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Effect of experimental analogs of contingency management treatment on cocaine seeking behavior

Mark K. Greenwald[a,*], **David M. Ledgerwood**[a], **Leslie H. Lundahl**[a], and **Caren L. Steinmiller**[a,b]

[a]Substance Abuse Research Division, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI 48201, USA

[b]Department of Pharmacology, University of Toledo, Toledo, OH 43614, USA

Abstract

Background—Contingency management (CM) treatment is effective for treating cocaine dependence but further mechanistic studies of its efficacy are warranted. This study aimed to determine whether: (a) higher vs. lower predictable money amounts ($3 vs. $1; analogs of standard voucher-based CM) increase cocaine demand elasticity; and (b) probabilistic amounts matched for expected value with the $3-predictable amount (50% chance of $6; 25% chance of $12; and 12.5% chance of $24; analogs of prize CM) similarly affect cocaine choice.

Methods—Each of 15 cocaine-dependent participants first completed a qualifying session to ensure that intranasal cocaine functioned as a reinforcer, then completed a 10-session, within-subject, randomized crossover study. During each of the 10 sessions, the participant responded on a progressive ratio schedule to earn units of cocaine (5-mg or 10-mg) and/or money (five monetary conditions above).

Results—During the reinforcement qualifying session (10-mg vs. 0-mg units; no money alternative), cocaine choice was high. The $3-predictable amount significantly decreased cocaine choice relative to both the $1-predictable amount and the qualifying session. Cocaine-choices in the probabilistic conditions were similar to the $3 predictable condition.

Conclusions—These findings indicate that CM interventions targeted at reducing cocaine self-administration are more likely to succeed with higher value non-drug reinforcement.

Keywords

Cocaine; Self-administration; Contingency management; Magnitude; Probability

[*]Corresponding author at: Department of Psychiatry and Behavioral Neurosciences, Tolan Park Medical Building, Suite 2A, 3901 Chrysler Service Drive, Detroit, MI 48201, USA. Tel.:+13139933965; fax:+13139931372. mgreen@med.wayne.edu (M.K. Greenwald).

Contributors

M.K.G. contributed to study design and implementation, data analysis and interpretation, and drafting the manuscript. D.M.L. and L.H.L. contributed to study design and implementation, and editing the manuscript. C.L.S. contributed to study design and implementation, and data analysis.

Conflict of interest

The authors declare no conflicts of interest in relationship to performing this study.

1. Introduction

Contingency management (CM) treatment is effective for reducing cocaine use in a magnitude-dependent manner (Higgins et al., 1991, 1994b, 2000, 2007; Petry et al., 2004; Rothfleisch et al., 1999). In standard CM treatment, economic consequences such as voucher earnings are scheduled *predictably* when the target behavior occurs, e.g., cocaine-negative urine. In prize-based CM treatment, clinically desired behavior earns access to a *probabilistic* lottery drawing that can yield a prize, e.g., 50% chance of no prize, 41.8% chance of a small-magnitude prize (≈$1), 8% chance of a moderate-magnitude prize (≈$20), and 0.2% chance of a large-magnitude prize ($80–100; Petry et al., 2005). Interpreting the efficacy of prize CM can be challenging because magnitudes and probabilities of prizes are confounded, i.e., low-value prizes are more likely than high-value prizes. Although the expected value of a single draw is small (e.g., $0.73 in Petry et al., 2005), these contingency arrangements can produce robust behavior change.

This study addressed two separate issues in one experiment, using analogs of standard (predictable) and prize-based (probabilistic) CM treatments. We determined whether: (1) higher vs. lower magnitude predictable money reinforcement would decrease cocaine choice; and (2) probabilistic and predictable money reinforcement conditions equated for overall expected value would differentially alter cocaine choice. We predicted that fewer cocaine choices would be made with (1) higher vs. lower magnitude predictable money alternative, consistent with prior findings on the effect of non-drug magnitude on cocaine choice (Higgins et al., 1994a; Donny et al., 2003, 2004); and (2) higher vs. lower probability money reinforcement, consistent with findings that human subjects exhibit a predictability bias (Sharp et al., 2012).

2. Methods

2.1. Participant recruiting and selection

The local Institutional Review Board approved this study, which was conducted according to the Declaration of Helsinki. A certificate of confidentiality was obtained. Male and female volunteers, aged 21–55 years, who were not seeking substance abuse treatment were screened using medical history, blood and urine chemistry, electrocardiogram and tuberculin testing, physical exam, and psychiatric interview (First et al., 1996).

All participants met DSM-IV criteria for current Cocaine Abuse or Dependence. Monitored urine specimens were positive for cocaine (≥300 ng/ml) and negative for opioids and methadone (<300 ng/ml), amphetamines (<1000 ng/ml) and barbiturates (<200 ng/ml). Benzodiazepine-positive (≥300 ng/ml) or THC-positive (≥50 ng/ml) samples were allowed but sedative and cannabis dependence diagnoses were exclusionary. Alcohol-free breath samples (<.002%) were required and alcohol dependence diagnosis was exclusionary. We excluded candidates for: abnormal ECG or laboratory test results; chronic health problems, serious psychiatric problems (e.g., psychosis, bipolar disorder, non-substance-induced depression) or taking medications to control these conditions; pregnancy (urine HCG), lactation or inadequate use of birth control methods (self-report); or cognitive impairment

(IQ < 80 on Shipley Institute of Living Scale; Zachary, 1991). Participants provided written informed consent.

2.2. Study design

A within-subject, randomized crossover design was used with two factors: cocaine unit dose (5-mg vs. 10-mg) *X* money alternative (two *predictable* unit amounts: $1 vs. $3; and three *probabilistic* unit amounts: 50% chance of earning $6; 25% chance of earning $12; and 12.5% chance of earning $24: odds-against of 1:1, 3:1, and 7:1, respectively). Predictable money conditions are analogs of lower value ($1) and higher value ($3) standard CM in which reinforcement is always delivered when the patient has abstained from drug use. Probabilistic alternatives, matched for expected value to the $3 predictable amount, mimic prize-based CM in which reinforcement is delivered via lottery when the person has abstained from drug use.

2.3. Protocol timeline

Participants lived on a residential unit for 16 nights that combined with staff observation and daily urinalysis, ensured abstinence from unsanctioned drug use. Participants earned $40 for each night on the residential unit.

2.3.1. Cocaine-reinforcement qualifying session—For each participant, we established that cocaine functioned as a reinforcer in a single-session procedure. The participant insufflated *Drug A* (4-mg or 110-mg) at 0900 and *Drug B* (110-mg or 4-mg) at 1100. An 11-trial Drug A vs. B choice progressive ratio task was conducted (1300–1600), during which the participant could earn 10-mg (active) and/or 0-mg (placebo) units. However, participants were not obligated to respond at all. Response requirements (computer mouse clicks) for each option increased independently across trials (100, 250, 505, 915, 1530, 2400, 3575, 5105, 7040, 9430, and 12,325). The maximum earned cocaine dose was 110-mg. The first mouse click “locked in” that choice; the non-selected option disappeared, the participant had to complete the remaining responses, after which a tone sounded and the point counter was updated. After a 5-s intertrial interval, the next trial began and the subject could respond on either option. The session ended after 3 h. If the subject completed all 11 choices before 3 h, the subject could only rest, drink water, or take a bathroom break for the remainder of that period, e.g., no smoking cigarettes, eating, watching TV, or phone use.

Cocaine reinforcement was defined a priori as occurring when cocaine (10-mg unit dose) maintained global preference (chosen ≥6/11 trials) and the subject chose cocaine ≥2 more trials than placebo.

2.3.2. Cocaine vs. money choice sessions—Each participant completed 10 choice sessions, in randomized order, involving all cocaine-dose and money-alternative combinations. In each session, the total available dose (55-mg or 110-mg on a given day) was insufflated at 0900. Participants were asked to attend to effects of the dose because that afternoon they could earn units of this total dose and/or money. After lunch, an 11-trial Drug vs. Money choice task was conducted (1200–1500); on each trial, the participant could earn

1/11th of the sampled cocaine dose (5-mg units of 55-mg, or 10-mg units of 110-mg) or money unit amount. Response requirements for Drug and Money options increased independently across trials using the same procedures as the reinforcement qualifying session. All earned money was paid at study discharge.

2.4. Drug administration

Cocaine HCl powder (Research Triangle Institute) was prepared in 110-mg constant-volume doses. Placebo contained 4-mg cocaine and 106-mg lactose; 55-mg doses contained 55-mg cocaine and 55-mg lactose; 110-mg doses contained only cocaine. Response-contingent doses contained all earned cocaine with lactose complement. The participant insufflated the powder through a plastic straw, while staff observed.

2.5. Data analyses

ANOVA was used to examine effects of cocaine unit dose (5-mg and 10-mg) and money alternative units (predictable: $1 vs. $3; probabilistic: $6 [50%], $12 [25%], and $24 [12.5%]) on cocaine responding. Huynh–Feldt adjusted P values were used for sphericity violations. Significance level was $P < .05$. One analysis determined whether cocaine choice decreased with a higher vs. lower magnitude predictable money amount, and the second analysis determined whether cocaine responding varied during variable-probability $3.00 reinforcement.

3. Results

3.1. Participant characteristics

Fifteen subjects (8 male, 4 female African Americans, 3 white males) completed the study. They were (*Mean* ± *SD*) 45.5 ± 4.1 years old and had completed 13.7 ± 2.4 years of education. All reported extensive histories of crack cocaine use (23.3 ± 6.6 years) and smoking tobacco cigarettes daily (17.1 ± 5.7). Seven smoked marijuana and one used benzodiazepines during the past month.

Participants reported past-month total income averaging $1892 ± 1547, spending 56 ± 27% of total income on cocaine ($1050 ± 119). Participants reported 7.2 ± 4.3 weekly cocaine purchases, estimated cocaine purity of 44 ± 28%, with round-trip purchase time of 29.1 ± 31.1 min, and purchase amount per episode of $44.67 ± 40.64.

3.2. Cocaine choice

3.2.1. Predictable money alternatives—Cocaine choice was significantly lower with the $3 vs. $1 predictable alternative and there was no effect of cocaine dose; see Fig. 1.

3.2.2. Probabilistic money alternatives—Cocaine choices in the probabilistic conditions did not significantly differ from the $3 predictable conditions, and, in most cases, were lower than the $1 condition; see Fig. 1. There were no significant differences in money amounts earned between the $3 predictable condition and probabilistic conditions that were matched a priori for expected value.

4. Discussion

This study compared effects of the amount and likelihood of money alternatives on cocaine-seeking behavior. Cocaine choice for both unit doses decreased when the money alternative amount was larger ($3) compared to when it was smaller ($1); this finding is consistent with results from preclinical studies (Nader and Woolverton, 1991; Nader et al., 1993; Woolverton et al., 1997; Rodefer et al., 1997; Peitz et al., 2013), human laboratory studies (Donny et al., 2003, 2004; Higgins et al., 1994a; Stoops et al., 2012) and clinical trials (Higgins et al., 1991, 1994b, 2000, 2007; Petry et al., 2004; Rothfleisch et al., 1999), which supports the validity of this study and provides a platform for the more novel investigation of reinforcement probability.

Clinical trials of CM treatment often use escalating schedules of reinforcement, in which consecutive drug abstinence over time leads to progressively greater economic gain for the patient. Use of a choice progressive ratio schedule in the human laboratory mirrors this process, such that consecutive choice of money despite increasing response requirements (and foregoing drug despite smaller response requirements) results in greater economic gain. Using this approach, we found that participants worked less for cocaine in the $3-equivalent conditions than $1 condition. Several studies that evaluated effects of schedules of reinforcement on behavior maintained by nicotine (Roll et al., 1996; Roll and Higgins, 2000; Roll and Howard, 2008) and methamphetamine (Roll and Shoptaw, 2006) found that escalating schedules of non-drug reinforcement reduce drug choice to a greater extent than fixed schedules. Together, these studies confirm that economic gain reduces drug-maintained responding not only as a function of magnitude, but also when effort required to earn the economic reinforcer escalates.

This study's novel finding was that cocaine choice did not significantly differ as a function of money probability. Given that humans exhibit a predictability bias (Sharp et al., 2012) and that probability discounting is routinely observed in animals and human subjects (Green et al., 2010; Mobini et al., 2002; Rachlin et al., 1991), this was unanticipated. Several factors may explain this result. First, to disentangle the effect of reinforcer probability from magnitude, we held constant monetary expected value; thus, the lack of difference between conditions could have been due to participants' computing and using expected value in their choices. Second, although point earnings were signaled after completing each money or cocaine ratio (i.e., displayed on the computer screen), probabilistic earnings were not determined until the end-of-session lottery (rather than after each trial), which could have influenced the findings. Third, most probability discounting studies evaluate discrete choices between a smaller/certain vs. larger/varying uncertainty reward; in addition, choices in the present study required escalating effort, which may complicate interpretation. Fourth, the flat-rate nightly pay may have influenced response-contingent choices. Finally, there was individual variation: seven subjects chose similar cocaine amounts (defined as ± 2 choices) across probabilistic money conditions at both cocaine unit doses, five subjects deviated from this definition of consistency for only one unit dose, and three subjects were more variable.

The present findings are largely consistent with Matching (Hernnstein, 1961; Baum, 1974) or Maximization (Graf et al., 1964; Shimp, 1966) theory at the overall session level, and

seem to argue that value-matched predictable and probabilistic conditions similarly decrease cocaine choice. However, individuals may respond differently when choices are perceived to be “bundled” rather than separate, introducing a bias toward delayed reward (Ainslie and Monterosso, 2003; Hofmeyr et al., 2010). Notably, participants in this study were not paid money earnings until the end of the study, possibly leading them to consider their chances of economic reinforcement across all choices rather than each choice separately. Our findings support the idea that choices were “bundled”: Participants made few cocaine-money choice shifts (trial-by-trial alternations) in all experimental conditions, i.e., they committed to one option and did not deviate often from this strategy (see Table 1). Thus, within-session behavior aligns with the picoeconomic theory of bundling, and overall-session choice data align with Maximization theory. This pattern of “self-controlled” responding has implications for treatment, in suggesting the need to: (1) schedule early, frequent opportunities for reinforcement (which patients may be inclined to bundle), (2) escalate value of non-drug reinforcers as rapidly as possible, and (3) teach patients cognitive strategies to attend to these contingencies to enhance salience of schedule parameters and their connection to behavior change.

In conclusion, this study provides the first human experimental demonstration that cocaine-maintained responding is susceptible to reduction by higher magnitude predictable non-drug reinforcement as well as objective value-equated probabilistic reinforcement.

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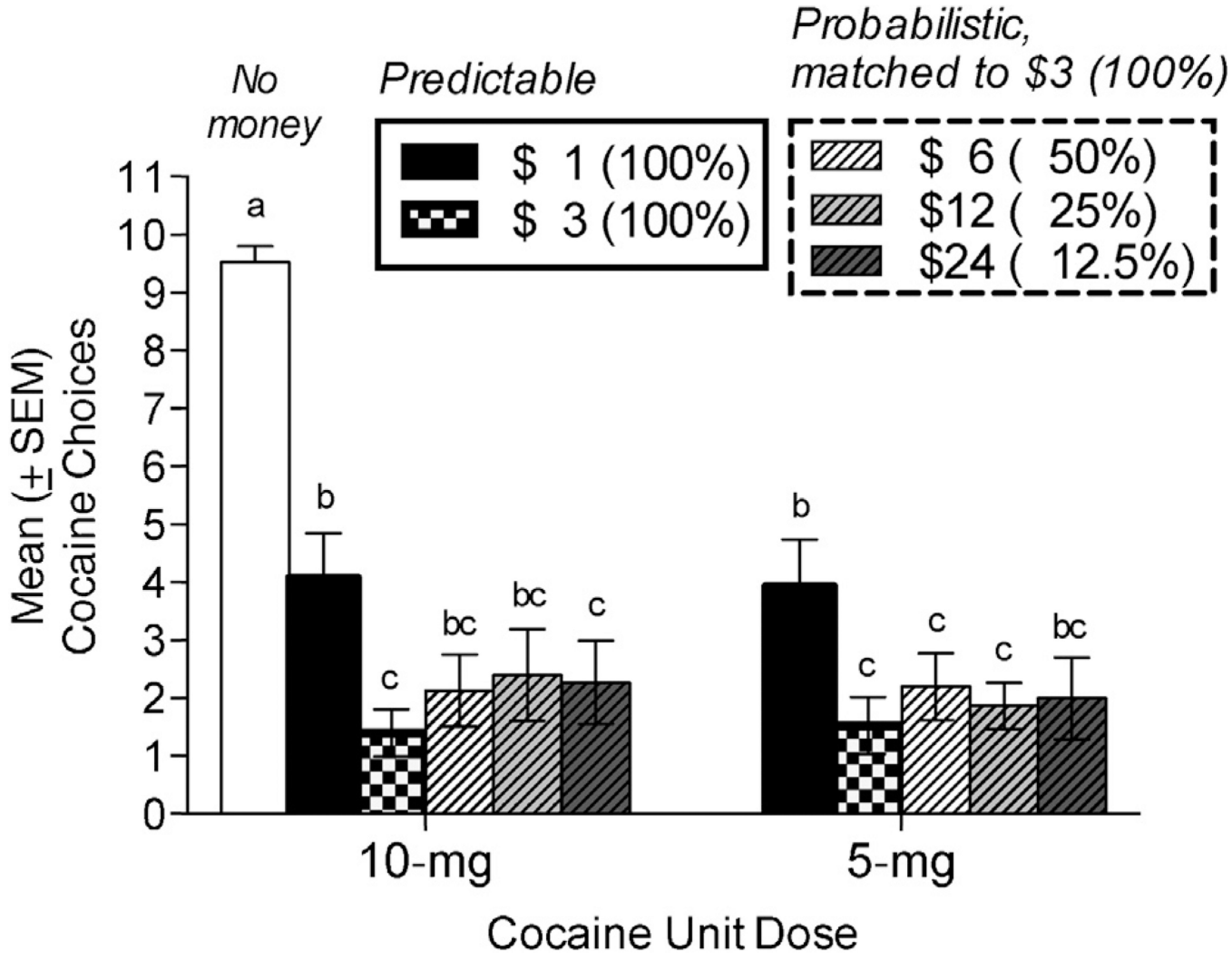

Fig. 1.

Mean ± 1 SEM choice for cocaine 10-mg units in the reinforcement qualifying session (white bar) and for cocaine 10-mg or 5-mg units in each of the money alternative conditions. Non-shared letters above the error bars indicate significant differences in cocaine responding. Within each unit dose, $3 predictable significantly suppressed cocaine choice relative to $1 predictable amount. Within each unit dose, probabilistic conditions did not significantly differ from the $3 predictable amount.

Table 1

Measures of cocaine and monetary responding during choice sessions.[A]

Measure[B]	10-mg vs. 0-mg	10-mg cocaine unit dose vs. money alternative					5-mg cocaine unit dose vs. money alternative				
		$1 (100%)	$3 (100%)	$6 (50%)	$12 (25%)	$24 (12.5%)	$1 (100%)	$3 (100%)	$6 (50%)	$12 (25%)	$24 (12.5%)
Total cocaine choices Money alternative $F(4,56) = 5.79$, $P = .002$, $\eta^2 = .293$	9.53 (.27)	4.07[b] (.78)	1.40[a] (.41)	2.13[a] (.62)	2.40[a] (.79)	2.27[a] (.72)	3.93[b] (.81)	1.53[a] (.49)	2.20[a] (.57)	1.87[a] (.40)	2.00[a] (.70)
Cocaine breakpoints Money alternative $F(4,56) = 4.92$, $P = .008$, $\eta^2 = .260$	8500 (616)	1957[b] (806)	270[a] (112)	689[a] (344)	1108[a] (531)	880[a] (395)	1893[b] (713)	359[a] (167)	621[a] (264)	330[a] (83)	778[a] (395)
Money-first choices Money alternative $F(4,56) = 4.34$, $P = .000$, $\eta^2 = .238$	N/A	5.93[b] (1.09)	8.53[a] (.80)	8.13[a] (.81)	7.80[a] (.92)	8.40[a] (.91)	4.73[b] (1.15)	9.13[a] (.55)	7.20[a] (1.10)	7.33[a] (1.10)	7.67[a] (1.09)
# Cocaine-money choice shifts Money alternative $F(4,56) = 1.61$, $P = .187$, $\eta^2 = .103$	N/A	1.73 (.47)	1.00 (.28)	1.40 (.38)	1.53 (.52)	1.13 (.48)	2.00 (.44)	1.00 (.26)	1.73 (.57)	1.33 (.36)	1.33 (.53)
Money earned Money alternative $F(4,56) = 11.37$, $P = .$	N/A	$6.93[b] (.78)	$28.60[a] (1.20)	$24.80[a] (2.54)	$21.60[a] (4.09)	$28.80[a] (5.34)	$7.00[b] (.85)	$28.00[a] (1.39)	$26.00[a] (2.60)	$32.00[a] (5.19)	$33.60[a] (8.05)

Measure[B]	10-mg vs. 0-mg	10-mg cocaine unit dose vs. money alternative					5-mg cocaine unit dose vs. money alternative				
		$1 (100%)	$3 (100%)	$6 (50%)	$12 (25%)	$24 (12.5%)	$1 (100%)	$3 (100%)	$6 (50%)	$12 (25%)	$24 (12.5%)
000, η^2 = .448											

[A] Sample means (±1 SEM), n = 15.

[B] For cocaine choice and breakpoint, there was a significant main effect of money alternative (the reinforcement qualifying session was excluded from these analyses), but no significant effects involving cocaine unit dose (i.e., no main effect or interaction with money alternative) based on the overall ANOVA. "η^2" = partial *eta*-squared (estimated effect size).

In post hoc tests, money alternative condition means that share superscript 'a' or 'b' do not significantly differ. Money-first choices provide an index of "resistance to cocaine lapse", i.e., higher numbers reflect "commitment" to money and delay to first cocaine choice. Number of choice shifts reflects the frequency of alternating between drug and money options (or vice versa) within each session, which relate to "bundling" of choices (see text). Money earned provides a manipulation check; these data provide a measure of substitutive action against cocaine reinforcing efficacy.