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Supplementary Materials for

Opposite effects of stress on effortful motivation in high and low anxiety are mediated by CRHR1 in the VTA

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The PDF file includes:

Figs. S1 to S6
Tables S1 and S2

Other Supplementary Material for this manuscript includes the following:

Source data

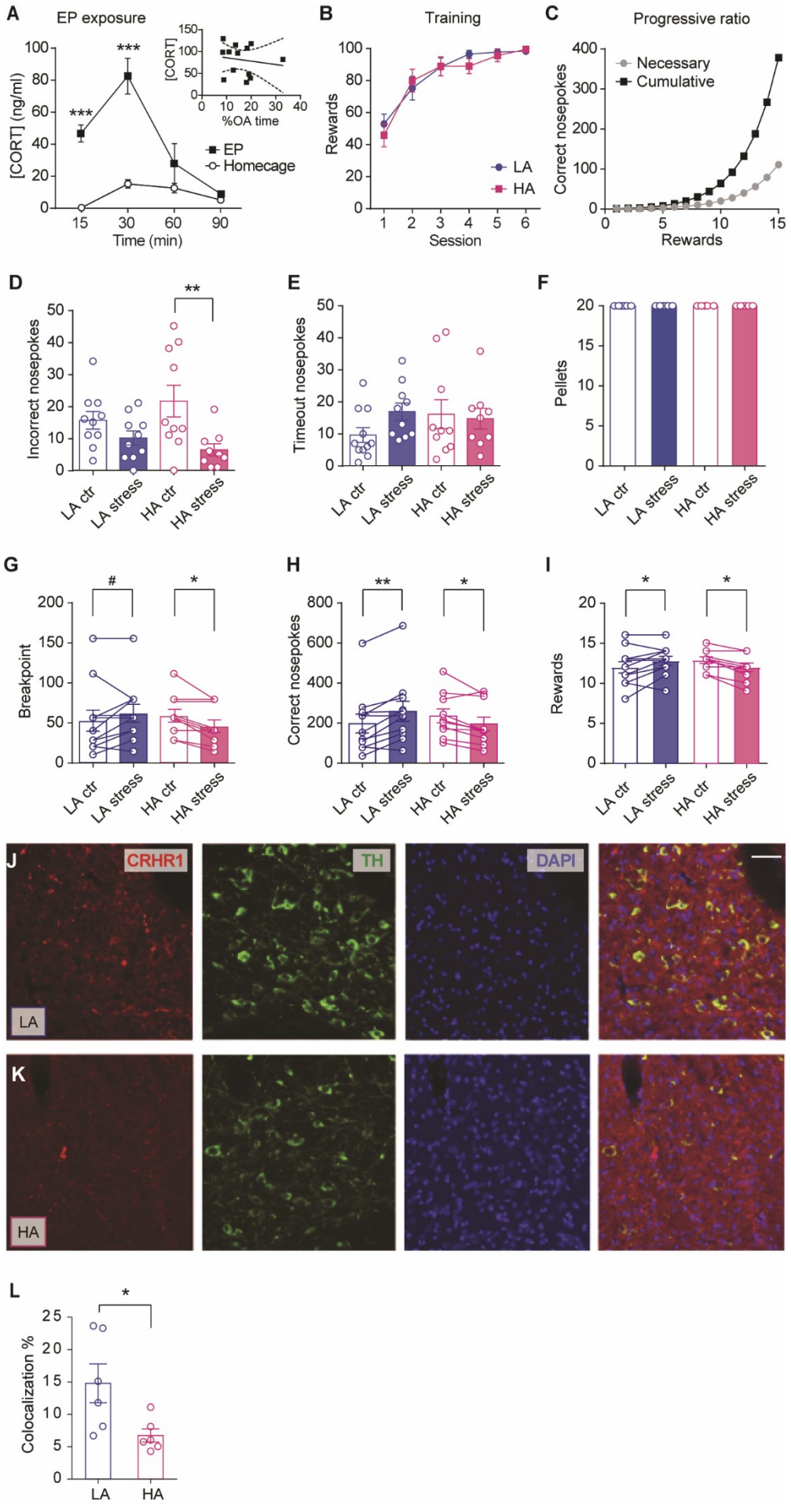
A
EP exposure
[CORT] (ng/ml)
Time (min)
%OA time
EP
Homecage
B
Training
Rewards
Session
LA
HA
C
Progressive ratio
Correct nosepokes
Necessary
Cumulative
Rewards
D
Incorrect nosepokes
E
Timeout nosepokes
F
Pellets
G
Breakpoint
H
Correct nosepokes
I
Rewards
LA ctr
LA stress
HA ctr
HA stress
J
CRHR1
TH
DAPI
LA
K
HA
L
Colocalization %
LA
HA

Fig. S1. Additional data on progressive ratio test performance. (A) Plasma corticosterone (CORT) levels at different time points following rats' exposure to the elevated platform (EP, n = 11) and in non-stressed rats in which blood samples were taken at equivalent time points (home cage, n = 8). Two-way ANOVA showed a significant effect of stress ($F_{(1,17)}$ = 22.49, p = 0.0002), a significant effect of time ($F_{(3,51)}$ = 14.07, p < 0.001) and a significant interaction ($F_{(3,51)}$ = 9.728, p < 0.0001). Insert, lack of correlation between peak CORT response and trait anxiety, as measured by % of time spent in the open arm (OA) of the elevated plus maze (r = -0.149, p = 0.628), supporting the view that all animals are stressed regardless their individual anxiety levels. **(B)** No difference in training performance was observed between LA and HA rats involved in stress experiments. Two-way repeated measures ANOVA revealed a non-significant session x anxiety interaction ($F_{(5,190)}$ = 0.6091, p = 0.693), a non-significant effect of anxiety ($F_{(1,38)}$ = 0.105, p = 0.748) and a significant effect of session ($F_{(5, 190)}$ = 36.00, p < 0.001). **(C)** Necessary (the number of nosepokes rats needed to carry out after acquiring the previous reward in order to acquire the next one) and cumulative nosepokes (all nosepokes rats needed to perform from the beginning of the task to reach each reward) for each reward in the PR test. **(D)** Two-way ANOVA showed a non-significant interaction effect ($F_{(1,36)}$ = 2.378, p = 0.132), a non-significant effect of anxiety ($F_{(1,36)}$ = 0.145, p = 0.705) and a significant effect of stress ($F_{(1,36)}$ = 10.70, p = 0.0024) on the number of incorrect nosepokes performed. **(E)** Two-way ANOVA showed a non-significant interaction effect ($F_{(1,34)}$ = 0.9755, p = 0.330), a non-significant effect of anxiety ($F_{(1,34)}$ = 0.729, p = 0.399) and a non-significant effect of stress ($F_{(1,34)}$ = 0.312, p = 0.580) on the number of timeout nosepokes. **(F)** All rats consumed 20 pellets when they were given access to them in a home cage-like environment, regardless of stress exposure, intra-VTA treatment or anxiety levels. **(G-I)** When the same rats were used for both conditions (control-stress) for the PR test session, the observed effect resembled the stress effect seen when rats were used either as controls or after stress exposure. **(G)** Two-way repeated measures ANOVA revealed a significant stress x anxiety interaction ($F_{(1, 19)}$ = 9.949, p = 0.0052), a non-significant effect of anxiety ($F_{(1, 19)}$ = 0.117, p = 0.736) and a non-significant effect of stress ($F_{(1,19)}$ = 0.2786, p = 0.604) on breakpoint. **(H)** Two-way repeated measures ANOVA revealed a significant stress x anxiety interaction ($F_{(1,19)}$ = 25.57, p < 0.0001), a non-significant effect of anxiety ($F_{(1,19)}$ = 0.043, p = 0.8384) and a non-significant effect of stress ($F_{(1,19)}$ = 1.175, p = 0.2919) on the number of correct nosepokes performed. **(I)** Two-way repeated measures ANOVA revealed a significant stress x anxiety interaction ($F_{(1,19)}$ = 13.04, p = 0.0019), a non-significant effect of anxiety ($F_{(1,19)}$ = 0.003, p = 0.958) and a non-significant effect of stress ($F_{(1,19)}$ = 0.0296, p = 0.865) on the number of obtained rewards. **(J-K)** Expression of CRHR1 protein (red) in TH^+ cells (green) (DA neurons), along with nuclear staining with DAPI (blue) and merged image in the VTA of LA (**J**) and HA rats (**K**). **(L)** LA rats had higher CRHR1 protein expression in DA neurons than HA rats (two-tailed t-test, $t_{(10)}$ = 2.546, p = 0.029). Asterisks denote significant differences at respective t-tests or post-hoc tests (***, p < 0.001, **, p < 0.01, *, p < 0.05, #, p < 0.1).

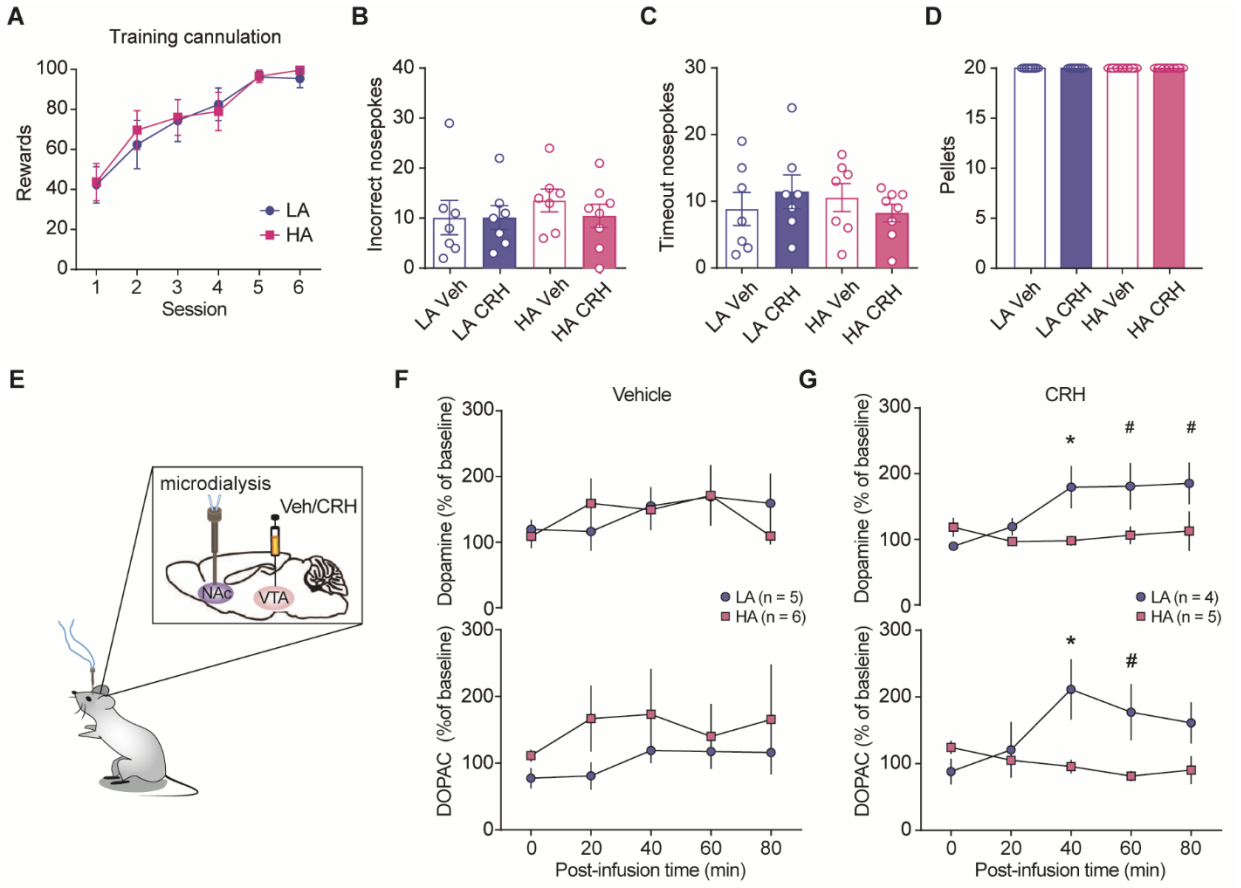

Fig. S2. Effects of intra-VTA CRH treatment on progressive ratio test performance and NAc DA release. **(A)** No difference in training performance was observed between cannulated LA and HA rats. Two-way repeated measures ANOVA revealed a non-significant session x anxiety interaction ($F_{(5,135)}$ = 0.162, p = 0.976), a non-significant effect of anxiety ($F_{(1,27)}$ = 0.055, p = 0.817) and a significant effect of session ($F_{(5, 135)}$ = 20.45, p < 0.001) in cannulated rats. **(B)** Two-way ANOVA showed a non-significant anxiety x treatment interaction effect ($F_{(1,25)}$ = 0.342, p = 0.564), a non-significant effect of anxiety ($F_{(1,25)}$ = 0.519, p = 0.478) and a non-significant effect of treatment ($F_{(1,25)}$ = 0.342, p = 0.564) on the number of incorrect nosepokes. **(C)** Two-way ANOVA showed a non-significant anxiety x treatment interaction effect ($F_{(1,25)}$ = 1.335, p = 0.259), a non-significant effect of anxiety ($F_{(1,25)}$ = 0.12, p = 0.732) and a non-significant effect of treatment ($F_{(1,25)}$ = 0.003, p = 0.9531) on the number of timeout nosepokes. **(D)** All rats consumed all 20 pellets when they were given free access to them, regardless of anxiety or treatment. **(E)** Scheme for measurement of DA and DOPAC release in the NAc following intra-VTA treatment with vehicle or CRH. **(F)**, Two-way ANOVA revealed no difference in DA and DOPAC release following intra-VTA vehicle treatment in HA and LA rats (DA: Interaction: $F_{(4,36)}$ = 1.177, p = 0.338, anxiety: $F_{(1,9)}$ = 0.014, p = 0.908, time: $F_{(4,36)}$ = 1.870, p = 0.133; DOPAC: interaction: $F_{(4,36)}$ = 0.425, p = 0.79, anxiety: $F_{(1,9)}$ = 0.757, p = 0.407, time: $F_{(4,36)}$ = 1.197, p = 0.329); n = 5-6 per group. **(G)** Effects of intra-VTA CRH treatment on NAc DA and DOPAC release. LA rats had higher DA and DOPAC release in the NAc compared to HA rats. DA: Two-way ANOVA revealed a significant anxiety effect ($F_{(1,7)}$ = 9.406, p = 0.018) and a marginally non-significant anxiety x time interaction ($F_{(4,28)}$ = 2.589, p = 0.058). DOPAC: Two-way ANOVA revealed a significant anxiety x time interaction ($F_{(4,28)}$ = 6.302, p = 0.001) and a non-significant anxiety effect ($F_{(1,7)}$ = 3.132, p = 0.12); n = 4-5 per group. (*, p < 0.05, #, p ≤ 0.07).

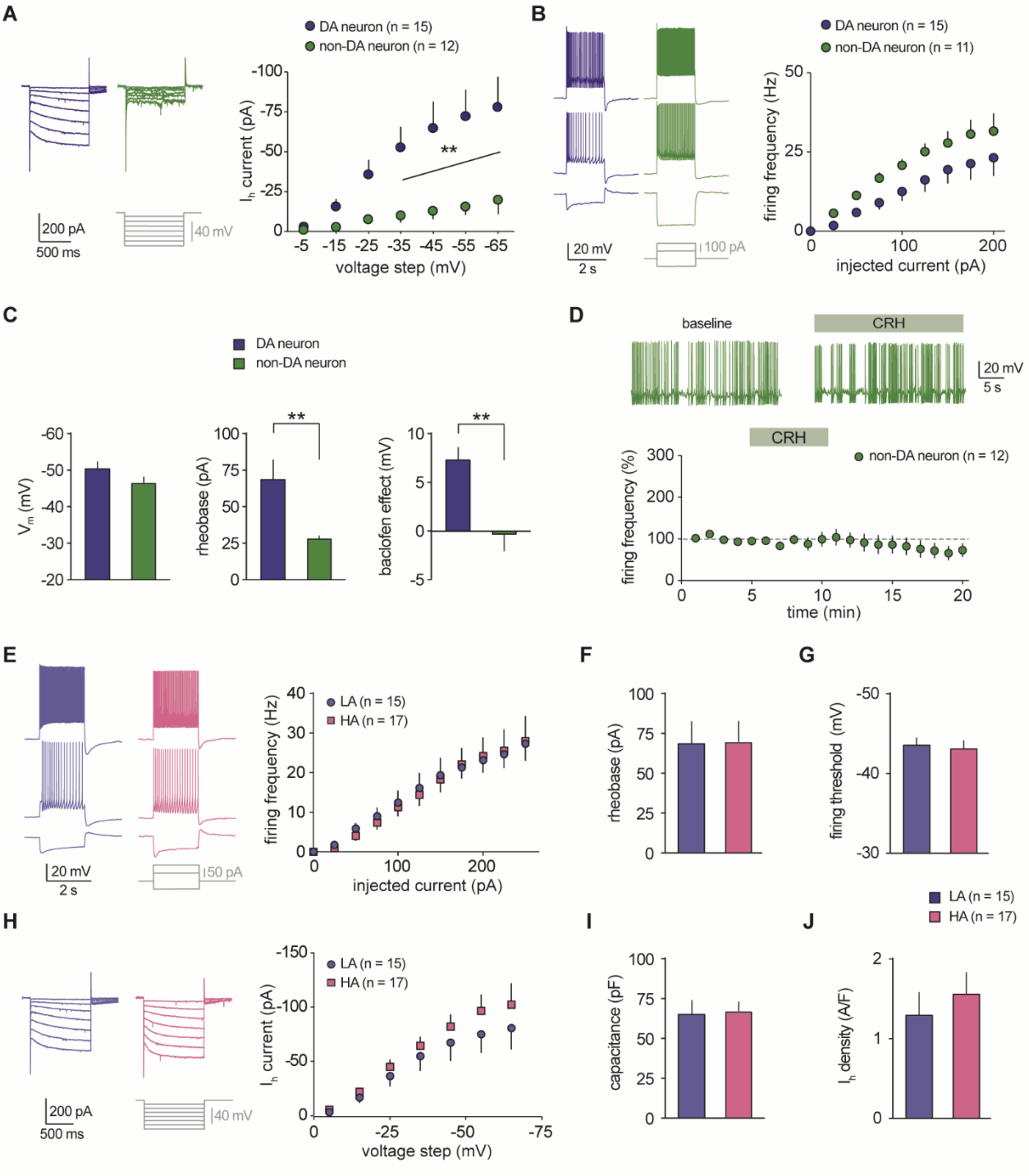

Fig. S3. Additional data on DA VTA firing. (A) Hyperpolarization-activated currents (I_h) induced by negative voltage steps in putative DA and non-DA neurons in the VTA (Two-way ANOVA for factor cell type, $F_{(1,172)} = 38.87$, $p < 0.0001$). Representative color-coded traces and voltage protocol are shown on the left. **(B)** Frequency-current (F-I) curves of cell firing evoked by 2-s-long somatic current injections in putative DA and non-DA VTA neuron (Two-way ANOVA for factor cell type, $F_{(1,216)} = 17.71$, $p < 0.0001$). Color-coded traces on the left are representative voltage responses elicited by -100 pA, 100 pA and 200 pA current steps. **(C)** Membrane potential (V_m, two tailed t-test, $t_{(24.79)} = 1.512$, $p = 0.143$), rheobase (Mann-Whitney test, $U = 38$, $p = 0.0087$) and hyperpolarization induced by $GABA_BR$-activation (baclofen effect,

Mann-Whitney test, U = 17, p = 0.0012) in putative DA and non-DA VTA cells. **(D)** Lack of effect on spontaneous firing of non-DA VTA neurons upon batch application of CRH (500 nM). **(E)** Frequency-current (F-I) curves of cell firing evoked by 2-s-long somatic current injections in DA VTA neurons from LA and HA rats held at -60 mV (Two-way ANOVA for factor anxiety, $F_{(1,330)} = 0.08$, p = 0.776). Color-coded traces on the left are representative voltage responses elicited by -50 pA, 50 pA and 100 pA current steps. **(F-G)** Rheobase and threshold of evoked firing did not differ between LA and HA rats (LA, n = 15 vs. HA, n =17; p = 0.81 for rheobase and p = 0.86 for threshold). **(H)** I_h currents in DA VTA neurons from LA and HA rats (Two-way ANOVA for factor anxiety, $F_{(1,209)} = 4.658$, p = 0.03; Fisher's LSD post-hoc comparison p > 0.05). Representative traces and voltage protocol are shown on the left. **(I-J)** Cell capacitance and I_h density (maximal I_h current normalized by cell capacitance) did not differ between LA and HA rats (p = 0.53 for capacitance and p = 0.20 for I_h density). (**, p < 0.01).

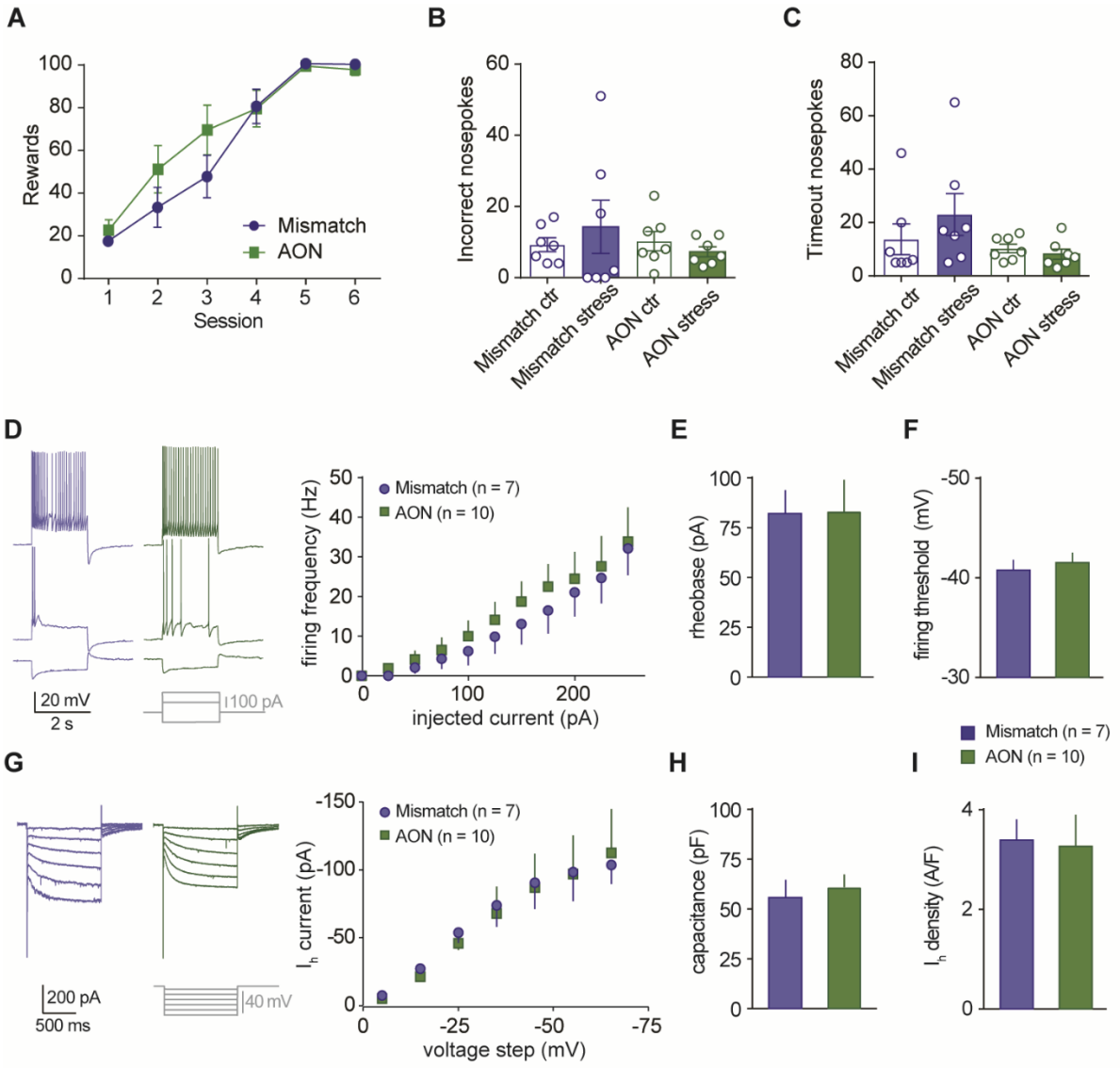

Fig. S4. Additional data on progressive ratio test performance in AON-treated rats. **(A)** Training performance was similar between the mismatch-treated and the AON-treated groups (Two-way repeated measures ANOVA: interaction effect $F_{(5,130)} = 1.486$, $p = 0.199$, AON effect $F_{(1,26)} = 1.117$, $p = 0.300$, Time effect $F_{(5,130)} = 54.87$, $p < 0.0001$). **(B)** No difference was observed between groups in incorrect nosepokes, regardless of AON treatment or stress exposure (Two-way ANOVA: interaction effect: $F_{(1,24)} = 0.931$, $p = 0.344$, AON effect $F_{(1,24)} = 0.524$, $p = 0.476$, Stress effect $F_{(1,24)} = 0.058$, $p = 0.81$). **(C)** No difference was observed between groups in timeout nosepokes, regardless of AON treatment or stress exposure (Two-way ANOVA: interaction effect $F_{(1,24)} = 1.291$, $p = 0.267$, AON effect $F_{(1,24)} = 3.306$, $p = 0.082$, Stress effect $F_{(1,24)} = 0.505$, $p = 0.484$). **(D)** Frequency-current (F-I) curves of cell firing evoked by 2-s-long somatic current injections in DA VTA neurons from mismatch-treated and AON-treated rats held at -60 mV (Two-way ANOVA for factor treatment, $F_{(1,163)} = 2.042$, $p = 0.155$). Color-coded traces on the left are representative voltage responses elicited by -100 pA, 100 pA and 200 pA current steps. **(E-F)** Rheobase and threshold of evoked firing did not differ between groups (mismatch, n = 7 vs. AON, n =10; $p = 0.98$ for rheobase and $p = 0.62$ for threshold). **(G)** I_h currents in DA VTA neurons from mismatch-treated and AON-treated rats (Two-way ANOVA for factor treatment, $F_{(1,103)} = 0.024$, $p = 0.877$). Representative traces and voltage protocol are shown on the left. **(H-I)** Cell capacitance and I_h density (maximal I_h current normalized by cell capacitance) did not differ between groups ($p = 0.88$ for capacitance and $p = 0.15$ for I_h density).

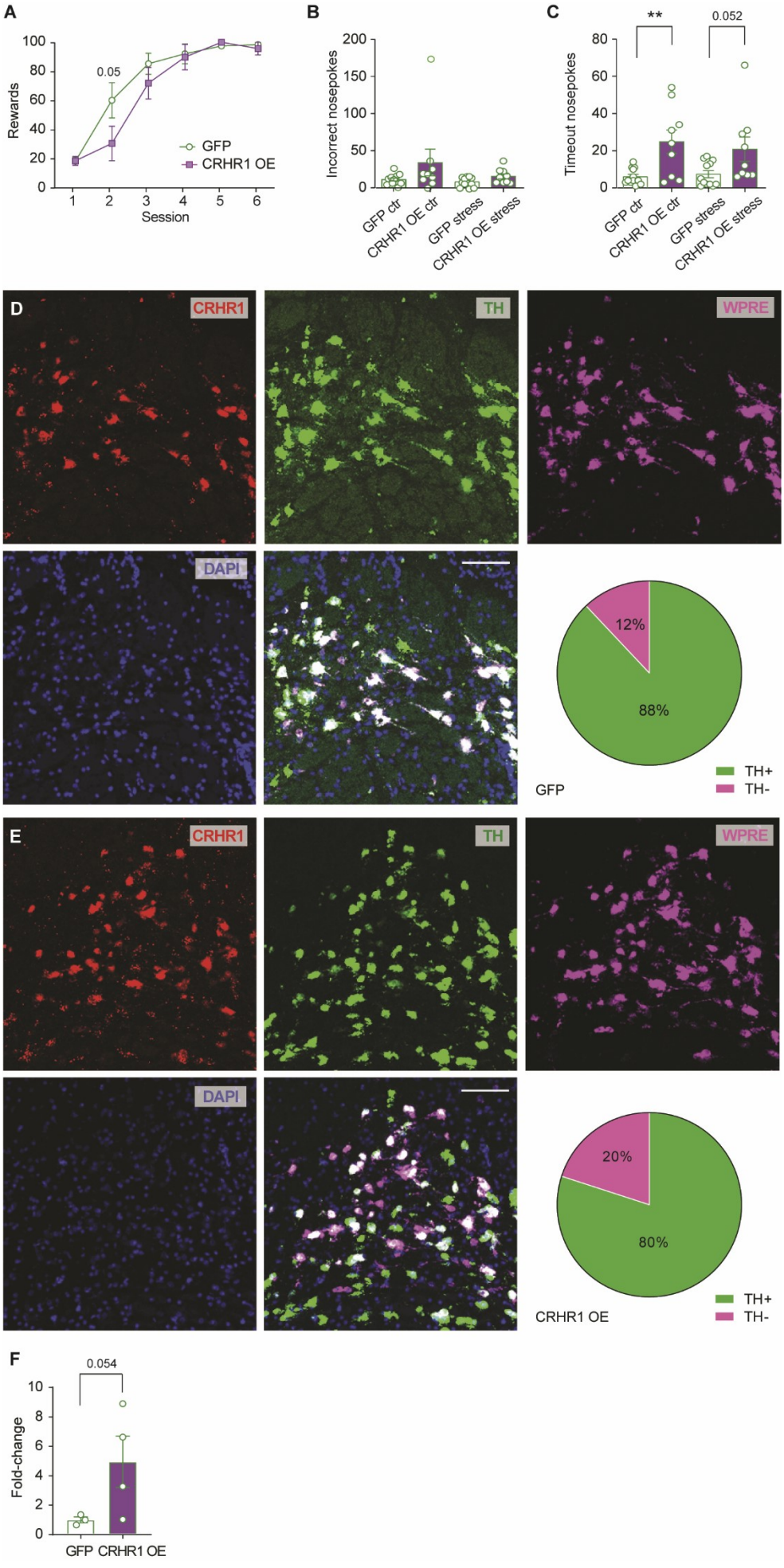
A
Rewards
Session
0.05
GFP
CRHR1 OE
B
Incorrect nosepokes
GFP ctr
CRHR1 OE ctr
GFP stress
CRHR1 OE stress
C
Timeout nosepokes
**
0.052
GFP ctr
CRHR1 OE ctr
GFP stress
CRHR1 OE stress
D
CRHR1
TH
WPRE
DAPI
12%
88%
TH+
TH-
GFP
E
CRHR1
TH
WPRE
DAPI
20%
80%
TH+
TH-
CRHR1 OE
F
0.054
Fold-change
GFP
CRHR1 OE

Fig. S5. Additional data on the effects of CRHR1 OE on PR test performance. (A) CRHR1 OE and GFP rats did not differ in their training performance (session x treatment interaction, $F_{(5,95)} = 1.580$, $p = 0.173$, treatment effect, $F_{(1,19)} = 2.839$, $p = 0.108$, session effect, $F_{(5,95)} = 45.68$, $p < 0.001$). **(B)** There was no difference in the number of incorrect nosepokes between GFP and CRHR1 OE rats (Two-way repeated measures ANOVA, treatment x stress interaction: $F_{(1,19)} = 1.057$, $p = 0.3168$; stress effect: $F_{(1,19)} = 2.059$, $p = 0.1675$; treatment effect: $F_{(1,19)} = 3.238$, $p = 0.0878$). **(C)** CRHR1 OE rats performed more timeout nosepokes than GFP rats (Two-way repeated measures ANOVA, treatment x stress interaction: $F_{(1,19)} = 0.840$, $p = 0.3709$; stress effect: $F_{(1,19)} = 0.210$, $p = 0.652$; treatment effect: $F_{(1,19)} = 10.19$, $p = 0.0048$)(**, $p < 0.01$). **(D-E)** Representative images of viral expression in TH+ cells in the VTA of GFP (**D**) and CRHR1 OE rats (**E**) (scale bar = 50 µm). Quantification of viral expression in TH+ cells. In both groups >80 % of WPRE+ cells were TH+, 88% in the GFP rats and 80% in the CRHR1 OE rats. **(F)** Treatment with the CRHR1 OE virus resulted in marginally non-significant upregulation of CRHR1 expression in DA neurons (one-tailed t-test $t_{(3.080)} = 2.248$, $p = 0.054$).

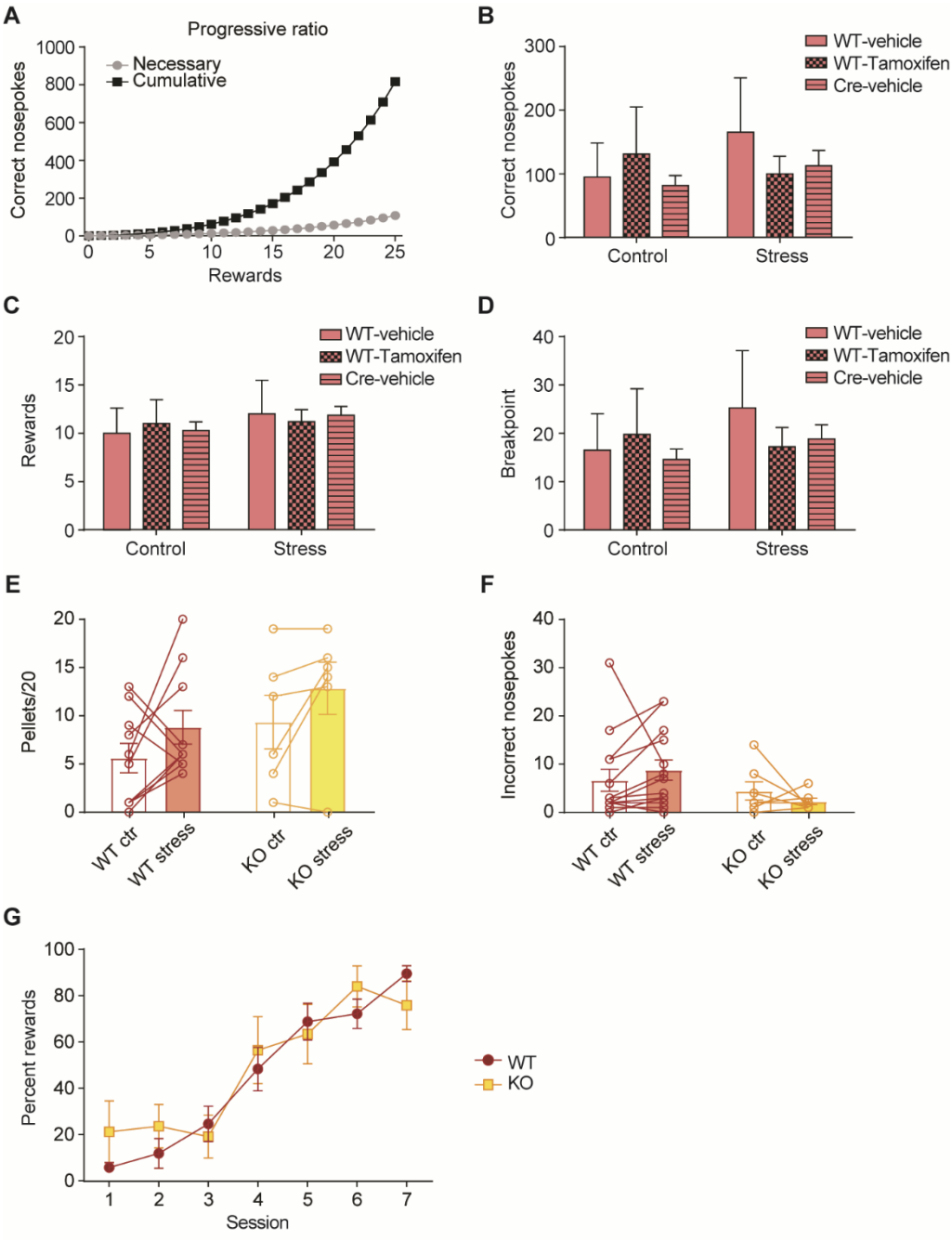

Fig. S6. Additional data on the effects of CRHR1 deletion in DA neurons in mice on PR test performance. **(A)** Necessary and cumulative nosepokes for each reward in the progressive ratio test for mice. **(B)** No difference between wild type groups ('WT-vehicle': Cre$^-$ vehicle-treated; 'WT-Tamoxifen': Cre$^-$ tamoxifen-treated; 'Cre-vehicle': DAT-CRHR1 vehicle-treated mice) under control conditions or after stress in the number of correct nosepokes (Two-way ANOVA, group effect $F_{(2,13)} = 0.166$, $p = 0.849$). **(C)** No difference between wild type groups was observed under control conditions or after stress in the number of rewards (Two-way ANOVA, group effect $F_{(2,26)} = 0.0013$, $p = 0.999$). **(D)** No difference between wild type groups was observed under control conditions or after stress in the breakpoint reached (Two-way ANOVA, group effect $F_{(2,13)} = 0.1381$, $p = 0.872$). **(E)** Number of pellets consumed out of 20, when WT and DAT-CRHR1 (KO) mice were allowed to freely eat them in a home cage-like setting. No significant stress x genotype interaction ($F_{(1,14)} = 0.009$, $p = 0.926$), no significant effect of genotype ($F_{(1,14)} = 2.368$, $p = 0.146$) and a

marginally non-significant effect of stress were observed ($F_{(1,14)}$ = 4.471, p = 0.053). **(F)** No difference was observed in the number of incorrect nosepokes between genotypes, or between control and stress. No significant interaction ($F_{(1,19)}$ = 1.641, p = 0.216), genotype ($F_{(1,19)}$ = 2.384, p =0.14) or stress ($F_{(1,19)}$ = 0.0, p > 0.99) effects were observed. **(G)** Two-way repeated measures ANOVA revealed a significant effect of session ($F_{(6,147)}$ = 22.31, p < 0.0001), but no effect of genotype ($F_{(1,147)}$ = 0.468, p = 0.495) or interaction effect ($F_{(6,147)}$ = 0.8025, p = 0.5695) in training performance.

Figure	Variable	Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	N1	N2	t	DF	P Value Holm-Sidak's test
1C	breakpoint	LA ctr vs. HA ctr	51.64	67.9	-16.26	11.22	11	10	1.45	36	0.1557
		LA ctr vs. LA stress	51.64	86.5	-34.86	11.22	11	10	3.109	36	0.0111
		HA ctr vs. HA stress	67.9	38.78	29.12	11.79	10	9	2.469	36	0.0363
		LA stress vs. HA stress	86.5	38.78	47.72	11.79	10	9	4.046	36	0.0012
1D	correct nosepokes	LA ctr vs. HA ctr	214.3	272.8	-58.53	45.33	11	10	1.291	36	0.2048
		LA ctr vs. LA stress	214.3	342.2	-127.9	45.33	11	10	2.822	36	0.023
		HA ctr vs. HA stress	272.8	169.6	103.2	47.66	10	9	2.166	36	0.0731
		LA stress vs. HA stress	342.2	169.6	172.6	47.66	10	9	3.622	36	0.0035
1E	rewards	LA ctr vs. HA ctr	12.45	13.2	-0.7455	0.6019	11	10	1.238	36	0.2236
		LA ctr vs. LA stress	12.45	14	-1.545	0.6019	11	10	2.567	36	0.0432
		HA ctr vs. HA stress	13.2	11.67	1.533	0.633	10	9	2.422	36	0.0407
		LA stress vs. HA stress	14	11.67	2.333	0.633	10	9	3.686	36	0.0027
3B	breakpoint	LA Veh vs. HA Veh	31.71	69.75	-38.04	12.97	7	8	2.933	26	0.0206
		LA Veh vs. LA CRH	31.71	81	-49.29	13.4	7	7	3.679	26	0.0043
		HA Veh vs. HA CRH	69.75	43.38	26.38	12.53	8	8	2.105	26	0.0451
		LA CRH vs. HA CRH	81	43.38	37.63	12.97	7	8	2.901	26	0.015
3C	correct nosepokes	LA Veh vs. HA Veh	132.3	329.1	-196.9	50.37	7	7	3.908	26	0.0024
		LA Veh vs. LA CRH	132.3	262.8	-130.5	48.77	7	8	2.675	26	0.0253
		HA Veh vs. HA CRH	329.1	167.5	161.6	48.77	7	8	3.314	26	0.008
		LA CRH vs. HA CRH	262.8	167.5	95.25	47.12	8	8	2.021	26	0.0536
3D	rewards	LA Veh vs. HA Veh	11	13.5	-2.5	0.6645	7	8	3.762	26	0.0027
		LA Veh vs. LA CRH	11	13.86	-2.857	0.6863	7	7	4.163	26	0.0018
		HA Veh vs. HA CRH	13.5	12	1.5	0.6419	8	8	2.337	26	0.0274
		LA CRH vs. HA CRH	13.86	12	1.857	0.6645	7	8	2.795	26	0.019
5C	breakpoint	mis. ctr vs. AON ctr	36.86	32.29	4.571	10.78	7	7	0.4241	24	0.6752
		mis. ctr vs. mis. stress	36.86	67.14	-30.29	10.78	7	7	2.81	24	0.0382
		AON ctr vs. AON stress	32.29	22.86	9.429	10.78	7	7	0.8748	24	0.6283
		mis. stress vs. AON stress	67.14	22.86	44.29	10.78	7	7	4.109	24	0.0024
5D	correct nosepokes	mis. ctr vs. AON ctr	147.4	127.3	20.14	48.68	7	7	0.4138	24	0.6741
		mis. ctr vs. mis. stress	147.4	284.6	-137.1	48.68	7	7	2.817	24	0.0283
		AON ctr vs. AON stress	127.3	91	36.29	48.68	7	7	0.7454	24	0.9266
		mis. stress vs. AON stress	284.6	91	193.6	48.68	7	7	3.976	24	0.0024
5E	rewards	mis. ctr vs. AON ctr	11.43	11	0.4286	0.8165	7	7	0.5249	24	0.597
		mis. ctr vs. mis. stress	11.43	13.29	-1.857	0.8165	7	7	2.275	24	0.064
		AON ctr vs. AON stress	11	10.14	0.8571	0.8165	7	7	1.05	24	0.9129
		mis. stress vs. AON stress	13.29	10.14	3.143	0.8165	7	7	3.849	24	0.0031
6B	breakpoint	GFP ctr vs. CRHR1OE ctr	26.75	63.11	-36.36	9.859	12	9	3.688	38	0.0014
		GFP stress vs. CRHR1 OE stress	30.17	55.67	-25.5	9.859	12	9	2.586	38	0.0271
6C	correct nosepokes	GFP ctr vs. CRHR1 OE ctr	109.75	261.11	-151.4	40.28	12	9	3.757	38	0.0012
		GFP stress vs. CRHR1 OE stress	125.92	224.67	-98.75	40.28	12	9	2.451	38	0.0375
6D	rewards	GFP ctr vs. CRHR1OE ctr	10.58	12.89	-2.306	0.6661	12	9	3.461	38	0.0027
		GFP stress vs. CRHR1 OE stress	10.92	12.67	-1.75	0.6661	12	9	2.627	38	0.0245
6F	breakpoint	WT - KO									
		Control	14	11.14	2.857	4.405	15	7	0.6486	40	0.5203
		Stress	19.07	5.857	13.21	4.405	15	7	2.999	40	0.0093
		Control - Stress									
		WT	14	19.07	-5.067	2.061	15	15	2.458	20	0.0459
		KO	11.14	5.857	5.286	3.017	7	7	1.752	20	0.0951
6G	correct nosepokes	WT - KO									
		Control	78.73	55	23.73	32.19	15	7	0.7372	40	0.7141
		Stress	116.3	24.14	92.12	32.19	15	7	2.861	40	0.0133
		Control - Stress									
		WT	78.73	116.3	-37.53	15.97	15	15	2.35	20	0.0574
		KO	55	24.14	30.86	23.38	7	7	1.32	20	0.3628
6H	rewards	WT - KO									
		Control	9.8	8	1.8	1.675	15	7	1.075	40	0.2889
		Stress	11.6	5.286	6.314	1.675	15	7	3.77	40	0.002
		Control - Stress									
		WT	9.8	11.6	-1.8	0.7996	15	15	2.251	20	0.0707
		KO	8	5.286	2.714	1.171	7	7	2.319	20	0.0926
S1D	incorrect nosepokes	LA ctr vs. HA ctr	15.55	21.6	-6.055	4.339	11	10	1.395	36	0.5109
		LA ctr vs. LA stress	15.55	10.1	5.445	4.339	11	10	1.255	36	0.4297
		HA ctr vs. HA stress	21.6	6.444	15.16	4.563	10	9	3.322	36	0.0082
		LA stress vs. HA stress	10.1	6.444	3.656	4.563	10	9	0.8012	36	0.4283
S1G	breakpoint	Control - Stress									
		LA	52.73	62	-9.273	4.873	11	11	1.903	19	0.0723
		HA	58.9	45.9	13	5.11	10	10	2.544	19	0.0392
		LA - HA									
		Control	52.73	58.9	-6.173	14.96	11	10	0.4126	38	0.6822
		Stress	62	45.9	16.1	14.96	11	10	1.076	38	0.494
S1H	correct nosepokes	Control - Stress									
		LA	196.5	257.8	-61.36	13.79	11	11	4.45	19	0.0005
		HA	234.6	194.9	39.7	14.46	10	10	2.745	19	0.0129
		LA -HA									
		Control	196.5	234.6	-38.15	60.75	11	10	0.6279	38	0.5338
		Stress	257.8	194.9	62.92	60.75	11	10	1.036	38	0.5196
S1I	rewards	Control - Stress									
		LA	12	12.82	-0.8182	0.3284	11	11	2.492	19	0.0339
		HA	12.9	12	0.9	0.3444	10	10	2.613	19	0.0339
		LA - HA									
		Control	12	12.9	-0.9	0.8036	11	10	1.12	38	0.4667
		Stress	12.82	12	0.8182	0.8036	11	10	1.018	38	0.4667
S2G	Dopamine	LA - HA									
		0	89.42	118.5	-29.03	30.05	4	5	0.966	35	0.5653
		20	119.4	96.58	22.78	30.05	4	5	0.758	35	0.5653
		40	179.6	97.83	81.74	30.05	4	5	2.72	35	0.0495
		60	180.9	106.3	74.56	30.05	4	5	2.481	35	0.0703
		80	185.3	112.6	72.64	30.05	4	5	2.417	35	0.0703
	DOPAC	LA - HA									
		0	88.15	124.4	-36.26	36.92	4	5	0.9821	35	0.5548
		20	120.7	105.1	15.61	36.92	4	5	0.4228	35	0.6751
		40	211.4	95.58	115.8	36.92	4	5	3.138	35	0.0171
		60	177	81.35	95.66	36.92	4	5	2.591	35	0.0543
		80	161	90.44	70.6	36.92	4	5	1.912	35	0.1802
S5C	timeout nosepokes	GFP ctr vs. CRHR1 OE ctr	6.08	24.89	-18.81	5.832	12	9	3.224	38	0.0052
		GFP stress vs. CRHR1 OE stress	7.42	20.89	-13.47	5.832	12	9	2.31	38	0.0521

Table S1. Details on statistical tests. Details from the *post hoc* Holm-Sidak's tests performed in datasets for which a Two-way ANOVA revealed a significant difference.

	Forward	Reverse
Primer pair 1	TGAAATCTGCTGCTTACTGAGCCC	TGGGCAAGGAATGCGTACCTCTTA
Primer pair 2	GCACTTTCCCTCCAACAACCCTA	ACTCTGTTCTCAGCACACTGGACA
Primer pair 3	ATCGCATGACCTACAGCAACTCCA	TCTTGAGTACCCAGAAGCACCGAA
Primer pair 4	TGGATCTTGTCCAGTGTGCTGAGA	AACTAAGCGTCTGTCTGTTTGGTC
Primer pair 5	GCCCGCTGTCTCCACTTATC	TGCTGAACCTCGTCTCCC
Primer pair 6	AGAGGAGGGAGAAAGAGGAGGG	CTTCAGAGATCCAGGTAGAGGACAT
Primer pair 7	CAGCCACCGGAGACCGCAG	GGTTCACCACCACCCTTTC

Table S2. List of primers.