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Hierarchical cue control of cocaine seeking in the face of cost

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Abstract

Rationale: Addiction is characterized by intermittent drug seeking despite rising costs. This behavior is heavily influenced by environmental stimuli that signal drug availability and reinforce drug seeking.

Objective: To establish the relationship between three key aspects of human drug use in rats: the intermittent, binge nature of drug intake, the motivational conflict of drug seeking in the face of escalating negative costs, and the ability of different drug cues to interact to modulate relapse.

Methods: Male and female rats were trained to self-administer cocaine on an intermittent access schedule, where brief drug-availability states were signaled by a shift in the ambient lighting of the environment and cocaine infusions were signaled by a separate proximal discrete cue. Rats then went through a conflict procedure, where foot shock intensity associated with cocaine seeking was escalated until intake was suppressed. We then completed relapse tests where the drug-delivery cue was non contingently presented alone, or in the context of dynamic drug-availability state transitions.

Results: Intermittent access spurred psychomotor sensitization and binge-like cocaine intake. The intensity of binge-like drug taking during training was predictive of later drug seeking despite escalating costs during conflict. In relapse tests, the ability of a proximal discrete drug cue to trigger relapse was gated by the presence of a global cue signaling drug-availability state transitions.

Conclusions: Our results suggest that the pattern of drug intake plays a role in many features of addiction, including modifying an individual's willingness to endure high costs associated with drug seeking. Further, our studies indicate that drug-related sensory information can be hierarchically organized to exert a dynamic modulating influence on drug-seeking motivation.

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Author Contributions

VC and BS were responsible for experimental design. VC and KB conducted behavioral experiments. VC, KB, AW, and SS analyzed the data. VC, KB, and BS wrote the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

cocaine; addiction; intermittent access; conflict; rat; footshock; relapse; individual differences

INTRODUCTION

Addiction is characterized by intermittent drug seeking despite rising costs, with a persistent threat of relapse (Robinson and Berridge 1993; Shaham et al. 2003; Everitt and Robbins 2005; Poisson et al. 2021). This behavior is heavily influenced by environmental stimuli that signal drug availability and receipt of drugs to invigorate and reinforce drug seeking actions. Drug-related cues take on many forms, including proximal, discrete cues and broader global cues signaling drug-related contexts and transient states (Weiss et al. 2000; Chaudhri et al. 2008; Crombag et al. 2008; Fraser and Holland 2019).

A growing body of preclinical work has made use of intermittent access schedules that promote rapid spikes in brain drug levels, which drive exaggerated motivation and striatal plasticity that is important in animal models of addiction (Zimmer et al. 2012; Bentzley et al. 2013; Calipari et al. 2013; Kawa et al. 2019b; Allain and Samaha 2019; Carr et al. 2020; Samaha et al. 2021). Earlier studies demonstrated that the pharmacokinetics of drugs, rather than the absolute amount of a drug, powerfully determines their ability to engage brain reward systems and behavior (Budney et al. 1993; Cone 1995; Samaha et al. 2002, 2005; Allain et al. 2015; Kawa et al. 2019a; Canchy et al. 2021). Drug cues are centrally positioned to modulate drug seeking motivation and in turn, the pattern of drug intake. Notably, there are considerable individual differences in the extent to which drug-related sensory information motivates behavior (Flagel et al. 2009; Robinson et al. 2014). In human patients with substance use disorder (SUD), the interplay of drug access patterns, dynamic environmental stimuli, drug seeking costs, and individual vulnerabilities produces a difficult landscape for effective treatments (Mahler and de Wit 2010; Bertz et al. 2018; Venniro et al. 2020; Poisson et al. 2021).

Here, we explored the intersection of drug cues, cost, and individual differences in rats. We integrated behavioral tasks that capture three key features of addiction: 1) the volitional, intermittent, binge nature of drug use, 2) continued use despite escalating costs, and 3) the interaction of different levels of drug-related sensory information in the control of relapse. We used an intermittent access cocaine self-administration procedure that leads to escalating, rapid drug intake that more closely models human drug use compared to traditional continuous access models (Allain et al. 2015; Kawa et al. 2019a). Additionally, we used a conflict procedure to assess motivation to continue drug taking in the face of escalating foot shock (Cooper et al. 2007; Saunders et al. 2013). Lastly, we compared the effect of noncontingent presentations of global drug-availability cues and proximal drug-delivery cues to promote relapse.

Our results motivate three main conclusions. First, sensory information signaling drug availability can dynamically regulate drug seeking in part via hierarchical modulation of the motivational value of other drug-related cues. Second, rapid, intermittent cocaine intake patterns promote cost insensitivity in future drug seeking. Third, there are considerable

individual differences in the extent to which rats use state-level/global versus discrete/proximal drug cues to guide drug seeking, suggesting unique trajectories to relapse. Together, our results underscore that the complex set of variables, including individual decision-making strategies, hierarchically organized drug-associated stimuli, dynamic patterns of access to drugs, and the cost of drug seeking, interact to regulate drug seeking motivation and addiction-like behaviors.

METHODS AND MATERIALS

Subjects

All procedures were conducted in accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals and were approved by the University of Minnesota Institutional Animal Care and Use Committee. Intact male (~300–350g) and female (~250–300g) Long Evans rats (Envigo, Indianapolis, Indiana, USA) served as the subjects for these experiments (Intermittent Access and Conflict phases n=35 (male=20, female=15), Cue-induced Relapse phase n=25 (male=13, female=12), Intermittent Access for video analysis n=12 (male=6, female=6), Unpaired n=12 (male=7, female=5); 12 additional rats were excluded due to catheter failure). Rats were initially group housed and then single housed post-catheter surgery and handled a week prior to the onset of the experiment. Experimentation took place during the light phase of their 12:12h light:dark cycle. Free access to water and food chow was provided in their home cage.

Intravenous Catheter Surgery

Catheter back ports were purchased from Instech (Plymouth Meeting, PA, USA) and prepared with 0.51 mm inner/0.94 mm outer diameter silastic tubing at 11.5 cm length with a silicone ball at 2.5 cm length. Rats were anesthetized with ketamine hydrochloride (10mg/kg; i.p.) and xylazine (10mg/kg; i.p.). Intra-jugular catheter placement was conducted as described previously (Saunders and Robinson 2010; Saunders et al. 2014). Briefly, after securing the end of the indwelling tubing within the right jugular vein, the connecting port was secured on the back and protected with a fitted cap (Instech). Following surgery, catheters were flushed daily with 0.1 ml of Gentamicin sulfate (5mg/ml; Vedco, MO) to prevent infection and line blockage. Catheter patency was tested prior to and at the end of each experimental phase with 0.1 ml methohexital sodium (10mg/ml, i.v.). Only patent rats, determined by ataxic response 3–5 s post-injection, were included in the analyses.

Cocaine self-administration: Acquisition

One week after catheter surgery, rats learned to self-administer cocaine in three continuous-access sessions. Med Associates chambers were outfitted with two ports on the left side that served as the active and inactive nose ports (counterbalanced between subjects). A nose-poke into the active nose port resulted in an IV infusion of cocaine (0.4 mg/kg/infusion in 50 ul sterile saline, delivered over 3.2 s; Boynton Pharmacy, Minneapolis, MN) on a fixed-ratio (FR)1 schedule of reinforcement with a 20-s timeout period, during which nose-pokes had no consequence. Active nose-pokes also resulted in the illumination of the nose port and 75dB white noise for 20 s (**the drug-delivery cue**). Nose-pokes in the inactive nose port had no consequences. These sessions were conducted with the ambient lighting

in the chambers (house and box lights) turned off. Throughout cocaine self-administration, each rat had access to a cocaine solution calculated from their weight that resulted in the same 0.4 mg/kg dose based on a 3.2-s infusion. Weights were updated twice per week for consistent cocaine dosing.

We included an unpaired control group to examine the effects of cocaine exposure that was not the result of a specific action-outcome contingency. This was achieved by unpairing the action (nose-poke) from the outcome (cocaine infusion) and the Pavlovian relationship (drug-delivery cue and cocaine infusion). The rate, pattern and magnitude of cocaine infusions and cue deliveries was matched for sex and session to the average levels achieved by the paired self-administration cohort. For pretraining in unpaired rats (n=12), a 20-s cue consisting of illumination of a nose port light and white noise - akin to the drug-delivery cue in paired rats - was presented noncontingently throughout a 4-hour session on a variable interval schedule based on sex (average female ITI (minutes) days 1–3: 6.0, 7.1, 6.9; average male ITI (minutes) days 1–3: 7.7, 6.5, 7.3). Rats also received noncontingent cocaine infusions (0.4 mg/kg/infusion, 3.2 s) via an intravenous catheter throughout the session with the same variable interval schedule based on sex. The number of infusions and cue presentations were matched to the average from the paired group of that day based on sex (female days 1–3: 40, 34, 35; male days 1–3: 31, 37, 33). In this way, the cue was not associated with cocaine delivery, and nose-pokes did not earn cocaine.

Cocaine self-administration: Intermittent Access

After acquisition, rats went through 14 days of intermittent access similar to previous studies (Zimmer et al. 2012; Calipari et al. 2013; Kawa et al. 2019b). Within each 4-hour session, there were 5-minute periods wherein active nose-pokes resulted in a cocaine infusion (0.4 mg/kg/infusion, 3.2 s) that coincided with drug-delivery cue (3.2 s) on an FR1 schedule of reinforcement. In this case, the timeout period lasted only 3.2 s, coinciding with the duration of each infusion. These **drug-available periods** were signaled by the extinguishing of the ambient lighting in the chamber - the house and box lights - for the entire 5-minute period. Following the drug-available period, the house and box lights illuminated, signaling the 25-minute **no-drug period**, wherein active nose-pokes had no consequence. This pattern (5-minute drug-available and 25-minute no-drug periods) repeated 8 times for a 4-hour session.

For unpaired rats, within each session a 5-minute drug-exposure period (signaled by house lights off) was followed by a 25-minute no-drug period (lights on) which patterned 8 times throughout the session, as with paired rats. In the drug-exposure period, rats received noncontingent cocaine infusions (3.2 s, 0.4 mg/kg) on a variable interval schedule based on sex (average female ITI (minutes) days 1–14: 3.0, 2.6, 2.0, 2.2, 1.9, 1.9, 1.8, 1.7, 1.8, 1.9, 1.6, 1.5, 1.3, 1.5; average male ITI (minutes) days 1–14: 1.6, 1.5, 1.7, 1.4, 1.4, 1.2, 0.9, 1.4, 1.1, 1.4, 1.1, 1.3, 1.2, 1.1). Throughout the entire session, rats received noncontingent 3.2-s cue presentations on a variable interval schedule based on sex (average female ITI (minutes): 17.7, 15.3, 12.0, 12.9, 11.3, 11.7, 10.8, 10.3, 11.1, 11.6, 9.6, 9.2, 8.0, 9.0; average male ITI (minutes): 9.5, 9.2, 10.1, 8.2, 8.4, 7.2, 5.5, 8.1, 6.7, 8.2, 6.7, 7.7, 7.2, 6.7). The number of infusions and cue presentations they received was the average from the paired group of that

day based on sex (female days 1–14: 14, 16, 20, 19, 21, 21, 22, 23, 22, 21, 25, 26, 30, 27; male days 1–14: 25, 26, 24, 29, 29, 33, 44, 30, 36, 29, 36, 31, 33, 36). In this way, unpaired rats received cocaine infusions at the same average rate during the drug-exposure period across sessions, compared to those volitionally taken by paired rats.

Cocaine self-administration: Conflict

After 14 days of intermittent access rats underwent a conflict phase (Cooper et al. 2007; Saunders et al. 2013). For each 1-hour session, 2/3 of the grid floor in front of the nose ports within the chamber was continuously electrified at escalating levels of shock between sessions (0, 0.13, 0.16, 0.2, 0.25, 0.32, 0.4 mA). The back 1/3 of the grid floor was not electrified, allowing rats to avoid shock. Rats received increasing shock intensities on successive sessions until the number of cocaine infusions was reduced by at least 2/3 below baseline levels determined by the 0 shock-level session. The house and box lights were extinguished throughout the entire 1-hour session. An active nose-poke resulted in a cocaine infusion (0.4 mg/kg/infusion in 50 ul over 3.2 s) that coincided with the drug-delivery cue for 20 s during which additional active nose-pokes had no further consequence.

For unpaired rats shock was increased over 6 1-hour sessions (0, 0.1, 0.13, 0.16, 0.2, 0.25 mA). The number of sessions was determined by the average amplitude at which rats in the paired group suppressed drug seeking behavior, as defined by 2/3 reduction in nose pokes from a no shock baseline. Rats received noncontingent cocaine infusions unpaired from noncontingent cue presentations at a variable interval schedule based on sex (average female ITI (minutes) days 1–6: 3.2, 3.3, 3.0, 4.0, 5.0, 6.7; average male ITI (minutes) days 1–6: 4.0, 4.0, 4.3, 5.5, 7.5, 7.5). Number of cocaine infusions and cue presentations was the average from the paired group of that day based on sex (female days 1–6: 19, 18, 20, 15, 12, 9; male days 1–6: 15, 15, 14, 11, 8, 8).

Cue-induced drug seeking

Following 14 days of abstinence, rats underwent tests for cue-induced relapse to assess the influence of noncontingent cue presentations on drug-seeking in the face of cost. During these sessions, 2/3 of the grid floor was electrified at the shock intensity 50% to the level of each rat’s individual conflict suppression shock level. To assess drug-seeking motivation in absence of drug intoxication, no cocaine was delivered during these tests. In the **single-cue test**, the drug-delivery cue (illumination of the active nose port and 75 dB white house) was non-contingently presented for 20 s with a fixed 3-minute intertrial interval (ITI) for 1-hr. The house and box lights were extinguished throughout the entire single-cue test. For the **multiple-cue test,** (order of single and multiple was counterbalanced between subjects), the drug-availability state (extinguished house and box lights) was presented for 2 minutes on a fixed 8-minute ITI, in a 1-hour test session. Within each 2-minute availability period, the 20-s drug-delivery cue (illumination of the active nose port and 75 dB white noise) was presented twice (at 40 s and 100 s). Nose-pokes had no consequences. For relapse tests in unpaired rats, shock was set at 0.13 mA. Both cue tests were run twice in the unpaired group, once with the drug-delivery cue (nose port light and white noise) and once with a neutral cue (other nose port light and a low tone), to examine spontaneous responding.

Conditioned Reinforcement

To assess the reinforcing value of the drug-delivery cue, rats underwent a conditioned reinforcement test. During this 1-hour session, active nose-pokes resulted in a 3.2-s presentation of the drug-delivery cue but no cocaine infusion. Inactive nose-pokes did not result in any consequence. Box and house lights were extinguished during the entire session. Unpaired rats also underwent conditioned reinforcement, once with the drug-delivery cue (nose port light and white noise) and once with a neutral cue (other nose port light and a low tone).

Video scoring

Med Associates chambers were fitted with overhead cameras (Vanxse CCTV 960H 1000TVL HD Mini Spy Security Camera 2.8–12mm Varifocal Lens Indoor Surveillance Camera) for a top-down video recording of self-administration behavior. We quantified locomotor activity during intermittent access via visual examination of these videos, similar to previous studies (Carr et al. 2020). The chamber was divided into four equal quadrants and locomotor activity was determined by counting the number of crossovers, defined as when the animal's back port fully crossed a line dividing the quadrants. Behavior was quantified for 3 separate epochs: 5 minutes before (pre), 5 minutes during, and 5 minutes after (post) the drug-available period. This was done for sessions 1 and 10.

DeepLabCut-based pose tracking

Markerless tracking of animal body parts was conducted using the DeepLabCut (DLC) Toolbox (Mathis et al. 2018) and analysis of movement features based on these tracked coordinates was conducted in Matlab R2020b (Mathworks). All DLC analysis was conducted on a Dell G7–7590 laptop running Windows 10 with an Intel Core i7–9750H CPU, 2.60Ghz, 16 GB RAM, and an NVIDIA GeForce RTX 2080 Max-Q 8GB GPU. DeepLabCut 2.1.10 was installed in an Anaconda environment with Python 3.7.7 and Tensorflow 1.13.1. Videos (944 × 480 resolution) were recorded with a sampling frequency of 30 frames per second using a TIGERSECU Super HD 1080P 16-Channel DVR system.

DeepLabCut Model

A previous DLC network trained for 500,000 iterations on 1700 manually labeled frames extracted from 17 videos (16 different rats, 9 different recording sessions) was updated for the current study. An additional 370 frames from this experiment were extracted (25 frames each uniformly extracted from 14 videos of 12 different rats), and 20 manually extracted frames for additional examples where the animal was rearing. Body parts were manually labeled in all frames for the nose, eyes, ears, center of head, catheter port, and tail base. Features of the environment were also labeled manually, including the 4 corners of the apparatus floor and the nose ports.

Labeled frames were split into a training set (95% of frames) and a test set (5% of frames) and trained using the training set for 500,000 iterations. An additional 267 outlier frames were extracted from 7 videos over 2 iterations. For each iteration, the network was retrained from the default Resnet50 model for 1,030,000 iterations using a newly generated 95% train–test split. The model was evaluated by comparing the labels acquired from the trained

network on the training and test sets with the manual user labels. Evaluation gave an error of 2.74 and 3.52 pixels for the training and test sets. Using a p-cutoff of 0.85 error was reduced to 2.63 pixels for the training set and 3.08 pixels for the test set. This model was then used to analyze videos from 24 rats (12 paired and 12 unpaired) for two separate intermittent access sessions (session 1 and session 10). Data for session 1 were re-analyzed for 2 rats after a further iteration. Pixel errors for this iteration were 2.65 and 2.93 pixels for the training and test datasets, 2.55 for the training set and 2.88 for the test set with a p-cutoff of 0.85.

Data Analysis

Self-administration behavior: Nose-pokes and cocaine infusions were the primary behavioral output measures. Data were processed with Microsoft Excel (Richmond, WA). Statistical analyses were conducted with GraphPad Prism (La Jolla, CA). For all hypothesis tests, the α level for significance was set to $p<0.05$. Data were analyzed with mixed effects ANOVA, Pearson correlation, and linear regression. Post-hoc comparisons and planned t-tests were used to clarify main effects and interactions.

Video analysis: Hand-scored locomotion data: Chamber crossover data was analyzed in GraphPad Prism with an ANOVA or mixed effects analysis comparing epoch (5-minute bins), group (unpaired or paired), and session (1 or 10).

DeepLabCut data: DLC data were analyzed with MATLAB and GraphPad Prism. All data for four rats, two from each group (paired/unpaired) were excluded from analysis due to the commutator obscuring the view of the active nose port in the recorded video. The x,y coordinates of fixed environment features were averaged across all frames where the likelihood (confidence-interval) value was > 0.7. The coordinates of the corners of the apparatus floor were used to calculate a pixel to cm conversion for each animal and session. This was calculated by taking the average pixel-to-cm ratio of all 4 sides and the two 2 diagonal measurements of the floor. For instances where not all points were visible in the video frame, only the available measurements were included in the average.

Frames where likelihood values for the body part x,y coordinates were < 0.7 were removed from the data before further processing. For all measures except movement speed, missing data for periods of <1 s due to low confidence was replaced using a moving average between the bordering coordinates before subsequent analysis. Movement speed and distance traveled were calculated using the x,y coordinates of the Catheter port. Speed was calculated from frame to frame using the formula: distance (cm)/time (s). Movement speed for each epoch was smoothed with a moving mean average over a window of 0.1 s, using the MATLAB function smoothdata. Distance traveled was calculated as the distance between x,y coordinates from frame to frame and converted to cm using that animal's pixel-to-cm ratio. Data were analyzed for 3 separate epochs: 5 minutes before (pre), 5 minutes during, and 5 minutes after (post) the drug available period. We also analyzed a shorter time window from 20 s before to 60 s after the drug availability period onset with data binned in 10-s increments. Analysis windows where >40% of coordinate data was missing for the catheter port were considered invalid and the measures dependent on these coordinates were not included in the analysis.

RESULTS

Intermittent access produced binge-like drug taking invigorated by drug-availability state onset

Rats first learned to self-administer cocaine in 3 continuous access sessions with a fixed ratio (FR)1 schedule of reinforcement (Supplemental Figure 1B). By the final day of pre training, rats discriminated between the active and inactive nose ports (Supplemental Figure 1C; Multiple paired t-test, $t_{(32)}$=p<0.0001). Males and females used similar amounts of cocaine throughout this pretraining (Supplemental Figure 3A; 2-way ANOVA, main effect of sex $F_{(5,97)}$=1.929, p=0.0964). Rats then underwent 14 days of intermittent access (Figure 1B). Behavior on days 1 versus 14 is compared in Figure 1C. Active nose pokes developed into a “sawtooth” pattern, discriminating the drug-available and no drug-periods. Across training, we found that females maintained a higher rate of nose poking during the no-drug period, relative to males, despite responding similarly during the drug-available period (Supplemental Figure 3D,E; unpaired t-test, $t_{(33)}$=2.431, p=0.0207). Responding in the unpaired group was low and showed no clear pattern (Supplemental Fig. 2B).

Overall, rats quickly learned to discriminate between no-drug and drug-available, and this discrimination grew across sessions (Figure 1D; main effect of period $F_{(1,34)}$=91.70, p<0.0001; session by period interaction $F_{(13,442)}$=5.283, p<0.0001. We directly compared the first and last days of training (Figure 1E; main effect of period $F_{(1.34)}$=39.39, p<0.0001; session x period interaction $F_{(1,34)}$=19.72, p<0.0001). Active nose-pokes during drug-available periods were significantly elevated above no-drug periods on session 14 (p<0.0001) but not session 1 (p=0.7676). Active nose-pokes during the no-drug periods significantly decreased from session 1 compared to 14 (p=0.0005). Rats in the unpaired group failed to discriminate between no-drug and drug-available periods across the 14 days (Supplemental Figure 2C; no main effect of period $F_{(1,11)}$=2.269, p=0.1602; no session x period interaction $F_{(1,11)}$=2.220, p=0.1643). Paired rats significantly escalated their cocaine-intake across the 14 days (Figure 1F; paired t-test, $t_{(34)}$ =3.362, p=0.0019) and inter-infusion interval significantly decreased from session 1 to session 14 (Figure 1G; $t_{(33)}$=3.079, p=0.0042) demonstrating rats took more cocaine more vigorously after 14 days of intermittent access. By the end of training, males and females similarly discriminated the drug-available and no-drug periods (Supplemental Figure 3F; no main effect of sex $F_{(1,35)}$=0.9735, p=0.3306) and self-administered similar amounts of cocaine at a similar rate (Supplemental Figure 3G,H; no main effect of sex $F_{(1,33)}$=0.002423, p=0.9610).

The temporal distribution of active-nose pokes within the 5-minute drug-available periods changed from session 1 to session 14 (Figure 1H; 2-way RM ANOVA, main effect of minute $F_{(2,68)}$=62.53, p<0.0001; main effect of session $F_{(1.34)}$=15.08, p=0.0005; minute x session interaction $F_{(2,68)}$=18.59, p<0.0001). Intermittent access produced brief robust drug-taking that primarily occurred in the first minute of the drug-available period. Active nose pokes within the first minute of the drug-available period were significantly elevated compared to the third and fifth minute in session 1 (Figure 1H; multiple comparisons test 1 v 3 p=0.0260; 1 v 5 p=0.0017) and session 14 (1 v 3 p<0.0001; 1 v 5 p<0.0001). Rats escalated their binge-like drug-taking, as active nose-pokes during the first minute increased from session

1 to session 14 ($p<0.0001$). Additionally, the time between the first and second cocaine infusions decreased from session 1 to session 14, demonstrating more vigorous binge-like drug taking with self-administration experience (Figure 1I; paired t-test, $t_{(33)}=3.506$, two-tailed, $p=0.0013$). This pattern of responding during the drug-available period was similar in males and females (Supplemental Figure 3F; no main effect of sex $F_{(1,38)}=1.104$, $p=0.3000$).

Active nose-pokes within the first minute of the drug-available period in session 1 positively correlated with active nose-pokes within the first minute in session 14 (Figure 1J; $F_{(1,33)}=11.84$, $p=0.0016$; $r^2=0.2640$), suggesting that initial binge-like drug use is associated with subsequent binging. This appears to be specific to behavior during intermittent access, as active nose-pokes during the third day of continuous access pretraining did not correlate with active nose pokes during the drug-available period in either session 1 (Supplemental Figure 1D; $F_{(1,33)}=0.6408$, $p=0.4292$; $r^2=0.01905$) or session 14 (Supplemental Figure 1E; $F_{(1,33)}=0.9946$, $p=0.3259$; $r^2=0.02926$) of intermittent access.

Drug-availability state transitions spur rapid movement

Chamber crossovers, a proxy for general locomotion, varied as a function of epoch (pre, during, or post drug-available period), session (1 or 10), and group (paired or unpaired) (Figure 2B; 3-way interaction epoch x group x session $F_{(2,44)}=7.055$, $p=0.0022$), increasing significantly during the drug-available period in paired ($p=0.0010$), but not unpaired ($p=0.5745$) rats. Making use of pose estimation with DeepLabCut (Figure 2C), we found that the transition to the drug-availability state almost instantly spurred psychomotor invigoration in paired rats. Distance traveled separated into 10-s bins (20 s before to 50 s after drug-availability cue) varied as a function of group (Figure 2D; 2-way interaction bin x group $F_{(7,154)}=3.463$, $p=0.0018$) and session (2-way interaction bin x session $F_{(7,154)}=2.622$, $p=0.0138$). In the 10–30 s after drug availability onset, Paired rats showed elevated distance traveled that significantly increased relative to unpaired rats across training days (Figure 2D,E; unpaired t-test $t_{(22)}=1.74$, $p=0.048$). Movement speed separated in 10-s bins also varied as a function of session and group (Figure 2F; 2-way interaction bin x group $F_{(7,154)}=2.356$, $p=0.0259$; 2-way interaction bin x session $F_{(7,154)}=2.139$, $p=0.0427$). Average speed in a group varied as a function of session (2-way interaction group x session $F_{(1,22)}=5.507$, $p=0.0283$). Speed increased rapidly in the ~40 s after drug-availability onset in the paired rats. Paired rats showed greater speed after drug-availability onset that significantly increased relative to unpaired rats across training days (Figure 2F,G; unpaired t-test $t_{(22)}=2.22$, $p=0.0185$).

Binge-like drug use predicts drug taking persistence in the face of escalating cost

After intermittent access, we used a conflict procedure to assess drug taking persistence in the face of escalating cost (Figure 3B). Figure 3C shows the conflict effect of reduced drug seeking as shock increases. Across our subject pool, we found a distribution in shock levels rats were willing to persist through (Figure 3D). Males and females suppressed at similar shock levels (Supplemental Figure 3I unpaired t-test; $t_{(33)}=0.9490$, two-tailed, $p=0.3495$). We found no relationship between cocaine intake at the end of continuous access pretraining and the levels of shock that rats later endured during conflict (Figure 3E; $F_{(1,33)}=0.9358$, $p=0.3404$, $r^2=0.0276$. We did find two predictors of conflict behavior, which were measures

taken after a history of intermittent cocaine binging: 1) the amount of cocaine initially taken during the baseline shock level 0 session (Figure 3F; $F_{(1,33)}$ =6.019, p=0.0196, r^2=0.1543), and 2) the amount of cocaine used in the last session of intermittent access (Figure 3G; $F_{(1,33)}$=9.462, p=0.0042, r^2=0.2228). This suggests that intermittent or binge-like cocaine intake promotes cost insensitivity.

Drug cues interact hierarchically to spur drug seeking

After a 14-day incubation period, we assessed the influence of drug-associated cues to spur drug seeking in the face of cost, under extinction conditions. Within **the single-cue test**, the drug-delivery cue was non-contingently presented for 20 s on a fixed 3-minute interval during a 1-hour long session where chamber lights were off the entire time (Figure 4B). For relapse tests, the level of shock was set at 50% of what that individual rat suppressed to within the conflict phase, as in previous studies (Saunders et al. 2013). In the single-cue test, there were no differences between active nose-pokes during the noncontingent drug-delivery cue presentation, active nose-pokes during the non-cued periods, and inactive nose-pokes (Figure 4C; $F_{(2,48)}$=2.879, p=0.0660) suggesting that the drug-delivery cue on its own was not sufficient to trigger drug seeking. Single cue test active nose-pokes were also not different in the paired cue group, compared to the unpaired group (Figure 4D; unpaired t-test, $t_{(35)}$=1.167, p=0.2512).

This single-cue session was conducted entirely in darkness, so the rats never experienced the *transition* to the drug-availability state, from light to dark. We hypothesized that global drug-availability state transitions may be an important mitigator of the motivational impact of this more proximal drug-delivery cue to spur drug seeking. We tested this with a **multiple-cue test**, wherein the drug-availability state (house lights going from on to off) was presented for 2 minutes every 8 minutes for a 1-hour long session (Figure 4E). Within a drug-available period, the 20-s drug-delivery cue was non-contingently presented at 40 s and 100 s. In the multiple-cue test, noncontingent presentation of the drug-delivery cue increased active nose poke rate compared to non-cued baseline periods (Figure 4F; multiple comparisons test, p<0.0001, n=25), suggesting that information about drug availability gated the motivational impact of the drug-delivery cue to spur drug seeking. Multiple-cue test active nose-pokes were significantly greater than inactive nose-pokes (Figure 4G; paired t-test, $t_{(24)}$=5.613, p<0.0001. Nose-poke rate and number of nose-pokes was significantly higher in the paired group compared to the unpaired group in the multiple-cue test (Figure 4H,I; unpaired t-test, $t_{(35)}$=4.059, p=0.0003; unpaired t-test, $t_{(35)}$=4.059, p=0.0003). Compared directly, active nose-pokes were significantly higher in the multiple-cue periods, compared to the single-cue periods, for paired rats (Figure 4J; paired t-test, $t_{(24)}$=4.882, p<0.0001). We found no sex differences in behavior during the multiple-cue test (Supplemental Figure 3L; no main effect of sex $F_{(1,23)}$=2.562, p=0.1231). We also tested the ability of the drug-delivery cue to reinforce nose poking on its own, in a 1-hr session conducted with house and box lights off. In contrast to noncontingent cue presentations in the single-cue test, contingent cues reinforced robust responding in paired rats, compared to the unpaired group (Supplemental Figure 2H; unpaired t-test, $t_{(35)}$=3.833, p=0.0005), with no sex differences (Supplemental Figure 3J; $F_{(1,23)}$=4.064, p=0.0556).

Individual variability in the influence of different drug-related cues to spur drug seeking

In the multiple-cue test, we saw individual differences in how rats responded to the drug-availability state transition versus the drug-delivery cue within those states. A subset showed an increase in drug seeking in response to the drug-availability transition, before the drug-delivery cue was presented. Another subset did not immediately respond to the drug-availability cue but showed elevated drug seeking during subsequent drug-delivery cue presentations (Figure 5B). To categorize this heterogeneity we set a criterion of at least a 2x increase in responding on the active nose port during the drug-delivery cue presentation compared to the periods where the drug-availability state was presented alone to be categorized in the **proximal cue group** (n=10). Rats in the proximal cue category increased their active nose-pokes during the drug-delivery cue presentations compared to baseline, but not during drug-available periods in the absence of the delivery cue (Figure 5C; baseline vs. drug-delivery cue $p<0.0001$, baseline vs. drug available $p=0.5603$). Figure 5D shows the pattern of responding on the active nose port for the proximal rats, ($F_{(4,36)}=7.577$, $p=0.0002$) wherein there was an increase in responding to the drug-delivery cue presentations compared to baseline ($p=0.0007$ DD1, $p=0.0033$ for DD2), but did not alter their drug seeking in response to the drug-availability state transition itself ($p>0.05$). This indicates that the impact of the drug-delivery cue to spur drug seeking is gated by the presence of drug-availability state information, as these rats did not respond above non-cued baseline periods within the single-cue test.

To categorize rats that were preferentially driven to seek cocaine directly by the drug-availability state transition, the **global cue group** (n=12), we set a criterion of at least 2x responding to the drug-availability state onset (first 40 s) compared to a no-cue baseline period. Rats in this group increased their active nose-pokes compared to the baseline period during both the drug-availability cue and the drug-delivery cue periods (baseline vs. drug-available $p=0.0003$, baseline vs. drug-delivery cue $p=0.0316$). The global rats pattern of responding is observed in Figure 5F, ($F_{(4,44)}=4.317$, $p=0.0049$) wherein rats increased their active nose pokes at drug availability cue onset ($p=0.0007$). To define a relapse subgroup predictor, we compared several variables in proximal and global rats. There were no differences between the subgroups in the number of cocaine infusions during intermittent access training, inter-infusion intervals during intermittent access training, level of shock reached during conflict, or conditioned reinforcement (Supplemental Figure 4; unpaired t-tests; $p>0.05$). The sex breakdown was similar within the two relapse subgroups (Proximal group: 4 males and 5 females; Global group: 7 males and 5 females; 3 rats did not fit the criterion for either group). Together this suggests that individual differences in sensory-guided relapse reflect an isolated phenotype from individual differences in binge-like cocaine intake and cost sensitivity.

DISCUSSION

We modeled three key features of addiction: binge-like drug use, persistent drug seeking in the face of escalating costs, and the interaction of multi-cue relationships to spur relapse. We demonstrate that intermittent access produced robust drug taking invigorated by the transition to the drug-availability state, which escalated across 14 days of self-

administration. By the end of training, the bulk of infusions were taken in a rapid, binge-like fashion within the first minute of drug availability, similar to previous studies (Allain et al. 2018). We made use of a combination of experimenter and machine-learning guided analyses to quantify the movement profiles of self-administering rats. This showed that the transition to drug-availability states rapidly (i.e., within seconds) induces psychomotor sensitization, before cocaine infusions are taken. Critically, this state-induced movement invigoration was stronger compared to rats receiving rapid but passively delivered cocaine infusions. Thus, volitional drug intake reflecting intact action-outcome contingencies in the presence of dynamic state shifts is necessary for intermittent drug experience to promote exaggerated motivation. This result builds on the notion that intermittent access to drugs promotes sensitization to a greater degree than continuous long access (Allain et al. 2017; Algallal et al. 2020), and that drug-induced sensitization is under transient contextual control (Anagnostaras and Robinson 1996; Crombag et al. 2000; Anagnostaras et al. 2002).

Hierarchically organized environmental control of drug seeking

Our results underscore the powerful role of the environment in regulating drug-related behaviors, emphasizing the influence of dynamic drug-availability states on drug seeking. Drug availability spurred rapid movement invigoration and cocaine infusions during training. Critically, the presence of state transitions - the shift from an environment signaling drug unavailability to one signaling drug availability - was necessary for proximal drug-associated cues to induce relapse. This indicates that different forms of sensory information can interact in a hierarchical fashion to control drug seeking (Rescorla 1988; Fraser and Holland 2019). We also found important differences between noncontingent and contingent drug cue presentations in the promotion versus maintenance of drug seeking. Noncontingent cue presentations evoked relatively weak relapse, compared to relapse supported by conditioned reinforcement. Our results suggest that one potential reason for this is that the motivational value of non-contingently presented drug cues is strongly tied to the current state of the animal. Transitions to a state of drug expectation or “craving” may “prime” individuals to be more vulnerable to the triggering influence of proximal drug cues. This distinction is notable because the majority of addiction studies in rodents examine relapse based on cue-reinforced responding, rather than noncontingent cue presentations (Saunders et al. 2013; Venniro et al. 2020; Poisson et al. 2021).

Given the modulating influence the drug-availability state had on the motivational value of proximal drug cues, it shares elements of hierarchical or configural associative learning that is demonstrated in studies of discriminative stimuli, contextual renewal, and occasion setting (Rescorla 1988; Weiss et al. 2000; Chaudhri et al. 2008; Crombag et al. 2008; Trask et al. 2017; Fraser and Holland 2019; Valyear and Chaudhri 2020; Valyear et al. 2020). Our work in particular builds on previous studies demonstrating that drug-related contexts can regulate the rate of drug intake and the ability of discrete drug cues to reinforce drug seeking (Crombag and Shaham 2002; Di Ciano and Everitt 2003; Sciascia et al. 2015; Valyear and Chaudhri 2020). Contextual control of drug seeking is typically demonstrated by extinguishing behavior in a new environment across different experimental phases, in so called “ABA” and related designs (Crombag and Shaham 2002; Bouton 2002; Hamlin et al. 2008; Chaudhri et al. 2008), which are distinct from our approach in these studies.

Static context changes can modify the motivational impact of proximal reward-paired cues, including drug cues (Chaudhri et al. 2008; Sciascia et al. 2015; Valyear and Chaudhri 2020).

Even though the drug-available period in our studies was signaled by a global change in the environment, given its transient nature, we do not conceive of it as a classic contextual stimulus. Instead, the drug-available period is a state that is toggled on and off within a session. During self-administration training, this makes the availability state akin to a discriminative stimulus that disambiguates when drug is available. In the relapse tests, the drug-availability state may function differently, as an occasion setter that disambiguates the relationship between proximal cues and reward. Notably, occasion setters not only modulate other cues, but can acquire their own incentive motivational value (Fraser and Holland 2019; Fraser and Janak 2019). Our relapse results could thus be partly explained by a Pavlovian-to-instrumental transfer process, where the presentation of a Pavlovian conditioned stimulus can invigorate instrumental reward-seeking actions (LeBlanc et al. 2012; Wassum et al. 2013; Collins et al. 2016). Given that we found rapid movement invigoration at the onset of drug-available periods suggests the drug-availability state itself developed incentive motivational properties. Notably, transfer or generalization between instrumental discriminative stimuli and Pavlovian occasion setters can occur (Davidson et al. 1988), which could be another feature of our results. Occasion setters can also directly support conditioned reinforcement (Fraser and Janak 2019). We did not test the conditioned reinforcing value of the drug availability state in our studies, nor look at the ability of the drug-availability state to modulate the conditioned reinforcing value of the proximal drug delivery cue. Therefore, questions remain regarding what associative versus incentive information is transmitted by the drug-availability state in intermittent access studies.

If the drug-availability state functions as a discriminative stimulus during instrumental training and as an occasion setter during relapse tests in our studies, this might explain why we found no relationship between self-administration behavior and individual differences in relapse phenotypes. Decision-making strategies motivated by discriminative stimuli, contexts, and occasion setters can be distinct (Crombag et al. 2008; Fraser and Holland 2019). Further work is needed to disambiguate these concepts to better understand state-dependent control of drug seeking and the intersecting influence of global and proximal drug cues.

Binge-like cocaine intake promotes cost insensitivity in future drug seeking

We investigated the relationship between binge-like intake during intermittent access and the propensity to seek cocaine in the face of escalating costs, using a conflict procedure (Cooper et al. 2007; Barnea-Ygael et al. 2012; Saunders et al. 2013). We found that self-administration training was predictive of seeking during conflict - rats taking more cocaine infusions at the end of intermittent access later endured higher shock levels to take cocaine. This suggests that rapid, intermittent cocaine intake facilitates cost-insensitive drug seeking, which may be a feature of compulsivity in addiction-like behavior. Continued drug seeking despite its unavailability has been conceptualized as an important aspect of addiction, and another proxy for compulsive or habitual behavior in animal models (Lüscher et al. 2020; Venniro et al. 2020; Poisson et al. 2021). In our studies, we did not see an increase in drug

seeking responses during the no-drug period, unlike some long access self-administration studies (Deroche-Gamonet et al. 2004; Belin et al. 2009). Taken together, these results suggest that different behavioral correlates of compulsivity are not interchangeable and may instead reflect unique components of addiction.

Individual differences in sensory-guided relapse trajectories

We find that state-level and proximal cocaine-related sensory information interact hierarchically to guide drug seeking. Notably, however, considerable individual differences existed in which specific sensory elements promoted relapse across our subject pool. Some rats renewed drug seeking preferentially in response to state transitions - right after the drug-available period began. Other rats renewed seeking preferentially in response to the proximal drug-delivery cue, following the transition to drug-availability state. Thus, among individuals (rats in this case), there is variability in what type of environmental information is predominantly used to guide drug-seeking behaviors.

Past work, including some of our own, demonstrated individual differences in the extent to which rats engage in cue-directed approach behavior (“sign tracking”), versus cue-evoked goal approach (“goal tracking”) predict drug cue-induced relapse and other addiction-like behaviors (Uslaner et al. 2006; Flagel et al. 2009; Saunders and Robinson 2010, 2013; Yager and Robinson 2013; Saunders et al. 2013). The potential relationship between sign/goal tracking variability and the individual differences we see here remains somewhat unclear. Goal tracker rats are known to preferentially relapse in response to cocaine-associated contexts in ABA experimental designs (Saunders et al. 2014). However, goal trackers also relapse more when drug availability is signaled by a discrete drug cue acting as a discriminative stimulus in intermittent access procedures (Pitchers et al. 2017). Given the different relapse conditions in our studies compared to this past work, future studies to unpack potential individual differences in hierarchical drug cue representations are needed.

We found that individual rats’ binge-like self-administration was correlated across intermittent access training, suggesting that an individual’s intake pattern set point was somewhat locked in, based on innate differences across subjects, rather than emergent from self-administration experience. Notably, neither variability in cocaine intake rates during training nor cocaine seeking during conflict predicted which relapse subgroup a rat later fell into. This suggests that different facets of addiction-like behavior in our dataset - cost insensitivity and cued relapse vulnerability - represent somewhat independent traits. It remains unclear how to conceptualize this individual variability in relapse, but it seems to reflect broad inter-individual heterogeneity in decision-making strategies that intersect with the environment to produce different relapse phenotypes.

Sex-based effects

Our studies included intact male and female Long Evans rats. One notable sex-related difference emerged. Female rats maintained a higher rate of nose poking during the no drug period, compared to males, similar to data reported previously (Kawa et al. 2019b). This difference was seen across several sessions before a similar level of discrimination was reached at the end of training. Given that we found no other sex differences, it is

difficult to interpret this effect. Continued drug seeking when it is no longer available is one behavioral variable considered to approximate compulsive or addiction-like behavior (Deroche-Gamonet et al. 2004; Robinson 2004; Poisson et al. 2021). In the case or our results, the distinction was seen early in cocaine use history, making drug-induced compulsivity specifically in females an unlikely interpretation. Further, male and female rats did not differ in conflict behavior or relapse tests, suggesting that overall addiction-like phenotyping was not different as a function sex in these studies.

We did not find sex differences in cocaine intake or rate of responding in the drug availabile period on the intermittent access schedule. This is somewhat unexpected based on recent evidence that female rats show elevated motivation for cocaine during intermittent access self-administration, resulting in more cocaine infusions, compared to males (Kawa and Robinson 2019; Algallal et al. 2020). The reasons for lack of sex differences in intake are unclear, but we note that the experimental protocols, including the length of pretraining acquisition and intermittent access training, differ substantially across the studies. Sex differences may be more apparent after longer periods of cocaine self-administration. Previous studies also used other rat strains, including Sprague Dawleys. A recent report investigating variability in drug self-administration across a broad sample of mouse strains showed that sex differences in drug seeking are not uniformly expressed, and instead depend heavily on the genetic background of animals (Bagley et al. 2022). There are also several reports demonstrating a lack of sex differences across different drug seeking models, including the conflict procedure (Fredriksson et al. 2020; Nicolas et al. 2022). Overall, rodent sex differences in drug-related behaviors appear to be subtle, variable, and heavily dependent on the details of experimental preparations.

Conclusion

Here, we describe studies that underscore the critical role of drug intake patterns and dynamic environments in regulating drug seeking motivation. Further, they suggest broad individual differences in sensory-guided relapse trajectories, which is an important consideration for the development of effectively targeted interventions for substance use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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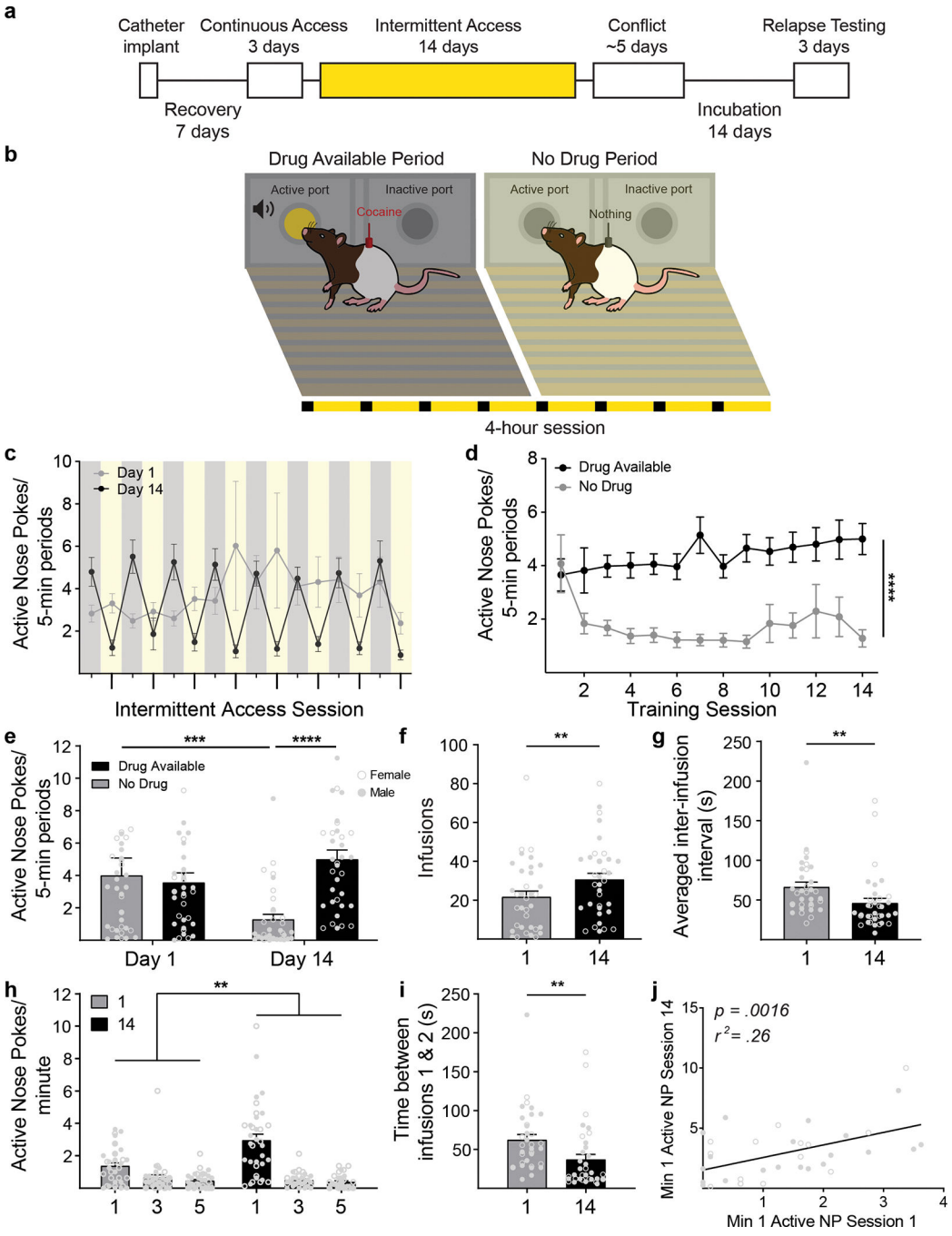

Figure 1. Intermittent access to cocaine promotes the development of rapid, binge-like intake that is under the control of drug availability state information.

Intermittent access to cocaine self-administration procedure and data. **a** Flow diagram of the experimental phases. Highlighted portion refers to the phase represented in the figure. **b** Schematic diagram of intermittent access showing the drug-available period (left), no-drug period (right), and pattern (bottom). **c** Rats learned to discriminate between the drug-available and no-drug periods across the 14 days. Gray and yellow boxes represent drug-available and no-drug periods, respectively. Gray and black circles represent session 1

and session 14, respectively. **d** Nose-pokes during the drug-available period increased across training, relative to the no-drug period. **e** Active nose pokes/5-minutes of drug-available and no-drug periods on sessions 1 versus 14. Nose-pokes decreased in the no-drug period across sessions. In session 14 nose-pokes during the drug-available period were elevated compared to the no-drug period. **f** Cocaine infusions increased from session 1 to 14. **g** Average inter-infusion intervals decreased from session 1 to session 14. **h** Within the drug-available periods, active-nose pokes differed across the 5-minute drug-available period and this changed from session 1 to session 14. There was a main effect of minute, main effect of session, and a minute x session interaction. Specifically, active nose pokes within the 1st minute of the drug-available period were significantly elevated compared to the 3rd and 5th minute in session 1 and 14. As training progressed, rats increased active nose-pokes during the 1st minute of drug availability periods. **i** The time between the 1st and 2nd cocaine infusions decreased from session 1 to session 14, demonstrating more vigorous binge-like drug taking with self-administration experience. **j** Initial binge-like drug use, defined as active nose-pokes within the first minute of the drug-available period, is positively correlated with binge-like drug use after 14-days of drug use. (n=35). Bars represent mean ± SEM. **p<0.01, ***p<0.001, ****p<0.0001.

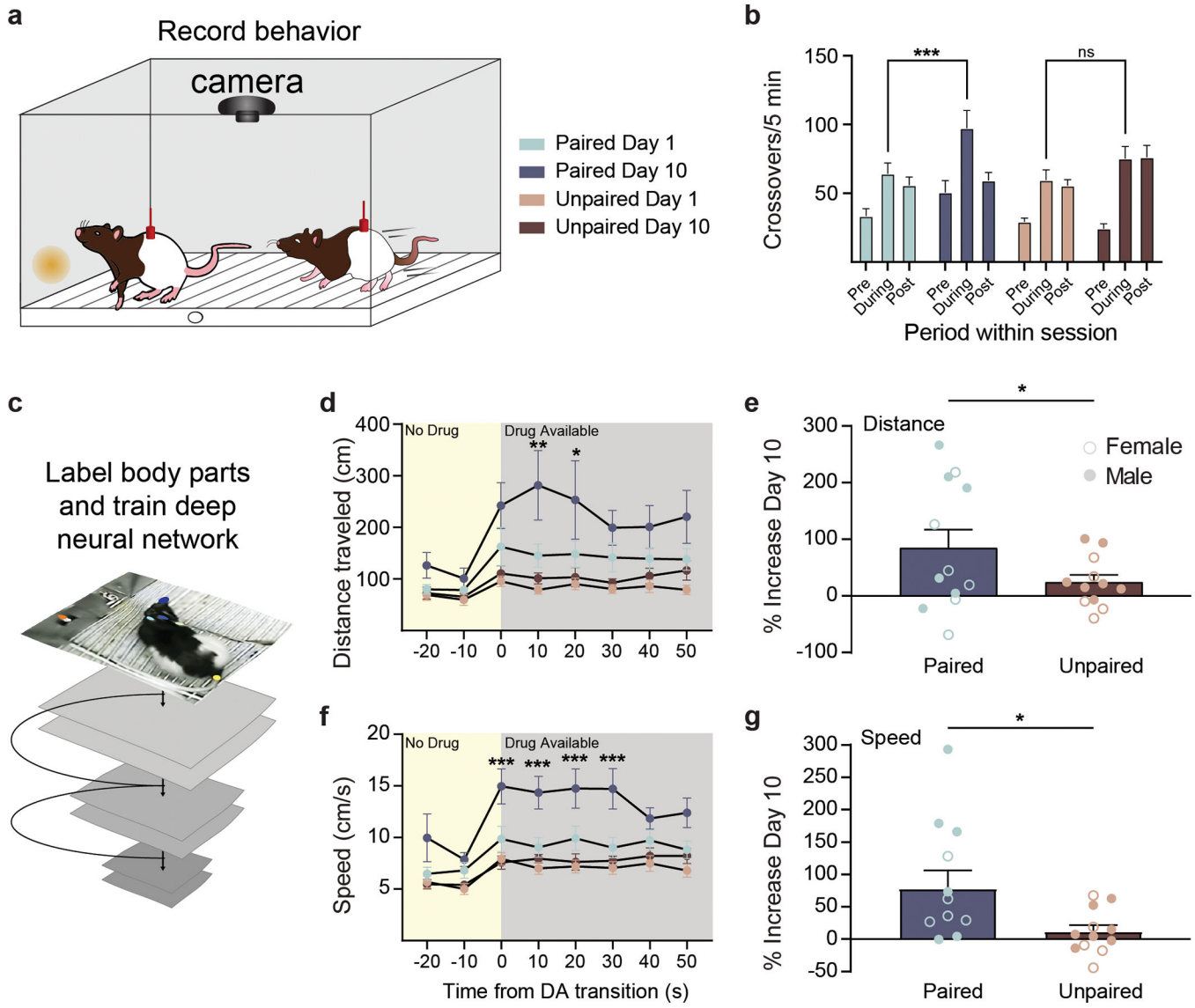

Figure 2. Drug availability states promote psychomotor sensitization when a drug seeking action-outcome contingency is intact.

a Behavior is video recorded from cameras positioned above behavioral chambers, for hand scoring by experimenters and detailed analysis with DeepLabCut. **b** Intermittent access to cocaine led to increased chamber crossovers during the drug available period in the paired (n=12) but not unpaired (n=12) rats. **c** Movement kinematics are interpolated from DLC-based pose estimation. **d-g** The transition to the drug-availability state spurs rapid psychomotor invigoration, with increased distance traveled **d-e** and speed **f-g**, in the first minute that sensitizes in paired compared to unpaired rats. Bars represent mean ± SEM. *p<0.05, **p<0.01, ***p<0.001.

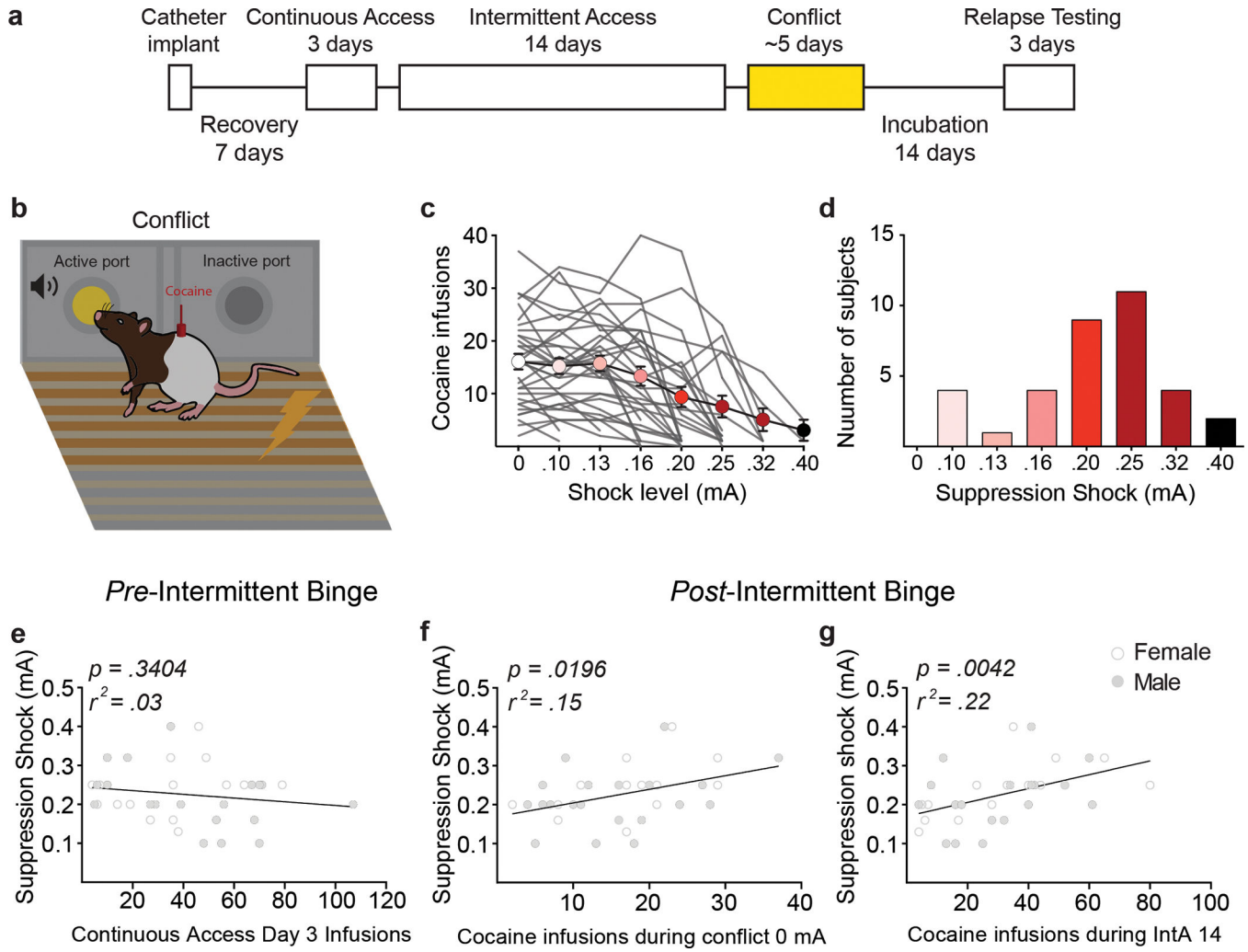

Figure 3. Binge-like cocaine self-administration history predicts motivation to seek cocaine in the face of escalating cost.

a Flow diagram of the experimental phases in which the phase represented in the figure is highlighted. **b** Schematic diagram of the conflict procedure. **c** Average number of cocaine infusions decreases over escalating shock values. Bars represent mean ± SEM. **d** There was a distribution in shock levels rats were willing to endure. **e** The amount of cocaine taken during the continuous access training phase, pre-intermittent binging, had no relationship with future shock cost the rats were willing to persist through. **f** The amount of cocaine initially taken within the baseline shock level 0 session predicted how much shock cost the rats were willing to persist through. **g** The amount of cocaine used in the last session of intermittent access was positively correlated with the shock intensity cost rats were willing to endure to continue taking cocaine. n=35.

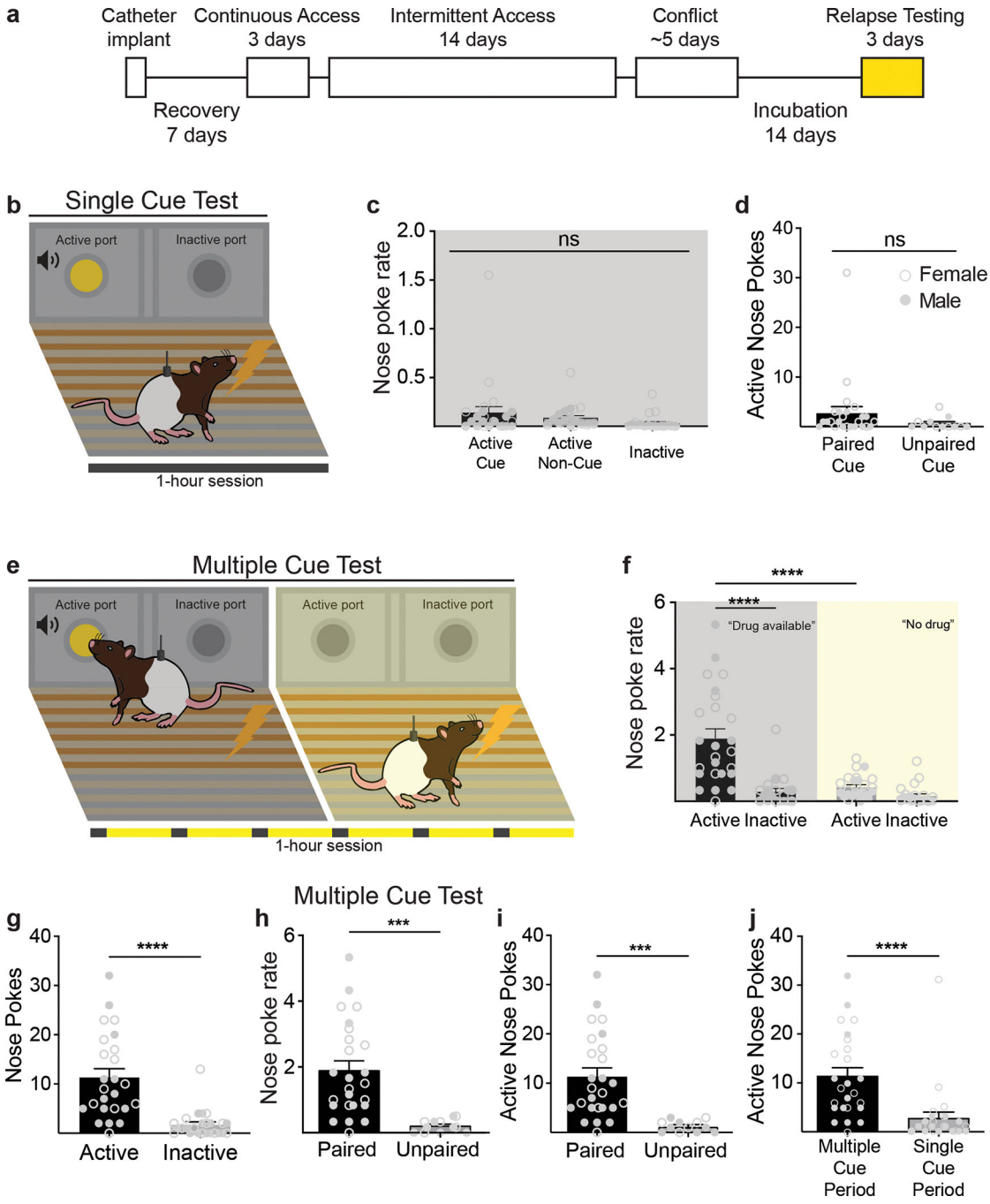

Figure 4. Drug-availability state transitions spur relapse in the face of cost and modulate the motivational value of proximal drug cues.

After a 14-day incubation period, we assessed the influence of drug-associated cues to spur drug seeking in the face of cost. **a** Flow diagram of the experimental phases in which the phase represented in the figure is highlighted. **b** Schematic of the single cue test, which consisted of a 20-s drug-delivery cue that was presented non-contingently with a fixed 3-minute ITI throughout a 1-hour session with the house and box lights off for the duration of the session. **c** In the single-cue test, active nose-pokes during the noncontingent drug-

delivery cue presentation did not differ from active nose-pokes during the non-cued periods (nose pokes/20 s), **d** nor from nose pokes made in a single cue test for unpaired cue control rats. **e** In the multiple cue test, the drug-availability cue (house and box lights going from on to off) was presented for 2 minutes every 8 minutes for a 1-hour long session. Within a drug-available period, the 20-s drug-delivery cue was then non-contingently presented at 40 s and 100 s. **f** In the multiple-cue test, noncontingent cue presentation of the drug-delivery cue increased active nose-poke rate compared to non-cued baseline periods (nose pokes/2 minutes) and **g** relative to inactive nose-pokes. **h,i** Only rats with a history of cocaine infusions paired with their drug seeking responses showed relapse in the multiple-cue test. **j** The multiple-cue test resulted in significantly more active nose-pokes than the single-cue test. n=25. *$p<0.05$, **$p<0.01$.

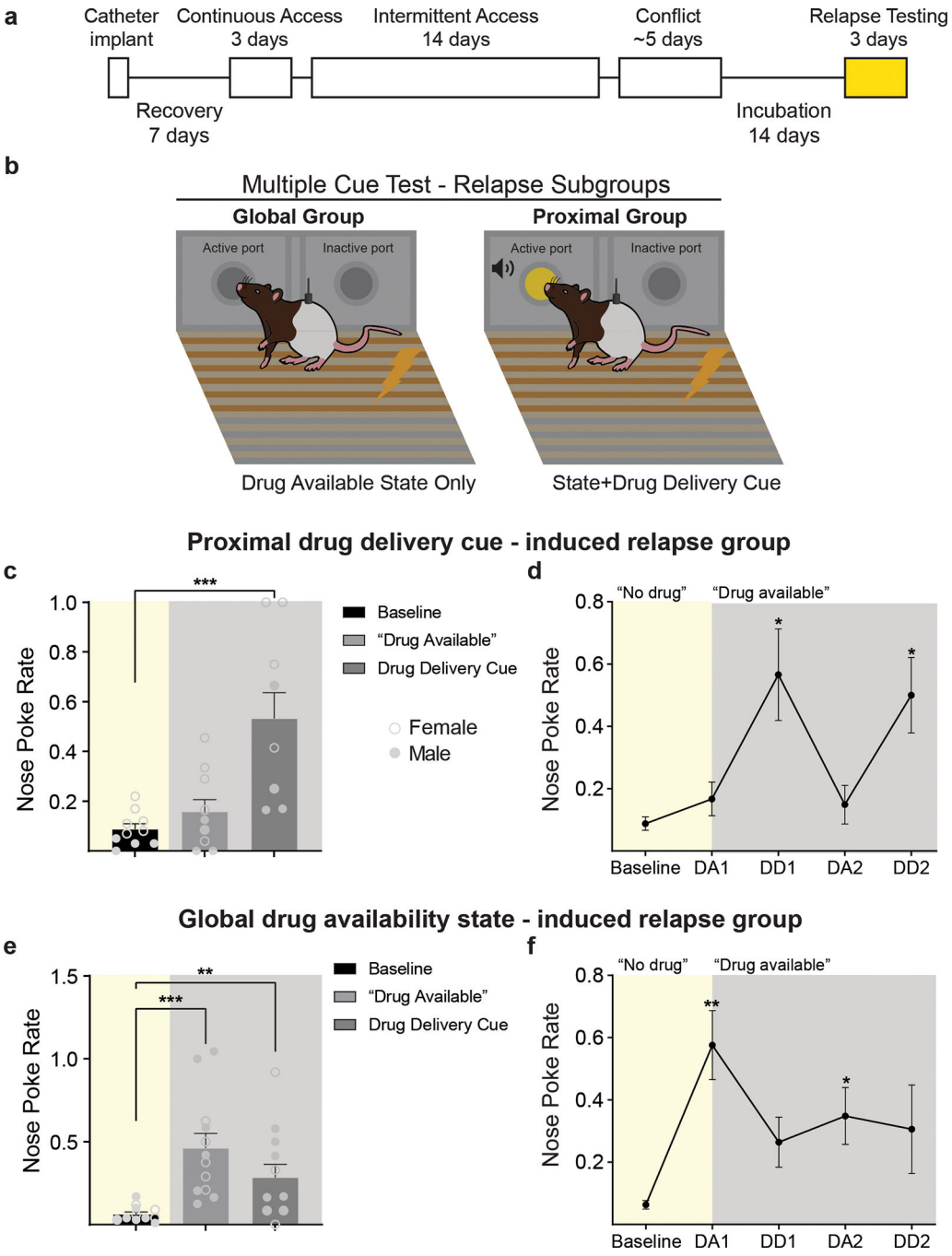

Figure 5. Individual differences in relapse behavior.

a Flow diagram of the experimental phases in which the phase represented in the figure is highlighted. **b** Within the multiple-cue test, relapse was preferentially triggered by proximal drug-delivery cues or global drug-availability state information in different subsets of rats. **c** Rats in the proximal group (n=10) increased their active nose-poke rate during the drug-delivery cue presentations, but not during the preceding drug-available period (nose pokes/20 s). **d** The pattern of responding in the proximal group where nose-pokes increase to the drug-delivery cues but not the drug-availability cue by itself. **e** For rats in the

global group (n=12), nose-poke rate increased immediately following the transition to the drug-availability state. **f** The pattern of responding in the global group where nose-pokes increase to the initial drug-availability cue. *p<0.05, **p<0.01.