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Contribution of Cocaine-Related Cues to Concurrent Monetary Choice in Humans

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Abstract

Rationale: Theoretical accounts highlight the importance of drug-related cues for the development and persistence of drug-taking behavior. Few studies have evaluated the ability of spatially contiguous drug cues to bias decisions between two concurrently presented non-drug reinforcers.

Objective: Evaluate the contribution of spatially contiguous cocaine cues to choice between two concurrently presented monetary reinforcers.

Methods: Participants with cocaine use disorder completed a cued concurrent choice task. Two cues (one cocaine and one control image) were presented side-by-side followed by concurrent monetary offers below each image. Concurrent choice was measured for cocaine-side advantageous, equal, and disadvantageous concurrent monetary offers. The primary dependent measure was bias for selecting cocaine-cued monetary reinforcers. Three experiments tested selectivity of cocaine-cued bias in individuals with a cocaine use history (Experiment 1), replication when including additional control trials (Experiment 2), and a potential attentional mechanism evaluated using eye-tracking technology (Experiment 3).

Results: Significant and robust cocaine-cue bias at equal monetary value was observed in three experiments (mean percent choice = 65%–77%) and higher Drug Abuse Screening Test (DAST) scores were associated with greater cocaine-choice bias. These experiments demonstrated that cocaine-cue bias was 1) selective to individuals with a cocaine use history, 2) specific to trials involving a cocaine cue, and 3) partially associated with attentional bias.

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Conclusions: These experiments provide evidence that drug-related cues can influence choice and potentially promote maladaptive decision-making during concurrent choice events. Future research evaluating prospective associations of drug-cued bias with drug-associated behaviors will help reveal the clinical relevance for substance use disorder.

Keywords

Addiction; Conditioning; Cue; Drug; Salience

Introduction

Numerous theoretical perspectives on addiction emphasize the significance of drug-related cues for the development, maintenance, and persistence of drug-taking behavior. Contemporary research and theory has emphasized this role of drug cues and cue reactivity in influencing choice and decision-making events (e.g., Hardy et al. 2017; Wang et al. 2012). For example, research in the behavioral economic literature has contributed to this understanding of drug-cued decision-making by showing that cue-associated incentive salience can drive suboptimal decision-making (Chow et al. 2017; Smith et al. 2018) and demonstrating that state-dependent changes in drug valuation occur following cue exposure (MacKillop et al. 2010, 2012; Metrik et al. 2016).

The specific role of cocaine-related cues in choice and decision-making has been studied in an elegant series of studies conducted by Moeller and colleagues (for review see Moeller and Stoops 2015). In studies using an explicit cue choice task, wherein participants were presented with a concurrent choice between a cocaine and non-drug image presented side-by-side, individuals with cocaine use disorder chose to view more cocaine images than controls and the percentage of cocaine image choice was correlated with cocaine use frequency and severity (Moeller et al. 2009, 2013). Other studies using comparable designs have found similar relationships between choice for visual drug cues (i.e., pictures) and severity measures for alcohol (e.g., Hardy and Hogarth 2017; Hogarth et al. 2018) and tobacco cigarettes (e.g., Miele et al. 2018). These findings indicate that explicit choice for a drug-related image broadly, and a cocaine-related image specifically, may provide a valid measure of drug dependence.

One gap in this literature is an understanding of how spatially contiguous drug cues may bias decisions between concurrently presented non-drug reinforcers. Spatial contiguity facilitates the formation of Pavlovian relationships (Rescorla and Cunningham 1979), which may result in particularly salient associations formed for cues spatially and temporally contiguous with drug reinforcement (e.g., drug paraphernalia). It is therefore likely that presenting a drug stimulus in a position that is spatially contiguous with a specific non-drug reinforcer would bias choice towards that response option. An implication of this effect is that biased choice could result in the decision to engage in high-risk activities that were otherwise undesirable without the influence of a salient drug cue. Evaluating decisions at varying levels of primary reinforcement on a standardized and matching scale is also notable as it allows for the study of potentially maladaptive decision-making promoted by these cues, the magnitude of which can be quantified on the primary reinforcer scale.

Here, we present a series of experiments evaluating the ability of cocaine-related cues spatially contiguous with a decision-making event to compete with non-drug cues and influence concurrent reinforcer choice in humans. Money was selected for this demonstration due to its ability to serve as a reinforcer of standardized and easily communicated magnitudes. Participants completed a cued concurrent choice task to evaluate bias for monetary choices spatially contiguous with cocaine and matched control cues. These experiments were designed to test the selectivity of this bias in individuals with a cocaine use history compared to controls without this history (Experiment 1), the reproducibility of this effect with the addition of categorically-distinct neutral cue trials (i.e., boxes and signs, which are stimuli with clear categorical boundaries, but with little inherent value) (Experiment 2), and a potential attentional mechanism underlying this bias (Experiment 3). The guiding hypothesis was that individuals with a history of cocaine use would show a bias for monetary choices spatially contiguous with cocaine relative to neutral cues. The specific hypotheses for each experiment were that 1) bias for cocaine- contiguous choices would be observed for cocaine-using, but not control, participants, 2) this bias would be replicated in an independent sample completing a task with additional categorically-distinct neutral trials, and 3) choice bias would be positively associated with cocaine-cue attentional bias.

Methods: Experiment 1

Participants

Twenty-four individuals participated in Experiment 1. Participants in the cocaine group were 12 adults who met DSM-IV criteria for cocaine use disorder and provided a urine sample positive for recent use. Participants in the control group were 12 adults who reported 10 or fewer lifetime cocaine uses. One control participant reported one day of cocaine use in the past month and removal of this individual's data did not change the results. All other control participants reported that their last cocaine use was more than one month ago. Controls also reported daily or near-daily cannabis use therefore representing individuals with frequent illicit substance use but with limited cocaine experience. This control group was selected to help account for illicit substance use (e.g., neurobiological, environmental) that could affect alterations in cognition associated with choice and decision-making. Participants were excluded if they reported drug use that could produce significant withdrawal symptoms during testing. The Institutional Review Board of the University of Kentucky approved all procedures. Participants provided written informed consent.

Procedures

Participants completed a single experimental session lasting approximately one hour. All participants were instructed not to use alcohol or other substances at least 12 hours prior to the session, which all participants verbally confirmed. Participants were allowed to use tobacco products prior to the session. Time since last cigarette and breath carbon monoxide (CO) were collected upon arrival. Urine samples were positive for a THC metabolite in 33.3% of the cocaine group and 91.7% of the cannabis group participants. Presence of urine positive for recent cannabis use was not related to choice bias in the cocaine group. A breath sample negative for alcohol and a successful field sobriety test were necessary to participate

in the session. Participants also did not exhibit acute signs of cannabis intoxication as observed by trained research staff. Participants were told to respond carefully because money would be received based on their choices. In actuality, all participants received \$10 for completing the task. Participants were informed of payment at the end of the session to avoid differential responses based on performance.

Cued Concurrent Choice Task

A cued concurrent choice task was used to evaluate the effects of cocaine-related cues on choice (Figure 1; Supplemental Materials for details). This task involved concurrent choices between two monetary values presented side-by-side (e.g., \$0.05 versus \$0.04). Monetary values were preceded by two visual stimuli, a cocaine-related and a neutral image, selected from previous studies on attentional bias in cocaine use disorder (Marks et al. 2014a, 2014b). Cocaine images contained powder or crack cocaine and paraphernalia. Neutral images were selected to match the number of objects, size, and color scheme. Trials began with a fixation point presented for 1000 ms in the screen center. Next, two visual stimuli (i.e., cocaine and neutral images) replaced the fixation point and were displayed for 2000 ms. Finally, a monetary value appeared under each stimulus and participants asked to select the value they would like to receive. The images disappeared after a response or 2000 ms elapsed and the next trial began.

Participants completed 10 practice trials followed by 120 experimental trials. All experimental trials presented a cocaine image (e.g., crack pipe) with a matched neutral image (e.g., pen). Monetary values from \$0.03 to \$0.07 in \$0.01 increments were presented in all possible side, location, and monetary combinations at least twice. Equal value trials presented the same monetary values on the cocaine- and neutral-cued side (e.g., \$0.05 on cocaine and \$0.05 on neutral) and were oversampled, with 8 trials per monetary increment pair. Other trials evaluated monetarily advantageous (e.g., \$0.05 on cocaine and \$0.04 on neutral) and disadvantageous (e.g., \$0.04 on cocaine and \$0.05 on neutral) cocaine-side selection. The location of cocaine and neutral images was randomized across trials. The primary outcome was percent choices for cocaine-cued values (cocaine-cued/[cocaine-cued + neutral-cued choices] * 100).

Questionnaires

A battery of questionnaires was collected including the Alcohol Use Disorder Identification Test (AUDIT; Babor et al. 2001), Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al. 1991), and Drug Abuse Screening Test (DAST; Skinner 1982), as well drug use frequency and quantity measures. Participants also completed a computerized version of the Structured Clinical Interview for the DSM-IV-TR to evaluate criteria for cocaine use disorder.

Data Analysis

Demographic and drug use variables in cocaine and control groups were first compared using independent samples *t*-tests (continuous) or Fisher's exact test (dichotomous). A mixed factor ANOVA was used to compare percent cocaine choice between groups (between-subject factor) and difference values (within-factor factor). Percent cocaine choice

on equal value trials was also compared between groups using an independent samples *t*-test. Additional one-sample *t*-tests were used to compare percent choice at equal value to indifference (50%). Finally, data were fit to a multiparameter logistic choice function to determine the minimum asymptote and inflection point (see Supplemental Materials for details). Bivariate correlations were used to determine the association between breath CO levels upon arrival and choice bias at equal value as well as demographic and drug use variables in the cocaine group. All tests were conducted using SPSS or R Statistical Language with a type I error rate of .05.

Results: Experiment 1

Sample Characteristics

Demographic and drug-use information are presented in Table 1. Cocaine and control groups differed in age, education, alcoholic drinks per week, DAST scores, and cocaine use, *p* values < .05. All participants reported lifetime cannabis use and groups did not differ in lifetime uses, *p* = .13.

Cocaine-Cued Choice

Figure 2 displays percent choice for cocaine-cued monetary values for cocaine and control groups. A 2×9 Mixed ANOVA (Group x Difference Value) indicated main effects of Group, $F_{1,22} = 11.15$, $p = .003$, and Difference Value, $F_{8,176} = 248.99$, $p < .001$, that were superseded by a Group x Difference Value interaction, $F_{8,176} = 2.682$, $p = .008$. Follow up *t*-tests indicated that the cocaine group showed a significant and large effect size difference from controls on equal value trials (i.e., when monetary values were equal), $t_{22} = 3.32$, $p = .003$, $d = 1.36$. One-sample *t* tests confirmed that the cocaine-cued choice was significantly greater than indifference in the cocaine group (65.2%), $t_{11} = 2.38$, $p = .037$, $d = 0.69$, and significantly lower than indifference in the control group (33.5%), $t_{11} = 2.33$, $p = .040$, $d = 0.67$. One significant group effect was observed when the cocaine choice was disadvantageous by one cent. This effect represented greater choice for the monetary value spatially contiguous with the cocaine images in the cocaine group compared to control group, $t = 2.549$, $p = .02$, $d = 1.04$. Consistent results were observed for the multiparameter logistic function which indicated significant parameter effects for the minimum asymptote, $p = .012$, and inflection point, $p = .017$. These coefficients indicated a higher minimum asymptote and lower inflection point in the cocaine group, both of which were indicative of increases in cocaine-cued choices at equal or negative expected value (i.e., when the cocaine side was of less value). Few omissions were recorded (mean omissions: Cocaine = 1.2; Control = 0.8). Choice bias was not related to breath CO levels upon arrival, $r = .14$. Female participants showed a lower cocaine choice bias. No other variables were associated with choice bias (Table 2).

Discussion: Experiment 1

Participants with cocaine use disorder showed a greater than chance bias towards cocaine-cued monetary values. This choice bias was of a large effect size and was not observed in controls who showed a greater than chance bias for neutral-cued monetary values. These

findings suggest that cocaine-related cues influence concurrent choice and that this effect is selective to one's substance use history.

Several methodological features of Experiment 1 deserve consideration. A between-subject design was used comparing cocaine users to cannabis-using controls. These controls were selected to provide a comparison group with frequent illicit substance use, but a limited history of cocaine effects. However, the inclusion of a cannabis-using control group resulted in several demographic characteristics that were nearly perfectly confounded with group (e.g., age). Post-hoc partial correlations controlling for group indicated that drinks per week, education, and DAST scores were not significantly associated with choice bias (r values $< .23$), but that age was associated ($r = .48$). The most parsimonious explanation for this is that cocaine use history rather than covarying demographics was proximally related to biased choice. However, the relatively small sample, between-subject design, and nearly perfect confounding of these characteristics by group makes conclusions about the impact of these demographic features difficult.

Experiment 2 was designed to replicate this cocaine-cue choice bias in an independent sample of cocaine-using individuals. Additional neutral filler trials were included in which categorically-distinct neutral cues (i.e., stimuli with categorical boundaries, but with little inherent value) were presented. These trials allowed for the within-subject comparison between trials in which we would expect bias (i.e., cocaine-cued trials) and those in which no bias was expected (i.e., neutral filler trials). The hypothesis was that participants would show a bias for cocaine-cued choices, reproducing Experiment 1 effects, but would not show a bias on categorically-distinct neutral trials.

Methods: Experiment 2

Participants and Procedures

Fourteen individuals participated in Experiment 2 with no duplications in participants from Experiment 1. All participants met DSM-IV criteria for cocaine use disorder, reported cocaine use, and provided a urine sample positive for recent use. Demographic and drug-use information are presented in Table 1. General procedures were identical to Experiment 1.

Within-Subjects Cued Concurrent Choice Task

A modified version of the task described in Experiment 1 was used in Experiment 2. This task included two trial types. *Cocaine trials* were identical to Experiment 1 and presented choices between monetary values with cocaine and matched neutral cues. *Categorized neutral trials* presented two categories of cues 1) road signs and 2) cardboard boxes. These stimuli were selected because they have clear categorical boundaries, but no value-laden characteristics. All categorized neutral trials presented a sign and box image, side-by-side. Other parameters were identical to Experiment 1 except that participants completed 240 experimental trials reflecting the two trial types. The primary outcomes were percent choices for cocaine-cued values (cocaine-cued/[cocaine-cued + neutral-cued choices] * 100) and percent choices for sign-cued values (sign-cued/[sign-cued + box-cued choices] * 100).

Data Analysis

Percent choice on equal value trials were compared within-group using a dependent samples *t*-test. Additional one-sample *t*-tests were used to compare to indifference (50%). Data were also fit to a multiparameter logistic choice function to determine minimum asymptote and inflection point.

Results: Experiment 2

Cocaine-Cued Choice and Categorized Neutral-Cued Choice

Figure 3 displays percent choices for cocaine-cued and sign-cued monetary values. A significant and large effect size difference was observed between percent choices for cocaine-cued (76.6%) and sign-cued (48.4%) monetary values on equal value trials, $t_{11} = 4.13$, $p = .001$, $d_z = 1.10$. One-sample *t* tests confirmed that the cocaine-cued choice was significantly greater than indifference, $t_{13} = 5.65$, $p < .001$, $d = 1.51$, whereas sign-cued choice did not differ, $t_{13} = 0.39$, $p = .701$, $d = 0.11$. Choices on neutral-neutral trials did reveal a modest right side bias (average left choice = 43%) that was unrelated to choice bias, $r = -.01$. Cocaine-cued and sign-cued choices were also not significantly correlated, $r = -.18$, $p = .55$. Only one significant cue effect was observed at other difference values, with greater disadvantageous responding for the cocaine-cued choice at -1 (i.e., cocaine side one cent less than neutral side), $t = 3.02$, $p = .01$, $d_z = 0.81$. Consistent results were observed for the multiparameter logistic function which indicated significant effects for the inflection point, $p < .001$ and a trend towards significance for the minimum asymptote, $p = .056$. These coefficients indicated a lower inflection point and suggested a higher minimum asymptote on the cocaine compared to neutral trials, both indicative of increases in cocaine cued choice at equal or negative expected value. On average, less than one omission was made on cocaine or categorized neutral cue trials. Choice bias was not related to breath CO levels upon arrival, $r = .11$. Male participants showed a lower cocaine choice bias at equal value (the opposite of Experiment 1). No other variables were associated with cocaine choice bias at equal value (Table 2).

Discussion: Experiment 2

Experiment 2 demonstrated a reproducible choice bias for cocaine-cued choices that did not extend to neutral cue trials. This specificity suggests that simple categorization and selection of one category type over another was unlikely to contribute to the choice bias observed, although additional experiments described in the General Discussion are needed to further test this conclusion. Experiment 2 also demonstrates that participants were able to engage in optimal decision-making on categorized-neutral trials resulting in maximum primary reinforcement delivery suggesting that suboptimal decisions on cocaine trials were a result of the drug cue rather than more global impairments in decision-making.

Experiments 1 and 2 demonstrate a reproducible bias for cocaine-cued choices in individuals with a history of cocaine use. One mechanism proposed to underlie the relevance of drug-related cues is attentional control (Fadardi et al. 2016; Field and Cox 2008; Franken and van de Wetering 2015; Sofuoglu et al. 2016). These theories state that drug-related cues come to

serve as conditioned stimuli and increased salience of these cues is behaviorally manifest in attentional capture. Attentional bias is the tendency for these cues to capture and/or hold attention. Supporting these theories is research showing greater visual attention to laboratory conditioned cues (e.g., Hogarth et al. 2003; Mayo and de Wit 2015). Recent research has demonstrated attentional bias in cocaine users by demonstrating a robust, reliable, and selective bias for cocaine cues (Leeman et al. 2014; Marks et al. 2014a, 2014b, 2015, 2016).

Experiment 3 evaluated an attentional mechanism that may underlie the bias observed in Experiments 1 and 2. Cocaine-using participants completed a cued concurrent choice task while eye-tracking technology was used to record fixation location and duration. The hypothesis was that cocaine-cue attentional bias and choice bias would be positively associated.

Methods: Experiment 3

Participants and Procedures

Twenty-five individuals participated in Experiment 3 (Table 1) with no duplications in participants from Experiments 1 and 2. Participants completed one session including an eye-tracking concurrent choice task. Other procedures were similar to Experiments 1 and 2.

Cued Concurrent Choice Task with Eye-Tracking

A modified version of the task described in Experiment 1 was used in Experiment 3. This task used three monetary values (\$0.05, \$0.10, and \$0.25) presented in all combinations with cocaine and neutral images. These values were selected to model common US denominations. Trials were randomized and equal value trials with cocaine images (e.g., crack pipe) matched with neutral ones (e.g., pen) and were oversampled (24 trials balanced by side and value). Filler trials included two neutral images unrelated in content to cocaine or matched neutral images. Other details are identical to Experiments 1 and 2.

Fixation data were collected using Tobii X2-60 (Tobii Technology, Sweden) as described previously (Marks et al. 2014a). Briefly, eye movement was sampled at 60 Hz, with onsets of fixations defined as periods of at least 100 ms during which the line of gaze had a standard deviation of less than 0.5 degrees of visual angle. Periods of at least 50 ms in which gaze position as 1 degree of visual angle away from the initial fixation were recorded as fixation offsets. Mean fixation time for cocaine and neutral images was computed during the 2000 ms stimulus stage. Additionally, the percentage of trials in which the final fixation was on the cocaine image (as opposed to neutral image) was computed. Fixation time calculations did not include the following choice period when monetary values were presented. One participant was removed from analysis due to technical problems recording fixations. Fixation time attentional bias scores were computed as difference scores (cocaine - neutral fixation time) (Marks et al. 2014a, 2014b). Final fixation scores were computed as a percentage with a higher number indicating a greater percentage of trials in which the final fixation was on the cocaine image.

Data Analysis

Percent cocaine choice on equal value trials was first compared to indifference (50%). Filler trials were evaluated for left-right side bias. Cocaine and neutral fixation time were compared using a dependent-samples *t*-test. Bivariate correlations compared attentional bias and choice bias.

Results: Experiment 3

Cocaine-Cued Choice

Figure 4 (left panel) displays percent choice for cocaine-cued monetary values (see Supplemental Figure 1 for choices across monetary combinations). Percent choice of cocaine-cued monetary values on equal value trials (67.1%) was significantly greater than indifference, $t_{24} = 3.22$, $p = .004$, $d = 0.64$. Few disadvantageous choices (mean = 0.6 choices) or omissions (mean = 0.6 choices) were observed. Choices on neutral-neutral trials did not reveal an apparent left-right bias (average left choice = 51%). Choice bias was not related to breath CO levels upon arrival, $r = -.08$. Higher DAST scores were associated with greater cocaine choice bias in Experiment 3, $r = .48$, and when pooled across the experiments, $r = .38$. Other variables were not associated with cocaine choice bias in Experiment 3 or the pooled sample.

Attentional Bias

A significant effect of cue was observed wherein participants fixated on cocaine-related images longer than neutral images, $t_{23} = 3.138$, $p = .005$, $d_z = 0.64$. This effect is represented by a fixation time attentional bias score that was positive for most participants (mean = 89.1 [SEM = 28.4] ms Figure 4; right panel). Percentage final fixation scores were significantly greater than 50% (mean = 58.6% [SEM = .02]), $t_{23} = 4.68$, $p < .001$, $d = 0.96$, indicating a greater percentage of trials with final fixation on the cocaine image than expected by chance. Fixation time and percentage final fixation attentional bias scores were not related to breath CO levels upon arrival, $r = -.24$ and $-.08$, respectively.

Relationship Between Choice Bias and Attentional Bias

The bivariate correlation between fixation time attentional bias and cocaine-cued choice bias was positive, but not statistically significant, $r = .33$, $p = .11$. Removal of two apparent outliers (Choice Bias = 10%) attenuated this relationship, $r = .19$, $p = .39$. The correlation between percentage final fixation scores and choice bias was positive and significant, $r = .47$, $p = .02$. Removal of two apparent outliers attenuated this relationship, $r = .24$, $p = .29$.

Discussion: Experiment 3

Participants showed a choice bias for cocaine-cued monetary reinforcers as well as attentional bias for those cues. The choice bias observed reproduced those effects observed in Experiments 1 and 2, indicating that the outcome was not bound by the specific task parameters used in those earlier experiments. The significance and magnitude of the fixation time attentional bias observed also reproduced similar outcomes in recent studies evaluating cocaine cue attentional bias using a visual probe method (Marks et al. 2014a, 2014b, 2015,

2016). Results with another measure (i.e., percentage final fixation scores) were also consistent with an attentional bias towards cocaine-related cues.

Fixation time attentional bias scores were not significantly related to choice bias. Participants with a greater percentage of trials in which the final fixation was on the cocaine image did show greater choice bias scores, however, two outliers seemed to drive this effect. These findings suggest that attentional bias may partly contribute to the biased choice in a concurrent setting, which is partially consistent with other studies evaluating the role of attentional bias in concurrent choice procedures. For example, Rose and colleagues (2013) found that approximately 30% of the change following alcohol devaluation on a concurrent alcohol-soda choice task was mediated by changes in attentional bias (see Rose et al. 2018 for a replication of this effect, however with a smaller indirect effect size of ~ 18%). Similar results have been observed for food reinforcers with one series of experiments demonstrating a 7%-11% increase in choices for snack foods presented for a long (900 ms) compared to short (300 ms) cue duration (Armel et al. 2008). The delivery of a commodity (or points directly redeemed for the commodity) rather than money may explain some of the discrepancies between the present results and previous studies. Alternatively, the effect of attentional bias may be modest (e.g., 18% indirect effect for alcohol or 11% maximal increase for food choice) and the relatively small and homogenous sample was not adequately powered or varied to detect these effects. Future studies with a larger sample that evaluates a battery of potential mediators (e.g., craving, demand) are needed to clarify these discrepancies.

General Discussion

The purpose of these experiments was to test the ability of cocaine-related cues to influence concurrent reinforcer choice in humans. A bias for cocaine-cued monetary values was observed across three separate experiments and samples and was supported by varied analytic approaches. As outlined in the discussions above, these experiments demonstrated that this choice bias was selective to individuals with a cocaine use history (Experiment 1) and reproducible with additional categorized control trials (Experiment 2). Modest support for an attentional bias mechanism was found (Experiment 3) suggesting that future studies will need to evaluate visual attention in combination with other potential factors underlying cue influenced decision-making.

Selection of cocaine-cued monetary choices in this concurrent choice procedure is consistent with and extends a series of recent studies using a cocaine-picture choice task (see review in Moeller and Stoops 2015). Across several studies, including explicit and implicit task variants, individuals with a cocaine use disorder chose to view more cocaine images than controls in a concurrent-choice setting (Moeller et al. 2009, 2010, 2013). Notably, one study found that the contrast of cocaine versus pleasant image selection prospectively predicted drug use in a group of treatment-seeking participants over a six-month period (Moeller et al. 2013). These findings suggest that cocaine-related images maintain responding and behavioral allocation even in the absence of the primary reinforcing effects of the drug. The results of the present study parallel these findings by demonstrating that biased responding can extend to choices for other reinforcers incidental to and spatially contiguous with drug-

related cues. Future research evaluating the prospective association of drug-cued choice with drug-taking behavior will help reveal the clinical relevance of these findings. Nevertheless, this study contributes to a growing literature developing tasks suitable for use in treatment-seeking individuals or other populations with whom traditional measurement of drug reinforcement are not possible due to ethical or medical contraindications (e.g., drug-picture choice tasks, commodity purchase tasks; Bruner and Johnson 2014; MacKillop 2016; Moeller et al. 2009; Moeller and Stoops 2015; Strickland and Stoops 2017).

Prior research evaluating concurrent choice for drug-related cues has demonstrated a relationship between bias for drug stimuli and measures of alcohol (Hardy and Hogarth 2017; Hogarth et al. 2018), tobacco cigarette (Hogarth and Chase 2011, 2012; Miele et al. 2018), and cocaine use severity (Moeller et al. 2009, 2013). Pooling participants across the three experiments revealed a medium effect size association between choice bias and DAST scores. This finding is consistent with prior reports of positive associations between use severity and drug choice biases and suggests that this relationship generalizes to situations in which drug is a cue incidental to the choice rather than the reinforcer being delivered. Significant associations with use frequency were not observed, however, which contrasts with the findings of Moeller and colleagues (2009, 2013), and could be due to the relatively homogenous characteristics of the study sample (i.e., all non-treatment seeking individuals with cocaine use disorder).

Significant effects at a -1 monetary difference were observed in Experiments 1 and 2. These outcomes represented greater disadvantageous selection for reinforcers on the cocaine side by cocaine participants compared to controls (Experiment 1) and on cocaine trials compared to categorized-neutral trials (Experiment 2). Varying the value of the primary reinforcer (i.e., money) across different dimensions permitted modeling of these data as a function of expected value using a multiparameter logistic choice function. Results from this function indicated a negative inflection point in the cocaine group (Experiment 1) and on cocaine trials (Experiment 2), suggesting increases in selections of negative expected value and maladaptive choices. Importantly, these effects were not observed on neutral trials in Experiment 2, which indicates that participants could still engage in advantageous and rational decisionmaking and that the cocaine stimulus, as opposed to inherent cognitive difficulties, was negatively affecting this decision-making process. These results are consistent with prior studies in the animal laboratory demonstrating the ability of cues to decrease sensitivity to primary reinforcement and promote maladaptive decision-making (Chow et al. 2017; Smith et al. 2018; Zentall 2014) and illustrate that this effect can occur in humans even when the primary reinforcer is explicitly cued and of a certain value.

Limitations of the current study provide a clear direction for future research. Only a single reinforcer type (i.e., money) was evaluated. Money was selected for this initial demonstration, as it is a reinforcer of a standardized and easily communicated magnitude. It would be of interest to evaluate how drug-related cues may influence other non-drug reinforcers (e.g., social interaction) and how these effects may differ when drug-cues are paired with distinct reinforcers that are perceived to be of similar value in a concurrent setting (e.g., drug cue with social interaction versus neutral cues with money or vice versa). Additionally, only one type of appetitive cue was evaluated in the choice procedure. Other

studies indicate similar cue-related increases in concurrent choice for alcohol (e.g., Hardy and Hogarth 2017; Hogarth et al. 2018) and tobacco cigarette (e.g., Miele et al. 2018) stimuli suggesting that the results observed here would generalize to these populations when the drug cue is incidental to the selected reinforcer. The addition of another approach-related cue in the task, such as food, would also help to determine whether the magnitude of cued choice bias generalizes to non-drug reinforcers. In this regard, it is of interest how drug-related cues may continue to bias choice when competing against other appetitive stimuli related to other drugs (e.g., cocaine versus cigarette cues) or non-drug reinforcers (e.g., cocaine versus food cues). The pitting of drug versus prosocial, appetitive cues would be of particular interest as such procedures may model the decision to engage in drug-related activities at the expense of beneficial alternatives or, conversely, the ability of alternatives to shift behavioral allocation.

Laboratory-conditioned cues were not used; instead each experiment relied on conditioning that would have occurred outside of the experimental setting. This choice was partially motivated by the preliminary nature of this study, given that the experimental conditioning of cues to cocaine-taking behavior requires more extensive medical oversight. Relatedly, measures of subjective liking or arousal were not collected, which precluded mediation testing the pathway between variations in stimulus valence and choice bias. The stimuli selected had previously been successful in generating cocaine cue attentional bias (Marks et al. 2014a, 2014b, 2015, 2016) and were successful in Experiment 3 suggesting salience and subjective liking. Nevertheless, future work should test whether biased responding extends to laboratory-conditioned cues and whether valence or arousal could mediate this effect.

Other limitations could be addressed with additional experiments in future work. The sample size in each individual experiment was small, however the systematic replications of the choice bias across each experiment diminish this concern. Although the inclusion criteria allowed for participants age 18–55, participants in the cocaine group tended to be older, consistent with the demographic composition of this population at the study site and in the United States (Center for Behavioral Health Statistics 2017). A relationship between age and bias in the cocaine group was also not observed. Targeted sampling of younger individuals and those with less extensive cocaine use histories would help clarify the extent to which the current results generalize. Selectivity could also be further examined with additional neutral trials containing one stimulus of a clear neutral category (e.g., boxes) with non-categorized neutral images. Similarly, tests such as cannabis cues with the control group in Experiment 1 could help reveal if the direction and magnitude of choice bias map on to a participant's favored drug or drug class.

These experiments represent a preliminary assessment of the effect of drug-related cues on concurrent choice in humans. The ecological impact of such behavioral allocation biased by drug cues supports continued research. The natural environment presents varied decision-making events, and in the case of a drug-involved individual, many of these decisions are preceded by drug cues. This study suggests that these drug cues may direct preference selection towards such decisions when the cue-contiguous choice is equal or, in some cases, of a negative expected value. The tasks described in this study also provide a simple way to measure this putative bias throughout various stages of disease course (e.g., by substance use

disorder severity; throughout treatment and relapse events). Future research evaluating parametric manipulations suggested above as well as prospective associations will help reveal the specific clinical relevance of these choice biases for cocaine use, specifically, and substance use, broadly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1. Overview of Cued Concurrent Choice Task

. Task trials began with a fixation point presented for 1000 ms. Two cues presented side-by-side replaced the fixation point and were displayed for 2000 ms. Monetary values then appeared under each stimulus and the participant was required to choose the value he or she would like to receive. Monetary choices and trial cues remained on the screen for up to 2000 ms during participant choice, after which a new fixation point was presented and a new trial began. Depicted is an equal value trial in which the reinforcer available was equal for each cue (for additional details see Supplemental Materials).

Fig. 2. Active cocaine users show cocaine-cued choice bias (Experiment 1)

. Active cocaine users ($n = 12$; circles and solid line) and controls ($n = 12$; squares and dotted line) completed a cued concurrent choice task for monetary reinforcers. Presented are mean percent choices for cocaine-cued monetary value across each quantitative difference in cocaine and neutral-cued values. The y-axis dotted line represents indifference (50%). Equal value trials occurred at 0 in which cocaine-cued and neutral-cued values were equal. Error bars represent standard error of the mean (SEM).

Fig. 3. Cued-choice bias is specific to cocaine-cued reinforcers (Experiment 2)

Active cocaine users ($n = 14$) completed a cued concurrent choice task for monetary reinforcers. Presented are mean percent choices for cocaine-cued reinforcers (circles and solid line) and for neutral sign-cued reinforcers across each quantitative difference reinforcer value. The y-axis dotted line represents indifference (50%). Equal value trials occurred at 0 in which cocaine-cued and neutral-cued values were equal. Error bars represent SEM.

Fig. 4. Cocaine-cued choice and attentional bias (Experiment 3)

Active cocaine users ($n = 25$) completed a cued concurrent choice task during laboratory eye tracking. Presented are individual participant percent cocaine-cued choices on equal value trials (i.e., when cocaine-cued and neutral cued values were equal) and individual participant attentional bias scores. Also presented are mean and SEM. The y-axis dotted line represents indifference.

Table 1.

Participant Demographics

	Experiment 1		Experiment 2		Experiment 3	
	Cocaine (n = 12)	Controls (n = 12)	Cocaine (n = 14)	Cocaine (n = 25)	Cocaine (n = 25)	Cocaine (n = 25)
Demographics						
Age	46.0 (4.3)	24.8 (7.0) ***	45.9 (6.9)		42.0 (6.8)	
Female	25.0%	16.7%	35.7%		36.0%	
White	16.7%	58.3%	21.4%		36.0%	
Education	12.2 (1.3)	13.8 (2.2) *	12.6 (1.9)		11.8 (1.6)	
Drug Use						
Drinks Per Week	27.5 (22.6)	4.3 (5.4) **	8.5 (10.4)		14.2 (14.7)	
AUDIT	11.8 (9.9)	5.9 (4.7)	5.3 (3.2)		5.9 (3.7)	
Alcohol Use Disorder	50.0%	41.7%	14.3%		28.0%	
Cigarette Smoker	83.3%	41.7%	78.6%		96.0%	
CPD ^a	9.8 (6.9)	9.5 (6.7)	8.5 (5.0)		12.9 (6.7)	
FTND ^a	3.4 (1.9)	2.8 (2.3)	3.5 (2.1)		4.2 (2.4)	
DAST	9.3 (3.6)	4.0 (2.3) ***	10.0 (3.7)		10.2 (5.2)	
Ever AMP	33.3%	50.0%	28.6%		48.0%	
Ever BENZ	41.7%	25.0%	28.6%		64.0%	
Ever OPI	58.3%	50.0%	64.3%		64.0%	
Ever THC	100%	100%	92.9%		100%	
Cocaine Use						
Ever Cocaine	100%	33.3% ***	100%		100%	
Past Week Cocaine Use	3.9 (2.2)	0.0 (0.0) ***	4.0 (1.6)		3.8 (2.0)	
Past Month Cocaine Use	17.5 (8.9)	0.3 (0.5) ***	17.0 (6.7)		15.6 (8.6)	
Years Since First Cocaine Use	21.8 (7.7)	3.3 (1.3) ***	17.6 (9.2)		17.9 (8.3)	
Lifetime Cocaine Use	4114 (3265)	4.8 (3.6) ***	4624 (4297)		3278 (2749)	
Cocaine Abuse	16.7%	0.0% ***	14.3%		12.0%	

	Experiment 1		Experiment 2	Experiment 3
	Cocaine (n = 12)	Controls (n = 12)	Cocaine (n = 14)	Cocaine (n = 25)
Cocaine Dependence	83.3%	0.0% ***	85.7%	88.0%

Note. AUDIT = Alcohol Use Disorder Identification Test; CPD = cigarettes/day; FTND = Fagerström Test for Nicotine Dependence; DAST = Drug Abuse Screening Test; AMP = stimulant use; BENZ = benzodiazepine; OPI = opioid; THC = cannabis; Lifetime Cocaine Use = number of times used cocaine.

^a Only participants reporting tobacco cigarette use

* $p < .05$

** $p < .01$

*** $p < .001$ comparing cocaine and control groups in Experiment 1

Table 2.

Demographic and Drug Use Correlates of Percent Cocaine-Cued Choice

Variable	Experiment 1	Experiment 2	Experiment 3	Pooled
Age	.53	-.26	.22	.17
Female	-.71*	.56*	.17	.08
White	.23	.25	-.07	.04
Education (Years)	-.06	.43	-.01	.12
AUDIT	.05	-.05	.01	-.04
DAST	.05	.34	.48*	.38**
Past Month Cocaine Use	-.12	-.22	.27	.10
Past Week Cocaine Use	-.13	-.27	.23	.06
Years Since First Cocaine Use	-.23	-.29	.07	-.09
Lifetime Cocaine Use	-.23	-.13	.17	.03
Cocaine Dependence	.56	.16	-.14	.09

Note. AUDIT = Alcohol Use Disorder Identification Test; DAST = Drug Abuse Screening Test; Lifetime Cocaine Use = number of times used cocaine. Correlations only for participants in the cocaine group in Experiment 1 ($n = 12$). Pooled correlations combine participants from all three experiments ($n = 51$)

*
 $p < .05$

**
 $p < .01$

 $p < .001$ (statistical significant correlations bolded)