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Relationship Between Drug Discrimination and Ratings of Subjective Effects: Implications for Assessing and Understanding the Abuse Potential of *d*-Amphetamine in Humans

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Abstract

The discriminative and subjective effects of drugs in humans are related, but the full extent of this relationship remains to be determined. To further explore this relationship, a retrospective analysis was conducted on data from six studies completed in our laboratory that used identical procedures. The relationship between the discriminative and subjective effects of a range of doses of *d*-amphetamine (i.e., 2.5–15 mg) was examined using correlational analyses. Significant correlations with discrimination performance were observed on 15 of 20 items from the Drug-Effect Questionnaire across a range of qualities (e.g., Pay For [a positive effect indicative of abuse potential] and Active [a stimulant-like effect]), but the magnitude of these relationships was modest ($r < 0.52$). The current findings demonstrate that diverse subjective effects contribute to the discriminative effects of *d*-amphetamine and indicate that the former are a more practical means to assess abuse potential of drugs. Although these procedures are fundamentally related in that they rely on the presence of an interoceptive drug state, they differ in the dimension(s) of the interoceptive effects that participants must quantify. The simultaneous use of drug discrimination and subjective effects may, therefore, reveal complimentary aspects of drug effects that underlie their potential for abuse.

Keywords

Abuse potential; *d*-amphetamine; drug discrimination; subjective effects

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Introduction

Drugs of abuse produce interoceptive stimulus effects that contribute to their abuse potential. The interoceptive stimulus effects of drugs in humans are typically assessed using subjective-effects questionnaires. These questionnaires require participants to quantify their subjective experiences, moods, and feelings on a standardized set of items following drug administration. These instruments are commonly used to compare the subjective responses to a drug of interest with those produced by a reference compound with known abuse potential and/or similar pharmacological properties (e.g., stimulants; Fischman and Foltin, 1991). The drug of interest is inferred to have abuse potential when it engenders a constellation of subjective effects that is similar to the reference compound. By contrast, the drug of interest is inferred to have limited abuse potential when it fails to engender a pattern of subjective effects similar to the reference compound. However, subjective-effects measures may be used to assess the abuse potential of the drug of interest without the inclusion of a reference compound (e.g., ratings of Like Drug; Fischman and Foltin, 1991). In one study, for example, methamphetamine (a widely abused stimulant), methylphenidate (a prescription stimulant used to treat attention-deficit hyperactivity disorder [ADHD]), and *d*-amphetamine (a prescription stimulant used to treat ADHD, narcolepsy, and obesity) produced similar subjective-effects profiles in humans (e.g., increased ratings of Drug Liking; Martin et al., 1971). Consistent with these findings, results from the National Survey on Drug Use and Health indicated that the prevalence rates of methamphetamine and prescription stimulant abuse (e.g., methylphenidate and *d*-amphetamine) in the past month were comparable (0.2% and 0.4% respectively; SAMSHA, 2012). In other studies, atomoxetine, a norepinephrine reuptake inhibitor (also used to treat ADHD), was devoid of subjective effects that are thought to suggest increased abuse potential (e.g., Drug Liking; Heil et al., 2002; Jasinski et al., 2008). Consistent with these findings, a recent review of neurochemical, preclinical, clinical, and post-marketing studies suggest that the prevalence of the abuse of atomoxetine is minimal (Upadhyaya et al., 2013). Collectively, the laboratory findings along with epidemiological data suggest that subjective-effects measures have predictive validity for determining the abuse potential of psychomotor stimulants in the natural ecology. Actual prevalence rates of abuse, however, may be influenced by a host of factors (e.g. drug availability; social factors [peer pressure]; economic circumstances [cost]) that are independent of the interoceptive stimulus effects of drugs.

An alternative procedure that may be used to assess the interoceptive effects of drugs in humans is drug discrimination. Drug discrimination procedures were initially developed to examine the interoceptive effects of drugs with preclinical models in animals (e.g., monkeys and rats), but have been adapted for use with humans (Preston, 1991). In a typical human drug discrimination procedure, participants learn to discriminate when they have received a drug (e.g., *d*-amphetamine) or placebo. After learning the discrimination (i.e., stimulus control of behavior has been established), a range of doses of the training drug and a novel compound are tested to see if the novel compound produces interoceptive effects that are similar to those of the training drug (Rush et al., 2011). The novel compound is often hypothesized to be from the same pharmacological class as the training drug (e.g., stimulants). If the novel compound occasions a pattern of responding similar to that of the

training drug, it may be inferred that it has enhanced abuse potential. A negative control (e.g., pentobarbital, a sedative-hypnotic) is often included to demonstrate the pharmacological specificity of the discrimination (i.e., participants are not responding to any interoceptive change). Importantly, the failure of the negative control or novel compound to occasion drug-appropriate responding does not preclude its potential for abuse.

Given that both procedures may be used to determine the relative abuse potential of drugs, considerable efforts have been devoted to investigating the relationship between discriminative and subjective effects. Traditionally, the relationship between these behavioral measures has been established by testing drugs from various pharmacological classes using within-subjects designs. Drugs that share discriminative-stimulus effects generally have similar subjective-effects profiles. By contrast, drugs that do not share discriminative-stimulus effects generally produce a different constellation of subjective effects. A high degree of concordance (i.e., corresponding dose-related increases on both outcome measures) has been observed between the discriminative and subjective effects of drugs that have diverse pharmacological mechanisms including stimulants, opioids, and sedatives (e.g., Rush et al., 2011; Preston et al., 1989; Oliveto et al., 1994). However, this relationship is not isomorphic. For example, there are instances in which drugs produce similar discriminative effects but dissimilar subjective effects (e.g., Chait et al., 1986). There are also instances in which drugs produce similar subjective effects but dissimilar discriminative effects (e.g., Rush et al., 1998).

The purpose of the present analysis was to further explore the relationship between the discriminative and subjective effects of *d*-amphetamine in humans. To accomplish this aim, we combined data from six studies that were conducted in the same laboratory that used identical procedures and measures to assess the discriminative and subjective effects of *d*-amphetamine. Each study was designed as a drug combination study in which the *d*-amphetamine doses were administered alone or following pretreatment with another drug. In the individual studies, the sample size was 6–8 participants per experiment. Although these studies were initially conducted for alternative purposes (i.e., to investigate underlying neuropharmacology), we chose to combine data from these studies in order to have a sample size large enough to support correlational analyses to determine the relationship between these two behavioral assays. To the best of our knowledge, this analytical strategy has not been used previously to determine the relationship between the discriminative and subjective effects of *d*-amphetamine in humans.

Methods

Data from six previous studies that were conducted in our laboratory were included in the current retrospective analysis (Lile et al., 2005a, 2005b; Rush et al., 2003, 2004; Stoops et al., 2006, Stoops et al., unpublished data). Each experiment was designed as a drug combination study in which *d*-amphetamine doses were administered alone or after pretreatment with an acute dose of a drug with antipsychotic activity (i.e., aripiprazole and risperidone; Lile et al., 2005a; Rush et al., 2003; Stoops et al., 2006; Stoops et al., unpublished data) or benzodiazepine (Lile et al., 2005b; Rush et al., 2004). Only data from sessions where *d*-amphetamine was administered alone were included in the present

analysis. All studies employed identical experimental procedures and were conducted in the same laboratory. The Institutional Review Board at the University of Kentucky approved all protocols and informed consent documents.

Participants

A total of 27 participants were enrolled in the six previous studies and were eligible for inclusion in the current report. If a participant was enrolled in more than one of the studies, only the data from the first study in which they participated were used. Participants provided their sober written informed consent and completed questionnaires that assessed drug use, medical, and psychiatric histories prior to participating. Participants were without contraindications to *d*-amphetamine.

General Procedures

Participants were enrolled as outpatients at the Laboratory of Human Behavioral Pharmacology at the University of Kentucky for up to 37 experimental sessions. On experimental session days subjective-effects and cardiovascular (i.e., heart rate and blood pressure) measures were assessed approximately 30 min before and 1, 2, 3, 4 and 5 h after drug administration. Cardiovascular measures were recorded for safety purposes and are not presented in the current report. The other procedural details are described at length in a previous report (Vansickel et al., 2007). Each drug discrimination experiment consisted of three phases, which were completed in fixed order: 1) sampling, 2) test-of-acquisition, and 3) test. This procedure has been described in detail previously (Rush et al., 2003).

Point-Distribution Task

A point-distribution drug discrimination task was completed 1, 2, 3, 4, and 5 h after oral drug administration on an Apple Macintosh computer (Apple Computer, Inc., Cupertino, CA). In this procedure, participants distributed 100 points between two options (i.e., DRUG A or NOT DRUG A). During sampling and acquisition sessions, points accumulated on the correct option were exchangeable for money at a rate of \$0.08/point. During test sessions, participants were credited with the greater number of points allocated to the DRUG A or NOT DRUG A option and were exchangeable at the same rate described above. Thus, participants were able to earn a maximum of \$40/session on this task. The dependent measure in this task was the percentage of *d*-amphetamine-appropriate responding.

Subjective-Effects Measures

Subjective-effects questionnaires included an Adjective Rating Scale (Oliveto et al., 1992), a Stimulant Sensitive Adjectives Scale (Di Marino et al., 1998), a short form of the Addiction Research Center Inventory (ARCI; Jasinski, 1977; Martin et al., 1971) and a locally developed Drug-Effect Questionnaire (Rush et al., 2003) with 20 items identical across all studies included in the present report. These behavioral measures are widely used in human laboratory studies and the procedural details were described in detail previously (Rush et al., 2003).

Drug Administration

All drug conditions were administered in a double-blind fashion. Participants learned to discriminate DRUG A (i.e., 15 mg oral *d*-amphetamine) from NOT DRUG A in all studies included in the current report. *d*-Amphetamine doses were administered in three capsules that were prepared by over-encapsulating commercially available generic drug in size 0 capsules. Each *d*-amphetamine capsule contained either 2.5 or 5 mg. Cornstarch or lactose was used to fill the remainder of all the capsules. Placebo capsules contained only cornstarch or lactose. Administering the appropriate number of active and placebo capsules varied the dose of *d*-amphetamine. Capsules were taken orally with water.

Data Analysis

Statistical significance refers to $p = 0.05$ for all analyses. Group data from the point-distribution task were analyzed as raw scores (Stat View 5.0.1, SAS Institute Inc., Cary, NC). Drug discrimination data were analyzed statistically as the total percentage of points allocated to the drug option across a five-hour session (i.e., percentage of *d*-amphetamine-appropriate responding). The percentage of *d*-amphetamine-appropriate responding was analyzed with a one-way repeated measures analysis of variance (ANOVA) with Dose (placebo, 2.5, 5, 10, and 15 mg *d*-amphetamine) as the within-subjects factor. For the Adjective Rating Scale, Stimulant Sensitive Adjectives Scale, each ARCI scale, and Drug-Effect Questionnaire items, area-under-the-time-action curve (AUC) was calculated as a composite score for each participant across the entire five-hour experimental session using the trapezoidal method and then analyzed in the same fashion as percentage of *d*-amphetamine-appropriate responding. Interpretation of the results was guided by *F*-values. For analysis and graphical representation, data were divided by the coefficient used for AUC calculation in order to return to the same scale that was used for the subjective-effects questionnaire. The relationship between drug discrimination performance under active doses of *d*-amphetamine with the Adjective Rating Scale, Stimulant Sensitive Adjectives Scale, each of the ARCI scales, and Drug-Effect Questionnaire items was analyzed using separate Pearson correlations (GraphPad Prism version 6.0 for Mac OS X, GraphPad Software, San Diego California USA, www.graphpad.com).

Results

Analysis of Variance (ANOVA)

Point-distribution task—*d*-Amphetamine significantly increased drug-appropriate responding above placebo levels ($F_{4,104} = 26.2, p < 0.001$). Figure 1 shows that *d*-amphetamine increased drug-appropriate responding on the point-distribution task as a function of dose.

Subjective-effects measures—*d*-Amphetamine dose-dependently increased subjective ratings on 17 items from the Drug-Effect Questionnaire: Active, Alert, Energetic; Any Effect; Bad Effects; Euphoric; Good Effects; High; Irregular-Racing Heartbeat; Like Drug; Nervous; Performance Improved; Restless; Rush; Shaky-Jittery; Stimulated; Talkative, Friendly; Willing to Pay For; and Willing To Take Again ($F_{4,104}$ values $> 2.5, p$ values < 0.05). Figure 1 shows that *d*-amphetamine increased subjective ratings in a dose-dependent

manner on Any Effect; Good Effects; High; Like Drug; Willing to Pay For; and Willing to Take Again. The magnitude and direction of subjective ratings for Active, Alert, Energetic; Bad Effects; Euphoric; Irregular-Racing Heartbeat; Nervous; Performance Improved; Restless; Rush; Shaky-Jittery; Stimulated; and Talkative, Friendly were similar to those shown in Figure 1 (data not shown).

d-Amphetamine also increased subjective ratings on the Stimulant Scale of the Adjective Rating Scale ($F_{4,104} = 18.3, p < 0.001$), the Stimulant Sensitive Adjectives Scale ($F_{4,104} = 24.4, p < 0.001$) and the A, BG, LSD and MBG scales of the ARCI ($F_{4,104}$ values $> 5.9, p$ values > 0.05) in a dose-dependent manner (data not shown).

Pearson Correlations

Significant correlations were observed between drug-appropriate responding for active doses of *d*-amphetamine and subjective ratings on 15 items from the Drug-Effect Questionnaire: Active, Alert, Energetic ($r = 0.51$); Any Effect ($r = 0.50$); Good Effects ($r = 0.37$); High ($r = 0.24$); Irregular-Racing Heartbeat ($r = 0.33$); Like Drug ($r = 0.37$); Performance Improved ($r = 0.28$); Nervous ($r = 0.33$); Restless ($r = 0.37$); Rush ($r = 0.38$); Shaky-Jittery ($r = 0.26$); Stimulated ($r = 0.45$); Talkative, Friendly ($r = 0.41$); Willing to Pay For ($r = 0.29$); and Willing To Take Again ($r = 0.35$). No significant correlations were observed between drug-appropriate responding for active doses of *d*-amphetamine and subjective ratings of Bad Effects ($r = 0.08$); Euphoric ($r = 0.13$); Nausea ($r = 0.11$); Performance Impaired ($r = -0.02$); and Sluggish, Fatigued, Lazy ($r = -0.02$). Figure 2 shows the positive correlations between drug-appropriate responding for active doses of *d*-amphetamine and subjective ratings of Any Effect; Good Effects; High; Like Drug; Willing to Pay For; and Willing to Take Again. Figure 3 shows the positive correlations between drug-appropriate responding for active doses of *d*-amphetamine and subjective ratings of Rush; Restless; Shaky-Jittery; and Talkative, Friendly. The magnitude and direction of correlations for subjective-effects items Active, Alert, Energetic; Irregular Heart-Beat; Performance Improved; Nervous; and Stimulated were similar to those shown in Figures 2 and 3.

Significant correlations were also observed between drug-appropriate responding for active doses of *d*-amphetamine and subjective ratings on the Stimulant Scale of the Adjective Rating Scale ($r = 0.20$), the Stimulant Sensitive Adjectives Scale ($r = 0.36$) and the LSD scale of the ARCI ($r = 0.29$; data not shown) but not the A ($r = -0.02$), BG ($r = -0.005$), MBG ($r = -0.11$), or PCAG ($r = -0.05$) scales. The magnitude and direction of these correlations were similar to those shown in Figures 2 and 3.

Discussion

The present retrospective analysis examined the relationship between the discriminative-stimulus and subjective effects of a range of doses of *d*-amphetamine. *d*-Amphetamine dose-dependently increased drug-appropriate responding and produced prototypical stimulant-like subjective effects. While statistically significant, the correlations between the discriminative and subjective effects of *d*-amphetamine were modest in magnitude. Below we discuss these findings as they relate to the combined use of drug discrimination and subjective-effects questionnaires to assess and further understand the abuse potential of drugs in humans.

Dose-Related Effects of *d*-Amphetamine

d-Amphetamine dose-dependently increased drug-appropriate responding. Across the range of doses included in the present analysis, levels of responding ranged from intermediate for the lower doses of *d*-amphetamine (i.e., 2.5–5 mg) to near maximal for the higher doses (i.e., 10–15 mg) that were tested. These findings are similar to the dose-related effects of *d*-amphetamine obtained in preclinical studies where monkeys and rats were trained to discriminate *d*-amphetamine through various routes of administration under different laboratory conditions (e.g., De La Garza and Johanson, 1987; Huang and Ho, 1974). For example, in rhesus monkeys trained to discriminate intragastric administration of *d*-amphetamine (0.56 or 1.0 mg/kg) using a signaled shock-avoidance procedure (De La Garza and Johanson, 1987), *d*-amphetamine increased drug-appropriate responding in a dose-dependent manner. More specifically, the lowest dose of *d*-amphetamine tested (0.03 mg/kg) did not engender drug-appropriate responding, intermediate doses (0.1–0.3 mg/kg) produced moderate levels of drug-appropriate responding (i.e., 50%), and high doses (0.56–1.0 mg/kg) produced near maximal responding. Similar dose-related effects were observed in the present experiment, although none of the doses tested produced minimal drug-appropriate responding. The inclusion of a lower *d*-amphetamine dose (e.g., 1.25 mg) in the present analysis would have likely produced minimal drug-appropriate responding. Overall, the dose-effect curve in the present analysis was graded and similar to those observed in preclinical experiments.

d-Amphetamine produced a constellation of stimulant-like subjective effects (e.g., increased ratings of Good Effects and Like Drug). These results are concordant with many previous human laboratory studies (e.g., Brauer and de Wit, 1996; Chait and Johanson, 1988; de Wit et al., 1997). In general, the magnitude of effects for the subjective-effects ratings was lower compared to the drug discrimination data and maximal responding was not observed for the subjective effects. The reasons for these effects are unknown, but could reflect a response bias in that participants may be reluctant to self-report maximal drug effects or measurement considerations (e.g., time course captured by AUC). Although not possible in the studies used in this analysis, the inclusion of a higher *d*-amphetamine dose (e.g., 40 mg) might have produced further increases in ratings of subjective drug effects.

The current findings using correlational analyses, along with the previous findings, suggest that the discriminative and subjective effects of *d*-amphetamine are related. More specifically, the degree to which drug discrimination and subjective effects are correlated may reflect parallel increases in drug-appropriate responding and ratings of subjective drug effects at corresponding drug doses. On the basis of the degree of correspondence between responses in drug discrimination and ratings of subjective effects, it seems reasonable to suggest that subjective effects contributed to the accurate discrimination of *d*-amphetamine in the present analysis. Given this, it seems that subjective-effects measures may be the most practical method for the assessment of abuse potential in humans (Rush et al., 2011). This is especially important considering that human drug discrimination studies involve a significant additional time investment on the part of both the investigator and participants. A drug discrimination experiment could involve as many 25–27 sessions to establish a dose-response curve for both the training and novel drug if 3–4 active doses of each compound

were tested. In contrast, the necessary information may be gleaned from a study involving as few as 7–9 sessions if the primary outcome measures were restricted to subjective-effects questionnaires.

Drug discrimination behavior may be influenced by a number of procedural factors. For example, previous preclinical and human laboratory studies have shown that training dose influences discrimination behavior (see Rush et al., 2011 for a review). In participants trained to discriminate 10 mg *d*-amphetamine or 20 mg *d*-amphetamine from placebo (Kollins and Rush 1999), participants in the 10 mg group were more sensitive to the discriminative-stimulus effects of *d*-amphetamine when tested across a range of doses (1.25–20 mg). This enhanced sensitivity was apparent as a statistically significant leftward shift in the dose-response function. However, training dose influenced the subjective-effects ratings of *d*-amphetamine to a lesser extent. *d*-Amphetamine dose-dependently increased responses on eight items on a Drug-Effect Questionnaire (i.e., Anxious/Nervous; Bad Effects; Feel the Drug; Good Effects; Improved Performance; Like Drug; Stimulated; and Feel Like Talking or Socializing). The *d*-amphetamine dose-response function was shifted leftward in the low-dose versus the high-dose group on only four of these items (i.e., Improved Performance; Like Drug; Stimulated; and Feel Like Talking or Socializing). *d*-Amphetamine also dose-dependently increased scores on the A, BG, and MBG scales of the ARCI, and neither the main effect of training dose nor the interaction of training dose and *d*-amphetamine dose were statistically significant. In a similar study, mazindol was tested to determine whether it shares discriminative-stimulus and subjective effects with *d*-amphetamine (Chait et al., 1986). The high dose of mazindol produced *d*-amphetamine-appropriate responding but did not produce subjective effects typically thought to reflect increased abuse potential (e.g., Elation and Positive Mood) consistent with epidemiological findings that suggest mazindol is not misused/abused like *d*-amphetamine. The authors indicated that measurement considerations such as a forced dichotomization between two response alternatives (e.g., DRUG A versus NOT DRUG A) could have influenced responding in the discrimination resulting in a false positive.

The findings of the current retrospective analysis provide information regarding the experimental efficiency of procedures that may be used to assess the abuse potential of drugs. Although drug discrimination and subjective-effects questionnaires rely on interoceptive changes produced by a drug, responding on these measures is likely to reflect distinct, albeit complimentary, dimensions of behavior that underlie their abuse potential. More specifically, drug discrimination procedures are geared toward the detection and identification of a specific set of interoceptive drug effects and are under an operant contingency. Subjective-effects measures, by contrast, provide information regarding the quality or nature of the drug's effects (e.g., Good Effects or Bad Effects) using standardized instruments and rely on common verbal conditioning histories. Therefore, one key consideration in determining the most appropriate and/or practical method to evaluate abuse potential is the inferences that may be made using these different investigational strategies. For example, if the primary aim of a study is to investigate whether a drug is likely to be abused, ratings of subjective effects are likely to be sufficient. However, the simultaneous

assessment of the discriminative and subjective effects of drugs is practical and yields data that justifies the conduct of a more intensive study in some circumstances.

Simultaneous Use of Drug Discrimination and Subjective Effect Questionnaires

Importantly, drug discrimination and subjective effects questionnaires have value and utility in the determination of abuse potential and they should not be viewed as mutually exclusive. Although not presented in this report, a composite score that was calculated from individual measures that significantly correlated with drug discrimination in the current analysis did not predict discrimination responding to a greater degree than individual items alone (e.g., Active, Alert, Energetic [$r = 0.52$] and Stimulated [$r = 0.45$]). Furthermore, negative subject-rated effects (e.g., Bad Effects and Nausea) did not contribute to the discriminative effects of *d*-amphetamine. Thus, it is likely that these specific stimulant-like effects, in addition to measures of drug strength and positive effects, contributed to the accurate discrimination of the *d*-amphetamine discriminative stimulus.

Although the use of subjective-effects questionnaires may be the most practical method for the assessment of the abuse potential of drugs, the combined use of drug discrimination and subjective effects may be appropriate when attempting to elucidate the neuropharmacological mechanisms that contribute to the abuse potential of stimulants and other drugs. Preclinical behavioral pharmacology studies have implicated central monoamine systems, namely dopamine, in the discriminative effects of amphetamines (e.g., Tidey and Bergman, 1998). However, human laboratory studies have not convincingly demonstrated the involvement of central monoamine systems in the subjective effects of amphetamines in humans (for a review, see Brauer et al., 1997). For example, the subjective effects of methamphetamine (placebo or 20 mg) were assessed following pretreatment with risperidone (placebo or 0.75 mg), a non-selective dopamine/serotonin receptor antagonist, and haloperidol (placebo or 3 mg), a dopamine D₂ receptor antagonist (Wachtel et al., 2002). Methamphetamine produced prototypical stimulant-like subject-rated effects and pretreatment with risperidone or haloperidol failed to significantly alter subject ratings.

Human drug discrimination procedures have been used less frequently to elucidate the neuropharmacological mechanisms that mediate the abuse potential of amphetamines but the extant literature suggests that the concomitant use of drug discrimination procedures and subjective-effects questionnaires produce results that are consistent with the notion that central monoamine systems mediate the behavioral effects of *d*-amphetamine in humans. In a previous drug discrimination experiment from our laboratory that was included in the present analysis, participants learned to discriminate 15 mg oral *d*-amphetamine from placebo (Rush et al. 2003). The behavioral effects of a range of doses of *d*-amphetamine (placebo, 2.5, 5, 10, and 15 mg) were assessed alone and following pretreatment with risperidone (placebo or 1 mg). *d*-Amphetamine functioned as a discriminative stimulus and produced prototypical stimulant-like subjective effects. Risperidone attenuated the discriminative-stimulus effects of *d*-amphetamine as well as many of the subjective effects (e.g., Like Drug, Good Effects and Willing to Take Again). Similar to the results of preclinical investigations, these findings suggest dopaminergic and serotonergic involvement in the discriminative and subjective effects of *d*-amphetamine in humans.

In addition, neuroanatomical and neurochemical data suggest that central dopamine systems are under the inhibitory control of γ -aminobutyric-acid (GABA) systems (Churchill et al., 1992; Dewey et al., 1997; Finlay et al., 1992; Invernizzi et al., 1991; Kalivas et al., 1990; Kita and Kitai, 1988; Morgan and Dewey, 1998; Zetterstrom and Fillenz, 1990). In one human laboratory study, the subjective effects of *d*-amphetamine (placebo and 20 mg/70 kg) were assessed alone and following pretreatment with triazolam (0.25 mg), a high-efficacy-positive GABA_A receptor modulator (Mintzer and Griffiths, 2003). *d*-Amphetamine alone produced a constellation of stimulant-like subjective effects (e.g., increased ratings of Good Effects) whereas triazolam alone produced sedative-like self-reported drug effects (e.g., increased ratings of sleepiness). In combination, triazolam generally did not attenuate the subjective effects of *d*-amphetamine and in several instances augmented them. In a previous drug discrimination experiment conducted in our laboratory (some data included in the present analysis), six healthy volunteers learned to discriminate 15 mg oral *d*-amphetamine from placebo (Rush et al. 2004). In this study, the effects of *d*-amphetamine (placebo, 2.5, 5, 10, and 15 mg) were tested alone and following pretreatment with alprazolam (placebo and 0.5 mg), another high-efficacy GABA_A receptor modulator. *d*-Amphetamine functioned as a discriminative stimulus and produced stimulant-like subjective effects (e.g., increased ratings of Good Effects) that generally increased as a function of dose. Alprazolam did not occasion *d*-amphetamine-appropriate responding, nor did it increase ratings of sedation or impair performance. Alprazolam in combination with *d*-amphetamine significantly attenuated the discriminative effects of *d*-amphetamine, as well as some of the subjective effects (e.g., Good Effects). Taken together, these findings suggest that the activity of GABA systems may modulate the discriminative and subjective effects that are produced by *d*-amphetamine.

The results of these studies collectively suggest that the concomitant use of human drug discrimination procedures and subjective-effects questionnaires may yield results that are more informative with regard to the pharmacology of amphetamines. Accurately elucidating the neuropharmacological mechanisms that mediate the abuse potential of amphetamines in humans may carry implications for the development of putative pharmacotherapies for stimulant dependence.

Future Directions

The results of the present analysis further support the notion that the discriminative and subjective effects of drugs are, to some degree, related. However, additional research is needed to fully examine this relationship. Although the sample size in the present analysis was comparatively much larger than in a typical human drug discrimination study, it was too small to support the use of more sophisticated statistical techniques. Given a larger sample size, hierarchical linear regression analyses could be used to identify the subjective-effect item(s) that best predicts drug discrimination performance. In addition, future studies should investigate the relationship between the discriminative and subjective effects of *d*-amphetamine across a greater range of doses and other routes of administration as the magnitude of this relationship may vary based on manipulation of these parameters. Furthermore, future studies should also seek to fully determine the relationship between the discriminative and subjective effects with drugs from other pharmacological classes (e.g.,

opioids and sedatives). A more rigorous and complete characterization of the relationship between drug discrimination performance and subjective-effects measures will provide investigators with the best information to determine the most appropriate experimental procedure to evaluate the relative abuse potential of novel drugs.

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Figure 1.

Dose-response function for *d*-amphetamine for drug discrimination performance expressed as the percent drug-appropriate responding and subjective ratings on Any Effect; Good Effects; High; Like Drug; Willing to Pay For; and Willing to Take Again on the Drug-Effect Questionnaire expressed as AUC. For analysis and graphical representation, data were divided by the coefficient used for AUC calculation so as to return to the same scale that was used for the subjective-effects questionnaire. X-axes: *d*-Amphetamine Dose (placebo, 2.5, 5, 10, 15 mg). Data points above PL indicate placebo values. Data points represent the mean for 27 participants. Brackets represent one standard error of the mean.

Figure 2.

Correlations between percent drug-appropriate responding and subjective ratings on Any Effect; Good Effects; Willing To Pay For; Like Drug; High; and Willing to Take Again on the Drug-Effect Questionnaire for all active doses of *d*-amphetamine (2.5, 5, 10, and 15 mg). For analysis and graphical representation, data were divided by the coefficient used for AUC calculation so as to return to the same scale that was used for the subjective-effects questionnaire. Y-axes: Percent drug-appropriate responding. X-axes: Subjective ratings. Symbols represent the active doses of *d*-amphetamine: 2.5 mg (circles; N=27), 5 mg

(triangles; N=27), 10 mg (squares; N=27), and 15 mg (diamonds; N=27). Each panel contains 108 data points but due to superimposition in graphing, not all are evident. Please note that the x-axes may be different across panels.

Figure 3.

Correlations between percent drug-appropriate responding subjective ratings of Rush; Shaky-Jittery; Restless; and Talkative, Friendly on the Drug-Effect Questionnaire for all active doses of *d*-amphetamine (2.5, 5, 10, and 15 mg). Remaining details are the same as for Figure 2.