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Caffeine choice prospectively predicts positive subjective effects of caffeine and *d*-amphetamine

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Abstract

Background—Individuals vary in their subjective and behavioral response to psychomotor stimulants and these differences may be associated with the likelihood of developing problematic use of these drugs. The present study sought to determine whether individual differences in caffeine choice prospectively predict subjective response to acute doses of caffeine and *d*-amphetamine.

Methods—In Phase 1, Choosers and Nonchoosers of caffeine were identified using 10 independent choice trials in which subjects repeatedly chose between caffeine (200 mg/70kg) or placebo. Choosers were defined as those who chose caffeine over placebo on ≥ 7 of the 10 trials; Nonchoosers were those who chose placebo on ≥ 7 trials. In Phase 2, Choosers and Nonchoosers were compared in their subjective response to caffeine (100, 200, 400 mg/70kg) and *d*-amphetamine (5, 10, 20 mg/70kg).

Results—Of the 22 participants completing the study, 11 met criteria for being a caffeine Chooser and 8 were Nonchoosers. In Phase 1, Choosers reported higher ratings of positive (i.e., pleasant) and lower ratings of negative (i.e., unpleasant) effects of caffeine during the sampling sessions. In Phase 2, caffeine Choosers reported more positive subjective effects and fewer negative effects of caffeine and *d*-amphetamine, particularly at the highest doses examined.

Conclusions—Individual differences in caffeine reinforcement predicted subsequent subjective response to both *d*-amphetamine and caffeine. This observation may have clinical utility for identifying individuals who are vulnerable to the reinforcing effects of abused psychomotor stimulants.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Dr. Griffiths obtained the grant that funded this project. Drs. Sigmon and Griffiths designed the study, wrote the protocol, conducted the study, conducted literature searches, were involved in the statistical analyses and wrote the manuscript. All authors contributed to and have approved the final manuscript.

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Keywords

Psychomotor stimulant; Caffeine; *d*-Amphetamine; Individual Differences; Subjective Effects; Reinforcement; Choice; Human

1. Introduction

While the abuse potential of psychomotor stimulants has been widely demonstrated (Foltin and Fischman, 1991), it is also the case that not everyone who tries a stimulant will develop abuse or dependence. Of people who use stimulants, such as cocaine or *d*-amphetamine at least once, only a small proportion go on to use them in excessive amounts or to develop problems (de Wit, 1998). Individual variability in subjective and behavioral response to abused stimulants has been especially well-demonstrated (de Wit et al., 1986; Singha et al., 1999; Sofuoglu et al., 2000; Gabbay, 2003).

As with the abused psychomotor stimulants, studies using choice and repeated drug self-administration have shown that the stimulant caffeine can function as a reinforcer in humans (Evans et al., 1994; Griffiths et al., 1989; Hughes et al., 1991; 1992). The average incidence of caffeine reinforcement across studies in normal caffeine users is about 40% (Griffiths et al., 2003; Griffiths and Woodson, 1988; Hughes et al., 1993). Individual differences in the reinforcing effects of caffeine have been shown to covary with individual differences in subjective response to caffeine (Griffiths and Woodson, 1988; Hughes et al., 1993; Stern et al., 1989). For example, in a choice study examining the subjective effects of placebo and caffeine on forced-exposure days prior to choice sessions, participants who chose caffeine over placebo in the choice sessions reported more positive subjective effects of caffeine relative to placebo, including increased alertness, contentedness, energy and liking (Evans and Griffiths, 1992). Those who chose placebo over caffeine reported more negative effects of caffeine relative to placebo, including increased anxiety, mood disturbance and jitteriness.

The purpose of the present study was to more fully investigate the individual differences in the reinforcing effects of caffeine and also evaluate the relationship between these individual differences and the subsequent assessment of caffeine and *d*-amphetamine subjective effects. Of particular interest was whether caffeine chooser status would prospectively predict subjective response to *d*-amphetamine. Prior studies have demonstrated individual differences in the reinforcing and subjective effects of *d*-amphetamine (de Wit et al., 1986; Gabbay, 2003; Sigmon et al., 2003; Uhlenhuth et al., 1981), and a recent study in college students has shown that consumption of caffeinated energy drinks prospectively predicts non-medical use of prescription stimulants (Arria et al., 2010). Identification of caffeine reinforcement as a predictor of *d*-amphetamine response would contribute important new information about individual differences in vulnerability to reinforcement and abuse of classic psychomotor stimulants such as amphetamine and cocaine. Toward this end, in the present study we first used a discrete-trial choice procedure with 10 experimentally-independent choice trials to categorize participants into caffeine Choosers or Nonchoosers. In a subsequent phase, the acute effects of a range of doses of caffeine and *d*-amphetamine were characterized.

2. Methods

2.1. Participants

Participants were recruited through newspaper advertisements and community postings. To be eligible, participants had to be adult volunteers between the ages of 18–60 years, report a history of regular or intermittent caffeine use, provide a urine specimen that tested negative

for illicit drugs of abuse, be in good health as determined by medical history and vital signs, be fluent in English, and be capable of understanding and complying with the protocol. Females were required to be non-pregnant and non-lactating. Exclusion criteria included: known hypersensitivity or medical contraindication to stimulants; a past or current significant medical or psychiatric condition; current diagnosis of any substance dependence other than nicotine; significant illness in the past 30 days; diastolic blood pressure >90 mmHg or a systolic pressure >140 mmHg; body weight 20% above or below their Ideal Body Weight, as calculated using the Metropolitan Life Insurance index; use of prescription or over-the-counter medications that could interfere with the study. The study was approved by the local institutional review board, and subjects provided written informed consent before participating.

Twenty-two participants (14 females and 8 males) completed the study; 17 were Caucasian, 4 were African American, and 1 was Asian. Participants had a mean (range) age of 32.4 (19–51) years, 15.5 (12–16) years of education, and reported drinking a mean of 2.7 (0–6) standard alcohol drinks per week. Subjects reported consuming 167 (14–410) mg caffeine per day. None reported recent use of illicit drugs, and urine samples for all subjects tested negative for illicit substances.

2.2. Intake screening

Individuals came to the Behavioral Pharmacology Research Unit (BPRU) at the Johns Hopkins University School of Medicine and completed a battery of questionnaires assessing demographic variables and drug use history (i.e., age, gender, ethnicity, education, body weight, cigarettes/day, use of alcohol (number of drinks/day), caffeine (mg/day) and illicit drugs (number of times used/lifetime)). They received a brief medical screening that included measurement of vital signs, urine toxicology, and a medical and psychiatric questionnaire. In order to accurately assess participants' dietary intake before the study, they also were asked to keep a food/medication diary for seven days, recording the amounts, types and timing of all foods, drinks and medications consumed. Questions about foods without caffeine were included to keep participants blind as to the exact drugs under study.

2.3. Study Design

This double-blind, placebo-controlled study was 10–14 weeks in duration (including an initial 1-week caffeine abstinence period). Subjects were informed that its purpose was to examine how commonly-used medications may influence mood and medication preference and that they could receive placebo or a variety of commonly-prescribed or over-the-counter sedatives, stimulants or antihistamines. Dietary restrictions were in place throughout the study to eliminate caffeine from each subject's diet; in addition to restricting caffeinated foods, non-caffeinated foods were also restricted in order to keep subjects blind to the exact drugs under study (e.g., foods containing NutraSweet, oysters, mussels, almonds, coconuts, poppy seeds and all beverages except milk, fruit juice and water). To further facilitate compliance with dietary restrictions, participants provided saliva samples at each study visit and were told that the samples would be analyzed for the various compounds contained in the restricted foods. Two samples were chosen from each participant for caffeine quantification and all were collected a minimum of two days after last caffeine exposure. These analyses provided an opportunity to confirm compliance with study dietary restrictions at a point when little or no caffeine should have been ingested. Salivary caffeine concentrations were analyzed by Gas Chromatography-Thermionic Specific Detection (Labstat Inc, Ontario, Canada) using methods previously described (Griffiths and Woodson, 1988; Jacob et al., 1981). The tested saliva samples were collected an average of 3.2 (range 2–6) days following last caffeine exposure and had a median caffeine concentration of 8.4 ng/ml, indicating that subjects were compliant with the caffeine restrictions during the study.

During the week before initiation of drug administration, subjects followed dietary restrictions and reported to the laboratory 3 times (e.g., Monday, Wednesday, Friday) to provide a saliva sample. Participants then began Phase 1, which consisted of 30 experimental sessions over a 6–10 week period depending on subjects' schedules. Participants visited the laboratory 3–5 times per week, during which they provided a saliva sample, completed a pre-capsule Drug Effect Questionnaire (DEQ), and ingested p.o. 2 identical color-coded capsules with water under double-blind conditions. The 30 sessions in Phase 1 were comprised of 10 sequences of 3 sessions (Sample-Sample-Choice) per sequence. Each test sequence began with two “no-choice” drug-sampling days during which participants received 2 different types of color-coded capsules on different days (e.g., red capsules on Monday and green capsules on Tuesday). Participants always received placebo on one sample day and caffeine anhydrous (200 mg/70 kg) on the other sample day, with the order of exposure to caffeine and placebo counterbalanced across trials. After leaving the laboratory, participants completed the DEQ at 1, 2, 4, and 8 hours after capsule ingestion, which assessed drug effects and drug liking (described in more detail below). On the subsequent “choice session” day, they were shown their self-report data from the prior two sample days to help them recall specific drug effects associated with each pair of capsules. They then chose to ingest one of the two color-coded capsule pairs. The content of the color-coded capsules was always the same as during the preceding 2 sample sessions (one pair contained placebo and the other 200 mg caffeine anhydrous). After leaving the laboratory, participants again completed the DEQ at 1, 2, 4 and 8 hours post-capsule. This 3-day test sequence (2 sample days followed by 1 choice day) was repeated for a total of 10 consecutive test sequences. Each 3-day sequence was experimentally independent (i.e., each sequence involved novel color-codes for the capsules and participants were told that capsule ingredients may or may not change across sequences).

Phase 2 of the study consisted of 7 experimental sessions over a 3–4 week period, during which participants reported to the laboratory approximately 2–3 times per week. At each visit, participants provided a saliva sample, completed a pre-capsule DEQ and then ingested p.o. 2 capsules with water under double-blind conditions. These sessions were similar to the drug sampling days of Phase 1 except that there was never an opportunity for choosing between capsules during Phase 2. Phase 2 capsules contained placebo, caffeine anhydrous (100, 200 or 400 mg/70 kg), or *d*-amphetamine sulfate (5, 10 or 20 mg/70 kg), with order of exposure to caffeine and *d*-amphetamine doses and to placebo counterbalanced across subjects and trials in a Latin Square sequence. Capsules were not color-coded but rather were identical across all 7 sessions. After leaving the laboratory, subjects completed the DEQ at 1, 2, 4 and 8 hours post-capsule. At least one non-experimental day was scheduled between sessions to eliminate any drug carryover effects. Subjects received approximately \$1300 for participating in the study.

2.4. Drug preparation and administration

Size 0, opaque hard gelatin capsules were used throughout the study. Two capsules were used for each instance of drug or placebo administration in both Phase 1 and 2. During Phase 1, caffeine capsules (200 mg/70 kg) were prepared using powdered lactose and caffeine anhydrous (USP). Placebo capsules were prepared using powdered lactose. The color of the caffeine and placebo capsules varied across experimental sessions within and across participants; there were 7 possible colors (e.g., red, yellow, blue) and a total of 28 possible color combinations (including solid-colored capsules and capsules with each half being a different color). During Phase 2, all capsules were blue. Caffeine capsules (100, 200 or 400 mg/70 kg) were prepared using powdered lactose and caffeine anhydrous (USP). *d*-Amphetamine capsules (5, 10 or 20 mg/70 kg) were prepared using powdered lactose and *d*-

amphetamine sulfate. Amphetamine doses are expressed as the salt. Identical placebo capsules were prepared using powdered lactose.

2.5. Subjective measures

Participants completed the Drug Effect Questionnaire (DEQ) immediately before and at 1, 2, 4, and 8 hours after capsule administration. This questionnaire was designed to assess subjective effects of drugs and included 25 items: Drug Effect, Arousing/Stimulant Effect, Depressant/Sedating Effect, Good Effects, Bad Effects, Liking, Alert/Attentive, Well-Being, Refreshed, Desire To Socialize/Talkativeness, Anxious/Nervous, Happy, Urge To Do Task/Work-Related Activities, Drowsy/Sleepy, Overjoyed, Ability To Concentrate, Energy/Active, Jittery/Shaky, Elated, Lethargy/Fatigued/Tired/Sluggish, Pleased, Muzzy/Foggy/Not Clear-Headed, Satisfied, Self-Confidence and Heart Pounding. Participants rated each item on a 5-point scale from 0 (not at all) to 4 (extremely). An additional 9-point item was included that asked participants to rate their "liking" of the drug effect they were feeling right now, using a scale that ranged from -4 (dislike very much) to +4 (like very much) and which also included the option of rating their liking of drug effect as 0 (neutral or no effect). For the items assessing general drug effects (i.e., Drug Effect, Arousing/Stimulant Effect, Depressant/Sedating Effect, Good Effects, Bad Effects, Liking), subjects were instructed to rate them as "0" for the pre-capsule timepoint.

2.6. Data analysis

SAS Proc Mixed (Version 9.2) was used to analyze the data with repeated measures regression models. These models allow for the specification of the covariance structure of the repeated measures and have better mechanisms for handling missing data and thus are preferable to traditional ANOVA models (Wolfinger and Chang 1995). We report Type III tests of fixed effects.

DEQ data are expressed as change scores from the precapsule timepoint. The subjective effects of caffeine vs. placebo in Phase 1 were first analyzed for the entire group (N=22) using a repeated measures regression model with AR(1) covariance structure and factors of drug (caffeine and placebo) and time, followed by Tukey's HSD post-hocs comparing caffeine and placebo conditions at each timepoint. This analysis included all participants (i.e., even individuals who did not meet subsequent criteria for Chooser or Nonchooser status). Subjective effects data from the drug sampling sessions were used for these analyses; data from the choice sessions were not included because those self-report ratings could be confounded by the fact that participants were rating the effects of the capsule which they had chosen to ingest on that day.

Participants were then dichotomized into Chooser or Nonchooser categories based on their number of caffeine or placebo choices during the 10 choice sessions in Phase 1. Choosers were defined as those who chose caffeine over placebo on ≥ 7 of the 10 choice trials; Nonchoosers were those who chose placebo over caffeine on ≥ 7 of the 10 trials. Participants who did not meet these criteria (e.g., those that made 5 or 6 choices for caffeine or placebo during Phase 1) were excluded from subsequent Chooser vs. Nonchooser comparisons. This criterion of 7/10 ($p=0.172$) for Chooser vs. Nonchooser membership produced two distinct groups while also not discarding participant data unnecessarily. Demographic and drug use characteristics were compared between Choosers and Nonchoosers using t-tests. In Phase 1, the subjective effects data for the Choosers and Nonchoosers were analyzed using a repeated measures regression model with AR(1) covariance structure and factors of chooser status (Chooser and Nonchooser) and time, followed by Tukey's HSD post-hocs comparing Choosers and Nonchoosers at each timepoint.

In Phase 2, data are expressed as peak change from baseline. Peak subjective effects of the dose conditions were analyzed for the entire group (N=22) using a repeated measures regression model with an exchangeable covariance structure and one factor of drug condition (placebo, 3 caffeine doses, 3 *d*-amphetamine doses), followed by Tukey's HSD post-hocs comparing each active drug dose to placebo. This analysis included all participants (i.e., even individuals who did not meet criteria for Chooser or Nonchooser status).

Because the primary focus of the study was on whether Choosers and Nonchoosers differ in their response to caffeine and *d*-amphetamine doses in Phase 2, planned comparisons were conducted between the two groups at each of the 7 dose conditions. For all statistical tests, results were considered significant when $p \leq .05$.

3. Results

3.1. Caffeine or placebo choice

Twenty-two participants completed the study, with 19 categorized as either a caffeine Chooser (N=11, 58%) or Nonchooser (N=8, 42%) based on the criteria of choosing caffeine or placebo ≥ 7 out of the 10 choice trials during Phase 1. Choosers chose caffeine over placebo an average of 80% of choice sessions; Nonchoosers chose placebo over caffeine an average of 83% (i.e., chose caffeine 17% of the time). Three participants failed to make ≥ 7 exclusive choices for either caffeine or placebo. There were no significant differences between Choosers and Nonchoosers, respectively, on pre-study caffeine intake (mean of 211 vs. 156 mg/day, $p=.16$), gender (55% vs. 75% female, $p=.39$), age (33.6 vs. 28.6 yrs; $p=.22$), cigarettes/day (1.2 vs. 0; $p=.17$), alcohol drinks/week (2.6 vs. 3.4; $p=.77$) or instances of lifetime illicit drug use (5.9 vs. 4.8; $p=.73$).

3.2. Subjective response to caffeine and placebo during Phase 1

Examination of subjective response to caffeine and placebo for the total sample (N=22) during Phase 1 showed significant effects of drug (caffeine vs. placebo) on 16 items on the Drug Effect Questionnaire ($F=5.02-23.14$, $p \leq .05$), and a significant drug x time interaction for 11 items ($F=3.16-15.32$, $p \leq .05$). For most of these items, caffeine effects were significantly different from placebo at the 1-, 2- and 4-hr post-capsule timepoints. Ratings typically peaked at 2-hrs post-capsule, remained significantly elevated at 4 hrs and decreased thereafter, with 7 of these measures remaining significant at 8 hrs post-administration. Caffeine increased ratings on 14 items (i.e., Drug Effect, Arousing Effect, Good Effects, Bad Effects, Refreshed, Talkativeness, Anxious, Happy, Elated, Overjoyed, Energy/Active, Jittery/Shaky, Self-confidence and Heart pounding) and decreased ratings on 3 items (i.e., Depressant Effect, Drowsy, Tired/Sluggish).

Examination of Phase 1 subjective ratings after 200 mg/70 kg caffeine showed a significant main effect of chooser status on 9 items (i.e., Liking, Well-being, Happy, Urge To Do Task/Work-Related Activities, Pleased, Satisfied, Foggy/Not Clear-headed, Heart Pounding, and Bad Effects, $F=4.88-11.72$, $p \leq .05$), and a significant chooser x time interaction on 6 items (i.e., Alert/Attentive, Energy/Active, Self-Confidence, Pleased, Happy, Bad Effects, $F=2.86-4.38$, $p \leq .05$). For all 12 items that showed a significant chooser effect or chooser x time interaction, Choosers and Nonchoosers were significantly different at 2 hours post-drug, with 7, 9, and 1 items being significantly different at 1, 4, and 8 hours, respectively. Relative to Nonchoosers, Choosers had significantly greater ratings on 9 items reflecting positive (i.e., pleasant) effects of caffeine: Liking, Well-Being, Happy, Urge To Do Task/Work-Related Activities, Pleased, Alert/Attentive, Energy/Active, Self-Confidence and Satisfied. Four representative measures are shown in Figure 1. Compared to Nonchoosers,

Choosers also had significantly lower ratings on 3 items reflecting negative (i.e., unpleasant) effects of caffeine: Foggy/Not Clear-Headed, Heart Pounding, and Bad Effects (Figure 2).

Four of the 25 items on the Drug Effect Questionnaire showed significant main effects of chooser status following placebo administration (i.e., Liking, Alert/Attentive, Refreshed and Urge To Do Task/Work-Related Activities, $F=4.63-8.15$, $p \leq .05$). There were no significant chooser x time interactions. In contrast to the robust time-dependent effects in response to caffeine, these 4 items showed a variable pattern of differences over time, with none showing a significant difference at 1 hour and only Liking showing a significant difference at 2 hours post-drug. When differences did occur, Choosers tended to report lower ratings on positive effects following placebo administration than Nonchoosers.

3.3. Subjective response to caffeine and d-amphetamine during Phase 2

Examination of peak subjective effects of the seven drug conditions in Phase 2 for the total sample ($N=22$) showed significant effects of drug condition on 11 items (i.e., Drug Effect, Arousing Effect, Good Effects, Bad Effects, Talkativeness, Anxious, Jittery/Shaky, Self-Confidence, Overjoyed, Energy/Active and Pleased, $F=2.27-8.65$, $p \leq .05$). For both caffeine and *d*-amphetamine, the magnitude of effects generally increased with dose, with the highest dose showing the largest effects. As shown in Figure 3, compared to placebo, both caffeine and *d*-amphetamine produced significant increases on ratings of Drug Effects, Arousing Effect and Good Effects, while only caffeine produced significant increases in Bad Effects ($p \leq .05$). For rated items that showed significant effects of drug condition, but that are not shown in Figure 3, the high dose of caffeine significantly increased ratings of Anxious and Jittery/Shaky, whereas the high dose of *d*-amphetamine significantly increased ratings of Talkativeness, Overjoyed, Energy/Active and Jittery/Shaky.

The effects of chooser status on peak subjective ratings in Phase 2 were examined using planned comparisons between Choosers and Nonchoosers at each of the 7 drug conditions. Of the 25 items on the Drug Effect Questionnaire, 18 items had one or more significant planned comparison. Differences between Choosers and Nonchoosers were generally greatest at the highest dose of *d*-amphetamine and caffeine. For example, of the 18 measures, Choosers and Nonchoosers significantly differed at the 400 mg dose of caffeine on 15 items (i.e., Good Effects, Liking, Alert/Attentive, Well-Being, Refreshed, Talkativeness, Happy, Urge To Do Task/Work-Related Activities, Overjoyed, Concentration, Tired/Sluggish, Pleased, Satisfied, Self-Confidence and Heart Pounding). Furthermore, Choosers and Nonchoosers significantly differed at the 20 mg dose of *d*-amphetamine on 6 items (i.e., Liking, Alert/Attentive, Well-Being, Concentration, Jittery/Shaky and Satisfied) and differed significantly at 10 mg of *d*-amphetamine on 1 item (i.e., Urge To Do Task/Work-Related Activities). Eight representative measures are shown in Figure 4. After placebo, Choosers and Nonchoosers differed on 3 items (i.e., Drowsy, Concentration, Energy/Active). Generally, Nonchoosers reported being more drowsy, less energetic and having less concentration following placebo administration compared to Choosers.

4. Discussion

The profiles of subjective effects of both caffeine and *d*-amphetamine for the entire subject group were similar to that reported in prior studies. Caffeine produced dose-related increases in ratings of general drug effects (e.g., Drug Effect, Arousing Effect, Talkativeness), pleasant effects (e.g., Good Effects, Happy, Energy/Active) and unpleasant effects (e.g., Bad Effects, Anxious, Heart Pounding). This mixed profile of pleasant and unpleasant effects of caffeine is consistent with that described previously (Griffiths et al., 2003; Griffiths and Woodson, 1988). *d*-Amphetamine significantly increased ratings of general drug effects and

pleasant effects (e.g., Drug Effects, Arousing Effects, Good Effects, Self-Confidence) but produced less evidence of unpleasant subjective effects, which is also similar to prior studies (Rush et al., 2001; Sigmon et al., 2003).

In Phase 1, individual differences in caffeine reinforcement were demonstrated. These data are consistent with prior studies showing individual differences in caffeine reinforcement and subjective effects (Evans and Griffiths, 1992; Griffiths and Woodson, 1988; Hughes et al., 1993; Stern et al., 1989). The incidence of caffeine reinforcement in the present study (50%) (11 of 22 participants) is similar to the 40% that has been demonstrated in previous studies in normal volunteers, most of whom were physically dependent (Griffiths et al., 2003).

The subjective effects of caffeine during sampling sessions differed between caffeine Choosers and Nonchoosers, with Choosers reporting significantly more positive effects and Nonchoosers more unpleasant effects of caffeine. Previous choice or reinforcement studies with caffeine reporting subjective effect differences are difficult to interpret because they have been confounded by the subjective effects of caffeine abstinence (Griffiths and Woodson, 1988; Stern et al., 1989). The differences between Choosers and Nonchoosers in the present study are analogous to subjective effect differences noted with drugs such as amphetamine and diazepam which were also tested in the absence of physical dependence (de Wit et al., 1986).

No significant differences were found between Choosers and Nonchoosers on demographic or other drug use characteristics. Further, while Choosers showed slightly greater intake of caffeine before the study compared to Nonchoosers, this was not statistically significant. While the limited sample size in this study may not be sufficient to address this issue definitively, the absence of demographic predictors of drug caffeine reinforcement is generally consistent with several prior studies that have examined the reinforcing and subjective effects of caffeine (Evans et al., 1994; Griffiths and Woodson, 1988). The only relationship shown in those studies was a measure of trait anxiety, which was negatively correlated with caffeine choice and suggested less caffeine choice among participants with higher trait anxiety (Griffiths and Woodson, 1988). Unfortunately, trait anxiety was not assessed in the present study.

A primary aim of the present study was to determine whether individual differences in caffeine choice prospectively predict subjective effects of *d*-amphetamine. In Phase 2, caffeine Choosers (as determined in Phase 1) reported significantly more positive (i.e., pleasant) subjective effects of caffeine and *d*-amphetamine, particularly at the highest doses, in contrast to Nonchoosers who reported more negative (i.e., unpleasant effects). These data show that caffeine choice predicts positive subjective effects of *d*-amphetamine. This is the first demonstration, to our knowledge, that caffeine reinforcement prospectively predicts the positive subjective effects of another drug. An analogous study with different drugs showed that stimulant subjective effects of ethanol and *d*-amphetamine were correlated across participants (Holdstock and de Wit, 2001). The present study extends this line of inquiry by using caffeine to prospectively predict the subjective response to *d*-amphetamine. Future research is warranted examining whether caffeine reinforcement predicts vulnerability to reinforcement and abuse of classic psychomotor stimulants such as amphetamine and cocaine, particularly considering data from studies showing that lifetime caffeine intake and dependence are significantly and positively associated with substance abuse (e.g., alcohol, nicotine, marijuana, cocaine abuse/dependence) (Arria et al., 2010, 2011; Kendler et al., 2006; Svikis et al., 2005). Studies should also further investigate the potential mechanisms underlying this relationship, including the role of a shared dopaminergically-mediated neuropharmacological mechanism (Ferré, 2008; Ferré et al., 1992, 1997; Fredholm et al.,

1999) as well as the role of possible genetic polymorphisms (Yang, Palmer and de Wit, 2010).

While not the primary aim, the present study also provided unique information about whether caffeine can function as a reinforcer in absence of physical dependence. In Phase 1, a meaningful proportion (i.e., 50%) of participants met the criteria for caffeine reinforcement despite the fact that they were maintained on a caffeine-free diet and received a moderate dose of caffeine (200 mg/70 kg) only 1 or 2 times a week. This level of caffeine exposure is likely below that required to produce physical dependence. Further, analysis of saliva samples indicated volunteers complied with the caffeine dietary restrictions, and there was no evidence of caffeine withdrawal symptoms (e.g., fatigue and headache) after ingestion of placebo. These results provide the strongest demonstration to date that caffeine can function as a reinforcer under conditions in which participants are not physically dependent on caffeine (Griffiths et al., 1989; Silverman et al., 1994).

Several limitations and strengths of this study should be noted. First, a single intermediate dose of caffeine was used for determining Chooser status. Although the dose was the same as that used in prior studies on this topic (e.g., Griffiths and Woodson, 1988), it is unknown whether higher or lower doses would produce different results. Second, participants were healthy volunteers without significant medical, psychiatric or substance abuse diagnoses. How these results may generalize to clinical populations of drug abusers is unknown. However, as a large literature suggests a concordance of use and potential pharmacological interactions among stimulants such as caffeine, nicotine and cocaine, it seems unlikely that the relationship observed in the present study would not extend to individuals with problematic drug use (Budney et al., 1993; Higgins et al., 1994; Istvan and Matarazzo, 1984; Jones and Griffiths, 2003; Roll et al., 1996, 1997; Swanson et al., 1994; Tanda and Goldberg, 2000). Third, although the present study used a larger sample size than prior studies examining individual variability in subjective and behavioral response to stimulants, future studies are needed to replicate these findings with still larger sample sizes. Strengths of the study included the rigorous prospective determination of caffeine Chooser vs. Nonchooser status prior to testing *d*-amphetamine and the range of caffeine and *d*-amphetamine doses that were tested in the final study phase.

In conclusion, individuals vary in their subjective and behavioral response to psychomotor stimulants, and these differences may be associated with their likelihood of developing problematic use of these drugs. In the present study, caffeine Choosers and Nonchoosers differed significantly in their subjective responses to *d*-amphetamine, with Choosers reporting more pleasant and fewer unpleasant effects of *d*-amphetamine than Nonchoosers. Results from this study demonstrate that individuals for whom a modest caffeine dose serves as a reinforcer are the same individuals who subsequently report more positive subjective effects of *d*-amphetamine. The use of caffeine choice as a predictor of an individual's subsequent response to *d*-amphetamine may hold significant clinical utility for identifying individuals who are particularly sensitive to the reinforcing effects of psychomotor stimulants and possibly at risk for developing abuse and dependence on psychomotor stimulants.

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References

- Arria AM, Caldeira KM, Kasperski SJ, O'Grady KE, Vincent KB, Griffiths RR, Wish ED. Increased alcohol consumption, nonmedical prescription drug use, and illicit drug use are associated with energy drink consumption among college students. *J Addict Med.* 2010; 4:74–80. [PubMed: 20729975]
- Arria AM, Caldeira KM, Kasperski SJ, Vincent KB, Griffiths RR, O'Grady KE. Energy drink consumption and increased risk for alcohol dependence. *Alcohol Clin Exp Res.* 2011; 35:365–75. [PubMed: 21073486]
- Budney AJ, Higgins ST, Hughes JR, Bickel WK. Nicotine and caffeine use in cocaine-dependent individuals. *J Subst Abuse.* 1993; 5:117–130. [PubMed: 8400835]
- de Wit, H. Individual differences in acute effects of drugs in humans: their relevance to risk for abuse. In: Wetherington, CL.; Falk, JL., editors. *Laboratory Behavioral Studies of Vulnerability to Abuse.* NIDA Research Monograph No. 169. National Institute on Drug Abuse; Rockville, MD: 1998. p. 176-187.
- de Wit H, Uhlenhuth EH, Johanson CE. Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. *Drug Alcohol Depend.* 1986; 16:341–360. [PubMed: 3698813]
- Evans SM, Critchfield TS, Griffiths RR. Caffeine reinforcement demonstrated in a majority of moderate caffeine users. *Behav Pharmacol.* 1994; 5:231–238. [PubMed: 11224272]
- Evans SM, Griffiths RR. Caffeine tolerance and choice in humans. *Psychopharmacol.* 1992; 108:51–59.
- Ferré S. An update on the mechanisms of the psychostimulant effects of caffeine. *J Neurochem.* 2008; 105:1067–1079. [PubMed: 18088379]
- Foltin RW, Fischman MW. Methods for the assessment of abuse liability of psychomotor stimulants and anorectic agents in humans. *Br J Addict.* 1991; 86:1633–40. [PubMed: 1686198]
- Fredholm BB, Chen JF, Cunha RA, Svenningsson P, Vaugeois JM. Adenosine and brain function. *Int Rev Neurobiol.* 2005; 63:191–270. [PubMed: 15797469]
- Gabbay FH. Variations in affect following amphetamine and placebo: markers of stimulant drug preference. *Exp Clin Psychopharmacol.* 2003; 11:91–101. [PubMed: 12622347]
- Griffiths RR, Bigelow GE, Liebson IA. Reinforcing effects of caffeine in coffee and capsules. *J Exp Anal Behav.* 1989; 52:127–140. [PubMed: 2794839]
- Griffiths, RR.; Juliano, LM.; Chausmer, AL. Caffeine pharmacology and clinical effects. In: Graham, AW.; Schultz, TK.; Mayo-Smith, M.; Ries, RK.; Wilford, BB., editors. *Principles of Addiction Medicine.* 3. American Society of Addiction Medicine; Chevy Chase, MD: 2003. p. 193-224.
- Griffiths RR, Woodson PP. Reinforcing effects of caffeine in humans. *J Pharmacol Exp Ther.* 1988; 246:21–29. [PubMed: 3392652]
- Higgins ST, Budney AJ, Hughes JR, Bickel WK, Lynn M, Mortensen A. Influence of cocaine use on cigarette smoking. *JAMA.* 1994; 272:1724. [PubMed: 7966914]
- Holdstock L, de Wit H. Individual differences in responses to ethanol and *d*-amphetamine: a within-subject study. *Alcohol Clin Exp Res.* 2001; 25:540–548. [PubMed: 11329494]
- Hughes JR, Higgins ST, Bickel WK, Hunt WK, Fenwick JW, Gulliver SB, Mireault GC. Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. *Arch Gen Psychiatr.* 1991; 48:611–617. [PubMed: 2069491]
- Hughes JR, Hunt WK, Higgins ST, Bickel WK, Fenwick JW, Pepper SL. Effect of dose on the ability of caffeine to serve as a reinforcer in humans. *Behav Pharmacol.* 1992; 3:211–218. [PubMed: 11224118]

- Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ. Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. *Drug Alcohol Depend.* 1993; 32:239–246. [PubMed: 8348875]
- Istvan J, Matarazzo JD. Tobacco, alcohol, and caffeine use: a review of their interrelationships. *Psychol Bull.* 1984; 95:301–326. [PubMed: 6544436]
- Jones HE, Griffiths RR. Oral caffeine maintenance potentiates the reinforcing and stimulant subjective effects of intravenous nicotine in cigarette smokers. *Psychopharmacol.* 2003; 165:280–290.
- Kendler KS, Myers J, Gardner OC. Caffeine intake, toxicity and dependence and lifetime risk for psychiatric and substance use disorders: an epidemiologic and co-twin control analysis. *Psychol Med.* 2006; 36:1717–1725. [PubMed: 16893482]
- Roll JM, Higgins ST, Budney AJ, Bickel WK, Badger GJ. A comparison of cocaine-dependent cigarette smokers on demographics, drug use and other characteristics. *Drug Alcohol Depend.* 1996; 40:195–201. [PubMed: 8861397]
- Roll JM, Higgins ST, Tidey JW. Cocaine use can increase cigarette smoking: evidence from laboratory and naturalistic settings. *Exp Clin Psychopharmacol.* 1997; 5:263–268. [PubMed: 9260074]
- Rush CR, Essman WD, Simpson CA, Baker RW. Reinforcing and subject-rated effects of methylphenidate and *d*-amphetamine in non-drug-abusing humans. *J Clin Psychopharmacol.* 2001; 21:273–286. [PubMed: 11386490]
- Sigmon SC, Tidey JW, Badger GJ, Higgins ST. Acute effects of *d*-amphetamine on progressive-ratio performance maintained by cigarette smoking and money. *Psychopharmacol.* 2003; 167:393–402.
- Silverman K, Mumford GK, Griffiths RR. Enhancing caffeine reinforcement by behavioral requirements following drug ingestion. *Psychopharmacol.* 1994; 114:424–432.
- Singha AK, McCance-Katz EF, Heck SA, Kosten TR, Oliveto A. Individual differences in humans responding under a cocaine discrimination procedure: discriminators versus nondiscriminators. *Exp Clin Psychopharmacol.* 1999; 7:391–398. [PubMed: 10609974]
- Sofuoglu M, Brown S, Dudish-Poulsen S, Hatsukami DK. Individual differences in the subjective response to smoked cocaine in humans. *Am J Drug Alcohol Abuse.* 2000; 26:591–602. [PubMed: 11097194]
- Stern KN, Chait LD, Johanson CE. Reinforcing and subjective effects of caffeine in normal human volunteers. *Psychopharmacol.* 1989; 98:81–88.
- Svikis DS, Berger N, Haug NA, Griffiths RR. Caffeine dependence in combination with a family history of alcoholism as a predictor of continued use of caffeine during pregnancy. *Am J Psychiatry.* 2005; 162:2344–2351. [PubMed: 16330600]
- Swanson JA, Lee JW, Hopp JW. Caffeine and nicotine: a review of their joint use and possible interactive effects in tobacco withdrawal. *Addict Behav.* 1994; 19:229–256. [PubMed: 7942243]
- Tanda G, Goldberg SR. Alteration of the behavioral effects of nicotine by chronic caffeine exposure. *Pharmacol Biochem Behav.* 2000; 66:47–64. [PubMed: 10837843]
- Uhlenhuth EH, Johanson CE, Kilgore K, Kobasa SC. Drug preference and mood in humans: preference for *d*-amphetamine and subject characteristics. *Psychopharmacol.* 1981; 74:191–194.
- Wolfinger, R.; Chang, M. SUGI Proceedings. 1995. Comparing the SAS GLM and MIXED Procedures for Repeated Measurements Analysis.
- Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. *Psychopharmacol.* 2010; 211:245–257.

Figure 1.

Positive (i.e., pleasant) subjective effects of 200 mg/70 kg caffeine as measured by self-report ratings on the Drug Effect Questionnaire in Choosers ($n=11$, filled circles) and Nonchoosers ($n=8$, open circles) during Phase 1 of the study. The four panels show representative measures (i.e., Liking, Happy, Well-Being, Urge To Do Task/Work-Related Activities) that differed between Choosers and Nonchoosers. Data points show means at each time point; brackets indicate ± 1 SEM. Each item is rated on a 5-point scale (0 to 4) except for Liking, which uses a 9-point scale (-4 to +4). Y-axes show mean ratings expressed as change scores from the pre-capsule timepoint. X-axes show each timepoint (i.e., 1, 2, 4 and 8 hours) following capsule ingestion at which the above measures were assessed. Asterisks indicate a significant difference between Choosers and Nonchoosers at that timepoint ($p \leq .05$, Tukey's HSD tests).

Figure 2. Negative (i.e., unpleasant) subjective effects of 200 mg/70 kg caffeine as measured by self-report ratings on the Drug Effect Questionnaire in Choosers ($n=11$, filled circles) and Nonchoosers ($n=8$, open circles) during Phase 1 of the study. The three panels show representative measures (i.e., Foggy/Not Clear-headed, Heart Pounding, Bad Effects) that differed between Choosers and Nonchoosers. Other details as in Figure 1.

Figure 3.

Peak subjective response after placebo, caffeine (100, 200 or 400 mg/70 kg) and *d*-amphetamine (5, 10 or 20 mg/70 kg) as measured by self-report ratings on the Drug Effect Questionnaire for the total sample (N=22) during Phase 2 of the study. Panels show data for four representative measures (i.e., Drug Effects, Good Effects, Arousing Effects, Bad Effects). Data points show mean peak change from pre-capsule timepoint; brackets indicate 1 SEM. Y-axes show change scores from the pre-capsule timepoint on the subjective measure. X-axes show each drug condition. Filled symbols indicate a significant difference between the drug dose and placebo ($p \leq .05$, planned comparisons).

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● Choosers
 □ Nonchoosers

Figure 4.

Peak subjective response after placebo, caffeine (100, 200 or 400 mg/70 kg), and *d*-amphetamine (5, 10 or 20 mg/70 kg) as measured by self-report ratings on the Drug Effect Questionnaire in Choosers ($n=11$, circles) and Nonchoosers ($n=8$, squares) during Phase 2 of the study. Panels show data for eight representative measures (i.e., Liking, Alert/Attentive, Well-Being, Satisfied, Good Effects, Refreshed, Heart Pounding, Jittery/Shaky) that significantly differed between Choosers and Nonchoosers. Data points show mean peak change from pre-capsule timepoint; brackets indicate 1 SEM. Y-axes show peak change scores from the pre-capsule timepoint on the subjective measure. X-axes show each drug

condition. Asterisks indicate a significant difference between Choosers and Nonchoosers at that dose condition ($p \leq .05$, planned comparisons).