SUPPLEMENTAL MATERIAL

MATERIALS AND METHODS

Food Training

To facilitate the acquisition of lever pressing for cocaine infusions in the absence of explicit conditioned stimuli that signaled drug delivery, rats were first trained to lever press for food reinforcement (45 mg pellets, Bio-Serv, Flemington, NJ) in standard operant-conditioning chambers (Coulbourn Instruments, Holliston, MA) during a 16-h overnight session as described previously [19]. Food training was conducted in a dedicated chamber without exposure to contextual stimuli used for subsequent cocaine conditioning.

Surgery

Twenty-four h after food training, rats were fully anesthetized using ketamine hydrochloride and xylazine (100 and 5 mg/kg, i.p., respectively; Dechara Veterinary Products, Overland Park, KS and Akorn, Lake Forest, IL). Jugular catheters were implanted into the right jugular vein. Stainless-steel guide cannulae (26-Ga, P1 Technologies, Roanoke, VA) were aimed at the BLA (-2.7 mm AP, ±5.0 mm ML, -6.6 mm DV relative to bregma) or pCPu (-2.7 mm AP, ±5.0 mm ML, -4.5 mm DV relative to bregma). Stainless-steel screws and dental acrylic anchored the cannulae to the skull. Rats received the analgesic, carprofen (5 mg/kg per day, p.o.; ClearH2O, Westbrook, ME) for 24 h before and 48 h after surgery. The catheters were maintained and periodically tested for patency, as previously described [19]. Rats received five days for post-surgical recovery.

Cocaine Self-administration and Extinction Training

Rats were randomly assigned to self-administer cocaine in one of two distinctly different environmental contexts (see **Table S1**). These contexts contained multimodal sensory (visual,

olfactory, tactile, and auditory) stimuli that were presented throughout each session independent of responding.

Table S1 | Context configurations in Experiment 1-6

Context	Visual	Auditory	Olfactory	Tactile
1	Continuous red house light	Intermittent tone (78 dB, 10 Hz)	Vanilla-scented air freshener	Wire mesh flooring
2	Flashing white light above inactive lever	Continuous tone (78 dB, 2kHz)	Pine-scented air freshener	Slanted tile bisecting a steel grid flooring

Habituation to the Intracranial Infusion Procedure

After extinction session 4, rats were removed from the operant-conditioning chamber and transported into a different room. The stylets protecting the indwelling guide cannulae were removed, and injection cannulae (33-Ga, P1 Technologies) were inserted 2 mm past the guide cannula tips. The injection cannulae remained in place for 4 min, while the rats were held gently by the experimenter. Fluid was not infused through the injection cannulae.

RESULTS

Behavioral History

There were no pre-existing differences between the subsequent treatment groups in drug intake or lever responding during the last 10 days of cocaine self-administration training, during the seven days of extinction training in Experiments 2, 3, 5, and 6. However, minor pre-existing group differences that could not account for the effects of the manipulations were observed in Experiments 1 and 4 (see results of ANOVAs and *post-hoc* pairwise comparisons in **Table S2**). Importantly, there were no differences between the treatment groups in lever responding during the memory retrieval session. Note: Behavioral testing concluded with the memory reactivation session in Experiment 5; therefore, data are not shown for post-treatment extinction responding for this experiment in **Table S2**.

Table S2 | Behavior History of Experimental Groups in Experiments 1-6

Experiment 1 - BLA AM251

		Treatment Main Effects				Time Main Effects				Treatment x Time				*Post-hoc* tests
Phase	**Measure**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	
Self-Administration	Active Lever	F	1,18	0.47	0.50	F	9,162	0.50	0.88	F	9,162	1.30	0.24	
	Inactive Lever	F	1,18	1.29	0.27	F	9,162	1.93	0.05	F	9,162	0.33	0.96	
	Cocaine Infusions	F	1,18	0.87	0.36	F	9,162	1.95	0.05	F	9,162	2.20	0.02	Day 1: AM251 > Vehicle
Extinction	Active Lever	F	1,18	0.02	0.89	F	6,108	26.27	<0.0001	F	6,108	0.77	0.60	
	Inactive Lever	F	1,18	1.33	0.26	F	6,108	6.32	<0.0001	F	6,108	2.36	0.03	Day 1: AM251 > Vehicle
Memory Retrieval	Active Lever	t	18	1.11	0.28									
	Inactive Lever	t	18	0.22	0.83									
Post-treatment Extinction (1st/last)	Active Lever	F	1,18	0.74	0.40	F	1,18	0.04	0.85	F	1,18	0.13	0.72	
	Inactive Lever	F	1,18	1.22	0.28	F	1,18	2.97	0.10	F	1,18	0.69	0.42	

Experiment 2 - *Delayed* BLA AM251

		Treatment Main Effects				Time Main Effects				Treatment x Time				*Post-hoc* tests
Phase	**Measure**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	
Self-Administration	Active Lever	F	1,12	1.33	0.27	F	9,108	1.02	0.43	F	9,108	0.82	0.60	
	Inactive Lever	F	1,12	0.87	0.37	F	9,108	2.65	0.01	F	9,108	0.59	0.80	
	Cocaine Infusions	F	1,12	0.24	0.63	F	9,108	5.00	<0.0001	F	9,108	1.19	0.31	
Extinction	Active Lever	F	1,12	0.00	0.95	F	6,72	13.69	<0.0001	F	6,72	0.38	0.89	
	Inactive Lever	F	1,12	0.57	0.46	F	6,72	0.89	0.50	F	6,72	0.56	0.76	
Memory Retrieval	Active Lever	t	12	0.25	0.81									
	Inactive Lever	t	12	1.38	0.19									
Post-treatment Extinction (1st/last)	Active Lever	F	1,12	0.07	0.80	F	1,12	0.08	0.78	F	1,12	0.90	0.36	
	Inactive Lever	F	1,12	0.24	0.63	F	1,12	3.41	0.09	F	1,12	0.65	0.44	

Experiment 3 - pCPu AM251

		Treatment Main Effects				Time Main Effects				Treatment x Time				*Post-hoc* tests
Phase	**Measure**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	
Self-Administration	Active Lever	F	1,14	2.52	0.14	F	9,126	0.72	0.69	F	9,126	1.14	0.34	
	Inactive Lever	F	1,14	1.19	0.29	F	9,126	2.10	0.03	F	9,126	1.87	0.06	
	Cocaine Infusions	F	1,14	0.07	0.79	F	9,126	2.69	0.01	F	9,126	1.47	0.17	
Extinction	Active Lever	F	1,14	1.07	0.32	F	6,84	3.44	0.00	F	6,84	0.94	0.47	
	Inactive Lever	F	1,14	0.94	0.35	F	6,84	5.26	<0.0001	F	6,84	0.42	0.86	
Memory Retrieval	Active Lever	t	14	0.08	0.94									
	Inactive Lever	t	14	0.09	0.93									
Post-treatment Extinction (1st/last)	Active Lever	F	1,14	1.18	0.30	F	1,14	0.10	0.76	F	1,14	0.22	0.65	
	Inactive Lever	F	1,14	0.43	0.52	F	1,14	1.62	0.22	F	1,14	0.08	0.79	

Experiment 4 - BLA WIN55212-2

		Treatment Main Effects				Time Main Effects				Treatment x Time				*Post-hoc* tests
Phase	**Measure**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	
Self-Administration	Active Lever	F	2,33	0.27	0.77	F	9,297	5.25	<0.0001	F	18,297	1.11	0.34	
	Inactive Lever	F	2,33	3.12	0.06	F	9,297	11.71	<0.0001	F	18,297	2.36	0.00	Day 1: WIN (0.5 µg) > WIN (5 µg),Vehicle
	Cocaine Infusions	F	2,33	0.22	0.80	F	9,297	3.83	0.00	F	18,297	0.88	0.60	
Extinction	Active Lever	F	2,33	6.10	0.01	F	6,198	39.25	<0.0001	F	12,198	1.59	0.10	Vehicle > WIN (5 µg)
	Inactive Lever	F	2,33	3.82	0.03	F	6,198	6.35	<0.0001	F	12,198	1.26	0.24	WIN (0.5 µg) > WIN (5 µg)
Memory Retrieval	Active Lever	F	2,33	0.44	0.65									
	Inactive Lever	F	2,33	0.24	0.79									
Post-treatment Extinction (1st/last)	Active Lever	F	2,33	5.50	0.01	F	1,33	0.01	0.93	F	2,33	0.03	0.98	Vehicle > WIN (5 µg)
	Inactive Lever	F	2,33	3.82	0.03	F	1,33	0.59	0.45	F	2,33	1.97	0.16	WIN (0.5 µg) > WIN (5 µg)

Experiment 5 - BLA AM251 Corticosterone

		Treatment Main Effects				Time Main Effects				Treatment x Time				*Post-hoc* tests
Phase	**Measure**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	
Self-Administration	Active Lever	F	3,18	0.79	0.51	F	9,162	0.36	0.95	F	27,162	1.01	0.46	
	Inactive Lever	F	3,18	0.73	0.55	F	9,162	2.51	0.01	F	27,162	1.18	0.27	
	Cocaine Infusions	F	3,18	0.98	0.43	F	9,162	16.45	<0.0001	F	27,162	1.07	0.38	
Extinction	Active Lever	F	3,18	2.49	0.09	F	6,108	13.19	<0.0001	F	18,108	0.80	0.69	
	Inactive Lever	F	3,18	0.54	0.67	F	6,108	3.39	0.00	F	18,108	1.27	0.22	
Memory Retrieval	Active Lever	t	9	1.42	0.19									
	Inactive Lever	t	9	0.01	0.99									

Experiment 6 - BLA Corticosterone

		Treatment Main Effects				Time Main Effects				Treatment x Time				*Post-hoc* tests
Phase	**Measure**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	**Test**	**df**	**Statistic**	**p**	
Self-Administration	Active Lever	F	2,17	0.35	0.71	F	9,153	0.54	0.84	F	18,153	1.03	0.43	
	Inactive Lever	F	2,17	0.48	0.63	F	9,153	1.42	0.18	F	18,153	1.32	0.18	
	Cocaine Infusions	F	2,17	0.10	0.91	F	9,153	1.90	0.06	F	18,153	1.05	0.40	
Extinction	Active Lever	F	2,17	0.80	0.47	F	6,102	38.69	<0.0001	F	12,102	1.51	0.13	
	Inactive Lever	F	2,17	0.53	0.60	F	6,102	5.02	0.00	F	12,102	1.20	0.29	
Memory Retrieval	Active Lever	F	2,17	0.31	0.74									
	Inactive Lever	F	2,17	0.49	0.74									
Post-treatment Extinction (1st/last)	Active Lever	F	2,17	0.09	0.92	F	1,17	4.65	0.05	F	2,17	0.96	0.40	
	Inactive Lever	F	2,17	0.04	0.96	F	1,17	0.40	0.53	F	2,17	0.89	0.43	

Experiment 1: Post-retrieval AM251 administration into the BLA does not alter inactive-lever responding at test

Inactive-lever responding remained low in both contexts (**Fig. S1A**; 2x2 ANOVA, treatment x context, $F_{(1,18)} = 0.25$, $p = 0.63$; treatment, $F_{(1,18)} = 0.78$, $p = 0.39$; context, $F_{(1,18)} = 3.96$, $p = 0.06$), and it declined during the test session (**Fig. S1B**; 2x6 ANOVA, time, $F_{(5,90)} = 10.45$, $p < 0.0001$, Tukey tests, interval 1 > 2-6, ps < 0.05; treatment x time, $F_{(5,90)} = 0.23$, $p = 0.95$; treatment, $F_{(1,18)} = 0.03$), independent of treatment.

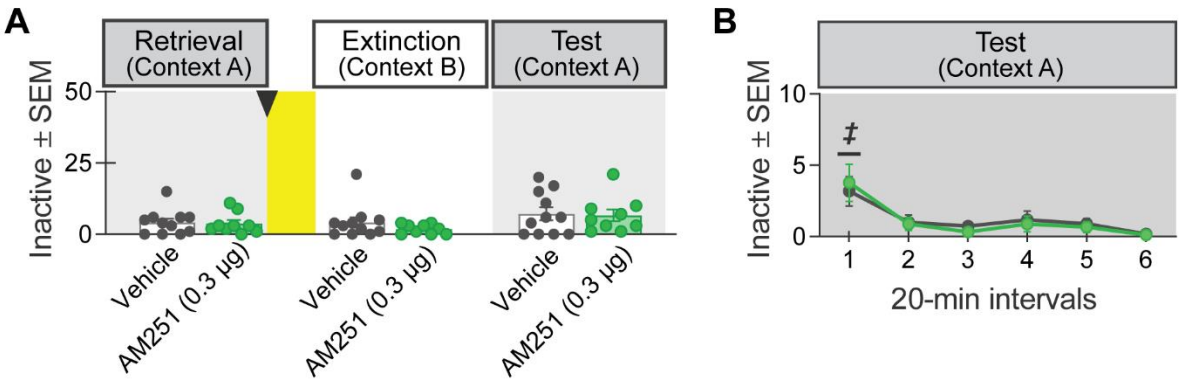

FIGURE S1. Intra-BLA AM251 administration *during* cocaine-memory reconsolidation does not alter inactive-lever responding at test. (A) Inactive-lever responses (mean ± SEM) during the 15-min memory-retrieval session (before treatment; see statistics in Table S2) and upon first re-exposure to the extinction context and the cocaine-paired context (after treatment) at test. Treatment involved bilateral intra-BLA administration of the CB1R antagonist, AM251 (0.3 µg/0.5 µL per hemisphere; *n* = 9) or vehicle (*n* = 11) immediately after the 15-min cocaine-memory retrieval session. **(B)** Time course of inactive-lever responding in the cocaine-paired context at test. ***Symbols***: ANOVA #context main effect; ‡time simple-main effect, Tukey's tests, intervals 1 > 2-6, ps < 0.05.

Experiment 2: Intra-BLA AM251 administration after memory reconsolidation does not alter inactive-lever responding at test

Inactive-lever responding remained low in both contexts (**Fig. S2A**; 2x2 ANOVA, treatment x context, $F_{(1,12)} = 0.0001$, $p = 0.99$; treatment, $F_{(1,12)} = 0.40$, $p = 0.54$; context, $F_{(1,12)} = 0.84$, $p = 0.38$), and it declined during the test session, but AM251 increased responding at the first interval relative to vehicle (**Fig. S2B**; 2x6 ANOVA, time x treatment, $F_{(5,60)} = 3.080$, $p = 0.02$, Tukey tests,

AM251 > vehicle at interval 1, AM251 interval 1 > 2-6, ps < 0.05; time, $F_{(5,60)} = 8.85$, $p < 0.0001$; treatment, $F_{(5,60)} = 4.05$, $p = 0.07$;).

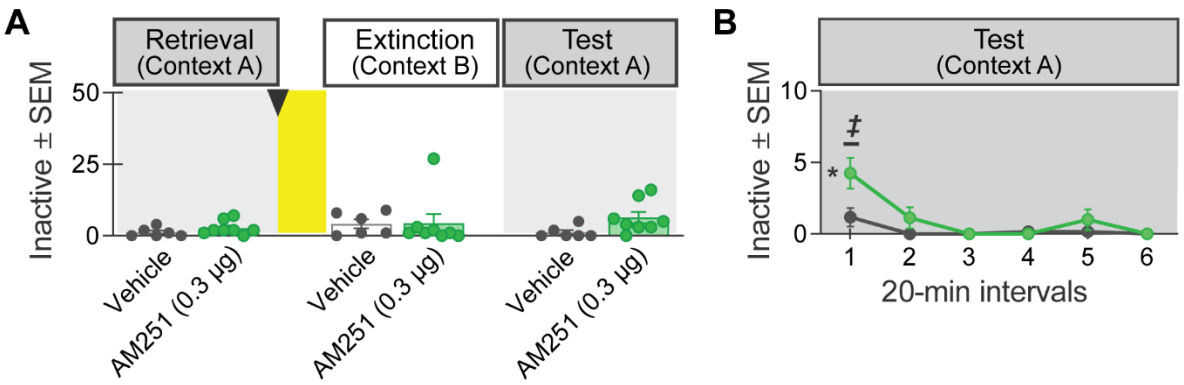

FIGURE S2. Intra-BLA AM251 administration *after* memory reconsolidation does not alter inactive-lever responding at test. (A) Inactive-lever responses (mean ± SEM) during the 15-min memory-retrieval session (before treatment; see statistics in Table S2) and upon first re-exposure to the extinction context and the cocaine-paired context (after treatment) at test. Treatment involved bilateral intra-BLA administration of the CB1R antagonist, AM251 (0.3 µg/0.5 µL per hemisphere; *n* = 8) or vehicle (*n* = 6) six hours after the 15-min cocaine-memory retrieval session. **(B)** Time course of inactive-lever responding in the cocaine-paired context at test. ***Symbol***: ANOVA *treatment simple-main effect, Tukey's test, $p < 0.05$.‡time simple-main effect, Tukey's tests, intervals 1 > 2-6, ps < 0.05,

Experiment 3: Post-retrieval AM251 administration into the pCPu anatomical-control region does not alter inactive-lever responding at test

Inactive-lever responding remained low in both contexts (**Fig. S3A**; 2x2 ANOVA, treatment x context, $F_{(1,14)} = 0.31$, $p = 0.58$; treatment, $F_{(1,14)} = 0.40$, $p = 0.54$; context, $F_{(1,14)} = 0.66$, $p = 0.43$), and it declined during the test session, (**Fig. S3B**; 2x6 ANOVA, time main effect $F_{(5,70)} = 10.35$, $p < 0.0001$, Tukey tests, interval 1 > 2-6, ps < 0.05; treatment x time, $F_{(5,70)} = 0.75$, $p = 0.59$; treatment, $F_{(1,14)} = 0.006$, $p = 0.94$), independent of treatment.

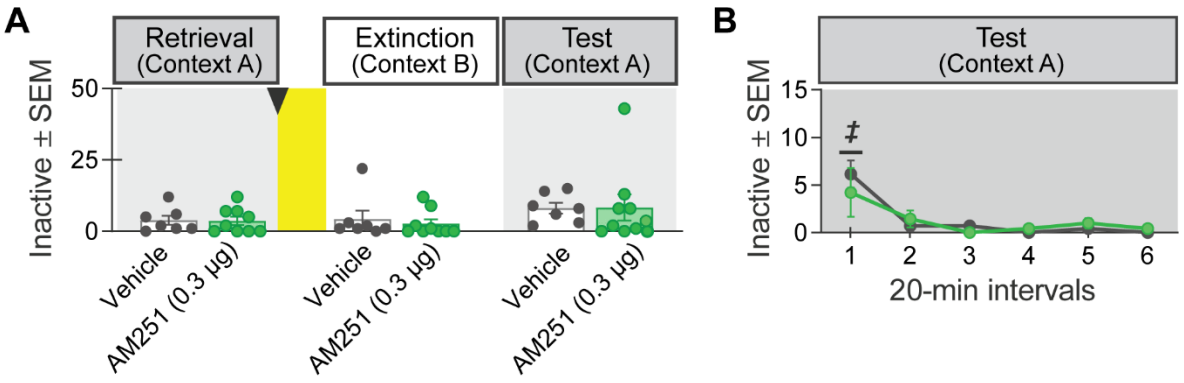

FIGURE S3. Intra-pCPu AM251 administration *during* cocaine-memory reconsolidation does not alter inactive-lever responding at test. (A) Inactive-lever responses (mean ± SEM) during the 15-min memory-retrieval session (before treatment; see statistics in Table S2) and upon first re-exposure to the extinction context and the cocaine-paired context (after treatment) at test. Treatment involved bilateral intra-pCPu administration of the CB1R antagonist, AM251 (0.3 µg/0.5 µL per hemisphere; *n* = 9) or vehicle (*n* = 7) immediately after the 15-min cocaine-memory retrieval session. **(B)** Time course of inactive-lever responding in the cocaine-paired context at test. ***Symbol***: ANOVA ‡time simple-main effect, Tukey's tests, intervals 1 > 2-6, ps < 0.05.

Experiment 4: Intra-BLA WIN55,212-2 administration during memory reconsolidation dose-dependently alters inactive-lever responding

Inactive-lever responding remained low in both contexts. Neither WIN55,212-2 dose (0.5 or 5 µg/hemisphere) altered inactive-lever responding relative to vehicle in either context, but the 0.5 µg/hemisphere dose of WIN55,212-2 administered after memory retrieval increased inactive-lever responding compared to the 5 µg/hemisphere dose independent of context (**Fig. S4A**; 3x2 ANOVA, treatment, $F_{(2,33)}$ = 5.11, p = 0.01, Sidak's test, p = 0.01; treatment x context, $F_{(2,33)}$ = 0.002, p = 0.99, context, $F_{(1,33)}$ = 2.965 p = 0.10), and it declined during the test session, independent of treatment (**Fig. S4B**; 3x6 ANOVA time, $F_{(5,165)}$ = 27.09, p < 0.0001, Tukey test, interval 1 > 2-6, p < 0.05; treatment x time, $F_{(10,165)}$ = 1.28, p = 0.25; treatment, $F_{(2,33)}$ = 2.45, p = 0.11).

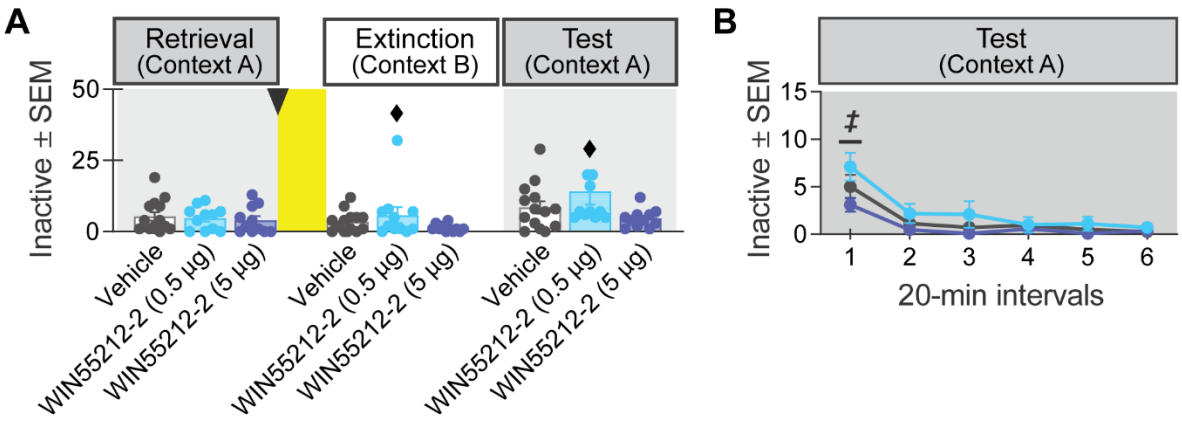

FIGURE S4. Intra-BLA WIN55,212-2 administration *during* cocaine-memory reconsolidation does not alter inactive-lever responding at test. (A) Inactive-lever responses (mean ± SEM) during the 15-min memory-retrieval session (before treatment; see statistics in Table S2) and upon first re-exposure to the extinction context and the cocaine-paired context (after treatment) at test. Treatment involved bilateral intra-BLA administration of the CB1/2R agonist, WIN55,212-2 (0.5 or 5 µg/0.5 µL per hemisphere; *n* = 11/group) or vehicle (*n* = 14) immediately after the 15-min cocaine-memory retrieval session. **(B)** Time course of inactive-lever responding in the cocaine-paired context at test. ***Symbols***: ANOVA ♦treatment simple-main effect (different from 5.0 µg dose only); ‡time simple-main effect, Tukey's tests, intervals 1 > 2-6, ps < 0.05.

Experiment 5: Intra-BLA AM251 administration prolongs the rise in serum corticosterone levels during cocaine-memory reconsolidation

The two groups did not differ in inactive-lever responding during the memory retrieval session ($t_{(9)}$ = 0.01, p = 0.99; **Fig. S5**), prior to treatment. Behavioral testing concluded with the memory reactivation session in Experiment 5.

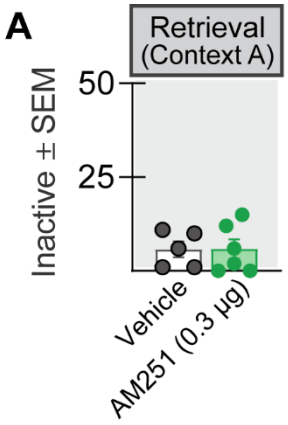

FIGURE S5. There are no pre-existing differences between the groups in inactive-lever responding at test. Inactive-lever responses (mean ± SEM; *n* = 5, 6) during the 15-min memory-retrieval session, before treatment.

Experiment 6: Post-retrieval corticosterone administration into the BLA fails to alter cocaine-memory strength

Inactive-lever responding remained low in both contexts (**Fig. S6A**; 3 x 2 ANOVA, treatment, $F_{(2,17)}$ = 0.52, p = 0.60; treatment x context, $F_{(2,17)}$ = 0.14, p = 0.87, context, $F_{(1,17)}$ = 1.98 p = 0.18), and it declined during the test session (**Fig. S6B;** 3 x 6 ANOVA, time, $F_{(1,17)}$ = 10.36, p < 0.0001, Tukey tests, interval 1 > 2-6, ps < 0.05; treatment x time, $F_{(2,17)}$ = 0.37, p = 0.70; treatment, $F_{(2,17)}$ = 0.39, p = 0.68), independent of treatment.

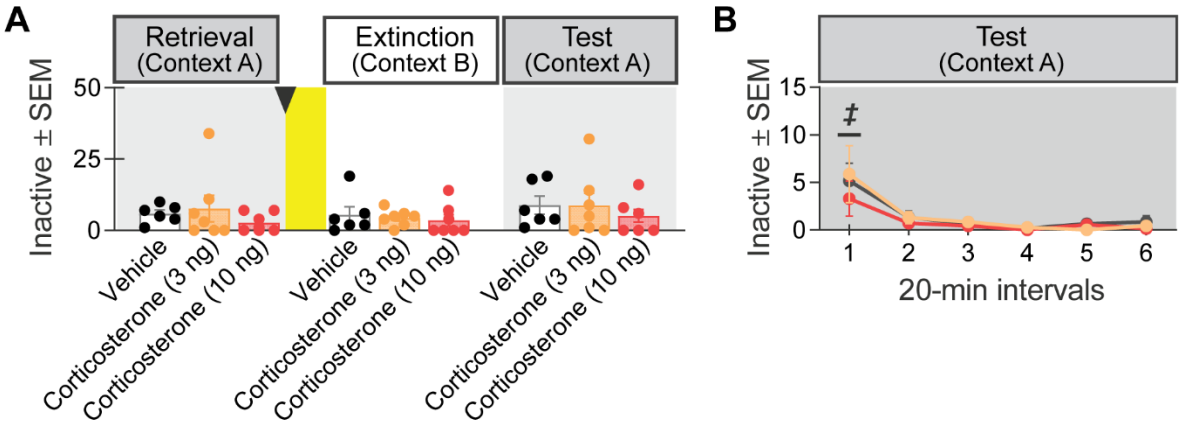

FIGURE S6. Intra-BLA corticosterone administration *during* cocaine-memory reconsolidation does not alter inactive-lever responding at test. (A) Inactive-lever responses (mean ± SEM) during the 15-min memory-retrieval session (before treatment; see statistics in Table S2) and upon first re-exposure to the extinction context and the cocaine-paired context (after treatment) at test. Treatment involved bilateral intra-BLA administration of the CB1/2R agonist, corticosterone (3 or 10 µg/0.5 µL per hemisphere; *n* = 7/group) or vehicle (*n* = 6) immediately after the 15-min cocaine-memory retrieval session. **(B)** Time course of inactive-lever responding in the cocaine-paired context at test. ***Symbols***: ANOVA ‡time simple-main effect, Tukey's tests, intervals 1 > 2-6, ps < 0.05.