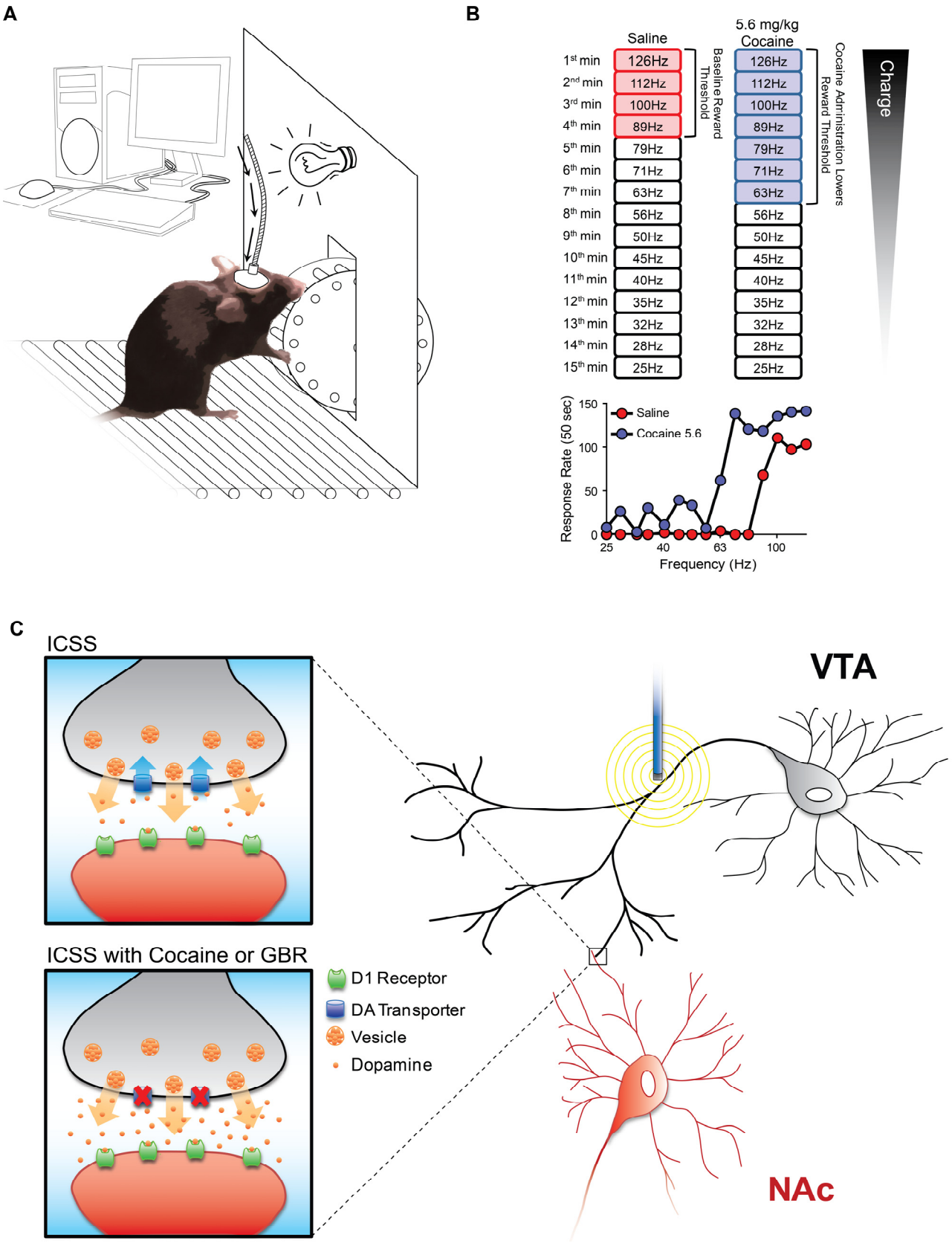
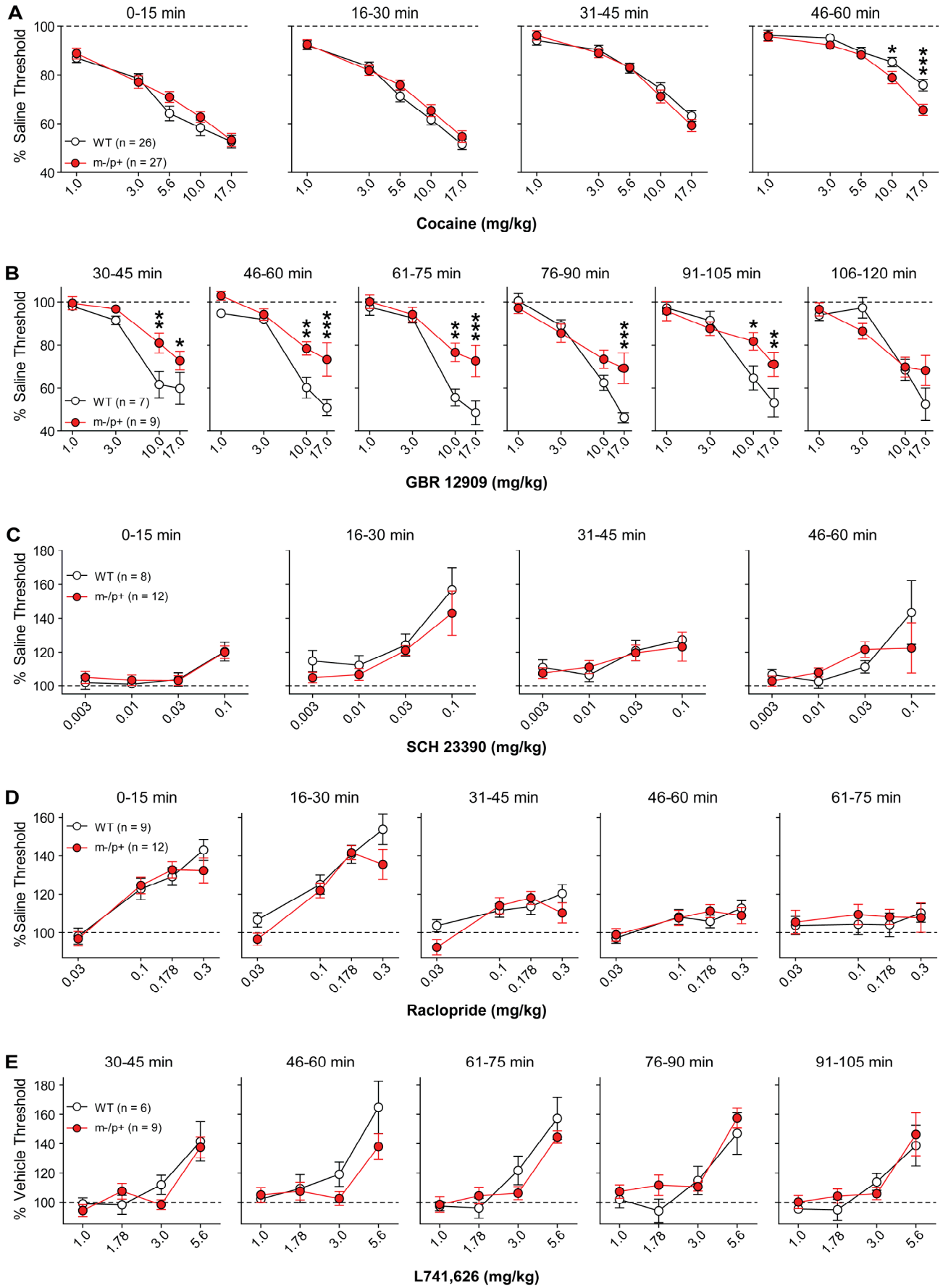
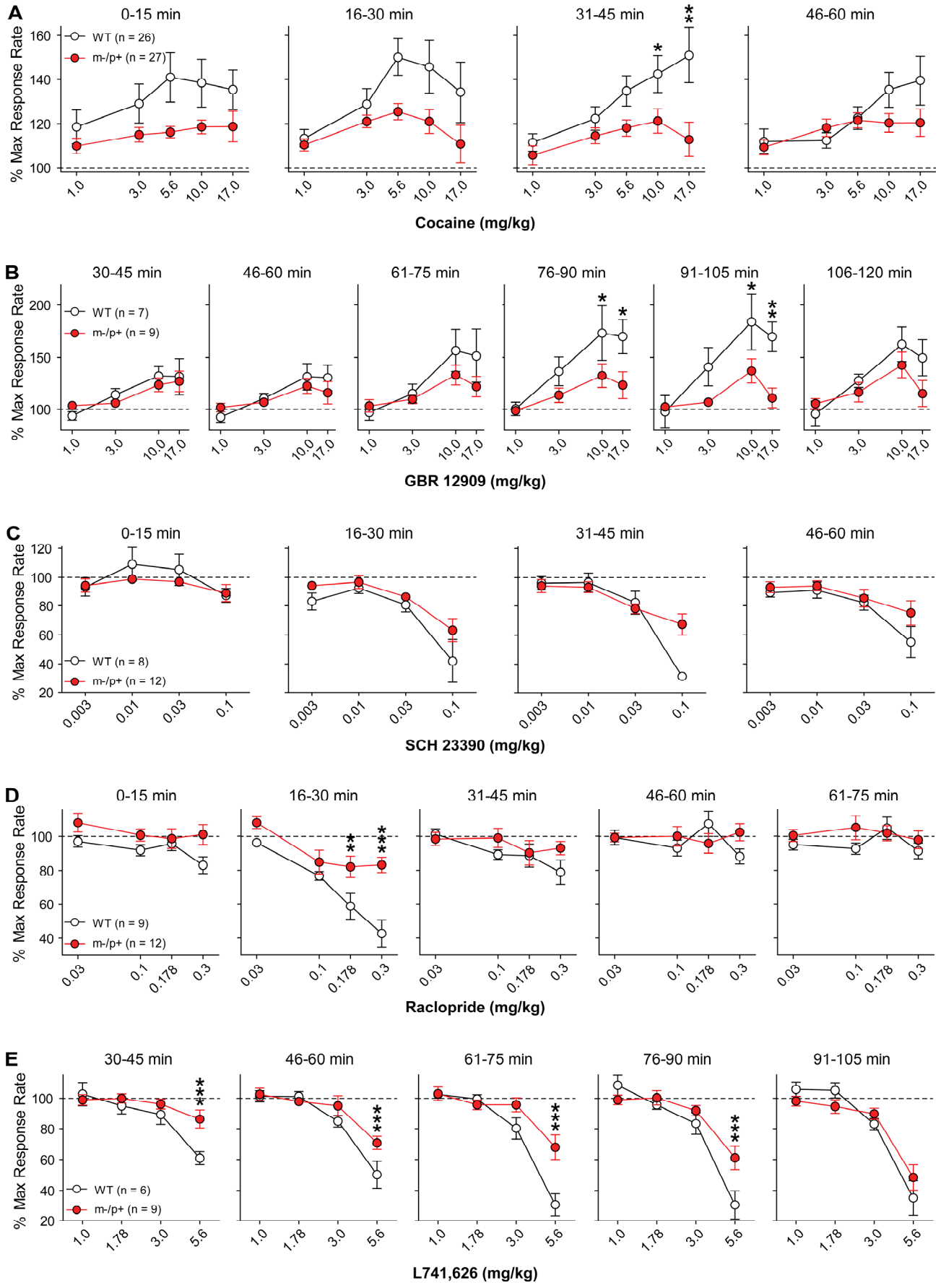
Online Supplemental Material



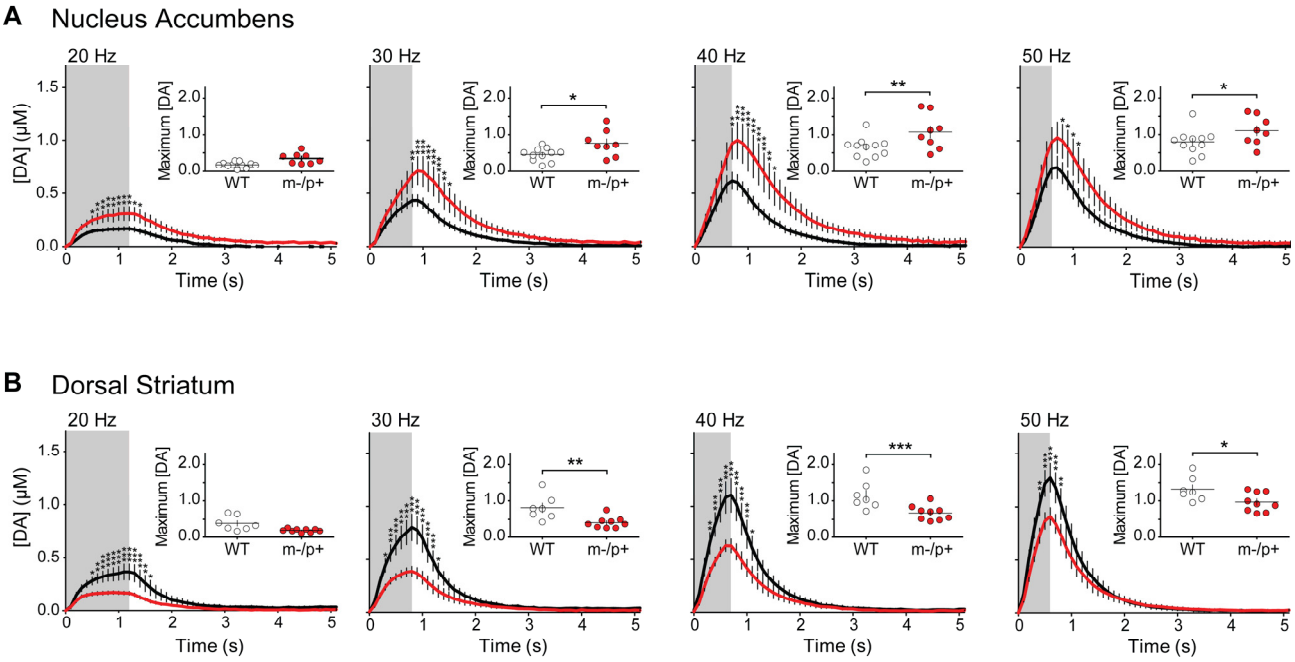
↑ **Supplemental Figure 1. Schematic of rate-dependent intracranial self-stimulation (ICSS)**
(**A**) Mice implanted with monopolar stimulating electrodes to the medial forebrain bundle (MFB) at the level of the lateral hypothalamus receive rewarding brain stimulation (BSR) for every quarter wheel turn, accompanied by illumination of the house light (500 ms). (**B**) Mice are presented with 15 discrete descending frequency steps (0.05 inverse log units) over 15 minutes. Mice have ad libitum access to BSR for 50 seconds during each frequency presentation. The minimum stimulus amplitude (μA) needed to initiate wheel turning for the top 3-5 frequencies is determined for each mouse and kept constant for the rest of the experiment. Injection of drugs that increase forebrain dopamine release (e.g., 5.6 mg/kg cocaine) decrease reward threshold (EF50) such that lower frequency stimulation sustains responding. (**C**) Schematic of the VTA-NAc reward circuit. Stimulation of ascending axons (MFB) from the VTA results in the release of dopamine from their terminal fields in the NAc. Dopaminergic release in the NAc can be increased pharmacologically by blocking dopamine transporters with cocaine or GBR 12909, increasing extracellular dopamine availability.


A
0-15 min
16-30 min
31-45 min
46-60 min
% Saline Threshold
WT (n = 26)
m-/p+ (n = 27)
Cocaine (mg/kg)
B
30-45 min
46-60 min
61-75 min
76-90 min
91-105 min
106-120 min
% Saline Threshold
WT (n = 7)
m-/p+ (n = 9)
GBR 12909 (mg/kg)
C
0-15 min
16-30 min
31-45 min
46-60 min
% Saline Threshold
WT (n = 8)
m-/p+ (n = 12)
SCH 23390 (mg/kg)
D
0-15 min
16-30 min
31-45 min
46-60 min
61-75 min
%Saline Threshold
WT (n = 9)
m-/p+ (n = 12)
Raclopride (mg/kg)
E
30-45 min
46-60 min
61-75 min
76-90 min
91-105 min
% Vehicle Threshold
WT (n = 6)
m-/p+ (n = 9)
L741,626 (mg/kg)

↑ **Supplemental Figure 2. Changes in BSR threshold following pharmacological treatment**
Reward threshold (EF50) was determined following i.p. administration of drugs that affect dopaminergic neurotransmission. (**A**) Cocaine lowered BSR threshold to the same extent in both *Ube3a*$^{m-/p+}$ and WT mice (0-45 min), but its effect decayed more rapidly in WT mice by 45-60 min (10 mg/kg, **p* = 0.025; 17 mg/kg, ****p* < *0.001*). (**B**) The highly-selective (DAT) blocker GBR 12909 consistently lowered reward threshold more in WT mice than m-/p+ littermates for the first 105 minutes following injection (30-45 min, 10.0 mg/kg, ***p* = *0.002*, 17.0 mg/kg, **p* < *0.036*; 46-60 min, 10.0 mg/kg, ***p* = *0.003*, 17.0 mg/kg ****p* < *0.001*; 61-75 min, 10.0 mg/kg, ***p* = *0.002*, 17.0 mg/kg, ****p* < *0.001*; 76-90 min, 17.0 mg/kg, ****p* < *0.001*; 91-105 min, 10.0 mg/kg, **p* = *0.014*, 17.0 mg/kg, ***p* = *0.01*). (**C**) There were no significant genotype differences in the threshold-elevating effects of the dopamine D1-receptor antagonist SCH 23390 Neither administration of the D2/D3 antagonist raclopride (**D**) nor the D2-selective antagonist L741,626 (**E**) elevated reward threshold to a greater extent in either genotype. Error bars indicate ±SEM.

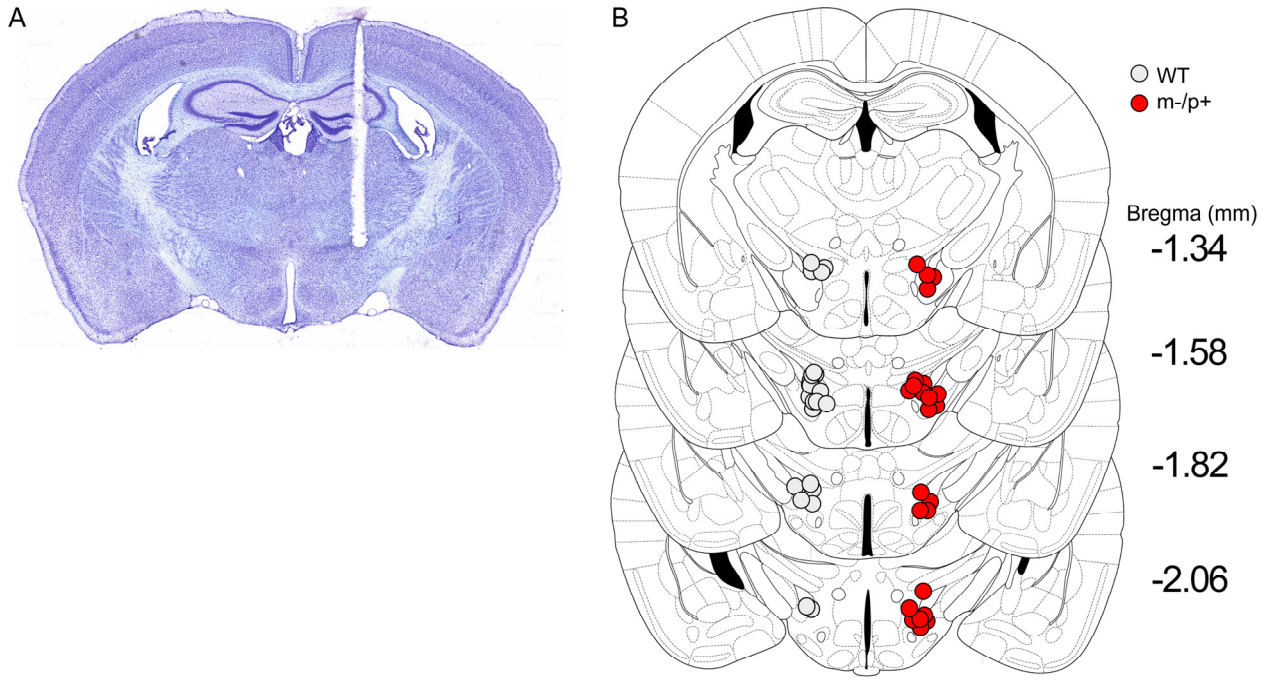

A
0-15 min
16-30 min
31-45 min
46-60 min
% Max Response Rate
WT (n = 26)
m-/p+ (n = 27)
Cocaine (mg/kg)
B
30-45 min
46-60 min
61-75 min
76-90 min
91-105 min
106-120 min
WT (n = 7)
m-/p+ (n = 9)
GBR 12909 (mg/kg)
C
WT (n = 8)
m-/p+ (n = 12)
SCH 23390 (mg/kg)
D
WT (n = 9)
m-/p+ (n = 12)
Raclopride (mg/kg)
E
WT (n = 6)
m-/p+ (n = 9)
L741,626 (mg/kg)

↑ **Supplemental Figure 3. Maximum operant response rate following pharmacological treatment** (**A**) WT mice exhibited a significantly larger increase in their maximum response rate 31-45 min after i.p. cocaine injection (10 mg/kg, *p = *0.028*; 17 mg/kg, **p = *0.001*). (**B**) WT mice also exhibited a significantly larger increase in their maximum response rate 76-105 min after i.p. GBR 12909 injection (76-90 min, 10 mg/kg, *p = *0.032*, 17 mg/kg, *p = *0.015*; 91-105 min, 10 mg/kg, *p = *0.018*, 17 mg/kg, **p = *0.004*). (**C**) There was no significant difference in reduction of maximum operant response rate following SCH 23350 injection between genotypes at any time point after i.p. administration. (**D**) *Ube3a*$^{m-/p+}$ mice were significantly less sensitive than WT littermates to the depressant effects of the D2/D3 antagonist raclopride on maximum operant response rate (16-30 min, 0.178 mg/kg, **p = 0.005, 0.3 mg/kg, ***p < 0.001). (**E**) *Ube3a*$^{m-/p+}$ mice were also less sensitive to the effects of the selective D2 antagonist L741,626 on maximum response rate (30-45 min, 5.6 kg/mg, ***p < 0.001; 46-60 min, 5.6 kg/mg, ***p < 0.001; 61-75 min, 5.6 kg/mg, ***p < 0.001; 76-90 min, 5.6 kg/mg, ***p < 0.001). Error bars indicate ±SEM.

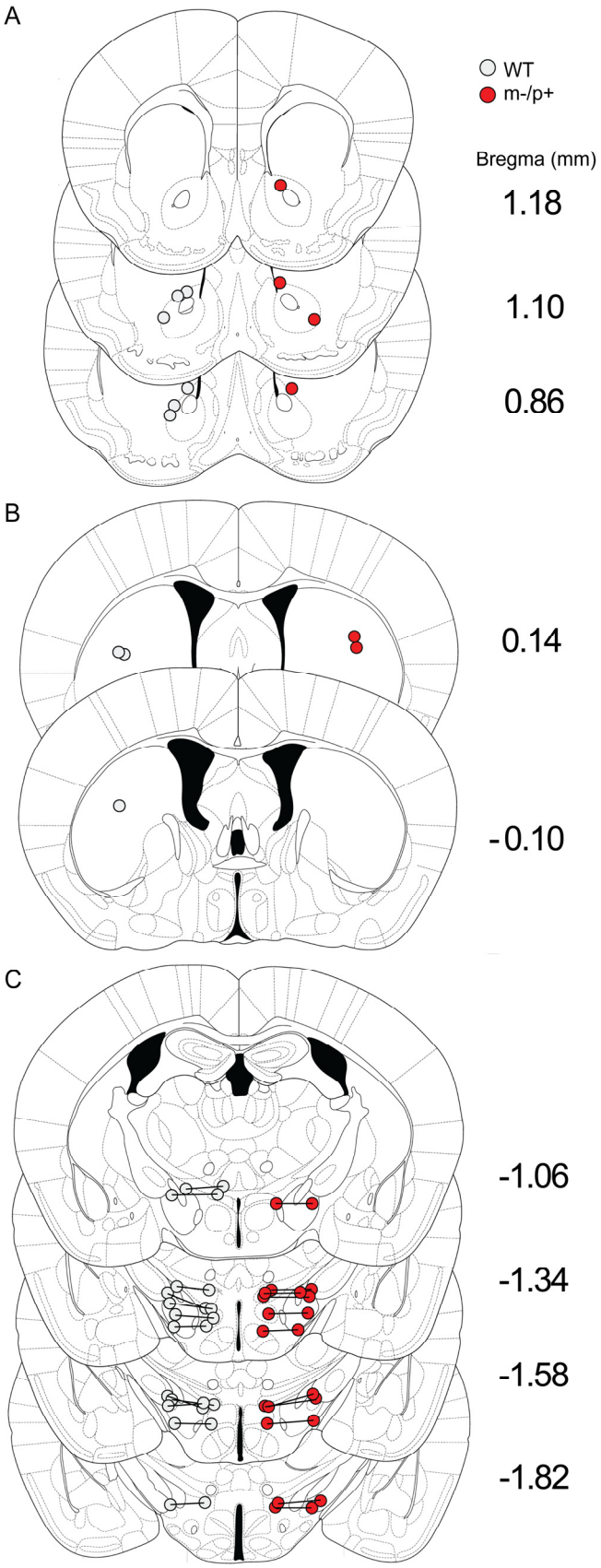


Supplemental Figure 4. Enhanced extracellular dopamine in the NAc and reduced extracellular dopamine in the dorsal striatum of *Ube3a*$^{m-/p+}$ mice

Change in extracellular dopamine concentration measured by voltammetry following electrical stimulation of the ascending dopaminergic fibers to either the NAc (**A**) or dorsal striatum (**B**). Insets show the peak dopamine concentration recorded from each mouse. The stimulus duration is shown in gray shading. (**A**) *Ube3a*$^{m-/p+}$ mice consistently exhibited greater accumbal NAc dopamine concentrations across all stimulation frequencies (20-50 Hz, above, and 60 Hz in Figure 5A). (**B**) Conversely, in the dorsal striatum extracellular dopamine was reduced in *Ube3a*$^{m-/p+}$ mice (20-50 Hz, above, and 60 Hz in Figure 5B). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Error bars indicate ±SEM.



Supplemental Figure 5. ICSS electrode placement
Mice used for ICSS experiments were perfused and their brains sectioned and stained for Nissl to determine electrode tip placements. (**A**) Representative coronal section (4x magnification) with a stimulating electrode tract directly above the MFB. (**B**) All electrodes were implanted on the right. The most ventral point of each electrode tract was determined and plotted on the left for WT mice (gray circles) and on the right for *Ube3a*$^{m-/p+}$ mice (red circles) for clarity.



Supplemental Figure 6. FSCV electrode placement
Mice used for FSCV experiments were perfused and their brains sectioned and Nissl stained to determine electrode tip placements. (**A**) Representative placements for carbon-fiber microelectrodes in the NAc. (**B**) Representative placements for carbon-fiber microelectrodes in the dorsal striatum. (**C**) Representative placements for bipolar stimulating electrodes in the MFB. The two tips of each bipolar electrode are connected with horizontal lines. The most ventral point of each electrode tract was determined and plotted on the left for WT mice (gray circles) and on the right for *Ube3a*$^{m-/p+}$ mice (red circles).