Supporting Information

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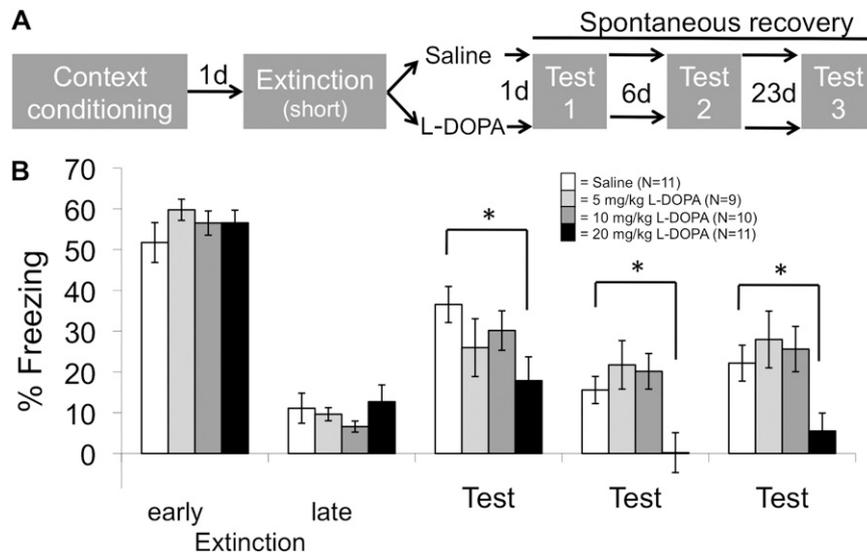
Fig. S1. Mouse study 1: Attenuation of spontaneous recovery of contextual fear by L-dopa (normalized data). Unlike Fig. 1, the figure shows the normalized data that were also used for statistics. Further, doses of 5 and 10 mg/kg are included. Administration of 20 mg/kg L-dopa directly after extinction learning (*A*) results in a long-term reduction of spontaneous recovery (*B*), as indexed by the percentage of time spent freezing. Gray fields in *A* indicate the context (identical on all days). Early extinction, first 4 min; late extinction, last 4 min. Data from tests 1–3 are normalized by subtraction to late extinction to appropriately quantify return of fear. *$P < 0.05$ (two-tailed planned post hoc *t* tests on normalized data).
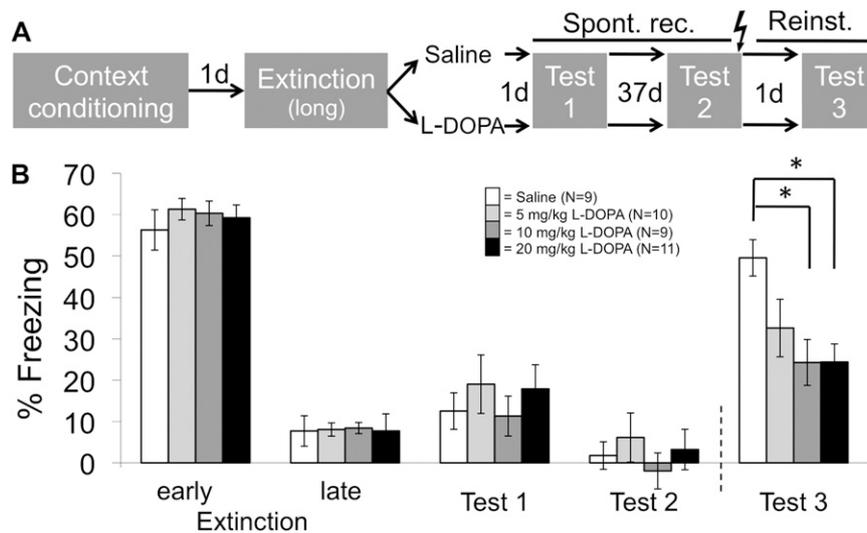
Fig. S2. Mouse study 2: Attenuation of reinstatement of contextual fear by L-dopa (normalized data). Unlike Fig. 2, this figure shows the normalized data that were also used for statistics. Further, doses 5 and 10 mg/kg are included. Administration of 10 and 20 mg/kg L-dopa directly after extinction learning (*A*) results in a reduction of reinstatement 40 d later (Reinst., Test 3) (*B*). Gray fields in *A* indicate the context (identical on all days). Lightning bolt denotes UCS. Data from tests 1 and 2 are normalized by subtraction to late extinction (to quantify spontaneous recovery); data from test 3 are normalized to data from test 2 (to quantify reinstatement). *$P < 0.05$ (two-tailed planned post hoc *t* tests on normalized data).
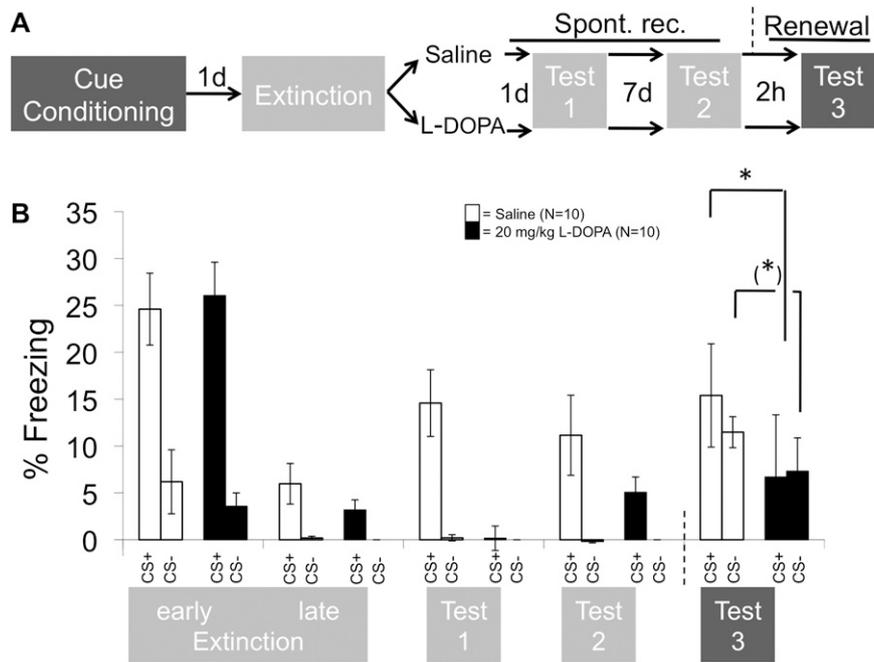
Fig. S3. Mouse study 3: Attenuation of spontaneous recovery and renewal of cued fear by L-dopa (normalized data). The figure is identical to Fig. 3 *A* and *B*, except showing that the normalized data that were also used for statistics. Administration of 20 mg/kg L-dopa directly after extinction learning (*A*) results in a reduction of spontaneous recovery (Spont. rec., tests 1 and 2, in the extinction context B; light gray shading) and ABA renewal (test 3, in the conditioning context A; dark gray shading) (*B*). Data from tests 1 and 2 are normalized by subtraction to late extinction (to quantify spontaneous recovery); data from test 3 are normalized to data from test 2 (to quantify renewal). $^{(*)}P < 0.1$; $*P < 0.05$ (two-tailed planned post hoc *t* tests on normalized data).

Fig. S4. Human study (renewal of cued fear): Fear and UCS expectancy ratings. (*A* and *B*) Fear (*A*) and UCS expectancy (*B*) rating data showed successful conditioning and extinction learning on day 1 as well as successful renewal in the original conditioning context A (dark gray shading; test 2) compared with the extinction context B (light gray shading; test 1) on day 2 [(CS+ > CS−)A > (CS+ > CS−)B; $P < 0.001$ on both days]. The predicted cue by context by group interaction, indicating attenuated renewal by L-dopa, failed to reach significance (fear: $P = 0.16$; expectancy: $P = 0.22$). (*C*) When restricting the analysis to the first rating provided for each cue and context combination on day 2, thus taking into account online extinction, differential fear ratings in context A [(CS+ > CS−)A] were larger in the L-dopa group than in the placebo group ($T_{1,36} = 2.15$; $P = 0.039$). We report this result descriptively only.

Table S1. Statistics mouse study 1 (spontaneous recovery of contextual fear): Percent time spent freezing

Effect	df, df error	F	P	Eta^2
Extinction				
Time (early, late)	1,37	581.64	<0.001*	0.94
Group (0, 5, 10, 20 mg/kg)	3,37	0.33	0.80	0.03
Time × group	3,37	1.5	0.23	0.11
Spontaneous recovery (tests 1–3)				
Time (tests 1, 2, 3)	2,74	16.2	<0.001[†]	0.30
Group (0, 5, 10, 20 mg/kg)	3,37	3.07	0.04[‡]	0.20
Time × group	6,74	1.71	0.13	0.12

*Early > late (indicating successful conditioning and extinction).
[†]Post hoc: Test 1 > test 2, $P < 0.001$; test 1 > test 3, $P < 0.004$; test 3 > test 2, $P = 0.01$.
[‡]Post hoc: 20 < 0, $P = 0.019$; 20 < 5, $P = 0.022$; 20 < 10, $P = 0.018$; all others $P > 0.94$ (indicating attenuated spontaneous recovery by L-dopa).

Table S2. Statistics mouse study 2 (reinstatement of contextual fear): Percent time spent freezing

Effect	df, df error	F	P	Eta^2
Extinction				
Time (early, late)	1,35	578.1	<0.001*	0.94
Group (0, 5, 10, 20 mg/kg)	3,35	0.2	0.9	0.02
Time × group	3,35	0.21	0.89	0.02
Spontaneous recovery (tests 1 and 2)				
Time (test 1, test 2)	1,35	39.6	<0.001†	0.53
Group (0, 5, 10, 20 mg/kg)	3,35	0.25	0.86	0.21
Time × group	3,35	0.63	0.6	0.05
Reinstatement (test 3)				
Group (0, 5, 10, 20 mg/kg)	3,35	3.13	0.038‡	0.21

*Early > late (indicating successful conditioning and extinction).
†Test 1 > test 2.
‡Post hoc: 20 < 0, P = 0.01; 10 < 0, P = 0.013; 5 < 0, P = 0.081; all others P > 0.36.

Table S3. Statistics mouse study 3 (renewal of cued fear): Percent time spent freezing

Effect	df, df error	F	P	Eta^2
Extinction				
Time (early, late)	1,18	56.65	<0.001*	0.76
Cue (CS+, CS−)	1,18	69.54	<0.001†	0.79
Group (0, 20 mg/kg)	1,18	0.31	0.58	0.02
Time × cue	1,18	19.80	<0.001‡	0.52
Time × group	1,18	0.07	0.80	0.00
Cue × group	1,18	0.06	0.81	0.00
Time × cue × group	1,18	0.87	0.36	0.05
Spontaneous recovery (tests 1 and 2)				
Time (tests 1 and 2)	1,18	0.3	0.59	0.02
Cue (CS+, CS−)	1,18	17.91	0.001†	0.5
Group (0, 20 mg/kg)	1,18	7.62	0.012§	0.3
Time × cue	1,18	0.3	0.59	0.02
Time × group	1,18	0.3	0.59	0.02
Cue × group	1,18	7.73	0.013¶	0.3
Time × cue × group	1,18	0.3	0.59	0.02
Renewal (test 3)				
Cue (CS+, CS−)	1,18	0.89	0.36	0.05
Group (0, 20 mg/kg)	1,18	6.25	0.022‖	0.26
Cue × group	1,18	2	0.18	0.1

As in earlier work, only the first two CS+ and CS− presentations each were counted based on repeated prior observations that CRs to CS+ strongly decrease after the first two presentations (online extinction).
*Early > late.
†CS+ > CS−.
‡(CS+ > CS−)early > (CS+ > CS−)late (indicating successful conditioning and extinction).
§0 > 20.
¶CS+ in 0 > CS+ in 20 (indicating attenuated spontaneous recovery by L-dopa).
‖0 > 20 (indicating attenuated general renewal by L-dopa).

Table S4. Statistics human study (renewal of cued fear): SCR

Effect	df, df error	F	P	Eta^2
Learning (day 1)				
Cue (CS+, CS−)	1,27	25.68	<0.001*	0.488
Context (A, B)	1,27	27.27	<0.001†	0.502
Cue × context	1,27	10.59	0.003‡	0.282
Group (0, 150 mg/kg)	1,27	0.045	0.83	0.002
Cue × group	1,27	0.75	0.4	0.027
Context x group	1,27	0.7	0.41	0.025
Cue × context × group	1,27	0.04	0.84	0.002
Expression test (day 2)				
Cue (CS+, CS−)	1,31	9.87	0.004*	0.242
Context (A, B)	1,31	10.01	0.003†	0.244
Cue × context	1,31	3.11	0.088§	0.091
Group (0, 150 mg/kg)	1,31	1.45	0.24	0.045
Cue × group	1,31	0.28	0.60	0.009
Context × group	1,31	0.64	0.43	0.020
Cue × context × group	1,31	5.23	0.029¶	0.144

*CS+ > CS−.
†A > B.
‡(CS+ > CS−)A > (CS+ > CS−)B (indicating successful conditioning and extinction).
§Testing in B corresponds to test 1 in Fig. 4 (spontaneous recovery), and testing in A corresponds to test 2 in Fig. 4 (renewal). Planned post hoc test (one-sided, based on directed a priori hypothesis): (CS+ > CS−)A > (CS+ > CS−)B, $P = 0.047$ (indicating successful context-specific renewal on day 2).
¶(CS+ > CS−)A > (CS+ > CS−)B in placebo > L-dopa (indicating attenuated renewal by L-dopa).

Table S5. Human study (renewal of cued fear): fMRI CS+ and CS− estimates

Cue	Placebo		L-dopa	
	Mean	SEM	Mean	SEM
CS+, context A	−3.96	2.38	−1.35	0.9
CS−, context A	−2.98	1.97	−2.56	1.01
CS+, context B	−2.68	1.69	−3.47	1.01
CS−, context B	−4.03	2.32	−2.6	0.85

Shown are estimates for the categorical regressors from the first half of the experiment on day 2 (early); see *Imaging data analysis* for details.