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Amygdala slices preparation. Horizontal brain slices containing amygdala area (400 μm) were prepared by Leica vibratome and maintained in an artificial cerebral spinal fluid (ACSF) solution at 30°C. To record inhibitory postsynaptic currents (IPSCs), the patch pipette was filled with a solution containing (in mM) 120 KCl, 20 K-gluconate, 10 HEPES, 10 phosphocreatine Na salt, 2 ATP Na salt, 0.4 GTP Na salt, and 2 $MgCl_2$, pH 7.35, while ASCF was supplemented with 10 μM CNQX and 50 μM D-APV. To record excitatory postsynaptic currents (EPSCs), the patch pipette was filled with a solution containing (in mM) 120 K gluconate, 20 KCl, 10 HEPES, 10 phosphocreatine Na salt, 2 ATP Na salt, 0.4 GTP Na salt, and 2 $MgCl_2$, pH 7.35, while ASCF was supplemented with 10 μM bicuculline.

Open field test. The apparatus was a clear Plexiglas arena (40 × 40 × 40 cm). Mouse was placed into the arena center for recording of their behavior for 5 min. Anxiety levels were measured by the percentage of time spent in the center square (20 × 20 cm) and entry times into the center square. An entry into the center square was registered if all four paws of mice were placed inside the center area.

Elevated plus maze test. The elevated plus-maze raised 70 cm above the floor consisted of two open arms (40 × 7 cm), and two closed arms (40 × 7 cm) with side and end walls of 10 cm in height. The arms were connected by a central area (7 × 7 cm). Mouse was placed in the center area facing an open arm for recording of their behavior for 5 min. The time spent in and number of entries into open arms were recorded when the mice put all four paws into open arms. Anxiety levels were quantified by the percentage of time spent in the open arms and the percentage of entries into the open arms.

Novelty-suppressed feeding test. After deprivation of food with free access to water for 24 h, mouse was placed for 6 min in a corner of a brightly lit test chamber (45 × 45 × 45 cm) unfamiliar to mice. One food pellet was placed on a piece of filter paper in the center floor of the arena. The time taken to explore the novel environment to the point when the animal was sitting on its haunches and eating food with its forepaws was measured. Then, mice were allowed to feed in their home cage for 5 min, during which food consumption was measured.

Delayed nonmatching to sample task (DNMTST) test. Sprague-Dawley rats were restricted food intake to maintain their body weight at about 85% of their normal weight. Spatial working memory (SWM) was examined in a wooden T-shape box (75-cm-long start alley connected to two 30-cm-long goal arms with 15 cm in width

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and 30 cm in height). DNMTST test consisted of pretest training, acquisition training and performance test. On pretest training day, rats were allowed to explore the open maze and eat the Graham Crumbs at the end of one goal arm. The acquisition training lasting 6 days with 10 trials per day had a sample run and then a choice run with 3-min inter-trial interval in each trial. Beginning 1 day after the acquisition training, rats were tested for the same 10 trials per day for 2 days as during acquisition with the exception of 30-sec retention intervals. The averaged values of these two-day data represent the ability of rat performance of SWM.

Table 1: Detailed information on statistical analysis.

Figure	size (n)	Statistical Analysis
Figure 1 A-B	n=9-11	LSD post-hoc test after one-way ANOVA $F_{2,27} = 21.66, p < 0.01$
Figure 1 D	n=8	LSD post-hoc test after one-way ANOVA $F_{2,21} = 7.007, p < 0.01$
Figure 1 E	n=8	LSD post-hoc test after one-way ANOVA $F_{2,21} = 0.327, p = 0.724$
Figure 2 A	n=5	LSD post-hoc test after one-way ANOVA $F_{2,12} = 28.995, p < 0.01$
Figure 2 B	n=5	Student's t test $p < 0.01$
Figure 2 C	n=5	Student's t test $p < 0.01$
Figure 2 D	n=12	Student's t test $p < 0.01$
Figure 2 E	n=9	LSD post-hoc test after one-way ANOVA $F_{2,24} = 23.301,$ $p < 0.01$

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Figure 2 F	n=5	LSD post-hoc test after one-way ANOVA $F_{2,12} = 28.787$, $p < 0.01$
Figure 2 G	n=5	Student's t test $p < 0.01$
Figure 3 A	n=9-10	LSD post-hoc test after two-way ANOVA left: $F_{1,35} = 4.929$, $p < 0.05$; right: $F_{1,35} = 6.793$, $p < 0.05$
Figure 3 B	n=9-10	LSD post-hoc test after two-way ANOVA left: $F_{1,35} = 3.653$, $p = 0.064$; right: $F_{1,35} = 5.533$, $p < 0.05$
Figure 3 C	n=8-11	LSD post-hoc test after one-way ANOVA left, $F_{4,40} = 4.328$, $p < 0.01$; right, $F_{4,40} = 3.347$, $p < 0.05$
Figure 3 D	n=8-11	LSD post-hoc test after one-way ANOVA left, $F_{4,40} = 5.83$, $p < 0.01$; right, $F_{4,40} = 6.247$, $p < 0.01$
Figure 3 E	n=7-10	LSD post-hoc test after one-way ANOVA left, $F_{3,31} = 7.295$, $p < 0.01$; right, $F_{3,31} = 4.175$, $p < 0.05$
Figure 3 F	n=7-10	LSD post-hoc test after one-way ANOVA left, $F_{3,31} = 5.979$, $p < 0.01$; right, $F_{3,31} = 9.939$, $p < 0.01$
Figure 3 G	n=8-10	LSD post-hoc test after one-way ANOVA left, $F_{3,33} = 6.747$, $p < 0.01$; right, $F_{3,33} = 6.853$, $p = 0.01$;

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Figure 3 H	n=8-10	LSD post-hoc test after one-way ANOVA left, $F_{3,33} = 8.877, p < 0.01$; right, $F_{3,33} = 9.928, p < 0.01$
Figure 4 A	n=10-11	LSD post-hoc test after one-way ANOVA $F_{2,29} = 19.14$, $p < 0.01$
Figure 4 B	n=10-11	LSD post-hoc test after one-way ANOVA $F_{2,29} = 8.68$, $p < 0.01$
Figure 4 C	n=10-11	LSD post-hoc test after one-way ANOVA $F_{2,29} = 4.265$, $p < 0.05$
Figure 4 D	n=10-11	LSD post-hoc test after one-way ANOVA $F_{2,29} = 5.530$, $p < 0.01$
Figure 4 E	n=9-11	LSD post-hoc test after one-way ANOVA $F_{2,27} = 3.455$, $p< 0.05$
Figure 4 F	n=9-11	LSD post-hoc test after one-way ANOVA $F_{2,27} = 0.177$, $p = 0.84$
Figure 4 G	n=10-13	LSD post-hoc test after one-way ANOVA $F_{3,40} = 3.601$, $p < 0.05$
Figure 4 H	n=10-13	LSD post-hoc test after one-way ANOVA $F_{3,40} = 3.395$, $p < 0.05$
Figure 4 I	n=10-13	LSD post-hoc test after one-way ANOVA $F_{3,40} = 5.863$, $p < 0.01$

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Figure 4 J	n=10-13	LSD post-hoc test after one-way ANOVA $F_{3,40} = 2.408$, $p = 0.081$
Figure 4 K	n=9-13	LSD post-hoc test after one-way ANOVA $F_{3,39} = 3.146$, $p < 0.05$
Figure 4 L	n=9-13	LSD post-hoc test after one-way ANOVA $F_{3,39} = 0.17$, $p = 0.92$
Figure 4 M	n=10-13	Student's t test $p < 0.05$
Figure 4 N	n=10-13	Student's t test $p < 0.05$
Figure 4 O	n=10-13	Student's t test
Figure 4 P	n=10-13	Student's t test
Figure 4 Q	n=10-13	Student's t test $p < 0.05$
Figure 4 R	n=10-13	Student's t test
Figure 5 B	n=24-31	LSD post-hoc test after one-way ANOVA $F_{3,111} = 9.083$, $p < 0.01$
Figure 5 C	n=24-31	LSD post-hoc test after one-way ANOVA $F_{3,111} = 13.658$, $p < 0.01$
Figure S 1 A-B	n=5	Student's t test $p < 0.01$
Figure S 1 C-D	n=5	Student's t test $p < 0.01$
Figure S 2 A	n=8-10	LSD post-hoc test after one-way ANOVA left, $F_{3,32} = 8.812$, $p < 0.01$; right,

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		F3,32 = 4.913, p < 0.01
Figure S 2 B	n=5-9	LSD post-hoc test after one-way ANOVA F3,25 = 4.188, p < 0.05
Figure S 2 C	n=7-9	LSD post-hoc test after one-way ANOVA left, F3,27 = 3.712, p < 0.05; right, F3,27 = 4.409, p < 0.05
Figure S 2 D	n=7-9	LSD post-hoc test after one-way ANOVA F3,26 = 5.246, p < 0.01
Figure S 2 E	n=7	LSD post-hoc test after one-way ANOVA left, F2,18 = 10.796, p <0.01; right, F2,18 = 8.332, p < 0.01
Figure S 2 F	n=7	LSD post-hoc test after one-way ANOVA left, F2,17 = 5.314, p < 0.05; right, F2,17 = 4.205, p < 0.05
Figure S 2 G	n=9-11	Student's t test left, p < 0.01; right, p < 0.01
Figure S 2 H	n=9-11	Student's t test left, p <0.05; right, p < 0.05
Figure S 2 I	n=9-11	Student's t test left, p <0.05
Figure S 3 A	n=7-11	LSD post-hoc test after one-way ANOVA left, F3,29 = 7.549, p < 0.01; right, F3,29 = 5.782, p < 0.01

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Figure S 3 B	n=7-11	LSD post-hoc test after one-way ANOVA left,$F_{3,29} = 6.156$, $p < 0.01$; right, $F_{3,29} = 5.552$, $p < 0.01$
Figure S 3 C	n=10-11	LSD post-hoc test after repeated measure two-way ANOVA left: $F_{1,38} = 6.031$, $p < 0.01$; right: $F_{1,38} = 2.559$, $p < 0.05$
Figure S 3 D	n=10-11	LSD post-hoc test after repeated measure two-way ANOVA left: $F_{1,38} = 4.001$, $p < 0.01$; right: $F_{1,38} = 7.54$, $p < 0.05$
Figure S 3 E	n=6-10	LSD post-hoc test after one-way ANOVA left: $F_{3,27} = 8.655$, $p < 0.01$; right: $F_{3,27} = 8.078$, $p < 0.05$
Figure S 3 F	n=6-10	LSD post-hoc test after one-way ANOVA left, $F_{3,27} = 8.543$, $p < 0.01$; right, $F_{3,27} = 10.321$, $p < 0.01$
Figure S 4 A	n=42	LSD post-hoc test after one-way ANOVA for repeated measure $F_{5,205} = 102.107$, $p < 0.01$
Figure S 4 B	n=7	LSD post-hoc test after one-way ANOVA $F_{5,36} = 48.220$, $p < 0.01$

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Fig. S1: AEA and AA-5-HT induce *in vivo* LTD at PFC-BLA synapses in rats. **(A-D)** Plots of normalized fEPSP amplitude in anesthetized rats (A, C) and histograms summarizing the average percent change of fEPSP amplitude (B, D) show that relative to vehicle injection, an intra-BLA injection of AEA (A, B) or an i.p. injection of AA-5-HT (C, D) at 0 min elicits LTD lasting for > 2 h. Representative fEPSP traces before (1) and after (2) vehicle, AEA or AA-5-HT administration are shown below each plot. All summary graphs show means ± SEMs; n = numbers of animals recorded in each group. ** $p < 0.01$, Student's *t* test (B, D).

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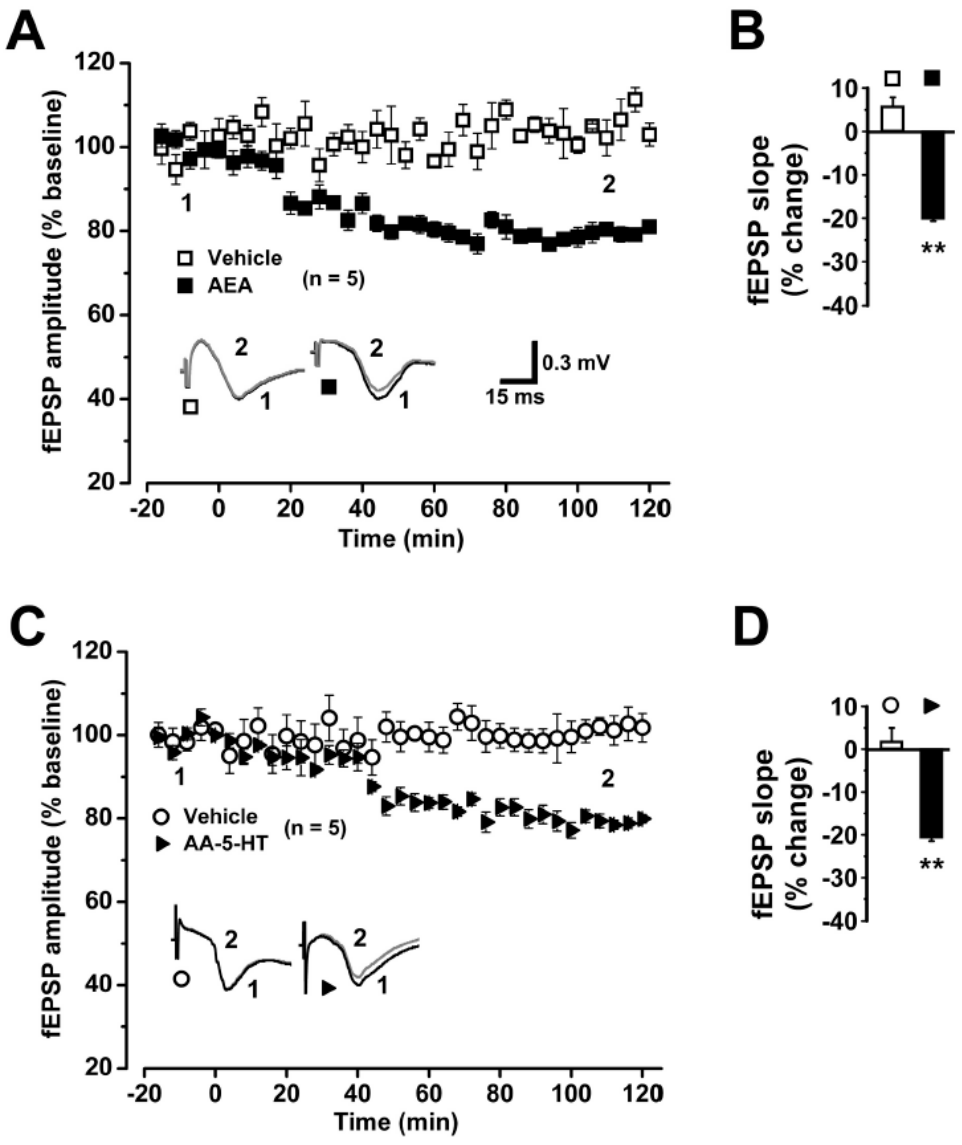

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Fig. S2: Acute stress and CORT exposure induce anxiogenic behavioral responses in mice. **(A, B)** Relative to control (Con), an acute inescapable swimming stress for 10 (FS10) or 20 min (FS20), but not 5 min (FS5), reduces time spent in and entrance times into EPMT open arms (A), while the acute stress for 5, 10 and 20 min decreases time spent in OFT center area (B). **(C, D)** Relative to control (Con), an acute injection of 40 or 80 but not 20 mg/kg CORT reduces time spent in and entrance times into EPMT open arms (C) and time spent in OFT center area (D). **(E, F)** Relative to control (Con), RU486 (RU) but not vehicle (Veh) prevents the acute stress (FS) to reduce time spent in and entrance times into EPMT open arms (E) and OFT center area (F). **(G-I)** Relative to chronic vehicle-exposed mice (Con), chronic CORT-exposed mice show a decrease of time spent in and entrance times into EPMT open arms (G) and OFT center area (H), and an increased latency to eat in a novel chamber without significant changes of food intake in home cages in the NSFT (I). All summary graphs show means ± SEMs; n = numbers of animals tested in each group. * $p < 0.05$ and ** $p < 0.01$ vs. control, LSD *post-hoc* test after one-way ANOVA (A: left, $F_{3,32} = 8.812$, $p < 0.01$; right, $F_{3,32} = 4.913$, $p < 0.01$; B: $F_{3,25} = 4.188$, $p < 0.05$; C: left, $F_{3,27} = 3.712$, $p < 0.05$; right, $F_{3,27} = 4.409$, $p < 0.05$; D: $F_{3,26} = 5.246$, $p < 0.01$; E: left, $F_{2,18} = 10.796$, $p < 0.01$; right, $F_{2,18} = 8.332$, $p < 0.01$; F: left, $F_{2,17} = 5.314$, $p < 0.05$; right, $F_{2,17} = 4.205$, $p < 0.05$) or Student's *t* test (G-I).

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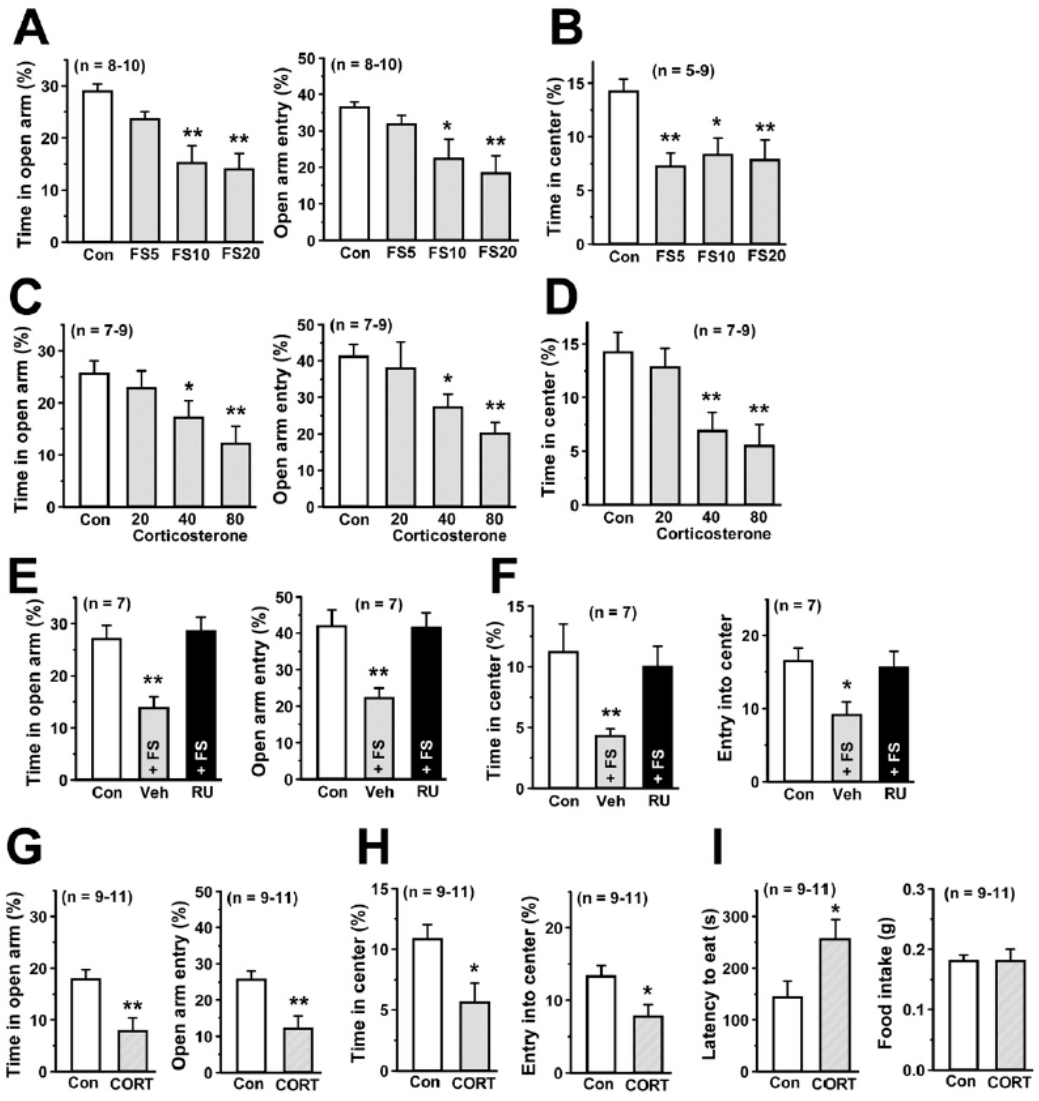

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Fig. S3: PF3845 and URB597 exert anti-anxiety effects in mice. **(A, B)** Relative to control mice (Con), PF3845 (PF: 4 mg/kg, i.p.) prevents acute stress (Veh) to reduce time spent in and entrance times into EPMT open arms (A) and OFT center area (B), all of which are abolished by AM281 (AM). **(C, D)** Relative to vehicle (Veh), PF3845 (4 mg/kg, i.p.) increases time spent in and entrance times into EPMT open arms (C) and OFT center area (D) in both CaMKII-CB_1R-WT (Ca-CB_1R-WT) and CaMKII-CB_1R-KO littermates (Ca-CB_1R-KO). **(E, F)** Relative to control mice (Con), Tat-GluR2s (sTat, i.p.) and URB597 (URB) together prevents acute stress (Veh) to reduce time spent in and entrance times into EPMT open arms (E) and OFT center area (F), both of which are abolished by Tat-GluR2 (Tat, i.p.). The Con and Veh in E and F are the same as the Con and Veh groups in A and B. All summary graphs show means ± SEMs; n = numbers of animals tested in each group. * $p < 0.05$ and ** $p < 0.01$ vs. control or vehicle, LSD *post-hoc* test after one-way ANOVA (A: left, $F_{3,29} = 7.549$, $p < 0.01$; right, $F_{3,29} = 5.782$, $p < 0.01$; B: left, $F_{3,29} = 6.156$, $p < 0.01$; right, $F_{3,29} = 5.552$, $p < 0.01$) or after repeated measure two-way ANOVA (C, left: $F_{1,38} = 6.031$, $p < 0.01$; right: $F_{1,38} = 2.559$, $p < 0.05$; D, left: $F_{1,38} = 4.001$, $p < 0.01$; right: $F_{1,38} = 7.54$, $p < 0.05$; E, left: $F_{3,27} = 8.655$, $p < 0.01$; right: $F_{3,27} = 8.078$, $p < 0.05$; F: left, $F_{3,27} = 8.543$, $p < 0.01$; right, $F_{3,27} = 10.321$, $p < 0.01$).

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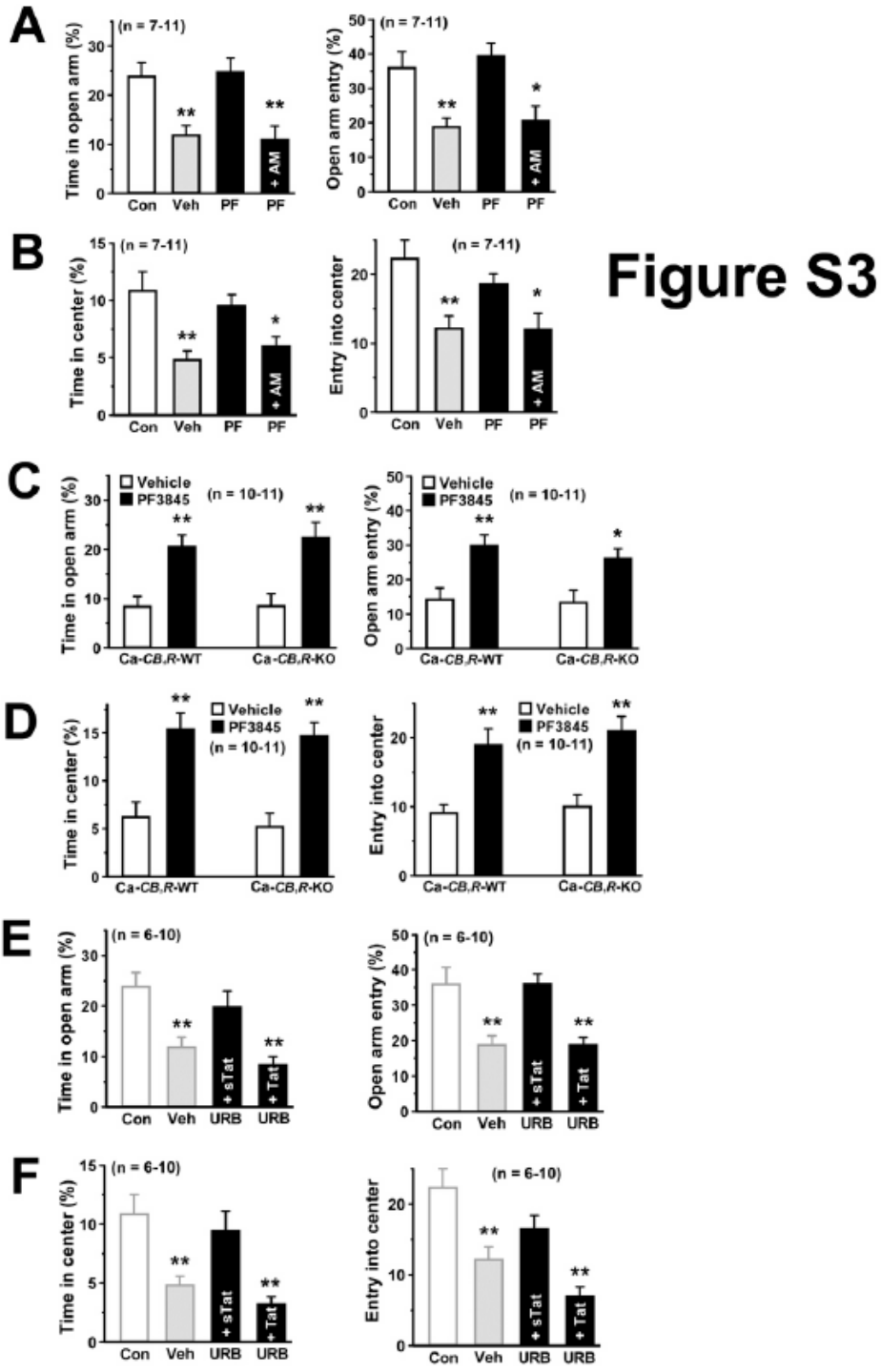

Figure S3

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Fig. S4: HU210 but not PF3845 impairs SWM in rats. **(A)** The learning curve of naïve rats during DNMTST test shows that naïve rats with 6-daily training sessions improve their ability of making correct choices from approximately 55% on day 1 to > 80% on day 6. **(B)** HU210, but not PF3845 injection (4 or 8 mg/kg, i.p.) 30 min or 2 h before test, suppresses SWM performance. All summary graphs show means ± SEMs; n = numbers of animals tested in each group. * $p < 0.05$ vs. day 1 or vehicle, LSD *post-hoc* test after one-way ANOVA for repeated measure (A: $F_{5,205} = 102.107$, $p < 0.01$) or one-way ANOVA (B: $F_{5,36} = 48.220$, $p < 0.01$).