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Relationship Between Intranasal Cocaine Self-Administration and Subject-Rated Effects: Predictors of Cocaine Taking on Progressive-Ratio Schedules

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Abstract

Objective—Subject-rated measures and drug self-administration represent two of the most commonly used methods of assessing abuse potential of drugs, as well as screening intervention efficacy in the human laboratory. Although the results from these methods are often consistent, dissociations between subject-rated and self-administration data have been observed. The purpose of the present retrospective analysis was to examine the relationship between subject-rated effects and intranasal cocaine self-administration to help guide future research design and intervention assessment.

Methods—Data were combined from two previous studies in which drug and an alternative reinforcer (i.e., money) were available on concurrent progressive-ratio schedules of reinforcement. Pearson correlation coefficients and regression model selection utilizing corrected Akaike information criterion were used to determine which subject-rated measures were associated with and best predicted cocaine self-administration, respectively.

Results—Eleven subject-rated effects were positively associated with cocaine maintained breakpoints. A combination of three of these subject ratings (i.e., Like Drug, Performance Improved, and Rush) best predicted cocaine taking.

Conclusions—The present findings suggest that, at least under certain conditions with intranasal cocaine, some, but not all, positive subject-rated effects may predict drug self-administration. These findings will be useful in guiding future examinations of putative interventions for cocaine-use disorders.

Keywords

abuse potential; cocaine; drug self-administration; humans; predictors; subject-rated effects

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Introduction

In 2012, 1.6 million Americans reported current cocaine use and 1.1 million individuals met the diagnostic criteria for cocaine dependence making cocaine the third most commonly abused illicit drug behind marijuana and prescription psychotherapeutics (Substance Abuse and Mental Health Service Administration [SAMHSA], 2013b). Despite efforts at identifying an effective pharmacotherapy or behavioral intervention for cocaine dependence, retention rates remain low, relapse remains high, and prevalence of use remains stable (Dutra *et al.*, 2008; SAMSHA, 2013b; Stoops and Rush, 2013). Although the use of smoked cocaine (i.e., crack) has received a great deal of attention in epidemiological reports (e.g., Falck *et al.*, 2004, 2008; Paim Kessler *et al.*, 2012) and in human laboratory studies (e.g., Foltin *et al.*, 2003; Haney *et al.*, 2006; Hart *et al.*, 2008), it is important to note that many cocaine users do not smoke cocaine (up to 2/3; Gossop *et al.*, 1994; Foltin and Haney, 2004; SAMSHA, 2013a). Many individuals report initiation of cocaine use via intranasal insufflation and a preference for this route of administration (Foltin and Haney, 2004; van der Meer Sanchez and Nappo, 2007). A focused examination of the factors related to intranasal cocaine self-administration is needed to help guide future investigations of putative interventions.

Historically, human laboratory studies have relied upon subject-rated measures to index the rewarding effects of a drug (i.e., abuse potential) and to investigate how putative interventions might change these effects (Fischman and Foltin, 1992; Carter and Griffiths, 2009; Comer *et al.*, 2012). Subjective ratings are a quantifiable measure of drug effects that occur in an otherwise unobservable realm. These measures are usually collected via responses on visual analog scales, True/False ratings, or Likert-type scales for a series of standardized items and then scored as single measures (e.g., Good Effects or Rush) or as multiple ratings grouped into a single scale (e.g., the Stimulant subscale of the Adjective Rating Scale; Oliveto *et al.*, 1992). The misuse and abuse of stimulants has been attributed to the production of positive subjective effects (e.g., Like Drug, Friendliness; Johanson *et al.*, 1983; Foltin and Fischman, 1992). Although subject-rated effects provide an easy and rapid assessment of abuse potential and the efficacy of potential interventions (Griffiths *et al.*, 2003), these methods are often criticized as they represent an indirect measure of the behavior of interest (i.e., drug-taking; Katz, 1990), may result in marked between-subjects variability due to variations in interpretation across time and individuals (Kelly *et al.*, 2003), and can produce false positives when used to screen putative pharmacotherapies (Haney and Spealman, 2008).

In part to address the concerns associated with subject-rated effects data and to better model the behavior of interest (i.e., drug taking), clinical researchers have increasingly relied upon drug self-administration procedures to assess intervention efficacy (Comer *et al.*, 2008a). The ability to vary experimental procedures and schedules of reinforcement (e.g., choice procedures, availability of alternative reinforcers, progressive-ratio schedules) allows researchers to dynamically model naturalistic drug-taking conditions (Stoops, 2008; Jones and Comer, 2013). Self-administration techniques provide a valid measure of abuse potential given the high concordance between laboratory drug self-administration outcomes and

predictors of abuse in the natural environment (e.g., Herman-Stahl *et al.*, 2007; Stoops *et al.*, 2007). These techniques also have a relatively high predictive validity when translating potential interventions into the clinical setting (e.g., Comer *et al.*, 2001; Donny *et al.*, 2005; see reviews by Comer *et al.*, 2008a; Haney and Spealman, 2008). Despite these benefits, self-administration techniques are less efficient than the use of subject-rated measures due to the relative difficulty in their design and implementation, particularly during early stages of intervention assessment, as well as the uncertainty surrounding the variables controlling drug-taking behavior in the laboratory environment. Information pertaining to those subject-rated effects that are most closely associated with drug self-administration would help researchers predict key clinical outcomes and optimize subsequent investigations of putative interventions.

Conflicting results have been observed when comparing changes in subject-rated effects and changes in cocaine self-administration following administration of a variety of pharmacotherapies (e.g., Haney *et al.*, 1999, 2006, 2011; Foltin *et al.*, 2003; Hart *et al.*, 2004, 2008; Stoops *et al.*, 2012). Although a majority of this research has been conducted using smoked or intravenous cocaine, a recent study from our laboratory indicated similar inconsistencies between intranasal cocaine self-administration and subject-rated effects (Stoops *et al.*, 2012). In that study, acute bupropion enhanced some positive subject-rated cocaine effects (e.g., Good Effect, Willing to Take Again) but reduced choices for intranasal cocaine versus money on a concurrent progressive-ratio schedule. The self-administration outcomes were more consistent with those of a clinical trial (Poling *et al.*, 2006). Studies such as these highlight the discordant results that can occur when comparing self-administration data and changes on a single subject-rated measure when screening potential interventions.

The purpose of the present retrospective analysis was to examine the relationship between subject-rated effects and the self-administration of intranasal cocaine in order to determine which subject-rated factors best predict cocaine-use behaviors. Regression techniques that examine the associations between multiple predictor variables and a drug-taking criterion can help to elucidate more complex relationships among subject-rated effects that bivariate correlation techniques fail to capture. This analysis strategy was applied to combined data from two previous studies using identical self-administration procedures (Stoops *et al.*, 2010; Stoops *et al.*, 2012). In order to more fully characterize the relationship between and relative importance of each subject-rated effect, model selection was used to determine the most predictive multiple regression model among the study measures. The correlation between model predicted and study derived cocaine breakpoints from bupropion pretreatment sessions (i.e., independent of the data used for model selection) was then determined in order to evaluate the validity of the derived model from the AICc criterion.

Methods

Data from two studies (Stoops *et al.*, 2010; Stoops *et al.*, 2012) that used identical cocaine self-administration procedures were included in this retrospective analysis. In these studies, the reinforcing effects of intranasal cocaine (4, 15, and 45 mg) were assessed using a drug choice procedure with concurrent progressive-ratio schedules of reinforcement. The

Institutional Review Board of the University of Kentucky Medical Center approved all protocols and subjects gave their written informed consent before participating.

Subjects

Data from 12 non-treatment seeking adult subjects (nine men and three women) with recent histories of cocaine use who met criteria for a cocaine use disorder as determined by a computerized version of the Structured Clinical Interview for the DSM-IV were included in this analysis. Exclusion criteria included current physical disease (e.g., high blood pressure) or serious psychiatric disorders (i.e., Axis I, DSM IV). Information regarding screening procedures is described elsewhere (see Stoops *et al.*, 2010; Stoops *et al.*, 2012). If subjects completed both studies, only results from the first data set were included in the present analysis.

Subjects were 40 (± 2) years of age and weighed 82 (± 4) kg on average ($\pm$ standard error of the mean [SEM]). In addition to cocaine use prior to screening (3 ± 1 days of use totaling US\$150 $\pm$ \$53 spent on cocaine in the past week), ten subjects reported weekly alcohol use (17 ± 5 drinks/week). All subjects reported marijuana use, three subjects reported benzodiazepine use, and three subjects reported opioid use in the month prior to screening. Subjects were paid \$400 (Stoops *et al.*, 2010) or \$800 (Stoops *et al.*, 2012) for completing the study.

General Procedures

Subjects were enrolled as outpatients at the University of Kentucky Chandler Medical Center Clinical Research and Development Operations Center (CRDOC) for 5 to 10 sessions. In order to proceed with a given session, subjects were required to provide an expired air specimen that was negative for the presence of ethanol (Alco-Sensor, Intoximeter, Inc., St. Louis, MO) and a urine sample negative for benzodiazepines, barbiturates, opiates, and amphetamines. All female subjects received urine pregnancy tests prior to each session, which were negative throughout their participation.

Practice and Experimental Sessions—Subjects completed one practice session to familiarize them with experimental measures including the progressive-ratio schedule and drug choice procedure. Four to nine experimental sessions were completed and conducted only on weekdays, at least 24 hours apart. Data from sessions testing 4, 15 and 45 mg intranasal cocaine alone are included here. The remaining sessions either tested a cocaine dose not used in both studies (i.e., 30 mg; Stoops *et al.*, 2010) or used a bupropion pretreatment condition (Stoops *et al.*, 2012). Data from those sessions were excluded except as described below. During each session, subjects sampled the cocaine dose available for that day, 4, 15, or 45 mg. They then made six choices between the available dose and a monetary reinforcer (US\$0.25) at 30-minute intervals. After making a choice, subjects had to complete a response requirement to earn that choice (see Progressive-Ratio Procedure below). Cocaine doses (4, 15, and 45 mg) were prepared by combining the appropriate amount of cocaine hydrochloride (Mallinckrodt, St. Louis, MO) with lactose to equal a total weight of 60 mg powder and administered in a double-blind fashion.

Progressive-Ratio Procedure

After sampling the dose available in each session, subjects made six choices between the drug and the monetary reinforcer available at 30-minute intervals by selecting one of two options presented to them on a computer screen (“Dose” or “Money”). Following this choice, subjects were then required to complete a number of responses (i.e., mouse clicks) to earn that choice. Cocaine and money were available on concurrent progressive-ratio schedules such that the ratio for the next choice increased only for the previously chosen option (Stoops *et al.*, 2010). The initial ratio for each reinforcer was 400 responses and response requirements increased by 200 following a choice for that reinforcer (i.e., full progression: 400, 600, 800, 1000, 1200, and 1400). If the subject chose drug, it was immediately provided to him or her. If a subject chose money, he or she was immediately provided with a token marked \$0.25 and the total money earned was added to his or her payment at the end of the session.

Subject-Rated Effects

All subject-rated effects measures were administered on an Apple Macintosh computer (Apple, Cupertino, CA, USA) in a fixed order. Subjects completed these measures prior to the initial dose administration and 15 minutes after each drug administration. Measures included the Drug-Effect Questionnaire consisting of 20 items rated on a 0–100 Visual Analog Scale anchored with “not at all” under the left anchor and “extremely” under the right anchor (see Rush *et al.*, 2003 for the items rated). Subjects also completed the Adjective-Rating Scale, which includes 32 Likert-type items classified into a Stimulant (e.g., active, excited) and Sedative (e.g., drowsy, dazed) subscale (Oliveto *et al.*, 1992).

Physiological Measures

Physiological measures including heart rate, blood pressure and oral temperature were recorded prior to the first dose administration and at 15-minute intervals thereafter. If systolic blood pressure exceeded 180 mmHg, diastolic blood pressure exceeded 120 mmHg, or heart rate exceeded 130 beats per minute, participation was terminated. No subjects were excluded from the protocols for exceeding these parameters, nor were any doses withheld in either study.

Data Analysis

Effects were considered significant for $p < .05$. Data from the progressive-ratio schedule were analyzed as breakpoint (i.e., the last ratio successfully completed to earn cocaine). Only subject-rated and physiological data from 15 minutes after the sampling dose were analyzed because subjects made differing selections between cocaine and money during choice sessions (i.e., after the sampling dose). This time point was selected because 1) numerous studies have demonstrated that the peak subjective effects of intranasal cocaine occur within 15 minutes of administration (e.g., Resnick *et al.*, 1977; Volkow *et al.*, 2000) and 2) it captures the subject-rated effects of the sampling dose immediately before subjects engaged in the progressive-ratio procedure. Breakpoints, subject-rated effects and physiological data were analyzed using a one way, repeated measures analysis of variance (ANOVA) with dose (4, 15, and 45 mg cocaine) as the within-subjects factor. To reduce

type I error, a Greenhouse-Geisser correction was applied to ANOVAs violating the assumption of sphericity (Greenhouse and Geisser, 1959). The relationship between cocaine-maintained breakpoints and subject-rated effects and physiological data were examined using separate Pearson bivariate correlations. All ANOVAs and correlations were conducted using GraphPad Prism (Version 6.00 for Mac OS X, GraphPad Software, San Diego, CA).

In order to systematically determine the most predictive model among significantly correlated subject-rated measures, model selection using corrected Akaike information criterion (AICc) was conducted with the *glmulti* package in R statistical language. AICc provides a method of model selection suited for small sample sizes that maximizes model fit while minimizing potential model overfitting (i.e., inclusion of excess variables; Burnham and Anderson, 2004). Relative weights were determined for model predictors to determine each factor's relative importance (Tonidandel and LeBreton, 2011). Relative weights represent the percentage of explained variance contributed by each factor and provide a measure of relative importance that, unlike standardized regression coefficients, are not affected by inappropriate variance partitioning for correlated predictors. In order to evaluate the validity of the derived model from the AICc criterion and determine the model's goodness of fit, the correlation between model predicted and study derived cocaine breakpoints during bupropion pretreatment sessions was determined. These data were collected on separate study days and were not included in the initial correlation and regression analyses (i.e., Stoops *et al.*, 2012). To examine if the derived model differentially predicted breakpoints as a function of cocaine or bupropion dose, we conducted a mixed ANOVA with breakpoint type (i.e., predicted versus observed) as the between subjects factor and cocaine and bupropion dose as the within subject factors.

Results

Analysis of Variance (ANOVA)

Cocaine Breakpoints—A one-way ANOVA revealed a significant effect of cocaine dose for breakpoints maintained by cocaine ($F_{2,22} = 13.90$, $p < .01$, eta-squared = .35) on the concurrent progressive-ratio schedule. Cocaine significantly increased cocaine-maintained breakpoints in a dose-dependent manner (Figure 1).

Subject-Rated Effects—A significant effect of cocaine dose was observed on four items from the Drug-Effect Questionnaire: Any Effect, Good Effect, Like Drug, and Willing to Take Again ($F_{2,22}$ values = 3.60, p values = .05, eta-squared values = .11). The magnitude and direction of the increase was similar for each item (Figure 1). Cocaine also significantly and dose-dependently increased ratings on the Stimulant subscale of the Adjective Rating Scale ($F_{2,22} = 4.32$, $p = .04$, eta-squared = .04; data not shown).

Physiological Measures—No significant effect of cocaine dose was observed on any physiological measure ($F_{2,22} = 1.22$, $p = .31$).

Pearson Correlations

A significant, positive correlation was observed between self-administration of cocaine and eleven items from the Drug-Effect Questionnaire: Alert/Active/Energetic, Any Effect, Good Effect, High, Like Drug, Performance Improved, Rush, Stimulated, Talkative/Friendly, Willing to Pay For and Willing to Take Again (r^2 values = .12 to .19, p values < .05; Table 1). No significant relationships were observed between cocaine-maintained breakpoints and the two subscales of the Adjective Rating Scale.

Model Selection

Model selection using AICc criteria among significant study predictors (see Pearson Correlations) indicated that the most parsimonious model predicting cocaine-maintained breakpoints included three items: Like Drug, Performance Improved, and Rush ($R^2 = .30$, $p < .01$). Notably, in this final model, Like Drug and Performance Improved were positively associated with ($b = 20.59$, 8.29 , respectively), whereas, Rush was negatively associated ($b = -16.42$) with cocaine breakpoints. Relative weight analysis indicated that Like Drug had the greatest relative importance (RW = 46%), whereas Performance Improved and Rush were similarly important in the model (RW = 28% and 23%, respectively). Critically, the addition of all other items from the Drug-Effect Questionnaire failed to significantly increase the adjusted or total variance explained when added to this final cocaine breakpoint model (R^2_{adj} values .00, R^2 values .01, p values .50).

Cross Validation

Cocaine-maintained breakpoints under bupropion pretreatment were predicted using the proposed regression model including Like Drug, Performance Improved, and Rush. A significant correlation was observed ($r^2 = .32$, $p < .01$) between predicted and actual breakpoints in this model supporting the model's goodness of fit when applied to a new data set and utility in predicting cocaine self-administration following bupropion pretreatment (Figure 2). A mixed ANOVA indicated that predicted values did not differ significantly from actual values (no main effect of value type; $F_{1,14} = .92$, $p = .35$). This effect was observed independent of bupropion or cocaine dose (no interactions between value type and drug doses; $F_{1,14}$ values < 2.95, $p > .11$) indicating that the model did not provide differentially better predictions for the drug doses under different conditions.

Discussion

In agreement with the individual studies, when data were combined in the present retrospective analysis, intranasal cocaine functioned as a reinforcer under a concurrent progressive-ratio schedule of reinforcement, significantly increasing breakpoints for drug choices as an orderly function of dose. Cocaine also produced dose-dependent increases in ratings for several positive, stimulant-like subject-rated effects questionnaire items. Cocaine self-administration was significantly correlated with ratings on eleven items from the Drug-Effect Questionnaire, all of which were measures of drug strength or the positive subjective effects of stimulants. Regression analysis of these relationships indicated that the combined effects of Like Drug, Performance Improved, and Rush provide the best predictive model of intranasal cocaine choice. This was confirmed by cross validating the predictive model

derived from these three ratings with cocaine self-administration outcomes following bupropion pretreatment. The data included in this cross-validation procedure were collected on separate study days and not included when deriving the subject-effects model. Consequently, the strong correlation between predicted and observed breakpoints in this alternative data set supports the predictive value and generalizability of the present findings.

These data are concordant with the results of several controlled laboratory studies demonstrating the greater choice for intranasal cocaine than available alternate reinforcers (e.g., Higgins *et al.*, 1994), as well as numerous studies indicating that intranasal cocaine increases positive subject-rated effects (e.g., Javaid *et al.*, 1978; Kouri *et al.*, 2001; Foltin *et al.*, 2003; Foltin and Haney, 2004; Collins *et al.*, 2007; Stoops *et al.*, 2008). The current findings support the robust literature demonstrating that intranasal cocaine produces dose dependent increases in positive rather than negative subject-rated effects. These data also further support the notion that laboratory drug self-administration procedures provide a valid behavioral measure of abuse potential (e.g., Herman-Stahl *et al.*, 2007; Stoops *et al.*, 2007).

That subjective measures of drug strength and positive subject-rated effects were correlated with the self-administration of intranasal cocaine is consistent with prevailing theory that drug-taking behavior and positive drug effects are directly related and reflective of common neurobiological processes (Johanson *et al.*, 1983; Foltin and Fischman, 1992; Ikemoto and Bonci, 2013). These data are also in agreement with a recent study wherein significant, positive relationships were observed between the positive subjective effects and self-administration of oral *d*-amphetamine (Bolin *et al.*, 2013). It is important to note that the present analysis does not rule out the possibility that the negative effects of drugs constitute a part of the user's total subjective experience as the dose range tested in the present study might limit the experience of these negative effects. Instead, these and other studies support the notion that the negative subjective effects experienced after drug-taking behavior might have a less robust influence on the reinforcing efficacy of cocaine than effects of a positive valence (e.g., Babalonis *et al.*, 2013).

Only four of the eleven measures that positively correlated with cocaine breakpoints also showed a significant dose-dependent relationship following cocaine administration (i.e., Any Effect, Good Effect, Like Drug, and Willing to Take Again). These findings suggest that the dose-dependent effects of a drug, as indexed by subjective-effects measures, are not isomorphic with dose-dependent drug-taking behavior. Factors including the dose range tested and the sensitivity of subjective measures may limit the observation of dose-dependency for subject-rated outcomes in the human laboratory. Taken together, these data indicate that simple examination of dose-dependent changes in the subjective effects of a drug using ANOVA might not reveal the specific interoceptive effects related to the likelihood of taking that drug.

Relative weight analysis indicated that Like Drug was the single most important predictor of intranasal cocaine self-administration. These results add to the extant literature documenting the sensitivity and reliability of drug liking measurements in assessing and predicting abuse potential (Griffiths *et al.*, 2003; Comer *et al.*, 2008b; Schoedel and Sellers, 2008; Comer *et al.*, 2012). However, the significant increase in the explained variance of our model with the

inclusion of Performance Improved and Rush highlights the multi-dimensional nature of positive subjective effects and need for multiple indices of the positive subjective effects of drugs.

Intranasal cocaine has previously been shown to improve performance on cognitive tasks (Higgins *et al.*, 1990). Increased ratings of Performance Improved were observed here despite any changes in subject performance on a digit symbol substitution task in one of the studies from which these data are derived (see Stoops *et al.*, 2012; no performance measure was included in Stoops *et al.*, 2010). These findings are consistent with epidemiological studies wherein individuals report cocaine use for enhanced performance (Weiss and Laties, 1962; Wagner, 1991). Moreover, laboratory studies have demonstrated the increased likelihood of stimulant administration when subjects were required to complete a performance task after self-administration relative to a relaxation task (Silverman *et al.*, 1994; Stoops *et al.*, 2005a, 2005b). This relationship suggests that interventions that incorporate means to enhance subjects' general cognitive performance (e.g., employment-based contingency therapy and skills training; DeFulio *et al.*, 2009) to replace the perceived performance improvement produced by cocaine warrant future empirical investigation as a means to reduce drug-taking behavior.

The negative association of Rush with drug-taking in our regression equation was surprising. Although Rush showed a positive association with cocaine-taking behavior as a single factor (i.e., bivariate correlation), when incorporating the influence of drug liking and performance enhancement in regression analysis a more complex relationship was observed. The model specifies that when holding ratings of Like Drug and Performance Improved constant, higher ratings of Rush will predict lower self-administration. For example, if two subjects rated Like Drug and Performance Improved equally, the model would predict the subject with higher ratings of Rush to self-administer less. These findings demonstrate the importance of regression techniques when examining the importance and predictive validity of factors related to drug-taking behavior. Real world behavior, including drug-taking, is normally associated with numerous, meaningful stimuli (i.e., as is analyzed with multiple regression) and not a single factor (i.e., as is analyzed with bivariate correlation). Regression techniques allow for the examination of multiple predictors (e.g., subject-rated effects) and association among these predictors in determining the criterion (e.g., drug-taking behavior). The use of regression models may provide a more nuanced view of how a particular subjective effect may predict drug-seeking or taking behavior when other potential factors are considered (i.e., the user's total subjective experience).

It is important to acknowledge several limitations of the present analysis. First, the small sample size limited the statistical power of our correlational and regression analyses and may limit the generalizability of these findings. In order to increase the statistical power of our analyses, subject-rated effects measures for all three cocaine doses were combined resulting in the potential bias of inter-correlated data (but see Banks *et al.*, 2013). The inclusion of data from all three doses of cocaine served to increase the range and variability of the criterion (i.e., breakpoint values), thereby reducing the artificial attenuation of bivariate correlations and regression coefficients due to restricted range in the criterion. The application of our findings to an alternative data set (i.e., following bupropion pretreatment)

also supported the importance of the factors identified in this study and lend greater credence to the generalizability of this small sample finding. Second, the relationship between the identified factors and clinical outcomes remains to be determined. Although concordant with several previous findings, our theoretical recommendations for clinical interventions should be viewed cautiously as they need further empirical investigation. Third, the present study only examined intranasal cocaine self-administration, so it is unclear if similar results would be observed for other drugs or routes of administration. As route of administration is an important determinant of the subjective effects of cocaine (Foltin and Fischman, 1992), it is possible that the relationship between subject-rated effects and self-administration might differ by mode of use. Fourth, these studies were conducted with a concurrent schedule where money acted as the alternative reinforcer, making it unclear if the same results would occur under other self-administration procedures. In addition, the relatively low amount of money available in the self-administration task could be viewed by subjects as insignificant in comparison to compensation for study participation, although the alternative monetary reinforcer did effectively compete with the lower cocaine doses (e.g., in Stoops *et al.*, 2012, the 15 mg dose was not chosen to a significantly greater degree than 4 mg cocaine). Finally, the limited sampling of physiological data (i.e., 15 minutes after administration) likely contributed to the lack of significant changes in these physiological measures.

Conclusion

Although these findings should be considered in the context of the small sample size, the present analysis provides several important recommendations for human laboratory researchers and clinical investigators. First, generally, these findings highlight the need to distinguish between data obtained via laboratory measures of subject-rated effects and drug self-administration. Second, in order to enhance the predictive validity of early intervention assessments that rely solely on subject-rated effects, researchers should focus on ratings of drug liking-, performance improvement- and rush-related effects as these effects may indicate future self-administration behavior, particularly for intranasal cocaine use. Third, and finally, regression analyses might provide a novel method to identify the factors predicting drug self-administration and to optimize intervention screening for substance-use disorders.

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Fig. 1.

Dose-response function for intranasal cocaine maintained breakpoints (Top Left) in a concurrent progressive ratio procedure; Any Effect, Good Effect (Middle Row); Like Drug; Willing to Take Again (Bottom Row) as a function of intranasal cocaine dose. X-axes: Cocaine dose (4, 15, or 45 mg). Y-axes: Breakpoints (Top Row) or Subject Ratings (Middle and Bottom Row). Data points represent mean value for twelve subjects and error bars represent one standard error of the mean.

Fig. 2. Comparison of model predicted (open square; dotted line) and observed (open circle; solid line) breakpoints under 100 mg (Left) and 200 mg (Right) bupropion maintenance. X-axes: Cocaine dose (4, 15, or 45 mg). Y-axes: Breakpoints. Data represent mean value for 8 subjects and error bars represent one standard error of the mean.

Table 1

Correlation Between Subject-Rated Factors & Cocaine-Maintained Breakpoints

Measure	Cocaine Breakpoints	
	<i>r</i>	<i>p</i>
Active/Alert/Energetic	.34	.04
Any Effect	.40	.01
Good Effect	.40	.02
High	.36	.03
Like Drug	.44	.01
Pay For	.35	.03
Performance Improved	.37	.03
Rush	.34	.04
Stimulated	.40	.02
Take Again	.39	.02
Talkative/Friendly	.37	.03