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REINFORCING, SUBJECTIVE, AND COGNITIVE EFFECTS OF METHAMPHETAMINE DURING D-AMPHETAMINE MAINTENANCE

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THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in
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By

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ABSTRACT OF THESIS

REINFORCING, SUBJECTIVE, AND COGNITIVE EFFECTS OF METHAMPHETAMINE DURING *D*-AMPHETAMINE MAINTENANCE

Translational research suggests that agonist replacement may be a viable treatment approach for managing methamphetamine dependence. This study sought to determine the effects of *d*-amphetamine maintenance on methamphetamine self-administration in stimulant using participants. A cognitive battery was used to determine the performance effects of methamphetamine alone and during *d*-amphetamine maintenance. During each maintenance condition, participants first sampled a dose of intranasal methamphetamine then had the opportunity to respond on a progressive ratio task to earn portions of the sampled dose. Subject-rated drug-effect and physiological measures were completed prior to and after sampling methamphetamine. Methamphetamine was self-administered as function of dose regardless of the maintenance condition. Methamphetamine produced prototypical subject-rated effects, some of which were attenuated by *d*-amphetamine maintenance. Methamphetamine was well tolerated during *d*-amphetamine maintenance and no adverse events occurred. The self-administration results are concordant with those of clinical trials that show *d*-amphetamine did not reduce methamphetamine use. Generally, there was no difference in cognitive performance after methamphetamine administration during both placebo and *d*-amphetamine maintenance. Overall *d*-amphetamine does not appear to be a viable treatment for preventing methamphetamine relapse, but translational literature suggests that other agonist medications or the combination of pharmacotherapy and behavioral therapies may be effective.

Keywords: methamphetamine, *d*-amphetamine, self-administration, subject-rated drug-effects, cognitive performance

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Chapter One. Significance and Background

Methamphetamine use disorders are a significant problem in the United States. In 2011, 439,000 individuals over 12 years of age reported using methamphetamine. The number of new users of methamphetamine 12 years of age and older increased between 2010 and 2011 (Substance Abuse and Mental Health Services Administration (SAMHSA), 2011; SAMHSA, 2012). Not only are the number of individuals using methamphetamine increasing, but the cost to society, including premature death, health care costs, and costs of incarceration, is staggering. Using the most recently available data, the estimated total cost of methamphetamine abuse in the United States was over $23 billion in 2005 (Nicosia, Pacula, Kilmer, Lundberg, & Chiesa, 2009). The increasing number of individuals using methamphetamine and the high cost to society contribute to the importance of identifying an effective treatment for methamphetamine abuse, as no universally effective treatments are currently available.

Below I review the available therapeutic approaches for methamphetamine dependence that have been empirically tested.

Behavioral Therapy

Behavioral therapies that have been tested for treatment of methamphetamine abuse include motivational interviewing, cognitive behavioral therapy, relapse prevention, the Matrix Model, and contingency management. Motivational interviewing is a type of therapy designed to help increase an individual's motivation to change their substance use patterns (Baker, Boggs, & Lewin, 2001; Baker, et al., 2002; Baker, et al., 2005). Cognitive behavioral

therapy is related to basic principles of conditioning and learning and involves teaching individuals skills to stop or reduce their substance use (Lee & Rawson, 2008; Vocci & Montoya, 2009). Cognitive behavioral therapy has been expanded into other more specific therapies, such as relapse prevention. Relapse prevention aims to help individuals recognize and cope with situations and feelings that may contribute to relapse in order to increase periods of abstinence (Baker, Boggs, & Lewin, 2001; Baker, et al., 2005; Lee & Rawson, 2008). The Matrix Model was designed specifically to address treatment needs of stimulant abusers and is an intensive multi-week program that includes many types of treatment such as relapse prevention, individual therapy, group sessions, and family education. This model also encourages individuals to become involved in social support groups, such as Alcoholics Anonymous (Obert, et al., 2000; Rawson, et al., 1994, Rawson, et al., 2004; Vocci & Montoya, 2009). Contingency management is a treatment model that provides incentives, such as vouchers for goods or services or payment, for meeting set behavioral goals (e.g., negative urine samples or self-reported abstinence) (for review see: Lee & Rawson, 2008; Roll, 2007; and Vocci & Montoya, 2009; Roll, et al., 2006).

One example of a behavioral intervention that has been tested is contingency management, which has shown promise as a potential treatment for methamphetamine abuse. Methamphetamine abusing participants receiving treatment, including contingency management, were more likely to provide amphetamine or methamphetamine negative urine samples, have increased retention in treatment, and have longer periods of abstinence (for review see:

Lee & Rawson, 2008 and Roll, 2007; Vocci & Montoya, 2009; Rebak, Peck, Dierst-Davies, Nuno, Kamien, & Amass, 2010; Roll, et al., 2006). While contingency management seems promising, results at follow-up are inconsistent. Some studies show maintained abstinence at follow-up, while others show that the differences between contingency management and treatment as usual or no treatment is not maintained at follow-up (for review see: Lee & Rawson, 2008 and Roll, 2007; Vocci & Montoya, 2009; Rebak, Peck, Dierst-Davies, Nuno, Kamien, & Amass, 2010; Roll, et al., 2006). Recent reviews have shown similar results with other cognitive and behavioral therapies (i.e., motivational interviewing, cognitive behavioral therapy, and Matrix Model treatment), with increased rates of stimulant negative urine samples, increased treatment retention, and increased continuous abstinence compared to treatment as usual or no treatment. However, beneficial effects of the treatments have not been shown to be present at follow-up (Lee & Rawson, 2008; Vocci & Montoya, 2009)

Overall, behavioral therapies have shown positive results in promoting methamphetamine abstinence during treatment, but do not produce lasting changes after treatment. This suggests that other strategies, like pharmacotherapy, are needed.

Pharmacotherapy

Methamphetamine belongs to a class of drugs called phenylethylamines and is lipophilic, which allows it to readily cross the blood-brain barrier. Methamphetamine increases the release of endogenous monoamines, primarily dopamine, through different biological processes. First, methamphetamine is

readily transported into the nerve terminal by diffusion across the cell membrane and is also transported by catecholamine-uptake transporters. Once in the nerve terminal, methamphetamine interacts with vesicular monoamine transporter-2 (VMAT-2) to redistribute monoamines from vesicles into the cytosol. Also, methamphetamine reverses catecholamine-uptake transporters causing monoamines that are free in the cytosol to be moved into the synapse. Finally, methamphetamine inhibits the activity of monoamine oxidase, which breaks down monoamines in the cell, and promotes tyrosine hydroxylase, which allows for increased synthesis of dopamine (reviewed in Schep, Slaughter, & Beasley, 2010).

Based on this neuropharmacology, the dopamine system has been targeted for medications development. Both antagonist treatment and agonist replacement have been tested (for reviews see Herin, Rush, & Grabowsi 2010; Karila, Weinstein, Aubin, Benyamina, Reynaud, & Batki, 2010; Rush, Vansickel, Lile, & Stoops, 2009). Antagonists block the effects of the abused drug to extinguish self-administration. Agonist replacement produces cross tolerance to the drug of abuse by diminishing the high that is achieved when the drug of abuse is taken, which leads to extinction of drug taking (for reviews see Herin, Rush, & Grabowsi 2010; Karila, Weinstein, Aubin, Benyamina, Reynaud, & Batki, 2010; Rush, Vansickel, Lile, & Stoops, 2009).

The first pharmacologic approach that was tested to treat methamphetamine abuse was typical antipsychotics as an antagonist treatment. Dopamine is thought to mediate the abuse of methamphetamine and typical antipsychotics are

D2 antagonists, which should block methamphetamine from binding to dopamine receptors. Pimozide is one example of an atypical antipsychotic that has been tested (for review: Brauer, Goudie, & de Wit, 1997). Pimozide has been shown to block the discriminative effects of 1 mg/kg amphetamine in amphetamine-trained rats (Nielsen & Jepsen, 1985). Also, rats pretreated with pimozide self-administered fewer doses of amphetamine and were slower to reinstate responding after extinction compared to placebo treated animals (Yokel & Wise, 1976). In a study using dogs, pretreatment with pimozide increased amphetamine self-administration, which has been linked to increased responding for drug early in extinction models (Risner & Jones, 1976). However, pimozide inconsistently blocked amphetamine discrimination in rhesus monkeys, with some doses effective in a subset of the sample and other animals in the sample displaying no effect of pimozide pretreatment. Additionally, because of a decrease in the response rate when pimozide and amphetamine were combined, higher doses were not tested (Kamien & Woolverton, 1989). In humans, results have also been mixed. One study showed that 2 mg of pimozide blocked increases in arousal after a 10 mg dose of *d*-amphetamine in healthy volunteers (Silverstone, Fincham, Wells, & Kyriakides, 1980). However, in another study with healthy volunteers, pretreatment with 1 or 2 mg pimozide had no effect on 10 or 20 mg doses of *d*-amphetamine (Brauer & de Wit, 1996). In a later study, a higher dose of pimozide (8 mg) was tested in healthy volunteers and found that pimozide had no effect on subjective effects after 10 or 20 mg of *d*-amphetamine. Additionally, some side effects including sedation, agitation, restlessness, facial

spasms, and rigidity were noted (Brauer & de Wit, 1997). Similar research has been done with other typical antipsychotics, including haloperidol, chlorpromazine, and fluphenizine (for review see Brauer, Goudie, & de Wit, 1997; Colpaert, Niemegeers, & Janssen, 1978; Schechter & Cook, 1975; Wilson & Schuster, 1972; Arnt, 1996).

In response to the mixed results and side effects associated with typical antipsychotics, atypical antipsychotics have been tested as a possible antagonist treatment. Atypical antipsychotics, including risperidone and aripiprazole, were considered as possible pharmacotherapies, because of their action on dopamine and serotonin receptors. Risperidone is a dopamine and serotonin antagonist, and it is believed that blocking monoamine binding through the use of an antagonist may decrease the rewarding effects of methamphetamine (Fletcher, 1998; Grabowski, et al., 2000; Meert, Dr Haes, Vermote, & Janssen, 1990; Meredith, et al., 2009; Rush, Stoops, Hays, Glaser, & Hays, 2003; Wachtel, Ortengren, & de Wit, 2002). Preclinical experiments have shown that risperidone reduced drug-appropriate responding to *d*-amphetamine in *d*-amphetamine trained rats (Arnt, 1996; Meert, De Haes, Vermote, & Janssen, 1990) and self-administration of *d*-amphetamine in rats (Fletcher, 1998). When tested in healthy human volunteers, acute risperidone pretreatment did not significantly reduce subject-rated drug-effects of methamphetamine, but did produce a trend toward decreased subject-rated drug-effects (Wachtel, Ortengren, & de Wit, 2002). In another study, healthy human volunteers trained to discriminate *d*-amphetamine showed that pretreatment with risperidone decreased drug-appropriate

responding to *d*-amphetamine and reduced subject-rated drug-effects of *d*-amphetamine. However, this study also showed some performance impairments after risperidone pretreatment (Rush, Stoops, Hays, Glaser, & Hays, 2003). In an open label clinical trial injectable risperidone was tested for the treatment of methamphetamine dependence, only forty-four percent of all possible urine samples were negative for methamphetamine, when analyzed using an intent-to-treat model (Meredith, et al., 2009). Also, patients experienced negative side-effects of risperidone including sedation, which occurred in eighty percent of participants, and akathisia, which occurred approximately seventeen percent of participants (Meredith, et al., 2009). A double-blind placebo-controlled trial was designed to test varying doses of risperidone for the treatment of cocaine dependence. Participants in the 8 mg risperidone condition had a greater proportion of cocaine positive urine samples in the first month of the trial compared to all of the other groups, including placebo (Grabowski, et al., 2000). None of the participants randomized to the highest dose condition, 8 mg risperidone, completed the study. Over all of the doses tested, risperidone treatment did not improve outcomes or retention. Additionally, participants experienced multiple negative side effects of the medication (Grabowski, et al., 2000). The increase in positive urine screens, poor retention, and multiple negative side effects suggest that risperidone is not likely to be an effective pharmacotherapy as treatment retention and compliance may be problematic.

Aripiprazole, another atypical antipsychotic, which is a dopamine and serotonin partial agonist, has also been tested as a potential pharmacotherapy

for methamphetamine dependence. Similar to risperidone, aripiprazole pretreatment showed promising results in healthy human volunteers (Sevak, et al., 2011; Stoops, 2006). Clinical trials testing aripiprazole for methamphetamine dependence have generally shown no significant reduction in methamphetamine use (Coffin, et al., 2012; Tiihonen, et al., 2007). Additionally, one of the trials was ended early when interim analysis showed that participants in the aripiprazole arm of the study were more likely to submit a urine sample positive for amphetamine than participants receiving placebo (Tiihonen, et al., 2007). This increase in drug use in the aripiprazole condition is disconcerting and suggests that antagonist treatment may not be an effective strategy for treating methamphetamine abuse. These studies suggest that a different approach is needed to identify a potential pharmacotherapy for treating methamphetamine dependence.

Agonist replacement may be an alternative to antagonist treatment for methamphetamine dependence. Dopamine agonists have been proposed as a potential pharmacotherapy as they may increase extracellular dopamine, which has been found to be depleted after long-term stimulant use, without the rewarding properties produced by methamphetamine (reviewed in: Herin, Rush, & Grabowski, 2010; Moeller, Schmitz, Herin, & Kjome, 2008). Agonist replacement is commonly used for other types of substance use, including methadone for opiate abuse and nicotine replacement for tobacco use. In addition, dopamine agonists have shown promising results when tested for

treating cocaine dependence (reviewed in: Herin, Rush, & Grabowski, 2010; Moeller, Schmitz, Herin, & Kjome, 2008).

Few studies have been conducted to test agonist replacement with methamphetamine. However there is an extensive literature related to agonist replacement for treating cocaine dependence that may be germane to the approach of using agonist replacement for methamphetamine abuse. Numerous dopamine agonists have been tested for treating cocaine dependence including *d*-amphetamine, which can provide translational evidence for the use of *d*-amphetamine for methamphetamine abuse. Preclinical studies with rats have shown that chronic maintenance with *d*-amphetamine decreases cocaine taking on a progressive-ratio schedule of self-administration (Chiodo & Roberts, 2009), decreases breakpoints of responding for cocaine (Chiodo, Läck, Roberts, 2008), and produces a rightward shift in the discrimination and self-administration curves of cocaine (Peltier, Li, Lytle, Taylor, & Emmett-Oglesby, 1996). Similarly, preclinical studies using rhesus monkeys have shown that chronic pretreatment with *d*-amphetamine reduced self-administration of cocaine (Czoty, Gould, Martelle, & Nader, 2011; Czoty, Martelle, & Nader, 2010; Foltin & Evans, 1998; Negus & Mello, 2003a; Negus & Mello, 2003b). Human laboratory studies with healthy non-treatment seeking cocaine users have shown that maintenance on *d*-amphetamine reduced some of the positive subjective effects of intranasal cocaine and decreased self-administration of 20 mg of cocaine (Rush, Stoops, & Hays, 2009; Rush, Stoops, Sevak, & Hays, 2010). Finally, clinical trials have shown positive results using *d*-amphetamine as a potential treatment for cocaine

dependence (Grabowski, et al., 2001; Grabowski, et al., 2004; Shearer, Wodak, van Beek, Mattick, & Lewis, 2003). Two clinical trials have shown decreases in cocaine positive urine samples with an escalating dose of 30 mg to 60 mg *d*-amphetamine (Grabowski, et al., 2001; Grabowski, et al., 2004). Another clinical trial tested 60 mg *d*-amphetamine and did not find a significant decrease in positive urine samples, but participants in the treatment group reported significantly less cocaine use and lower levels of craving compared to those receiving placebo treatment (Shearer, Wodak, van Beek, Mattick, & Lewis, 2003). These findings provide evidence for the use *d*-amphetamine as a potential pharmacotherapy for cocaine dependence, which may also translate to methamphetamine dependence.

Similar to the findings with cocaine, dopamine agonists that have been tested for methamphetamine dependence and show promise as a potential pharmacotherapy, with fewer unpleasant side effects or performance impairments than other classes of medications that have been tested (Herin, Rush, & Grabowsi, 2010; Karila, Weinstein, Aubin, Benyamina, Reynaud, & Batki, 2010). A recent study tested subject-rated drug-effects of varying doses of methamphetamine during *d*-amphetamine maintenance compared to placebo in chronic stimulant abusing individuals. It was found that 45 mg/day *d*-amphetamine reduced subject-rated drug-effects of methamphetamine significantly compared to placebo (Rush, Stoops, Lile, Glaser, & Hays, 2011). This suggests that *d*-amphetamine may be effective for treating methamphetamine abuse, but this study did not test to see if *d*-amphetamine

would reduce self-administration of methamphetamine in a controlled laboratory or clinical setting. One clinical trial showed that pretreatment with *d*-amphetamine decreased illicit amphetamine use in intravenous drug users (Moeller, Schmitz, Herin, & Kjome, 2008). Another clinical trial was designed to test the efficacy of sustained release *d*-amphetamine for the treatment of methamphetamine abuse in treatment seeking methamphetamine users. The data showed that treatment with 60 mg of sustained-release *d*-amphetamine did not reduce methamphetamine use compared to placebo maintenance (Galloway, et al., 2011). Similarly, another clinical trial demonstrated that maintenance on 110 mg *d*-amphetamine for the treatment of methamphetamine did not reduce methamphetamine abuse compared to placebo maintenance (Longo, et al., 2009). The results from clinical trials are mixed, which along with a promising signal from the human laboratory, suggests that more research is needed to determine if *d*-amphetamine may be an effective pharmacotherapy for methamphetamine abuse.

Overall, a universally effective pharmacotherapy for methamphetamine abuse has not been identified. While there has not been much work done testing agonist replacement as a pharmacotherapy for methamphetamine, previous work shows a good signal that agonist replacement may be effective and so far agonist replacement has shown the best signal as a pharmacotherapy for cocaine dependence. These findings suggest that more work is needed to test agonist replacement for methamphetamine dependence.

Cognitive Impairment as a Target for Medications Development

A recent target for medication development is the remediation of cognitive deficits related to chronic stimulant abuse. This has stemmed from studies that have associated poorer treatment outcomes and early treatment drop-out with performance on various measures of cognitive functioning (Ahronovich, Hasin, Brooks, Liu, Bisaga, & Nunes, 2006; Ahronovich, Nunes, & Hasin, 2003; Brewer, Worhunsky, Carroll, Rounsville, & Potenza, 2008; Hester, Lee, Pennay, Nielson, & Ferris, 2010; Moeller, Dougherty, Barratt, Schmitz, Swann, & Grabowski, 2001; Turner, LaRowe, Horner, Herron, & Malcolm, 2009).

The cocaine Stroop task assesses for a bias toward drug related stimuli by recording the reaction time for participants to respond to the color of both neutral and drug related words. The cocaine Stroop has consistently shown that chronic stimulant using individuals show an attention bias toward salient (i.e., drug related) words (Brewer, Worhunky, Carroll, Rounsaville, & Potenza, 2008; Gardini, Caffarra, & Venneri, 2009; Hester, Lee, Pennay, Nielson, & Ferris, 2010; Liu, Lane, Schmitz, Waters, Cunningham, & Moeller, 2011; Sharma & Money, 2010). There is an inverse relationship between performance on the cocaine Stroop and treatment retention, such that a higher attention bias is associated with less time in treatment (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Hester, Lee, Pennay, Nielson, & Ferris, 2010).

Other studies have investigated impulsivity in stimulant users, as individuals who are more impulsive may choose short-term reinforcement from using a drug

as opposed to longer-term reinforcement associated with abstinence. These studies have found that chronic stimulant users tend to be more impulsive compared to controls on the Barratt Impulsiveness Scale and tend to choose less advantageous decks on the Iowa Gambling Task (Kjome et al., 2010; Moeller, Dougherty, Barratt, Schmitz, Swann, & Grabowski, 2001).

Cognitive performance on a battery of tests has also been assessed as part of two clinical trails. These studies showed differences in cognitive performance of treatment completers compared to dropouts, with dropouts displaying significantly poorer performance on measures of attention, memory, spatial ability and processing, and mental reasoning (Ahronovich, Hasin, Brooks, Liu, Bisaga, & Nunes, 2006; Ahronovich, Nunes, & Hasin, 2003).

Further research is needed to assess different domains of cognitive function to see if deficits can be identified. Additionally, research has not yet been done to determine if cognitive performance of stimulant users can be improved using pharmacological methods.

Summary

Methamphetamine abuse is a significant problem in the United States, with over four hundred thousand people reporting past month use of methamphetamine and increasing numbers of people initiating use (SAMHSA, 2012). Also, methamphetamine abuse is associated with a very high cost to society (Nicosia, Pacula, Kilmer, Lundberg, & Chiesa, 2009). Behavioral therapies, especially contingency management, have shown some potential as a treatment for methamphetamine abuse. However, differences in use observed

between treatment groups and either treatment as usual or no treatment do not always persist at follow-up (for review see: Lee & Rawson, 2008 and Roll, 2007; Vocci & Montoya, 2009; Rebak, Peck, Dierst-Davies, Nuno. Kamien, & Amass, 2010; Roll, et al., 2006). It is possible that behavioral therapies combined with pharmacotherapy could produce more robust patterns of abstinence, but an effective pharmacotherapy has yet to be identified. Studies testing *d*-amphetamine as a potential pharmacotherapy for methamphetamine abuse have shown decreases in illicit stimulant abuse in intravenous amphetamine users and decreases in subject-rated drug-effects after methamphetamine administration (Moeller, Schmitz, Herin, & Kjome, 2008; Rush, Stoops, Lile, Glaser, & Hays, 2011, respectively). However, a clinical trial testing *d*-amphetamine as a treatment for methamphetamine abuse in treatment seeking methamphetamine users did not show a reduction in methamphetamine use compared to placebo (Galloway, et al., 2011). Finally, remediation of cognitive deficits associated with chronic stimulant abuse have become a target for medications development, since recent studies have shown that poor performance on cognitive measures are associated with poor treatment outcomes and retention (Ahronovich, Hasin, Brooks, Liu, Bisaga, & Nunes, 2006; Ahronovich, Nunes, & Hasin, 2003; Brewer, Worhunsky, Carroll, Rounsville, & Potenza, 2008; Hester, Lee, Pennay, Nielson, & Ferris, 2010; Moeller, Dougherty, Barratt, Schmitz, Swann, & Grabowski, 2001; Turner, LaRowe, Horner, Herron, & Malcolm, 2009). It is likely that a successful methamphetamine intervention will need to encompass each of these approaches.

Chapter Two. Purpose of Project

The aim of the present study was to evaluate *d*-amphetamine as a potential pharmacotherapy for methamphetamine abuse. This was accomplished by examining the subject-rated drug effects, self-administration, cognitive performance, and physiological measures after the administration of varying doses of methamphetamine during chronic maintenance on either *d*-amphetamine or placebo. These measures have previously been shown to be sensitive to the effects of methamphetamine (Lile, Stoops, Glaser, Hays, & Rush, 2011; Rush, Stoops, Lile, Glaser, & Hays, 2011; Sevak, Stoops, Hays, & Rush, 2009; Sevak, Vansickel, Stoops, Glaser, Hays, & Rush, 2011).

Chapter Three. Hypothesis

Behavioral

Methamphetamine will be self-administered by participants more than placebo. During *d*-amphetamine maintenance, participants will self-administer fewer doses of methamphetamine than during placebo maintenance. Methamphetamine administered alone will dose dependently increase positive subject-rated drug-effects (e.g., Like Drug; Willing to Take Again). During *d*-amphetamine maintenance, participants will report lower levels of drug-effects compared to placebo maintenance.

Cognitive

d-Amphetamine maintenance. *d*-Amphetamine alone will improve participants' performance on the cognitive battery compared to placebo maintenance.

Methamphetamine challenge. Methamphetamine administered alone and in combination with *d*-amphetamine will dose-dependently improve participants' performance on the cognitive battery compared to performance after placebo administration. *d*-Amphetamine maintenance will attenuate impairments observed after methamphetamine administration.

Physiological

Methamphetamine will dose dependently increase heart rate and blood pressure. *d*-Amphetamine, when administered alone, will increase physiological measures. Administration of methamphetamine during *d*-amphetamine maintenance will increase heart rate and blood pressure, but will be safe and well-tolerated.

Chapter Four. Method

The proposed experiment and informed consent document were approved by the Institutional Review Board of the University of Kentucky Medical Center.

Participants

Eight participants who reported stimulant dependence were recruited through the use of flyers, newspaper, online and radio ads, and by word of mouth for participation in this experiment. Prior to enrollment in the experimental protocol, all participants were screened using health-history, drug-use history, and psychiatric history questionnaires. Questionnaires included: the Beck Depression Inventory (BDI), Brief Symptom Index (BSI), assessments for attention deficit hyperactivity disorder (ADHD), mental status, and drug and alcohol dependence. Drug histories were collected including time since first use, frequency and

quantity of use, and drugs used over the lifetime. Laboratory values were collected for all participants, including a complete blood count and chemistry panel, urinalysis, and electrocardiogram (ECG). Laboratory values outside of the normal range were reviewed by Dr. Lon R. Hays (University of Kentucky, Department of Psychiatry) or Dr. Paul E. A. Glaser (University of Kentucky, Department of Psychiatry) to determine if the levels were clinically significant before admittance into the study. ECGs were interpreted by Dr. John Gurley (University of Kentucky, Department of Cardiology) and any participant with an ECG determined to be abnormal was excluded from participation from the study. Participants with a history of clinically significant medical conditions, CNS disorders, impaired heart functions, history of chronic pulmonary obstructive disease, history of seizures, family history of sudden death, or any contraindications to the administration of stimulant medications (e.g. allergic reaction to stimulant medications or heart problems) were excluded from participation. Also, participants with a current or past history of psychiatric illness that in the opinion of the study physicians would interfere with performance were excluded from participation. All participants were physically and psychologically healthy, as determined by the medical staff, and were within 20% of their ideal body weight (BMI tables).

Payment and Follow-Up

Participants earned $80 for each experimental session, with $40 being paid for each session completed and $40 paid as a bonus if all sessions were completed. Participants also had the opportunity to earn approximately $6 on the

Balloon Analog Risk Task (BART) completed twice on each cognitive testing day and once during each experimental session (shown in Tables 1 and 2). In total, participants were able to earn approximately $2000. At the end of their participation, participants returned to the Laboratory of Human Behavioral Pharmacology (LHBP) and received a check for up to $500 once per week until they were paid all of the money they earned. When participants received their weekly payments, they also completed a brief follow-up to assess recent drug use. These data were not analyzed as part of the proposed study, but were collected in case future analyses look for changes in drug use after enrollment in a study. During this assessment, participants provided an expired breath sample to test for the presence of alcohol as well as provided a urine sample to test for the presence of illicit substances.

General Procedures

Prior to admission to the Clinical Research Development and Operations Center (CR-DOC) and before all study sessions (cognitive and experimental), participants provided a urine sample that was tested for the presence of drugs of abuse. Urine samples were tested using the Integrated E-Z Split Key Cup (Iminia, Los Angeles, CA) and Fastect Drug Screen Dipstick Test MTH 300 and OXY 100 (Branan Medical Corp., Irvine, CA) to test for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, methadone, methamphetamine, opiates, oxycodone, PCP, and THC. Participants who provided a urine sample positive for drugs other than cocaine or THC were not admitted at that time. On session days, urine samples could test positive for

THC, amphetamines, or methamphetamine, depending on marijuana use prior to admittance or drugs administered during study sessions on previous days and were evaluated by Dr. William Stoops to determine if the study session could continue as planned. Any participant, who provided a urine sample that tested positive for a drug that was not administered as part of the study protocol, was discharged from the study. Expired breath samples were collected to assess for the presence of alcohol using a hand-held Alcosensor (Intoximeters, St. Loius, MO). Also, participants were asked to complete a sobriety test and participants who passed the sobriety test were allowed to participate in the day's session.

Female participants were required to use an effective form of birth control prior to admittance to the CR-DOC and received a pregnancy test using a urine HCG test (confirms II, I.M. Isbell Marthé Diagnostics, Inc., Naples, FL) prior to admittance to the CR-DOC as well as before every study session. Any female participant who tested positive for pregnancy was discharged from the study.

Participants resided at the CR-DOC for approximately 28 days and completed one practice and eight experimental sessions. Participants had a full day to acclimate prior to beginning maintenance medications. Timeline for maintenance medications and sessions are shown in Table 1. Participants were informed that during the study they would be given medications that may be placebo or an FDA approved prescription stimulant, such as *d*-amphetamine or methamphetamine. Participants were informed that the purpose of the study was to see how the drugs affect mood and behavior, if they like the drug and would be willing to take it again, and the affect of the drugs on cognitive and performance tasks.

Participants were not informed of the specific drugs they received, possible outcomes, or performance expectations.

Table 1. Timeline for maintenance medications and sessions

Day 1	Admission to CR-DOC
Day 2	Practice Session
Days 3-24	Drug maintenance. Doses administered at 0700 and 1900 daily
Day 9	Cognitive and performance task battery completed twice
Days 10-13	Experimental Sessions (timeline shown in Table 2)
Day 20	Cognitive and performance task battery completed twice
Days 21-24	Experimental Sessions (timeline shown in Table 2)
Day 25	Discharge

Practice session. Participants completed a practice session prior to beginning maintenance medication to familiarize them with the behavioral tasks, progressive ratio, and timeline of experimental sessions, which are described below. No medications were administered during the practice session.

Instructions for practice session. Today, you will not receive any medications, but will periodically complete behavioral tasks to familiarize you with the study routine. One of these tasks will be the progressive ratio task that you will do in experimental sessions to earn drug. The number of responses required for completing each of the opportunities to earn drug will increase as you proceed in the task. You will have to complete the full task today. In the future, you will decide how much of the task you want to complete to earn intranasal drug.

Experimental sessions. Participants completed four experimental sessions after at least 7 days of maintenance in each maintenance condition. Participants completed a pre-session task at 0900 and at 0930 sampled intranasally the medication that they had the opportunity to work for later in the session. Participants completed subject-rated drug-effects questionnaires at 0945 and 1000. Between 1005 and 1100, participants completed an abbreviated cognitive battery (visual probe, cued go/no-go, and BART). Then participants completed the subject-rated drug-effects questionnaires again at 1100 and 1130, followed by a break from 1145 until 1330. During the break, participants were allowed to eat lunch and engage in any desired activities, except smoking. At 1330 participants' vitals were recorded and the self-administration portion of the

session began. Between 1345 and 1430 participants completed the progressive ratio and subject-rated drug-effects questionnaires. At 1430 the participants received the dose that they worked for in the progressive ratio and completed subject-rated drug-effect questionnaires every 15 minutes for the next hour. After 1530, participants completed the subject-rated drug-effect questionnaires every 30 minutes for another hour. A timeline of experimental sessions is illustrated in Table 2. It is possible that two participants were enrolled in the study simultaneously and participants were instructed not to discuss drug effects with any other participants.

Instructions for medication-administration during sampling. You will now receive a drug. Please pay attention to how the drug makes you feel, because later today you will be given the opportunity to earn all, some or none of this drug. The drug will be in the form of a powder. Please follow along with the research assistant as he/she reads the instructions for you for preparing the powdered medication.

1) The nurse will empty the powdered medication on the mirror for you.
2) With the single-edged razor blade, please separate the powdered medication into two (2) lines that are approximately equal in volume.
3) When told to do so by the research assistant and nurse, please use the straw to inhale or snort one of the "lines" into each of your nostrils.
4) You will have a total of two (2) minutes to inhale or snort the drug.

Instructions for medication administration during self-administration. You will now have the opportunity to work for the drug you sampled this morning.

Please refer to your notes about the drug effects from the previous session because today you will be able to work for all, or some, of the drug from this morning.

You will have a total of ten (10) opportunities to respond by clicking on a mouse to receive the drug from this morning, and can earn the full dose from this morning's session. As you complete each segment, you will earn 1/10th of the drug. The total amount of drug that you earn today will be given to you all at once when you are done.

You should understand that you do not have to work for any drug today. However, if you choose not to work for any drug, you will not receive any drug today. You should also understand that you can stop working at any time. However, if you start a segment on the computer and do not finish it, you will only receive the total drug that you earned by completing earlier segments. Whether or not you choose to work for drug, you will have to complete the rest of the 3-hour session.

Baseline cognitive testing. Participants completed a baseline testing session, which served as a practice session to familiarize them with the battery of cognitive and performance tasks that were administered during the maintenance cognitive testing days. Baseline study sessions followed the same timeline and procedures as the maintenance cognitive testing days, except they were conducted at the Laboratory of Human Behavioral Pharmacology, rather than the CR-DOC inpatient unit. No medications were administered.

Maintenance cognitive testing. Participants completed the cognitive battery at 0830 and 1300 or 1000 and 1430, with the participant completing the battery at the same pairing of times on each testing day. Maintenance testing was conducted on the last day of maintenance before study sessions began for each maintenance condition (0 mg *d*-amphetamine and 40 mg *d*-amphetamine). The cognitive battery consisted of the grooved pegboard task, visual probe task, cued go/no-go task, n-back, cocaine Stroop task, balloon analog risk task (BART), and digit symbol substitution task (DSST).

Table 2. Experimental Session Timeline

0830	Vitals, sobriety test, pre-session paperwork completed
0900	Pre-session subject-rated drug-effects, vitals recorded
0930	Sample dose administered, subject-rated drug-effects, vitals recorded
0945	Subject-rated drug-effects, vitals recorded
1000	Subject-rated drug-effects, vitals recorded
1005	Abbreviated cognitive battery, vitals recorded after each task
1100	Subject-rated drug-effects, vitals recorded
1130	Subject-rated drug-effects, vitals recorded
1145	Participant had a 2 hour break
1330	Vitals recorded
1345	Progressive ratio, pre-dose subject-rated drug-effects, vitals recorded
1430	Dose administered, subject-rated drug-effects, vitals recorded
1445	Subject-rated drug-effects, vitals recorded
1500	Subject-rated drug-effects, vitals recorded
1515	Subject-rated drug-effects, vitals recorded
1530	Subject-rated drug-effects, vitals recorded
1600	Subject-rated drug-effects, vitals recorded
1630	Subject-rated drug-effects, vitals recorded

Modified Progressive-Ratio Procedure

The modified progressive-ratio procedure has been used in previous studies and has been shown to be a reliable measure of human drug reinforcement (Comer, Collins, & Fischman, 1997; Comer, Collins, MacArthur, Fischman, 1999; Comer, Collins, Wilson, Donovan, Foltin, & Fischman, 1998; Rush, Essman, Simpson, & Baker, 2001; Stoops, 2008). During the self-administration portion of each experimental session participants had 10 opportunities to work to earn a portion of the drug sampled that morning. Participants were presented with the progressive-ratio task on a computer screen and they were instructed to use the computer mouse to click on a button to work to earn a portion of the drug, each completed ratio earned 1/10th of the sampled dose. Participants were instructed that they might choose to work to earn all, a portion of, or none of the sampled dose. To complete the first ratio, participants were required to click 400 times and each additional ratio increased by 100 (i.e. 500, 600, 700, 800, 900, 1000, 1100, 1200, and 1300). To earn all of the sampled dose, participants were required to click a total of 8500 times. The participant was allowed quit the task at any time if they clicked a button labeled stop and the task was terminated. They received the dose for the highest ratio that was completed. This was verified by a research assistant in the data file for the task. Data was collected on the breakpoint (i.e. the highest ratio that was completed).

For each ratio completed the participant earned 1/10th of the drug that was sampled that morning. The doses of methamphetamine were mixed with lactose monohydrate powder, N.F. so that all doses were 60 mg of powder. After taking

the self-administered dose intranasally, participants completed the subject-rated drug-effect questionnaires every 15 minutes for the first hour then every 30 minutes for another hour. If the participant chose not to work for any of the sampled dose they still completed the scheduled tasks, which eliminated the possibility of a participant choosing no drug to end a session early. All sessions were conducted as shown in Table 1, regardless of the drug dose earned.

Subject-Rated Drug-Effect Questionnaires

All of the subject-rated drug-effect questionnaires were administered using an Apple microcomputer with a mouse attached in a fixed order. Participants completed the tasks as indicated on the daily schedule in Table 1 during experimental sessions.

Adjective Rating Scale. The adjective rating scale is a measure that consists of 32 questions divided into two subscales: sedative and stimulant. Participants were shown questions on a computer screen and were asked to indicate their answer by using a computer mouse to select one of 5 buttons: “not at all,” “A little bit,” “moderately,” “quite a bit,” or “extremely” (scored as 0-4 respectively). The sedative subscale consists of the following adjectives: *Clumsy*, *Dizzy*, *Confused*, *Dazed*, *Sleepy*, *Depressed*, *Difficulty Walking*, *Drowsy*, *Nausea*, *Drunk*, *Fatigued*, *Lazy*, *Relaxed*, *Tired*, *Sluggish*, and *Spaced Out*. The stimulant subscale consists of the following adjectives: *Active*, *Alert*, *Irregular Heartbeat*, *Good Mood*, *Muscles Twitching*, *Agitated*, *Energetic*, *Excited*, *Euphoric*, *Irritable*, *Nervous*, *Restless*, *Shaky*, *Sweaty*, *Talkative*, and *Heart Racing*. Composite

scores were produced for each subscale, with a maximum score of 64 on each subscale.

Visual Analog Scale (True/False). The Visual Analog Scale (VAS) True/False is a measure of subject-rated drug-effects. Participants were presented with statements and a sliding scale that is 101 mm long on a computer screen. The sliding scale was labeled "false" on the left and "true" on the right and participants were asked to indicate how much they agree with the statement presented by using a computer mouse to place a marker on the scale. Each item was scored as how many millimeters the participant placed the marker from the end of the scale indicating false (i.e. "false" would be scored as 0 and "true" would be scored as 100). The maximum possible score was 100 for any item. The statements presented were as follows: "Is the drug producing *any effect* right now?; Is the drug producing any *bad effects* right now?; Is the drug producing any *good effects* right now?; Is the drug making you feel *high* right now?; Are you experiencing a *rush* from the drug right now?; How much do you *like* the drug right now?; Is the drug making you feel *stimulated* right now?; Is the drug *impairing your performance* right now?; Is the drug *improving your performance* right now?; Based on how the drug effect feels right now, would you be willing to *take this drug again*?; Based on how the drug effect feels right now, would you be willing to *pay for this drug*?; Is the drug making you feel *active, alert or energetic* right now?; Is the drug making you feel *shaky or jittery* right now?; Is the drug making you feel *euphoric* right now?; Is the drug making you experience an *irregular or racing heartbeat* right now?; Is the drug making you feel *talkative*

or friendly right now?; Is the drug making you feel *nauseous, queasy, or sick to your stomach* right now?; Is the drug making you feel *nervous or anxious* right now?; Is the drug making you feel *restless* right now?; Is the drug making you feel *sluggish, fatigued or lazy* right now?

Cognitive and Performance Measures

The cognitive measures were administered using the grooved pegboard, a Dell laptop computer (visual probe, cued go/no-go, n-back, cocaine Stroop, and BART), and an Apple Macintosh microcomputer (DSST) in a fixed-order. These measures were administered twice daily on cognitive testing sessions and an abbreviated battery (i.e. visual probe, cued go/no-go, and BART) was administered once during experimental sessions. These tasks have been validated and used in previous studies (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Gardini, Caffarra, & Venneri, 2009; Hester, Dixon, & Garavan, 2006; Kaufman, Ross, Stein, & Garavan, 2003; Lejuez, et al., 2002; Liu, Lane, Schmitz, Waters, Cunningham, & Moeller, 2011; MacLeod, Mathews, & Tata, 1986; Oliveria, Barroso, Silveira, Ponce, Vaz, & Nappo, 2009; Waters, Sayette, Franken, & Schwartz, 2005).

Grooved Pegboard Task. The grooved pegboard task was an assessment of manual dexterity (Trites, 1977). Participants were presented with a pegboard that consists of a dish to hold the pegs, enough pegs to fill the pegboard with some extra, and a pegboard with 25 holes with the pegs oriented in varying directions. Participants were asked to use only their dominant hand and place the pegs into the pegboard as quickly as they could. Data was collected as a composite of the

number of holes filled on the pegboard, time to complete the task in seconds, and number of pegs dropped.

Instructions for the grooved pegboard task. This is a pegboard and these are the pegs.

All the pegs are the same. They have a groove, that is, a round side and a square side and so do the holes in the board. What you must do is match the groove of the peg with the groove of the board and put these pegs into the holes like this. (Demonstrate by filling the first row, then remove the pegs and return them to the tray)

When I say go, begin here and put the pegs in the boards as fast as you can using only your dominant hand. Fill the top row completely from (right handed: left to right or left handed: right to left). Do not skip any: fill each row the same way you filled the top row. Any questions? Ready, as fast as you can, go.

Visual Probe Paradigm. The visual probe paradigm measured attention bias toward salient images, such as images of a drug of abuse (MacLeod, Mathews, & Tata, 1986). Participants were presented pairs of images, either a cocaine image and a neutral image or two neutral images, oriented with one on the right side of the computer screen and one on the left. After a set period of time, the images disappeared and a target replaced one of the images. Participants were asked to identify which side of the screen the target appeared on by responding on one of two keys on a computer keyboard. Data were collected on reaction times when the target replaced a cocaine image and when the target replaced a

neutral image and the attention bias score was obtained by subtracting reaction times to cocaine images from reaction times to neutral images.

Instructions for the visual probe task. This is a reaction task. You will be presented with a fixation point (a tiny cross) at the center of the screen followed by a pair of images. These are images of various objects. Again, you are to look at the pictures while they are on the screen. Once the images disappear from the screen, an X will appear on either the left or right side of the screen. Your task is to respond as quickly as possible to the X by pressing the yellow key if the X is on the left side of the screen or the green key if the X is on the right side of the screen. Once you make your response, another fixation point will appear followed by the presentation of a new set of images. You will perform several of these trials.

Cued Go/No-Go Task. The cued go/no-go task was a measure of inhibitory control (Miller, Schaffer, & Hackley, 1991). Participants were shown a cue, an outline of a rectangle, which was oriented either horizontally or vertically. The orientation of the rectangle signified it as a go or a no-go cue. Participants were asked to respond on a computer keyboard when the rectangle filled in green, but to inhibit responding when the rectangle filled in blue. For example, when a vertical rectangle was a go cue, 80% of the time it filled in green, which indicated to the participant that they should respond. However, 20% of the time go cues filled in blue, which required participants to inhibit responding after being primed to respond. Data were collected on the percent of responses that were correctly inhibited after being presented with a go cue.

Instructions for the cued go/no-go task. This is a reaction time task that I would like you to perform. While you are performing the task you sit in front of the computer screen just you as are doing. You place your index finger on the '?' key.

Presented on the screen will be rectangular boxes that are standing upright or lying flat.

The boxes are empty when they first appear on the screen. If the box turns green then you are to press the '?' button as quickly as possible. If the box turns blue then no response is required.

Now, before a box appears, you will see a plus sign in the middle of the screen. It serves as a fixation point so that you know where to focus your attention on the computer screen. After the plus sign disappears, a box will appear on the screen. Again, if the box turns green, respond as quickly as possible by pressing the '?' key. If the box turns blue then no response is required.

To help you respond quickly, the computer will display how fast you are pressing the key when the green target appears. Once you respond to a green target, the screen will show the amount of time it took for you to make that response. The time is presented in milliseconds. The fewer the milliseconds, the faster the response. So lower numbers are better. If you accidentally respond to a blue target, the screen will say "Incorrect Response".

N-Back Task. The N-Back task assessed working memory by asking participants to identify if letters presented on a computer screen were the same or different than previous letters in a specific pattern (Kirchner, 1958). The task consisted of three pattern conditions: one back, two back, and three back. In one back, participants were asked to respond to each letter presented on the computer screen to identify if it was the same as the letter immediately before the letter presented or not the same. Two back required participants to respond if the current letter was the same as or different than the letter presented two letters before. Finally, the three back required participants respond to identify if the current letter was the same as or different than the letter presented three letters before. Data was collected on reaction time and accuracy to letters that are targets (i.e. the same as) and not-targets (i.e. different than) for each of the conditions.

Instructions for the n-back task. You will see letters on the screen, one letter at a time.

When the letter on-screen matches the last letter presented (two letters back for two back or three letters back for three back), press TARGET (1).

When the letter on-screen is not the same as the letter that came before it, press NOT A TARGET (2).

Cocaine Stroop Task. The cocaine Stroop task was a modified version of the Stroop task, which required participants to identify the color of cocaine words and neutral words (Hester, Dixon, & Garavan, 2006; Liu, Lane, Schmitz, Waters, Cunningham, & Moeller, 2011). Participants were presented words that are either

blue, red, or green and they were asked to identify the color of the text by pressing a key on a computer keyboard. Data were collected on the reaction time to respond to neutral and cocaine words and an attention bias score was obtained by subtracting the reaction time to cocaine words from the reaction time to neutral words.

Instructions for the cocaine Stroop task. In this task you will be presented with words that are either red, blue, or green. You will be asked to respond on the keyboard with the color that the word is written in.

For red text respond with the number 1 (red dot)

For blue text respond with the number 2 (blue dot)

For green text respond with the number 3 (green dot)

Balloon Analog Risk task. The balloon analog risk task (BART) was a measure of risk taking (Lejuez et al., 2002). Participants were presented with a screen where they can click a computer mouse to pump a balloon, each trial consisted of 20 balloons and each pump was worth $0.01. Each time the participant clicked the mouse, $0.01 was added to a temporary bank, and at any time participants may choose to end a balloon and save their earnings in a permanent bank, which was paid to them at the end of the session. Participants were instructed that they could pump the balloon as many times as they chose, but that the balloon may pop after as few as one or two clicks or could fill the screen, and if the balloon pops they lose all of the money stored in their temporary bank. Data were collected on the percentage of balloons that pop.

Instructions for the balloon analog risk task. Now you are going to see 20 balloons, one after another, on the screen. For each balloon, you will use the mouse to click on the box that will pump up the balloon. Each click on the mouse pumps the balloon up a little more.

BUT remember, balloons pop if you pump them up too much. It is up to you to decide how much to pump up each balloon. Some of these balloons might pop after just one pump. Others might not pop until they fill the whole screen.

You get MONEY for every pump. Each pump earns 1 cent(s). But if a balloon pops, you lose the money you earned on that balloon. To keep the money from a balloon, stop pumping before it pops and click on the box labelled "Collect $$$".

After each time you collect $$$ or pop a balloon, a new balloon will appear.

At the end of the experiment, you will be paid the amount earned on the game.

Digit-Symbol Substitution Task (DSST). A computerized version of the DSST was used in this experiment (McLeod, Griffiths, Bigelow, & Yingling, 1982). Participants used a numeric keypad to reproduce patterns that were associated with one of nine patterns associated with numbers shown on the computer screen. Participants had 90 seconds to enter as many patterns as possible. Data were collected on the number of patterns attempted and number of patterns correctly entered.

Physiological Measures

Heart rate, blood pressure, temperature, and heart rhythmicity (*via* ECG) were measured using a Dinamap digital monitor (Critikon, Pro 1000, Tampa, FL). Vitals were collected during experimental sessions every 30 minutes for 1.5 hours before medication administration starting at 0830 and then every 15 minutes until the participant went on break at 1145. After the break, vitals were recorded at 1330, 1345, and 1430 followed by the self-administered dose. Vitals were then recorded every 15 minutes until 1530 and after that they were recorded every 30 minutes until 1630.

Drug Administration

All medications were administered in a double blind fashion, such that the nurses, research assistant, and participant were not aware of the dose that is being given. Dr. Stoops determined the dose order so that the nurse and research assistant were not aware of the dose order. Maintenance medications were prepared by over-encapsulating a commercially available 5 mg *d*-amphetamine spansule and loose filling the capsule with lactose monohydrate powder, N.F. Participants received escalating doses of sustained release *d*-amphetamine twice daily until the target dose of 40 mg per day is reached. Participants received 5 mg twice daily on the first day of *d*-amphetamine maintenance, 10 mg twice daily on the second and third days, and 20 mg twice daily for the remaining days. Placebo capsules were prepared in the same way as the *d*-amphetamine, except only contained lactose monohydrate powder, N.F.

Methamphetamine doses were prepared by weighing out the appropriate dose (0, 10, 20 or 30 mg) of methamphetamine and then were mixed with lactose monohydrate powder, N.F. to make a total of 60 mg of powder. Participants sampled the entire dose in the morning the session and had the opportunity to work for a portion of the sampled dose in the afternoon self-administration portion of the session. Sampled doses were divided into 10 parts for self-administration and were prepared into 10 vials that contained each of the possible doses that the participant may earn (i.e., 10% to 100% of the sampled dose). Each of the vials contained the appropriate tenth of methamphetamine powder and were mixed with lactose monohydrate powder, N.F. so that all doses consisted of 60 mg of powder, regardless of the weight of methamphetamine.

Data Analysis

Statistical analysis was used to investigate drug effects on progressive-ratio task, subject-rated drug-effects questionnaires, performance tasks, cognitive tasks, and physiological indices. For all statistical analyses, effects with $p \leq .05$ were considered significant.

Progressive ratio. Data from the progressive-ratio task were analyzed using a two-factor repeated-measures analysis of variance (ANOVA). The factors were *d*-Amphetamine (i.e., 0 or 40 mg/day) and Methamphetamine (i.e., 0, 10, 20, and 30 mg). F statistics were used to interpret the ANOVA outcomes. During self-administration sessions, participants determined the amount of drug that they ingested. Thus, varying amounts of drug was administered to participants during the self-administration session. Due to participants ingesting varying amounts of

drug, data from subject-rated drug-effects questionnaires, performance measures, and physiological indices were not statistically analyzed.

Subject-rated drug-effects and physiological indices. Two analyses were conducted to analyze subject-rated drug-effect and physiological data. First, peak-effect data, which is the maximum response reported during data collection for that session, were calculated for each participant. Second, data were analyzed as area-under-the-time-action curve (AUC), which was calculated for each participant using the trapezoidal method. Peak effect and AUC were analyzed in the same fashion as breakpoint data from the progressive ratio task.

Cognitive Performance During Methamphetamine Challenge. Cognitive data collected during experimental sessions were analyzed in the same fashion as the break-point data.

Cognitive Performance During Maintenance. Cognitive data collected from each of the tasks, excluding the N-Back Task, during each of the maintenance conditions were analyzed using a *t*-test to compare placebo and *d*-amphetamine (40 mg/day). For these analyses, the data were averaged across time (i.e., morning and afternoon). The N-Back Task was analyzed using a three-factor repeated-measures ANOVA with *d*-Amphetamine (i.e., 0 or 40 mg/day), Time (i.e., morning or afternoon), and Trial (i.e., one-, two-, or three-back) as factors.

Power Analysis

In a previous study from our laboratory, we assessed cocaine choice during *d*-amphetamine and placebo maintenance (Rush et al., 2010). During *d*-amphetamine maintenance, subjects made significantly fewer choices for 20 mg

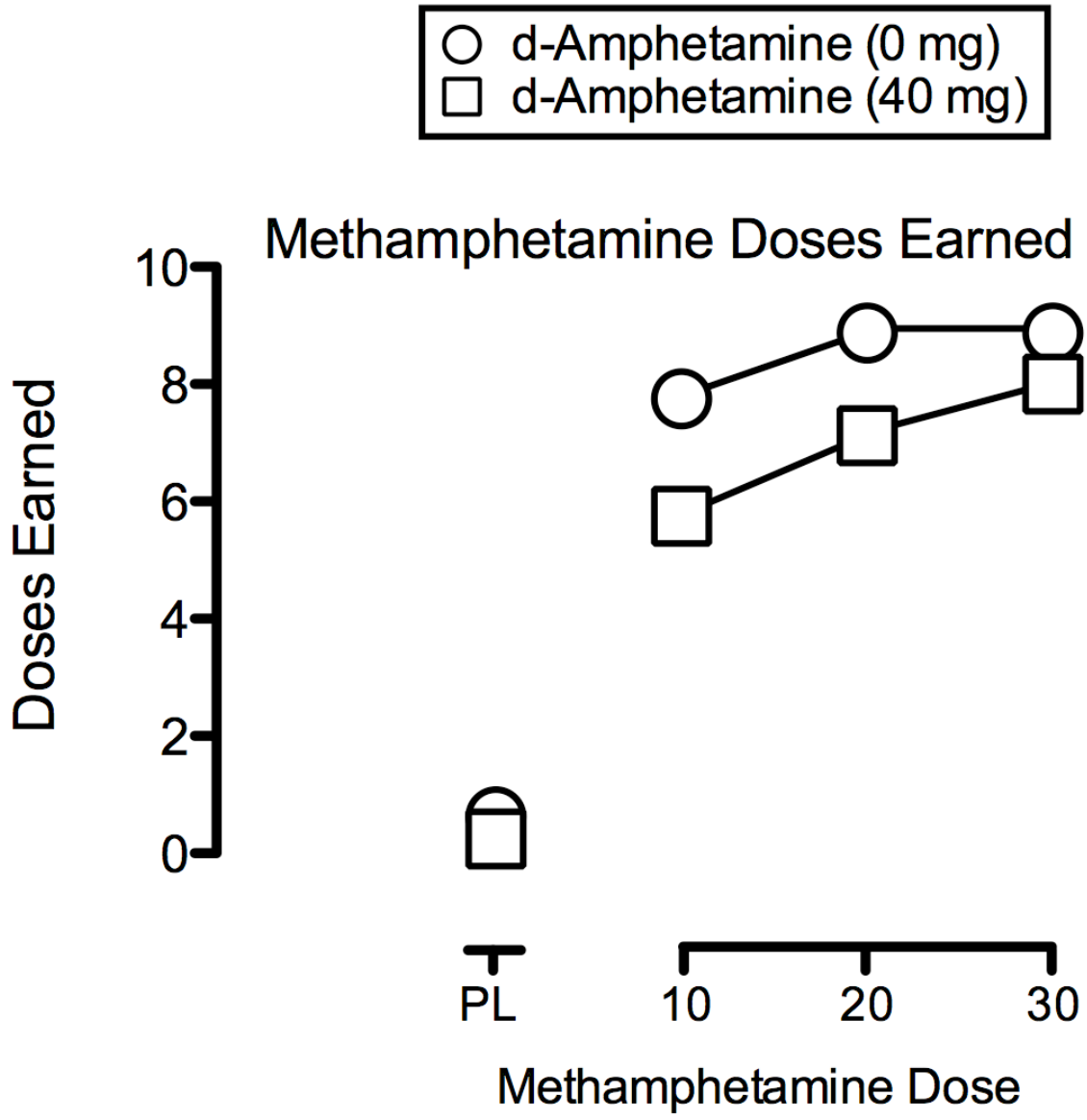
intranasal cocaine relative to placebo maintenance. That study enrolled 9 subjects, which was sufficient to detect the small effect size (f=0.16) for *d*-amphetamine to reduce the reinforcing effects of cocaine. Enrolling a similar number of subjects (n=8) was estimated to provide us with sufficient power to detect a significant effect of *d*-amphetamine on methamphetamine choice, which was the primary outcome variable for this study.

Chapter Five. Results

Methamphetamine Self-Administration During *d*-Amphetamine Maintenance

Progressive-Ratio Responding. ANOVA revealed a significant main effect of methamphetamine on number of doses earned. Methamphetamine dose-dependently increased the number of doses earned regardless of the maintenance condition (Figure 1). There were no other significant effects on number of doses earned.

Figure 1.



Subject-Rated Effects of Methamphetamine During *d*-Amphetamine Maintenance

Adjective Rating Scale

Peak Effect. ANOVA revealed only a main effect of methamphetamine for scores on the Stimulant scale of the Adjective Rating Scale. Methamphetamine increased these scores as function of dose regardless of the maintenance condition. There were no significant effects on the Sedative scale of the Adjective Rating Scale. F-values and means are shown in Tables 3 and 4, respectively.

Table 3. F-values from peak-effect analysis for physiological indices and subject-rated drug-effects measures (Bold indicates a significant F-value**).**

Outcome Measures	*d*-AMPH	METH	METH x *d*-AMPH
Physiological			
Diastolic Pressure	1.8	1.9	0.5
Heart Rate	1.8	1.2	0.6
Mean Arterial Pressure	4.1	**3.4**	0.0
Systolic Pressure	**8.6**	**4.4**	1.1
Temperature	0.8	0.2	0.3
Adjective Rating Scales			
Sedative	2.1	**0.4**	0.4
Stimulated	3.1	**8.9**	1.1
Visual Analog Scales			
Active/Alert/Energetic	1.6	**5.3**	0.7
Any Effects	**7.4**	**10.5**	0.5
Bad Effects	0.4	2.6	0.3
Euphoric	4.6	2.7	2.0
Good Effects	**10.4**	**9.8**	0.6
High	**5.8**	**9.2**	0.3
Irregular Heartbeat	**5.5**	**5.3**	1.8
Like Drug	**13.9**	**9.8**	0.6
Nauseous/Sick to Stomach	4.4	2.3	1.7
Nervous/Anxious	1.8	2.1	0.9
Pay For	**10.7**	**6.2**	0.9
Performance Impaired	2.6	**2.9**	1.9
Performance Improved	3.8	2.0	0.4
Restless	4.2	2.5	1.6
Rush	**13.4**	**5.8**	0.1
Shaky/Jittery	3.8	**3.4**	**3.6**
Sluggish/Fatigued/Lazy	2.3	1.8	1.3
Stimulated	**6.2**	**6.1**	0.5
Talkative/Friendly	2.2	**3.2**	0.6
Willing to Take Again	**5.6**	**9.3**	1.2

Table 4. Peak means for physiological indices and subject-rated drug-effects measures (Means [SEM]).

Peak Outcome Measures	Placebo	*d*-Amphetamine (0 mg) METH 10 mg	METH 20 mg	METH 30 mg
Physiological				
Diastolic Pressure	80.8 (3.7)	83.1 (2.8)	81.5 (1.5)	83.9 (3.4)
Heart Rate	79.2 (3.8)	85.9 (5.0)	83.5 (4.9)	87.0 (3.6)
Mean Arterial Pressure	94.2 (3.3)	99.9(2.1)	98.2 (1.7)	100.8 (2.7)
Systolic Pressure	120.5 (3.7)	133.0 (3.9)	131.5 (1.8)	133.1 (3.9)
Temperature	98.1 (0.2)	98.1 (0.2)	98.0 (0.2)	98.0 (0.1)
Adjective Rating Scale				
Sedative	3.9 (1.3)	4.4 (1.2)	3.4 (1.2)	4.4 (1.6)
Stimulated	6.8 (2.6)	10.9 (1.9)	11.8 (1.8)	14.1 (2.2)
Visual Analog Scale				
Active/Alert/Energetic	7.9 (3.1)	30.1 (11.0)	32.4 (12.3)	37.5 (12.1)
Any Effect	6.1 (3.3)	29.9 (9.8)	34.2 (10.4)	46.2 (9.8)
Bad Effect	2.1 (1.0)	2.6 (1.4)	3.9 (1.8)	5.4 (2.6)
Euphoric	2.0 (0.8)	6.6 (4.0)	5.8 (2.8)	17.8 (8.8)
Good Effect	5.8 (3.2)	30.4 (9.5)	34.1 (10.7)	44.2 (9.7)
High	6.5 (3.3)	29.2 (9.5)	33.0 (10.4)	42.5 (9.8)
Irregular/Racing Heartbeat	2.9 (1.2)	5.9 (2.7)	7.4 (5.6)	22.5 (8.9)
Like Drug	6.8 (2.9)	36.0 (10.4)	39.1 (11.0)	44.8 (10.0)
Nauseous/Sick to Stomach	3.8 (1.4)	8.5 (3.4)	5.0 (2.2)	9.1 (3.7)
Nervous/Anxious	2.6 (1.1)	11.4 (7.7)	4.8 (2.5)	13.6 (6.6)
Pay For	4.6 (2.3)	30.5 (10.9)	31.2 (12.6)	39.2 (12.2)
Performance Impaired	2.4 (1.0)	6.1 (3.0)	5.2 (2.8)	22.4 (11.3)
Performance Improved	6.0 (2.8)	21.2 (11.3)	21.2 (12.5)	19.6 (11.2)
Restless	2.1 (0.7)	7.5 (2.5)	9.4 (4.4)	11.1 (4.0)
Rush	5.0 (2.9)	23.1 (10.0)	28.0 (10.8)	34.0 (11.3)
Shaky/Jittery	2.2 (0.9)	26.1 (11.4)	5.2 (2.6)	21.9 (8.7)
Sluggish/Fatigued/Lazy	4.8 (2.2)	10.4 (6.4)	11.6 (6.6)	11.1 (5.8)
Stimulated	7.1 (3.7)	27.2 (10.0)	28.9 (11.0)	35.8 (10.6)
Talkative/Friendly	13.2 (5.4)	31.4 (11.8)	30.5 (12.5)	38.8 (12.9)
Willing to Take Again	6.2 (2.8)	45.0 (13.0)	47.0 (13.6)	53.1 (12.1)

Table 4 (continued). Peak means for physiological indices and subject-rated drug effects measures (Means [SEM]).

Peak Outcome Measures		*d*-Amphetamine (40 mg)		
	METH 0 mg	METH 10 mg	METH 20 mg	METH 30 mg
Physiological				
Diastolic Pressure	75.4 (3.6)	82.5 (2.0)	80.6 (2.0)	81.8 (2.5)
Heart Rate	86.9 (3.2)	88.0 (4.3)	84.0 (3.1)	88.4 (4.1)
Mean Arterial Pressure	91.1 (2.6)	97. 0 (1.7)	95.8 (2.1)	97.9 (2.2)
Systolic Pressure	119.6 (2.1)	125.1 (3.1)	125.0 (2.3)	128.0 (2.4)
Temperature	97.9 (0.2)	98.0 (0.2)	98.0 (0.1)	97.9 (0.2)
Adjective Rating Scale				
Sedative	2.1 (0.6)	3.0 (0.9)	3.2 (1.1)	4.0 (1.2)
Stimulated	6.2 (1.8)	9.2 (2.0)	9.8 (1.8)	10.2 (1.9)
Visual Analog Scale				
Active/Alert/Energetic	11.5 (7.3)	22.4 (11.3)	29.4 (9.0)	31.2 (9.5)
Any Effect	3.8 (1.4)	20.1 (11.4)	26.9 (7.0)	33.8 (7.0)
Bad Effect	1.9 (1.0)	2.8 (1.4)	2.9 (1.2)	4.6 (2.1)
Euphoric	2.1 (1.0)	4.2 (2.7)	5.8 (3.7)	7.5 (4.2)
Good Effect	3.8 (1.5)	18.4 (11.7)	25.8 (7.4)	34.5 (7.6)
High	4.1 (1.6)	20.8 (11.5)	27.9 (7.3)	33.5 (7.3)
Irregular/Racing Heartbeat	1.9 (0.7)	3.5 (1.5)	4.1 (1.7)	6.9 (2.9)
Like Drug	3.5 (1.3)	21.2 (11.2)	29.2 (8.7)	35.2 (7.9)
Nauseous/Sick to Stomach	2.4 (0.9)	4.2 (2.0)	4.6 (2.5)	5.6 (2.2)
Nervous/Anxious	2.6 (1.2)	5.2 (2.6)	4.0 (2.5)	7.6 (4.1)
Pay For	3.2 (1.4)	18.2 (11.2)	27.1 (9.0)	30.0 (9.3)
Performance Impaired	2.2 (1.3)	3.1 (1.2)	5.0 (2.8)	5.1 (2.2)
Performance Improved	2.6 (1.2)	13.8 (10.9)	14.8 (8.1)	15.6 (9.2)
Restless	3.5 (1.6)	4.2 (1.4)	6.6 (3.2)	7.8 (3.1)
Rush	1.6 (0.8)	16.0 (12.0)	20.8 (8.3)	28.4 (9.6)
Shaky/Jittery	2.9 (1.2)	5.0 (2.3)	7.6 (3.9)	8.5 (4.1)
Sluggish/Fatigued/Lazy	6.8 (4.2)	3.2 (1.3)	9.8 (5.7)	7.6 (3.8)
Stimulated	3.6 (1.6)	17.5 (10.8)	25.0 (7.9)	26.6 (8.6)
Talkative/Friendly	11.8 (7.8)	23.6 (12.8)	27.2 (10.0)	27.6 (10.2)
Willing to Take Again	4.0 (1.8)	22.0 (11.6)	28.8 (9.2)	42.8 (11.8)

Area-Under-the-Time-Action Curve. Analyses of area-under-the-time-action curve data revealed a pattern of effects similar to those observed with analysis of peak effect data. F-values and means and for these analyses are shown in Tables 5 and 6.

Table 5. F-values from area-under-the-time-action curve analysis for physiological indices and subject-rated drug-effects measures (Bold indicates a significant F-value).

Outcome Measures	*d*-AMPH	METH	METH x *d*-AMPH
Physiological			
Diastolic Pressure	0.9	0.4	0.3
Heart Rate	0.9	0.4	0.3
Mean Arterial Pressure	**6.0**	**5.1**	0.2
Systolic Pressure	**12.4**	**7.7**	0.5
Temperature	0.1	0.3	0.7
Adjective Rating Scale			
Sedative	2.0	0.3	0.1
Stimulated	3.4	**10.5**	2.9
Visual Analog Scale			
Active/Alert/Energetic	**5.5**	**5.0**	0.2
Any Effects	**16.9**	**7.8**	1.0
Bad Effects	0.5	2.5	0.3
Euphoric	4.5	2.6	2.4
Good Effects	**21.9**	**7.4**	0.8
High	**11.3**	**7.0**	0.7
Irregular/Racing Heartbeat	**7.0**	**7.5**	1.8
Like Drug	**17.3**	**7.2**	0.6
Nauseous/Sick to Stomach	4.2	2.3	0.8
Nervous/Anxious	1.6	2.0	2.1
Pay For	**9.4**	**4.9**	0.7
Performance Impaired	2.2	**3.6**	2.0
Performance Improved	3.2	2.0	0.2
Restless	**6.2**	2.4	1.4
Rush	**9.9**	**3.9**	0.1
Shaky/Jittery	2.2	**3.1**	3.6
Sluggish/Fatigued/Lazy	2.2	1.9	1.2
Stimulated	**7.7**	**4.7**	0.1
Talkative/Friendly	**6.8**	**3.5**	0.6
Willing to Take Again	**12.3**	**7.9**	0.8

Table 6. Means for area-under-the-time-action curve for physiological indices and subject-rated drug-effect measures (Means [SEM]).

AUC Outcome Measures	Placebo	*d*-Amphetamine (0 mg) METH 10 mg	METH 20 mg	METH 30 mg
Physiological				
Diastolic Pressure	75.9 (3.9)	77.1 (3.2)	77.9 (4.3)	79.5 (3.1)
Heart Rate	75.9 (3.9)	77.1 (3.2)	77.9 (4.3)	79.5 (3.1)
Mean Arterial Pressure	90.1 (2.8)	9.8 (1.9)	94.0 (1.4)	97.0 (2.9)
Systolic Pressure	115.8 (2.9)	123.0 (2.8)	125.5 (2.1)	128.0 (3.2)
Temperature	97.8 (0.2)	97.7 (0.2)	97.7 (0.2)	97.8 (0.1)
Adjective Rating Scale				
Sedative	2.7 (0.8)	3.2 (0.9)	2.7 (0.9)	3.2 (1.2)
Stimulated	5.5 (2.0)	8.8 (1.5)	10.0 (2.0)	12.2 (1.9)
Visual Analog Scale				
Active/Alert/Energetic	6.1 (2.8)	22.2 (8.6)	25.9 (10.9)	30.3 (10.1)
Any Effects	4.2 (2.5)	19.2 (6.5)	23.6 (8.9)	33.6 (8.1)
Bad Effects	1.3 (0.6)	2.0 (1.1)	2.5 (1.3)	3.3 (1.5)
Euphoric	1.3 (0.5)	4.1 (2.6)	4.0 (2.2)	10.0 (5.1)
Good Effects	3.9 (2.2)	18.1 (6.7)	23.5 (9.1)	33.2 (7.7)
High	4.1 (2.5)	19.1 (6.8)	23.6 (9.0)	32.0 (8.4)
Irregular/Racing Heartbeat	1.7 (0.7)	4.2 (2.0)	5.1 (2.5)	10.7 (3.3)
Like Drug	3.9 (2.2)	22.9 (7.9)	28.4 (10.4)	34.7 (8.3)
Nauseous/Sick to Stomach	2.0 (0.8)	4.5 (1.6)	3.6 (1.7)	6.2 (3.0)
Nervous/Anxious	1.6 (0.6)	4.2 (2.3)	3.2 (1.7)	10.0 (5.7)
Pay For	2.4 (1.2)	21.6 (8.5)	25.6 (11.3)	30.6 (9.6)
Performance Impaired	1.5 (0.7)	3.6 (1.9)	3.1 (1.7)	6.9 (2.8)
Performance Improved	4.0 (2.0)	14.6 (8.2)	17.1 (10.7)	14.1 (8.1)
Restless	1.5 (0.6)	4.8 (1.8)	6.4 (3.3)	6.9 (2.4)
Rush	3.9 (2.5)	15.3 (7.4)	19.4 (9.8)	23.3 (7.9)
Shaky/Jittery	1.5 (0.6)	7.9 (4.0)	3.4 (2.0)	13.5 (6.3)
Sluggish/Fatigued/Lazy	3.3 (1.8)	8.6 (5.7)	7.8 (4.6)	8.2 (4.5)
Stimulated	4.4 (2.5)	16.8 (7.3)	22.3 (9.6)	22.8 (7.1)
Take Again	3.7 (2.1)	27.8 (8.4)	33.3 (10.5)	39.4 (9.2)
Talkative/Friendly	7.1 (3.0)	22.5 (9.6)	25.6 (11.4)	29.7 (10.7)

Table 6 (continued). Means for area-under-the-time-action curve for physiological indices and subject-rated drug-effect measures (Means [SEM]).

AUC Outcome Measures	Placebo	*d*-Amphetamine (0 mg) METH 10 mg	METH 20 mg	METH 30 mg
Physiological				
Diastolic Pressure	80.5 (3.2)	80.5 (3.5)	78.3 (3.2)	81.2 (3.8)
Heart Rate	80.5 (3.2)	80.5 (3.5)	78.3 (3.2)	81.2 (3.8)
Mean Arterial Pressure	86.6 (2.6)	91.8 (2.1)	91.0 (1.8)	92.7 (2.2)
Systolic Pressure	112.8 (2.4)	120.0 (3.2)	119.7 (2.0)	121.4 (2.2)
Temperature	97.7 (0.2)	97.6 (0.2)	97.9 (0.2)	97.6 (0.2)
Adjective Rating Scale				
Sedative	1.8 (0.5)	2.4 (0.9)	2.5 (0.8)	2.8 (0.6)
Stimulated	6.0 (1.7)	7.6 (2.0)	8.5 (1.9)	8.2 (1.8)
Visual Analog Scale				
Active/Alert/Energetic	3.9 (1.7)	18.0 (10.1)	21.9 (8.3)	22.8 (8.3)
Any Effects	2.4 (1.0)	13.6 (9.1)	17.0 (6.4)	21.4 (6.4)
Bad Effects	1.2 (0.6)	1.8 (0.9)	1.9 (0.8)	3.1 (1.5)
Euphoric	1.4 (0.7)	2.8 (1.7)	3.4 (2.4)	3.6 (2.2)
Good Effects	2.5 (1.0)	13.5 (10.2)	18.0 (6.6)	22.7 (6.7)
High	2.6 (1.1)	14.8 (10.0)	18.3 (6.4)	21.0 (6.5)
Irregular/Racing Heartbeat	1.2 (0.5)	2.0 (0.8)	2.6 (1.0)	4.4 (1.7)
Like Drug	2.4 (1.0)	15.9 (10.0)	21.1 (8.0)	24.2 (7.2)
Nauseous/Sick to Stomach	1.4 (0.5)	2.5 (1.3)	3.0 (1.5)	3.9 (1.6)
Nervous/Anxious	2.0 (0.9)	2.5 (1.1)	2.8 (1.7)	4.6 (2.1)
Pay For	2.2 (0.9)	13.4 (10.0)	21.0 (8.8)	21.2 (8.0)
Performance Impaired	1.4 (0.7)	1.9 (0.8)	3.0 (1.7)	3.2 (1.4)
Performance Improved	1.3 (0.6)	11.9 (10.1)	12.1 (7.2)	12.1 (8.0)
Restless	2.4 (1.1)	2.5 (0.8)	3.9 (1.7)	4.5 (1.5)
Rush	1.1 (0.5)	12.9 (10.3)	14.3 (6.4)	18.2 (7.6)
Shaky/Jittery	2.2 (1.0)	2.9 (1.3)*	3.7 (1.9)	5.0 (2.4)
Sluggish/Fatigued/Lazy	2.6 (1.4)	2.2 (0.9)	7.5 (5.0)	5.1 (2.8)
Stimulated	2.4 (1.2)	10.9 (7.0)	17.8 (6.7)	18.2 (7.4)
Take Again	2.2 (1.0)	18.0 (10.4)	21.8 (8.8)	29.7 (8.6)
Talkative/Friendly	5.8 (3.0)	18.7 (10.9)	20.7 (9.2)	20.6 (9.0)

Visual Analog Scales

Peak Effect. ANOVA revealed a significant interaction of methamphetamine and *d*-amphetamine for ratings of *Shaky or Jittery* (Table 3). This interaction was attributable to 10 and 30 mg methamphetamine increasing these ratings above placebo levels during placebo maintenance but not during *d*-amphetamine maintenance (Table 4).

ANOVA revealed a main effect of methamphetamine and *d*-amphetamine, but not an interaction of these factors, for ratings of *Any Effect*, *Good Effects*, *High*, *Like Drug*, *Pay For*, *Rush*, *Stimulated*, *Talkative or Friendly* and *Willing to Take Again*. Methamphetamine generally increased these ratings as a function of dose during both placebo and *d*-amphetamine maintenance. However, these ratings were lower during *d*-amphetamine maintenance relative to placebo maintenance. F-values and means are shown in Tables 3 and 4, respectively. Figures 2 and 3 show data for two of these measures, ratings of *Like Drug* and *Willing to Take Again*, respectively.

ANOVA revealed only a main effect of methamphetamine for ratings of *Active, Alert, Energetic*; *Irregular or Racing Heartbeat*; and *Talkative or Friendly*. Methamphetamine increased these ratings as function of dose regardless of the maintenance condition. F-values and means are shown in Tables 3 and 4, respectively.

Figure 2.

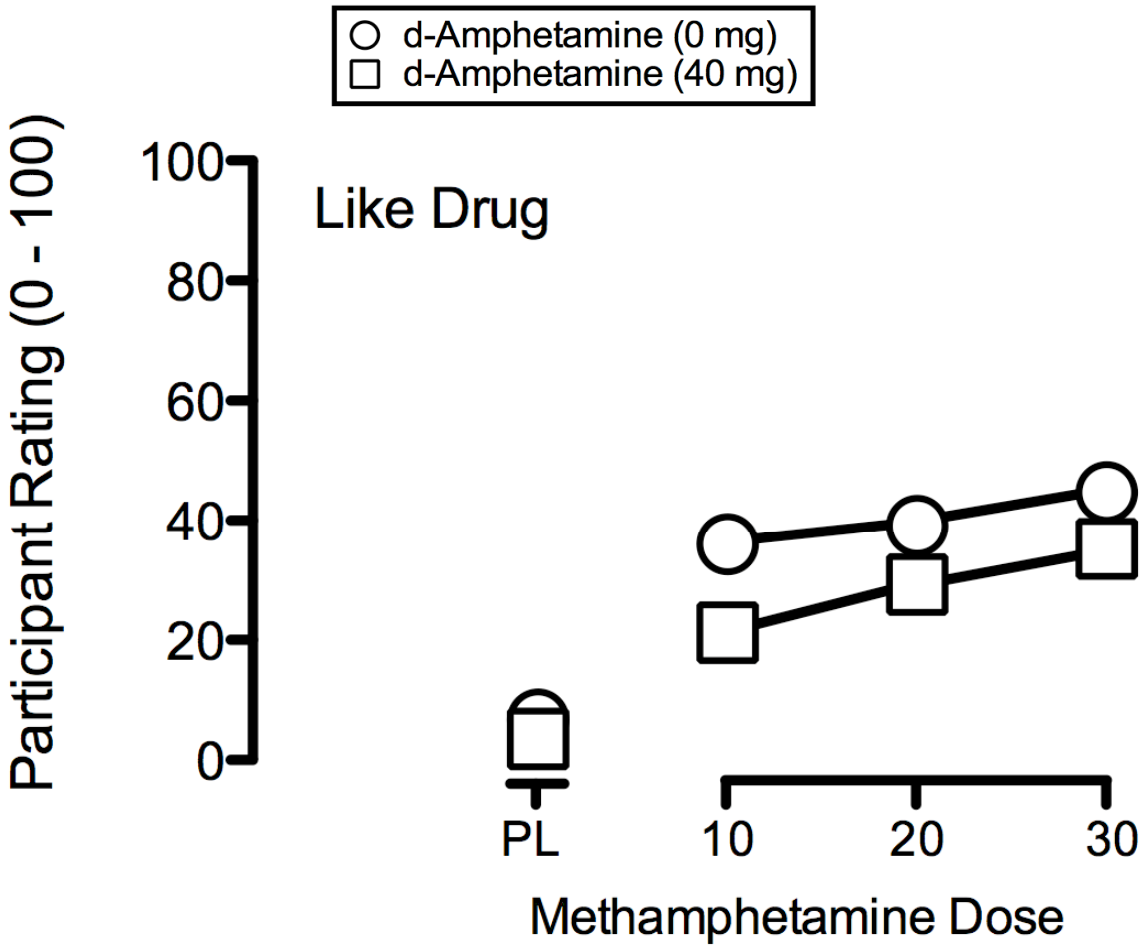
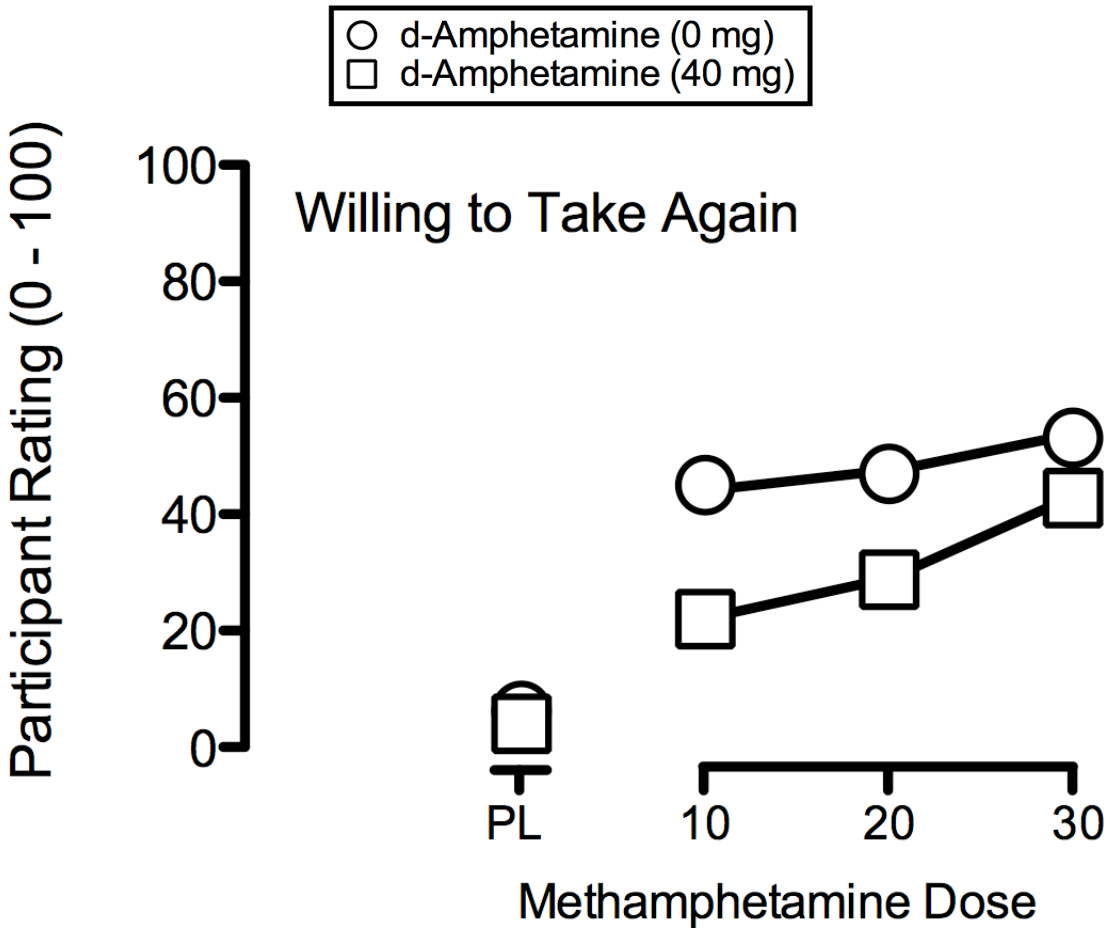


Figure 3.



Area-Under-the-Time-Action Curve. Analyses of area-under-the-time-action curve data revealed a pattern of effects similar to those observed with analysis of peak effect data. F-values and means and for these analyses are shown in Tables 5 and 6, respectively.

Cognitive Effects of Methamphetamine During *d*-Amphetamine Maintenance

Cued Go/No-Go Task. ANOVA revealed a significant interaction of methamphetamine and *d*-amphetamine for inhibitory failures to a no-go target following a no-go cue on the Cued Go/No-Go task (Table 7). This interaction was due to the methamphetamine having little effect during placebo maintenance, but dose-dependently increasing inhibitory failures during *d*-amphetamine maintenance (Table 8; Figure 4). There were no significant effects on inhibitory failures for a no-go target following a go cue or on reaction time to go targets following either go or no-go targets.

Table 7. F-values of cognitive tasks after methamphetamine administration (Bold indicates a significant F-value).

Outcome Measures	*d*-AMPH Dose	METH Dose	METH x *d*-AMPH
Visual Probe Task			
Reaction Time Cocaine	0.0	0.4	0.0
Reaction Time Neutral	0.0	0.6	0.6
Attention Bias Score	0.0	0.0	1.7
Cued Go/No-Go Task			
Reaction Time			
Go Cue	0.4	1.9	0.6
No Go Cue	2.7	2.1	1.3
Inhibitory Failures			
Go Cue	0.8	0.5	0.7
No Go Cue	1.6	1.3	**3.2**
Balloon Analog Risk Task			
Percent Exploded	0.6	0.9	1.8

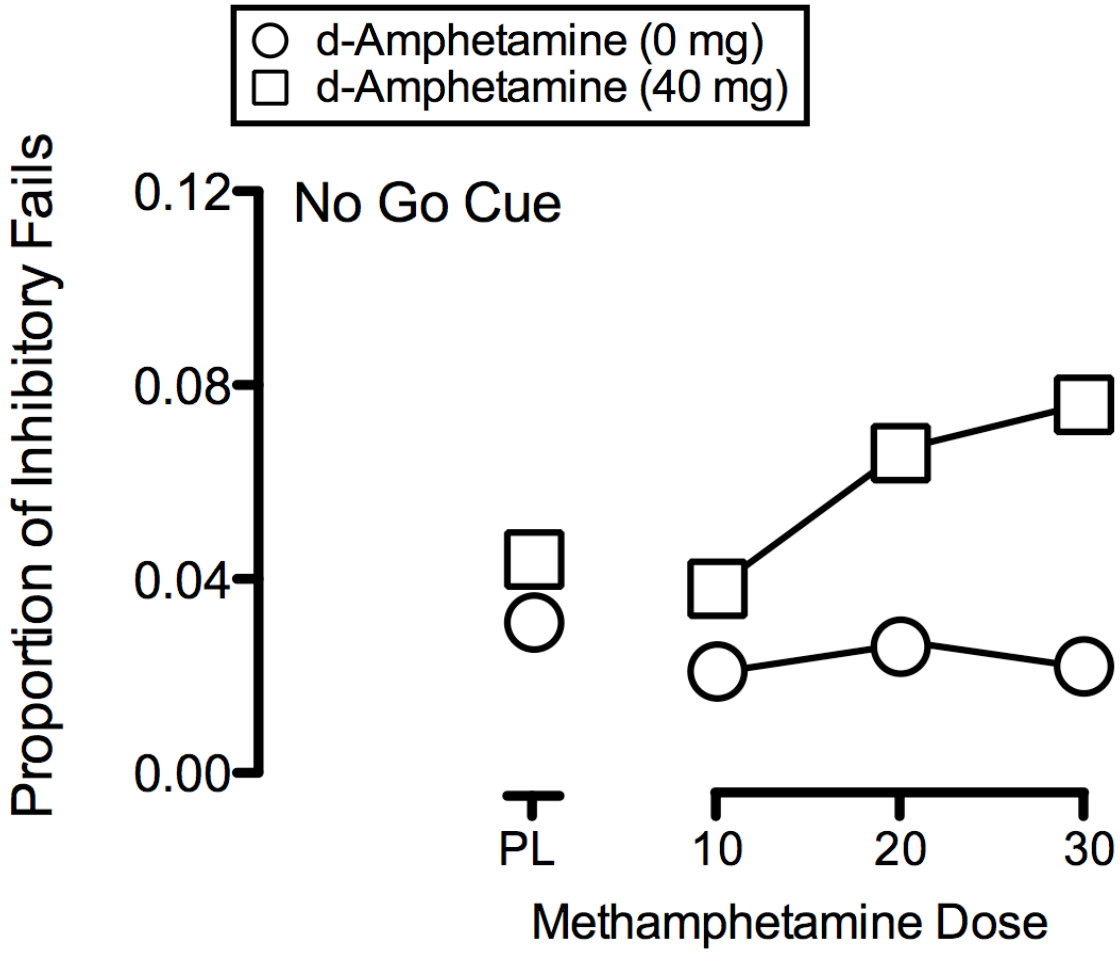
Table 8. Means of cognitive tasks after methamphetamine administration (Means [SEM]).

Outcome Measures	Placebo	*d*-Amphetamine (0 mg) METH 10 mg	METH 20 mg	METH 30 mg
Visual Probe Task				
Reaction Time Cocaine	396.6 (32.5)	391.6 (26.3)	378.5 (25.0)	392.1 (29.5)
Reaction Time Neutral	406.6 (33.4)	393.6 (28.2)	397.4 (31.4)	402.8 (26.9)
Attention Bias Score	10.0 (11.6)	2.0 (6.1)	18.9 (7.7)	10.6 (12.7)
Cued Go/No-Go Task				
Reaction Time				
Go Cue	291.8 (16.0)	285.6 (12.6)	280.0 (6.5)	285.6 (9.4)
No Go Cue	328.4 (17.4)	326.9 (13.2)	326.5 (14.9)	322.2 (12.8)
Inhibitory Failures				
Go Cue	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)
No Go Cue	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Balloon Analog Risk Task				
Percent Exploded	0.4 (0.0)	0.3 (0.0)	0.4 (0.0)	0.3 (0.0)

Table 8 (continued). Means of cognitive tasks after methamphetamine administration (Means [SEM]).

Outcome Measures	*d*-Amphetamine (40 mg)			
	METH 0 mg	**METH 10 mg**	**METH 20 mg**	**METH 30 mg**
Visual Probe Task				
Reaction Time Cocaine	393.5 (30.2)	388.0 (20.3)	382.4 (22.7)	389.9 (30.1)
Reaction Time Neutral	403.2 (31.0)	408.9 (18.3)	381.0 (23.9)	399.7 (30.6)
Attention Bias Score	9.7 (6.3)	20.9 (9.1)	-1.3 (6.2)	9.8 (5.9)
Cued Go/No-Go Task				
Reaction Time				
Go Cue	299.3 (20.7)	284.4 (10.5)	274.9 (8.1)	274.7 (5.1)
No Go Cue	337.8 (22.8)	314.0 (16.1)	312.9 (16.3)	311.6 (13.4)
Inhibitory Failures				
Go Cue	0.2 (0.1)	0.2 (0.0)	0.2 (0.0)	0.2 (0.1)
No Go Cue	0.0 (0.0)	0.0 (0.0)	0.1 (0.0)	0.1 (0.0)
Balloon Analog Risk Task				
Percent Exploded	0.3 (0.0)	0.3 (0.0)	0.3 (0.0)	0.3 (0.0)

Figure 4.



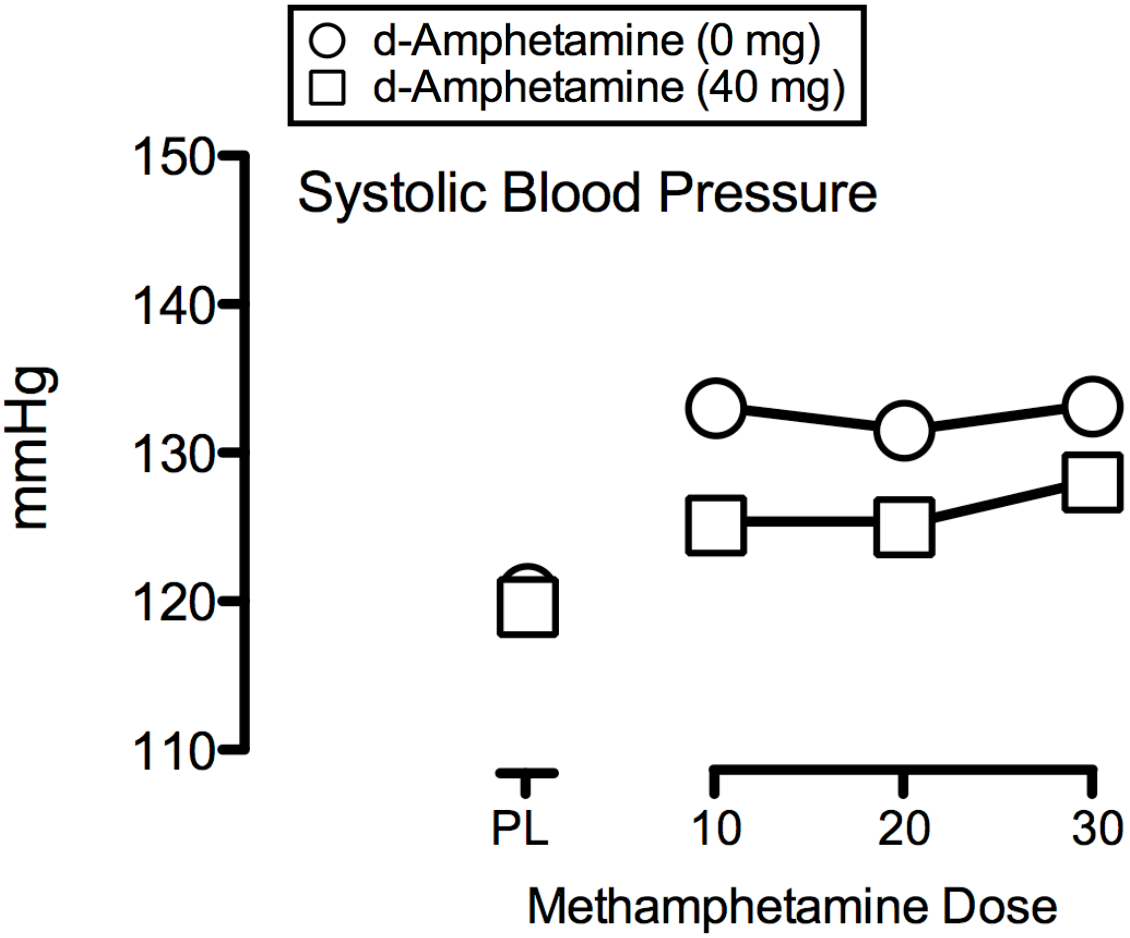
Visual Probe Task. There were no significant effects on the Visual Probe task. F-values and means for this task after the administration of methamphetamine are shown in Tables 7 and 8, respectively.

Balloon Analog Risk Task (BART). There were no significant effects on the BART. F-values and means for this task after the administration of methamphetamine are shown in Tables 7 and 8, respectively.

Physiological Effects of Methamphetamine During *d*-Amphetamine Maintenance

Peak Effect. ANOVA revealed a main effect of methamphetamine and *d*-amphetamine, but not an interaction of these factors, for systolic blood pressure (Figure 5). Methamphetamine generally increased systolic blood pressure as a function of dose during placebo and d-amphetamine maintenance. The pressure-increasing effects of methamphetamine on systolic blood pressure were attenuated during *d*-amphetamine maintenance relative to placebo maintenance. There were no significant effects on heart rate, diastolic pressure of body temperature. F-values and means are shown in Tables 3 and 4, respectively.

Figure 5.



Area-under-the-time-action curve (AUC). Analyses of area-under-the-time-action curve data revealed a pattern of effects similar to those observed with analysis of peak effect data. F-values and means and for these analyses are shown in Tables 5 and 6, respectively.

Cognitive Effects of *d*-Amphetamine and Placebo Maintenance

Visual Probe Task. *d*-Amphetamine maintenance did not significantly affect of the measures on the Visual Probe Task. T-values and means and for these analyses are shown in Tables 9 and 10, respectively.

Table 9. T-values of cognitive tasks during maintenance days (Bold indicates a significant t-value).

Outcome Measure	T-Value
Visual Probe Task	
Reaction Time Cocaine	1.0
Reaction Time Neutral	0.5
Attention Bias Score	1.0
Cocaine Stroop	
Reaction Time Cocaine	0.0
Reaction Time Neutral	2.1
Attention Bias Score	1.2
Cued Go/No-Go Task	
Reaction Time	
Go Cue	1.2
No Go Cue	**3.6**
Inhibitory Failures	
Go Cue	0.0
No Go Cue	1.1
Balloon Analog Risk Task	
Percent Exploded	0.5
Digit Symbol Substitution Task	
Trials Completed	0.0
Trails Correct	0.9

Table 10. Means of cognitive tasks during maintenance days (Means [SEM]).

Outcome Measure	*d*-AMPH (0 mg) AM	*d*-AMPH (0 mg) PM	*d*-AMPH (40 mg) AM	*d*-AMPH (40 mg) PM
Visual Probe Task				
Reaction Time Cocaine	396.9 (23.9)	385.1 (22.6)	382.9 (26.7)	380.0 (33.5)
Reaction Time Neutral	401.4 (26.0)	385.2 (22.2)	390.9 (27.9)	386.6 (29.2)
Attention Bias Score	4.5 (7.2)	0.1 (4.1)	8.0 (6.2)	6.5 (6.4)
Cocaine Stroop				
Reaction Time Cocaine	761.9 (41.4)	751.2 (39.6)	751.8 (43.7)	760.7 (43.0)
Reaction Time Neutral	770.3 (40.8)	745.6 (39.6)	733.4 (37.6)	732.2 (38.2)
Attention Bias Score	-8.4 (17.8)	5.6 (7.5)	18.4 (19.1)	28.5 (12.6)
Cued Go/No-Go Task				
Reaction Time				
Go Cue	295.5 (11.8)	285.2 (9.3)	287.6 (9.8)	282.3 (8.2)
No Go Cue	324.2 (12.6)	324.7 (12.4)	304.8 (13.0)	308.6 (13.4)
Inhibitory Failures				
Go Cue	0.1 (0.0)	0.2 (0.1)	0.1 (0.0)	0.2 (0.0)
No Go Cue	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Balloon Analog Risk Task				
Percent Exploded	0.3 (0.1)	0.3 (0.0)	0.2 (0.0)	0.3 (0.0)
Digit Symbol Substitution Task				
Trials Completed	44.8 (3.2)	46.9 (3.2)	45.2 (3.7)	46.4 (3.7)
Trails Correct	42.0 (3.2)	43.5 (2.8)	40.2 (4.1)	40.4 (6.3)

Cocaine Stroop Task. *d*-Amphetamine maintenance did not significantly affect any of the measures on the Cocaine Stroop Task. T-values and means and for these analyses are shown in Tables 9 and 10, respectively.

Cued Go/No Go Task. *d*-Amphetamine maintenance did not significantly affect inhibitory failures to a no-go target following a no-go cue on the Cued Go/No-Go task nor did *d*-amphetamine significantly affect inhibitory failures to a no-go target following a go cue on the Cued Go/No-Go task. *d*-Amphetamine maintenance decreased reaction time to a go target following a no-go cue. *d*-Amphetamine maintenance did not affect reaction time to a go target following a go cue. T-values and means and for these analyses are shown in Tables 9 and 10, respectively.

Balloon Analog Risk Task (BART). *d*-Amphetamine maintenance did not significantly affect the percent of balloons exploded. T-values and means and for these analyses are shown in Tables 9 and 10, respectively.

Digit-Symbol-Substitution Task (DSST). *d*-Amphetamine maintenance did not significantly affect the number of trials completed and trials correct. T-values and means and for these analyses are shown in Tables 11 and 12, respectively.

Grooved Pegboard Task. *d*-Amphetamine maintenance did not significantly affect performance on the Grooved Pegboard Task. F-values and means and for these analyses are shown in Tables 11 and 12, respectively.

Table 11. F-values for grooved pegboard during maintenance days (Bold indicates a significant F-value).

Outcome Measure	*d*-AMPH	Time	Replication	*d*-AMPH x Time	*d*-AMPH x Replication	Time x Replication	*d*-AMPH x Time x Replication
Grooved Pegboard	4.2	**11.1**	**12.5**	0.3	2.7	0.8	0.4

Table 12. Means of grooved pegboard during maintenance days (Means [SEM]).

	***d*-AMPH (0 mg) Maintenance**		***d*-AMPH (40 mg) Maintenance**	
Trial Number	**AM**	**PM**	**AM**	**PM**
One	91.4 (2.8)	86.7 (2.7)	93.5 (2.9)	92.1 (2.6)
Two	86.8 (2.0)	84.9 (2.3)	87.3 (3.0)	85.4 (2.2)

N-Back Task. *d*-Amphetamine maintenance did not significantly affect performance on the N-Back Task. F-values and means and for these analyses are shown in Tables 13 and 14, respectively.

Table 13. F-values for N-Back Task during maintenance days (Bold indicates a significant F-value).

Outcome Measure	Number Back	*d*-AMPH	Time	Back x *d*-AMPH	Back x Time	*d*-AMPH x Time	Back x *d*-AMPH x Time
N-Back							
Accuracy							
Target	3.0	2.1	0.3	0.3	3.1	0.0	0.1
Non-Target	0.4	0.5	0.5	0.5	0.5	0.5	0.1
Reaction Time							
Target	1.64	1.59	0.03	2.22	2.09	**5.20**	4.56
Non-Target	3.1	0.0	0.1	0.2	0.0	2.1	2.2

Table 14. Means of N-Back Task during maintenance days (Means [SEM]).

	d-AMPH (0 mg)		*d*-AMPH (40 mg)	
N-Back	**AM**	**PM**	**AM**	**PM**
One Back				
Accuracy				
Target	1.0 (0.0)	0.9 (0.1)	0.8 (0.1)	0.7 (0.1)
Non-Target	0.8 (0.1)	0.9 (0.0)	0.8 (0.1)	0.8 (0.1)
Reaction Time				
Target	643.8 (63.8)	637.0 (58.5)	646.1 (68.6)	669.7 (71.9)
Non-Target	569.8 (98.2)	563.4 (70.2)	589.0 (77.2)	575.9 (73.0)
Two Back				
Accuracy				
Target	0.8 (0.1)	0.9 (0.0)	0.7 (0.1)	0.8 (0.1)
Non-Target	0.9 (0.0)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)
Reaction Time				
Target	838.6 (113.0)	762.0 (96.9)	653.1 (99.0)	777.7 (117.7)
Non-Target	768.4 (143.7)	661.8 (65.3)	683.2 (106.0)	750.7 (105.8)
Three Back				
Accuracy				
Target	0.7 (0.1)	0.8 (0.1)	0.6 (0.1)	0.7 (0.1)
Non-Target	0.9 (0.0)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)
Reaction Time				
Target	847.9 (146.3)	688.4 (95.6)	718.9 (138.8)	787.6 (130.7)
Non-Target	787.1 (116.9)	666.0 (70.4)	662.7 (104.7)	761.6 (113.3)

Chapter Six. Discussion

Overall, methamphetamine acted as a reinforcer and was self-administered significantly more than placebo regardless of maintenance condition. *d*-Amphetamine maintenance attenuated some of the subject-rated drug-effects of methamphetamine. There were generally no significant differences after placebo or methamphetamine administration on the cognitive battery during placebo and *d*-amphetamine maintenance. Methamphetamine was safe and well-tolerated during both placebo and *d*-amphetamine maintenance. Below is a discussion of these findings as they pertain to the current literature.

Behavioral

Intranasal methamphetamine was self-administered by participants more than placebo. This was shown across the range of doses with participants earning between eight and nine of the ten possible drug choices. This is consistent with previous research that has shown that intranasal methamphetamine functions as a robust reinforcer (Kirkpatrick, et al., 2011). Intranasal dosing was selected as the route of administration as it produces robust reinforcing effects.

However, *d*-amphetamine maintenance did not significantly reduce self-administration of methamphetamine. This result is similar to the results of two recent clinical trials that showed *d*-amphetamine treatment did not reduce methamphetamine use significantly compared to placebo (Galloway, et al., 2011, Longo, et al., 2009). However, these findings are inconsistent with results of another clinical trial that showed that *d*-amphetamine pretreatment reduced illicit use of amphetamine (Moeller, Schmitz, Herin, & Kjome, 2008). Similar to this

clinical trial, the data from the present study shows a clear trend of a downward shift in self-administration during *d*-amphetamine maintenance, however this decrease was not statistically significant. This suggests that it may be that a higher dose would be necessary to show a significant decrease in self-administration. However, the higher doses, up to 110 mg/day have been tested in previous studies and did not significantly reduced methamphetamine self-administration compared to placebo (Galloway, et al., 2011, Longo, et al., 2009), which suggests that the lack of a reduction of self-administration of methamphetamine during *d*-amphetamine maintenance may not be solely due to the dose tested. Overall, the concordance between the self-administration data and results of clinical trials shows that self-administration has predictive validity for outcomes that have been observed in clinical trials.

Methamphetamine administered alone dose dependently increased positive subject-rated drug-effects (e.g., Like Drug; Willing to Take Again). This is consistent with previous literature that shows methamphetamine increases ratings of positive subject-rated drug-effects (Hart, et al., 2008; Hart, et al., 2011; Lile, Stoops, Glaser, Hays, & Rush, 2011; Perez, et al., 2008; Rush, Stoops, Lile, Glaser, & Hays, 2011; Rush, Stoops, Lile, Glaser, & Hays, 2011; Sevak, et al., 2011; Stoops, 2006). *d*-Amphetamine maintenance attenuated some of the positive subject-rated drug-effects. The reduction of subject-rated drug-effects of methamphetamine during *d*-amphetamine maintenance is consistent with a previous study that showed 45 mg/day *d*-amphetamine reduced the subject-rated drug-effects of methamphetamine (Rush, Stoops, Lile, Glaser, & Hays, 2011).

The positive results of *d*-amphetamine to reduce subject-rated drug-effects of methamphetamine suggest that subject-rated drug-effects have poor predictive validity to model results observed in the clinic, producing false positives. Other medications have reduced the subject-rated drug-effects of stimulants, but were not effective clinically. Representative medications that have decreased subject-rated drug-effects, but failed to decrease drug use in the clinic include risperidone (Grabowski, et al., 2000; Meredith, et al., 2009; Wachtel, Ortengren, & de Wit, 2002) and aripiprazole (Sevak, et al., 2011; Stoops, 2006; Tiihonen, et al., 2007).

While the data from the current study combined with the findings of recent clinical trials (Galloway, et al., 2011, Longo, et al., 2009) suggest that *d*-amphetamine may not be a viable pharmacotherapy for methamphetamine dependence, translational literature from studies testing agonist replacement for the treatment of cocaine suggest that a different agonist medication may be found that is an effective treatment (reviewed in: Herin, Rush, & Grabowski, 2010; Moeller, Schmitz, Herin, & Kjome, 2008). Preclinical studies with rats and rhesus monkeys have shown that maintenance with *d*-amphetamine decreases cocaine self-administration (Chiodo, Läck, Roberts, 2008; Chiodo & Roberts, 2009; Czoty, Gould, Martelle, & Nader, 2011; Czoty, Martelle, & Nader, 2010; Foltin & Evans, 1998; Negus & Mello, 2003a; Negus & Mello, 2003b; Peltier, Li, Lytle, Taylor, & Emmett-Oglesby, 1996). Human laboratory studies with healthy non-treatment seeking cocaine users have shown that maintenance on *d*-amphetamine reduced some of the positive subjective effects of intranasal

cocaine and decreased self-administration of 20 mg of cocaine (Rush, Stoops, & Hays, 2009; Rush, Stoops, Sevak, & Hays, 2010). Finally, clinical trials have shown positive results using *d*-amphetamine as a potential treatment for cocaine dependence (Grabowski, et al., 2001; Grabowski, et al., 2004; Shearer, Wodak, van Beek, Mattick, & Lewis, 2003).

Cognitive

Effects of d-Amphetamine and Placebo Maintenance. Generally there were not significant differences in performance on the cognitive battery between *d*-amphetamine and placebo maintenance. The only difference observed was that during *d*-amphetamine maintenance participants were quicker to respond to a go target following a no-go cue on the cued go/no-go task. As *d*-amphetamine is used to treat psychiatric disorders with deficits that have been proposed to be found in chronic stimulant abusers, the lack of difference in performance between maintenance conditions suggests that there may not be deficits present.

Effects of Methamphetamine during d-amphetamine maintenance. Generally there were not differences in performance observed after methamphetamine administered either alone or in combination with *d*-amphetamine. The only significant difference observed was that participants had increased inhibitory failures to a no-go target following a no-go cue on the cued go/no-go task. This difference was attributed to a dose dependent decrease in performance when methamphetamine was administered during *d*-amphetamine maintenance only. This increase in inhibitory failures may be attributed to participants having

received two stimulant medications and the behavioral effects of a general increase activity.

It is possible that the participants did not have significant deficits in cognitive functioning, as suggested in a recent review (Hart, Marvin, Silver, & Smith, 2012). This review compiled previous studies that investigated cognitive performance in methamphetamine users and compared the results found to normative data for the assessments used when normative data was available. It was found that while deficits may be apparent when performance is compared to a control sample these deficits are not present when compared to age and education matched normative data (Hart, Marvin, Silver, & Smith, 2012). It would be expected that if impairments in cognitive functioning had existed, there should have been significant improvements observed after *d*-amphetamine was administered alone, but the only changes observed were a general reduction in time for participants to respond to go targets on the cued go/no-go task. Additionally, when methamphetamine and *d*-amphetamine were administered in combination there was a decrease in inhibitory control observed on the cued go/no-go task. The results of the present study combined with the recent review of cognitive performance in chronic stimulant users suggest that cognitive deficits may not be a viable target for treatment.

Physiological

Methamphetamine dose dependently increased systolic blood pressure during both *d*-amphetamine and placebo maintenance. However, these increases were attenuated during *d*-amphetamine maintenance. Additionally,

while the increases in systolic blood pressure were statistically significant, it was considered clinically insignificant and no participants were discharged from the study for medical reasons. There were no significant effects on heart rate, diastolic blood pressure, or temperature. Administration of methamphetamine during *d*-amphetamine maintenance produced an attenuated increase in systolic blood pressure, compared to administration of methamphetamine alone. This attenuation during *d*-amphetamine maintenance may be attributed to cross tolerance to the stimulating effects of methamphetamine. These findings are consistent with prior studies that have shown that intranasal methamphetamine administered is safe and well-tolerated (Hart, et al., 2008; Kirkpatrick, et al., 2011; Lile, Stoops, Glaser, Hays, & Rush, 2011; Perez, et al. 2008; Rush, Stoops, Lile, Glaser, & Hays, 2011; Rush, Stoops, Lile, Glaser, & Hays, 2011; Sevak, Stoops, Hays, & Rush, 2009; Sevak, et al., 2011; Stoops, 2006).

Future Directions

Future research should investigate the use of other agonist medications and combinations of medications for the treatment of methamphetamine dependence. It is possible that a dopamine transporter blocker would be best used for the treatment of methamphetamine abuse, as methamphetamine is a dopamine releaser. This is supported by past research that has shown that *d*-amphetamine, which is a dopamine releaser, has shown positive results for cocaine dependence, however methylphenidate, a dopamine transport blocker was ineffective. It is possible that methylphenidate may be an effective treatment for methamphetamine abuse, which is currently being assessed in a clinical trial.

Combinations of medications that are modestly effective alone, such as bupropion and naltrexone, should also be tested to see if the interaction of the medications is more effective than either medication alone. The combination of pharmacotherapy and behavioral therapy should also be assessed. Previous research has shown that the combination of levodopa and contingency management was more effective for cocaine dependence than levodopa or contingency management alone (Schmitz, et al., 2008). Additionally, future research is needed to investigate cognitive performance in chronic stimulant users to determine if it is a viable target for medications development.

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EDUCATION:
University of Michigan – Flint
B.S.

- Graduation Date: May 2009
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- Graduated with Honors from the Honors Program in Psychology

RESEARCH PROJECTS AND PRESENTATIONS:

Pike, E. Stoops, W.W., Glaser, P.E.A., Hays, L.R., & Rush, C.R. (June 2013). *Methamphetamine self-administration in humans during d-amphetamine maintenance*. Poster accepted to be presented at the 75th annual meeting of the College on Problems of Drug Dependence, San Diego, CA.

Marks, K.R., Stoops, W.W., Pike, E., Roberts, W., Fillmore, M.T., & Rush, C.R. (June 2013). *Gaze time as a sensitive measure of cocaine-related attentional bias.* Poster accepted to be presented at the 75th annual meeting of the College on Problems of Drug Dependence, San Diego, CA.

Marks, K.R., Stoops, W.W., Pike, E., Roberts, W., Fillmore, M.T., & Rush, C.R. (April 2013). Measuring attentional bias to cocaine using eye-tracking technology. Poster accepted to presented at the 2nd annual Tobii Eye Tracking Conference on Behavioral Research, Boston, MA.

Marks, K.R., Pike, E., Stoops, W.W., & Rush, C.R. (August 2012). *Agonist replacement therapy for cocaine dependence: A translational review*. Poster session presented at the 120th Annual American Psychological Association Convention, Orlando, FL.

Pike, E., Marks, K.R., Stoops, W.W., Rush, C.R. (June 2012). *Years of stimulant use as a biobehavioral marker for methamphetamine dependence*. Poster session presented at the 74th Annual Meeting of the College on Problems of Drug Dependence, Palm Springs, CA.

Pike, E. (May 2009). *Investigating the relationship between perceived control of attention deficit hyperactivity disorder symptoms and substance use in college students*. Poster session presented at the annual Meeting of Minds Undergraduate Conference, University of Michigan-Dearborn, Dearborn, Michigan.

Shaughnessy, S., Pike E., Wojtkowicz, M., Berkuchel, S., Abu-Aita, A. (May 2007). *What would Mickey do? A behavioral analysis of mice response to cat hair*. Poster session presented at the annual Meeting of Minds Undergraduate Conference, University of Michigan-Flint, Flint, Michigan.

Pike, E. (April 2007). *The problem of prescription stimulant misuse among high school and college students*. Paper presented at the Honors Colloquium- Papers on independent study topics, University of Michigan-Flint.

Pike, E. (2006, April). *Breaking Barriers: Pilar and Sam in John Sayles' Lone Star*. Paper presented at the Honors Colloquium- Papers on Shakespeare, Emile Zola, and John Sayles' Lone Star, University of Michigan-Flint.

PUBLICATIONS:

Pike, E. (2006) Breaking barriers: Pilar and Sam in John Sayles' Lone Star. In S. Koehler (Ed.), *Journal of the University of Michigan-Flint's First Annual Critical and Creative Writing Conference* (201-203). Flint, MI: University of Michigan-Flint Printing.

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GRANTS:

Pike, E. (2007). Proposal to create a Women in Service to Appalachia scholarship for college women. *Women in Service to Appalachia*, Women in Service to Appalachia Board of Directors. Cost per year: 500.

EXPERIENCE:

University of Kentucky, Department of Psychology, Lexington, KY
Teaching Assistant, 2011-2012

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University of Kentucky, Psychiatry Research, Lexington, KY
Research Assistant, 2008

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AFFILIATIONS:

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AWARDS:

- Chancellor's Scholarship, University of Michigan – Flint
- Ralph M. and Emmalyn E. Freeman Honors Scholarship 2008-2009
- Ralph M. and Emmalyn E. Freeman Psychology and Honors Scholarships 2007-2008
- Honors Program Scholarship, University of Michigan – Flint 2005-2007
- Michigan Merit Award, University of Michigan – Flint 2005-2007
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