Supplementary information

Supplementary methods

Experimental design							
rl/+							
	days	1	8-29				
batch1	rl/+ n=12	OF	CS	saline n=6; cocaine n=6			
	wt n= 12			saline n=6; cocaine n=6			
	days	1					
batch2	rl/+ n=10	NSF					
	wt n=7						
	days	1	7				
batch3	rl/+ n=6	BW	FST				
	wt n=6						
	days	1-21	22				
batch4	rl/+ n=12	cort	FST				
	wt n=8						
	days	1	7	14			
batch5	rl/+ n=9	PPI	PPI (0.15)	PPI (0.3)			
	wt n=9						
Reelin-OE							
	days	1					
batch1	Reelin-OE n=6	activity					
	wt n=6						
	days	1	3	4	8-29		
batch2	Reelin-OE n=13	OF	NSF	FST	CS	saline n=5; cocaine n=8	
	wt n=26					saline n=9; cocaine n=17	
	days	1					
batch3	Reelin-OE n=13	BW					
	wt n=12						
	days	1-13					
batch4	Reelin-OE n=5	SA					
	wt n=5						
	days	1					
batch5	Reelin-OE n=5	rotor-rod					
	wt n=5						
	days	1-21	22				
batch6	Reelin-OE n=10	control / cort	FST	control n=5; cort n=5			
	wt n=21			control n=15; cort n=6			
	days	1	7	14			
batch7	Reelin-OE n=10	PPI	PPI (0.15)	PPI (0.3)			
	wt n=7						
	days	1-21	22				
batch8	Reelin-OE n=6	cort/control	Electro	control n=3; corticosterone n=3			
	wt n=6			control n=3; corticosterone n=3			

Table S1: Experimental design. OF: Open field, BW: black-white box, NSF: Novelty suppressed feeding, FST: Forced-swim-test, CS: Cocaine sensitization, cort: corticosterone treatment, PPI: Pre-pulse inhibition, activity: 24h activity box, SA: cocaine self-administration, Electro: electrophysiology studies.

Supplementary results

Figure S1

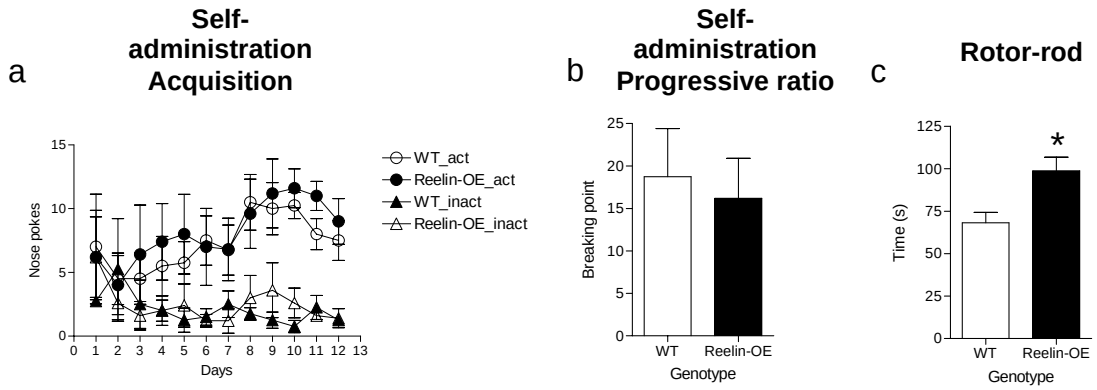

Figure S1: Differences in cocaine sensitization were not due to differences in the rewarding effects of cocaine or to variations in motor performance. a) Reelin-OE and wild-type mice acquired preference for the reinforced hole in the self-administration paradigm. WT/Reelin-OE_act – number of nose pokes in the active hole (reinforced). WT/Reelin-OE_inact – number of nose pokes in the inactive hole (non-reinforced). b) There were no differences in the breaking point between wild-type and Reelin-OE mice in a 3 h progressive ration session. c) Reelin-OE mice spent more time in the rotor-rod (accelerating from 4-40 rpm over 5 min) than wild-type mice ($P<0.05$). Values represent mean ± SEM.

Figure S2

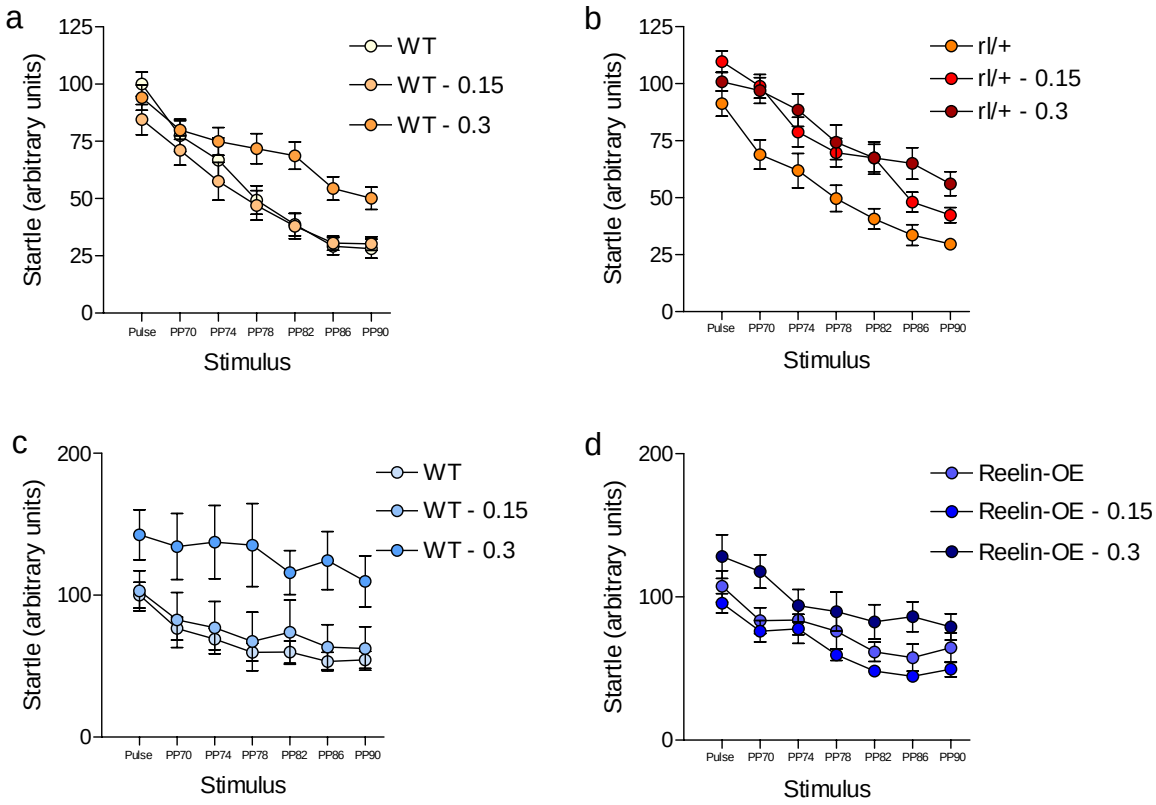

Figure S2: a-d) Startle amplitude in arbitrary units. a-b) Startle amplitudes of WT (a) and rl/+ (b) mice after treatment with Mk-801 (0; 0.15 and 0.3 mg/kg). c-d) Startle amplitudes of WT (a) and Reelin-OE (d) mice after treatment with Mk-801 (0; 0.15 and 0.3 mg/kg).

Figure S3

We have found no significant disruption of PPI in untreated rl/+ when compared with their WT littermate controls without treatment (Figure S3a; genotype x PP: $F_{(5,80)}$=0.48, p=0.79; genotype: $F_{(1,16)}$=0.88, p=0.36; PP: $F_{(5,80)}$=0.48, p<0.001), after treatment with 0.15mg/kg of MK-801 (Figure S3b; genotype x PP: $F_{(5,80)}$=1.58, p=0.18; genotype: $F_{(1,16)}$=1.23, p=0.28; PP: $F_{(5,80)}$=93.94, p<0.001) and after treatment with 0.3 mg/kg of MK-801 (Figure S3c; genotype x PP: $F_{(5,80)}$=2.03, p=0.08; genotype: $F_{(1,16)}$=0.37, p=0.55; PP: $F_{(5,80)}$=33.61, p<0.001).

Also, we found no differences in PPI between untreated WT and Reelin-OE mice (Figure S3d; genotype x PP: $F_{(5,80)}$=0.74, p=0.59; genotype: $F_{(1,16)}$=0.36, p=0.55; PP: $F_{(5,80)}$=11.59, p<0.001) or after treatment with 0.15 mg/kg of MK-801 (Figure S3e; genotype x PP: $F_{(5,50)}$=2.06, p=0.09; genotype: $F_{(1,10)}$=0.13, p=0.73; PP: $F_{(5,50)}$=9.17, p<0.001), except after 0.3mg/kg of MK-801 (Figure S3f; genotype x PP: $F_{(5,75)}$=2.51, p=0.04; LSD test p<0.05).

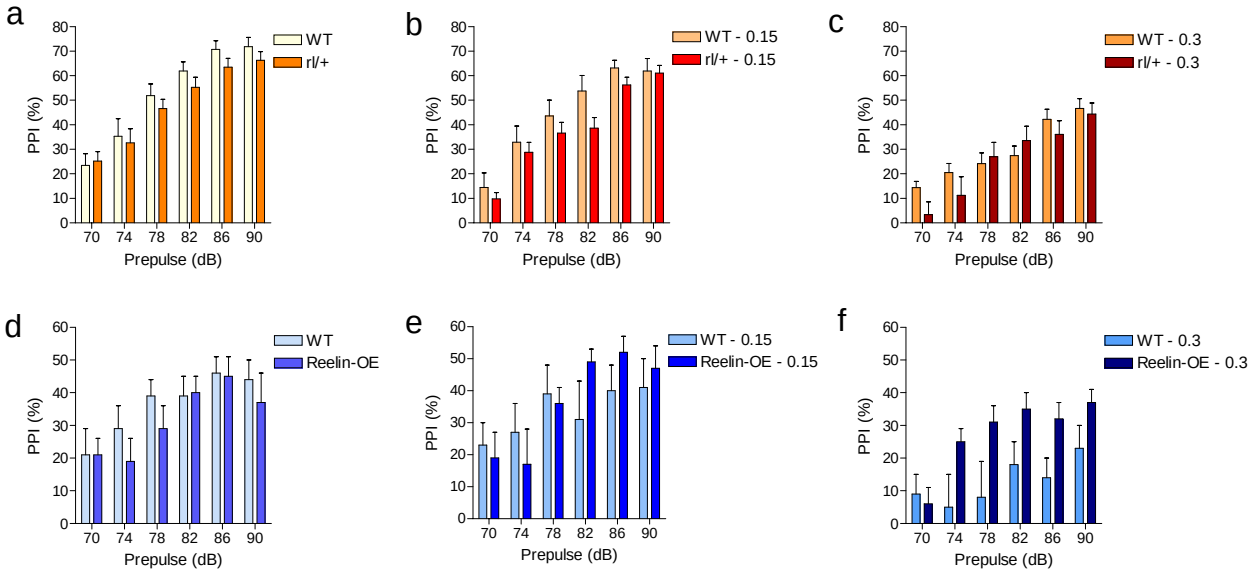

Figure S2: a-c) PPI levels in WT vs rl/+ mice untreated (a), after 0.15 mg/kg of MK-801 (b) and after 0.3 mg/kg of MK-801 (c). d-f) PPI levels in WT vs Reelin-OE mice untreated (d), after 0.15 mg/kg of MK-801 (e) and after 0.3 mg/kg of MK-801 (f).

Figure S4

Measurements of the fiber volleys from Reelin-OE and wild-type (WT) slices were similar (Supplemental Fig 4a) and there was no difference in an input/output curve (Supplemental Fig 2b). We also studied the presynaptic function to exclude the possibility that Reelin over-expression alters the probability of neurotransmitter release. Paired-pulse (PPF) ratios of fEPSP slopes at interstimulus intervals ranging from 25 ms to 400 ms were normal in both genotypes (Supplemental Fig 4c), thereby suggesting that the probability of neurotransmitter release was not modified by Reelin.

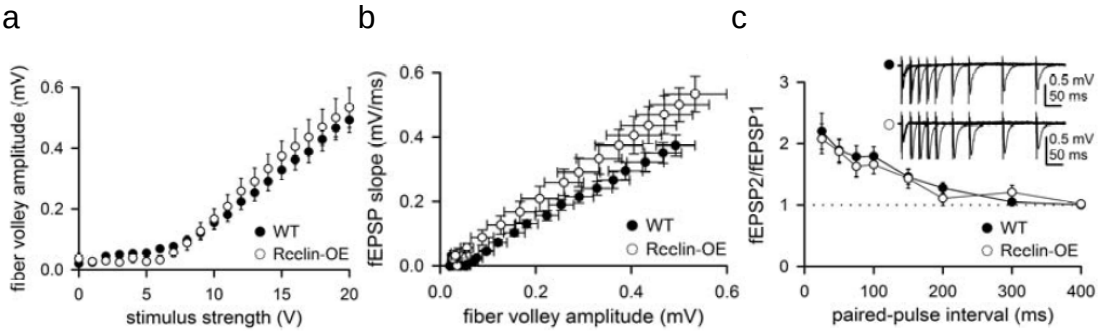

Figure S4: Basal synaptic transmission at CA1 synapses in the Reelin-OE mice. a) Fiber volley amplitudes were similar between WT (filled circle, n = 12 slices from 3 mice) and Reelin-OE (open circle, n = 10 slices from 3 mice) slices for a given range of stimulus intensities. b) Input/output relationships for WT (filled circle, n = 12 slices from 3 mice) and transgenic (open circle, n = 10 slices from 3 mice) mice. c) Paired-pulse facilitation of fEPSPs was similar in WT (n = 12 slices from 3 mice) and Reelin-OE (n = 10 slices from 3 mice) mice. The mean slope of the paired EPSP is plotted against interpulse interval. Inset shows representative fEPSP recorded in the stratum radiatum of slices from WT (top) and Reelin-OE (bottom) mice at a range of inter-stimulus intervals. Data are presented as mean ± SEM.

Figure S5

Measurements of the fiber volleys from Reelin-OE and wild-type (WT) slices treated with corticosterone were similar (Supplemental Fig. 5a) and showed no differences with control animals (compare with Supplemental Fig. 4a). For a range of stimulation intensities, the slopes of Reelin-OE fEPSP responses were not significantly different from the fEPSP responses of WT mice treated with corticosterone (Supplemental Fig. 5a). Interestingly, Reelin-OE mice treated with corticosterone showed a significant reduction of fEPSP response when compared with control conditions (Supplemental Fig. 5c). This observation indicates that corticosterone treatment abolishes the basal glutamatergic neurotransmission potentiation induced by Reelin. In addition, Reelin-OE mice treated with corticosterone showed an inadequate activation of NMDA-dependent glutamatergic neurotransmission evoked by a three-stimuli train (Supplemental Fig. 5d).

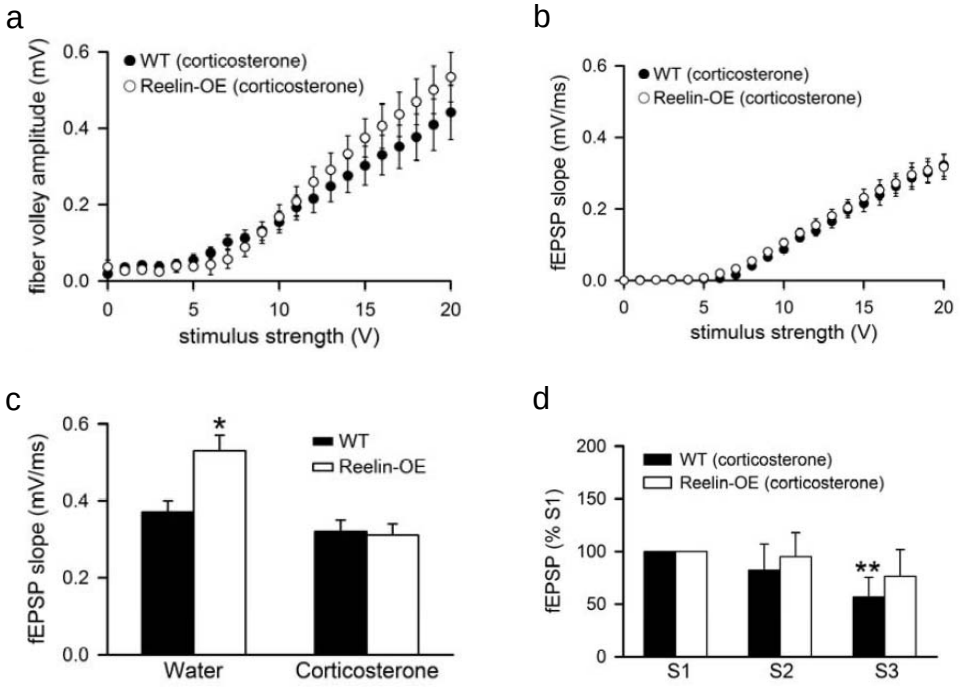

Figure S5: Corticosterone treatment abolished basal fEPSP Reelin-induce potentiation and produces an inadequate synaptic activation of NMDA receptors in Reelin-OE mice. a) fEPSP slopes for wild-type (WT) (filled circle, n = 7 slices from 3 mice) and Reelin-OE (open circle, n = 8 slices from 3 mice) mice treated with corticosterone for a given range of stimulus intensities. b) Fiber volley amplitudes were similar between WT (filled circle, n = 7 slices from 3 mice) and Reelin-OE (open circle, n = 8 slices from 3 mice) in the same animals. c) Summary of mean fEPSP slope in WT (filled bar) and Reelin-OE (open bar) slices in control conditions (data taken

from Figure 5, panel a) and after treatment with corticosterone (data taken from present figure, panel b). While fEPSPs in Reelin-OE control were significantly potentiated at high stimulus strengths (when compared with that in WT slices), they were reduced to basal values after treatment with corticosterone. Significant differences were established at *$p < 0.05$. d) Summary data showing mean NMDA component evoked by a three-stimuli train (given at 100 Hz) in WT (filled bar, n = 6 slices from 3 mice) and Reelin-OE (open bar, n = 6 slices from 3 mice) mice, recorded in the presence of 20 µM CNQX to block AMPA component. The fEPSP slope was significantly smaller in the WT for the 3rd stimulus when compared with 1st. Significant differences were established at **$p < 0.01$. Data are presented as mean ± SEM.