

Cocaine-induced decision-making deficits are mediated by miscoding in basolateral amygdala

Thomas A Stalnaker¹, Matthew R Roesch¹, Theresa M Franz¹, Donna J Calu², Teghpal Singh² & Geoffrey Schoenbaum^{1,3,4}

Addicts and drug-experienced animals have decision-making deficits in reversal-learning tasks and more complex ‘gambling’ variants. Here we show evidence that these deficits are mediated by persistent encoding of outdated associative information in the basolateral amygdala. Cue-selective neurons in the basolateral amygdala, recorded in cocaine-treated rats, failed to change cue preference during reversal learning. Further, the presence of these neurons was critical to the expression of the reversal-learning deficit in the cocaine-treated rats.

Addicts make poor decisions. These deficits have been modeled in addicts and drug-experienced animals using reversal-learning tasks and more complex ‘gambling’ variants. In these settings, subjects first learn to associate different cues with different probabilities of reward and punishment, and then the meanings of the cues are reversed. After this reversal, addicts and animals exposed to psychostimulants have difficulty learning to stop responding to previously rewarded cues^{1–4}. Similar reversal deficits caused by damage to orbito-frontal cortex are mediated by miscoding of associative information in the basolateral

amygdala^{5,6}. Here we test whether miscoding of associative information in the basolateral amygdala (ABL) also mediates cocaine-induced reversal deficits in rats.

In the first experiment (Fig. 1, Experiment 1 and **Supplementary Methods** online for procedures), neural activity was recorded in ABL in rats previously exposed to saline or cocaine (30 mg per kg of body weight, intraperitoneal \times 14 d, locomotor data in **Supplementary Results** and **Supplementary Fig. 1** online). Recording began \sim 4 weeks after drug exposure and was conducted in a different room and boxes than those used for drug exposure. We recorded 118 neurons in saline-treated rats ($n = 4$) and 228 neurons in cocaine-treated rats ($n = 3$) during acquisition and reversal of a series of novel two-odor go, no-go discrimination problems. In each problem, one odor predicted the delivery of sucrose, and another odor predicted the delivery of quinine; after learning, these predictive relationships were reversed (see **Supplementary Methods**). Recording locations (Fig. 2a,b) and baseline firing rates (see **Supplementary Results** and **Supplementary Fig. 2** online) were similar between groups, and as expected, rats exposed to cocaine were slower to learn the reversals (Fig. 1b; detailed analysis available in **Supplementary Results** and **Supplementary Fig. 3** online).

To assess encoding of the odor-outcome associations, we analyzed neural activity to the sucrose- and quinine-predictive cues during learning and after reversal (description and additional analyses of other time periods available in **Supplementary Methods** and **Supplementary Results**). We found little effect of cocaine on the development of activity to either cue during learning (Table 1, Fig. 2a,b and **Supplementary Results**). However, cocaine-treatment markedly reduced the changes in cue-evoked activity that are normally observed across reversal. In controls, 48% of the cue-selective neurons evident during learning switched their cue preference after reversal, and only a single neuron maintained the same preference (Table 1). These

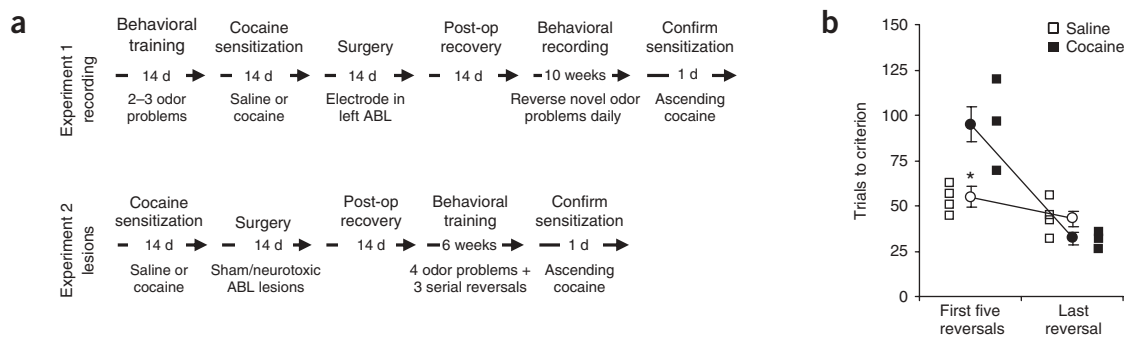


Figure 1 Experimental design and effect of cocaine exposure on reversal learning during recording. **(a)** Experimental timelines. Animal testing procedures were approved by the Institutional Animal Care and Use Committee at the University of Maryland School of Medicine. **(b)** Individual and group trials to criterion after reversal during the initial and final recording sessions (* $P < 0.05$). Error bars represent s.e.m.

¹Department of Anatomy and Neurobiology, ²Program in Neuroscience and ³Department of Psychiatry, University of Maryland School of Medicine, 20 Penn St., HSF-2 S251, Baltimore, Maryland 21201, USA. ⁴Department of Psychology, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, Maryland 21250, USA. Correspondence should be addressed to T.A.S. (tstal002@umaryland.edu).

proportions are nearly identical to those in two prior studies of neural activity in ABL in this task^{6,7}, in which 55% (10/18 cue-selective ABL neurons in 4 rats) and 53% (34/64 cue-selective ABL neurons in 3 rats) switched cue preference after reversal (see **Supplementary Results** and **Supplementary Fig. 4** online for comparison of individual rats). Thus, the effect of reversal on cue-evoked activity in controls in the current experiment reflects a highly reliable and reproducible result. Indeed, similar results have been reported in primates⁸.

Flexibility of cue-evoked activity in ABL is evident in the population responses (**Fig. 2a**), which reversed cue preference during reversal learning, tracking the outcomes predicted by the odor cues rather than their sensory features. This is also evident in the ‘cue-selectivity index’, calculated for each neuron in each population as $(\text{firing}_{\text{odor1}} - \text{firing}_{\text{odor2}}) / (\text{firing}_{\text{odor1}} + \text{firing}_{\text{odor2}})$ (**Fig. 2a**, scatterplot). These indices were inversely correlated across reversal ($r = -0.68, P = 0.00001$), indicating that the neurons fired according to the outcomes predicted by the cues and not to the cues’ specific sensory features.

By contrast, cue-evoked activity in the cocaine-treated rats was significantly less likely to reverse and significantly more likely to persist to the same odor across reversal (**Table 1**; $\chi^2 = 11.98, P = 0.0005$, and $\chi^2 = 10.1, P = 0.0015$, respectively). There were no differences between animals within groups in the proportion of neurons that reversed (P values = 0.27–0.97), indicating that this effect was not carried by any one animal in the cocaine-treated group (see **Supplementary Results** and **Supplementary Fig. 4** for comparison of individual rats).

Inflexibility of cue-evoked activity in ABL in cocaine-treated rats is evident in the population responses (**Fig. 2b**) and in the cue-selectivity indices (**Fig. 2b**, scatterplot), which showed a highly significant positive correlation across reversal ($r = 0.46, P = 0.0004$). Because these neurons developed cue-selective firing during initial learning (see **Supplementary Results** for details), this positive correlation indicates that these neurons continued to fire on the basis of the pre-reversal significance of the cues. This effect was particularly apparent in neurons that were selective for the sucrose-predictive odor before reversal;

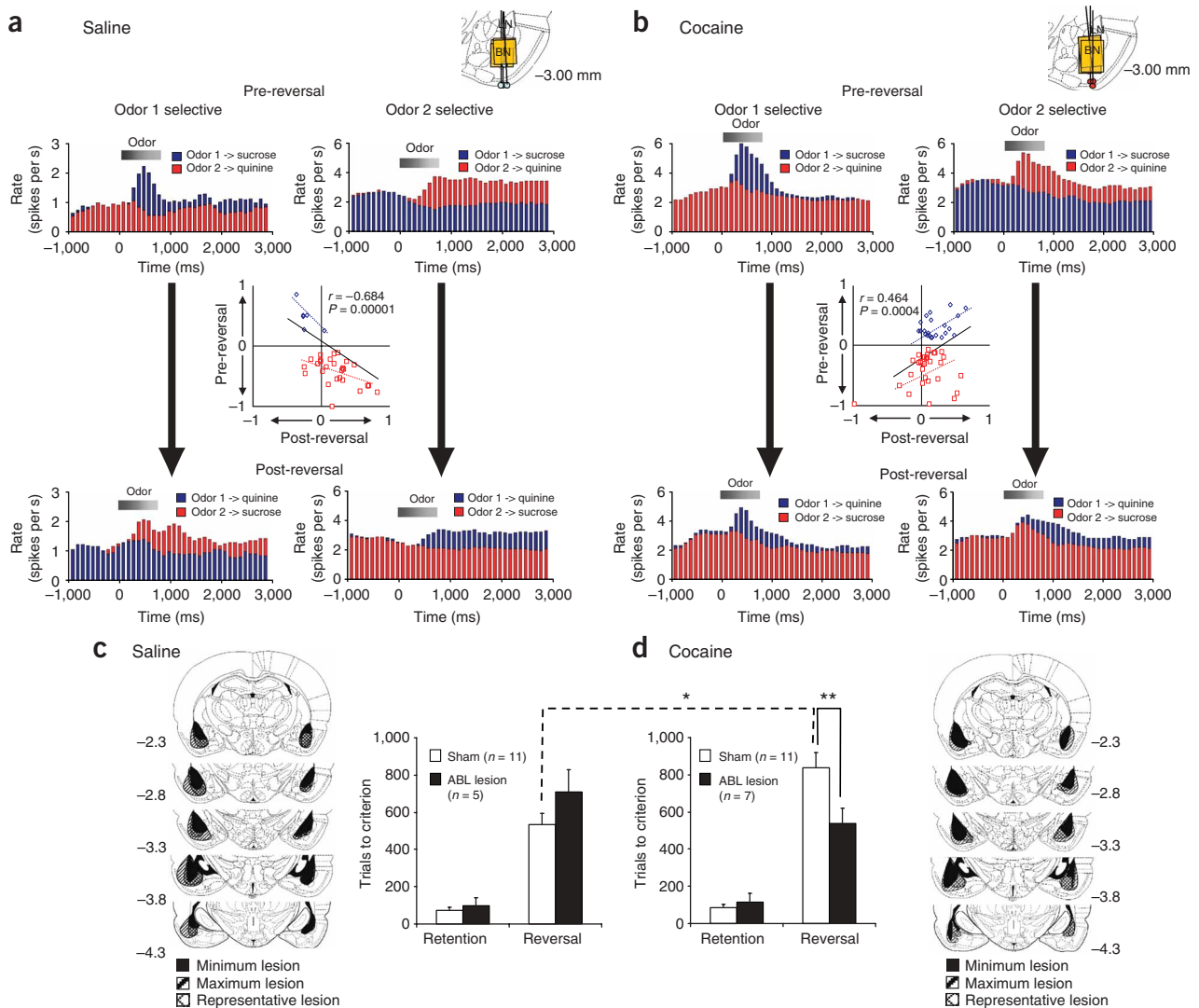


Figure 2 Cocaine-induced decision-making deficits are mediated by miscoding in basolateral amygdala. (**a,b**) Population histograms show average activity in neurons selective for each odor cue after learning and after reversal. Scatterplots show selectivity indices calculated from cue-evoked firing before and after reversal for each neuron. (**c,d**) Drawings show size and extent of lesions; bar graphs show average trials to criterion for retention and reversal. Planned comparisons after three-factor ANOVA: * $P = 0.0046$, ** $P = 0.013$. No other comparisons, planned or unplanned, were significant. Error bars represent s.e.m.

Table 1 Effect of reversal on cue-evoked activity in ABL in cocaine- and saline-treated rats

Pre-reversal	Post-reversal		
	Same odor	Opposite odor	Nonselective
All cue-selective neurons			
Saline (<i>n</i> = 33)	1 (3%)	16 (48%)	16 (48%)
Cocaine (<i>n</i> = 55)	15* (27%)	8* (15%)	32 (58%)
Odor 1 + selective neurons			
Saline (<i>n</i> = 6)	0 (0%)	4 (67%)	2 (33%)
Cocaine (<i>n</i> = 23)	13* (57%)	0* (0%)	10 (43%)
Odor 2- selective neurons			
Saline (<i>n</i> = 27)	1 (4%)	12 (44%)	14 (52%)
Cocaine (<i>n</i> = 32)	2 (6%)	8 (25%)	22 (69%)

Values indicate the number of cue-selective neurons (with percentages in parentheses) that were selective for the same odor cue versus the opposite odor cue (or were nonselective) after reversal. Odor 1 is the sucrose-predictive odor before reversal, and Odor 2 is the quinine-predictive odor cue before reversal. Thus, although many neurons reversed their cue-selectivity across reversal in saline-treated rats, very few neurons did so in cocaine-treated rats. * indicates difference from saline-treated controls at $P = 0.01$ or better by χ^2 (no others were significant at $P < 0.05$ or better).

however, inflexible encoding was also apparent in neurons selective for the quinine-predictive odor (see **Supplementary Results** for analyses by outcome).

Although ABL is not normally critical for reversal learning^{9,10}, persistent encoding of outdated associative information in ABL could slow reversal learning by interfering with normal processing in other structures^{1,2,10}. We have demonstrated such a mechanism for reversal deficits caused by orbito-frontal cortex lesions^{5,6}. To test whether drug-induced reversal deficits might be mediated by a similar mechanism, we tested the effects of ABL lesions on the reversal deficit caused by cocaine (see **Fig. 1a**, Experiment 2 and **Supplementary Methods** for procedures). Groups included saline/sham = 11, saline/lesion = 5, cocaine/sham = 11 and cocaine/lesion = 7. Lesion size (**Fig. 2c,d**) and sensitization to cocaine did not differ between relevant groups (locomotor data available in **Supplementary Results** and **Supplementary Fig. 5** online). Rats were trained 4 weeks after drug exposure on four discriminations followed by three reversals of the final problem. There was no effect of lesions or cocaine on learning (see **Supplementary Results**). As expected, cocaine impaired reversal learning in rats with sham lesions, but this reversal deficit was completely abolished by ABL lesions (**Fig. 2c,d** and **Supplementary Results**). Improved reversal learning was not a result of a general blockade of cocaine's effects by ABL lesions, as lesioned rats showed normal locomotor sensitization at the end of reversal training (see **Supplementary Results** and **Supplementary Fig. 5**). The failure of ABL lesions to alter performance in normal rats also suggests that lesions did not alter rats' normal learning strategy. Nor did ABL lesions independently facilitate reversal learning; lesioned controls performed no better than shams on the reversals

(**Fig. 2c**). Instead, cocaine created a pathological role for ABL in reversal learning.

The observation that cocaine exposure affects decision-making by diminishing the flexibility of associative encoding in ABL suggests a mechanism whereby drug-associated cues may persistently affect behavior, even after extinction and in the face of adverse consequences. Thus in addicts and animal models, inflexible associative representations in ABL might contribute to relapse and compulsive drug-seeking. Indeed, ABL neurons fire strongly to drug-associated cues¹¹, and ABL is critical to cue-induced relapse^{12–14}. Manipulations designed to disrupt reconsolidation of memories in ABL reduce cue-evoked drug-seeking¹⁴. Inflexible encoding in ABL may be related to pathological changes in prefrontal areas, as has been suggested in other neuropsychiatric disorders¹⁵ (see **Supplementary Discussion** online).

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

T.A.S. and G.S. conceived the experiments; T.A.S., M.R.R. and D.J.C. carried out the recording work; T.A.S. and T.S. carried out the lesion work; and T.M.F. assisted with electrode construction, surgeries and histology. The data were analyzed by T.A.S. and G.S., who also cowrote the manuscript with assistance from each of the other team members.

COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

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