Supporting Information

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SI Materials and Methods

Generation of Conditional DRD2 Mutant Mice and Genotyping. Mutant mice with targeted loxP sites flanking DRD2 exon 2 ($DRD2^{flox/flox}$) were crossed with a homologous recombinant mice that drives the expression of Cre recombinase by the PV promoter in a C57/BL6 background. We established a mouse colony by mating $DRD2^{flox/flox}$ with $PV^{+/Cre}$::$DRD2^{flox/flox}$, which yields littermates of both genotypes in equal amounts. Only male mice were used for experiments. Animals were maintained in a controlled environment (20–22 °C, 12 h light/dark cycle) and were group housed in individual ventilated cages with food and water ad libitum. For interneuron electrophysiological recordings, a tdT reporter line (ai14)[3] was used to identify PV-positive (PV^{+}) interneurons. The used groups were $PV^{+/Cre}$::$DRD2^{flox/flox}$::tdT and $PV^{+/Cre}$::tdt. Genomic DNA was obtained from ear punch biopsies and the purified material was used to perform PCRs to identify each genotype. The sequence of the primers used to genotype the animals were as follows: for $DRD2^{flox/flox}$: forward, 5′-GCTTCACAGTGTGCTGCCTA-3′, and reverse, 5′-CCATTGCTGCCTCTACCAAG-3′; for $PV^{+/Cre}$: forward, 5′-GCATAACCAGTGAAACAGCATTGCTG-3′, and reverse, 5′-AAAATTTGCCTGCATTACCG-3′; for tdT, 5′-CTCTGCTGCCTCCTGGCTTCT-3′, 5′-CGAGGCGATCACAAGCAATA-3′, and 5′-TCAATGGGCGGGGGTCGTT-3′. Experiments were performed in accordance with the Principles of Laboratory Animal Care and with the guidelines approved by the Institutional Animal Care and Use Committee.

Preparation of Brain Slices. Adult (P60) mice were anesthetized with a ketamine/xylazine solution (ketamine, 80–100 mg/kg, and xylazine, 2%; 10 mg/kg, i.p.) followed by an intracardiac perfusion with ice-cold low sodium/antioxidants solution containing the following (in mM): 200 sucrose, 2.5 KCl, 26 $NaHCO_3$, 1.25 NaH_2PO_4, 20 glucose, 0.4 ascorbic acid, 2 pyruvic acid, 1 kynurenic acid, 1 Cl_2Ca, and $MgSO_4$, gassed with 95% O_2/5% CO_2. Animals were decapitated, and the brain was rapidly removed and placed into an ice-cold low-Ca^{2+} artificial cerebrospinal fluid (aCSF). This solution contained the following (in mM): 125 NaCl, 2.5 KCl, 3 $MgSO_4$, 0.1 $CaCl_2$, 1.25 NaH_2PO_4, 0.4 ascorbic acid, 3 myoinositol, 2 pyruvic acid, 25 D-glucose, and 25 $NaHCO_3$ saturated with 95% O_2 and 5% CO_2. Sagittal slices (300 μm) from prefrontal cortex (PFC) and hippocampus (Hipp) were obtained using a vibratome (Vibratome 1000 Plus, Pelco; Ted Pella). Slices were cut sequentially and transferred to an incubation chamber containing aCSF (in mM): 125 NaCl, 2.5 KCl, 2.3 NaH_2PO_4, 25 $NaHCO_3$, 2 $CaCl_2$, 1.3 $MgCl_2$, 1.3 Na^{+}-ascorbate, 3.1 Na^{+}-pyruvate, and 10 dextrose (315 mOsm) at 37 °C for 30 min. After incubation, slices were allowed to return to room temperature. The pH was 7.4 when gassed with 95% O_2/5% CO_2. All used drugs and chemicals were purchased at Sigma, unless otherwise stated.

Recordings of Pyramidal Cells in Hippocampal Slices. Slices were transferred to an experimental chamber. During recording, slices were continuously perfused with carbogenated (95% O_2 and 5% CO_2) aCSF maintained at room temperature (22–25 °C). Hippocampal slices were mounted on an Olympus BX51 microscope.

Pyramidal neurons in CA1 cell layer were recorded with infrared DIC video microscopy. Whole-cell recordings were performed using microelectrodes (4–8 MΩ) filled with the following (in mM): 130 CsOH, 130 D-gluconic acid, 2 $MgCl_2$, 0.2 EGTA, 5 NaCl, 10 Hepes, 4 ATP-Tris, 0.3 GTP-Tris, and 10 phosphocreatine. Field recordings were performed using patch pipettes (4–8 MΩ) filled with 3 M NaCl. Recordings were obtained using Axopatch 200B and Multiclamp700B amplifiers, digitized, and acquired at 20 kHz onto a personal computer using the pClamp10 software. Membrane capacitance and input resistance were obtained from current traces evoked by a hyperpolarizing step of 10 mV. Evoked monosynaptic EPSCs and IPSCs were recorded after Schaffer collateral (SC) stimulation. EPSCs were isolated by voltage-clamping pyramidal neurons at the reversal potential of the IPSC measured for each individual neuron (approximately −70 mV). In turn, IPSCs were recorded at the reversal potential of the EPSC (~0 mV). Synaptic excitatory and inhibitory conductances were computed as the EPSC or IPSC divided by the driving force at which the synaptic currents were recorded. For spontaneous activity, cells were recorded at the reversal potential of inhibition (obtained after measuring evoked currents) to measure sEPSCs and at the reversal potential of excitation to measure sIPSCs.

Calibration of Input Strength for Pyramidal Cell Activation. The input strength is proportional to the number of activated SC axons. The slope of the field excitatory postsynaptic potential (fEPSP) increases linearly with the number of activated axons. Therefore, the input strength was assessed as percentage fEPSP slope. For this purpose, a field-recording microelectrode was placed in CA1 pyrimidal neuron layer to record the fEPSP and the population spike (pop spike) in response to the SC stimulation. To compare input strengths across experiments, the fEPSP slope elicited at any given stimulus intensity was normalized to the fEPSP slope evoked at a stimulus intensity that evokes a maximal pop spike (100%). Input strength was kept ≤50% for all experiments. A similar approach for input strength calibration has been previously used (49).

Recordings from Interneurons. Slices were mounted on a Zeiss Axioskop microscope. Recordings were made with patch pipettes pulled from thin-walled borosilicate glass (1B100F-4; World Precision Instruments). Electrodes had resistances of 3.2–4.2 MΩ when filled with internal solution. Solutions for voltage-clamp recordings contained the following (in mM): 120 Cs-methanesulfonate, 20 CsCl, 10 Hepes, 10 Na_2-phosphocreatine, 10 TEA-Cl, 0.5 EGTA, 4 Mg-ATP, and 0.3 Li-GTP. The pH was adjusted to 7.2 with CsOH. We added TTX (1 μM) and bicuculine (20 μM) to isolate mEPSCs. Cesium methanesulfonate was replaced by K-gluconate in the intracellular solution for current-clamp recordings. The following parameters were rapidly measured after the patching of the tomato-expressing interneurons: resting membrane potential, membrane resistance, membrane capacitance, threshold potential for spikes, and maximum firing frequency. Whole-cell patch-clamp recordings were made using an Axopatch 200A (Molecular Devices) amplifier, a Digidata 1322 A/D converter (Molecular Devices), and pClamp 10.2 software (Molecular Devices). Data were sampled at 50 kHz and filtered at 4–6 kHz (low-pass Bessel filter).

For whole-cell patch-clamp recordings in interneurons, $PV^{+/Cre}$::$DRD2^{flox/flox}$::tdT and $PV^{+/Cre}$::tdt expressing cells were excited at 594 nm. Interneurons were identified using a 40× water-immersion objective and a camera with contrast enhancement (Dage-MTI).

Local Field Potential Recordings. Mice were anesthetized with urethane (1.8 g/kg, i.p.) and secured in a stereotaxic frame, testing the proper state of anesthesia by observing the absence of the paw reflex. Body temperature was measured by a rectal probe and held constant at 37 °C using a controlled pad. The skull was exposed

and two craniotomies were drilled in the mPFC and Hipp coordinates [mPFC: anteroposterior (AP) = 1.7 mm, lateral (L) = 0.3 mm, dorsoventral (DV) = 2 mm; dHipp: AP = −2.1 mm, L = 1.2 mm, DV = 1.5 mm; bregma as reference]. A stainless-steel screw was inserted in the occipital bone as reference, and one stainless-steel macroelectrode (surface, 0.038 mm^2) was introduced in each area for local field potential (LFP) recordings. Electrodes were preimmersed in a DiI solution for posterior localization of the recording sites. One recording (30 min long) was performed in each animal. Signals were preamplified 10×, and then amplified 1,000×. Data were acquired with a National Instruments device at a sampling frequency of 30 kHz, and downsampled to 2.5 kHz. Power spectra and coherence were computed with the multitaper method (time-bandwidth product = 3, number of tapers = 5; Chronux package, chronux.org/). To estimate the phase-amplitude coupling, the phase locking value (PLV) was computed as follows:

$$\mathrm{PLV} = \frac{1}{N}\left|\sum_{n=1}^{N} e^{-i(\phi_H(n)-\phi_L(n))}\right|,$$

where N stands for the total number of samples in a given recording, $\phi_H(n)$ is the phase angle at sample n of the envelope of the high-frequency band (gamma, 30–70 Hz), and ϕ_L is the phase angle at sample n of the low-frequency band (alpha, 8–15 Hz). To obtain these two values, we first used a zero phase filter onto the downsampled signal to obtain low- and high-frequency bands. To obtain ϕ_H, we first computed the envelope of the high-frequency band as the amplitude of its Hilbert transform. Then, we computed the Hilbert transform once again over the envelope and took its phase angle as ϕ_H. To obtain ϕ_L, we computed the Hilbert transform of the low-frequency band and took its phase angle.

Immunohistochemistry and Image Analysis. Mice were transcardially perfused with 4% paraformaldehyde (PFA), and the brain was removed and postfixed in the same fixative for 180 min at 4 °C. The tissue was cryoprotected sequentially in 10%, 20%, and 30% sucrose solution in PBS and then cut serially in a cryostat in 40-μm-thick coronal brain sections. Primary antibodies were as follows: monoclonal anti-PV (1:2,000; Swant), rabbit anti-Calretinin (1:2,000; Swant), chicken anti-GFP (1:2,000; Aves Labs), and rat anti-somatostatin (1:250; Millipore). Secondary antibodies were as follows: anti-mouse AF-594 (1:400; Jackson ImmunoResearch), anti-rabbit 555 (1:400; Life Technologies), anti-chicken 488 (1:400; Life Technologies), anti-rat 594 (1:400; Jackson ImmunoResearch), and anti-mouse 647 (1:400; Jackson ImmunoResearch). Stained sections of control and mutant mice were imaged during the same imaging session. Images were acquired using an Olympus IX83 microscope. For cell counting, images were processed using ImageJ.

In Situ Hybridization. Animals were perfused with 4% PFA and brains were fixed overnight in the same solution, cryoprotected in 30% sucrose in RNase-free PBS, embedded in Cryoplast (Biopack), and stored frozen at −80 °C. Twenty-five-micrometer coronal sections were cut on a cryostat and subsequently postfixed in 4% PFA for 10 min. After three washes in PBT [PBS plus Tween 0.1% (Sigma)], sections were treated with 10 μg/mL proteinase K (Roche) in PBT for 10 min, transferred to 4% PFA for 5 min, and then briefly washed with PBT. Subsequently, sections were acetylated for 10 min [1.3% triethanolamine (Sigma), 0.25% acetic anhydride (Merck), and 21 mM HCl], then washed with PBT three times 5 min each, and transferred to a hybridizing chamber for an incubation with the prehybridization solution [50% Formamide (Millipore), 20% dextran sulfate (Sigma), 1 mg/mL tRNA (Sigma), 1× Denhardt's solution (Sigma), SSC 5× [from a 20× stock solution containing 3 M NaCl (Sigma), 0.3 M sodium citrate (Sigma), Tween 0.1%, EDTA 5 mM (Sigma)] for 3 h at room temperature (RT). Prehybridization solution was heated to 85 °C for 15 min and also digoxigenin (DIG)-labeled RNA probes for 5 min. Heated probes were then added to heated prehybridization solution to a final concentration of 1 ng/μL and maintained at 85 °C for other 5 min. Prehybridization solution was then poured off the slides, and 250 μL of the solution containing the probe was added to each slide, which was subsequently covered with a coverslip and incubated overnight at 62 °C. The next day, the coverslips were gently removed and slides were washed with a solution containing 50% formamide, 1× SSC, 0.1% Tween three times for 30 min each at 62 °C. Slides were then washed in PBST [PBS plus 0.1% Triton (Merck)] for 10 min and incubated for 2 h in blocking solution [1× PBS, 2 mg/mL BSA (Sigma), 0.1% Triton, 10% goat serum (Natocor)] and subsequently incubated overnight with anti-DIG antibody (Roche) diluted 1:2,000 in blocking solution. The next day, slides were washed 10 min in a solution containing 100 mM Tris·HCl, pH 7.5, 150 mM NaCl (Sigma), and 0.1% Triton. Afterward, slides were washed in alkaline phosphatase buffer [100 mM Tris·HCl, pH 9.5, 50 mM $MgCl_2$ (Sigma), 100 mM NaCl (Sigma), 0.1% Tween 20] for 10 min and incubated in the dark at RT in nitroblue tetrazolium (NBT)/5-bromo-4-chloro-3-indolyl phosphate (BCIP) solution [300 μL/mL NBT (Sigma): 175 μL/mL BCIP (Sigma)]. Slides were checked periodically and the reaction was stopped in Tris-EDTA buffer. Finally, slides were dried overnight, dehydrated, and covered with DPX mounting medium (Sigma).

RT-PCR. Animals were killed by cervical dislocation, and brains were quickly removed and flash frozen. Brains were cut in a cryostat at 300 μm at the level of the PrL and IL region [bregma, 1.94 mm (50)] or at the level of the ventral hippocampus [bregma, −3, 64 (50)]. One or two of these 300-μm sections were used to specifically dissect the PrL/IL or the ventral subiculum region from the rest of the brain tissue. The dissected tissues were transferred to Tripure isolation reagent to obtain total RNA (Roche). The mRNA was extracted and transcribed into cDNAs with Transcriptor First Strand cDNA Synthesis Kit (Roche). The following primers were used for RT-PCR: DRD2, forward primer, 5′-CCACACTGGTTATGCCCTGG-3′; reverse, 5′-GGTTCAAGATGCTTGCTGTGC-3′; DRD1, forward, 5′-GATGGCTCCTAACACTTCTACC-3′; reverse, 5′-GGCTGTGAGGATGCGAAAG-3′; GAD67, forward, 5′-CATGGCGGCTCGGTACAAAGTA-3′; reverse, 5′-AACAGTCGTGCCTGCGGTTGC-3′; NR2A, forward, 5′-GCCTGAGAATGTGGACTTCC-3′; reverse, 5′-TTCTGTGACCAGTCCTGC-3′; NR2B, forward, 5′-GCATTTGCCACAATGAGAAGAA-3′; reverse, 5′-CACAGTCATAGAGCCCATCAA-3′; PV, forward, 5′-CTGCCCGCTCAAGTTG-3′; reverse, 5′-TCTGCAGCAAAGGCTC-3′; Cyclofilin, forward, 5′-TGGAGATGAATCTGTAGGACGA-3′; reverse, 5′-GAAGTCTCCACCCTGGATCA-3′.

Western Blots. Mice were killed by decapitation and PFC tissue was rapidly dissected out and homogenized in lysis buffer containing the following (in mM): 50 Tris·HCl, pH 7.5, 150 NaCl, 1% IGEPAL with protease and phosphatase inhibitor mixture. Samples were denatured and run on 12% SDS/PAGE gels. Gels were electrophoretically transferred onto PVDF membranes. Membranes were blocked with 5% BSA in TBST 0.1% (50 mM Tris base, pH 7.5, 150 mM NaCl, and 0.1% Tween 20) for 1 h and probed with the following primary antibodies overnight at 4 °C: anti–α-tubulin (1:4,000, Millipore) or anti-Gsk3β (1:1,000; Cell Signaling). Subsequently, immune complexes were revealed by using appropriate peroxidase-conjugated secondary antibodies (Jackson ImmunoResearch) along with ECL Western blotting detection reagents (Thermo Scientific). Signals were acquired as 8-bit images and quantified in ImageJ.

HPLC. The neurochemical detection of DA and DA metabolites were performed by HPLC using the electrochemical detector (BAS LC-4C). Tissues were weighed, homogenized, and deproteinized in 0.2 M perchloric acid (1/20 mg/μL). Homogenates were centrifuged, and supernatants (20 μL) were injected onto a 12.5 cm × 4 mm Nova-Pak C18 (Waters) reverse-phase column. Mobile phase contained 0.076 M $NaH_2PO_4 \cdot H_2O$, 0.99 mM EDTA, 5.24 mL/L PICB8, and 6% methanol. Endogenous concentrations of DA, DOPAC, and HVA were determined in equipment with a Shimadzu LC-1OAS bomb and electrochemical detector (Bioanalytical Systems). Peak heights were measured by Peak Simple Chromatography Data System (Model 302 Dix Channel USB) and were quantified based on standard curves.

Brain Viral Injection and Dendritic Spine Analysis. Mice were anesthetized by i.p. injection of ketamine (100 mg per kg of body weight) and xylazine (10 mg per kg) and placed on a stereotaxic frame (Stoelting). An incision was made through the midline to expose the skull. The bregma was identified and a hole was drilled at the appropriate coordinates. A 10.0-μL Hamilton syringe coupled to a 36-gauge stainless-steel needle was used to inject 2 μL of lentiviral suspension (0.6×10^7 transduction units) carrying the GFP reporter cassette under control of ubiquitin promoter on both hemispheres into the prelimbic cortex at the following coordinates (50): AP, +1.94 mm; L, ± 0.4 mm; DV, −2.5 mm, measured from the bregma. Injection rate was 0.2 μL/min. During the surgery and until full recovery, animals were kept in constant temperature conditions. Immediately after surgery, mice received the analgesic flunixin meglumine (1 mg/kg, s.c.).

Fourteen days after lentivirus injection, mice were perfused with 4% PFA in PBS 1×, and 60-μm coronal brain sections were cut in a cryostat. Brain sections were mounted onto slides in mounting media and imaged with an Olympus IX83 microscope. Secondary dendrites (20–80 μm from the soma) from each neuron were analyzed for spine analysis. The number of dendritic protrusions was counted with ImageJ.

Behavioral Analyses. Behavioral experiments were conducted during the dark phase of the light/dark cycle between 6 PM and 11 PM, and performed by an observer blind to genotype. All tests were videotaped using a computer-assisted data acquisition system (VirtualDub 1.4 auxiliary setup). The order of tests was as follows: open field (locomotor activity), elevated plus maze (anxiety), marble-burying test (anxiety), Y maze (spatial memory), novel object recognition test (NOR) (short-term memory), and nesting test (motivation).

Locomotor activity. Spontaneous locomotor activity in an open field was measured using ANY-maze Video Tracking System. Total distance traveled (horizontal activity) was analyzed. For drug experiments, mice were injected with vehicle (saline solution) or drug (10 mL/kg body weight, i.p.), placed into the open field, and monitored for 30 or 60 min.

For the stress test, animals were separated in naive or stress groups. Naive animals were transferred to an open field arena to measure total locomotion and grooming events during 10 min. Stress group animals were given an i.p. injection of saline (200 μL) before the open field test.

For the amphetamine-induced locomotion, animals were placed in the open field and monitored for 60 min.

The concentrations of used drugs were as follows: MK-801, 0.2 mg/kg (Sigma); aripiprazole, 0.6 mg/kg (Maprimed); risperidone, 0.025 mg/kg (Maprimed); and amphetamine, 5 mg/kg (Sigma).

Elevated plus maze. The elevated plus maze was used to study anxiety-related behavior. The apparatus consists of a cross-shaped platform (four arms faced two to two with a length of 30 cm and 8 cm width) elevated 50 cm from the floor. Two opposing arms are protected by walls (without roof) and the other two are left unprotected. Because it is elevated from the ground, the open arms represent an aversive environment for the mouse. The proportion of time spent in open arms during 8 min is considered a measure of anxiety. Traveled distance was also analyzed as a measure of the activity in the apparatus.

Marble burying. Empty cages (30 × 24 × 15 cm) were filled with woodchip bedding up to 5 cm from the cage floor, and 12 marbles were positioned in a grid pattern throughout the cage. Mice were allowed to freely explore the cage for 30 min. Afterward, the number of successfully buried marbles was counted. A marble was defined as buried when <30% of its surface was visible. After the test time period, a photograph was taken to analyze the result.

Spontaneous alternation in Y maze. Testing was carried out on a Y-shaped maze (35 × 5 cm each arm). Mice were placed into the end of one arm and allowed to freely explore for 7 min. The sequence of arm entries was recorded. The spontaneous alternation behavior was calculated as the number of triads containing entries into all three arms divided by the total number of entries.

Novel object recognition test. A mouse was placed in an empty arena and was allowed to explore it for 5 min. Twenty-four hours later, during familiarization session, the mouse was presented with two identical objects and was allowed to freely explore them for 5 min. Two hours later, during the test session, one of the two objects was replaced by a new one and mice were allowed to explore for 3 min. The amount of time taken to explore the new object provides an index of recognition memory. Total locomotion was also determined during the test.

Nesting test. To study the motivation to build a nest, one piece of pressed cotton fiber (~3 g each), was introduced in a cage in which a mouse was individually housed. Each piece of pressed cotton was weighed before the test. After the test, the unthreaded and identifiable pieces of nesting material were weighed. Pictures of the nests were also taken at the end of the experiment.

Statistical Analysis. Statistical analysis was carried out in GraphPad Prism 5. The data are presented as mean ± SEM. Behavioral data were evaluated by *t* test, one- or two-way ANOVA, followed by post hoc tests. A value of $P < 0.05$ was considered significant. Mann–Whitney–Wilcoxon test ($P < 0.05$) was used to analyze nesting and marble-burying test.

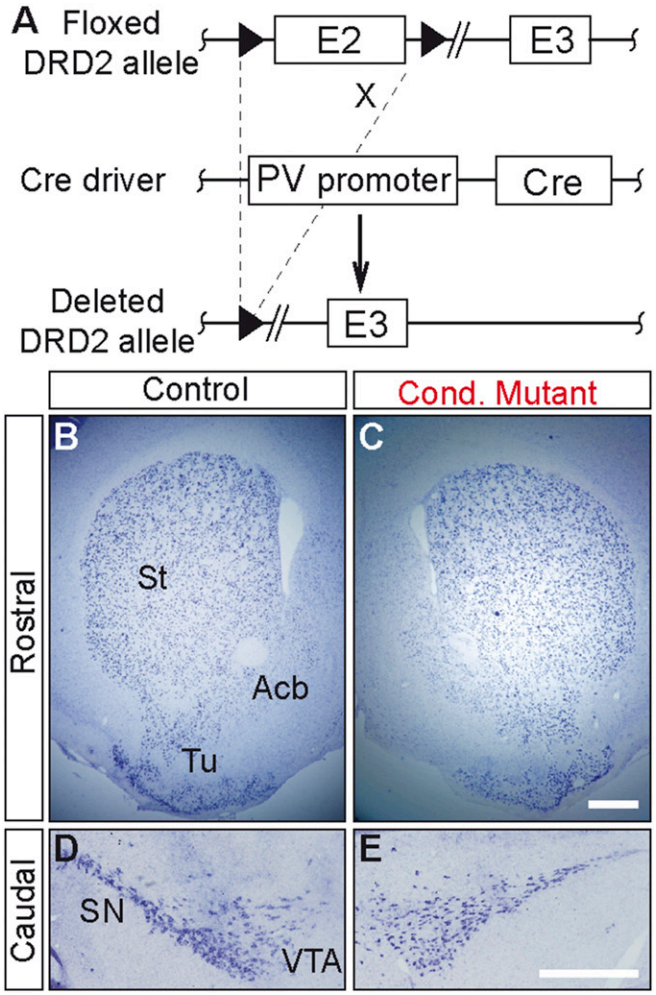

Fig. S1. (*A*) Schematic representation of DRD2 locus with exon 2 flanked by loxP sites (black triangles), Cre recombinase under the transcriptional control of PV promoter and deleted exon 2 after Cre recombination. (*B*–*E*) Normal DRD2 mRNA expression by in situ hybridization in both control (*B* and *D*) and conditional mutants (*C* and *E*) in the striatum (St) (rostral) (*B* and *C*) and substantia nigra (SN) and ventral tegmental area (VTA) (caudal) (*D* and *E*) regions. (Scale bar: 500 μm.) Acb, accumbens nucleus; Tu, Olfactory tubercle.

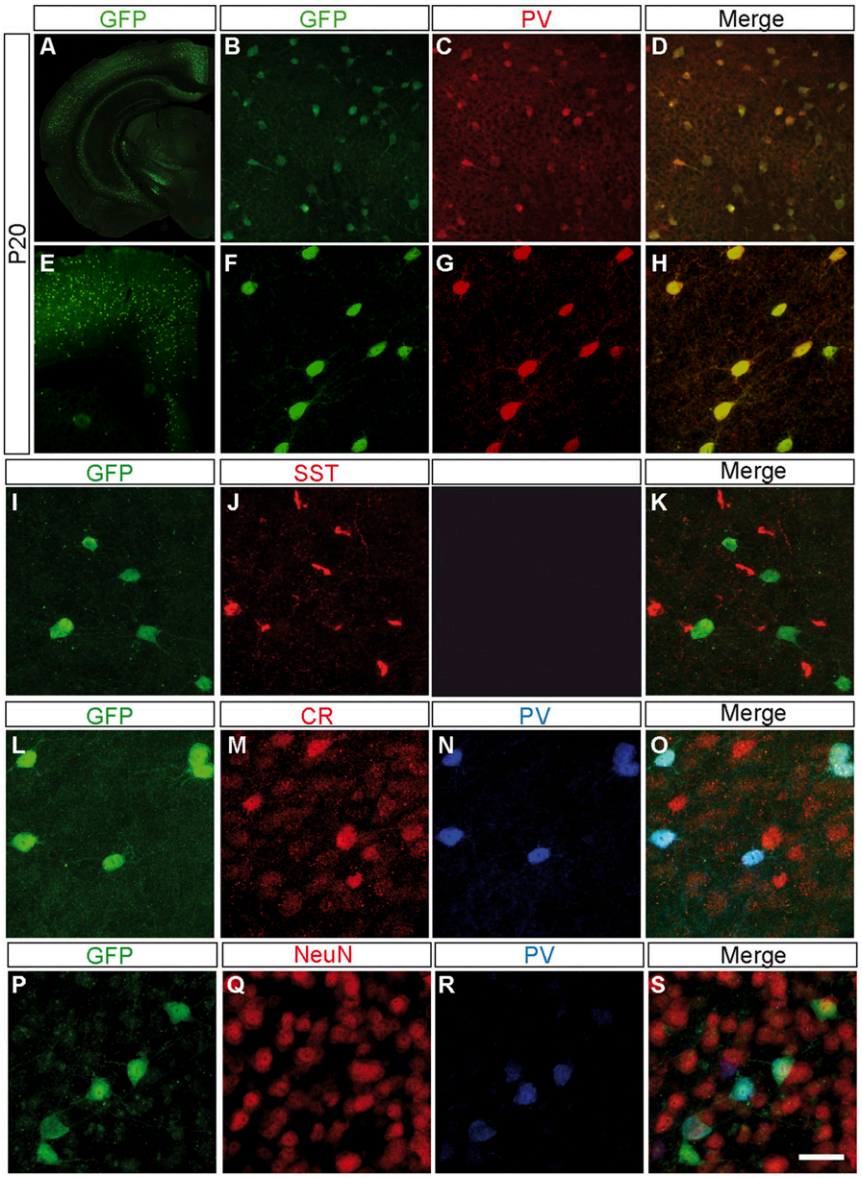

Fig. S2. Cre recombinase is already expressed at P20 and is restricted to PVIs. (*A*) Immunofluorescence of P20 coronal brain sections from a PV-Cre::GFP reporter. GFP (*B*, *D*, *F*, and *H*) and PV (*C*, *D*, *G*, and *H*) immunofluorescence from the ventral hippocampus (*A–D*) or PFC (*E–H*). PVIs express the Cre reporter GFP by this age. (*I–S*) GFP expression is restricted to PVIs. GFP (*I*, *K*, *L*, *O*, *P*, and *S*) do not colocalize with somatostatin (*J* and *K*) or calretinin (*M* and *O*) and is restricted to PVIs (*N*, *O*, *R*, and *S*) but not other type of neurons (*Q* and *S*). (Scale bar: 50 μm; *F–S*.)

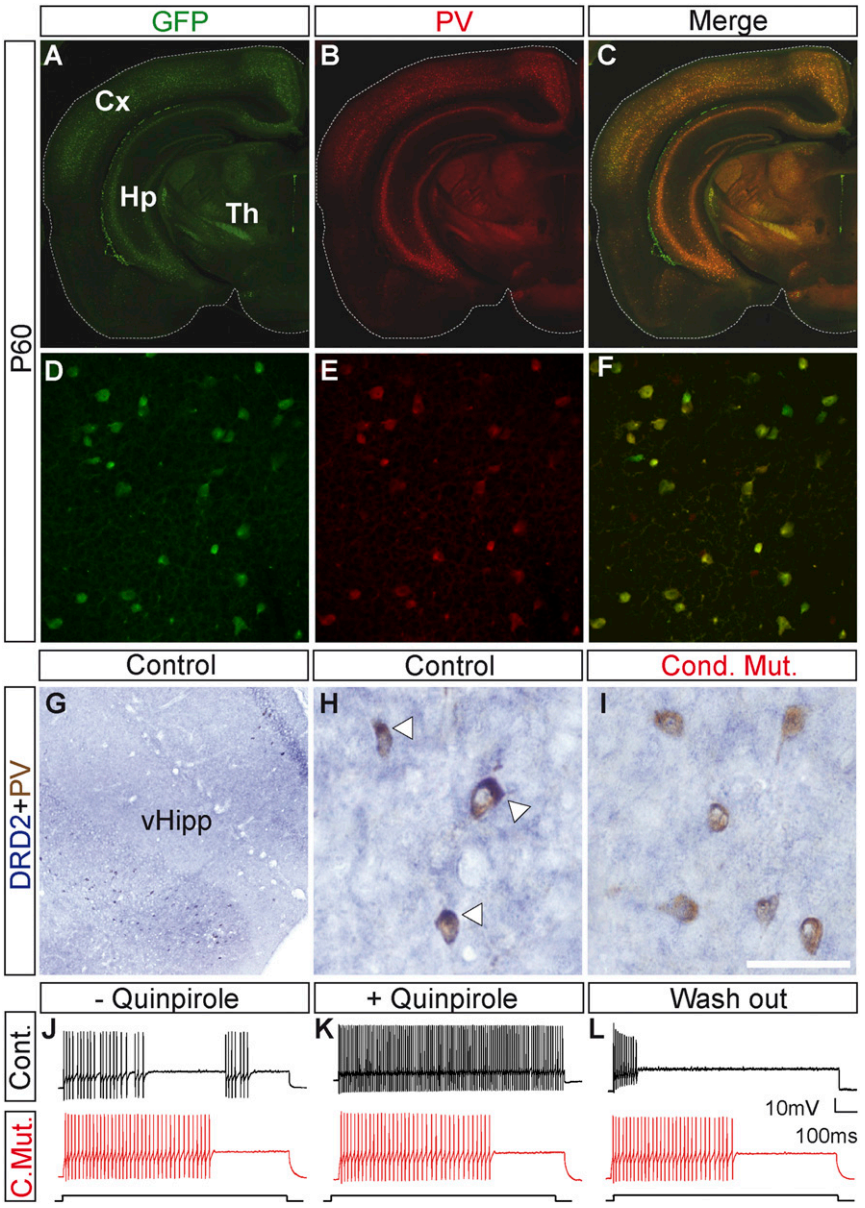

Fig. S3. Reliable expression of Cre recombinase causes selective DRD2 deletion from PVIs at P60. (*A–F*) The micrographs show immunofluorescence experiments to label PV and GFP from a reporter line in coronal brain sections at the level of the thalamus (*A–C*) and the ventral hippocampus (*D–F*). The GFP reporter (*A*, *C*, *D*, and *F*) is expressed only in PVIs (*B*, *C*, *E*, and *F*). (*G–I*) Combined in situ hybridization and immunohistochemistry to label DRD2 receptor mRNA and PV, respectively. (*G*) Micrographs at the level of the ventral hippocampus. (*H*) Control animals show DRD2 mRNA (purple) in PVIs (brown, white arrowheads). (*I*) In contrast, conditional DRD2 mutant animals are labeled for PV, but not for DRD2 mRNA. (Scale bar: 50 μm.) (*J–L*) Functional experiment to test the deletion of DRD2 from PVIs. Bath application of an effective dose of the selective DRD2 agonist quinpirole (1 μM) increased excitability only in FS interneurons expressing DRD2 receptor. Excitability was assessed by counting the number of action potentials evoked by a constant-amplitude intracellular current injection. Current amplitude was adjusted to initially evoke a few (5–20) spikes per second (i.e., not a saturating stimulation). Following 5–7 min of quinpirole (1 μM), the number of evoked spikes increased in control animals but had no effect in conditional DRD2 mutant animals. Cx, cortex; Hp, hippocampus; Th, thalamus.

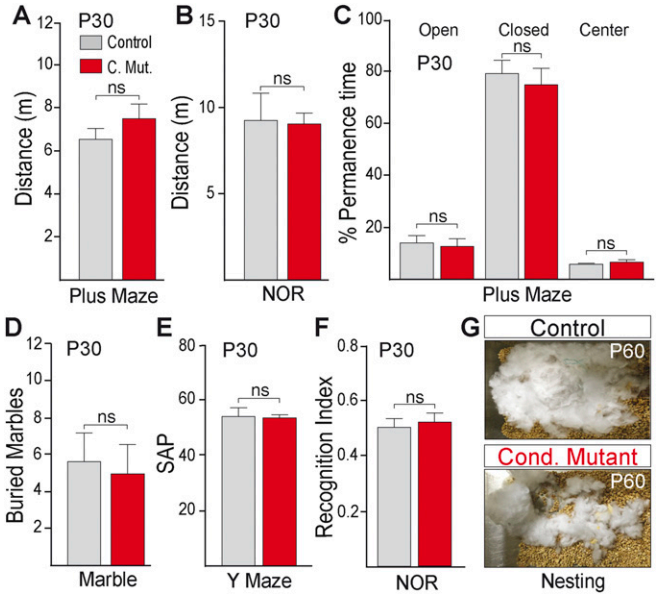

Fig. S4. Young animals did not show behavioral phenotypes. Behavioral performance in young (P30) control and conditional DRD2 mutants. (*A*) Total distance from young animals in plus maze and (*B*) novel object recognition (NOR) test. (*C*) Percentage of permanence time in the open arms, closed arms and center of the plus maze. (*D*) Number of buried marbles in the marble-burying test. (*E*) Spontaneous alternation percentage (SAP) in the Y maze. (*F*) Recognition index in the NOR test. (*G*) Representative images from the nests of adult (P60) control and conditional mutants. ns, not significant. Data are presented as mean ± SEM (*A*–*F*). Unpaired *t* test (*A*–*F*).

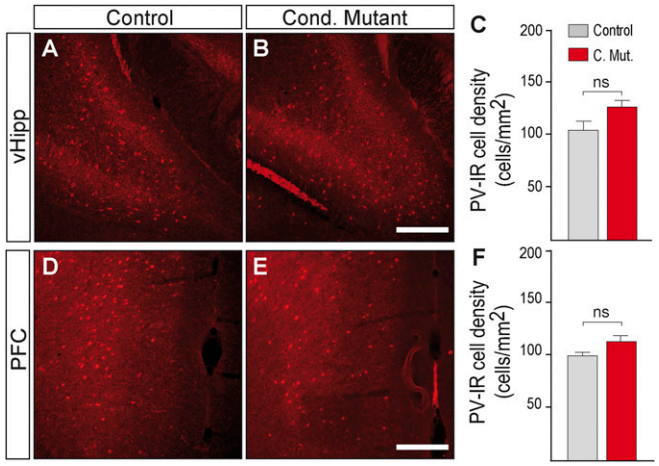

Fig. S5. PVI density in PFC and vHipp. Micrographs of a PV immunofluorescence in the vHipp (*A* and *B*) and PFC (*D* and *E*) from control (*A* and *D*) or conditional DRD2 mutants (*B* and *E*). (Scale bar: 250 μm.) Quantification of PVI density in (*C*) the vHipp and in (*F*) the PFC. ns, not significant; data are presented as mean ± SEM. Unpaired *t* test, $n = 8$–12 animals per genotype (*C* and *F*).

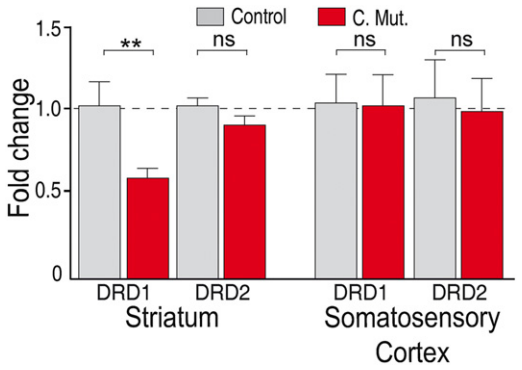

Fig. S6. Quantification of dopamine receptor mRNA levels in the striatum and somatosensory cortex. DRD1, but not DRD2, mRNA level is reduced in the striatum of conditional DRD2 mutants. In the somatosensory cortex, a region not prominently innervated by dopaminergic fibers, DRD1 and DRD2 mRNA levels did not change between genotypes. $^{**}P \leq 0.01$; ns, not significant; data are presented as mean ± SEM. Unpaired *t* test, $n = 5$ animals per genotype.

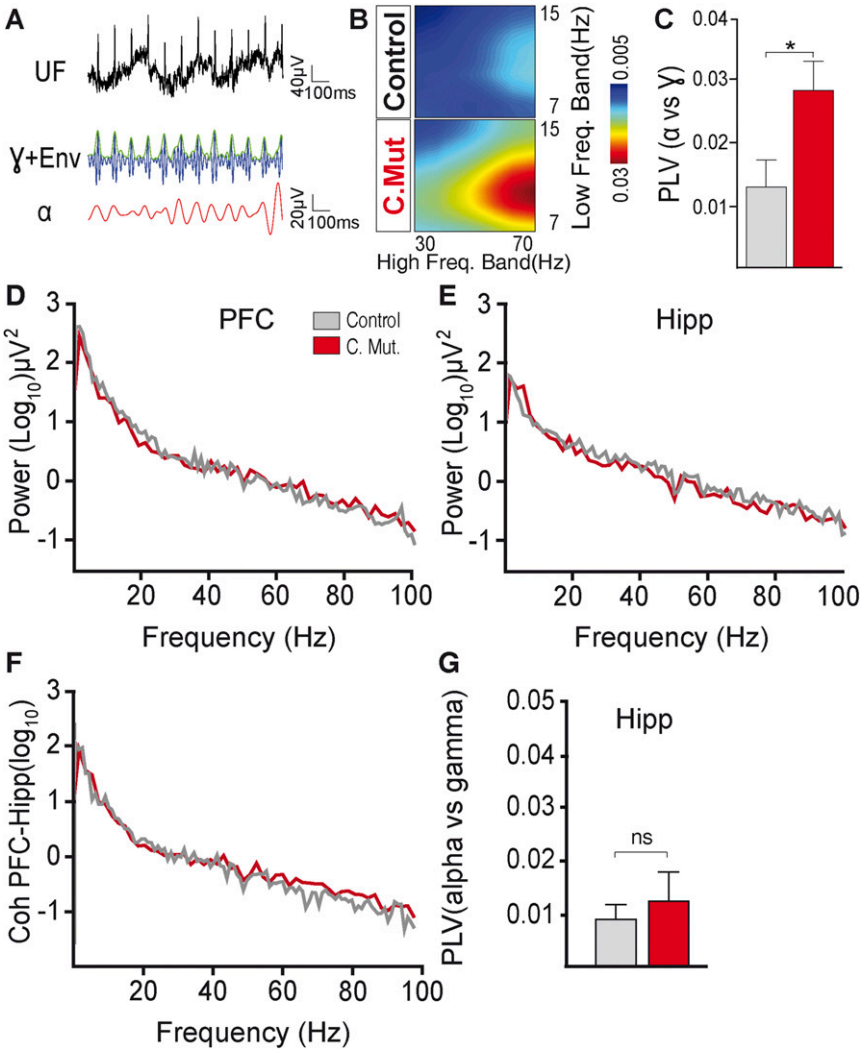

Fig. S7. (*A*–*C*) Local field potential (LFP) recordings in PFC. (*A*) Representative traces of the unfiltered signal (UF-black), gamma (γ) trace (blue) plus its envelope (Env, green) and alpha (α) trace (red). (*B*) Correlation between amplitude and phase frequency for control and conditional DRD2 mutants in a range of frequencies corresponding to gamma (*x* axis) and alpha bands (*y* axis). (*C*) Increased phase-locking value (PLV) in conditional mutant animals between alpha and gamma bands ($n = 6$ animals from each genotype). Power spectrum along the range of frequencies in the (*D*) PFC and (*E*) hippocampus and coherence (*F*) between these structures. (*G*) PLV between alpha and gamma bands in the Hipp. $^{*}P \leq 0.05$; ns, not significant. Data are presented as mean ± SEM. Unpaired *t* test (*C* and *G*); five to six animals per genotype. Coh, coherence.

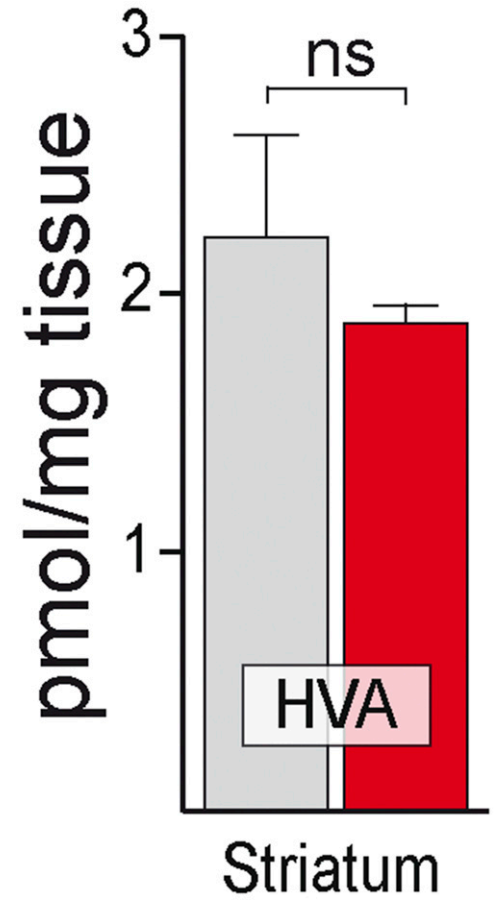

Fig. S8. HPLC measurement of the dopamine metabolite HVA in the striatum. ns, not significant; data are presented as mean ± SEM. Unpaired *t* test, $n = 8$–10 animals per genotype.

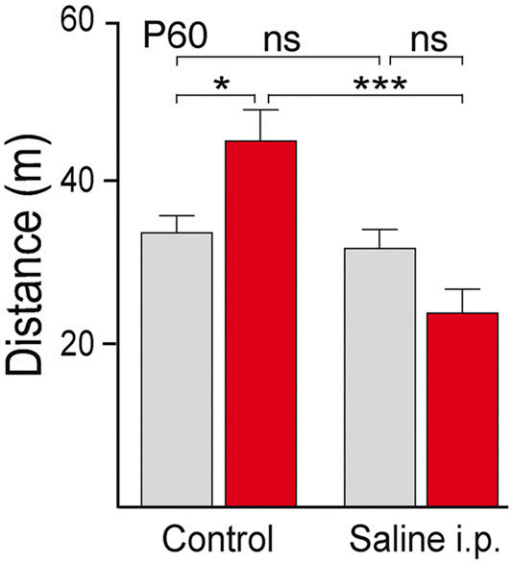

Fig. S9. Conditional DRD2 mutant animals show susceptibility to an i.p. injection. Total distance traveled by control and conditional mutant animals in noninjected (control) and i.p. injected (saline i.p.) animals. Conditional DRD2 mutant animals show a reduced locomotor activity after the injection, while control animals are not affected. $*P < 0.05$; $***P < 0.001$; ns, not significant; data are presented as mean ± SEM. Unpaired *t* test, $n = 10$–20 animals per genotype.

Table S1. Basic membrane properties of PVIs in the PFC of control and conditional DRD2 mutants

Properties evaluated	Control (*n*)	Conditional mutant (*n*)	*P* value
RMP, mV	−75.55 ± 2.73 (8)	−76.66 ± 1.62 (13)	0.357
Rm, MΩ	178.98 ± 15.54 (8)	219.61 ± 26.31 (13)	0.136
APT, mV	−36.88 ± 1.84 (8)	−39.98 ± 1.32 (13)	0.089
Delay first AP, ms	0.695 ± 0.045 (8)	0.679 ± 0.017 (13)	0.354
APA, mV	42.21 ± 3.91 (8)	44.62 ± 1.89 (13)	0.272
APA peak to peak, mV	124.55 ± 3.74 (8)	133.23 ± 2.97 (13)	*(0.043)
APD, ms	0.346 ± 0.01 (8)	0.343 ± 0.01 (13)	0.397
AHP, mV	−82.33 ± 1.39 (8)	−88.62 ± 2.08 (13)	*(0.022)
MFF, Hz	81.63 ± 9.01 (8)	74.67 ± 9.67 (12)	0.312

AHP, afterhyperpolarization; AP, action potential; APA, action potential amplitude; APD, action potential delay; APT, action potential threshold; MFF, maximum firing frequency; Rm, membrane resistance; RMP, resting membrane potential.
*$P < 0.05$.