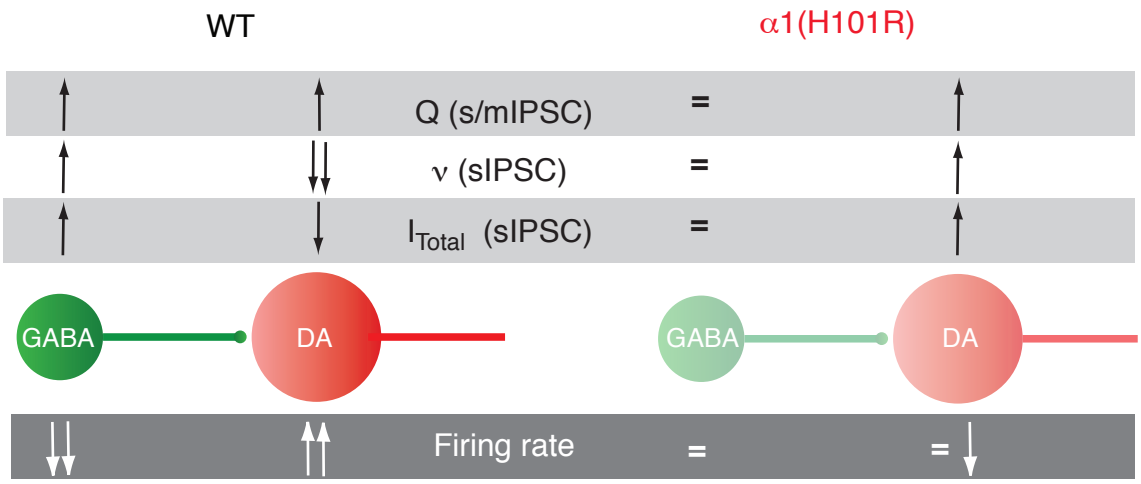
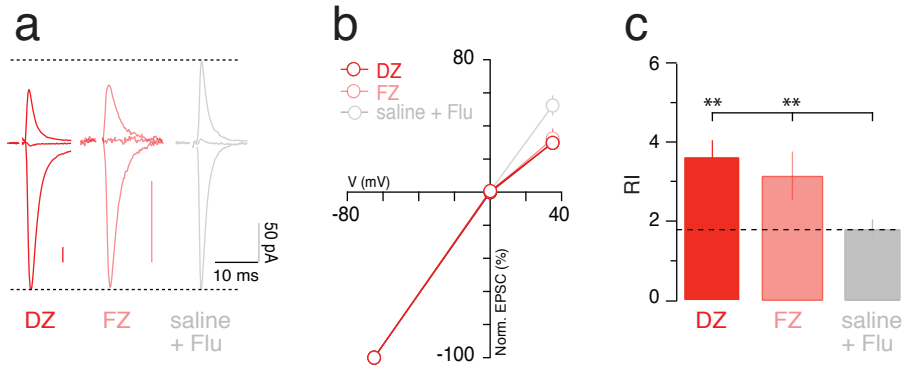
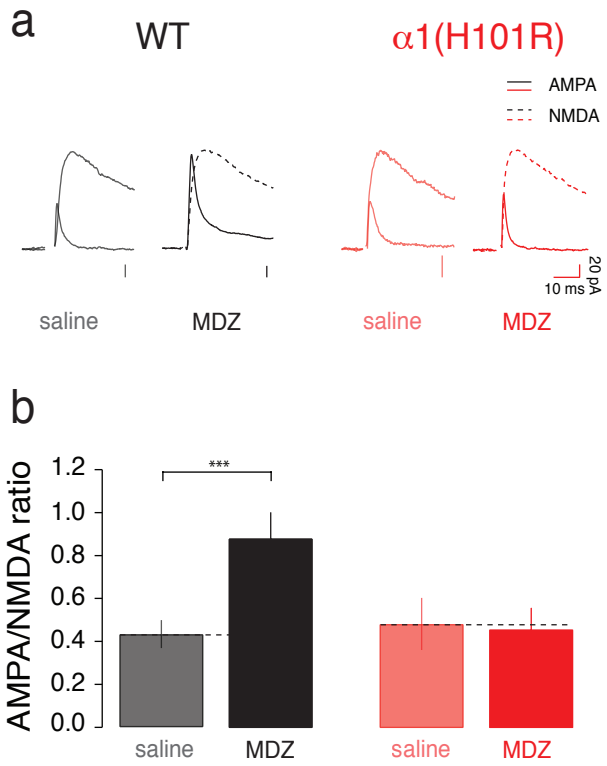
SUPPLEMENTARY INFORMATION



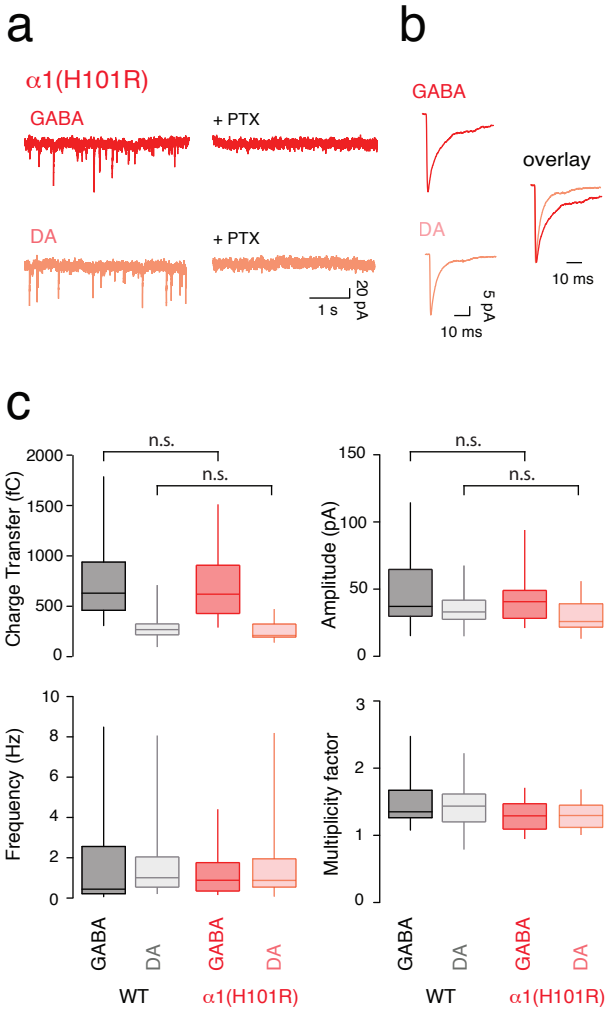
Supplementary Figure 1. Schematic of the proposed cellular mechanism underlying disinhibition of DA neurons by BDZs. Summary of main effects of MDZ in WT and α1(H101R) mice. The parameters measured are charge transfer (Q) of mIPSCs and sIPSCs, frequency (ν) of sIPSCs, the total current generated by sIPSCs and the *in vivo* firing rate. Since DA neurons are much larger than GABA neurons a similar change in the total current leads only to a modest decrease in the firing rate. For discussion see text.



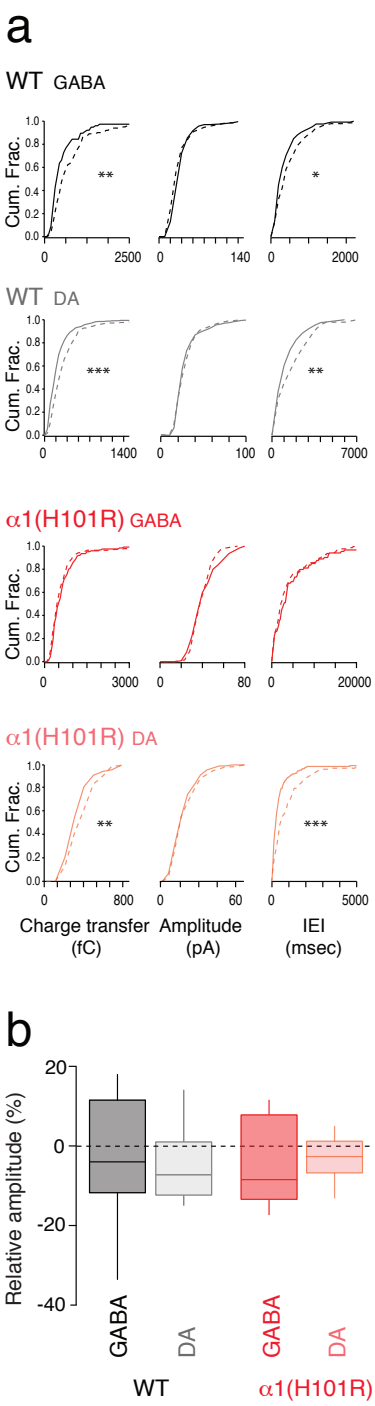
Supplementary Figure 2. DZ- and FZ-evoked synaptic plasticity in DA neurons of the VTA. a, Normalized AMPAR-EPSCs obtained at –65, 0 and +35 mV in slices from WT mice injected i.p. with DZ (5 mg/kg), FZ (5 mg/kg), and saline followed by Flu, 24 h prior to sacrifice. b, Corresponding iv-curves. c, bar graphs representing group data for the RI. $F_{(2,28)} = 8.98$. n = 6-8.



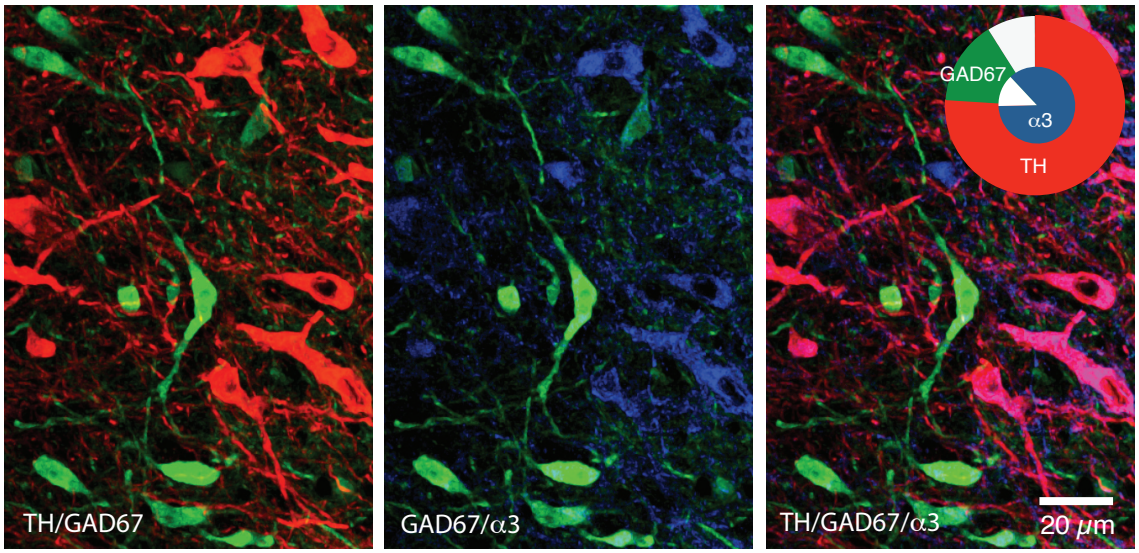
Supplementary Figure 3. MDZ-evoked increase of AMPA/NMDA ratio is abolished in α1(H101R) mutant mice. a, Representative AMPAR-EPSCs (solid trace) and NMDAR-EPSCs (dotted trace), recorded at +35 mV in slices from WT (black) and α1(H101R) (red) mice injected i.p. with saline (or not) or MDZ (0.5 mg/kg), 24 h prior to sacrifice. b, Bar graphs representing group data for the AMPA/NMDA ratio, which was increased in WT mice injected with MDZ. $t_{(14)} = 8.20$. n = 6-8.



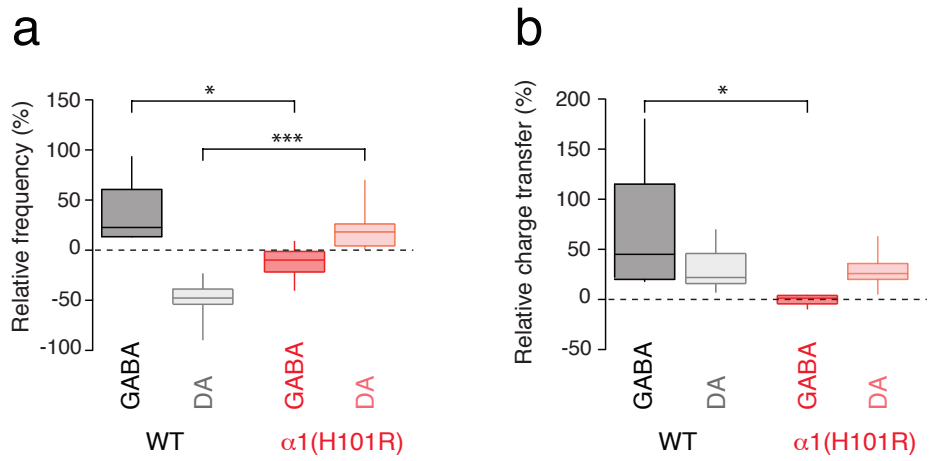
Supplementary Figure 4. Normal $GABA_AR$ mediated inhibitory neurotransmission in α1(H101R) mice. a, Example traces of mIPSCs recorded in GABA and DA neurons in slices obtained from α1(H101R) mice. mIPSCs were abolished with picrotoxin (PTX, 100 μM). b, Representative averaged mIPSCs from a GABA and a DA neuron. The overlay shows the difference in kinetics when the two currents are normalized to the average GABA mIPSC peak amplitude. c, Box plots represent group data for charge transfer, amplitude, frequency of mIPSCs and multiplicity factor in GABA and DA neurons in slices obtained from WT and α1(H101R) mice. None of the comparison between genotypes reached significance. Data from WT mice are the same as in Fig. 3, n = 25-48.



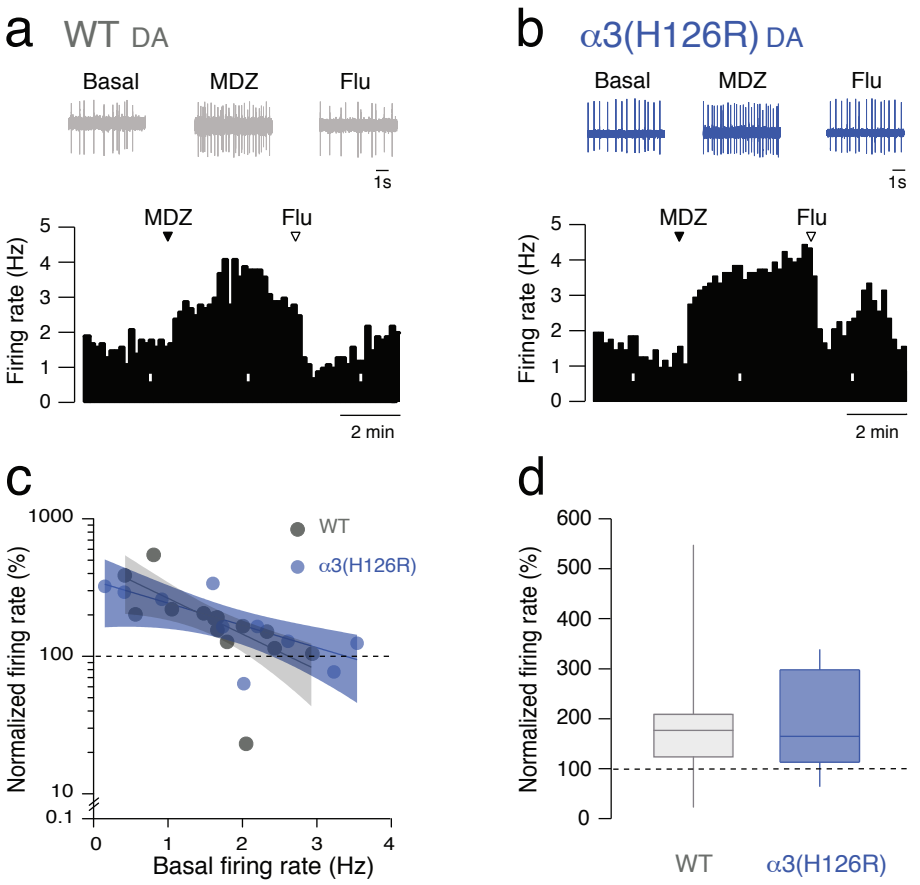
Supplementary Figure 5. Effects of MDZ on charge transfer, amplitude and inter event interval of mIPSCs. a, Cumulative fractions for charge transfer (left panel), amplitude (middle panel), and inter-event-interval (IEI, right panel) before (solid line) and after (dotted line) bath-application of MDZ when mIPSCs are recorded in GABA or DA neurons in slices from WT and α1(H101R) mice. All comparisons are before and after MDZ application. WT/GABA/charge transfer: KS = 1.81; WT/GABA/IEI: KS = 1.08; WT/DA/charge transfer: KS = 2.74; WT/DA/IEI: KS = 1.68; α1(H101R) /DA/charge transfer: KS = 1.80; WT/DA/IEI: KS = 5.09. Note that the cumulative fraction for charge transfer and frequency remained unchanged after MDZ application in GABA neurons in slices from α1(H101R) mice. b, Box plots represent group data for relative amplitude of mIPSCs after MDZ application in slices from WT and α1(H101R) mice. n = 5-10.



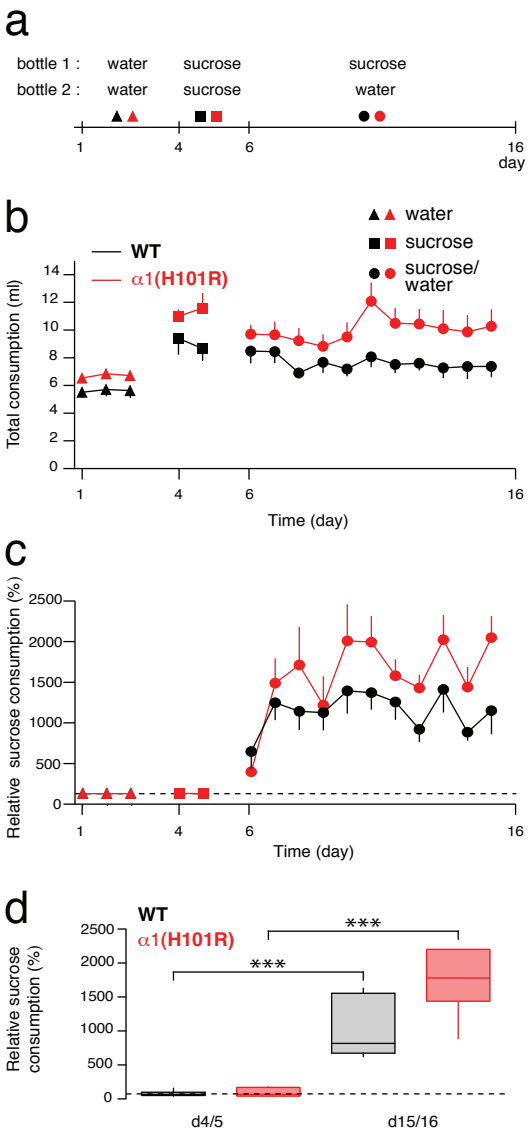
Supplementary Figure 6. Preferential expression of the α3 subunit isoform in DA neurons of the VTA. Immunohistochemical staining for Tyrosine hydroxylase (TH, red) and the α3 subunit isoform of the $GABA_AR$ (blue) in VTA slices of GAD67-GFP (green) knock-in mice. Inset with concentric pie charts representing quantification from 4 mice. The inner segment corresponds to the fraction of α1-positive cells, while the outer reflects the quantification of the two cell types. Overlap between inner and outer segments represents colocalization.



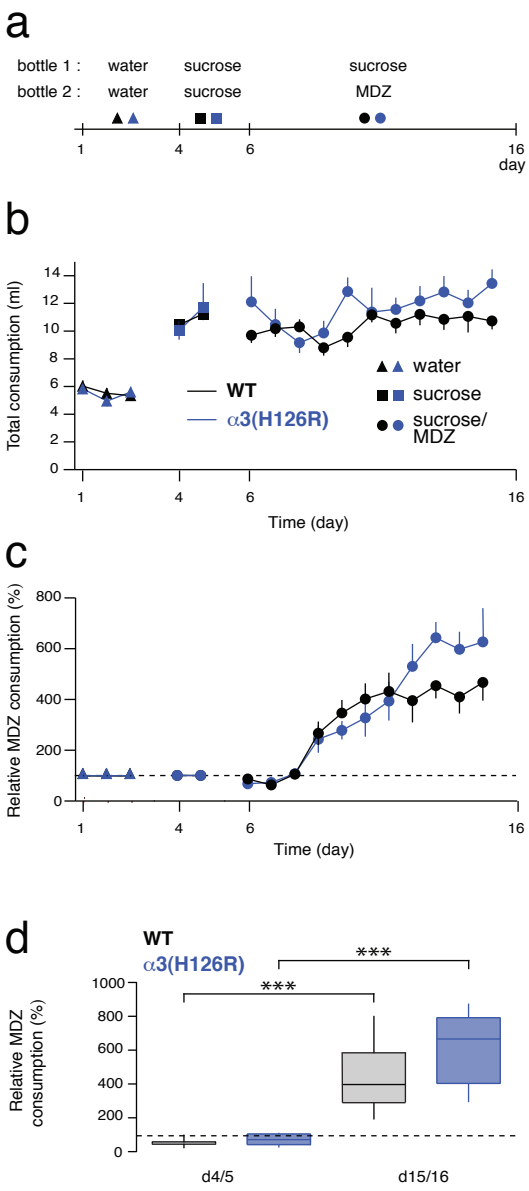
Supplementary Figure 7. Effects of MDZ on frequency and charge transfer of sIPSCs. a, Box-plots representing group data for the relative frequency of sIPSCs in GABA and DA neurons after MDZ bath-application in slices from WT and α1(H101R) mice. GABA/WT vs GABA/α1(H101R) $t_{(9)}$ = 2.98, DA/WT vs DA/α1(H101R) $t_{(15)}$ = 7.35. n = 6-8. b, Box-plots representing group data for the relative charge transfer of sIPSCs after MDZ bath-application in slices from WT and α1(H101R) mice. GABA/WT vs GABA/α1(H101R) $t_{(9)}$ = 2.33



Supplementary Figure 8. MDZ increases firing rate of DA neurons in α3(H126R) mice. a, Representative *in vivo* extracellular single unit recording of a DA neuron during the i.v. (lateral tail vein) injection of MDZ (0.5 mg/kg) in WT mice. Corresponding firing frequency plot (lower panel; Flu 1 mg/kg). b, Same experiment in α3(H126R) mice. White bars indicate time windows of traces shown above. c, Normalized firing rate in response to MDZ as a function of the basal activity in WT and α3(H126R) mice. A linear regression fitting was used to compare the two sets of data, which are superimposable. d, Box-plots representing group data for relative change in firing rate. Solid lines: regression curves; shaded area: 95% confidence intervals. For all experiments n = 10-15. Data from WT mice are the same as in Fig. 5.



Supplementary Figure 9. Oral-self administration of sucrose in α1(H101R) mice. a, Protocol for behavioral experiment. b, Total consumption successively with water, sucrose, and sucrose + water in WT mice (black) and α1(H101R) mice (red). c, Relative sucrose consumption in WT and α1(H101R) mice. d, Corresponding box plots for relative average consumption of sucrose at days indicated. n = 18 mice in 6 cages. $F_{(3;20)}$ = 35.15.



Supplementary Figure 10. Oral-self administration of MDZ in α3(H126R) mice. a, Protocol for behavioral experiment. b, Total consumption successively with water, sucrose, and MDZ (0.005 mg/ml) + sucrose (4 %) in WT mice (black) and α3(H126R) mice (blue). Note that WT and α3(H126R) mice drink similar amounts of liquids. c, Relative MDZ consumption in WT and α3(H126R) mice. d, Corresponding box plots for relative average consumption of MDZ at days indicated. n = 11 α3(H126R) mice in 5 cages and 22 WT mice in 8 cages. $F_{(3;24)} = 22.96$.