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The Effects of Oral d-Amphetamine on Impulsivity in Smoked and Intranasal Cocaine Users

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Abstract

BACKGROUND—Effective treatments for cocaine use disorders remain elusive. Two factors that may be related to treatment failures are route of cocaine used and impulsivity. Smoked cocaine users are more likely to have poorer treatment outcomes compared to intranasal cocaine users. Further, cocaine users are impulsive and impulsivity is associated with poor treatment outcomes. While stimulants are used to treat Attention Deficit Hyperactivity Disorder (ADHD) and attenuate certain cocaine-related behaviors, few studies have comprehensively examined whether stimulants can reduce behavioral impulsivity in cocaine users, and none examined route of cocaine use as a factor.

METHODS—The effects of immediate release oral d-amphetamine (AMPH) were examined in 34 cocaine users (13 intranasal, 21 smoked). Participants had three separate sessions where they were administered AMPH (0, 10, or 20 mg) and completed behavioral measures of impulsivity and risk-taking and subjective measures of abuse liability.

RESULTS—Smoked cocaine users were more impulsive on the Delayed Memory Task, the GoStop task and the Delay Discounting Task than intranasal cocaine users. Smoked cocaine users also reported more cocaine craving and negative mood than intranasal cocaine users. AMPH produced minimal increases on measures of abuse liability (e.g., Drug Liking).

CONCLUSIONS—Smoked cocaine users were more impulsive than intranasal cocaine users on measures of impulsivity that had a delay component. Additionally, although AMPH failed to attenuate impulsive responding, there was minimal evidence of abuse liability in cocaine users. These preliminary findings need to be confirmed in larger samples that control for route and duration of cocaine use.

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Contributors

Authors Stephanie Collins Reed and Suzette M. Evans designed the study and wrote the protocol. Author Stephanie Collins Reed did the statistical analyses, managed the literature research and summaries of previous work and wrote the first draft of the manuscript. Author Suzette M. Evans participated in data interpretation and writing of the manuscript. Both authors have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Keywords

Impulsivity; Amphetamine; Abuse Liability; Cocaine users; Route

1. INTRODUCTION

Although illicit drugs such as marijuana and non-medical use of prescription-type psychotherapeutics (primarily pain relievers) now exceed the use cocaine, cocaine continues to remain a persistent public health problem in the United States (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014a). The number of initiates to cocaine use, the number who report using cocaine and the number who are dependent on cocaine has not decreased over the past 4 years (SAMHSA, 2014a). Based on a recent Treatment Episode Data Set (TEDS), primary cocaine admissions represented 7% of all admissions for substance abuse treatment in 2012, with 69% of those admissions for smoked cocaine (SAMHSA, 2014b).

One often-ignored factor that can influence potential treatment outcome is the route of cocaine being used by individuals. It has been well established that drugs with a rapid onset of action can enhance the reinforcing effects or have greater abuse liability than drugs with delayed onsets (e.g., Abreu et al., 2001; Balster and Schuster, 1973; see reviews by Hatsukami and Fischman, 1996 and Lile, 2006). In the case of cocaine, route of administration is directly related to the onset of action and the reinforcing efficacy. Specifically, smoked cocaine achieves peak venous plasma concentrations within 4-5 minutes and subjective ratings of “High” within as little as 1 minute (Evans et al., 1996), and lasts only about 15 minutes (Cone et al., 1995; Foltin and Fischman, 1991; Evans et al., 1996). In contrast, intranasal cocaine is more delayed with plasma levels and ratings of “High” peaking around 30-40 minutes and lasting for an hour or longer (Cone, 1995; Javaid et al., 1978). Additionally, Volkow et al. (2000) found that ratings of “high” were the greatest for smoked cocaine and lowest for intranasal cocaine, corresponding to the onset of peak subjective effects. Route of administration is considered an important factor in the likelihood of developing a cocaine use disorder, the severity of the use disorder, and other problems associated with cocaine use (e.g., Chen and Anthony, 2004; Gossop et al., 1994; Hatsukami and Fischman, 1996), with several studies demonstrating that smoked cocaine users have less successful treatment outcomes than intranasal users (e.g., Bisaga et al., 2005; Gossop et al., 2003; Grella et al., 2003; Kiluk et al., 2013).

Another potentially related factor that may limit success in treatment is impulsivity, which has been associated with substance abuse (e.g., Aragues et al., 2011; Brady et al., 1998; Dawe and Loxton, 2004). Greater impulsivity is associated with poorer treatment outcomes, including retention and relapse to drug use (Moeller et al., 2001; Patkar et al., 2004; Pattij and De Vries, 2013; Staiger et al., 2014; Winhusen et al., 2013). It is important to note that the construct of impulsivity is multifaceted (e.g., Dawe and Loxton, 2004; Depue and Collins, 1999; Dick et al., 2010; Evenden, 1999; Fineberg et al., 2014) and laboratory studies using a variety of behavioral tasks (see review by Reynolds et al., 2006 and meta-

analyses by Lipszyc and Schachar, 2010 and MacKillop et al., 2011) have demonstrated an association between substance abuse and impulsivity.

Relevant to the present study, cocaine-dependent individuals consistently report greater impulsivity on self-report measures and show more impulsive responding on behavioral tasks compared to non-drug users (e.g., Coffey et al., 2003; Colzato et al., 2007; Liu et al., 2011; Moeller et al., 2002, 2005). Regrettably, these studies, and others (Moreno-López et al., 2012; Vonmoos et al., 2013), did not examine the impact of route of cocaine use on impulsivity. However, there is some indirect evidence that impulsivity may differ as a function of preferred route of cocaine use. One study found that lower white brain matter was associated with increased impulsivity in cocaine users compared to healthy controls (Moeller et al., 2005) and a subsequent study by the same group showed that smoked cocaine users had lower white brain matter compared to intranasal users (Ma et al., 2009). Taken together, these data suggest that smoked cocaine users may be more impulsive than intranasal cocaine users. To build on this hypothesis, one goal of this study was to directly compare smoked cocaine users to intranasal cocaine users on a range of impulsivity questionnaires and behavioral tasks.

Despite the continued use of cocaine by various routes of administration, there has been limited success in identifying an effective treatment medication for cocaine use disorders. Agonist or substitution/replacement treatment medications, such as d-amphetamine (AMPH) and methylphenidate, have shown some efficacy (e.g., Castells et al., 2010; Grabowski et al., 2001, 2004; Herin et al., 2010; Mariani and Levin, 2012; Shearer, 2008; see Stoops and Rush, 2013, for review), but these have not been embraced due to concerns about abuse liability, even with sustained-release formulations (Negus and Henningfield, 2014; Rush and Stoops, 2012). However, stimulants have long been used as the first line of treatment for Attention Deficit Hyperactivity Disorder (ADHD), and the concerns about abuse liability have not been substantiated to date (e.g., Biederman et al., 2008; Swanson et al., 2011). Two relatively recent studies in non-treatment seeking cocaine users did not find any evidence that oral AMPH produced increases in subjective positive drug effects (Comer et al., 2013; Lane et al. 2014) and previous studies have shown that sustained-release oral AMPH actually decreased the subjective effects (Rush et al., 2009) and self-administration (Rush et al., 2010) of intranasal cocaine.

A benefit of stimulant treatment for cocaine use disorders would seemingly be reduced impulsive behavior given that stimulants are used to treat ADHD, a disorder defined by impulsive behaviors. However, literature on stimulants and impulsivity in cocaine users has been mixed. One study showed that neither methylphenidate nor modafinil attenuated impulsive responding on a cued Go/No-Go task (Vansickel et al., 2008), while other studies have shown that methylphenidate decreased impulsive responding on the stop signal reaction time task (Li et al., 2010) and the color-word Stroop task (Goldstein and Volkow, 2011) in cocaine users. However, two other studies showed that inhibitory responding was impaired, suggesting an increase in impulsivity, by oral AMPH on a cued Go/No-Go task (Fillmore et al., 2003) and oral cocaine on a stop signal task (Fillmore et al., 2002). These findings have important clinical implications but need to be interpreted cautiously given that these studies

had very small sample sizes (8 participants), utilized limited impulsivity measures, and did not examine route of cocaine use, which may be an important variable.

The purpose of the present study was to fill this gap in the literature by determining whether impulsivity, determined by multiple behavioral measures, is altered by acute oral AMPH administration in cocaine users and if this varies depending on drug use history (i.e., route of cocaine use). We hypothesized that smoked cocaine users would be more impulsive than intranasal cocaine users. Since previous studies have found that frequency and amount of cocaine used is generally lower in intranasal cocaine users than smoked cocaine users (e.g., Gossop et al., 2006a, b; Grella et al., 2003), we hypothesized that AMPH might decrease impulsivity in intranasal cocaine users compared to smoked cocaine users. Lastly, we also hypothesized that oral AMPH would produce less positive subjective drug effects in smoked cocaine users compared to intranasal cocaine users due to the slower onset and greater duration of action of oral AMPH.

2. METHODS

2.1. Participants

Cocaine users were recruited via advertisements posted on the internet, flyers and local newspapers to participate in a research study examining the effects of common medications on mood and performance. All participants were medically and psychiatrically healthy based on a detailed medical history, laboratory tests, ECG, physical examination and clinical interview. The Structured Clinical Interview for DSM-IV-TR (SCID I, First et al., 1995) was conducted by a trained Master's or Ph.D. level clinical interviewer to rule out a current Axis I psychiatric disorder (excluding cocaine or nicotine abuse or dependence). Participants were not seeking treatment and reported using cocaine predominately by either the smoked route or the intranasal route; cocaine use was verified by participants testing positive for cocaine on urine toxicology tests during screening. None of the participants were taking any prescription medications. Females were currently using effective non-hormonal contraceptives and were not pregnant (based on blood pregnancy tests) or nursing. All participants signed a consent form that was approved by the New York State Psychiatric Institute Institutional Review Board and were financially compensated for their participation.

2.1.1. Cocaine Users—Fifty-five cocaine users, 32 who smoked cocaine (27 M, 5 F) and 23 (18 M, 5 F) who used cocaine intranasally, signed study consent. However, 13 participants never started due to scheduling issues, 5 participants (3 cocaine smokers and 2 cocaine inhalers) were medically excluded prior to starting the study, and 3 participants (2 cocaine smokers and 1 cocaine inhaler) were discontinued for failing to provide drug negative urines on experimental sessions. Therefore, 21 smoked cocaine users (17 M, 4 F) and 13 intranasal cocaine users (12 M, 1 F) completed the study. Table 1 shows that both groups reported using cocaine approximately 4 days per week, but smoked cocaine users spent significantly more money per week on cocaine compared to intranasal users whereas intranasal cocaine users reported using cocaine for significantly more years than smoked cocaine users.

2.2. Procedures

The volunteers participated as outpatients at the New York State Psychiatric Institute. A within-subjects repeated measures design was employed; participants had a total of 5 sessions on separate days, and each session was approximately 7.5 hr long. The first session was a practice session to familiarize participants with the routines to be followed and session 5 was a lottery session (described below); data from these two sessions were not analyzed. On sessions 2-4, oral AMPH (0, 10 or 20 mg) was administered in a randomized order.

2.3. d-Amphetamine Dosing

Oral AMPH (10 and 20 mg; Cardinal Health, Dublin, OH) was prepared as capsules (size 00) with lactose powder as filler; placebo capsules contained only lactose powder. Participants ingested two identically appearing capsules each session (two placebo capsules, one 10 mg AMPH and one placebo capsule, or two 10 mg AMPH capsules). Both the staff and the participants were blind to study medication.

2.4. Experimental Sessions

Participants reported to the laboratory at approximately 8:30 a.m. and remained until approximately 4:00 p.m. each session. They were instructed not to eat breakfast before reporting to the laboratory and to refrain from using cocaine, alcohol and any other drugs (with the exception of tobacco and caffeinated products) or medications the day before an experimental session. Upon arrival each session, a urine specimen was collected and analyzed for the presence of illicit drugs and a breath alcohol test was conducted to test for the presence of alcohol in expired air. On any session day, if illicit drug use was evident (except marijuana since marijuana metabolites remain in urine for several weeks), the participant was rescheduled; if this occurred on two consecutive occasions, the participant was discontinued. Since it is challenging for cocaine users to abstain from cocaine use, to encourage compliance attempts were made to schedule sessions consecutively within the same week and participants were paid \$10 for providing a drug-free urine each session.

After participants consumed a light breakfast (the same on all sessions) that included a caffeinated beverage for those who regularly consumed caffeine, they completed a baseline assessment battery of various computerized self-report questionnaires, impulsivity tasks and performance tasks. After the baseline assessment battery, participants ingested two capsules of oral AMPH (total of 10 or 20 mg) or placebo under the supervision of an investigator. Then participants completed computerized questionnaires and tasks at specified times, described below. Tobacco cigarette smokers were allowed to smoke a single tobacco cigarette after lunch each session.

At the end of each session, participants were required to pass a field sobriety test and cardiovascular measures had to be stable (blood pressure 140/90; heart rate 90). As a safety precaution, they were not allowed to drive to and from the laboratory and were provided subway fare at the end of each session. In the event a participant was still impaired, he/she either remained at the laboratory until the drug effects subsided and cardiovascular measures stabilized or was transported home in a taxicab. Participants were instructed not to

operate a vehicle for 8 hours after drug administration and not to use any drugs, medications or alcohol for the remainder of the day.

2.5. Measures

Unless otherwise specified, measures were conducted before drug administration (−0.75 hr) and 0.25, 1, 2, 3, 4 and 5 hr after drug administration each session.

2.5.1. Abuse-Liability Measures

Drug Effects Questionnaire (DEQ): The DEQ (Evans et al., 1994) asked participants to rate “good effects,” “bad effects,” “strength of the drug effect,” and the degree they would be “willing to take the drug again” on a 5-point scale and rate how much they liked the drug effect on a 9-point scale from −4 (“dislike very much”) to 4 (“like very much”). The DEQ was not completed at baseline since no drug had been administered yet.

Biphasic Alcohol Effects Questionnaire (BAES): The BAES (Martin et al., 1993) is a 14-item adjective rating scale that contains 2 subscales measuring stimulant (BAES Stimulant) and sedative (BAES Sedative) effects.

Multiple Choice Procedure: This procedure assesses the reinforcing effects of drugs in humans (Griffiths et al., 1993, 1996). Four times each session participants made a series of 9 discrete choices between the drug dose administered that session and various amounts of money. Data from this procedure were analyzed as the maximum dollar amount that participants chose drug over money (i.e., the cross-over point). The last session was a lottery session when participants randomly selected a poker chip that corresponded to one of their previous choices from sessions 2-4. This choice was then implemented and regardless of the outcome, participants completed the standard session. The Multiple Choice Procedure was not completed at baseline since no drug had been administered yet.

Drug Craving: This questionnaire consisted of four 100 mm visual analog scales (VAS) labeled ‘not at all’ (0 mm) at one end and ‘extremely’ (100 mm) at the other end used to operationalize drug craving, and were labeled “I want...”, “...cocaine”, “... alcohol”, “... marijuana”, and “...nicotine”.

2.5.2. Mood Questionnaires

Beck Depression Inventory II (BDI II): This 21-item self-report questionnaire (Beck et al., 1996) was completed during screening and at −0.75, 2 and 4 hr of each session.

State-Trait Anxiety Inventory (STAI): The 40-item STAI self-report questionnaire (Spielberger et al., 1970) was completed during screening. The 20-item State component of the STAI was completed at −0.75, 2 and 4 hr of each session.

Profile of Mood States (POMS): For the 72-item Profile of Mood States questionnaire (POMS; McNair et al., 1971), 10 subscales were analyzed (see Evans et al., 1998 for details). Participants rated each item on a 5-point scale from 0 (“not at all”) to 4

(“extremely”). To have all subscales on a similar 5-point scale, total scores for each subscale were divided by the number of items used to determine the subscale score.

2.5.3. Cognitive Tests

Wechsler Adult Intelligence Scale 3rd edition (WAIS-III): The WAIS-III (Wechsler, 1997) provided scores for Verbal IQ, Performance IQ, and Full Scale IQ, along with four secondary indices (Verbal Comprehension, Working Memory, Perceptual Organization, and Processing Speed). For this study, the only the Vocabulary subscale (for Verbal IQ) and Block subscale (for Performance IQ) scores were calculated.

Stroop Color and Word Test: The Stroop color and word test (Golden, 1978) yielded three scores based on the number of items completed on each of three stimulus sheets (a Word Page with color words printed in black ink, a Color Page with ‘Xs’ printed in color, and a color-Word Page with words from the first page printed in colors from the second page). An Interference score, which is the extent of delay in naming the color of an incongruent color word relative to naming the color of a congruent color word or of a neutral non-color word, was calculated. These two cognitive tests were only completed during screening.

2.5.4. Impulsivity Self-Report Questionnaires

Barratt Impulsiveness Scale, version 11 (BIS-11): The BIS-11 (Patton et al., 1995) is a 30-item questionnaire that measures three 2nd order factors of impulsivity (attentional, motor, and non-planning) and six 1st order factors (attention, cognitive instability, motor, perseverance, self-control, and cognitive complexity), and generates a total impulsivity score (Patton et al., 1995). Only the total score and the 2nd order factors were analyzed for the purposes of the present study.

Impulsivity Questionnaire (EIQ): The EIQ is a 54-item questionnaire that measures three dimensions of impulsivity: impulsiveness, venturesomeness, and empathy, and also generates a total impulsivity score (Eysenck et al., 1985).

Sensation-Seeking Scale (SSS): The SSS is a 40-item questionnaire that measures four dimensions of sensation seeking: thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility and also generates a total sensation-seeking score (Zuckerman et al., 1978). These three impulsivity self-report questionnaires were only completed during screening.

2.5.5. Impulsivity Tasks

Immediate Memory Task/Delayed Memory Task (IMT/DMT): The IMT/DMT measures response initiation (Dougherty and Marsh, 2003; Dougherty et al., 2002, 2003a). In the IMT, participants were instructed to respond when the stimulus on the monitor was identical to the one that immediately preceded it. In the DMT, participants were instructed to respond when the stimulus on the monitor was identical to another stimulus after a delay of 3.5 sec; during this delay distractor stimuli were presented. The primary dependent measures were the IMT ratio and DMT ratio, respectively. The ratio is defined as the proportion of commission

errors to correct detections (Dougherty et al., 2002, 2008). The IMT/DMT was completed at -0.75, 1, 2 and 4 hr of each session.

The GoStop Task: The GoStop task measures response inhibition (Dougherty et al., 2003b, 2005). In the GoStop task, participants were instructed to respond to the identically matching numbers before the number disappeared from the screen, but *not* to respond to a number that turns red after its presentation. The primary dependent measure was the 150 msec GoStop ratio, which is the number of response inhibition failures for the 150 msec delay relative to the number of responses to go trials (Dougherty et al., 2008). The GoStop task was completed at -0.75, 1, 2 and 4 hr of each session.

The Delay Discounting Task (DDT): The DDT is a measure of temporal discounting (Kirby and Marakovic, 1996; Kirby et al., 1999; Petry et al., 2002). The primary dependent measure is the overall k value, which determines the discount rate, or the steepness of the reduction in the present value of a reward with increases in delay to that reward (Kirby et al., 1999). Higher overall k values indicate higher levels of impulsivity. To encourage attentive responding, participants were informed that on the last session, they would be given a 1 in 6 chance of receiving the reward that they chose on one of the trials based on the roll of a die (see Reed et al., 2012 for details). The DDT was completed at -0.75, 0.25, 1, 2 and 4 hr of each session.

2.5.6. Measure of Risk-Taking

Balloon Analogue Risk Task (BART): The BART is a measure of risk taking (Lejuez et al., 2002). The primary dependent measure was the number of adjusted pumps, defined as the average number of pumps on balloons on the computer screen, excluding balloons that exploded before money collection. To ensure consistent effort participants were instructed that they would receive a percentage of the actual money earned on this task at the end of the study. The BART was completed at -0.75, 0.25, 1, 2 and 4 hr of each session.

2.5.7. Food Selection and Consumption—Approximately 2 hr after dosing, corresponding to the expected time of peak plasma levels of AMPH (Asghar et al., 2001), participants selected their lunch and approximately 3.5 hr after dosing they had 30 min to consume lunch (see Reed et al., 2008 for details). The amount of food consumed was measured and total food intake at lunch was calculated [(total energy intake, g-intake of carbohydrate, fat, and protein, percent of energy intake derived from each macronutrient estimated as kcal from g-intake using Atwater factors (McLaren, 1976) based on the caloric and macronutrient information provided by the manufacturers].

2.5.8. Vital Signs—Heart rate (HR) and systolic (SP) and diastolic (DP) blood pressure were measured each session at -0.75, 0.25, 1, 2, 3, 4 and 5 hr of the session using a Sentry II vital signs monitor (Model 6100; NBS Medical Services, Costa Mesa, CA).

2.6. Data Analysis—All analyses included route of cocaine use as a grouping variable using data from the 21 smoked cocaine users and the 13 intranasal cocaine users. The results from the practice session (session 1) and the lottery session (session 5) were not included in

the data analyses. *T*-tests were used to compare demographics and data collected during screening as a function of route of cocaine use. For food intake, mean data were analyzed using a 2×3 mixed-model ANOVA with a between groups comparison with two levels (smoked and intranasal cocaine users) and a within groups comparison with three levels (0, 10, and 20 mg).

For all other measures examined across time, mean peak data were analyzed using a 2×3 mixed-model ANOVA with a between groups comparison with two levels (smoked and intranasal cocaine users) and a within groups comparison with three levels (0, 10, and 20 mg). The direction of the peak effect (maximum or minimum) for each participant on each measure was based on initial inspection of the time-course data. Planned comparisons were used to compare 10 and 20 mg AMPH to 0 mg AMPH within each group (2 comparisons within each group) and to compare each AMPH dose between groups (3 comparisons between groups) for all measures. For all analyses, results were considered statistically significant if $p \leq 0.05$. To reduce the potential for Type I errors due to unequal sample sizes and to avoid reporting results that were too liberal or too conservative (i.e., underestimate or overestimate sphericity), the Huynh-Feldt correction was reported when epsilon was $> .75$ and the Greenhouse-Geisser correction when epsilon was $< .75$ (Girden, 1992).

3. RESULTS

3.1. Demographics and Impulsivity Self-reports

Demographic characteristics for smoked and intranasal cocaine users are presented in Table 1. There were no significant group differences in age, race/ethnicity and education level. Of note, there were also no significant group differences in BDI, STAI and Stroop test scores or scores on select subscales of the WAIS-III during screening. However, the groups did differ in their drug use history. Specifically, intranasal cocaine users reported using cocaine for more years than smoked cocaine users ($p \leq 0.05$), although both groups had a long history of cocaine use (> 15 years). In contrast, smoked cocaine users reported spending more money on cocaine per week than intranasal cocaine users ($p \leq 0.05$). Smoked cocaine users also reported more current alcohol and tobacco cigarette use than intranasal cocaine users ($p \leq 0.05$). Cocaine users in general reported little marijuana use, though marijuana use per month was greater in smoked cocaine users than intranasal users; the most frequent use of marijuana reported by any participant was 2 times per month (in 4 smoked cocaine users).

Total scores on impulsivity self-report questionnaires completed during screening are also presented in Table 1. Self-reported impulsivity was significantly greater in smoked cocaine users than intranasal cocaine users based on the total BIS-11 scores ($p = 0.03$); the attentional subscale was also significantly greater ($p = 0.02$) in smoked cocaine users. Self-reported impulsivity on the EIQ was not significantly different between the groups, although the venturesomeness subscale was marginally greater in smoked cocaine users ($p = 0.06$). There were no group differences in total SSS or subscale scores (p 's > 0.05).

3.2. Abuse Liability and Mood Measures

As shown in Figure 1, AMPH did not reliably increase subjective effects measures that would have been indicative of increased abuse liability in either group of cocaine users. In fact, ratings of Good Drug Effect dose-dependently decreased in intranasal cocaine users, in part due to the elevated ratings for placebo, but not in smoked cocaine users [AMPH dose $\times$ group interaction: $F(2,64) = 3.71$, $p = 0.03$]. For ratings of Drug Liking, there were no significant differences as a function of AMPH dose or group, although smoked cocaine users actively disliked all doses. Further, cocaine craving was overall greater in smoked cocaine users than intranasal cocaine users [AMPH dose $\times$ group interaction: $F(2,60) = 3.81$, $p = 0.03$], but following 20 mg AMPH, cocaine craving showed a slight increase in intranasal cocaine users, though this did not reach significance. There were a number of other group effects, such that smoked cocaine users had higher BAES Sedation scores [group effect: $F(1,32) = 7.51$, $p = 0.01$], higher scores on the Confusion [group effect: $F(1,32) = 6.70$, $p = 0.02$] and Fatigue [group effect: $F(1,32) = 8.63$, $p = 0.006$] subscales of the POMS and higher state anxiety scores [group effect: $F(1,32) = 4.18$, $p = 0.05$] compared to intranasal cocaine users (data not shown). However, there was no effect of AMPH on these ratings and AMPH also did not alter BAES Stimulant scores in either group (data not shown). There were no group differences or effects of AMPH on the choice of drug over money using the Multiple Choice Procedure, or any other DEQ or POMS ratings (p 's > 0.05 ; data not shown).

3.3. Behavioral Measures of Impulsivity and Risk-Taking

Figure 2 documents peak IMT, DMT, GoStop Task, and DDT performance as a function of AMPH dose and group. Overall, there was no evidence that AMPH altered these behavioral measures of impulsivity relative to placebo. However, on three of the behavioral impulsivity tasks (the DMT, GoStop Task and DDT), smoked cocaine users responded more impulsively than intranasal cocaine users. Specifically, the DMT ratio was significantly greater in smoked cocaine users than intranasal cocaine users [group effect: $F(1,32) = 4.26$, $p = 0.05$]; post hoc comparisons revealed significant group differences following 10 mg AMPH ($p = 0.04$) and a trend following 20 mg AMPH ($p = 0.09$). A similar pattern was observed for the IMT, but this did not reach statistical significance. There was also a dose $\times$ group interaction on the GoStop Task [$F(1,32) = 4.62$, $p = 0.04$] where performance was slightly elevated in smoked cocaine users and slightly decreased in intranasal cocaine users after 10 mg AMPH compared to placebo (and compared to 20 mg AMPH); however these simple comparisons did not reach significance in post hoc tests, likely due to large amount of variability. Lastly, smoked cocaine users had higher discounting rates on the DDT (per the overall k value) than intranasal cocaine users regardless of AMPH dose [group effect: $F(1,32) = 5.89$, $p = 0.02$]; a similar pattern was observed when the k values for the small, medium and large delayed reward categories were examined separately. There were no group differences or AMPH effects on the BART (data not shown; p 's > 0.05).

3.4. Cardiovascular Effects

Figure 3 shows maximal SP, DP, and HR as a function of AMPH dose and group. As expected, AMPH produced dose-dependent increases in HR [AMPH dose effect: $F(2,64) =$

7.67, $p = 0.001$], SP [AMPH dose effect: $F(2,64) = 21.80$, $p < 0.0001$] and DP [AMPH dose effect: $F(2,64) = 19.51$, $p < 0.0001$]. HR peaked 5 hrs after AMPH administration and did not differ between the two groups. Both AMPH doses produced peak SP and DP at 4 hrs after AMPH administration, but 20 mg AMPH produced significantly greater increases in SP and DP compared to 10 mg AMPH (p 's < 0.05). Further, SP was greater in smoked cocaine users than intranasal cocaine users [significant SP group effect: $F(1,32) = 5.26$, $p = 0.03$], particularly after 20 mg AMPH ($p = 0.03$). Of note, after receiving 20 mg AMPH, eight participants (seven smoked cocaine users and one intranasal cocaine user) had to remain in the laboratory an average of 60 min (range of 12 – 143 min) past the completion of the 7.5 hr session due to vital signs that continued to be elevated above our discharge criteria; four participants had elevated SP, three had elevated DP and one had elevated HR. Vital signs resolved within an hour, with the exception of one smoked cocaine user; his vital signs remained elevated for more than two hours past the end of the session, and as per our protocol he was taken to the emergency room for further monitoring and released when his vital signs stabilized.

3.5. Food Intake

AMPH produced an overall decrease in the number of calories eaten (i.e., food intake) at lunch [AMPH dose effect: $F(2,64) = 5.47$, $p = 0.006$] (data not shown). Under placebo conditions, participants consumed an average of 957 calories (± 64) and this decreased to 781 calories (± 60) after 10 mg AMPH and 736 calories (± 79) after 20 mg AMPH, with no overall group differences.

4. DISCUSSION

4.1. Subjective Effects, Abuse Liability, Mood and Performance

Though previous studies in non-drug users have demonstrated that oral AMPH increases positive subjective effects (de Wit et al., 2002; Kelly et al., 2006; Reed et al., 2010; Stoops et al., 2007; Vansickel et al., 2010), in the present study AMPH failed to increase any subjective effects that would have been indicative of increased abuse liability (e.g., drug liking, good drug effects) in a relatively large sample of cocaine users. This study confirms and extends two recent studies that also showed a blunted subjective response to 20 mg AMPH compared to placebo in 12 smoked cocaine users (Comer et al., 2013) and 13 cocaine users (route of administration not reported; Lane et al., 2014).

The only significant effect of AMPH was in intranasal cocaine users where AMPH *decreased* Good Drug Effect, in contrast to what generally has been shown in non-drug users. Interestingly, there was a slight *increase* in cocaine craving in response to a higher dose of AMPH in intranasal cocaine users. This was surprising given the lack of positive subjects ratings of AMPH. In contrast to the current results and the previous studies mentioned above, another laboratory study in non-treatment seeking smoked cocaine users (Fillmore et al., 2003) showed that oral AMPH, at doses similar to the current study, increased subjective ratings of Good Drug Effect. However, that was a small ($N = 8$) sample of smoked cocaine users who used considerably less cocaine, in terms of frequency (3 x/

week vs. 4-5 x/week), amount (\$88/week vs. \$229-442/week) and years of use (8 yrs vs. 15-20 yrs), than both the smoked and intranasal cocaine users in the current study.

The current findings are important, especially in light of the fact that agonist medications such as AMPH have been assessed for the treatment of cocaine abuse in previous preclinical (e.g., Czoty et al., 2010, 2011; Negus and Mello, 2003a,b) and clinical (e.g., Greenwald et al., 2010; Rush et al., 2009, 2010) studies. Promising results have been found with the sustained-release formulation of AMPH (AMPH-SR) on the effects of intranasal cocaine. AMPH-SR decreased some positive subjective effects of intranasal cocaine in a small (N = 7) group of smoked cocaine users (Rush et al., 2009). In a subsequent study (N = 9), the AMPH-induced decrease in cocaine's subjective effects was not replicated, but maintenance on AMPH-SR produced a slight decrease in the choice to self-administer intranasal cocaine (Rush et al., 2010). In treatment-seeking cocaine and opioid dependent individuals stabilized on buprenorphine, maintenance on AMPH-SR also decreased cocaine-related subjective effects and choice to self-administer intranasal cocaine (Greenwald et al., 2010), further supporting the potential of the SR formulation of AMPH for cocaine treatment. Additionally, we have shown that the SR formulation of another stimulant, methylphenidate, decreased the positive subjective effects and self-administration of intravenous cocaine among cocaine users with ADHD (Collins et al., 2006).

Though AMPH had no effect on mood in either group, smoked cocaine users appeared to have greater negative mood and anxiety compared to intranasal users. It has been shown that cocaine users in general reported greater depression than non-drug users (Mahoney et al., 2014), though smoked and intranasal cocaine users reported using alcohol and cocaine simultaneously at a similar level in order cope with negative affect (Martin et al., 2014). We are not aware of any other studies that have examined mood as a function of primary route of cocaine use. However, given that the smoked cocaine users used a greater amount of cocaine than the intranasal cocaine users in the current study, in terms of days/week of cocaine use and dollars/week spent on cocaine, it is possible that this variable (rather than, or in addition to, route of cocaine use) led to the difference in negative mood scores since chronic heavy cocaine use has been associated with self-reported depressive symptoms (Narvaez et al., 2014; Vonmoos et al., 2013).

4.2. Impulsivity and Risk-Taking

Contrary to our hypothesis, there was also little effect of AMPH on impulsivity in cocaine users. The only other study that examined the effects of AMPH on impulsivity in cocaine users assessed a single behavioral measure of impulsivity, a cued go no-go task, similar to the GoStop task in the current study, after similar doses of oral AMPH (0, 5, 10 and 20 mg) in eight smoked cocaine users (Fillmore et al., 2003). That study showed that AMPH increased inhibitory failures in response to invalid go cues but not invalid no-go cues, and did not have an effect on reaction time. Interestingly, in the current study, there was a group effect on DMT performance, where impulsivity was greater in smoked cocaine users than intranasal users, and upon closer inspection this was only the case after both doses of AMPH (i.e., no difference between the groups after placebo). This was due to a slight, non-significant decrease in intranasal users and increase in smoked cocaine users in DMT

performance after AMPH. Further, GoStop performance appeared worse in smoked cocaine users after 10 mg AMPH compared to placebo and compared to intranasal cocaine users. Therefore, AMPH's effect on impulsivity in smoked cocaine users in our study were more in line with the findings in the Fillmore study (2003), whereas intranasal users may have a profile more similar to non-drug users who have historically shown decreases or no change in impulsivity in response to AMPH (e.g., de Wit et al., 2002; Reed et al., 2010). This is supported by the group differences in DDT performance as well, where smoked cocaine users showed greater impulsivity than intranasal cocaine users, though there was no direct effect of AMPH on DDT performance.

Although both groups had been using cocaine for an extensive number of years (> 15), intranasal users reported using cocaine significantly longer than smoked cocaine users. Since years of cocaine use may be associated with behaviors such as impulsivity (Liu et al., 2015), we examined whether group differences on performance on the impulsivity tasks were correlated with years of cocaine use, using a Pearson's product-moment correlation. We found that DMT, GoStop and DDT scores were not correlated with years of cocaine use after any of the AMPH doses, supporting the notion that the group differences in impulsive responding were not related to differences in years of cocaine use.

It may not be surprising that there were relatively few differences between the groups on many of the impulsivity self-report questionnaires and behavioral measures since both groups were expected to be impulsive based on their long history of frequent cocaine use; however it is interesting to note that the few group differences in impulsivity that were observed occurred in a specific subset of impulsive behaviors. Smoked cocaine users scored higher on the attentional subscale of the BIS-11, were more likely to choose smaller more immediate rewards over larger delayed rewards (per the DDT), were less able to inhibit responding when there was a 150 ms delay (per the GoStop task), and had poorer memory recall when there was a delay (per the DMT) compared to intranasal users. Conversely, motor and non-planning subscale BIS-11 scores, immediate memory recall (IMT), and risk-taking (BART) behaviors were similar between the groups. While we are cautious in any overarching interpretation of these data due to the small changes observed, smoked cocaine users may have more difficulty with impulse inhibition when encountering a delay, which may be due to an attentional impulse deficit. Attentional impulsivity refers to task-focus (Patton et al., 1995) or an inability to sustain attention for prolonged periods of time (Zhou et al., 2014), whereas motor impulsivity is a tendency to act on the spur of the moment (Patton et al., 1995); motor impulsivity may play a greater role in tasks requiring more immediate responding, such as the IMT where there is little delay between the presentation of numbers on the screen. Importantly, the differences in observed in DMT, GoStop task and DDT performance did not appear to be due to greater cognitive deficits in cocaine smokers compared to intranasal cocaine users since there were no differences in WAIS-III and Stroop test scores between groups.

4.3. Cardiovascular Effects

AMPH produced the expected increases in SP, DP and HR in cocaine users; of note, the increases in SP were more pronounced in smoked cocaine users particularly after 20 mg

AMPH. These cardiovascular increases are consistent with previous studies that administered similar doses of immediate-release AMPH (Comer et al., 2013; Fillmore et al., 2003) and even AMPH-SR (Rush et al., 2009) to cocaine users. While a recent study (Lane et al., 2014) did not show an increase in cardiovascular effects after 20 mg AMPH in cocaine users, potential increases might not have been captured since vital signs were not measured beyond 90 min; based on our findings, peak cardiovascular effects were not observed until at least 4 hrs after AMPH administration, over 2 hrs after the time that peak plasma levels of AMPH occur (Asghar et al., 2001).

Although it is possible that higher doses of AMPH may have produced positive subjective effects or changes in impulsive responding, the moderate doses of AMPH used in the current study produced prolonged cardiovascular increases, mainly SP in the smoked cocaine users who also tended to have higher baseline SP than intranasal cocaine users (although still well within our safety criterion). As mentioned above, after the highest dose of AMPH, 26% of the participants (all but one were smoked cocaine users) had to remain in the laboratory an average of 60 min (range of 12 – 143 min) after the end of the session to wait for their vital signs to decrease before leaving the laboratory. These increases in cardiovascular response after oral AMPH prohibited the testing of higher doses and suggest that AMPH may not be an ideal medication for cocaine users, particularly smoked cocaine users, who are already vulnerable to cardiovascular issues (e.g., Awtry and Philippides, 2010; Bigi et al., 2008; Brecklin and Bauman, 1999). However, AMPH-SR or other SR stimulants that produce less of an increase in cardiovascular effects in cocaine users (Collins et al., 2006; Greenwald et al., 2010; Rush et al., 2010; but see Rush et al., 2009) may be safer.

4.4. Strengths and Limitations

This study had a number of procedural strengths not previously addressed in other studies. First, this study comprehensively examined the effects of AMPH on a range of impulsivity measures in cocaine users and these were assessed repeatedly each session. Second, to our surprise, this is the only study to date comparing smoked cocaine users to intranasal cocaine users under controlled laboratory conditions. Third, we systematically collected detailed information on drug use history which allowed us to determine that our sample was comprised of chronic heavy users (i.e., frequent use and a dollar amount used each week), which is a group of cocaine users that are thought to be challenging to treat (e.g., Bisaga et al., 2005) and warrant continued attention in treatment research studies.

This study also had several limitations. (1) The sample size of smoked cocaine users was greater than intranasal cocaine users (62% vs. 38%). However, we attempted to deal with this in a statistical manner that would render our results meaningful and the sample sizes in this study were larger than previous laboratory studies. (2) The cocaine users in the current study were not currently seeking treatment for their cocaine use. Although they were required to have cocaine negative urines each session, it is possible that treatment-seekers may have had a different response to AMPH, such as in the study by Greenwald et al. (2010), particularly with respect to cocaine craving. Moreover, individuals who are motivated to seek treatment may have a different profile of impulsivity than either non-treatment seeking cocaine users and/or non-drug using controls, and this may play a role in

the success of treatment (e.g., Poling et al., 2007; Schmitz et al., 2009). (3) Higher doses of oral AMPH could not be tested in this study due to the extended elevations in cardiovascular reactivity observed, but it was apparent that the cocaine doses administered in this study were behaviorally active as evidenced by the increased cardiovascular effects and decreased food intake observed in both groups.

Agonist or substitution medications have been successful for treating heroin and nicotine use disorders and there is evidence that this may also be true for cocaine use disorders. The current study is one of a few studies to examine the effects of oral AMPH in cocaine users, which is a group that remains prevalent (Centers for Disease Control and Prevention, 2013; Johnston et al., 2014; SAMHSA, 2014a), is likely to engage in other risky behaviors (e.g., Lim et al., 2011; Ropelewski et al., 2011) and for which HIV and other sexually transmitted diseases are also pervasive (e.g., Hagan et al., 2011; Kuo et al., 2011; Pagano et al., 2015). Importantly, this study is the only one we are aware of that examined the effects of AMPH on a range of measures as a function of preferred route of cocaine use. This is clinically relevant because smoked cocaine users have been shown to be more difficult to treat than intranasal cocaine users (Bisaga et al., 2005, 2006; Kiluk et al., 2013; Nunes et al., 1995).

While AMPH did not increase any subjective measures related to abuse liability, it also did not decrease impulsivity. Additionally, AMPH produced extended increases in cardiovascular activity, particularly in smoked cocaine users, which is not a favorable outcome for a treatment medication. However, this was most likely due to the fact that immediate-release AMPH was administered rather than AMPH-SR. Based on previous literature, extended-release formulations of stimulants have been shown to be safe and should be further examined as a potential treatment for cocaine use disorders. Since a number of groups have suggested that other agonist-like medications, such as modafinil and methylphenidate, may have utility as cocaine treatment medications (e.g., Dackis et al., 2003, 2005; Grabowski et al., 2001; Mariani and Levin, 2012; Martínez-Raga et al., 2008; Vansickel et al., 2008; Winhusen et al., 2006; see review by Stoops and Rush, 2013), it would also be of interest to directly compare the effects of AMPH and these other potential medications on cocaine-related behaviors. An essential component for such a study would be to account for preferred route of cocaine use since it has been overlooked in the majority of cocaine studies but may be an important variable in developing successful pharmacotherapies.

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Highlights

- Overall, smoked cocaine users were more impulsive than intranasal cocaine users.
- Group differences occurred primarily in impulsive measures with a delay component.
- Cocaine craving was greater in smoked cocaine users than intranasal cocaine users.
- Oral d-amphetamine did not alter impulsivity in cocaine users.
- Oral d-amphetamine did not increase positive subjective effects in cocaine users.

Fig. 1. Peak Good Drug Effect and Drug Liking ratings on the DEQ and peak ratings of cocaine craving as a function of group and AMPH dose. * denotes a significant difference compared to 0 mg AMPH within each group ($p < 0.05$). # denotes a significant difference between groups ($p < 0.05$). Error bars represent + 1 S.E.M.

Fig. 2.
Peak performance on the IMT, DMT, GoStop Task, and DDT as a function of group and AMPH dose. See Fig. 1 for details.

Fig. 3. Peak systolic pressure, diastolic pressure, and heart rate as a function of group and AMPH dose. See Fig. 1 for details.

Table 1

Demographic characteristics of study participants.

	<u>Smoked</u>	<u>Intranasal</u>
N	21	13
Age (Yrs)	40.8 (4.6)	42.2 (4.4)
Male/Female	17/4	12/1
Race (Blk/Hispanic/White/Other)	14/3/2/2	8/2/1/2
Education (Yrs)	12.3 (1.4)	12.5 (1.1)
Beck Depression (BDI) Score	5.2 (5.6)	2.0 (3.5)
State Anxiety (STAI) Score	34.0 (9.1)	27.9 (10.0)
WAIS		
Vocabulary Subscale Score	40.5 (12.2)	42.0 (8.9)
Block Subscale Score	31.5 (8.1)	32.5 (11.8)
Stroop Interference Score	-2.3 (9.1)	-2.5 (5.2)
Cocaine Use:		
Years *	15.0 (7.9)	20.9 (7.6)
Days/week	4.5 (1.5)	3.7 (1.1)
\$/week *	401.2 (217.6)	228.9 (115.4)
Alcohol:		
# drinkers	17	12
#drinks/week *	17.3 (16.0)	6.1 (6.7)
Cigarettes:		
# smokers *	21	8
# smoked/week *	9.0 (6.4)	3.5 (3.7)
Marijuana:		
# smokers	9	4
Times smoked/month *	0.7 (0.9)	0.1 (0.3)
Impulsivity Self-report Total Scores:		
Barratt Impulsiveness Scale (BIS-11) *	66.1 (9.6)	58.7 (8.8)
Eysenck Impulsivity Questionnaire (IQ)	28.4 (6.1)	26.1 (6.8)
Zuckerman Sensation-Seeking Scale (SSS)	21.6 (3.3)	21.6 (3.0)

Note: All demographics are presented as means $\pm$ SD unless otherwise denoted. Raw scores are reported for the WAIS and Stroop Test.

* Significant difference between groups ($p < 0.05$).