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# Differential effects of acute and prolonged morphine withdrawal on motivational and goal-directed control over reward-seeking behaviour

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## Abstract

Opioid addiction is a relapsing disorder marked by uncontrolled drug use and reduced interest in normally rewarding activities. The current study investigated the impact of spontaneous withdrawal from chronic morphine exposure on emotional, motivational and cognitive processes involved in regulating the pursuit and consumption of food rewards in male rats. In Experiment 1, rats experiencing acute morphine withdrawal lost weight and displayed somatic signs of drug dependence. However, hedonically driven sucrose consumption was significantly elevated, suggesting intact and potentially heightened reward processing. In Experiment 2, rats undergoing acute morphine withdrawal displayed reduced motivation when performing an effortful response for palatable food reward. Subsequent reward devaluation testing revealed that acute withdrawal disrupted their ability to exert flexible goal-directed control over reward seeking. Specifically, morphine-withdrawn rats were impaired in using current reward value to select actions both when relying on prior action-outcome learning and when given direct feedback about the consequences of their actions. In Experiment 3, rats tested after prolonged morphine withdrawal displayed heightened rather than diminished motivation for food rewards and retained their ability to engage in flexible goal-directed action selection. However, brief re-exposure to morphine was sufficient to impair motivation and disrupt goal-directed action selection, though in this case, rats were only impaired in using reward value to select actions in the presence of morphine-paired context cues and in the absence of response-contingent feedback. We suggest that these opioid-withdrawal induced deficits in motivation and goal-directed control may contribute to addiction by interfering with the pursuit of adaptive alternatives to drug use.

## KEYWORDS

goal-directed, habit, incentive, opiate, reward, sensitization, withdrawal

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## 1 | INTRODUCTION

Opioid addiction is a major public health crisis with devastating costs for individuals, communities and society at large. A defining characteristic of opioid addiction is *goal-narrowing*, which involves the excessive and uncontrolled urge to use drugs<sup>1</sup> as well as reduced interest in alternative, non-drug rewards.<sup>2,3</sup> This loss of adaptive goal-directed behaviour is multifaceted, comprising distinct emotional, motivational and cognitive components<sup>4</sup> and is positively correlated with withdrawal symptoms and craving in abstinent opioid users.<sup>5,6</sup> Cognitive impairments associated with opioid use tend to persist into drug abstinence and are often exacerbated during early withdrawal.<sup>7-9</sup> However, even after prolonged drug abstinence, exposure to opioid-related cues can trigger cognitive dysfunction<sup>10</sup> and induce a disruptive attentional bias that is associated with eventual relapse.<sup>11,12</sup>

Endogenous opioid systems are important regulators of feeding and food-motivated behaviour<sup>13</sup> and are persistently altered by chronic opioid exposure.<sup>14</sup> However, it remains unclear precisely how chronic opioid exposure and withdrawal impact the way food rewards are valued and pursued. For instance, animals with a history of opioid exposure display either diminished<sup>15-17</sup> or heightened<sup>18-22</sup> palatable food reward seeking and consumption, depending on study parameters such as withdrawal interval. Specifically, feeding and food motivation tend to be depressed during the first few days of opioid withdrawal but recover and may even become elevated after more prolonged withdrawal.<sup>23-26</sup> Opioid withdrawal may also impact certain feeding processes differently than others. For instance, studies focusing on hedonic-emotional measures of feeding have typically found either no change or increased responsivity in animals undergoing opioid withdrawal,<sup>21,27</sup> whereas homeostatic feeding tends to be suppressed.<sup>23-25</sup>

Repeated opioid exposure can also disrupt various aspects of action selection including simple visual discrimination learning<sup>28</sup> as well as more complex neuroeconomic processes such as discounting delayed rewards<sup>24,29</sup> and correcting 'snap' decisions.<sup>30</sup> However, whether or how chronic opioid exposure specifically impacts the goal-directed processes that support flexible decision making based on expected behavioural outcomes has yet to be studied. This cognitive capacity for goal-directed control can be readily assayed using the reward devaluation task,<sup>31</sup> which requires animals to evaluate the *current* value of potential outcomes using previously learned action-outcome relationships. It has been proposed that this capacity for adaptive goal-directed control breaks down in drug addiction,<sup>2,32-34</sup> such that drug pursuit becomes disconnected from the many adverse consequences of this behaviour. Such an impairment may also *indirectly* contribute to goal-narrowing in addiction by disrupting the processes through which alternative non-drug goals are evaluated and flexibly pursued.

Although there is a specific gap in knowledge regarding the effects of chronic opioid exposure on goal-directed action selection, there have been multiple reports that repeated exposure to psychostimulant drugs can promote the development of devaluation-resistant instrumental performance.<sup>35-38</sup> However, such effects are strongly

influenced by the nature of the task and may reflect an accentuation of habit formation (i.e., stimulus-response learning) rather than a frank loss of goal-directed control.<sup>33,34</sup> When more complex two-option choice tasks are used to assay goal-directed choice under conditions that prevent habit formation, repeated drug treatments tend to have either little or no effect<sup>39-41</sup> or produce transient, context-dependent deficits in goal-directed behaviour.<sup>42-44</sup> For instance, rats have been shown to temporarily lose their ability to flexibly choose between actions following reward devaluation when tested in the presence of cues that signal alcohol,<sup>42</sup> methamphetamine<sup>44</sup> or ad lib access to alternative, highly palatable junk foods.<sup>43</sup> Such findings suggest that conditioning factors related to drugs or other affectively-charged stimuli can interfere with the expression of flexible, goal-directed behaviour.

The current study examined the impact of spontaneous withdrawal from chronic morphine exposure (10–30 mg/kg) on hedonic, motivational and cognitive processes supporting the pursuit and consumption of palatable food rewards in male rats. Experiment 1 characterized the behavioural signs of early acute morphine withdrawal (24–48 h) and examined how this impacted hedonic feeding behaviour. Experiments 2 and 3 examined motivational vigour and goal-directed control over instrumental food-seeking actions during early (Experiment 2) and late (Experiment 3) stages of morphine withdrawal. The influence of morphine-related contextual cues on goal-directed choice was also characterized. Our findings indicate that motivation and goal-directed action selection are both disrupted during early but not late morphine withdrawal. However, even after prolonged withdrawal, brief re-exposure to morphine was sufficient to reestablish a reduction in motivational vigour as well as a partial, context-dependent deficit in goal-directed choice.

## 2 | MATERIALS AND METHODS

### 2.1 | Subjects

Adult male (300–440 g) Long-Evans rats ( $N = 65$ ) were used as subjects. Ad lib food and water were provided except when rats were food-restricted for behavioural procedures (see below). All experimental procedures were approved by the UC Irvine Institutional Animal Care and Use Committee and conducted in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals.

### 2.2 | Apparatus

Operant behavioural procedures were conducted in identical operant chambers (ENV-007, Med Associates), each housed in a sound- and light-attenuated cubicle. Each chamber was equipped with two retractable levers positioned on each side of a food-delivery port. Separate cups within this port were used to deliver 0.1-ml infusions of 50% sweetened condensed milk (SCM) solution (Eagle Brand) via a

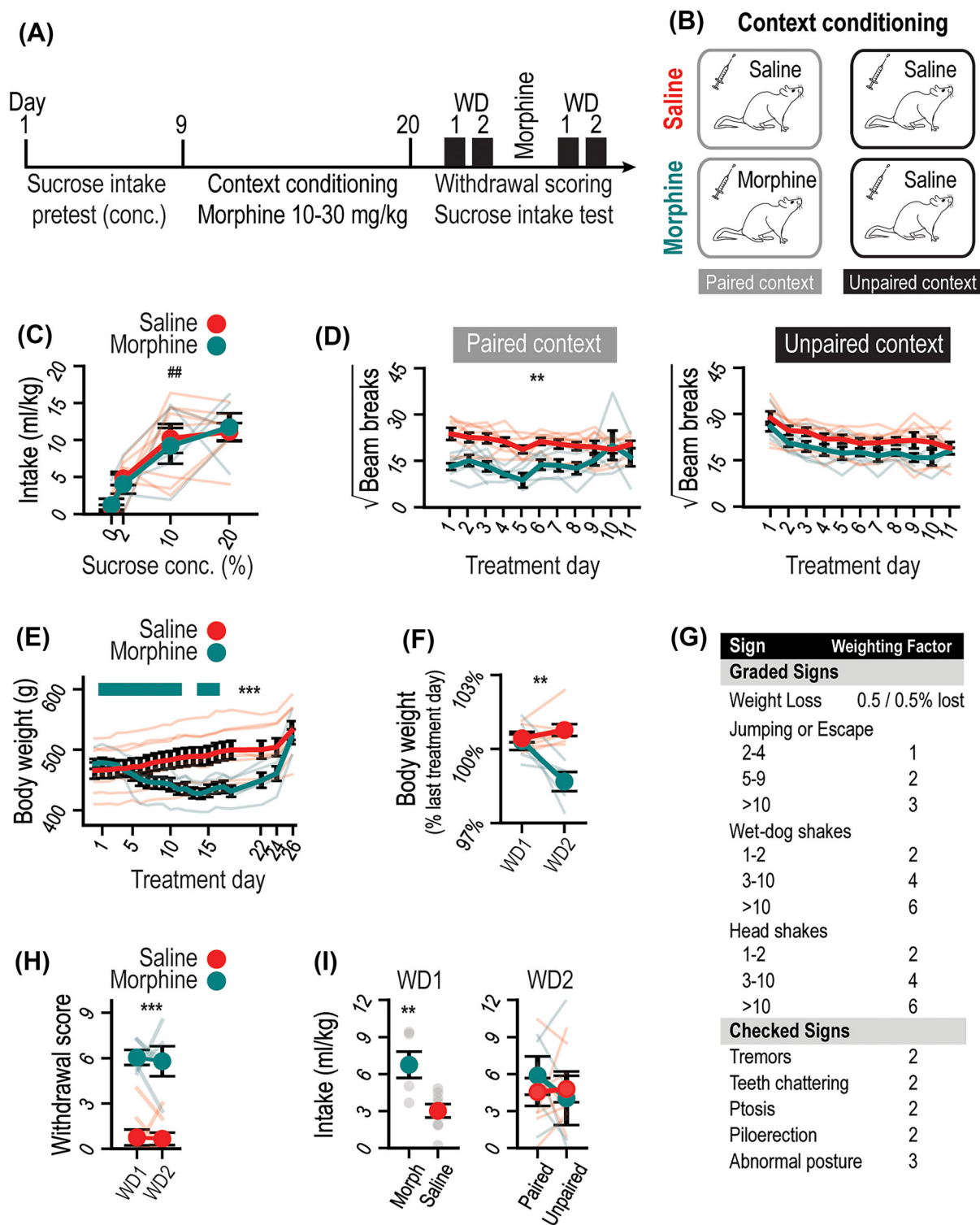


FIGURE 1 Legend on next page.

**FIGURE 1** Effects of morphine exposure on somatic withdrawal signs and hedonic feeding in rats (Experiment 1). (A) Schematic representation of behavioural testing during withdrawal from morphine ( $n = 5$ ) or saline ( $n = 8$ ) exposure in rats. Rats were tested for somatic signs and sucrose intake during withdrawal days (WDs) 1 and 2. (B) Schematic diagram illustrating context conditioning in rats from the morphine or saline groups. (C) Initial sucrose intake increases across a range of concentrations (conc.; ## main effect of concentration,  $p < 0.001$ ) during pretesting (i.e., before morphine exposure) but does not differ with planned exposure groups. (D) Locomotor activity is differently altered by morphine and saline treatments exposures in paired or unpaired contexts. It is initially reduced by morphine exposure (paired context; day X group  $**p = 0.002$ ). However, activity in the unpaired context is similar following morphine and saline exposure. (E) Morphine exposure induces significant weight loss that persists during withdrawal (group X day  $***p < 0.001$ ). Horizontal green mark shows morphine exposure days. (F) Discontinuation of morphine exposure elicits further weight loss, which is apparent on WD2 (% of last exposure day for WD1 and WD2; group X day<sup>2</sup>  $**p = .002$ ). (G) Graded and checked withdrawal signs and their corresponding weighing factors for withdrawal scoring. (H) Morphine exposure induces significant somatic withdrawal signs on WDs 1 and 2 (group  $***p < 0.001$ ). (I) Sucrose intake is significantly elevated in WD1 ( $**p = 0.007$ ). On WD2, there is no effect of drug exposure or test context

syringe pump located outside of the cubicle or 45-mg grain pellets (BioServ) via a pellet dispenser. A photobeam detector positioned across the food-port entrance was used to monitor head entries. Locomotor activity was monitored with four photobeams positioned in a horizontal plane  $\sim 2$  cm above the grid floor. A house light (3 W, 24 V) at the top of the opposite end-wall provided general illumination and a fan mounted on the cubicle provided ventilation and background noise. All experimental events were controlled and recorded with a 10-ms resolution using MED-PC IV software.

The above description refers to the bare chamber, which served at the *Training Context* during instrumental conditioning sessions. During drug administration sessions and behavioural test sessions, we added visual, tactile and olfactory cues to create two distinctive contexts. For *Context A*, panels with black-and-white vertical stripes were positioned outside the transparent sidewall and door, a PVC perforated sheet covered the grid floor and a paper towel scented with 0.4 ml of artificial vanilla extract (McCormick and Co. Inc.) was placed in the waste pan (below the grid floor). For *Context B*, white panels with black filled circles were placed outside the sidewall and door, the floor was covered with metal mesh sheet and a paper towel scented with 0.4 ml of artificial lemon extract (McCormick and Co. Inc.) was placed in the waste pan.

Sucrose licking procedures were conducted in a different set of identical operant chambers equipped with a retractable stainless steel 18-gauge gavage needle that served as a delivery spout. The tip of the spout was extended through an  $18 \times 12$  mm oval aperture during sucrose consumption sessions to provide unrestricted access. Sucrose licking responses were continuously recorded during consumption test sessions using a contact lickometer device (ENV-250B, Med Associates).

## 2.3 | Morphine treatment

Morphine sulfate provided by the NIDA Drug Supply Program was prepared daily in solution with 0.9% sterile saline. During initial morphine exposure (11 days; Figure 1A), rats were injected immediately before being placed in the behavioural chamber for 30 min. Rats were treated twice per day. Morphine groups (Figure 1B) were injected with saline each morning before being placed in the

*unpaired context (Context A or B)*. Each afternoon, these rats were injected with morphine and placed in the alternate, *paired context*. Morphine dose increased over days as follows: 10 mg/kg for 2 days, 20 mg/kg for 2 days, 25 mg/kg for 1 day and 30 mg/kg for the 6 last days.<sup>21–24</sup> This dosing regime was previously shown to induce signs of physical dependence and alter reward-seeking behaviours during withdrawal.<sup>24</sup> Saline groups received saline injections in both the morning (*unpaired context*) and afternoon (*paired context*). Given attrition due to morphine overdose, the *Ns* reported below refer to the number of rats that completed each experiment.

## 2.4 | Experiment 1

### 2.4.1 | Sucrose intake training

Ad lib fed rats were trained to consume 20% sucrose solution from a retractable metal drinking spout (5 days; 30 min each), before assessing the influence of sucrose concentrations (0%, 2%, 10% and 20%, randomized order). Our primary measure was bodyweight-normalized sucrose intake during the first 3 min of licking behaviour, as in Marshall et al.<sup>45</sup> and Halbout et al.,<sup>46</sup> which selectively assays hedonic feeding with minimal influence of satiety.<sup>47</sup>

### 2.4.2 | Morphine exposure

Rats in the morphine group ( $n = 5$ ) received one saline injection and one morphine injection each day, which were paired with distinct context cues. In contrast, a saline-only group ( $n = 8$ ) received two saline injections each day, which were also paired with the two distinct contexts.

### 2.4.3 | Sucrose intake during withdrawal

Within 24 h of the last injection (WD1), rats underwent morphine withdrawal assessment (see below) and followed by a 2% sucrose intake test in the training context. On the next day (WD2), rats

underwent the same procedures except that contexts A or B (paired or unpaired, counterbalanced) were added to chambers during sucrose intake testing. Rats were then re-exposed to morphine (15 mg/kg for 1 day and 30 mg/kg for 2 days) and/or saline using the context-treatment arrangements in place during initial drug exposure. Rats were tested in the bare chamber on WD1 and then in the alternate context on WD2, so that each rat was tested in both paired and unpaired contexts.

#### 2.4.4 | Morphine withdrawal assessment

Prior to each sucrose intake test (WD1 and WD2), rats were placed in a transparent plastic cylinder and continuously video recorded over a 30-min observation period. Trained observers blind to the treatment scored withdrawal signs<sup>48,49</sup> (weighting factors shown in Figure 1G). Withdrawal scores were averaged for each withdrawal interval (WD1 and WD2).

### 2.5 | Experiment 2

#### 2.5.1 | Instrumental training

Rats were food restricted and underwent instrumental training (as in Ostlund et al.<sup>42</sup> and Halbout et al.<sup>46</sup>) in the Training Context. Rats were given two daily sessions of magazine training, during which they received 15 grain pellets and 15 SCM infusions (0.1 ml) delivered in random order using a 90-s random time schedule with the levers retracted. They were then trained on two distinct instrumental action-outcome contingencies (e.g., left press → grain pellet and right press → 50% sweetened condensed milk, or vice versa) (Figure 2A,B). The left and right lever-press responses were trained in separate sessions each day, at least 60 min apart. Action-outcome contingencies were counterbalanced across subjects. Each session began with the insertion of the appropriate lever and ended after 30 min elapsed or 20 rewards were earned. Lever pressing was reinforced on a fixed ratio-1 (FR-1) schedule for 1 day. Rats were given additional FR-1 sessions, as needed, until they had earned at least 15 rewards with each response within a single session. Rats were then trained with increasingly effortful random ratio (RR) schedules, with 2 days of RR-5, 3 days of RR-10 and 3 days of RR-20.

#### 2.5.2 | Morphine exposure

After instrumental training, rats were returned to ad lib food access before receiving 11 days of both saline and morphine injections (morphine group:  $n = 9$ ) or saline-only injections ( $n = 10$ ), using distinct treatment-context pairing as described above. Rats were returned to food restriction on Day 10 of exposure and remained restricted for the rest of the experiment.

#### 2.5.3 | Devaluation tests

On WD1, rats were given instrumental retraining with both action-outcome contingencies. These retraining sessions (two sessions per day, one with each action) took place in the training context and were identical to the instrumental sessions described above, with the exception that the schedule of reinforcement shifted from FR-1 to RR-20 within the session (three rewards at FR-1, two rewards at RR-5, one reward at RR-10 and the remainder at RR-20). Retraining sessions lasted 30 min or until 20 rewards were earned. On WD2, rats were given a reward devaluation test, which began with given 60 min unrestricted access to grain pellets or SCM (counterbalanced with drug treatment and training contingencies) to induce outcome-specific satiety. Rats were then placed in the chamber with Context-A cues (either morphine-paired or unpaired, counterbalanced with drug, satiety and training conditions) (Figure 2F). Both levers were inserted after a 10-min exploration period. For the next 5 min (*Extinction Phase*), rats were able to freely press the left and right lever but received no food reinforcement/feedback. This was immediately followed by a 15-min period (*Reinforced Phase*), during which rats received feedback, as each action was reinforced with its respective outcome (FR-1 for the first five rewards, followed by a RR-20 for the remainder of the session). Rats were then re-exposed to morphine and/or saline (with the same context-treatment pairings; as in Experiment 1). They were then retrained on WD1 before undergoing a second round of reward devaluation testing on WD2, this time in the presence of Context-B cues.

### 2.6 | Experiment 3

#### 2.6.1 | Instrumental training

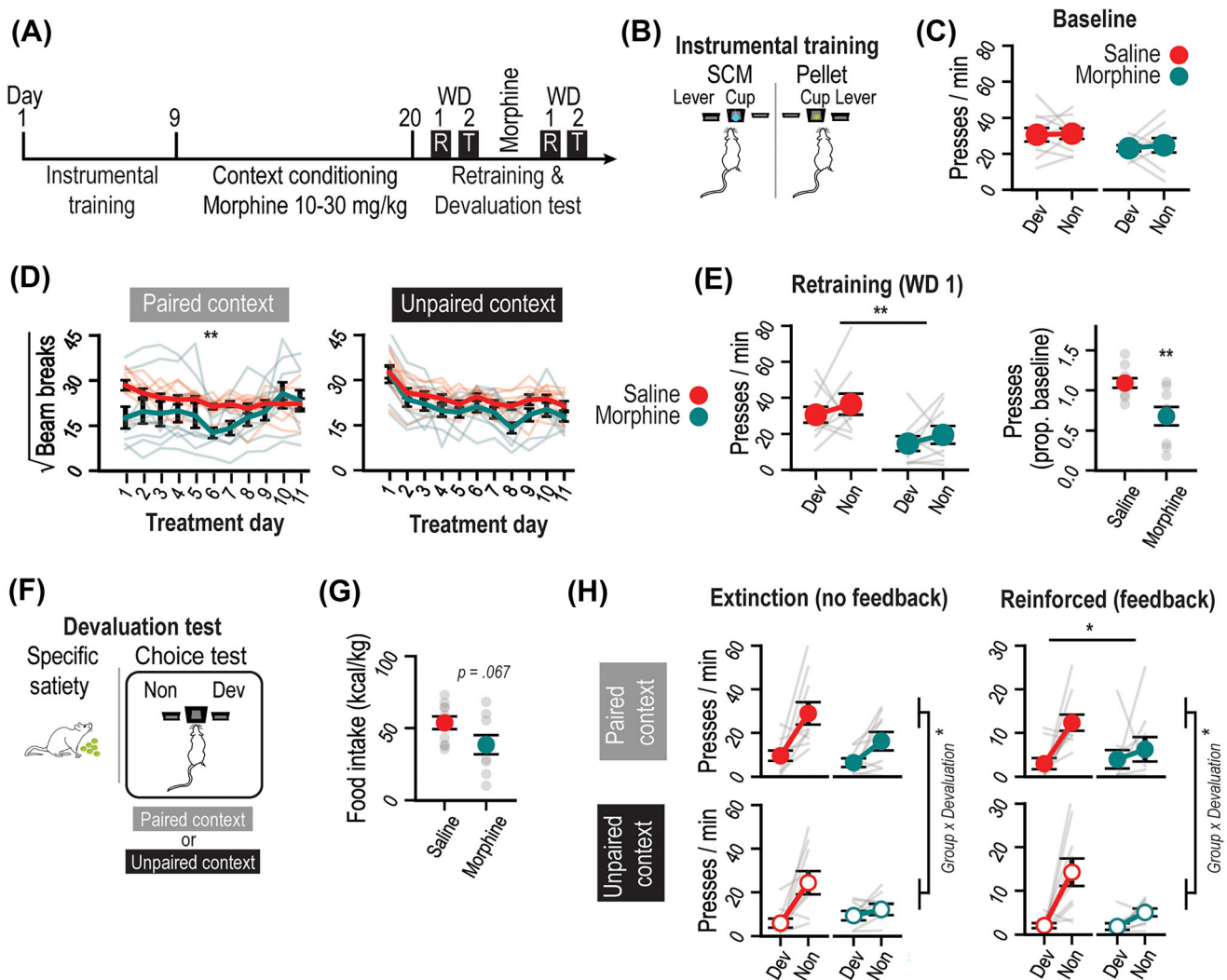
Rats were food-restricted and given instrumental training as described in Experiment 2. Ad libitum access to food was then provided following the last training sessions.

#### 2.6.2 | Initial morphine exposure

Rats were given 11 days of saline and morphine injections (morphine group:  $n = 13$ ) or saline-only injections ( $n = 13$ ) in distinct contexts. Rats were rested for the next 14 days before returning to food restriction.

#### 2.6.3 | Devaluation tests

Rats received instrumental retraining sessions in the training context during withdrawal Days 19–21, and a devaluation test in Context-A on WD22, as described in Experiment 2 (see Figure 3A). Rats were retrained before undergoing a second devaluation test on WD26 in Context-B.

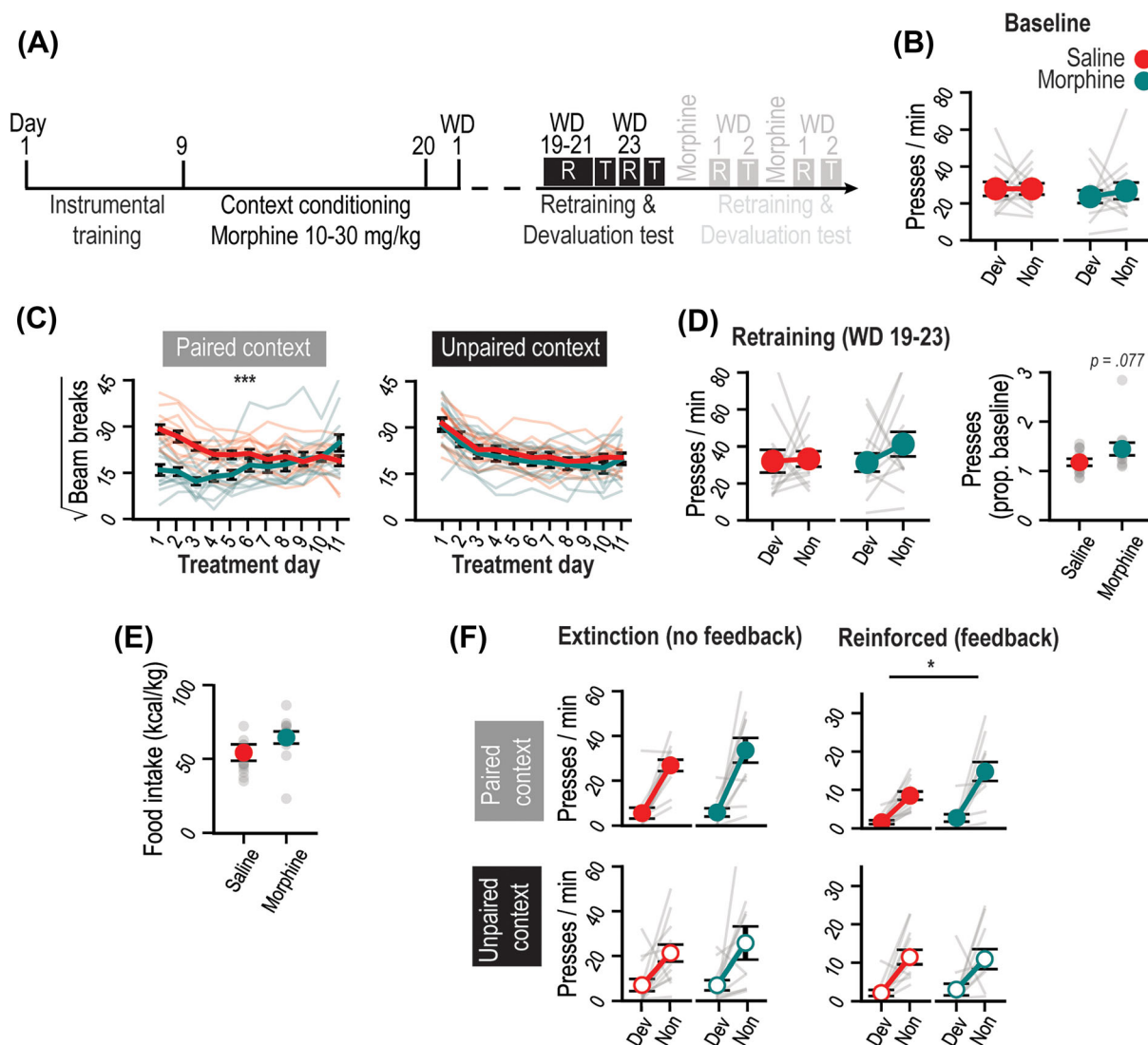


**FIGURE 2** Early morphine withdrawal impairs motivation and goal-directed control over instrumental behaviour in rats (Experiment 2). (A) Schematic representation of behavioural testing during early morphine withdrawal ( $n = 9$ ) or following saline exposure ( $n = 10$ ). Rats were assessed for motivation vigour during instrumental retraining on withdrawal day (WD) 1. On WD2, rats were given a reward devaluation test in either paired or unpaired contexts to assess their capacity for goal-directed control. (B) Schematic representation of instrumental training contingencies. (C) Baseline press rates during initial instrumental training did not differ between groups or planned devaluation treatment. (D) As in Experiment 1, locomotor activity is differently altered during morphine and saline exposures in paired or unpaired contexts. For paired context sessions, morphine-exposed rats displayed a suppression of activity that was less apparent over days (day  $\times$  group  $**p = 0.001$ ). The groups did not differ and showed similar rates of habituation of locomotor activity during unpaired context sessions. (E) Instrumental performance is reduced in morphine-exposed rats during instrumental retraining on WD1. Left, press rates are separated by group and by planned devaluation conditions, showing an overall decrease in press rate (group  $**p = 0.006$ ) but not as a function of planned devaluation treatment. Right, press rates were averaged across actions and plotted as a proportion of baseline performance ( $**p = 0.004$ ). (F) Schematic of the outcome-specific reward devaluation test. (G) Food intake during the prefeeding period (specific-satiety induction) was slightly reduced in morphine exposed rats ( $p = 0.067$ ). (H) Morphine-exposed rats show impaired sensitivity to reward devaluation in the extinction (left; group  $\times$  devaluation  $*p = 0.046$ ) and reinforced (right; group  $\times$  devaluation  $*p = 0.033$ ) phases of the test. During the reinforced phase, press rates were significantly lower in the morphine group ( $*p = 0.025$ ). Press rates during the test session are separated by devaluation (dev or non), group (morphine or saline), test phase (extinction and reinforced) and context (paired or unpaired). See the main text for detailed statistical analysis. Dev, devalued; Non, nondevalued; R, retraining; SCM, sweetened condensed milk; T, test.  $*p < 0.05$ ;  $**p < 0.01$

## 2.6.4 | Morphine re-exposure and devaluation tests

To assess the impact of acute withdrawal after brief morphine re-exposure on instrumental performance, rats were given 3 days of morphine exposure (15 mg/kg for 1 day and 30 mg/kg for 2 days) and saline (or saline only) using the original treatment-context pairings.

Rats then received 1 day of instrumental retraining in the training context on WD1, as in Experiment 2, followed by a devaluation test in Context-A on WD2. Rats were then re-exposed to morphine (30 mg/kg) and saline (or saline only) for 2 days and then retrained on WD1 before undergoing a final devaluation test in Context-B on WD2 ( $n = 13$ , saline-only group;  $n = 11$ , morphine group).



**FIGURE 3** Prolonged morphine withdrawal spares motivation and goal-directed control in rats (Experiment 3). (A) Schematic of behavioural testing during prolonged morphine withdrawal ( $n = 13$ ) or following saline exposure ( $n = 13$ ). Rats were assessed for motivation vigour during instrumental retraining on withdrawal days (WDs) 19–23. On WDs 22 and 24, rats were given a reward devaluation test in either paired or unpaired contexts to assess their capacity for goal-directed control. Rats were retested during early withdrawal following morphine re-exposure (see Figure 4). (B) Baseline press rates during initial instrumental training did not differ between groups. (C) Locomotor activity during morphine and saline exposures in paired or unpaired contexts. Morphine exposure influences locomotor activity, which varies across exposure days. For paired context sessions, morphine injections initially suppress locomotor activity (day  $\times$  group \*\*\* $p < 0.001$ ). Saline and morphine groups show a similar decline in activity over days in the unpaired context. (D) Instrumental performance during instrumental retraining on WDs 19–21 and 23. Left, press rates in rats separated by group and by planned devaluation conditions do not differ. Right, press rates averaged across actions and plotted as a proportion of baseline performance show a slight elevation in responding in the morphine group ( $p = 0.077$ ). (E) Food intake during the prefeeding period (specific-satiety induction) does not differ between groups. (F) Morphine-exposed rats show intact sensitivity to reward devaluation and elevated press rates during the reinforced phase of the test (\* $p = 0.041$ ). See THE main text for detailed statistical analysis. Press rates during the test session are separated by devaluation (dev or non), group (morphine or saline), test phase (extinction and reinforced) and context (paired or unpaired). Dev, devalued; non, nondevalued; R, retraining; T, test

## 2.7 | Data analysis

Data were analysed using mixed ANOVAs or unpaired tests, as appropriate, in SPSS(v29). Significance was set at  $p < 0.05$ . Significant interactions were followed by an analysis of lower order interactions or simple effects, as appropriate, to identify contributing factors. For sucrose consumption tests, we analysed bodyweight

normalized intake (ml/kg) using ANOVAs with the between-subjects factor group (morphine vs. saline) and within-subjects factors Concentration (0%, 2%, 10% and 20%) or context (paired and unpaired), as appropriate. For morphine/saline exposure sessions, locomotor activity (total photobeam breaks, square-root transformed to correct for excessive positive skewness) was analysed using Day  $\times$  Group  $\times$  Context ANOVAs. Bodyweight (g) was



analysed using a two-way ANOVA with group and day as factors. To further expose withdrawal-dependent changes in bodyweight, we analysed weight change as a percent difference from last treatment day using a Group X Day ANOVA. Withdrawal symptoms (composite weighted score) were analysed with a Group X Day ANOVA. Instrumental response rates (presses per minute) were analysed using an ANOVA with group, devaluation, and context as factors, as appropriate. Effect size estimates (partial  $\eta^2 = SS [\text{effect}]/SS (\text{effect}) + SS [\text{error}]$ ) are reported in Experiment 2 to highlight the significant difference in devaluation effect size across groups. To target the effect of withdrawal on instrumental performance, we computed the rate of lever pressing during the most recent (i.e., post-drug exposure) retraining sessions as a proportion of baseline (i.e., pre-drug) press rates during the last 3 days of instrumental training. For Experiment 3, press rates during the two instrumental training days during late withdrawal were used as baseline to assess the effect of early withdrawal following morphine re-exposure. For Figure 5, unpaired *t* tests were used to assess the effect of drug group on this measure. Consumption of SCM solution and grain pellets during specific-satiety was analysed as kcal/kg (calorie content- and bodyweight-normalized) using an unpaired test. We assessed overall and group-specific correlations (Pearson, two-tailed) between this consumption measure and sensitivity to devaluation (presses for devalued reward/[total presses for both devalued and nondevalued rewards]). A similar analysis was also performed to assess correlations between devaluation sensitivity and total response rate during devaluation tests. See Section 3 for further details.

### 3 | RESULTS

#### 3.1 | Early morphine withdrawal increases hedonic feeding

Experiment 1 investigated the effect of morphine withdrawal on hedonic sucrose intake (Figure 1A,B). Prior to drug exposure, we confirmed that initial sucrose intake was highly sensitive to sucrose palatability (concentration:  $F_{3,33} = 24.01, <0.001$ ) and did not differ across planned drug groups (concentration X group and group,  $F$ 's  $< 1$ ; Figure 1C). The morphine group then received repeated saline and morphine injections paired with distinct unpaired and paired contexts, respectively, whereas the saline group received saline in both contexts (see Figure 1A,B). Morphine, as opposed to saline treatment, suppressed locomotor activity in the paired context, particularly during early exposure sessions (day X context X group:  $F_{1,10} = 3.55, p < 0.001$ ; paired context: day X group:  $F_{10,110} = 3.05, p = 0.002$ ; Figure 1D). Activity in the unpaired context was similar in the morphine or saline exposed rats (group:  $F_{1,11} = 0.16$ ; day:  $F_{10,110} = 122.43, p < 0.001$ ; day X group:  $F_{10,110} < 1$ ). Rats lost weight during morphine exposure (day X group:  $F_{10,110} = 47.16, p < 0.001$ ; Figure 1E), which was exacerbated during early withdrawal (day X group:  $F_{1,11} = 16.41, p = 0.002$ ; Figure 1F). Bodyweights had return

to control levels by WD6 (Day 26 in Figure 1E;  $t_{11} = 0.46, p = 0.65$ ). Morphine-treated rats also showed increased somatic withdrawal signs (Figure 1G for details) on WD1 and WD2 (group:  $F_{1,11} = 70.07, p < 0.001$ ; day and day X group:  $F$ 's  $< 1$ ; Figure 1H). Initial sucrose intake on WD1 was significantly elevated in the morphine group ( $t_{11} = 3.30, p = 0.007$ ; Figure 1I, left). On the following day (WD2), we assessed the influence of drug context on sucrose intake but found no group or context effect or interaction between these factors ( $F$ 's  $< 1$ ; Figure 1I, right).

#### 3.2 | Motivation and goal-directed control are impaired during early morphine withdrawal

Experiment 2 investigated the effect of morphine withdrawal on instrumental responding for palatable food rewards (Figure 2A,B). Baseline press rates at the end of training did not significantly differ across planned groups ( $F_{1,17} = 3.26, p = 0.089$ ) or planned devaluation conditions (devaluation and devaluation X group,  $F$ 's  $< 1$ ; Figure 2C). Rats were then exposed to morphine and/or saline as in Experiment 1, again leading to locomotor suppression after early morphine injections (day X context X group:  $F_{10,170} = 4.58, p < 0.001$ ; day X group for paired sessions:  $F_{10,170} = 3.12, p = 0.001$ ; Figure 2D). The groups did not differ in their locomotor activity during unpaired context sessions (group:  $F_{1,17} = 3.19, p = 0.09$ ; day:  $F_{10,170} = 20.75, p < 0.001$ ; day X group:  $F_{10,170} = 1.024, p < 0.43$ ).

Rats were then administered a pair of reward devaluation tests to assess rats' ability to select instrumental actions in a flexible, goal-directed manner (Figure 2A). Brief morphine re-exposure was provided between tests to keep the withdrawal interval fixed, such that both tests (one in paired and one in unpaired context) were conducted on WD2. Rats received instrumental retraining on WD1 to assess their motivation to work when both food rewards were highly valued. Retraining press rates were generally depressed in the morphine group ( $F_{1,17} = 9.78, p = 0.006$ ; Figure 2E left), which was also apparent after normalizing for individual differences in baseline performance ( $t_{17} = 3.32, p = 0.004$ ; Figure 2E right). There was no difference in press rates as a function of planned devaluation treatment (devaluation:  $F_{1,17} = 1.40, p = 0.25$ ; devaluation X group:  $F < 1$ ).

Prior to testing, rats were fed to satiety on one of the two food rewards (Figure 2F). The morphine group consumed marginally less food ( $t_{17} = 1.96, p = 0.067$ ; Figure 2G; see Section 3.3.1 for discussion). The test began with an *extinction* phase, allowing us to probe rats' ability to flexibly choose between actions based on *expected outcomes* (Figure 2H; left). Rats selectively reduced their rate of responding for the devalued reward (devaluation:  $F_{1,17} = 18.56, p < 0.001$ ), an effect that varied with group (group X devaluation:  $F_{1,17} = 4.64, p = 0.046$ ) but not context (other  $F$ 's  $\leq 1.37$ ;  $p$ 's  $\geq 0.26$ ). While both groups displayed a devaluation effect, this effect was larger (group X devaluation: partial  $\eta^2 = 0.214$ ) for the saline group ( $F_{1,9} = 14.20, p = 0.004$ ; partial  $\eta^2 = 0.612$ ) than for the morphine group ( $F_{1,8} = 5.82, p = 0.042$ ; partial  $\eta^2 = 0.421$ ). Relative to controls, the morphine group showed a significantly lower rate of responding for

the nondevalued ( $F_{1,17} = 5.0$ ,  $p = 0.039$ ) but not for the devalued reward ( $F < 1$ ).

In the *reinforced* test phase (Figure 2H, right), which allowed us to assess the rats' ability to use *experienced outcomes* to modify their behaviour, overall press rates were significantly lower in the morphine group ( $F_{1,17} = 6.04$ ,  $p = 0.025$ ). The morphine group also showed continued insensitivity to reward devaluation (devaluation X group:  $F_{1,17} = 5.37$ ,  $p = 0.033$ ; partial  $\eta^2 = 0.24$ ; devaluation effect in saline group:  $F_{1,9} = 17.18$ ,  $p = 0.003$ ; devaluation effect in morphine group:  $F_{1,8} = 1.54$ ,  $p = 0.25$ ) despite receiving feedback about current reward values (other  $F$ 's  $\leq 1.40$ ;  $p$ 's  $\geq 0.25$ ). Relative to controls, the morphine group responded at a lower rate for the nondevalued ( $F_{1,17} = 7.03$ ,  $p = 0.017$ ) but not the devalued ( $F < 1$ ) reward. Altogether, findings from Experiment 2 indicate that acute morphine withdrawal induces a motivational deficit and specifically impairs flexible, goal-directed behaviour.

### 3.3 | Motivation and goal-directed control are restored after protracted morphine withdrawal but impaired again after brief morphine re-exposure

Experiment 3 investigated motivation and goal-directed control after protracted morphine withdrawal. Rats in this experiment trained as in Experiment 2. Baseline response rates (Figure 3B) did not differ across planned drug or devaluation conditions ( $F$ 's  $< 1$ ). Rats then received daily morphine and/or saline exposure as in Experiments 1 and 2, resulting in locomotor suppression following early morphine exposure (day X context X group:  $F_{10,240} = 9.91$ ,  $p < 0.001$ ; day X group for paired sessions:  $F_{10,240} = 17.03$ ,  $p < 0.001$ ; Figure 3C). The groups did not differ in their locomotor activity during unpaired context sessions (day:  $F_{10,240} = 43.55$ ,  $p < 0.001$ ; group and day X group:  $F$ 's  $< 1$ ).

After protracted morphine withdrawal (WD19–23), rats received instrumental retraining (see Figure 3A). Press rates did not significantly vary across groups or planned devaluation conditions ( $F$ 's  $< 1$ ), although the morphine group had marginally elevated responding after normalizing for baseline response rate ( $t_{24} = 1.85$ ,  $p = 0.077$ ; Figure 3D).

Pre-test food intake did not differ between groups ( $t_{24} = 1.48$ ,  $p = 0.15$ ; Figure 3E). During the *extinction test phase*, morphine and saline groups responded at similar levels ( $F < 1$ ; Figure 3F, left) and selectively withheld the action associated with the devalued reward to a similar degree ( $F_{1,24} = 36.61$ ,  $p < 0.001$ ). Although a context X devaluation interaction was detected ( $F_{1,24} = 4.73$ ,  $p = 0.04$ ), this effect did not vary with group (context X group X devaluation:  $F < 1$ ) and was thus not attributable to morphine expectancy ( $F$ 's  $< 1$  for all other effects and interactions).

Both groups remained sensitive to devaluation during the *reinforced test phase* (devaluation:  $F_{1,24} = 43.21$ ,  $p < 0.001$ ; devaluation X group:  $F_{1,24} = 1.72$ ,  $p = 0.20$ ; Figure 3F, right). Interestingly, the morphine group had generally higher rates of responding (Group:

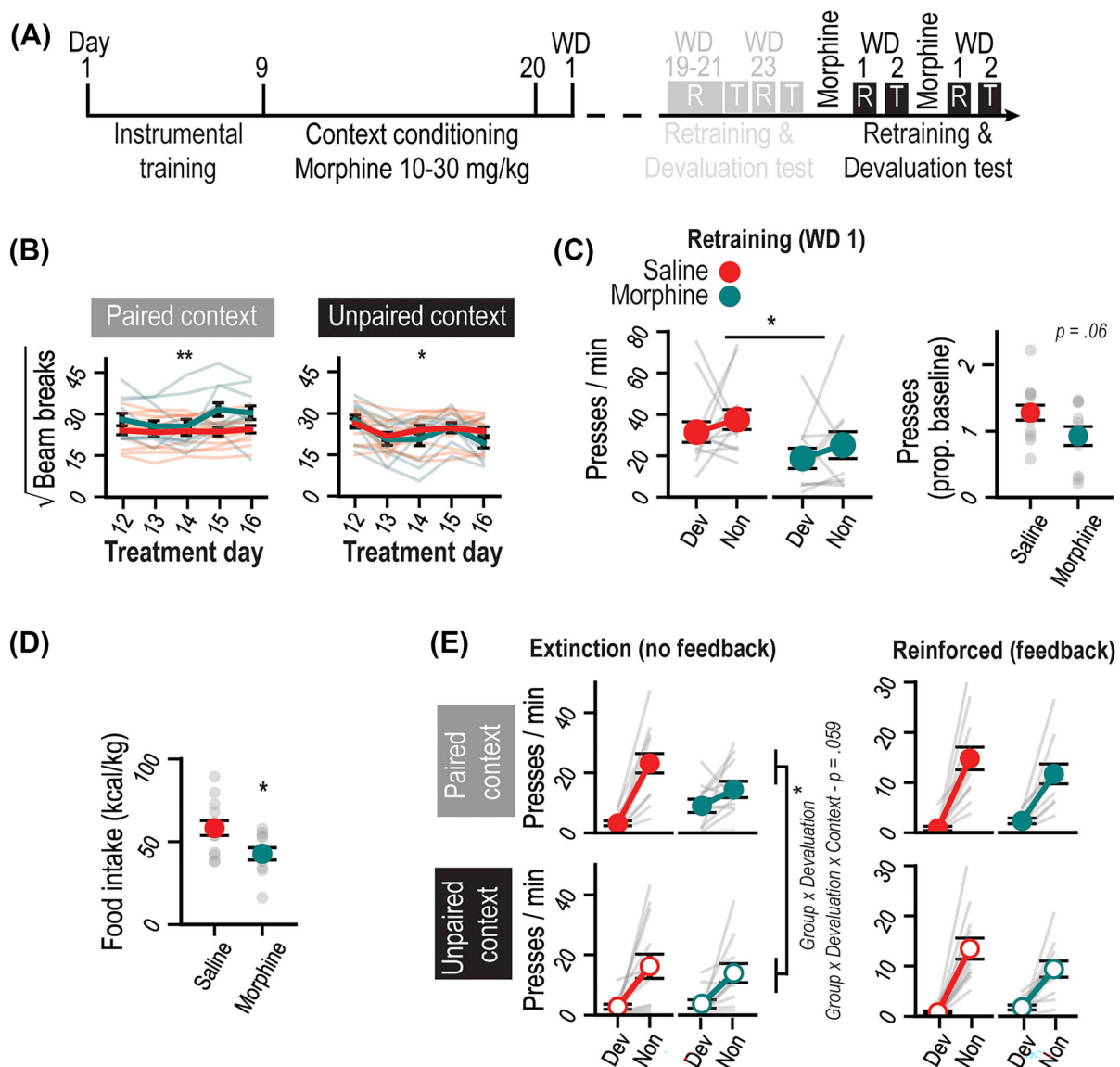
$F_{1,24} = 4.66$ ,  $p = .041$ ), which marginally interacted with test context ( $F_{1,24} = 3.68$ ,  $p = 0.067$ ; other  $F$ 's  $\leq 1.34$ ;  $p$ 's  $\geq 0.26$ ).

Rats were then briefly re-exposed to morphine (and/or saline) before undergoing retraining and devaluation testing in a state of acute withdrawal (see Figure 4A). During re-exposure, morphine now increased locomotor activity (group X day X context:  $F_{4,88} = 2.71$ ,  $p = 0.035$ ; group X day for paired sessions:  $F_{4,88} = 4.44$ ,  $p = 0.003$ ; group X day for unpaired sessions:  $F_{4,88} = 2.52$ ,  $p = 0.048$ ; Figure 4B). As in Experiment 2, retraining press rates during early morphine withdrawal (WD1) were generally suppressed (group:  $F_{1,22} = 5.16$ ;  $p = 0.032$ ) independently of planned devaluation conditions (other  $F$ 's  $\leq 1.50$ ;  $p$ 's  $\geq 0.23$ ; Figure 4C), though there was only a trend towards suppression when press rates were normalized to baseline rates ( $t_{22} = 1.96$ ,  $p = 0.06$ ; Figure 4C).

The morphine group consumed less food during the pre-feeding period ( $t_{22} = 2.61$ ,  $p = 0.016$ ; Figure 4D; see Section 3.3.1). During the *extinction phase* of the devaluation test (Figure 4E, left), the influence of reward devaluation over action selection was disrupted in the morphine group (devaluation X group:  $F_{1,22} = 5.20$ ,  $p = 0.032$ ). There was also a marginally significant interaction between devaluation X group X context ( $F_{1,22} = 3.97$ ,  $p = 0.059$ ). Both groups responded similarly in the unpaired context (devaluation:  $F_{1,22} = 19.45$ ,  $p < 0.001$ ; devaluation X group:  $F < 1$ ) but differed in their sensitivity to reward devaluation in the paired context (devaluation X group:  $F_{1,22} = 11.83$ ,  $p = 0.002$ ). Whereas the saline group displayed a selective devaluation effect in the paired context ( $F_{1,12} = 50.52$ ,  $p < 0.001$ ), the morphine group did not ( $F_{1,10} = 2.95$ ,  $p = 0.12$ ). Moreover, for the paired context test, the morphine group displayed a significantly higher response rate for the devalued reward ( $F_{1,22} = 6.78$ ,  $p = 0.016$ ) and a marginally lower response rate for the nondevalued reward ( $F_{1,22} = 4.04$ ,  $p = 0.057$ ), relative to the control group. In contrast, during the *reinforced* test phase (Figure 4E, right), there was a significant main effect of devaluation ( $F_{1,22} = 78.18$ ,  $p < 0.001$ ) that did not interact with group or context (other  $F$ 's  $\leq 1.50$ ;  $p$ 's  $\geq 0.23$ ). Thus, the impairment in goal-directed control observed after limited morphine re-exposure was not as widespread or persistent as the impairment observed early after chronic morphine exposure in Experiment 2.

### 3.4 | Alternative accounts of reduced sensitivity to reward devaluation during early withdrawal

Our findings indicate that acute morphine withdrawal disrupts rats' tendency to flexibly adjust their choice between actions based on current outcome value but also tends to generally suppress the vigour of instrumental performance, raising the possibility that a floor effect may have interfered with our ability to accurately measure their sensitivity to reward devaluation. Moreover, rats experiencing acute withdrawal also tended to consume less food during prefeeding sessions and therefore may not have been sufficiently satiated to selectively devalue the prefed food reward.



**FIGURE 4** Early withdrawal following morphine re-exposure impairs motivation and goal-directed control in rats (Experiment 3). (A) Schematic of behavioural testing following morphine ( $n = 11$ ) or saline re-exposure ( $n = 13$ ). (B) Locomotor activity during morphine and saline re-exposure. Saline or morphine exposures were given in the original paired or unpaired contexts. Morphine increased locomotor activity in an experience-dependent manner, which was more apparent in paired (day X group  $***p = 0.003$ ) than in unpaired sessions (day X group  $*p = 0.048$ ). (C) Instrumental performance was depressed in morphine-exposed rats during instrumental retraining on WD1 following morphine re-exposure. Left, press rates in rats are separated by group and by planned devaluation conditions. General suppression of lever press rate (group effect  $*p = 0.032$ ) is not dependent on planned devaluation conditions. Right, press rates were averaged across actions and plotted as a proportion of baseline performance showing a marginal suppression after morphine re-exposure ( $p = 0.06$ ). (D) Food intake during the prefeeding period (specific-satiety induction) is reduced in the morphine group ( $*p = 0.016$ ). (E) Morphine-exposed rats show a deficit in sensitivity to reward devaluation that was specific to the extinction phase of the test that was conducted in the paired context (devaluation X group  $*p = 0.032$  and devaluation X group X context  $p = 0.059$ ). See the main text for detailed statistical analysis. Press rates during the test session are separated by devaluation (dev or non), group (morphine or saline), test phase (extinction and reinforced) and context (paired or unpaired). Dev, devalued; non, nondevalued; R, retraining; T, test.  $*p < 0.05$

We performed some additional analyses to assess these alternative accounts. To maximize our statistical power, we pooled data from early withdrawal tests in Experiments 2 and 3. We focused our analysis on data from the extinction phase of reward devaluation tests since withdrawal-induced impairments were detected during this period in both experiments. Data from Experiment 2 were averaged

across test contexts since rats in this experiment showed a context-independent impairment. Given the context-specific effect observed in Experiment 3, data from this experiment were restricted to the test conducted in the morphine-paired context. From these data, we computed each rats' tendency to avoid choosing the action that had produced the devalued reward as a proportion of total actions performed

(devaluation score:  $\text{Dev}/[\text{Dev} + \text{Non}]$ ) and confirmed that morphine-withdrawn rats displayed a significant impairment in devaluation sensitivity on this measure (Group:  $t_{41} = 3.95$ ,  $p = 0.0003$ ; Figure 5A). We then assessed if this impairment was caused by a floor effect. According to this account, morphine withdrawal does not interfere with goal-directed action selection per se but instead induces a general suppression of responding at test that makes it difficult to measure any further action-specific response suppression related to reward devaluation. If this were the case, then impairments in goal-directed choice (devaluation score) should be restricted to rats showing low levels of responding at test (i.e., near the behavioural floor). However, this does not align with the data. Although morphine-withdrawn rats respond at a lower rate during retraining sessions (Figures 2E and 4C), their overall rate of responding (both actions) during devaluation tests was not significantly different from controls (unpaired  $t_{41} = 1.66$ ,  $p = 0.10$ ; Figure 5B). More importantly, inspection of individual differences in these measures reveals that withdrawal-induced impairments in goal-directed choice (i.e., devaluation scores approaching or exceeding indifference at 0.5) were not associated with low rates of responding at test (morphine group:  $r_{18} = 0.12$ ,  $p = 0.61$ ; saline group:  $r_{21} = 0.09$ ,  $p = 0.68$ ; all rats:  $r_{41} = -0.05$ ,  $p = 0.75$ ; Figure 5D). Thus, there is no indication that a floor effect interfered with assessment of the reward devaluation effect in morphine-withdrawn rats.

Likewise, our analysis of the individual differences indicates that reduced food intake during satiety induction was not responsible for the loss of sensitivity to reward devaluation during early morphine withdrawal. Although morphine-withdrawn rats consumed significantly less

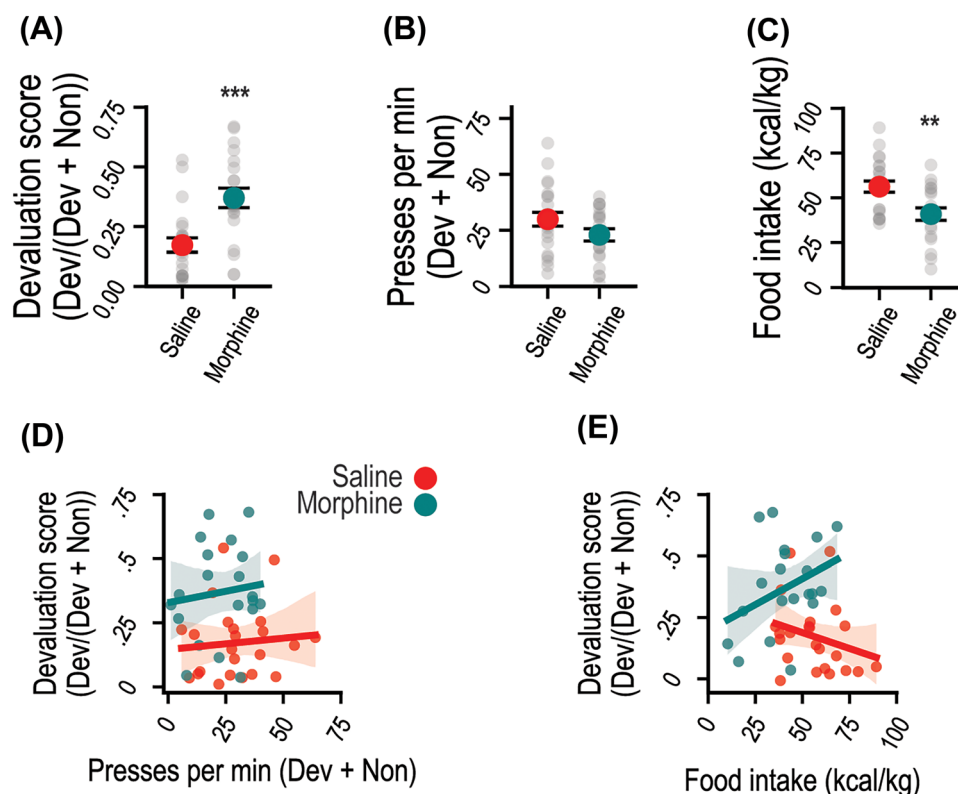
food prior to testing (Figure 5C;  $t_{41} = 3.29$ ,  $p = 0.0021$ ), there was no significant relationship in either group between pre-test food intake or sensitivity to reward devaluation (Figure 5E, morphine group:  $r_{18} = 0.36$ ,  $p = 0.12$ ; saline group:  $r_{21} = -0.27$ ,  $p = 0.21$ ; All rats:  $r_{41} = -0.19$ ,  $p = 0.22$ ). Indeed, careful inspection of these data indicates that withdrawal-induced deficits in reward devaluation sensitivity were if anything associated with high-levels of food consumption equivalent to that seen in the control group ( $>30$  kcal/kg).

These findings indicate that the loss of flexible, goal-directed control observed during acute morphine withdrawal is not a simple byproduct of a reduction in response rate or reward consumption. These alternative accounts are also difficult to reconcile with the limited deficit in goal-directed choice displayed by morphine-withdrawn rats in Experiment 3, which was restricted to the morphine-paired context and the extinction test phase, even though these rats showed more wide-ranging, context-independent deficits in instrumental performance and food intake. However, this does not preclude a link between the effects of morphine withdrawal on motivation and goal-directed choice under certain conditions, such as the generally low and non-selective pattern of lever pressing displayed by morphine-withdrawn rats during the reinforced phase of devaluation testing in Experiment 2 (Figure 2H).

## 4 | DISCUSSION

We investigated how morphine withdrawal impacts processes controlling the pursuit and consumption of palatable food rewards. Rats

**FIGURE 5** Individual differences in reward devaluation sensitivity do not vary with response rate or prefeeding levels. Data are combined from early withdrawal tests in Experiments 2 and 3 (see text for details). (A) Devaluation sensitivity is significantly impaired in the morphine group ( $***p < 0.001$ ). (B) Overall press rates during the extinction phase of the devaluation test do not significantly differ between morphine and saline groups. (C) Food intake during the prefeeding (specific satiety) period is significantly lower in the morphine group ( $**p < 0.01$ ). (D) Devaluation sensitivity does not correlate with response rate at test. (E) Devaluation sensitivity does not correlate with pre-test food intake. Dev, devalued; non, nondevalued



experiencing acute morphine withdrawal displayed elevated levels of hedonic feeding behaviour but showed reduced motivation and impaired goal-directed control over their food-seeking instrumental actions. These deficits were no longer apparent after prolonged morphine withdrawal but were at least partly reinstated following a brief period of morphine re-exposure. We believe these findings have important implications for understanding and studying goal-narrowing in opioid addiction.

A defining feature of addiction is that abruptly discontinuing drug use can trigger a so-called *motivational withdrawal syndrome*,<sup>3</sup> which is thought to involve a range of negative emotional changes (dysphoria, irritability and anxiety) and a loss of sensitivity to (anhedonia) and motivation for (amotivation) non-drug rewards. Our findings align with previous reports that motivation for palatable food rewards is attenuated during the early phase of opioid withdrawal.<sup>50–52</sup> Such effects are believed to be driven at least in part by reduced mesolimbic dopamine system function.<sup>3,14</sup> Although persistent motivational deficits have also been observed after more protracted periods of opioid withdrawal,<sup>15–17,53</sup> other findings suggest that motivational function recovers over time.<sup>51,52</sup> There have also been numerous reports of food-motivated behaviour becoming elevated during opioid withdrawal, particularly after long drug-free periods.<sup>18–20,22,50,51</sup> Such findings seem to align with the incentive-sensitization theory of addiction, which posits that repeated drug exposure can lead to a persistent increase in reward ‘wanting’ due to sensitizing adaptations in mesolimbic dopamine system.<sup>54</sup> Consistent with this, we found that after prolonged morphine withdrawal rats displayed a trend towards heightened motivation for food reward during instrumental retraining sessions and significantly enhanced motivation for food during the reinforced phase of the devaluation test. Such findings suggest that opioid withdrawal can trigger a biphasic pattern of motivational change in which an initial apathy-like motivational deficit is supplanted by a more persistent state of heightened incentive motivation. This interpretation is in line with reports that the mesolimbic dopamine system undergoes dynamic, bidirectional changes across early and late stages of opioid withdrawal.<sup>55,56</sup>

Our findings indicate that morphine withdrawal can have complex effects on feeding behaviour. Total food consumption during 1-h free-feeding sessions (prior to devaluation testing) was reduced during early but not protracted morphine withdrawal, which aligns with some earlier reports.<sup>23–26</sup> However, food intake during long-access periods such as these does not reliably measure hedonic feeding and is instead strongly influenced by homeostatic mechanisms (e.g., hunger/satiety) and appetitive motivation.<sup>47,57,58</sup> Experiment 1 therefore assessed rats' initial rate of sucrose intake (prior to satiety induction), an established measure of hedonic feeding.<sup>45–47,58</sup> We found that this aspect of feeding was significantly elevated rather than suppressed during acute morphine withdrawal. This finding is more in line with prior research showing unchanged or heightened hedonic responses to palatable food stimuli during morphine withdrawal.<sup>21,27</sup> This can be contrasted with reports that morphine withdrawal suppresses gross consumption of maintenance diet and tap water<sup>23–25</sup> and preferentially reduces intake of low- versus high-palatability sucrose

solutions.<sup>50</sup> We therefore suggest that hedonic food processing is not impaired and may be upregulated during acute morphine withdrawal, even when other factors (e.g., motivational deficit or increased satiety) may reduce total consumption. This combination of decreased homeostatic feeding and increased hedonic feeding may explain the generally poor nutrition and increased preference for sugary foods displayed by chronic opioid users.<sup>59–61</sup> Such findings also raise questions about whether opioid withdrawal induces a state of *true* anhedonia (i.e., a decrease in the experience of pleasure when consuming a reward stimulus) or whether other affective, motivational or even cognitive changes produce symptoms interpreted as anhedonia.<sup>62–64</sup>

To our knowledge, the current study is also the first to show that morphine withdrawal disrupts goal-directed action selection. Rats in early morphine withdrawal were impaired in flexibly adjusting their choice between actions following reward devaluation, regardless of whether they were tested in a morphine-paired or unpaired context. This impairment was observed both when rats were forced to rely solely on previously learned action-outcome associations to guide their choice (*extinction* test phase) as well as when they were given response-contingent feedback about the consequences of their actions (*reinforced* test phase). Given that normal (drug-naïve) rats will rapidly re-exert goal-directed control and suppress a habitual action when this behaviour actually produces a devalued reward, it has been argued that persistent responding for reward despite negative feedback reflects a profound loss of goal-directed control rather than a simple habit.<sup>33</sup>

A similar loss of flexible, goal-directed control during reinforced devaluation testing has been observed in rats with lesions of the dorsomedial striatum,<sup>65</sup> a key component of the brain's goal-directed behavioural control system<sup>66</sup> and in rats with a history of repeated cocaine<sup>37</sup> or methamphetamine<sup>44</sup> exposure. However, such impairments are more commonly observed in animals that have been trained on a simple one action-outcome training protocol that promotes habit formation. The more complex two action-outcome training protocol used here is known to support flexible, goal-directed control even after over-training.<sup>67–69</sup> Previous studies using this more complex task have found that rats' capacity to choose between actions based on reward value is not generally disrupted by prior methamphetamine,<sup>39</sup> cocaine<sup>41</sup> or amphetamine<sup>40</sup> exposure (though, as noted below, drug-context specific impairments have been reported<sup>42–44</sup>). Given these null results, the loss of flexible action selection in response to reward devaluation observed here during early morphine withdrawal is particularly notable and suggests a deficit in goal-directed choice and not an increase in normal habit formation or control.

However, this impairment was not permanent, in that rats tested after an extended withdrawal period displayed normal sensitivity to reward devaluation. This state was also associated with heightened rather than diminished motivation for food reward. Thus, the impairments in motivation and goal-directed control observed during early morphine withdrawal were relatively short-lived and not the result of long-term cognitive dysfunction, consistent with clinical findings that cognitive and executive deficits at least partially recover with extended opioid abstinence.<sup>7–9</sup> It is also notable that prior preclinical

research showing that repeated psychostimulant exposure does not impair flexible, goal-directed choice behaviour<sup>39–41</sup> has typically evaluated performance after at least 1 week of drug cessation. Thus, it remains to be determined whether goal-directed control is more markedly impaired during early than late psychostimulant withdrawal.

Importantly, we found that even after a protracted drug-free period, brief exposure to morphine was sufficient to reestablish an opioid-dependent state such that acute withdrawal once again impaired motivation and goal-directed control. However, in this case the deficit in devaluation sensitivity was restricted to the extinction test phase, suggesting a more limited loss of goal-directed control than the feedback-insensitive deficit observed after initial withdrawal from chronic morphine. This conclusion is also supported by the context-specificity of the deficit observed after brief morphine re-exposure, which was only apparent when rats were tested in the morphine-paired context. Although it remains unclear why morphine re-exposure produced a more modest and context-specific impairment in goal-directed control, it is important to note that these animals received only 2–3 days of morphine re-exposure prior to testing, which may not be sufficient to fully recapitulate the level of morphine dependence produced by the initial 11-day exposure period. We suggest that acute withdrawal from this initial morphine exposure may produce a more profound and wide-ranging impairment in goal-directed control that obscures the more subtle disruptive influence of morphine-paired cues. Indeed, similar context-specific deficits in goal-directed choice have been observed when rats are tested in the presence of cues that predict other salient stimuli including alcohol,<sup>42</sup> methamphetamine<sup>44</sup> or unrestricted access to highly-palatable junk foods.<sup>43</sup> Interestingly, in these prior reports, drug/food contexts disrupted choice behaviour for at least several weeks after the last drug/food-context pairings. Although we did not observe such a persistent deficit in the current study, this may relate to differences in study design (e.g., whether exposure occurred before or after instrumental training). Nevertheless, our findings together with these earlier results suggest that affectively charged environmental cues can perturb the cognitive processes responsible for goal-directed action selection. Such effects may be particularly relevant to understanding mechanisms of relapse, which is known to be strongly influenced by drug-related cues.<sup>70</sup>

There are some important caveats to the current study. First, since we exclusively used adult male rats as subjects, our findings do not address how factors such as sex and age influence the impact of opioid withdrawal on reward pursuit and consumption. Future research should address these questions, particularly given previous reports of sex-<sup>71–73</sup> and/or age-dependent<sup>74,75</sup> effects on other measures of morphine withdrawal. Another consideration is that withdrawal-induced alterations in food intake and motivation may have interfered with our ability to fully and accurately characterize the impact of withdrawal on goal-directed action selection. However, a more in-depth analysis of individual differences in these measures suggests this was not the case, at least when testing was conducted in extinction, without response-contingent feedback about behavioural consequences. Although morphine-withdrawn rats tended to

consume less than control rats during prefeeding sessions, variability in this measure was not associated with rats' ability to flexibly choose actions based on expected reward value in either group. Likewise, the loss of flexible, goal-directed control displayed by morphine-withdrawn rats was not likely caused by a simple floor effect, since deficits in value-based choice were not associated with low rates of responding at test.

Although the current study did not investigate the neural mechanisms underlying the behavioural effects of morphine withdrawal outlined above, it is known that repeated morphine exposure profoundly dysregulates endogenous opioid systems,<sup>14</sup> which are known to play critical roles in hedonic food evaluation, motivation and goal-directed action selection.<sup>13,62,76,77</sup> Importantly, acute morphine withdrawal triggers pronounced activation of the dynorphin-kappa opioid receptor (KOR) system,<sup>3,14,78</sup> which is notable given reports that KOR stimulation disrupts motivation<sup>79</sup> and cognition<sup>78</sup> but can promote hedonic reactivity to food stimuli.<sup>77</sup> However, chronic morphine exposure also leads to widespread changes in other neurochemical systems and neural circuits that are known to mediate food reward consumption and pursuit,<sup>3,14</sup> which may contribute to findings reported here. As noted earlier, a reduction in dopamine system function during early morphine withdrawal may contribute to the motivational deficit observed in this state without impinging on hedonic reward processing, given dopamine's well established role in reward 'wanting' but not 'liking'.<sup>57,62,63,80</sup>

We suggest that the deficits in motivation and goal-directed control reported here may contribute in important and potentially distinct ways to goal-narrowing in opioid addiction. For instance, a drop in motivation may reduce the amount of time and effort that one is willing to invest when pursuing goals, whereas a cognitive deficit impacting goal-directed control may instead prevent one from selecting and maintaining adaptive goals to pursue. These deficits may also interact in important ways. For instance, rather than inducing a global impairment in goal-directed control, opioid withdrawal may selectively reduce the cognitive resources allocated to pursuing non-drug goals based on their relatively low value versus the more highly valued goal of using opioid drugs. This interpretation is also compatible with a growing body of evidence that putatively compulsive drug-seeking behaviours may actually represent highly motivated and goal-directed actions rather than reflexive habits.<sup>81–83</sup> Future studies will be needed to refine our understanding of how these motivational and cognitive effects of opioid withdrawal interact and how they specifically contribute to the addiction cycle. Ultimately, identifying the unique motivational and cognitive needs of recovering addicts may be critical for developing more effective, patient-focused addiction therapies.

#### AUTHOR CONTRIBUTIONS

Briac Halbout and Sean B. Ostlund designed and conceptualized the study, performed the data analyses and wrote the manuscript. Stuti Agrawal, Collin Hutson, Briac Halbout and Zachary A. Springs carried out the experiments. All authors reviewed the content and approved the final version prior to submission.

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## CONFLICT OF INTEREST STATEMENT

The authors have nothing to disclose.

## DATA AVAILABILITY STATEMENT

All code and processed data used to generate figures and statistical analysis may be requested from the corresponding authors.

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