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Research report

Adrenergic manipulation inhibits pavlovian conditioned approach behaviors

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A B S T R A C T

Environmental rewards and Pavlovian reward cues can acquire incentive salience, thereby eliciting incentive motivational states and instigate reward-seeking. In rats, the incentive salience of food cues can be measured during a Pavlovian conditioned approach paradigm, in which rats engage in cue-directed approach ("sign-tracking") or approach the food delivery location ("goal-tracking"). While it has been shown that dopamine signaling is necessary for sign-tracking, some studies have suggested that norepinephrine is involved in learning to sign-track as well. Thus, in order to investigate the influence of norepinephrine in Pavlovian conditioned approach, we administered three adrenergic drugs while rats learned that a food cue (an illuminated, retractable lever) preceded the delivery of banana-flavored food pellets into a food-cup. We found that pre-session injections of disulfiram (a dopamine-β-hydroxylase inhibitor) inhibited the development of sign-tracking, but goal-tracking was only affected at the high dose. In one experiment, post-session injections of disulfiram blocked the development of sign-tracking, although this effect was not replicated in a separate set of rats. Post-session injections of prazosin (an α1-adrenergic receptor antagonist) and propranolol (a β-adrenergic receptor antagonist) also blocked the development of sign-tracking but not goal-tracking. Taken together, these results suggest that adrenergic transmission mediates the acquisition of sign-tracking but not goal-tracking, and thus plays a selective role in the attribution of incentive salience food cues.

1. Introduction

Environmental stimuli associated with rewards (conditioned stimuli or "cues") can acquire incentive salience and thus strongly influence motivated behaviors such as feeding and drug-taking. For example, incentive cues can elicit approach, reinforce new behaviors, and elicit conditioned motivational states [2–5]. However, there is substantial individual variability in the degree to which reward cues acquire incentive salience. In extreme cases, the attribution of incentive salience to reward cues can lead to maladaptive behaviors, including cue-triggered feeding and cue-induced relapse to drug-seeking [6–9].

In rodents, the incentive salience of reward cues can be inferred using a Pavlovian conditioned approach (PavCA) procedure, during which a conditioned stimulus (insertion of a retractable lever) predicts delivery of a food pellet [10,11]. During this paradigm, subjects will either approach the lever-cue ("sign-tracking") or the reward delivery location ("goal-tracking"). While both responses require associative learning, the degree of sign-tracking reflects the incentive salience attributed to the cue by the subject. Rats that tend to sign-track ("sign-trackers"), relative to "goal-trackers", also attribute incentive salience to cues in other paradigms, including conditioned reinforcement [12,13], cue-induced reinstatement of food and drug seeking, [14–16] and Pavlovian drug conditioning paradigms [17,18].

While several studies have focused on the role of dopamine in the development and expression of sign- and goal-tracking [10,19–23], norepinephrine (NE) has been implicated in this process as well. For example, Tomie et al. [1] showed an increase in NE levels in the prefrontal cortex (PFC) only when a food reward was paired with a lever cue (but not in unpaired controls), suggesting that this increase was related to the sign-tracking responses observed during the paired condition. In other Pavlovian paradigms, NE was increased in the PFC during appetitive and aversive conditioning [24,25], administration of NE or noradrenergic agonists facilitated cue-shock learning [26–29], and NE antagonists had the opposite effect on both aversive and appetitive Pavlovian conditioning [27,30,31]. Further, NE is involved in the consolidation of fear and drug memories [31–34], in that learned responses are sensitive to pharmacological interference for several hours after the learning event has occurred [30,35,36]. However, while the adrenergic system is critically involved in aversive and appetitive Pavlovian learning, no studies have determined whether NE manipulations differentially affect sign-tracking and goal-tracking during a PavCA paradigm.

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Thus, for the current experiments, we hypothesized that the adrenergic system is involved in the attribution of incentive salience during PavCA. To test this, we inhibited the adrenergic system using disulfiram (DSF), which inhibits dopamine-β-hydroxylase (DβH) and prevents the formation of NE and epinephrine peripherally and centrally [37]. Given that adrenergic systems are involved in memory consolidation [30,38,39], we also tested whether post-session administration of DSF would attenuate sign- and goal-tracking behaviors. Then, to determine the receptor subtypes involved in these effects, we gave post-session injection of the specific α- and β-adrenergic antagonists prazosin and propranolol. We show that the attribution of incentive salience to reward cues is mediated by adrenergic receptors through interference with memory consolidation.

2. Methods and materials

2.1. Subjects and housing

One hundred and twenty male Sprague-Dawley rats (48 each in Experiments 1 and 2, 24 in Experiment 3) were purchased from Envigo (250–275 g; Indianapolis, IN). Rats were handled for at least 3 days prior to testing. Rats were pair-housed in Plexiglas cages (45 length × 24 cm width × 20 cm height) with aspen shavings. Water and standard laboratory chow were freely available except during testing. Testing began at least one hour after the onset of the dark cycle (12:12 h, lights off at 7 AM). All procedures were approved by the University at Buffalo Institutional Animal Care and Use Committee.

2.2. Drugs

Disulfiram (DSF) was obtained from Sigma-Aldrich (PHR1690) and dissolved in 0.9% saline and 0.5% Tween 80. The DSF stock solutions were all sonicated for at least 30 min and briefly vortexed before each administration. DSF was administered intraperitoneally (50, 100, or 200 mg/kg). In Experiment 3, prazosin (α1-adrenergic receptor antagonist; 3 mg/kg) and propanolol (β-adrenergic receptor antagonist; 10 mg/kg) were obtained from Sigma-Aldrich (P7791; P0884) and dissolved in 0.9% saline solution. All solutions were vortexed before administration. All solutions were injected in a volume of 1 mL/kg.

2.3. Apparatus

MED Associates operant chambers (20.5 × 24.1 cm floor area, 29.2 cm high, Med-Associates Inc., St. Albans, VT) were housed in sound- and light-attenuating cabinets (A & B Displays, Bay City, MI) equipped with an exhaust fan for background noise and ventilation. Each chamber had a red house light located near the ceiling of the left chamber wall. The chambers contained a parallel bar floor (Med Associates, Model ENV-005A) over aspen shavings. The right wall of the chamber was equipped with a retractable lever containing a backlight (Med Associates, Model ENV-112CML) on the left or right side (counterbalanced) of a central food cup receptacle (Med Associates, Model 200R1M-6). An automated pellet dispenser (Med Associates, Model ENV-203M-45) delivered banana-flavored food pellets (45 mg, BioServ, #F0059, Frenchtown, NJ) as described below. All data were collected using MED-PC IV.2 software.

2.4. Procedures

For all experiments, on the two days before testing, rats were given ~50 banana flavored food pellets in their home cages to familiarize them with these pellets. For each day of testing, rats were transferred from the colony to the testing room in individual Sterilite Narrow Modular clear drawers (17.13 × 8 × 7) with holes drilled for ventilation. On the first day (food cup training), rats were placed into the chambers and, after a 5-min period, the house light was illuminated and 25 banana-flavored pellets were delivered into the food cup on a variable interval (VI) 30 (0–60 s) schedule. On the subsequent testing days, rats were placed into the chambers and the house light was illuminated after one min. There were 25 trials during each testing day; each trial consisting of an 8-s lever extension (the conditioned stimulus; CS) that preceded delivery of a banana-flavored food pellet (the unconditioned stimulus; US) into the food receptacle. Trials were delivered on a VI 90 s schedule (30–150 s). Food-cup entries were counted at all times and lever deflections were recorded during the CS period. Sign-tracking responses were defined as the number of lever deflections, while goal-tracking responses were defined as the number of food cup entries during the CS period. Probability of a sign-/goal-tracking response (number of trials in which a response occurred/25) was calculated as well as latency to approach the lever or the food cup.

2.5. Experiment 1: effects of pre-Session disulfiram on pavlovian conditioned approach

Rats were injected i.p. with DSF (50, 100, or 200 mg/kg) or saline 25 min *before* being placed in the chambers. Testing occurred over 5 consecutive days. On days 6 and 7, DSF was removed and all rats received saline injections in order to determine whether latent learning had occurred during drug treatment.

2.6. Experiment 2: effects of post-Session disulfiram on pavlovian conditioned approach

Rats were injected with 100 or 200 mg/kg DSF or saline immediately *after* completion of the Pavlovian conditioned approach sessions for 5 days.

2.7. Experiment 3: effects of post-Session prazosin and propranolol on pavlovian conditioned approach

This study was conducted similarly to Experiment 2, except that rats received prazosin (3 mg/kg), propranolol (10 mg/kg), or saline upon removal from the chambers. Because control rats learned more slowly in this experiment (no change in sign-tracking during days 1–4, see Fig. 6), rats were tested for 8 consecutive days instead of 5.

2.8. Statistics

Data for all experiments were analyzed with Statistica (Dell; Tulsa, OK) using repeated-measures ANOVAs with Drug Treatment as the between-groups variable and Session as the within-groups variable. Our primary measures for these studies were total numbers of lever contacts (presses) and food-cup contacts (entries) as well as the probability of making these responses (number of trials with a response/25 trials) and the average latency (0–8 s) to making each response. In addition, we have previously utilized a PavCA index score [11] that can be calculated for individual rats, and includes the average of three measures of conditioned approach: 1) The *probability differential* (average lever contact probability − average food-cup contact probability), 2) the overall *response bias* for either the lever or the food-cup CS (# lever contacts − # food-cup contacts/# lever + # food-cup contacts), and 3) *average latency difference* (food-cup latency − lever latency/8). This measure was used to characterize individual differences in sign- and goal-tracking behavior. Post hoc analyses were conducted using Fisher's least significant difference ($p < 0.05$). In Experiment 1, planned comparisons were used to test the *a priori* hypothesis that drug removal would result in the emergence of sign-tracking response on day 7 relative to day 5 in the previously drug-treated groups.

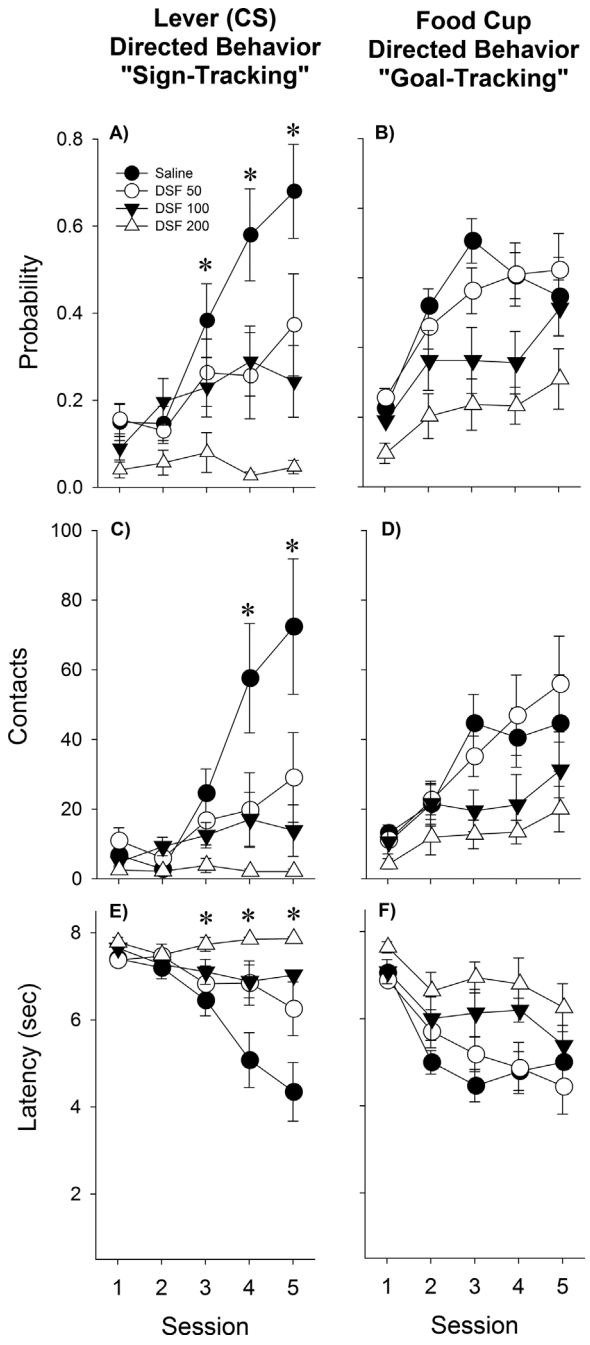

Fig. 1. Exp. 1. Pre-session administration of DSF inhibits the acquisition of sign-tracking responses in naïve Sprague-Dawley rats. Data show mean (± SEM) on probability of approaching the lever (A) or food cup (B) during the CS period, number of lever deflections (C) or food cup entries (D), and latency to contact the lever (E) or make a food cup entry (F) during the CS period, over 5 days of Pavlovian training. DSF doses (50, 100, 200 mg/kg) are indicated in the legend. $n = 12$ for all groups, asterisks indicate higher/faster responding in the saline-treated group compared to all other groups, $p < 0.05$.

3. Results

3.1. Experiment 1: effects of pre-Session disulfiram on pavlovian conditioned approach

DSF administered before the PavCA session attenuated sign-tracking behavior as measured by reduced response probability, reduced number of contacts, and increased latency to respond [Fig. 1; main effects of Treatment: $F(3, 44) = 8.30, 6.02, 7.58$, respectively, $ps < 0.01$; Treatment x Session interactions: $F(4, 176) = 4.43, 5.01, 5.40$, $ps < 0.01$]. Post hoc analyses revealed that, for the 200 mg/kg dose, lever response probability and latency to contact the lever differed from controls on days 3–5, and days 4–5 for number of contacts. Similarly, all three measures differed from controls days 4–5 for the 50 and 100 mg/kg doses. DSF also decreased goal-tracking behavior as measured by response probability and increased latency to enter the food cup [main effects of Treatment: $F(3, 44) = 8.85, 8.84$, $ps < 0.01$; no Treatment x Session interactions]. Post hoc analyses indicated that both probability and latency in the 200 mg/kg group were significantly reduced on days 2–5, with the 100 mg/kg group differing on days 3–4, relative to saline controls ($ps < 0.05$).

To determine whether saline control rats were indeed learning to goal-track, we calculated the rate of intertrial (ITI) entries (entries/sec; total ITI entries/total ITI time) and compared it to the rate of CS entries [total CS entries/(25 trials × 8 s per trial)] Indeed, the saline-treated rats increased their CS entries over days, while ITI entries did not change (Fig. 2). We then ran a Dose x CS/ITI x Day analysis on this rate measure [$F(12, 176) = 1.99$, $p < 0.05$ for the 3-way interaction]. Post-hoc analyses of this effect showed that only the rats given 200 mg/kg did not increase their head entries during CS to the NCS, thus rats in all groups except the 200 mg/kg group learned to goal-track during treatment.

Even though in our study we report levels of sign-tracking and goal-tracking as a group, it is likely that there were individual differences in terms of whether rats predominately sign- or goal-tracked, as we have published previously [11,40]. Unfortunately, it is not possible to isolate which rats will become “sign-trackers” or “goal-trackers” before testing and treatment begins. However, to illustrate individual differences in the propensity to sign- or goal-track, we calculated PavCA index scores for individual animals (Fig. 3A), subdivided by whether they sign-tracked more across learning (PavCA index increased from day 1 to day 5) or goal-tracked more across days (PavCA index decreased). We also show the average magnitude of these changes (Fig. 3B). While unequal and low sample sizes preclude statistical analyses of the individual differences, it is apparent that rats given DSF showed smaller increases in sign-tracking while DSF did not affect the magnitude of goal-tracking increases in rats that increased their goal-tracking behavior. This provides additional support for DSF preferentially affecting sign-tracking relative to goal-tracking behavior.

When DSF treatment was removed during sessions 6–7, animals increased their sign-tracking response as indicated by a main effect of session [Fig. 4A; $F(2, 88) = 12.74$, $ps < 0.01$]. Planned comparisons indicated that the sign-tracking responses of all groups previously treated with DSF increased significantly on day 7 relative to day 5 (the last day of drug treatment; $ps < 0.5$). However, by continuing to pair the CS with the US during these sessions, one cannot necessarily conclude whether rats had learned previously because new learning can take place during these sessions. To address this, we measured the sign-tracking and goal-tracking during trial 1 of day 6, which is before there are any additional CS-US pairings (Fig. 4B). Previous treatment with DSF affected sign-tracking [$F(3, 44) = 18.7$, $p < 0.05$] at the 100 and 200 mg/kg doses ($ps < 0.05$), but had no effect on goal-tracking. Together, these experiments indicate that DSF blocked the acquisition of sign-tracking, and that rats learned to sign-track upon DSF removal.

3.2. Experiment 2: effects of post-Session disulfiram on pavlovian conditioned approach

We then tested the effects of post-session DSF in naïve Sprague Dawley rats. However, while the magnitude of sign-tracking was lower in drug treated rats (particularly at the 100 mg/kg dose), this effect was not significant, and there was no effect of drug nor an interaction with either sign- or goal-tracking (Fig. 5).

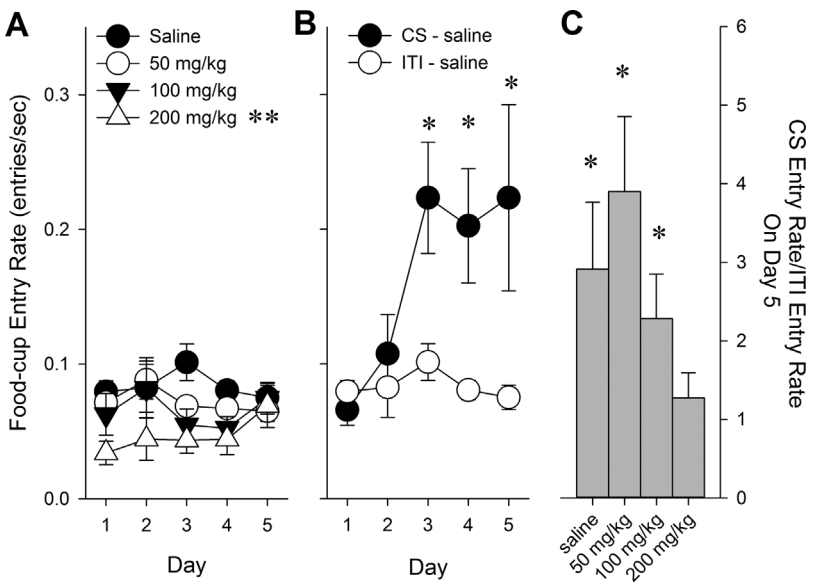

Fig. 2. Exp. 1. DSF did not affect goal-tracking except at the 200 mg/kg dose, which also reduced activity in general. Panel A shows the frequency of food-cup entries during the intertrial intervals (ITIs). Panel B shows only the saline-treated rats demonstrating that conditioned stimulus (CS) responding increased while responses during theITIs did not. Panel C shows the ratio of CS/ITI entries on day 5 only, subdivided by treatment group. All groups except the 200 mg/kg group increased their responding during the CS relative to the ITI. Asterisks denote significantly more CS vs. ITI entries ($p < 0.05$). Double asterisks indicate lower ITI entries in the 200 mg/kg group ($p < 0.05$).

3.3. Experiment 3: effects of post-Session prazosin and propranolol on pavlovian conditioned approach

Despite the lack of effect of post-session DSF, it is possible that the delayed onset of DSF, caused us to miss the critical window for consolidation. In addition, we did see an effect of DSF in a pilot study involving Long-Evans rats that had a history of nicotine and alcohol using an identical procedure (not shown). This inconsistency may be due to the limited solubility of DSF, thereby resulting in unreliable results when injecting suspensions of this drug. Given this mixed evidence for DSF post-session injections altering sign-tracking behavior, we next determined whether post-session interference with specific adrenergic receptors would interfere with sign- or goal-tracking. Because learning progressed slowly in this cohort of animals, we tested for eight sessions. Drug treatment inhibited sign-tracking behavior across days as measured by response probability, number of contacts, and latency to approach the cue [No effect of treatment; Treatment x Session interactions: $F(14, 147) = 5.30, 2.90, 4.70$, $ps < 0.01$; Fig. 6]. Post hoc analyses indicated that both propranolol and prazosin differed from controls on probability to sign-track from sessions 5–8. Number of contacts and latency to approach differed on days 6–8 for propranolol and days 7–8 for prazosin. There were no significant effects on goal-tracking responses (Fig. 6). Thus, this experiment further supports a role for noradrenergic signaling in the consolidation of sign-tracking.

4. Discussion

The incentive salience of reward cues enables them to instigate motivated behavior. In rats, Pavlovian conditioned approach paradigms can be used dissociate the incentive salience attribution to cues from general associative learning processes. Specifically, cue-directed approach (sign-tracking) is one index of the incentive salience assigned to that cue, while approach to the reward location (goal-tracking) reflects general associative learning [12]. In these experiments, the DβH inhibitor DSF prevented the development of sign-tracking when administered before the test session, and post-session injections of α1- and β-adrenergic receptors also blocked the consolidation of sign-tracking behaviors without affecting goal-tracking. Collectively, these results reveal that adrenergic signaling is required for the consolidation of incentive salience to attribution to reward cues, but not for associative learning *per se*.

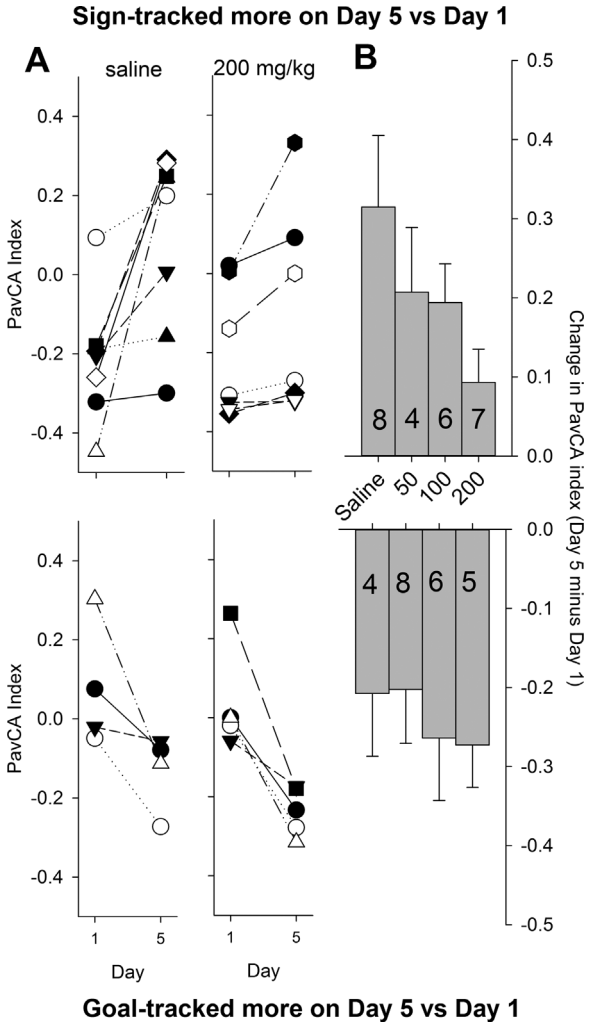

Fig. 3. Exp. 1. DSF selectively affected PavCA index scores in rats that increased sign-tracking from day 1 to day 5. A) PavCA index scores for individual animals, subdivided by whether they sign-tracked (top) or goal-tracked (bottom) more on day 5 vs day 1. 50 and 100 mg/kg groups are not shown for simplicity. B) The average magnitude of these changes. The numbers in the bars indicate sample sizes. Error bars indicate SEM.

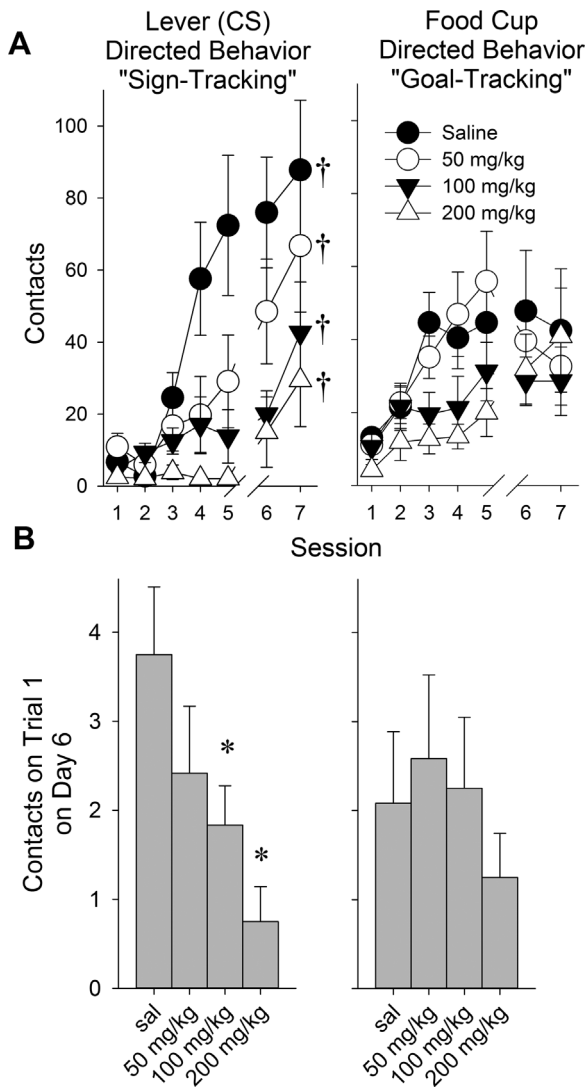

Fig. 4. Exp. 1. Stopping pre-session treatment with DSF (signified by axis break) allowed animals to acquire a sign-tracking behavior. Data from Fig. 1 are shown in panel A, with the addition of days 6–7, during which all rats received saline. Panel B shows only the first trial of Day 6, during which no additional learning had yet occurred. All values are mean (± SEM) lever contacts or food cup entries during the CS period; $n = 12$ for all groups. Daggers indicate an increase in sign-tracking behavior during session 7, relative to session 5, $p < 0.5$. Asterisks indicate a significant reduction in sign-tracking in the 100 and 200 mg/kg groups.

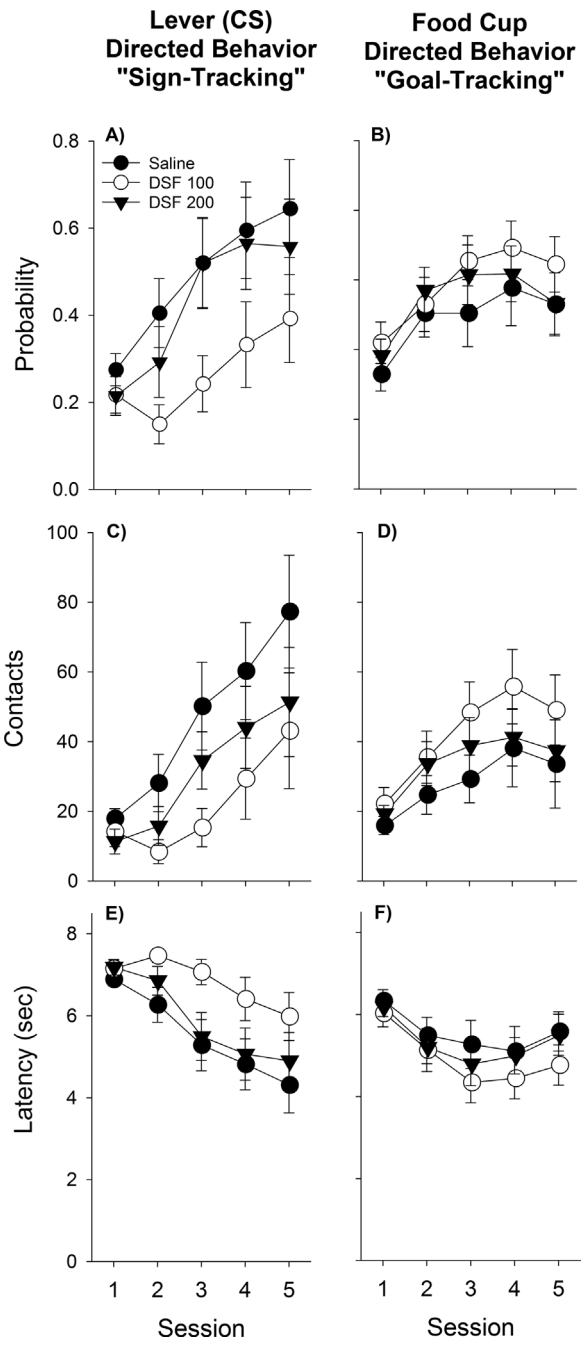

Fig. 5. Exp. 2. Post-session DSF did not significantly affect conditioned responding in naïve Sprague-Dawley rats. Data show mean (± SEM) probability of approaching the lever (A) or food cup (B) during the CS period, number of lever deflections (C) or food cup entries (D), and latency to contact the lever (E) or make a food cup entry (F) during the CS period, over 5 days of Pavlovian training. DSF doses (100, 200 mg/kg) are indicated in the legend. $n = 16$ for all groups.

4.1. Adrenergic mechanisms of incentive salience attribution

Previous studies from our laboratory and others have characterized individual differences in the tendency to attribute incentive salience to reward cues, as measured by the degree of sign-tracking during PavCA [10–12]. By categorizing rats as "sign-trackers" or "goal-trackers," these studies have shown that sign-tracking predicts the response to food and drug cues in several paradigms [7,13,16–18,41–43]. These individual differences have further been exploited to show that dopamine plays a selective role in promoting incentive salience attribution to reward cues [10,19,20,23,44] rather than a general role in reward learning. Specifically, these studies show that dopamine is necessary for both the learning (acquisition) and expression of sign-tracking responses, whereas only the expression of goal-tracking requires dopamine.

It may be that dopamine interacts with NE to produce some of these effects, because others have shown that adrenergic receptors mediate stress- and drug-induced increases in dopamine [45–49]. For example, Darracq et al. [49] showed that NE action within the PFC is critical for the effects of amphetamine on dopamine release in the nucleus accumbens and for amphetamine-induced locomotion. Inasmuch as drug-induced dopamine release is analogous to cue-induced dopamine release and incentive salience attribution, it may be that NE is also critical for the activation of dopamine by incentive cues. While the current experiments did not characterize individual differences in sign- and goal-tracking, they do raise the possibility that individual differences in cue-induced NE release may underlie the behavioral and neurochemical differences in sign-trackers and goal-trackers.

However, only a few studies have assessed the involvement of the

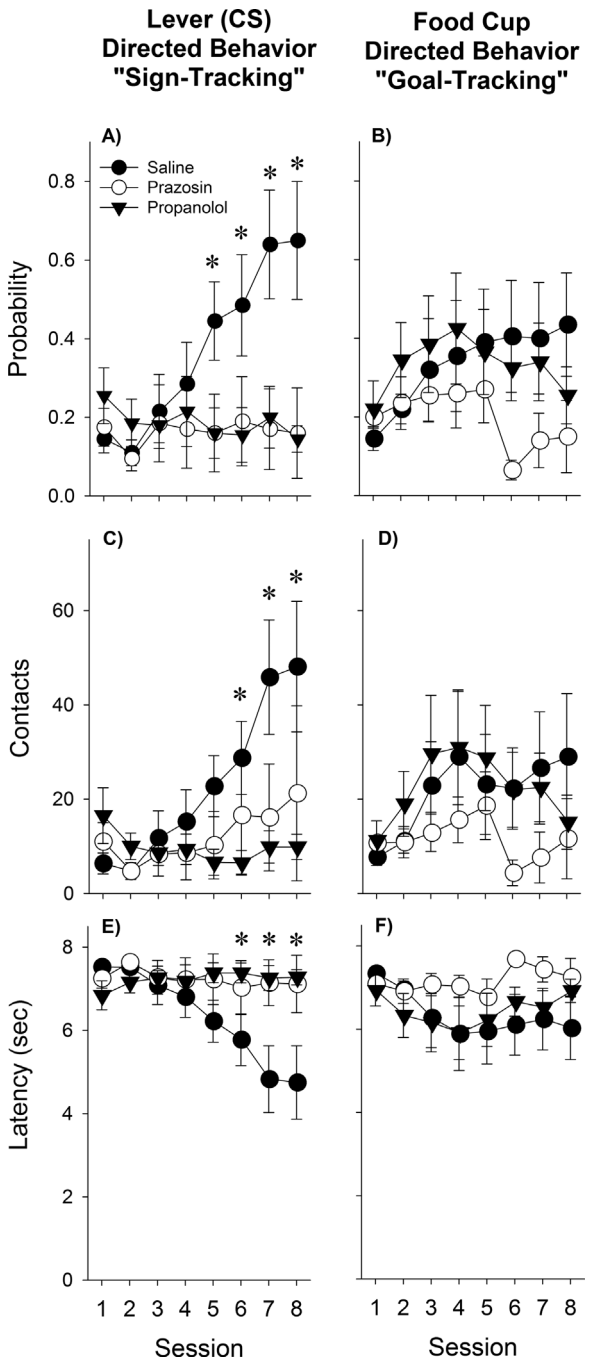

Fig. 6. Exp. 3. β-adrenergic receptor antagonist propranolol (10 mg/kg) and α-adrenergic receptor antagonist prazosin (3 mg/kg) blocked the development of sign-tracking without affecting goal-tracking. Data show mean (± SEM) of post-session administration on probability of approaching the lever (A) or food cup (B) during the CS period, number of lever deflections (C) or food cup entries (D), and latency to contact the lever (E) or make a food cup entry (F) during the CS period, over 5 days of Pavlovian training; $n = 8$ for all groups, asterisks reflect significant differences between saline- and drug-treated groups ($p < 0.05$).

adrenergic system on the attribution of incentive salience to reward cues during Pavlovian reward paradigms. For example, increases in NE in the PFC only when a food reward was paired (but not unpaired) with a lever cue suggests a relation to the sign-tracking responses observed during the study [1]. Supporting this, Milton et al. [31] showed that β-adrenergic receptor blockade disrupted the conditioned reinforcing properties of food- and drug-paired cues. Ventura et al. [50,51] showed that NE signaling was required for approach or avoidance responses to food- and aversive stimuli during place conditioning, but only when the salience of the unconditioned stimulus was sufficiently high [52]. This is consistent with the present findings, in that NE blockade only inhibited sign-tracking, which is associated with incentive salience attribution to reward cues.

The abovementioned studies also suggest that NE may exert its effects on incentive salience attribution via its actions within the PFC, and other studies suggest that this may involve the cholinergic system. For example, sign-trackers exhibit lower PFC acetylcholine levels during an attention-based task [53], and basal forebrain projections to the PFC are involved in the response to contextual drug cues in goal-trackers [54]. Further, nicotine increases the sign-tracking response to food cues, although it is not known if this involves activation of cholinergic input into the PFC. Given other studies showing that the PFC is involved in salience attribution and cue-guided behaviors [55], it may be that NE interacts with cholinergic inputs into the PFC in a way that heightens responsivity to incentive cues during PavCA at the expense of other cues in other tasks such as the sustained attention task [53].

4.2. Adrenergic modulation of incentive memory consolidation

These findings suggest that the noradrenergic system is responsible for the consolidation of incentive salience attribution to cues (as measured by sign-tracking), but not for reward learning in general (as measured by goal-tracking). However, Zhang et al. [56] have reported that, whereas cues initially acquire incentive salience as a result of learning processes, this incentive salience is dynamic in that it is sensitive to changes in motivational and physiological states without additional learning. While we do not dispute that this is a key feature of incentive salience (as measured by sign-tracking), our data suggest that the effects of NE manipulation are not due to dynamic changes in the cue's incentive salience for two reasons. First, when DSF was removed on day 6 in Experiment 1, the response to the cue on the first trial was still reduced. Given that rats were in a drug-free state during this test, an alteration of motivational or physiological state is unlikely. Instead, animals showed a similar rate of learning as naïve rats (Fig. 2), suggesting that sign-tracking acquisition had been blocked. Second, for Experiment 3, the drugs were given after the session, and thus testing occurred in a drug-free state. Therefore, the reduction in sign-tracking was unlikely due to a dynamic reduction in incentive salience. Instead, studies on the role of NE in the formation of fear memories have indicated that learned associations must be stabilized to become long-term memories. During this stabilization phase, which lasts for several hours, the memory trace is 'labile', i.e. vulnerable to pharmacological or procedural interference [57–60]. Our data indicate that prazosin and propranolol disrupt incentive salience attribution similarly by disrupting consolidation, because post-session injections of these drug prevented the acquisition of sign-tracking but not goal-tracking. As a result, we conclude that the most parsimonious explanation for the effect of these drugs is a disruption of the consolidation of incentive salience attribution.

4.3. Limitations and conclusions

A limitation of this study is that noradrenergic manipulations may have altered the microstructure of the approach, rather than altering the approach *per se*. For example, during omission studies, in which the US is omitted if the subject contacts the CS, subjects will still approach the CS without engaging with it directly [61]. While we do not have video recordings of the rats to assess this directly, results from the saline substitution tests indicate that subjects learn to approach and interact with the CS as if learning was occurring anew (Fig. 4). If the subjects had learned different conditioned approach response that did not involve contact with the CS, then the relearning of a new conditioned response that involved interaction with the CS might be expected to occur at a slower rate. Further, we have found that DSF injections do not affect the expression of an already learned sign-tracking response

(not shown). These things noted, we cannot definitively rule out an alteration of the topography of the conditioned response by noradrenergic manipulation.

Studies examining fear- and drug-related memories suggest that associations, once formed and consolidated, can be reactivated and are subject to reconsolidation [31,62–64]. It remains to be determined whether the reconsolidation of sign-tracking could be interfered with by adrenergic antagonists. For example, a single dose of propranolol in rats that had already learned to sign-track may attenuate the response during the following session. However, the overlap between the mechanisms of consolidation and reconsolidation is only partial [e.g. 65], and thus reconsolidation of sign-tracking may involve mechanisms distinct from the NE system. Yet, given that the reconsolidation of drug memories appears to involve the noradrenergic system [see 34 for review], there may be translational uses for pharmacological agents that specifically target the reconsolidation of incentive salience attributed to reward cues. Such pharmacotherapies could have potential use for treating cue-controlled disorders such as obesity, alcoholism, drug addiction, obsessive-compulsive disorder, and gambling in a similar way as these drugs have been used to treat disorders associated with traumatic memories such as post-traumatic stress disorder [39,66].

Acknowledgements

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