Published in final edited form as:

Pharmacol Biochem Behav. 2013 January ; 103(3): 481–486. doi:10.1016/j.pbb.2012.09.025.

Alternative Reinforcer Response Cost Impacts Methamphetamine Choice in Humans

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Abstract

Methamphetamine use disorders are a persistent public health concern. Behavioral treatments have demonstrated that providing access to non-drug alternative reinforcers reduces methamphetamine use. The purpose of this human laboratory experiment was to determine how changes in response cost for non-drug alternative reinforcers influenced methamphetamine choice. Seven subjects with past year histories of recreational stimulant use completed a placebo-controlled, crossover, double-blind protocol in which they first sampled doses of oral methamphetamine (0, 8 or 16 mg) and completed a battery of subject-rated and physiological measures. During subsequent sessions, subjects then made eight discrete choices between 1/8th of the sampled dose and an alternative reinforcer (\$0.25). The response cost to earn a methamphetamine dose was always 500 responses (FR500). The response cost for the alternative reinforcer varied across sessions (FR500, FR1000, FR2000, FR3000). Methamphetamine functioned as a positive reinforcer and produced prototypical stimulant-like effects (e.g., elevated blood pressure, increased ratings of “Stimulated”). Choice for doses over money was sensitive to changes in response cost for alternative reinforcers in that more doses were taken at higher FR values than at lower FR values. Placebo choices changed as a function of alternative reinforcer response cost to a greater degree than active methamphetamine choices. These findings suggest that manipulating the effort necessary to earn alternative reinforcers could impact methamphetamine use.

Keywords

Methamphetamine; Humans; Self-Administration; Alternative Reinforcer

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The authors declare no conflicts of interest relevant to this work.

Authors Stoops and Rush designed the study. Author Stoops and Rush oversaw the conduct of the research. Author Stoops and Bennett conducted data analysis. Author Bennett managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

1. Introduction

Methamphetamine use remains a persistent public health concern. Data from the National Survey on Drug Use and Health (NSDUH) suggest that 353,000 Americans reported past-month methamphetamine use and 105,000 individuals indicated past-year initiation of methamphetamine use in 2010 (Substance Abuse and Mental Health Services Administration [SAMHSA] 2011). Additionally, methamphetamine use is commonly associated with comorbid psychiatric problems and disorders as well as needle sharing and risky sexual behaviors, which can lead to increased risk of contracting HIV (see Semple et al., 2004; Shoptaw et al., 2005; Shoptaw et al., 2006; Zweben et al., 2004). Because of these risks, methods for preventing or reducing methamphetamine use need be investigated.

Efforts to identify a pharmacotherapy for methamphetamine dependence have yet to produce a widely effective medication (see Karila et al., 2010; Rush et al., 2009, for reviews). Behavioral treatments, by contrast, show promise. Contingency management procedures are effective for substance-use disorders in general (see Petry, 2000, for a review) and for methamphetamine-use disorders in particular (e.g., Petry, et al., 2005; Reback et al., 2010; Roll et al., 2006a; Roll et al., 2006b; Roll and Shoptaw, 2006). Contingency management programs encourage methamphetamine users to abstain from methamphetamine-taking behavior by using alternative reinforcers to increase objectively verified drug abstinence (e.g., providing drug-negative urine samples). For example, Roll et al. (2006b) assessed the efficacy of a contingency management program relative to the Matrix model in individuals who met DSM-IV criteria for methamphetamine abuse or dependence. Subjects in the contingency management group were allowed to earn tokens, which were exchangeable for prizes. Some of these tokens provided praise for negative samples (i.e., were marked “Good Job”), while others could be exchanged for prizes of differing values (e.g., bus tokens, snacks, compact disc players, telephones). Subjects in the contingency management group submitted significantly more negative samples and had significantly longer periods of abstinence. Contingency management programs not only effectively reduce drug use; they may also reduce some of the associated behaviors associated with use of drugs like risky sexual behaviors and needle sharing (Hanson et al., 2008; Petry et al., 2010; Petry et al., 2011; Reback et al., 2010; Shoptaw et al., 2005).

Because contingency management programs have proven successful in reducing methamphetamine use and attendant problem behaviors associated with use, the parameters of such treatments need be investigated to determine how the efficacy of contingency management can be enhanced. Researchers in preclinical and human laboratories have used drug versus alternative reinforcer choice paradigms as models of contingency management to determine the factors critical to treatment efficacy (Higgins et al., 2004). The outcomes of this research show that schedules with increasing magnitudes of alternative reinforcer value for consecutive drug negative urines that reset for positive tests (Roll and Shoptaw, 2006; Roll et al., 2006a), higher magnitude reinforcers (Nader and Woolverton, 1991; Petry et al., 2004; Rowan-Szal et al., 1994), lower response requirements for alternative reinforcers or higher requirements for drug reinforcers (Nader and Woolverton, 1992), schedules without built-in negative consequences (Iguchi, et al., 1988), monetary alternative reinforcers (Stoops, et al., 2010a) and schedules without delays to reinforcement or exchange (Roll, et al., 2000; Rowan-Szal, et al., 1994) are most effective for reducing drug taking. Through the conduct of studies such as these, the optimal parameters of contingency management may be determined, providing clinicians with guidance in developing the most effective means of reducing drug-taking behavior.

Although there is a rich literature of laboratory studies that have investigated manipulations of drug versus alternative reinforcer choice, no laboratory studies have assessed the impact

of “cost” of alternative reinforcers on methamphetamine self-administration. Therefore, the purpose of this study was to assess the extent to which altering response cost requirements for alternative reinforcers (i.e., money) would mediate methamphetamine choice. Seven adults with past-year recreational stimulant use sampled oral doses of methamphetamine (0, 8 or 16 mg). Following sampling sessions, subjects then completed self-administration sessions in which they made eight discrete choices between 1/8th of the sampled dose and an alternative reinforcer (US\$0.25). The response cost requirement to earn a dose of methamphetamine was fixed across sessions (FR500), whereas the response cost requirement for the monetary reinforcer varied across sessions (FR500, FR1000, FR2000 or FR3000). We hypothesized that methamphetamine choice would increase as a function of dose and alternative reinforcer response requirement.

2. Materials and methods

2.1 Subjects

Seven non-treatment-seeking adult subjects (5 men, 2 women; 5 Caucasian, 2 African American) with past-year histories of recreational stimulant use completed the protocol. One other subject was enrolled into the protocol but was lost to follow-up before completing. Data from this individual were not included in the analyses. All subjects reported recreational stimulant use in the past year (i.e., mixed salt amphetamine [Adderall], 3,4-methylenedioxymethamphetamine [MDMA; ecstasy], methylphenidate or cocaine). Three subjects reported using Adderall (i.e., mixed amphetamine salts); one reported using ecstasy (i.e., 3,4-methylenedioxymethamphetamine [MDMA]); one reported using cocaine, Adderall and Ritalin (i.e., methylphenidate); one reported using cocaine, Adderall, and ecstasy; one reported using Adderall and Ritalin within the past year. Only one subject reported using mixed amphetamine salts during the past month and another subject tested positive for cocaine use during initial screening procedures. Throughout the study, only one subject tested positive for a substance (oxycodone) that prevented him from running an experimental session. This subject was sent home and his session was rescheduled for when he could provide a drug-negative urine. Subjects were 25 (± 7) years of age and weighed 75 (± 19) kg on average ($\pm$ SEM). Two of the seven subjects reported daily use of cigarettes (13 $\pm$ 4 cigarettes/day) and all reported weekly alcohol use (10 $\pm$ 10 drinks/week). In addition to weekly cigarette and alcohol use, subjects reported recent recreational use of other drugs. In the month prior to screening, four subjects used marijuana, four used opioids and two used benzodiazepines. Three subjects met DSM-IV criteria for alcohol abuse and one subject met DSM-IV criteria for cannabis abuse.

The Institutional Review Board of the University of Kentucky Medical Center approved this experiment and all subjects gave their written informed consent prior to participating. Subjects were paid \$40 per session and earned an additional \$40 per session completion bonus if they finished the study. Subjects underwent extensive screening prior to enrollment (e.g., Sevak, et al., 2010). To meet inclusion criteria, subjects had to (1) report past-year recreational use of stimulant drugs (e.g., amphetamine, ecstasy, methylphenidate, cocaine) and (2) be in good health with no contraindications to stimulant medications.

2.2. General Procedures

Subjects reported to the University of Kentucky Laboratory of Human Behavioral Pharmacology (LHBP) at the University of Kentucky Chandler Medical Center for a total of 17 sessions (2 practice and 15 experimental). Subjects were informed that during their participation they would receive methamphetamine or placebo. Other than receiving this general information, subjects were blind to the dose of methamphetamine to be administered during each session. Subjects were told that the purpose of the study was to determine (1)

how the drug effects feel and influence mood, (2) the effects of drugs on physiology, and (3) whether subjects like the drug and are willing to take it again. Other than this general explanation of purpose, subjects were not given any information concerning what outcomes might be expected.

For all sessions (practice and experimental), subjects arrived daily at 0800 h to the LHBP. Sessions lasted approximately 7 h. Upon arrival, urine and expired breath samples were collected to confirm drug and alcohol abstinence, respectively. Female subjects also received urine pregnancy tests prior to each session, which were negative throughout their participation. If subjects tested positive for alcohol or other drugs (save THC and tests positive for methamphetamine as a result of experimental administration), they were sent home and their session rescheduled. To ensure that subjects were not acutely intoxicated, subjects had to pass a field sobriety test prior to beginning each session. To further enhance safety, no methamphetamine was administered until at least 2 h after subjects arrived at the laboratory.

Vital signs were recorded at 15 min intervals between 0800 h and 0830 h and subjects were provided a standard breakfast (i.e., 2 Nutri-grain® bars and a juice box or 1 standard single-serving cereal with skimmed milk and a juice box). At approximately 0830 h, subject-rated questionnaires and the choice task (only during practice and experimental self-administration sessions) were completed. Sampling doses or the amount of drug earned on the choice task was administered at 1000 h. For all sessions, subject vitals were recorded, subject-rated questionnaires were administered at 1 h intervals after drug administration (i.e., from 1100 h to 1500 h). Between these measures, subjects were allowed to engage in sedentary, quiet recreational activities (e.g., read newspapers or magazines, complete puzzles, watch television). At 1300 h, subjects were allowed to eat lunch, which was provided by the LHBP. If no drug effects (physiological or behavioral) were detected at 5 h post-administration, subjects were released from the laboratory.

2.2.1 Practice sessions—Subjects completed two practice sessions to familiarize them with (1) subject-rated questionnaires and (2) the methamphetamine versus alternative reinforcer choice task and the different fixed ratio requirements that would be in place in subsequent sessions. These tasks/measures were administered at approximately 0830 h each day. Subject-rated questionnaires and the drug versus alternative reinforcer choice task were administered on a Macintosh iMac computer (Apple Computer Inc., Cupertino, California). During the first practice session, subjects completed only the subject-rated questionnaires. During the second practice session, subjects completed both measures. The FR responses were described as small (i.e., FR500), medium (i.e., FR1000), large (i.e., FR2000), and extra large (i.e., FR3000), but actual numerical response requirements were not specifically disclosed to subjects. Experimental medications were not administered during either of these practice sessions.

2.2.2 Sampling Sessions—A total of 3 sampling sessions (i.e., one for each dose of methamphetamine) were conducted to familiarize subjects with the doses of drug they could work choose to earn in subsequent sessions. Sampling sessions for each dose condition always preceded four self-administration sessions (i.e., one for each FR requirement). At approximately 1000 h, subjects received eight identical blue and white capsules (each containing 1/8th of the drug dose which could be earned during the following self-administration sessions) to acquaint them with the effects of the drug dose. Doses were identified as Drug A (first dose tested), Drug B (second dose tested) or Drug C (third dose tested). Subjects were instructed to pay attention to and make notes about the effects of the drug, as they would later be given the opportunity to choose between receiving the capsules again and receiving money.

2.2.3 Self-Administration Sessions—Four self-administration sessions (i.e., one for each alternative reinforcer FR requirement) followed each sampling session until all doses were tested. During these self-administration sessions, subjects completed a drug versus alternative reinforcer choice task in which they made eight choices between a capsule containing 1/8th of the dose administered during the most-recent sampling session and \$0.25. Prior to each of the 8 choices, subjects were asked if they wanted to work for one of the capsules administered during the sampling session or \$0.25. Each capsule required 500 responses (i.e., mouse clicks). The response requirement for \$0.25 changed across sessions in random order. These response requirements were 500, 1000, 2000, and 3000 mouse clicks. Subjects were instructed which response requirement was in place each day using a descriptor: small, medium, large, extra large. After completing the first response requirement, subjects then chose between a capsule and money seven more times. Each of these 8 discrete choices was separated by 10 min. Following completion of the choice task and approximately 2 h after arrival to the LHBP (i.e., 1000 h), subjects ingested all of the capsules they had earned. Each capsule contained 12.5% of the total dose of the test drug administered during the sampling session. Thus, if a subject responded for all eight capsules during a self-administration session, he/she earned the total dose received during the corresponding sampling session. The number of alternative reinforcer choices determined the amount of money earned during each session; subjects could earn a maximum of \$2.00 each session if they made all eight choices for money. If a subject responded only for money, he/she still completed the subject-rated drug-effects questionnaires, and vital signs were recorded at hourly intervals for 5 h. The dependent measure on this choice task was the number of capsules earned.

2.3 Subject-Rated Measures

Subject-rated questionnaires were administered periodically throughout each session on a computer in fixed order.

2.3.1 Adjective-Rating Scale—This questionnaire consisted of 32 items and contained two subscales: Sedative and Stimulant (Oliveto et al., 1992), with each item rated on a 5-point (0-4) Likert-type scale.

2.3.2 Drug-Effect Questionnaire—This questionnaire consisted of 20 items that were presented one at a time (see Rush et al., 2003 for the items rated) on a 0-100 Visual Analog Scale.

2.4 Physiological Measures

Heart rate and blood pressure were recorded using an automated blood pressure monitor (GE Dinamap® Pro Series 400V2, GE Medical System Information Technologies, Tampa, FL), immediately prior to drug administration and at hourly intervals thereafter until the subject met release criteria at the end of each session.

2.5 Drug Administration

Methamphetamine was administered in a double-blind fashion. Doses were prepared weighing methamphetamine HCL powder (supplied by the National Institute on Drug Abuse/Research Triangle Institute, Research Triangle Park, NC) and admixing the appropriate dose with cornstarch. Each methamphetamine capsule contained either 1 mg (8 mg self-administration dose) or 2 mg (16 mg self-administration dose). Cornstarch was used to fill the remainder of all capsules. Placebo capsules contained only cornstarch. The order of dose administration was mixed.

During each sampling session, subjects ingested eight capsules, each containing 1/8th of the total dose of methamphetamine for that condition. During each self-administration session, subjects ingested up to eight capsules, each containing 1/8th of the total dose of methamphetamine, depending upon choice task performance.

2.6 Data Analysis

Effects were considered significant for $p < 0.05$. Data from the choice task were analyzed as number of drug choices. Choice data were analyzed with a two-factor repeated-measures analysis of variance (ANOVA) with Methamphetamine Dose (i.e., 0, 8, and 16 mg) and Alternative Reinforcer FR Requirement (i.e., 500, 1000, 2000, and 3000 mouse clicks) as factors (StatView, Cary, **NC**). F statistics were used to interpret the ANOVA outcomes.

Because amount of drug ingested during self-administration sessions varied as a function of choice, subject-rated drug-effect questionnaires and cardiovascular data from these sessions were not analyzed statistically. Thus, only subject-rated and physiological data from sampling sessions were analyzed (i.e., these data could not be analyzed as a function of alternative reinforcer response cost). Subject-rated and physiological data were analyzed using a two-factor, repeated-measures ANOVA with Methamphetamine Dose (i.e., 0, 8, and 16 mg) and time (Pre, 1, 2, 3, 4, 5 hours after administration) as the factors (StatView, Cary, **NC**). F statistics were used to interpret the ANOVA outcomes. For the sake of brevity, only those subject-rated and physiological measures in which dose and time interactions were observed are presented.

3. Results

3.1 Methamphetamine Versus Alternative Reinforcer Choice Procedure

Significant main effects of Methamphetamine Dose ($F_{2,18} = 6.30$, $p < 0.05$) and Alternative Reinforcer FR Requirement ($F_{3,18} = 6.54$, $p < 0.05$) were observed on number of drug choices. Figure 1 shows that methamphetamine was chosen to a greater degree than placebo. Moreover, choice for doses over money was sensitive to changes in response cost for alternative reinforcers in that more doses were taken at higher FR values than at lower FR values. Placebo choices changed as a function of alternative reinforcer response cost to a greater degree than active methamphetamine choices.

3.2 Subject-Rated Measures

Methamphetamine increased subject ratings as an orderly function of dose and time. Significant methamphetamine dose by time interactions ($F_{10,60}$ values > 2.14 , p values < 0.05) were observed on 9 items from the Drug-Effect Questionnaire: Active/Alert/Energetic, Any Effect, Good Effects, High, Like Drug, Willing to Pay For, Stimulated, Willing to Take Again, and Talkative/Friendly. Figure 2 (top and middle panel) shows data for two representative measures: High and Willing to Pay For. A significant methamphetamine dose by time interaction ($F_{10,60} = 3.63$, $p < 0.05$) also was observed on the Stimulant subscale from the Adjective Rating Scale, with methamphetamine increasing scores as an orderly function of dose and time (data not shown).

3.3 Physiological Measures

A significant methamphetamine dose by time interaction ($F_{10,60} = 2.17$, $p < 0.05$) was observed for systolic blood pressure (Figure 2; bottom panel). Both active methamphetamine doses increased this outcome relative to placebo. Additionally, a significant methamphetamine dose by time interaction ($F_{10,60} = 2.32$, $p < 0.05$) was observed on heart rate, with methamphetamine increasing heart rate as an orderly function

of dose and time (data not shown). No significant effects were observed for diastolic blood pressure.

4. Discussion

Methamphetamine functioned as a positive reinforcer (i.e., was chosen to a greater degree than placebo) and produced prototypical stimulant like effects in a time-dependent manner (e.g., increased ratings of Stimulated; elevated blood pressure). Overall drug choice was sensitive to changes in alternative reinforcer response cost in that more drug was generally chosen at higher FR requirements for money than lower FR requirements. Placebo choice was more sensitive to changes in FR requirements than active drug choice, however.

The finding that oral methamphetamine functioned as a reinforcer is consistent with the results of the seminal study investigating oral methamphetamine self-administration in humans (Hart et al., 2001). That study also demonstrated the reinforcing effects of oral methamphetamine in a drug versus alternative reinforcer choice task and found equivalent levels of self-administration behavior regardless of methamphetamine dose but it did not manipulate response cost to earn alternative reinforcers. In another study, Kirkpatrick et al. (2009) assessed self-administration of methamphetamine vs. monetary vouchers in a simulated work environment in which subjects experienced both day- and night-shift work. Night-shift work produced greater performance decrements and a greater number of methamphetamine choices were made prior to the first night shift that subjects experienced when compared to the first day shift experienced. Those results suggest that methamphetamine taking behavior is sensitive to environmental demands like working on a night shift as opposed to a day shift. The present study extends those findings by demonstrating that response cost for alternative reinforcers also impacts methamphetamine self-administration.

Although other studies assessing the effectiveness of manipulating the effort required to obtain alternative reinforcers on methamphetamine self-administration have yet to be conducted in animal or human laboratories, germane research with other stimulants like cocaine and d-amphetamine is available. In early research with monkeys, higher magnitude food alternative reinforcers decreased cocaine self-administration (Nader and Woolverton 1991). Those results were extended in a subsequent study, which demonstrated that fewer drug choices were made when the response requirements for the alternative reinforcers were lower than those for drug (Nader and Woolverton 1992). Similarly, Foltin (1997) found evidence of increased responding for d-amphetamine when pellet cost increased in baboons trained to respond for d-amphetamine and food. Research from our laboratory showed that increasing the effort required to earn alternative reinforcers increased the number of cocaine choices in a discrete-trials procedure similar to that used here (Stoops et al., 2012). In the current study, methamphetamine was clearly a robust reinforcer that was resistant, but not immune, to behavioral manipulations. In fact, the maximum change (i.e., approximately two choices) in methamphetamine choice behavior as a function of FR requirement for alternative reinforcers was comparable to what we previously demonstrated with cocaine (Stoops et al., 2012).

In recent years, our laboratory has conducted several experiments designed to refine human drug self-administration procedures to enhance our ability to determine the initial efficacy of potential pharmacotherapies for stimulant dependence (Sevak et al., 2010; Stoops et al., 2010b). Sevak et al. (2010) noted that previous studies conducted in our laboratory using progressive ratio schedules to assess a drug's reinforcing efficacy might have produced significant (but relatively low) self-administration of drugs because of high levels of responding to placebo (i.e., a ceiling effect). The procedures implemented in the current

study may therefore present a useful means for medication screening and assessing initial efficacy of putative pharmacotherapies, as we effectively reduced placebo taking (under FR500 and FR1000 response requirements) while observing high levels of active drug-taking behavior. These procedures, along with others that we have tested (Stoops et al., 2010a; 2010b; 2012) may now be used to determine the potential efficacy of putative pharmacotherapies for stimulant dependence.

There are several limitations that may impact the ecological validity of this study. First, methamphetamine is most commonly abused via smoked and intranasal routes, while oral use accounts for a small percentage of abuse (Community Epidemiology Work Group, 2011). Route of administration, and in turn, rate of onset of effects, is an important pharmacological variable known to influence the behavioral effects of drugs (Griffiths et al., 1980). Indeed, oral administration of methamphetamine is associated with relatively low abuse potential (Hart et al., 2008) with peak subject-rated effects occurring approximately 90 minutes post-administration (Hart et al., 2001), whereas peak subject-rated effects for other routes of administration (intranasal and smoked) occur as early as 15 minutes post-administration (see Harris et al., 2003; Hart et al., 2008). Future work should therefore determine whether route of administration influences the efficacy of alternative reinforcers in reducing methamphetamine self-administration in humans. In addition, the maximum dose of methamphetamine administered in this study was 16 mg. Previous studies have assessed the effects of smoked and intranasal doses of methamphetamine up to 50 mg (Harris et al., 2003; Hart et al., 2008). The doses administered in these previous studies may better approximate those used naturalistically and therefore should be tested to assess the effects of higher doses of methamphetamine on this self-administration paradigm.

A final limitation is that active drug was chosen to a high degree over money at all alternative reinforcer FR values. Thus, it is possible that the reinforcing effects of a small magnitude of the alternative reinforcer (US\$0.25) were insufficient to compete with the reinforcing effects of methamphetamine. Increasing the amount of the alternative reinforcer might be necessary to more substantially reduce methamphetamine choice. Similarly, including a condition in which the FR for alternative reinforcement was below that for drug (e.g., FR 250) could have also decreased active drug-taking behavior.

5. Conclusion

Both active doses of methamphetamine functioned as reinforcers relative to placebo and drug choice was impacted by response cost for alternative reinforcers, although placebo choice changed to a greater degree than methamphetamine choice when alternative reinforcer response cost was manipulated. The resistance of methamphetamine use disorders to treatment indicates that methamphetamine is a very potent reinforcer, so our findings that methamphetamine was relatively resistant to a behavioral manipulation aimed at reducing methamphetamine self-administration are not completely unexpected. Because there was less decrease in methamphetamine choice behavior as a function of increasing response cost requirements relative to placebo choice, these findings may assist in the design and implementation of treatment programs by suggesting that smaller response costs to earn alternative reinforcers be used in contingency management programs. Additionally, decreases in methamphetamine choice behavior may be achieved by increasing the alternative reinforcer value. Moreover, future human laboratory studies should investigate more potent behavioral manipulations (i.e., decreased cost for those alternative reinforcers as well as larger alternative reinforcers) on methamphetamine self-administration.

Acknowledgments

The authors wish to thank the staff at the University of Kentucky Laboratory of Behavioral Pharmacology for expert technical and medical assistance.

This research was supported by NIDA Grant R01 DA 025032 to CRR. This funding agency had no role in study design, data collection or analysis or preparation and submission of the manuscript.

Abbreviations

ANOVA	Analysis of Variance
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
FR	fixed ratio
h	hours
mg	milligrams
min	minute
SEM	Standard Error of the Mean
US\$	United States Dollar

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Highlights

- We tested how alternative reinforcer response cost impacts methamphetamine choice
- Methamphetamine functioned as a positive reinforcer
- Drug choice increased with higher alternative reinforcer response cost
- Changes in response cost impacted placebo choice more than methamphetamine choice
- Manipulating alternative reinforcers response cost could alter methamphetamine use

Fig. 1. Mean number of drug choices for 7 subjects. X-axis: methamphetamine dose. Symbols represent the FR values for the alternative reinforcer: FR500 (circles), FR1000 (squares), FR2000 (triangles), FR3000 (diamonds).

Fig. 2.

Dose- and Time-response functions for sampling doses of methamphetamine. Data show means ($n = 7$) for subject ratings (Top Panel: High; Middle Panel: Willing to Pay For) and systolic blood pressure. X-axis: time (hours). Data are from sampling sessions and represent measures collected pre- and post-methamphetamine administration.