with each virus. Each point is a cell. 4 and 3 mice per group. Nested *t* test: $p = 0.02$. **E.** *CRH-Cre* mice injected in ILA with AAV2/9 hSyn.FLEX.dsRed-shRNA(*vGAT*) or control AAV2/9 hSyn.FLEX.dsRed-shRNA(scrambled) (top). In situ hybridization picture against *vGAT* and *dsRed* showing viral expression (bottom). Scale bar 500 µm. **F.** Normalized interaction times during repetitive social presentation following expression of a shRNA against *vGAT* or a scrambled shRNA in ILA^{CRH} cells. Two-way ANOVA; $F(\text{trial}_{1\text{-}4} \times \text{virus})_{3,60} = 1.204$, $p = 0.3$; $F(\text{trial})_{3,60} = 12.77$, $p < 0.0001$; $F(\text{virus})_{1,60} = 0.031$, $p < 0.9$. **G.** Interaction time during recall trial of the SNP test following expression of a shRNA against *vGAT* or a scrambled shRNA in ILA^{CRH} cells. Paired *t* tests $p = 0.01$, $p = 0.008$. **H.** Discrimination index during time during recall trial of the SNP test. One sample t test vs. 0: $p = 0.01$ and $p = 0.006$. Unpaired *t* test, $p = 0.7$. **I.** C57BL/6 mice injected with HSV hEF1a.Cre in rdLS and AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(anti-*Crh*) or AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(scrambled) in ILA (top). Immunohistochemistry picture of ILA (bottom). Scale bar 500 µm. **J.** Normalized interaction times during repetitive social presentation following expression of a shRNA against *Crh* or a scrambled shRNA in retrogradely targeted ILA cells. Two-way ANOVA; $F(\text{trial}_{1\text{-}4} \times \text{virus})_{3,32} = 5.19$, $p = 0.005$; $F(\text{trial})_{3,32} = 17.98$, $p < 0.0001$; $F(\text{virus})_{1,32} = 42.01$, $p < 0.0001$ followed by Tukey's multiple comparison test comparing anti-*Crh* and scrambled expressing mice for each trial (trial 2, $p = 0.004$; trial 3, $p = 0.03$, trial 4, $p = 0.0002$). **K-L.** Total interaction time during learning (K) and recall (L) trials of the SNP test. **M.** Interaction time during recall trial of the SNP test. Paired *t* tests $p = 0.03$, $p = 0.06$. **N.** Discrimination index during time during recall trial of the SNP test. One sample t test vs. 0: $p = 0.02$ and $p = 0.07$. Unpaired *t* test, $p = 0.002$. **O-P.** Total interaction time during learning (O) and recall (P) of the social novelty preference test following Arch or mCherry expression in ILA^{CRH} and silencing of their terminals in LS. For the entire figure, bar graphs represent mean ± S.E.M. Grey dots are different mice.



Supplementary Figure 10 related to Figure 4. Arch-mediated silencing of ILA^{CRH} neuron terminals in rdLS reduces CRH release. A. *CRH-Cre* mice injected with AAV2/2 CAG.FLEX.ArchT-tdTomato in ILA and AAV2/9 syn.CRF1.0 in rdLS and implanted with two optical ferrules above rdLS. **B.** Immunohistochemistry picture showing fiber tracts and viral expression. Scale bars: 1 mm and 200 µm. **C.** Schematic of the experiment. **D.** CRH-related events per minute. 7 mice, 1-2 observations per mice. Nested ANOVA, $F_{2, 18} = 8.578$, $p = 0.002$. Tukey's multiple comparison tests: T1 vs. T2, $p = 0.002$; T2 vs. T3, $p = 0.2$. **E.** Amplitude of CRH-related events. 7 mice, 1-2 observations per mice. Nested ANOVA, $F_{2, 18} = 1.492$, $p = 0.3$ **F.** Interaction times. 7 mice, 1-2 observations per mice. Nested ANOVA, $F_{2, 18} = 5.649$, $p = 0.008$. Tukey's multiple comparison tests: T1 vs. T2, $p = 0.01$; T2 vs. T3, $p = 0.02$.

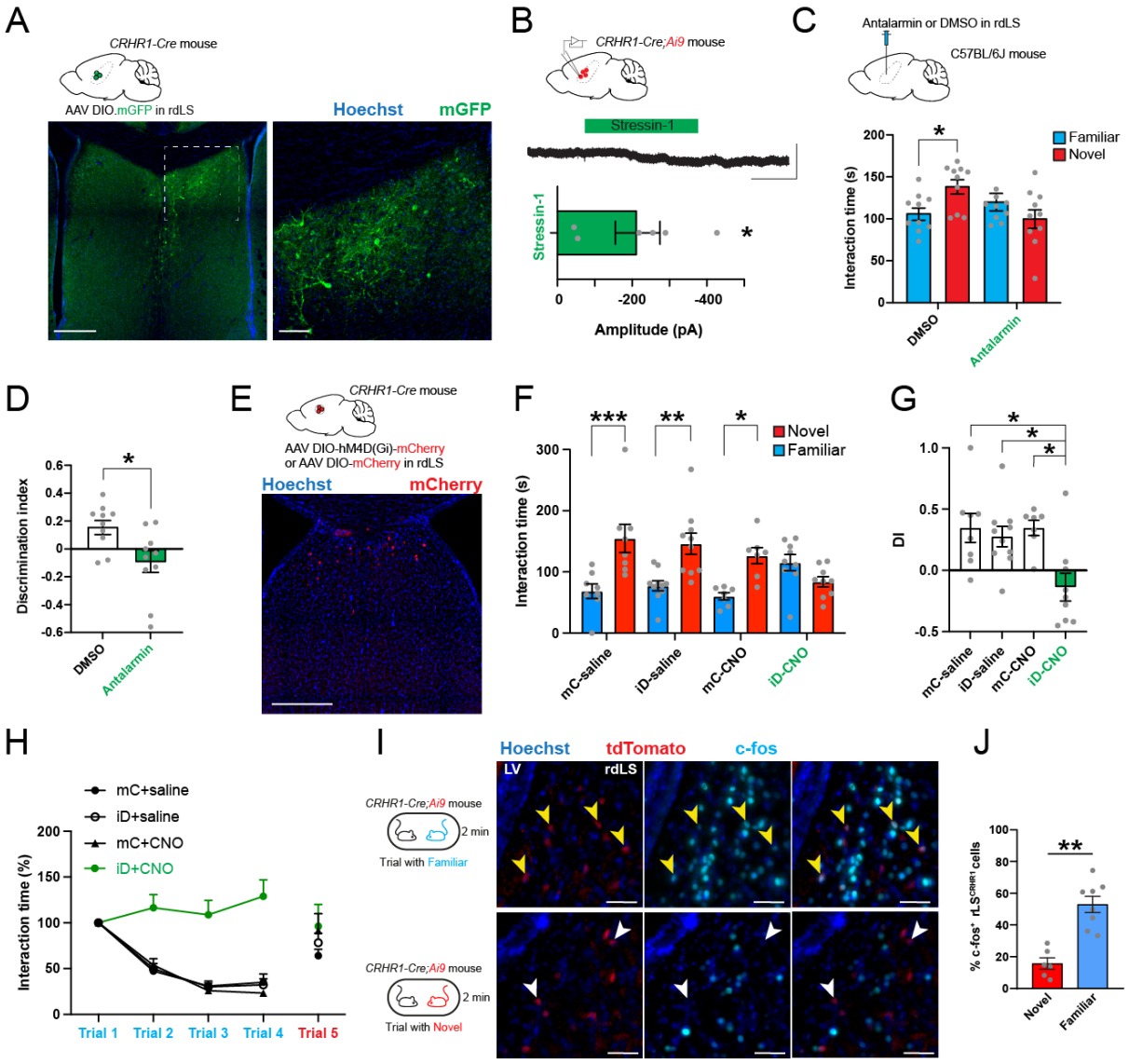
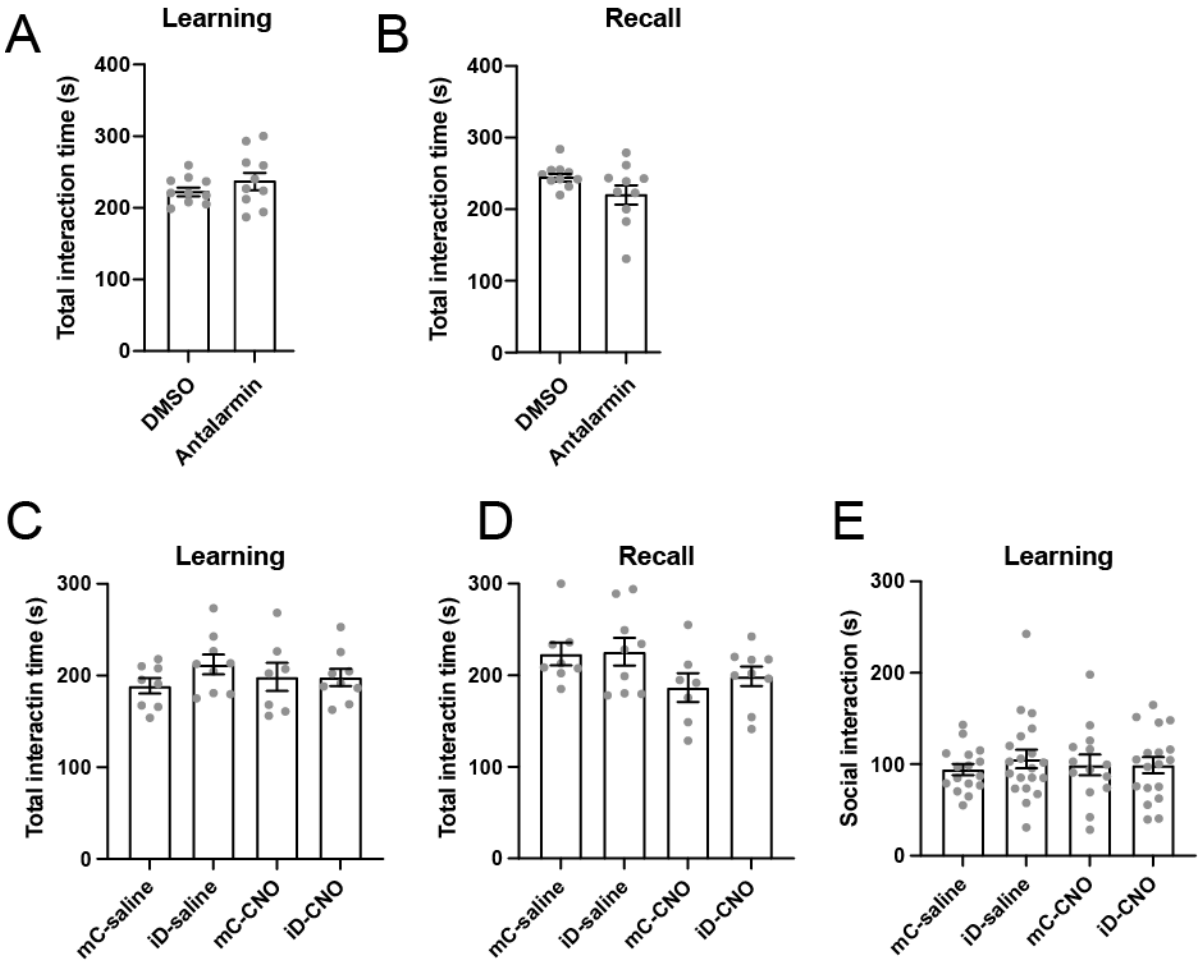


Figure 5. CRHR1^{+} neurons in rdLS are activated by social familiarity and regulate SNP and familiarization. A. *CRHR1-Cre* mice injected in rdLS with AAV2/5 hSyn.DIO.mGFP. Scale bars: 300 µm (left), 50 µm (right). **B.** Whole-cell patch-clamp recording of CRHR1-tdTomato cells in rdLS of *CRHR1-Cre;Ai9* mice (top). Voltage-clamp trace during bath application of 300 nM stressin-1 (middle). Scale bars: 100 pA and 2 min. Bar graph showing the amplitude of the decrease (bottom). **C.**C57BL/6J wild-type mice infused in rdLS with 2 µg of antalarmin dissolved in 0.6 µL of DMSO or DMSO as a control (top). Interaction time with familiar (blue) or novel (red) mouse during the recall trial of the social novelty preference test in mice infused with antalarmin or DMSO (bottom). Grey dots are different mice. 2-way ANOVA F(novelty x injection)$_{1,36}$ = 7.699, p = 0.009. Sidak's multiple comparison tests novel vs. familiar: DMSO, p = 0.04; antalarmin, p = 0.3. **D.** Discrimination index for social novelty preference during recall trial. Grey dots are different mice. One-sample t tests: p = 0.003 and p = 0.2. Unpaired t test:

p = 0.01. **E.** *CRHR1-Cre* mice injected in rdLS with AAV2/8 hSyn.DIO.hM4D(Gi)-mCherry (iDREADD) or AAV2/8 hSyn.DIO.mCherry (top). Immunohistochemistry pictures of iD-mCherry expression in rdLS. Scale bar: 300 µm (bottom). **F.** Interaction time with novel (red) or familiar (blue) mouse during the recall trial of the social novelty preference test in mice expressing mCherry (mC) or hM4Di (iD). Grey dots are different mice. 3-way ANOVA F(novelty x injection x virus)$_{1,60}$ = 3.845, *p* = 0.04. Sidak's multiple comparison tests novel vs. familiar: mC + saline, *p* = 0.0003; iD + saline, *p* = 0.001; mC + CNO, *p* = 0.01; iD + CNO, *p* = 0.4. **G.** Discrimination indexes for social novelty preference of the four groups during recall trial. One-sample *t* tests compared to 0: mC + saline, *p* = 0.02; iD + saline, *p* = 0.009; mC + CNO, *p* = 0.001; iD + CNO, *p* = 0.3. 2-way ANOVA: F(virus x injection)$_{1, 30}$ = 4.3, *p* = 0.04; F(virus)$_{1, 30}$ = 7.654, *p* = 0.009; F(injection)$_{1, 30}$ = 4.263, *p* = 0.05. Tukey's multiple comparison tests compared to the iD + CNO group: mC + saline, *p* = 0.009; iD + saline, *p* = 0.02; mC + CNO, *p* = 0.01. **H.** Normalized interaction times during repetitive social presentations. 7-8 mice per group. Two-way ANOVA, F(trial$_{1\text{-}4}$ x virus)$_{9,104}$ = 6.612, *p* < 0.0001; F(trial)$_{3,104}$ = 28.05, *p* < 0.0001; F(virus)$_{3,104}$ = 52.74, *p* < 0.0001. **I.** Immunohistochemistry pictures against c-fos of CRHR1-tdTomato mouse rdLS of following interaction with a familiar or novel mice. Scale bars: 50 µm. **J.** Percentage of CRHR1^{+} neurons expressing c-fos. 3 and 4 mice. 2 observations per mice. Nested *t* test, *p* = 0.007.



Supplementary Figure 11, related to Figure 5: Antalarmin infusion and rdLS^{CRHR1} neurons chemogenetic silencing controls. **A-B.** WT mice infused with DMSO or antalarmin. Total interaction time during the learning (A) and recall (B) phases of the social novelty preference test. **C-E.** *CRHR1-Cre* mice injected in rdLS with AAV2/8 hSyn.DIO.hM4D(Gi)-mCherry (iD) or AAV2/8 hSyn.DIO.mCherry (mC). **C-D.** Total interaction times during learning (C) or recall trial (D) of the social novelty preference test. **E.** Interaction time with each novel mouse during the learning trial of the social novelty preference test.

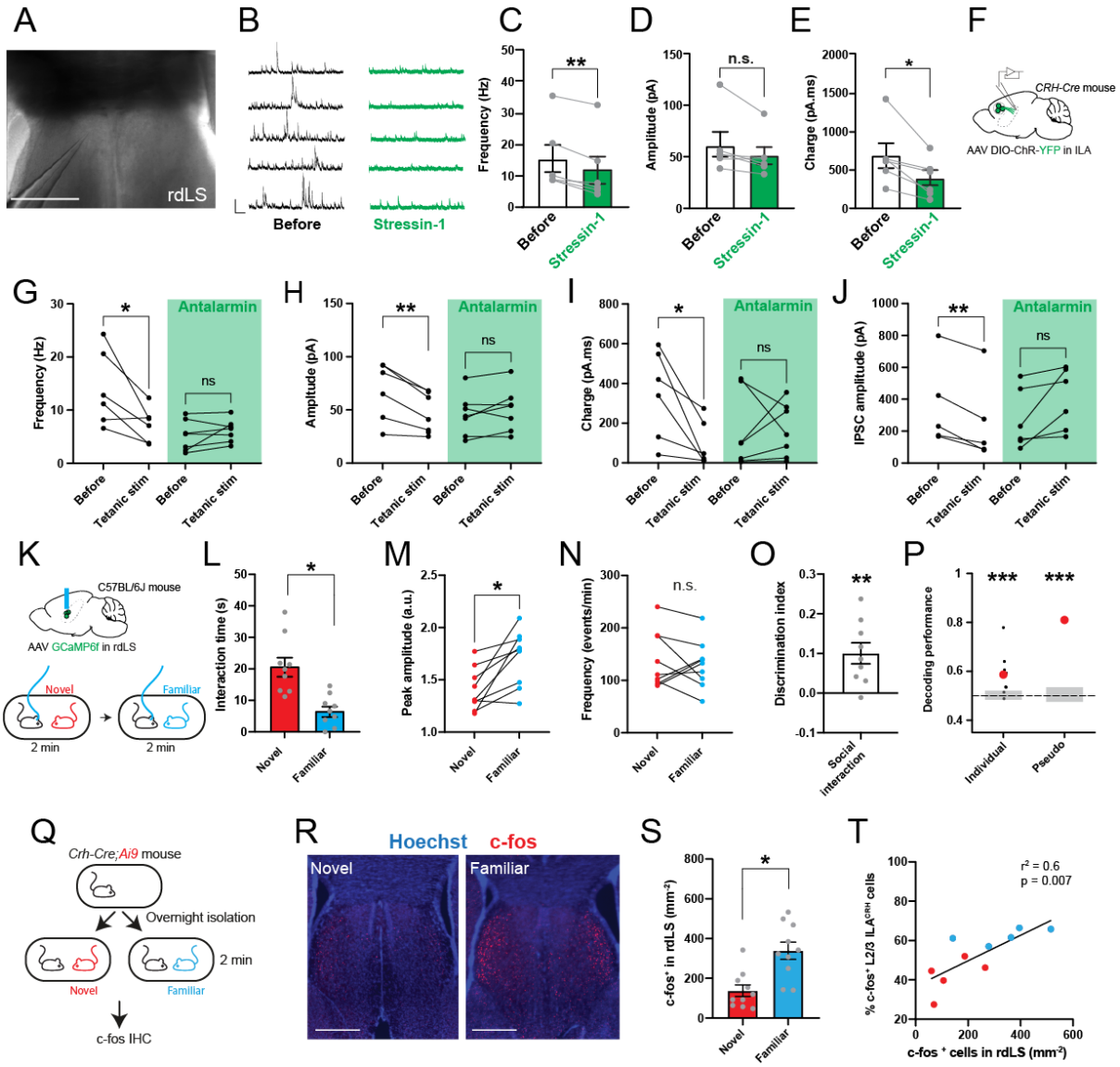
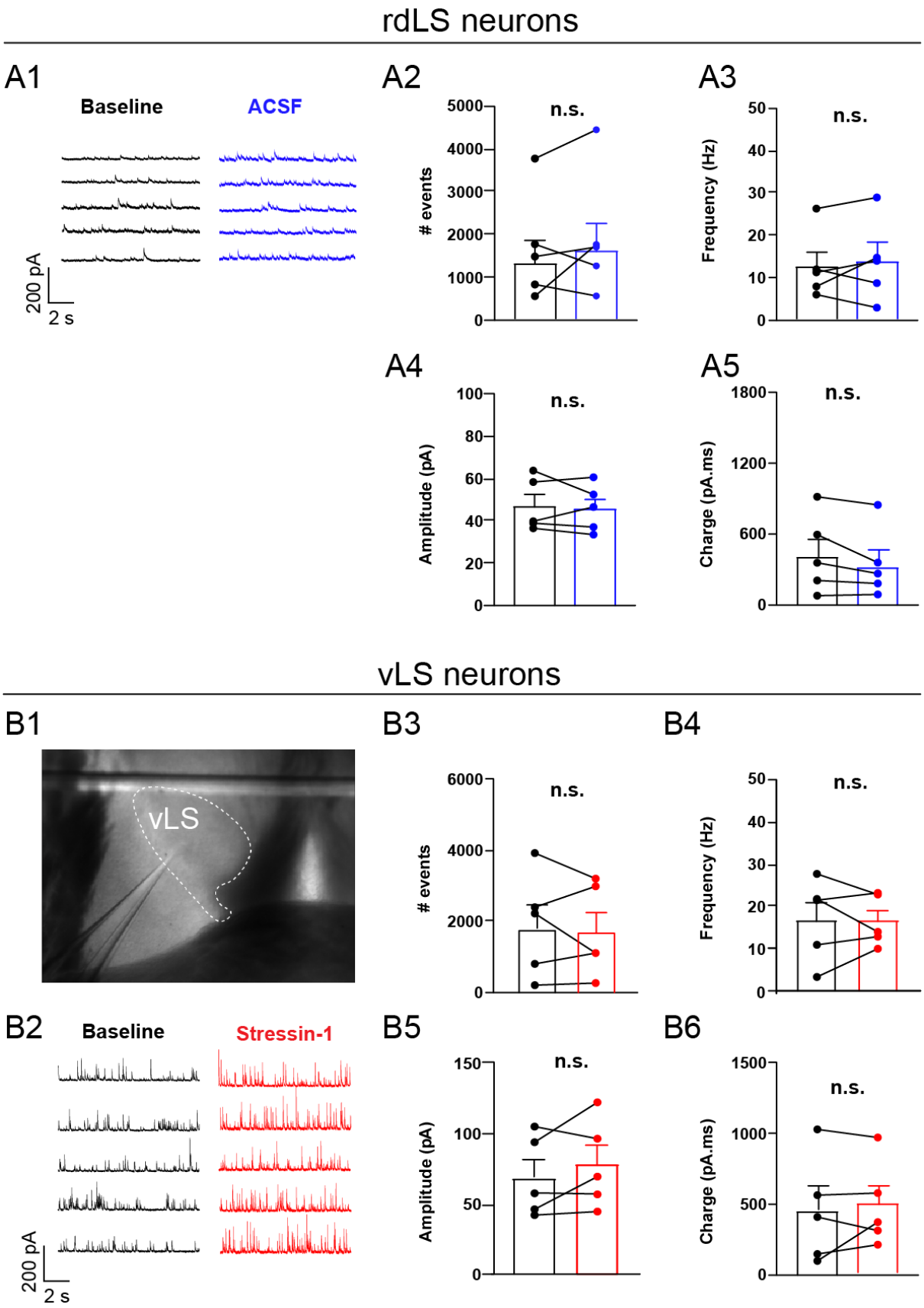


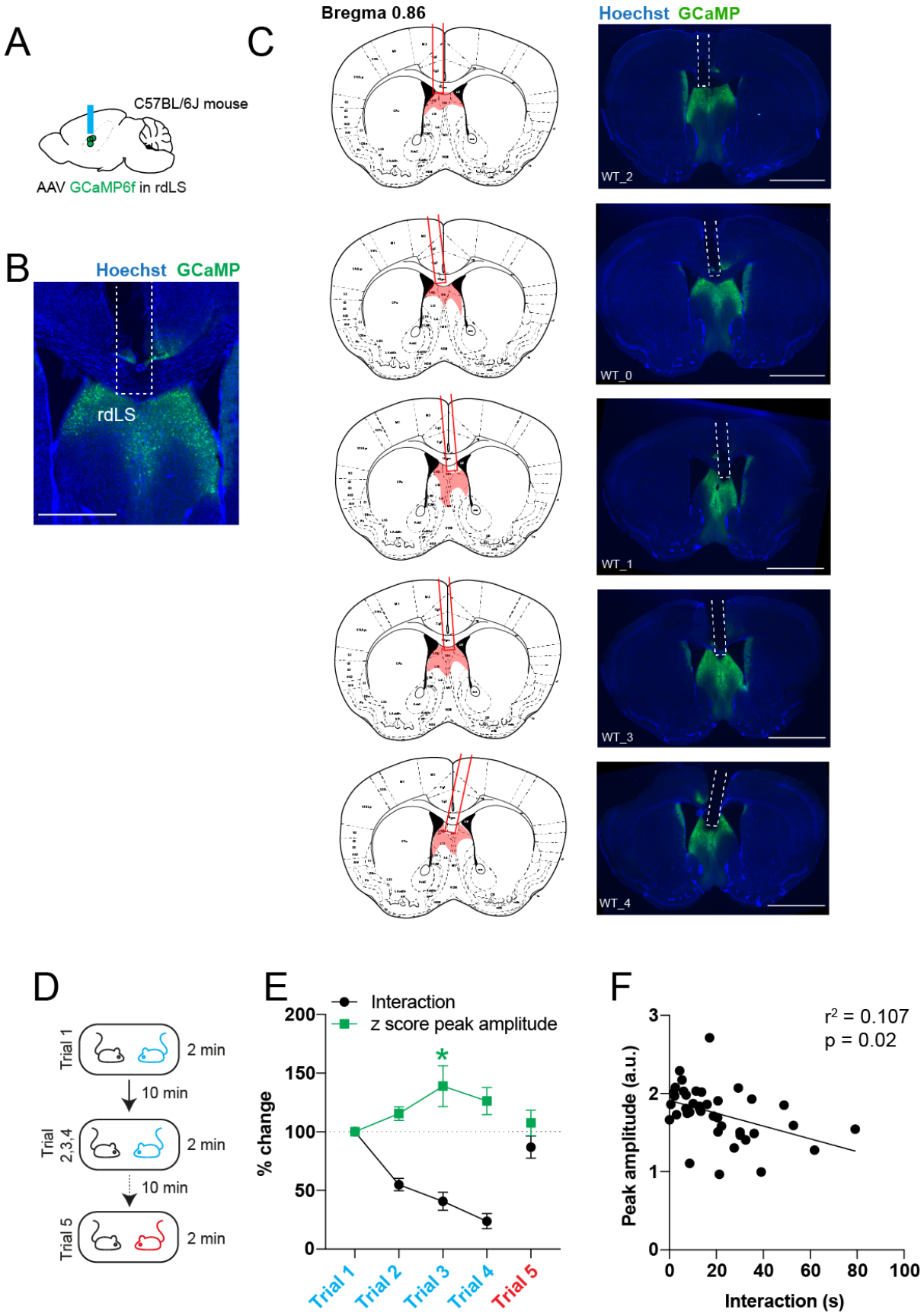
Figure 6: CRH signaling from ILA and familiar social interaction disinhibit rdLS. A. Differential interference contrast microscopy image of rdLS during patch-clamp recording. Scale bar: 500 µm. **B.** Example traces of IPSCs before or 15 min after application of 300 nM stressin-1. **C.** Frequency of IPSCs. **D.** Amplitude of IPSCs. **E.** IPSCs area under the curve. For C-E, points are obtained from individual cells recorded from separate slices in 6 mice. **F.** *CRH-Cre* mice injected with AAV2/9 EF1a.DIO.hChR2(E123T/T159C)-eYFP in ILA. **G-I.** Frequency (G), amplitude (H) and charge (I) of rdLS neuron spontaneous inhibitory events before and after tetanic light stimulation with or without 300 nM antalarmin. Each observation is from a different cell in separate brain slices obtained from 6 mice and 5 mice respectively. Paired *t* tests: p = 0.03, 0.2, 0.0003, 0.2, 0.03 and 0.9. **J.** Electrically evoked IPSC of rdLS neuron spontaneous inhibitory events before and after tetanic light stimulation with or without 300 nM antalarmin. Paired *t* tests: p = 0.006 and 0.07. **K.** C57BL/6J wild-type mice injected in rdLS

with AAV2/1 Syn.GCaMP6f and implanted with an optical ferrule above rdLS. Implanted mice were presented with novel then familiar mice. **L.** Interaction time during social presentation (left). 9 recording sessions using 5 mice. Nested *t* test, $p = 0.01$. **M.** Average peak amplitude of the z-score during presentation of a novel or familiar mouse. Nested *t* test: $p = 0.03$. **N.** Frequency of events during presentation of a novel or a familiar mouse. Nested *t* test: $p = 0.8$. **O.** Discrimination index for social familiarity preference calculated from z-scores. Nested *t* tests compared to 0: $p = 0.002$. **P.** Decoding performance for familiarity versus novelty from individual recordings or pseudo-simultaneous data. Small black dots on the left are the results from each individual recording sessions using 20 cross-validation iterations, large red dot is the average. Red dot on the right is the result of pseudo-population analysis from 100 cross-validation iterations. Grey areas denote chance level computed using permutation tests (2.5 – 97.5 percentiles in distribution of shuffled decoding performances). In both cases, statistical significance is determined by the probability of drawing the observed decoding performance from the distribution of shuffled decoding performances (null-hypothesis). $p < 0.001$ (two-tailed permutation test, see *Methods*). **Q.** *CRH-Cre;Ai9* mice were presented with novel or familiar mice after overnight isolation before being processed for immunohistochemistry against c-fos. **R.** Immunohistochemistry images of c-fos labelling in rdLS following social presentation with a novel or familiar mouse (same experiment than Fig. 3N). Scale bars: 500 µm. **S.** Density of rdLS cells positive for c-fos. For each mouse, one observation on each side of a rLS section. 5 mice per group. Nested *t* test, $p = 0.02$. **T.** Percentage of layer 2/3 ILA^{CRH} cells positive for c-fos (cf. Fig. 3) vs. density of rdLS cells positive for c-fos following social interactions. Each point represents a mouse.



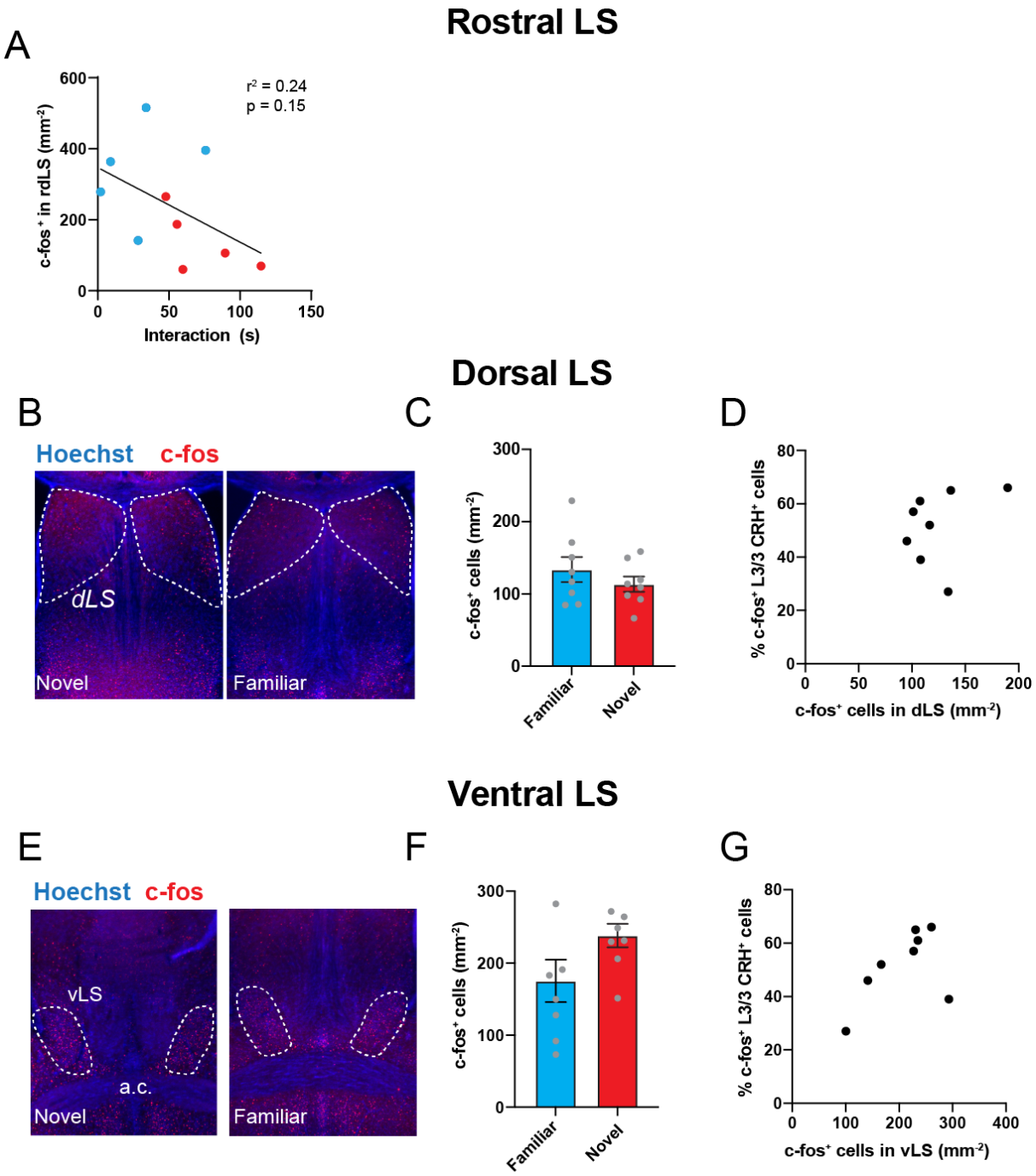
Supplementary Figure 12, related to Figure 6: Controls for in vitro electrophysiology recordings in LS. A. In vitro whole-cell patch-clamp of rdLS neurons. **A1.** Example trace of

IPSCs before or 15 min after application of ACSF. **A2.** Number of IPSCs. Points are individual cells recorded in 5 mice. **A3.** Frequency of IPSCs. **A4.** Amplitude of IPSCs. **A5.** IPSCs area under the curve. **B.** Neurons recorded in vLS before and after application of 300 nM stressin-1. **B1.** DIC image of the LS region where cells were recorded. Scale bar: 200 µm. **B2.** Example trace of IPSCs before or after 15 min 300 nM stressin-1. **B3.** Number of IPSCs. Points are individual cells recorded in 5 mice. **B4.** Frequency of IPSCs. **B5.** Amplitude of IPSCs. **B6.** IPSCs area under the curve. For the entire figure, bar graphs represent mean ± S.E.M.



Supplementary Figure 13, related to Figure 6: Fiber-photometry recordings in rdLS. A. C57BL/6J wild-type mice injected in rdLS with AAV2/1 Syn.GCaMP6f and implanted with an

optical ferrule above rdLS. **B.** Immunohistochemistry image showing GCaMP expression in rdLS and the optical ferrule implanted above the injection site. Scale bar: 500 µm. **C.** Detail of every recorded mouse. Scale bars 2 mm. **D.** Schematic of the repetitive social presentation test. **E.** Fiber-photometry recording during repetitive social presentation test (10 recording sessions in 5 mice). One-way ANOVA $F(\text{trial 1-4})_{3,27} = 3.389$, $p = 0.03$ followed by Dunnett's multiple comparison tests compared to trial 1: trial 2 $p = 0.5$, trial 3 $p = 0.01$ and trial 4 $p = 0.1$. **F.** Interaction times (trial 1 to trial 4) vs. z-scores during the same experiment.



Supplementary Figure 14, related to Figure 6: Dorsal and ventral posterior LS do not respond to social familiarity versus social novelty. A. Density of rdLS cells positive for c-fos vs. interaction time during social interaction with novel (red) or familiar (blue) mice. Each point represents one mouse, N = 5 mice. **B.** Immunohistochemistry images of c-fos labelling in posterior dorsal LS (dLS). Scale bars: 500 µm. **C.** Density of dLS cells positive for c-fos. Each point is from a different image obtained from 4 mouse. Unpaired *t* test, $p = 0.3$. **D.** Percentage of ILA^{CRH} cells positive for c-fos in layer 2/3 vs. density of dLS cells positive for c-fos following social interaction. Each point represents one mouse. **E.** Immunohistochemistry images of c-

fos labelling in posterior ventral LS (vLS). Scale bars: 500 µm. **F.** Density of vLS cells positive for c-fos. Each point is from a different image obtained from 4 mouse. Unpaired *t* test, p = 0.08. **G.** Percentage of ILA^{CRH} cells positive for c-fos in layer 2/3 vs. density of vLS cells positive for c-fos following social interaction. Each point represents one mouse. For the entire figure, bar graphs represent mean ± S.E.M.

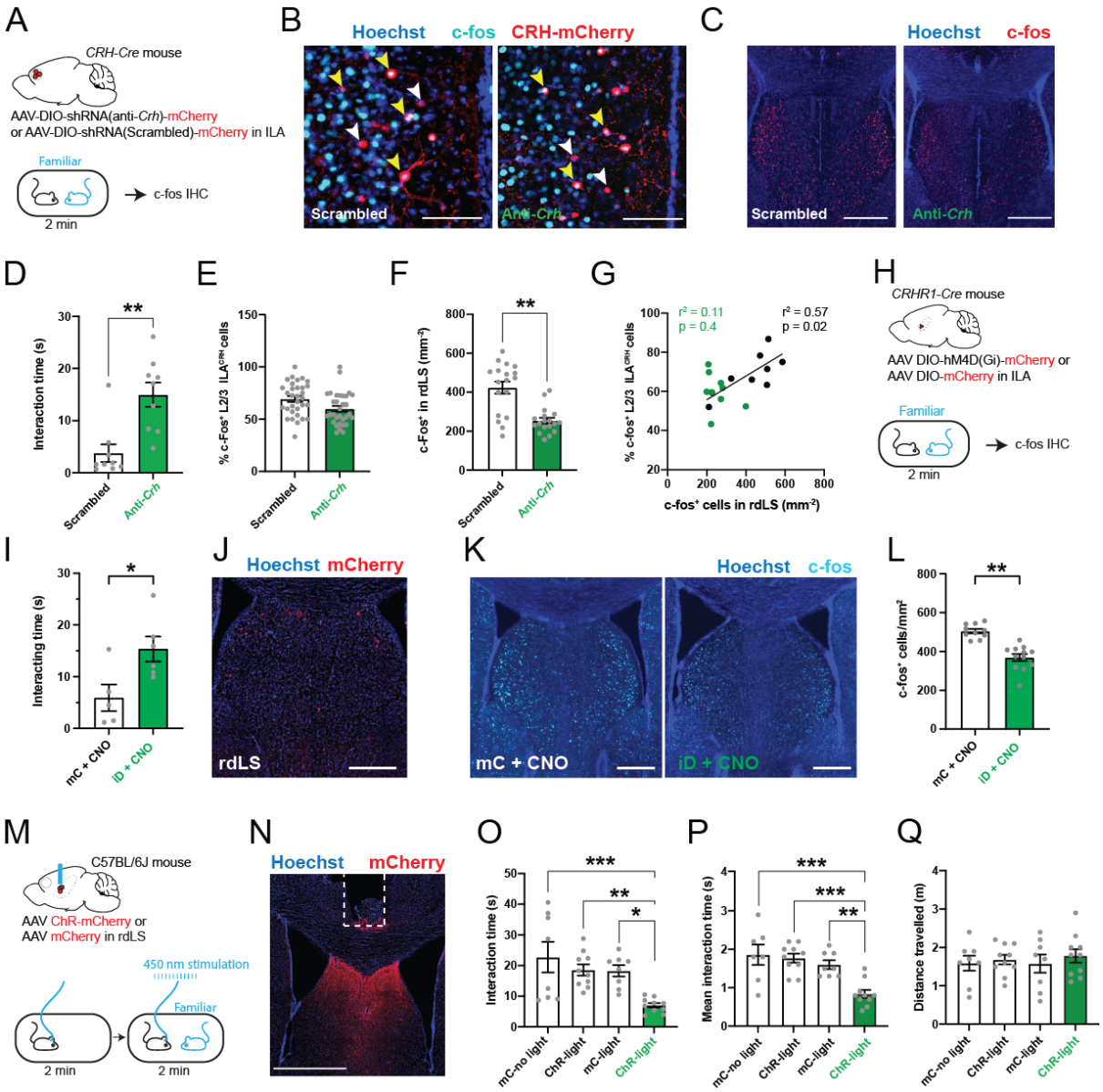


Figure 7: CRH release from ILA and rdLS^{CRHR1} neurons regulate rdLS disinhibition and social interaction with a familiar mouse. A. *CRH-Cre* mice injected in ILA with AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(anti-*Crh*) or AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(scrambled) presented with a familiar mouse for 2 min before being processed for immunohistochemistry against c-fos. **B-C.** Immunohistochemistry images of c-fos labelling in ILA (B) and rdLS (C). Yellow arrowheads: c-fos$^+$ / tdTomato$^+$ cells. White arrowheads: c-fos$^-$ / tdTomato$^+$ cells. Scale bars: 100 µm and 300 µm. **D.** Duration of interaction during familiar presentation. Each point is one mouse. Unpaired *t* test, $p = 0.001$. **E.** Percentage of layer 2/3 ILA^{CRH} cells positive for c-fos in layer 2/3 of ILA. Each point corresponds to each side of 2 sections. 9 mice per group. **F.** Density of rdLS cells positive for c-fos. We made one observation on each side of a rLS section. 9 mice per group. Nested *t* test, $p = 0.002$. **G.** Percentage of layer 2/3 ILA^{CRH} cells positive for

c-fos vs. density of rdLS cells positive for c-fos following social interaction with a familiar mouse. Each point represents one mouse. **H.** *CRHR1-Cre* mice injected in rdLS with AAV2/8 hSyn.DIO.hM4D(Gi)-mCherry (iDREADD) or AAV2/8 hSyn.DIO.mCherry presented with a familiar mouse for 2 min before being processed for immunohistochemistry against c-fos. **I.** Interaction time with familiar mouse. Each point is one mouse. Unpaired *t* test, $p = 0.03$. **J.** Immunohistochemistry picture of mCherry expression in rdLS. Scale bar: 400 µm. **K.** Immunohistochemistry pictures of c-fos expression in rdLS. Scale bar: 400 µm. **L.** Density of rdLS cells positive for c-fos. For each mouse, one observation on each side of a rLS section. 5 and 6 mice per group. Nested *t* test, $p = 0.002$. **M.** C57BL/6J wild-type mice were injected with AA2/2 hSyn1.hChR2(H134R)-mCherry or AA2/2 hSyn1.mCherry as control and an optical fiber was implanted above the injection site. Mice were then presented to a familiar mouse for 2 min meanwhile 450 nm light was applied (20 Hz, 1 ms). Mice were also run without light as additional controls. **N.** Immunohistochemistry picture of viral injection. Scale bar: 1 mm. **O.** Total interaction time with familiar mouse. Each point represents one mouse. One-way ANOVA: $F_{3,32} = 7.01$, $p < 0.0001$. Dunnett's multiple comparison tests: ChR-light vs. YFP-no light $p = 0.0005$, ChR-light vs. ChR-no light $p = 0.006$, ChR-light vs. YFP-light $p = 0.01$. **P.** Average duration of each bout of social interaction. Each point represents one mouse. One-way ANOVA: $F_{3,31} = 10.62$, $p < 0.0001$. Dunnett's multiple comparison tests: ChR-light vs. YFP-no light $p = 0.0001$, ChR-light vs. ChR-no light $p = 0.0001$, ChR-light vs. YFP-light $p = 0.003$. **Q.** Total distance travelled. Each point represents one mouse. For the entire figure, bar graphs represent mean ± S.E.M.

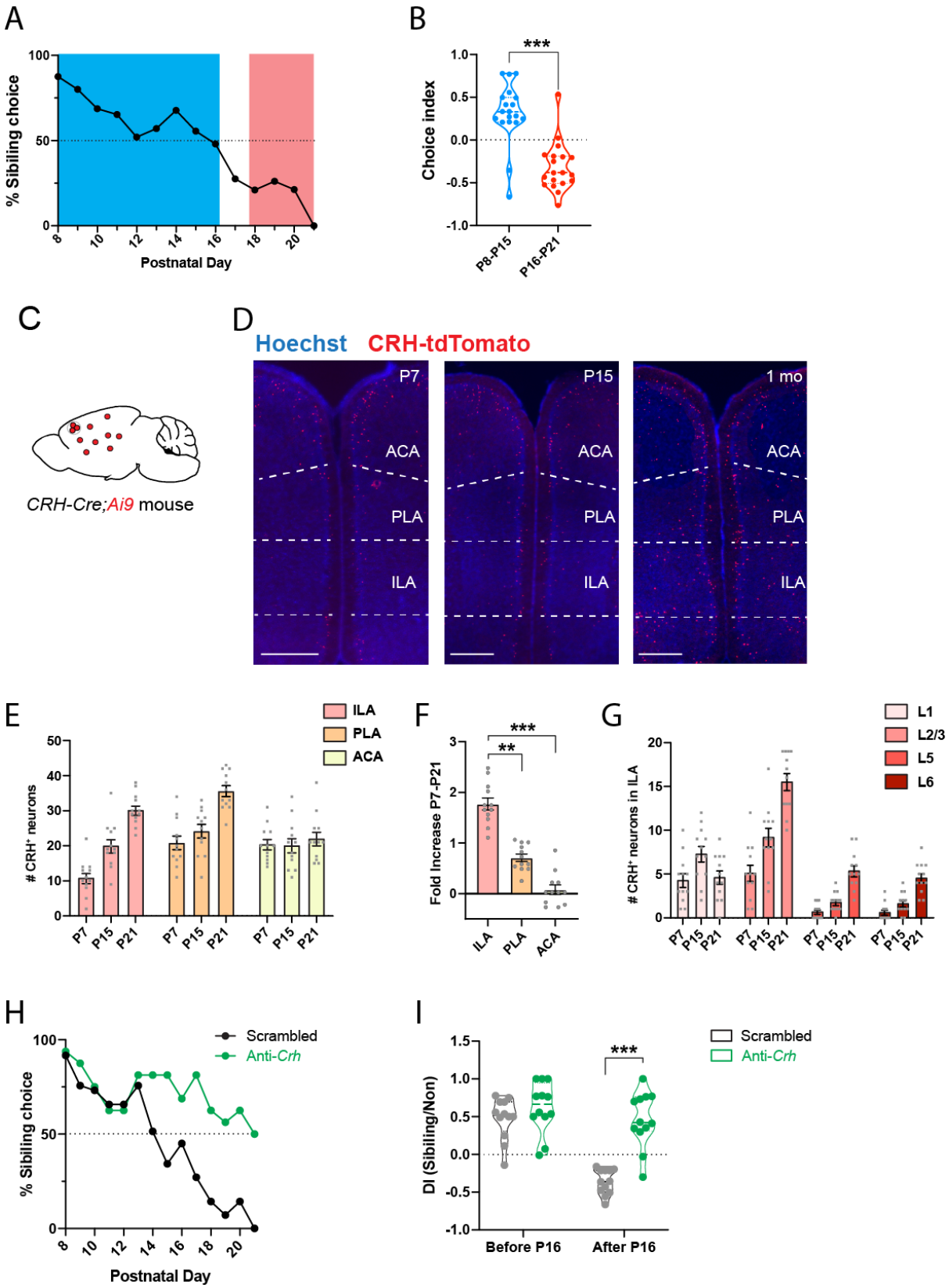
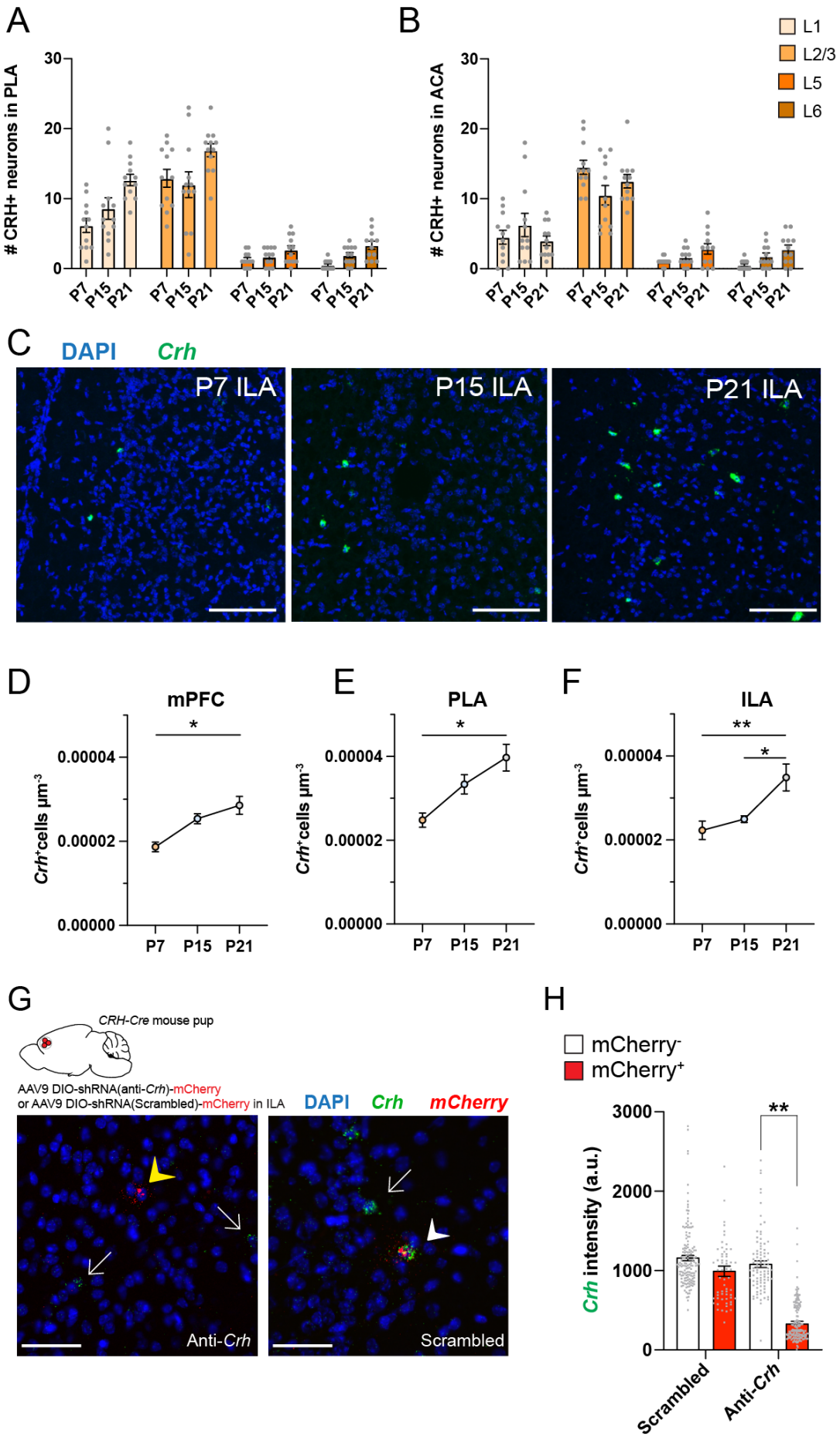


Figure 8: Increased CRH expression in ILA supports a shift in social preference in young mice.

A. Percentage of familiar choice during development, 19 mice. **B.** Discrimination index for familiar kin before and after postnatal day 16. Each point represents a mouse, 19 mice.

Unpaired *t* test, $p < 0.001$. **C.** *CRH-Cre;Ai9* mice. **D.** mPFC images of *CRH-Cre;Ai9* mice at P7, P15 or P21. Scale bars: 500 µm. **E.** Number of CRH^+ cells in ILA, PLA and ACA during development. Each point represents one observation made on each side of 2 section, 3 mice per group. Nested one-way ANOVA tests comparing CRH cells along postnatal day: $F(ILA)_{2,6} = 18.64$, $p = 0.003$; $F(PL)_{2,6} = 11.47$, $p = 0.009$; $F(ACA)_{2,6} = 0.22$, $p = 0.8$. **F.** Fold-increase of CHR^+ cells between P7 and P21. P21 values compared to the average P7 value. Nested one-way ANOVA $F_{1,6} = 63.03$, $p < 0.0001$. Post-hoc Tukey's multiple comparison test: ILA vs. PLA $p = 0.001$; ILA vs. ACA $p < 0.0001$. **G.** Number of CRH^+ cells per ILA layers during development. Each point represents one observation made on each side of 2 section, 3 mice per group. **H.** Percentage of familiar choice during development in *CRH-Cre* mice injected in ILA with AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(anti-*Crh*) to downregulate *Crh* or control AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(scrambled). 12 pups per group. Chi-square test: $p < 0.0001$. **I.** Discrimination index for familiar kin before and after postnatal day 16. Each point represents a mouse, 12 pups per group. Unpaired *t* tests: $p = 0.3$ and $p < 0.0001$. For the entire figure, bar graphs represent mean ± S.E.M.


A
CRH+ neurons in PLA
30
20
10
0
P7
P15
P21
B
CRH+ neurons in ACA
L1
L2/3
L5
L6
C
DAPI
Crh
P7 ILA
P15 ILA
P21 ILA
D
mPFC
E
PLA
F
ILA
Crh+cells µm-3
0.00004
0.00002
0.00000
*
**
G
CRH-Cre mouse pup
AAV9 DIO-shRNA(anti-Crh)-mCherry
or AAV9 DIO-shRNA(Scrambled)-mCherry in ILA
DAPI
Crh
mCherry
Anti-Crh
Scrambled
H
mCherry-
mCherry+
Crh intensity (a.u.)
3000
2000
1000
0
Scrambled
Anti-Crh

Supplementary Figure 15, related to Figure 8: CRH^+ cell distribution per layers in PLA and ACA, *Crh* expression in ILA across ages and *Crh* knock-down in young pups. A. Evolution of the number of CRH^+ cells per PLA layers. **B.** Evolution of the number of CRH^+ cells per ACA layers. Each point represents one observation made on each side of 2 section, 3 mice per group. **C.** In situ hybridization pictures against *Crh* of ILA at P7, P15 and P21. Scale bars 100 µm. **D-F.** Density of Crh^+ cells in mPFC, PLA and ILA. 3 mice per age. Nested one-way ANOVAs followed by Tukey's multiple comparison tests. $F_{2,28} = 6.731$, $p = 0.03$; $F_{2,28} = 8.088$, $p = 0.02$; $F_{2,27} = 7.766$, $p = 0.002$. **G.** *CRH-Cre* pup mice injected in ILA with AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(anti-*Crh*) to downregulate *Crh* or control AAV2/9 CMV-DIO-(mCherry-U6)-shRNA(scrambled) (top). In situ hybridization images of ILA slices expressing shRNA against *Crh* (left) or a scrambled shRNA (right) labelled for *mCherry* and *Crh*. White arrows denote CRH^+ neurons that do not express virus. Yellow arrowhead denotes CRH^+ cells expressing the anti-*Crh* shRNA, with reduced level of *Crh*. White arrowheads denote CRH^+ neurons expressing the scrambled shRNA, with intact *Crh* level. Scale bars: 50 µm. **H.** Quantification of *Crh* expression in cells using in situ hybridization images in ILA slices from mice injected with AAV expressing scrambled or anti-*Crh* shRNAs. In each slice neurons were classified as to whether they were uninfected or infected with virus based on *mCherry* expression (3 mice per group; each point is from a different neuron). Note the reduction in *Crh* expression in neurons infected with anti-*Crh* shRNA. Nested one-way ANOVA $F_{3,8} = 16.44$, $p = 0.0009$ followed by Tukey's multiple comparison test, anti-*Crh* + $mCherry^+$ vs. anti-*Crh* + $mCherry^-$, $p = 0.0012$. Bar graphs represent mean ± S.E.M.