Supplemental information

Kappa opioid receptor in nucleus accumbens

regulates depressive-like behaviors following

prolonged morphine withdrawal in mice

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Supplementary tables

Table S1 HAMD scores of placebo treatment in moderate depression patients (n=17). Related to Table 2.

No.	HAM-D scores	2W	4W	6W	8W
1	19	15	17	19	19
2	20	22	17	10	12
3	23	16	15	15	8
4	19	21	23	20	20
5	24	20	23	15	22
6	18	12	17	10	15
7	22	20	17	14	9
8	24	21	18	19	21
9	22	19	14	21	17
10	23	22	17	20	22
11	24	24	23	24	24
12	22	17	13	11	9
13	18	14	10	13	15
14	20	14	10	7	6
15	18	18	14	15	18
16	22	24	25	20	22
17	21	20	21	25	20

Table S2 HAMD scores of escitalopram treatment in moderate depression patients (n=21). Related to Table 2.

No.	HAM-D scores	2W	4W	6W	8W
1	23	17	18	15	11
2	19	19	22	20	20
3	20	18	14	11	10
4	24	19	23	15	15
5	18	10	13	11	8
6	24	18	13	15	10
7	21	22	19	20	22
8	22	20	18	20	14
9	19	19	23	20	18
10	20	22	17	15	16
11	24	17	12	11	11
12	22	16	14	11	13
13	18	15	9	8	5
14	19	22	19	16	16
15	18	13	12	7	6
16	22	24	25	20	18
17	20	15	10	7	7
18	21	20	21	25	22
19	19	15	9	8	6
20	23	23	17	19	16
21	22	16	12	14	12

Table S3 HAMD scores of placebo treatment in severe depression patients (n=12). Related to Table 3.

No.	HAM-D scores	2W	4W	6W	8W
1	24	22	24	25	19
2	26	28	22	24	24
3	25	18	21	16	10
4	22	19	16	20	18
5	24	23	24	20	21
6	22	19	12	17	20
7	28	24	18	13	12
8	26	24	26	19	21
9	27	23	22	19	21
10	26	25	21	24	25
11	24	24	23	22	25
12	26	21	22	15	20

Table S4 HAMD scores of escitalopram treatment in severe depression patients (n=11). Related to Table 3.

No.	HAM-D scores	2W	4W	6W	8W
1	26	20	23	16	12
2	28	28	25	24	25
3	29	26	23	25	18
4	29	26	24	21	20
5	28	20	22	18	14
6	25	20	21	16	11
7	27	22	23	19	16
8	26	26	19	23	25
9	24	20	23	22	18
10	25	26	29	24	19
11	26	20	22	16	10

Supplementary figures and legends
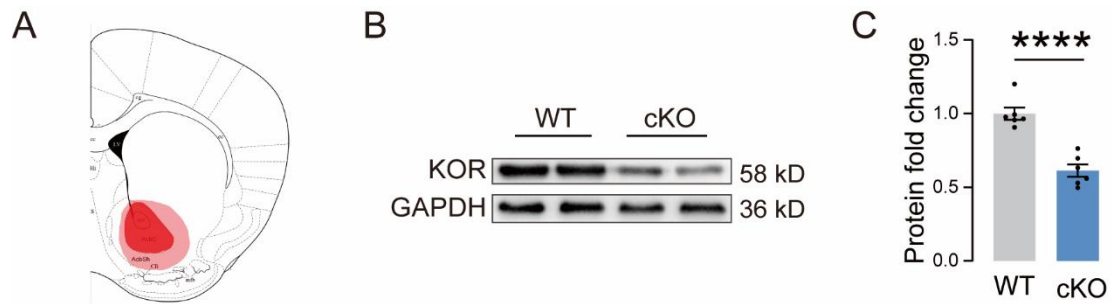
FIGURE S1 Knockdown of KOR in the NAc in KOR$^{loxp/loxp}$ **mice. Related to Figure 4.** (A) The schematic diagram of showing the maximum and minimum scope of virus diffusion. (B) Representative Western blot images. (C) KOR protein expression levels in the NAc of the cKO mice were decreased. The protein levels of the WT control group are set as 1. n=6 per group for analysis. ****$p < 0.0001$. Protein levels were analyzed with Unpaired t test. The WT control group was compared with cKO group. The values represent the mean ± SEM.
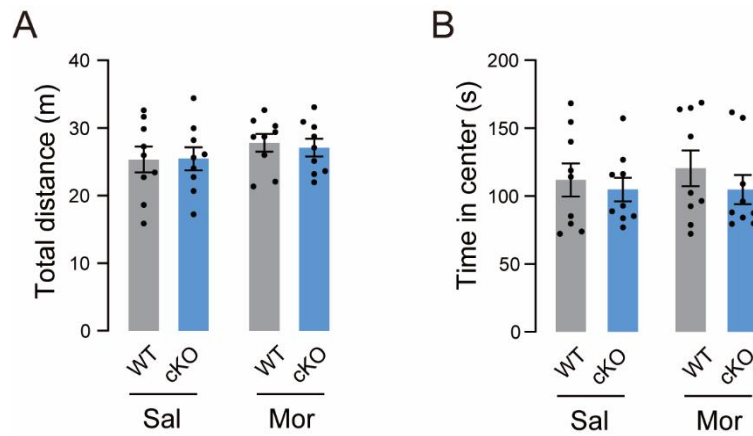
FIGURE S2 The locomotor activity after morphine withdrawal in KOR$^{loxp/loxp}$ mice. Related to Figure 4. (A) The total distance. (B) The time spent in center of the open field. n=9 per group. The data of locomotor activity were analyzed with two-way ANOVA, followed by Sidak's post hoc test. Sal-treated WT mice were compared with Mor-treated WT mice. Mor-treated WT mice were compared with Mor-treated cKO mice. The values represent the mean ± SEM.
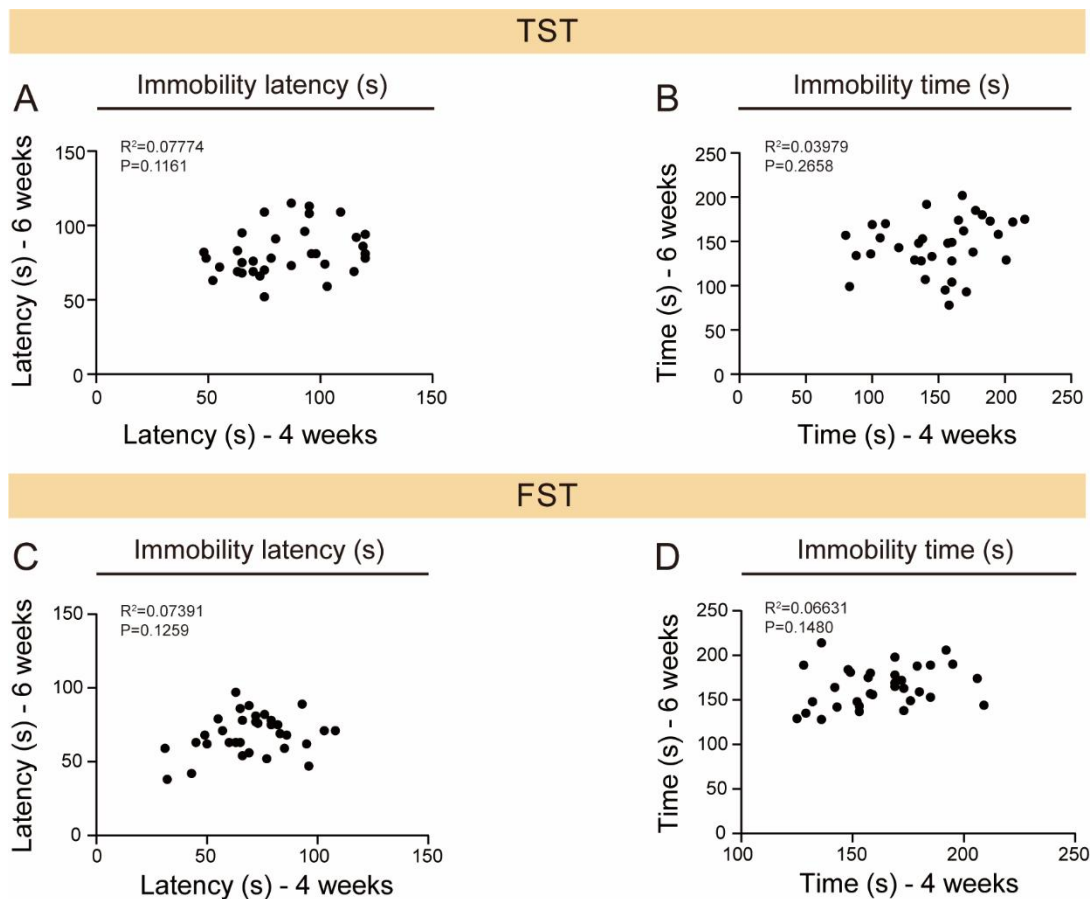
FIGURE S3 The correlation analysis of immobility behavior 4 weeks and 6 weeks after morphine withdrawal in the experiment of the single norBNI application. Related to Figure 5. (A) The correlation analysis of immobility latency in TST 4 weeks and 6 weeks after morphine withdrawal. Pearson correlation, $R^2 = 0.07774$, $P= 0.1161$. (B) The correlation analysis of immobility time in TST 4 weeks and 6 weeks after morphine withdrawal. Pearson correlation, $R^2 = 0.03979$, $P= 0.2658$. (C) The correlation analysis of immobility latency in FST 4 weeks and 6 weeks after morphine withdrawal. Pearson correlation, $R^2 = 0.07391$, $P= 0.1259$. (D) The correlation analysis of immobility time in FST 4 weeks and 6 weeks after morphine withdrawal. Pearson correlation, $R^2 = 0.06631$, $P= 0.1480$.
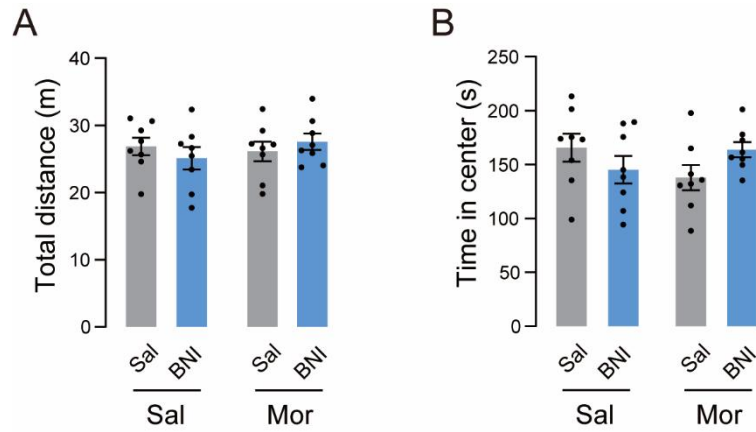
FIGURE S4 The locomotor activity after morphine withdrawal in mice with repeated norBNI application. Related to Figure 6. (A) The total distance. (B) The time spent in center of the open field. n=8 per group. The data of locomotor activity were analyzed with two-way ANOVA, followed by Sidak's post hoc test. Sal-Sal-treated mice were compared with Mor-Sal-treated mice. Mor-Sal-treated mice were compared with Mor-BNI-treated mice. The values represent the mean ± SEM.