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AN EVALUATION OF METHYLPHENIDATE PREFERENCE IN ADULTS  
DIAGNOSED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

by

Emily Kathleen MacDonald

A Dissertation  
Submitted to the  
Faculty of The Graduate College  
in partial fulfillment of the  
requirements for the  
Degree of Doctor of Philosophy  
Department of Psychology

Western Michigan University  
Kalamazoo, Michigan  
June 2003

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THE GRADUATE COLLEGE  
WESTERN MICHIGAN UNIVERSITY  
KALAMAZOO, MICHIGAN

Date April 11, 2003

WE HEREBY APPROVE THE DISSERTATION SUBMITTED BY

Emily Kathleen MacDonald

ENTITLED An Evaluation of Methylphenidate Preference in Adults Diagnosed with

Attention-Deficit/Hyperactivity Disorder

AS PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE


DEGREE OF Doctor of Philosophy

Psychology

(Department)

Psychology

(Program)

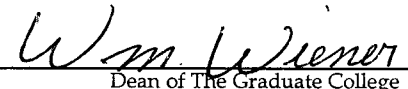
  
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## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed childhood psychiatric disorder in the United States, functionally impairing approximately 3–5% of the preadolescent population (American Psychiatric Association [APA], 1994). ADHD is characterized by a persistent pattern of inattention and/or impulsivity-hyperactivity that is more frequent and severe than typically observed in individuals at comparable levels of development (APA, 1994).

The prevalence of ADHD among adults was not recognized until recently. It had previously been assumed that children “outgrow” ADHD symptoms by adolescence (Laufer & Denhoff, 1957; Arnold, Strobl & Weisenburg, 1972). Recent studies have acknowledged that symptoms of ADHD persist into adolescence. In one such study, over 70% of children with ADHD were found to have met criteria for the disorder in adolescence (Barkley, 1990). Furthermore, studies have reported that 5–60% of children with ADHD continue to experience residual or full symptoms of this disorder into adulthood (Biederman et al., 1993; Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Wilens, Prince, Biederman, Spencer & Frances, 1995).

Children diagnosed with ADHD may be unable to sit still and pay attention in class, have poor peer relations, and exhibit disruptive behavior. These behaviors can often lead to academic, social and behavioral difficulties (APA, 1994). The symptoms of ADHD in adults appear to be developmentally related to those in children and include manifestations of inattention and distractibility, impulsivity and hyperactivity (Ward,

Wender, & Reimherr, 1993). The common presenting symptoms for adults diagnosed with ADHD include inattention, poor concentration, distractibility, daydreaming, boredom, forgetfulness, impulsivity, intrusiveness, low frustration tolerance, and temper tantrums, (e.g., Faraone et al., 2000, Wilens, Biederman et al. 1995). In addition, adults diagnosed with ADHD have been shown to have high rates of psychopathology, social dysfunction, academic difficulties, and occupational failure, (Biederman et al, 1993), substance abuse (Levin & Kleber, 1995; Wilens, Prince, et al., 1995) and depression (Alpert et al., 1996).

### Pharmacological Treatment of ADHD

To address the clinical symptoms of ADHD, 85–95% of individuals diagnosed with ADHD receive pharmacological treatment, and approximately 70–90% of the psychostimulant products prescribed for ADHD are methylphenidate-based (e.g., Concerta<sup>®</sup>, Metadate<sup>®</sup>, Ritalin<sup>®</sup>; Robison, Sclar, Skaer & Galin, 1999; Zarin, Suarez, Pincus, Kupersanin & Zito, 1998; Zito et al., 2000). Methylphenidate (MPH) has been shown to have positive effects in children across a wide range of domains (DuPaul, Barkley & Conner, 1998; Greenhill, 1998) including: academic productivity and accuracy (DuPaul, Barkley & McMurray, 1994; Elia, Welsh, Gulotta & Rapoport, 1993); fidgetiness and motor restlessness (DuPaul et al., 1994); parent and teacher behavior ratings (Barkley, 1991); aggression and other antisocial behavior (Bukstein & Kolko, 1998) and social functioning and peer relations (Barkley & Cunningham, 1979; Barkley, 1989).

Although the efficacy of MPH has been documented in children and adolescent populations, the efficacy of MPH in adult populations has not been clearly established. Despite the more than 200 controlled studies of stimulant treatment in children with ADHD (for reviews see Wilens & Biederman, 1992; Swanson, McBurnett, Wigal, & Pfiffner, 1993; MTA Group, 1999), there have been only six controlled studies of stimulants in adults diagnosed with ADHD (for review see Wilens, Spencer & Biederman, 2002; Wilens, Biederman, et al., 1995). Controlled outcome studies examining the efficacy of MPH in adults diagnosed with ADHD have yielded inconsistent results. Overall, the results of these studies suggest that the response rate in adults with respect to ADHD symptom reduction is more ambiguous than those found in children, ranging from 25% to 78% (Wood, Reimherr, Wender & Johnson, 1976; Mattes, Boswell & Oliver, 1984; Wender, Reimherr, Wood & Ward, 1985; Gualtieri, Ondrusek & Finley, 1985; Shekim, Asarnow, Hess, Zaucha & Wheeler, 1990; Spencer et al., 1995).

The most robust findings resulted from a randomized placebo-controlled crossover study of MPH in 23 adults diagnosed with ADHD using DSM-III-R defined criteria (Spencer et al., 1995). Results indicated that the overall response rate for ADHD symptoms, as measured by the ADHD Rating Scale (Barkley, 1990), was significantly higher during MPH treatment as compared to placebo (78% vs. 4%;  $p < 0.0001$ ). Overall, the variability observed across these six controlled studies could be attributed to differences in diagnostic criteria, methodology, MPH doses, comorbid psychiatric disorders, and outcome measures (Wilens, Biederman, et al., 1995). Yet, across studies, participants who responded favorably reported experiencing improved attention, and decreased restlessness, impulsivity and impatience (Shekim et al., 1990), and less

anxiety, anger and irritability (Wood et al., 1976). Several of these controlled studies suggest that MPH treatment for adults can lead to robust, dose-dependent improvement in ADHD symptoms (Biederman & Spencer, 2002).

Despite the equivocal results, MPH appears to be associated with improvements in attention span, behavior, cognitive aptitude, memory processing, mood stability, and sensorimotor coordination in adults (Greenhill, 1995). The amelioration of the symptoms of ADHD may lead to improvements in everyday abilities, academic or occupational performance and social adaptability (Bhandary, Fernandez, Gregory, Tucker & Masand, 1997). Thus, in spite of the limited number of controlled studies examining the efficacy of MPH, it appears to be well tolerated and is associated with improvement of symptoms in adults diagnosed with ADHD.

#### Mechanism of Action

MPH is associated with a wide range of clinically beneficial effects, yet the specific mechanisms by which the drug alters behavior have not been conclusively determined. From a neuropharmacological standpoint, MPH is believed to exert clinical effects by acting on noradrenergic and dopaminergic pathways by blocking dopamine (DA) and norepinephrine (NE) transporters (Solanto, 2000). By increasing the intrasynaptic dopamine by blocking the dopamine transporter, it is hypothesized that MPH attenuates deficits in inhibitory control and working memory that are hallmarks of ADHD (Greenhill, 1998).

MPH also demonstrates dopaminergic effects in the ventral tegmental area and nucleus accumbens via the mesolimbic pathway, thus MPH has been hypothesized to

affect behavior by altering behavioral reinforcement processes (Solanto, 2000). Several studies have provided some support for this theory of the behavioral mechanism of action of MPH. For example, one study demonstrated that MPH functions as an establishing operation by altering the rewarding properties of different kinds of stimuli in children with ADHD (Northup, Fusilier, Swanson, Roane & Borrero, 1997). While other studies have reported that when compared to non-drug conditions, MPH also changes the manner in which children with ADHD allocate their behavior across alternatives that produce rewards at different rates (e.g., Kollins, Lane, & Shapiro, 1997; Murray & Kollins, 2001).

#### Abuse Potential

The neuropharmacological profile of MPH is similar to that of other commonly abused stimulants such as cocaine and d-amphetamine (Hoffman & Lefkowitz, 1996). As such, concern regarding the abuse potential of MPH has arisen (see Kollins, MacDonald & Rush, 2001 for review). Recently, attention has focused on the misuse and abuse of MPH among adolescents, college students, and parents of children with prescriptions for MPH for the treatment of ADHD (e.g., Drug Enforcement Administration, 2000; Llana & Crimson, 1999; Safer, 2000; Popper, 1995). One study examined the rates of MPH misuse in adolescents assessed at an outpatient substance abuse treatment facility and reported that there was a significant increase in MPH misuse from 1992–1996 (Marsh, Key & Payne, 2000). Also, in a survey of school-aged children, one out of six reported having been approached to buy, sell or trade MPH (Musser, Ahmann, Mundt, Broste, Mueller-Rizner, 1998), while a recent survey of college-aged students revealed that 16% of survey responders (N=283) reported trying



MPH recreationally, and 12.7% reported using the drug intranasally (Babcock & Byrne, 2000).

Several case reports have also suggested more clinically significant patterns of MPH misuse, with users taking the drug to induce euphoria by crushing the tablet and administering it intranasally or intravenously (Fulton & Yates, 1988; Jaffe, 1991; Parran & Jasinski, 1991; Weiner, 2000). Though some individuals may use MPH to achieve euphoric drug highs, others may use MPH to improve attention and alertness. Among college students, MPH is reportedly used to stay awake to “party” longer, improve study skills by increasing mental concentration, or to increase alertness and decrease fatigue following “all-nighters” (Babcock & Byrne, 2000). Moreover, anecdotal reports of MPH use generally involve MPH being used to enhance social interactions or academic performance (Drug Enforcement Administration, 2000). Thus, the misuse of MPH has been documented and may be increasing.

Laboratory studies support the abuse potential of MPH in nonhumans and humans. MPH is behaviorally similar to other abused drugs such as d-amphetamine and cocaine (for review see Kollins et al., 2001). Specifically, in relation to these other stimulants, MPH produces comparable discriminative stimulus effects (e.g., Perkins, Eckman, & MacPhail, 1991; Wood & Emmett-Oglesby, 1988; Rush, Kollins, Pazzaglia, 1998; Kollins, Shapiro, Newland & Abramowitz, 1998), subjective effects (e.g., Chait, 1994; Heishman & Henningfield, 1991; Martin, Sloan, Sapira & Jasinski, 1971; Roehrs, Papineau, Rosenthal & Roth, 1999; Rush et al., 1998; Rush, Essman, Simpson & Baker, 2001; Smith & Davis, 1977) and reinforcing effects (e.g., Aigner & Balster, 1979;

Bergman et al., 1989; Risner & Jones, 1975; Chait, 1994; Roehrs, Papineau, Rosenthal & Roth, 1999; Rush et al., 2001).

One paradigm for assessing the abuse potential of a drug involves measuring its subjective effects in human participants. The subjective effects of a drug are considered to be strongly correlated with a drug's abuse potential (Jaskinski & Henningfield, 1989). Specifically, if a drug is associated with ratings of drug-liking, euphoria, or produces ratings comparable to other known drugs of abuse, the drug is believed to have abuse potential. Methylphenidate exerts clear participant rated effects across instruments when compared to placebo in human adults (e.g., Chait, 1994; Heishman & Henningfield, 1991; Martin, Sloan, Sapira & Jasinski, 1971; Roehrs, Papineau, Rosenthal & Roth, 1999; Rush et al., 2001; Rush et al., 1998; Smith & Davis, 1977). These studies demonstrated that MPH increased ratings of "Arousal," "Anxiety," "High," "Talkative," "Euphoric," "Like Drug," and "Like to Take Again" (for review see Kollins et al., 2001).

Although MPH is associated with subjective effects in adults, it is not associated with clear participant-rated effects in children (Kollins et al., 1998; MacDonald & Kollins, 2000). Rather, the patterns of participant-rated effects obtained in children were variable, and clear trends were not observed. The idiosyncratic participant-rated effects observed in children could be due to a developmental difference in the ability to self-report drug effects.

Another paradigm used to measure the abuse potential of a drug involves assessing a drug's reinforcing effects by determining whether it maintains self-administration (Brady, Heinz, & Ator, 1990). MPH has been shown to function as a reinforcer itself as demonstrated by self-administration paradigms in nonhuman species

(Aigner & Balster, 1979; Johanson & Schuster, 1975; Risner & Jones, 1975). Although the reinforcing effects of a drug are considered to be one of the most powerful predictors of abuse, only three published studies have directly examined the reinforcing effects of MPH in humans (Chait, 1994; Roehrs et al., 1999; Rush et al., 2001). The results of these studies do not provide conclusive evidence with respect to the reinforcing effects of MPH in humans. Of these published studies, one study did not report consistent reinforcing effects (Chait, 1994); one study reported significant reinforcing effects compared to placebo using a progressive-ratio procedure (Rush et al., 2001); and one study reported reinforcing effects under the specific environmental conditions of sleep deprivation (Roehrs et al., 1999).

In the first study, Chait (1994) measured the subjective and reinforcing effects of methylphenidate in 35 non-drug abusing human participants using a choice procedure. Participants were administered MPH and placebo on alternating days. Following this sampling phase was a choice day, wherein the participants could choose between MPH (20–40 mg), placebo or no capsules/neither drug. The results yielded inconsistent reinforcing effects. Out of 105 total choices across participants (three choices each), MPH was chosen 29 (27.6%) times, placebo was chosen 9 (8.6%) times, and no capsules were chosen on 67 (63.8%) occasions.

The second study assessed the reinforcing effects of MPH (20–40 mg), d-amphetamine (10–20 mg) and placebo in eight healthy adults using a modified progressive-ratio schedule, which are frequently used to assess the reinforcing effects of abused drugs (Rush et al., 2001). During sampling sessions participants ingested eight identical capsules, wherein each capsule contained 12.5% of the total dose. During self-

administration sessions, participants could earn capsules by responding on a progressive-ratio task. Participants had eight opportunities to work on a computer task in order to earn all or some of the eight capsules administered during the sampling session. In order to earn the first capsule, participants were required to click the mouse 50 times. The number of mouse clicks required to earn additional capsules doubled (e.g., 100, 200, 400, 800, 1600, 3200, 6400). Participants ingested all of the capsules they had earned after completing the progressive-ratio schedule. The dependent measure in this study was the break-point, which is the last ratio completed. Results indicated that the highest dose of MPH (40 mg), and both doses of d-amphetamine, increased the break-point values significantly above placebo, demonstrating that MPH functioned as a reinforcer in these healthy adult participants.

Finally, in the third study, the impact of sleepiness on the reinforcing effects of MPH was studied in six healthy volunteers 21–30 years of age (Roehrs et al., 1999). On sampling days, the participants received 10-mg of MPH or placebo after four or eight hours in bed and then, on separate choice days after four or eight hours in bed, participants chose their preferred capsule. The results indicated that MPH was chosen significantly more after four hours in bed (88%) as compared to choices made following eight hours in bed (29%). The authors interpreted the findings as supportive of the idea that the reinforcing effects of a drug are influenced by environmental circumstances (Roehrs et al., 1999). As such, in healthy adult volunteers sleep deprivation functioned as an establishing operation that altered the reinforcing effects of MPH.

Another recently completed study examined the reinforcing effects of MPH in five children diagnosed with ADHD (MacDonald & Kollins, 2000). Results

demonstrated that the difference between the number of choices for MPH, Placebo and Neither was statistically significant ( $X^2=9.6$ ;  $p<0.01$ ). Out of 30 total choices across all participants (six choices for each of five participants), MPH was chosen 18 times (60%). Placebo and Neither were each chosen six times (20%). This study was the first to document the reinforcing effects of MPH in a sample of individuals receiving the drug for clinical purposes.

Relatively few studies have examined the reinforcing effects of psychoactive drugs in individuals who receive them for clinical purposes (Roache, Stanley, Creson & Schmitz, 1996; Roache, Stanley, Creson, Shah, & Meisch, 1997; deWit, Uhlenhuth, Hedeker, McCracken & Johanson, 1986). As described previously, MacDonald & Kollins (2000) examined the reinforcing effects of MPH in children diagnosed with ADHD. However, to date this is the only study that has experimentally assessed the reinforcing effects of MPH in individuals diagnosed with ADHD who are prescribed the drug for clinical purposes. In the past decade, the therapeutic use of MPH has increased, leading to debates surrounding the prescription rates and safety of this stimulant drug (Rappley, 1997). There continues to be concern surrounding the use of stimulant medications to treat individuals, specifically children, diagnosed with ADHD. Specifically, critics argue that MPH is over-prescribed and is inherently dangerous (Safer, 2000; Safer, Zito, & Fine, 1996). Thus, in light of these arguments, it is critical to evaluate the reinforcing effects and abuse potential of MPH in a clinical sample.

## PURPOSE OF PRESENT STUDY

The purpose of the present study was to examine the reinforcing effects and participant-rated effects of MPH in adults diagnosed with ADHD. Such research may provide important information regarding: (a) the behavioral mechanism of action of MPH and how the drug interacts with other environmental events to produce meaningful clinical change, and (b) insight into the abuse potential of this drug in clinical populations.

## METHODS

### Participants

Participants for this study were 7 males (ages 18–22) and 3 females (ages 20–21). The participants were recruited through local physicians and psychologists, recruitment flyers, and word of mouth on the basis of two criteria: (1) an established diagnosis of ADHD, and (2) a current prescription for MPH for the treatment of symptoms associated with ADHD. All participants had been receiving MPH treatment for at least six months prior to selection for the study.

To corroborate the ADHD diagnostic status of participants and to ensure a homogeneous group, participants were required to receive a score of 36 or higher on the Wender Utah Rating Scale (WURS; Wender et al., 1985), and obtain a T-score of 65 or higher on the ADHD symptoms scale of the Conners Adult ADHD Rating Scale (CAARS; Conners, Erhardt, & Sparrow, 1999). Participants were excluded if they were taking any other type of psychoactive medication, exhibited any gross neurological,

sensory or motor impairment, had a history of other significant learning or psychiatric problems, or any current severe psychiatric disturbances (e.g., suicidality, homicidality, criminality). A total of 17 individuals were screened and 7 were excluded for the following reasons: not currently receiving MPH treatment (4), not willing to receive placebo (2), did not meet diagnostic criteria on the CAARS (1). Table 1 shows demographic information for the participants.

Participants received monetary compensation for their participation in the 13 sessions. Participants received \$5 for each session and an additional \$20 for completing all 13 sessions. In addition, by returning their daily questionnaires, participants were entered into weekly drawings for the opportunity to win gift certificates and coupons to local businesses and restaurants.

The Human Subjects Institutional Review Board at Western Michigan University approved this work (Appendix A).

## Dependent Variables

### Drug Preference

Drug choice was the primary dependent measure. The number of times one option (MPH, Placebo, Neither) was chosen over the other served as an indicator of its relative reinforcing effects (e.g., de Wit, 1991).

### Participant-Rated Effects

In order to assess the subjective effects of MPH, the participants completed various self-report measures. The participant-rated effects are important in that they may

Table 1  
Participant Demographics

Participant	Sex	Age	Dose	CAARS (ADHD Total)	WURS (Total Score)
1	F	21	10-mg	T=81	37
2	F	20	10-mg	T=83	59
3	F	20	15-mg	T=67	46
4	M	18	20-mg	T=71	59
5	M	22	20-mg	T=72	54
6	M	20	30-mg	T=74	59
7	M	20	10-mg	T=90	63
8	M	19	10-mg	T=78	36
9	M	21	20-mg	T=88	79
10	M	21	20-mg	T=75	54

be useful in predicting reinforcing and clinical efficacy of MPH. The participant-rated effects were assessed pre-drug administration, 1.5 hours and 4 hours post-drug administration. The participant-rated effects measures are as follows:

1. Participant-Rated Effects Scale (PRES). The Participant Rated Effects Scale (PRES) is a 25-item scale developed for this study to assess the subjective effects of MPH in adults diagnosed with ADHD. This scale was developed to streamline the assessment of subjective effects and to provide the least intrusive and time intensive assessment of participant-rated effects in these volunteers as they were requested to complete these forms in their natural environment.

Items from the questionnaire (Appendix B) were rated on a 5-point scale (1–5) where each numeric value corresponded to a phrase describing the frequency or intensity of the item (1= not at all, 2= a little bit, 3 = moderately, 4= quite a bit, 5= extremely).



Participants were instructed to rate each item according to how they felt “at that moment.” Items on this form were derived from four primary sources: (1) Addiction Research Center Inventory (ARCI; Martin et al., 1971); (2) Profile of Mood States (POMS; McNair, Lorr & Droppleman, 1971); and (3) Conners Adult ADHD Rating Scale (CAARS, Conners, Erhardt, & Sparrow, 1999 and the DSM-IV (APA, 1994). Items included those that had been used to measure the participant-rated effects of many drugs and are sensitive to the effects of stimulants (e.g., Heishman & Henningfield, 1991; Roache, Grabowski, Schmitz, Creson, & Rhoades, 2000). The items from the CAARS and the DSM-IV included symptoms of ADHD and were selected because of clinical utility in determining the effects of stimulant medications in this population.

2. End of the Day Questionnaire. This five-item questionnaire was administered approximately four hours after capsule ingestion to measure the overall effect of the drug received. Participants rated “Drug Strength,” “Drug Liking,” “Good Effects,” “Bad Effects,” and “Like to Take Again” on a 5-point scale (0 = Not at all, 1 = A little bit, 2 = Moderately, 3 = Quite a bit, 4 = Very much). Participants were also prompted to provide reasons for their pill choice, and to report any untoward effects.

3. Daily Activity Record. Participants used this form to record any academic or job requirements that occurred during the four hours post-drug administration. Participants also rated their performance on these tasks.

### Procedures

Volunteers participated in 13 sessions. The first session was a screening session wherein the participant completed self-report assessment measures. In addition, medical

history, comorbid mental health diagnoses, length of time on MPH and dosing information were obtained. Participants provided informed consent to participate in the study and all subjects received medical clearance for participation from their prescribing physician. After the participant received medical clearance from the prescribing physician, a collaborating physician from Western Michigan University Health Center wrote prescriptions for placebo pills and the participant's normal dose of MPH.

All drugs were prepared in a standardized manner by a pharmacist at the University Health Center who had experience preparing medications for similar research and clinical activities. The participant's maintenance dose of MPH and an inert placebo were each prepared in opaque capsules (size 01) to ensure that the enclosed substance was unknown to the subject and to the researcher. Each participant's maintenance dose was encapsulated in one capsule, so that only one capsule was administered at a time. The capsules were placed in separate bottles labeled as "Bottle A" and "Bottle B" with the MPH represented by one letter (e.g., "A") and the placebo being the other (e.g., "B"). The capsule letter assignments were varied across participants. However, the participants were informed that the same lettered capsule always contained the same substance.

### Screening Session

During the screening session, participants completed the WURS and the CAARS, and provided information regarding medication history. If entry criteria were met, participants provided consent to contact their physicians to obtain medical clearance. An independent physician served as a consultant on this study and provided the prescriptions following documentation of medical clearance from the participant's individual

physician. During the screening session, the researcher and the participant discussed the participant's class and/or work schedule in order to schedule the next 12 sessions so as to minimize the interference in the individual's work and class performance. Thus, the specific time that participants arrived at the laboratory was arranged on an individual basis in order to minimize the influence of this study on their class and/or work schedules.

Participants were asked to maintain their normal caffeine and nicotine use and to refrain from eating one hour before the session. Participants were provided with a standard light snack upon arrival to the laboratory. They were asked to refrain from taking their MPH prescription for at least four hours prior to coming into the laboratory. There were three sessions each week for four weeks. The methods used in the present study are modeled after similar drug self-administration studies (e.g., Chait, Uhlenhuth & Johanson, 1987; deWit, Uhlenhuth & Johanson, 1984; Johanson, Kilgore & Uhlenhuth, 1983; Johanson & Uhlenhuth, 1982).

### Sampling Sessions

The first four sessions were sampling sessions. The sampling sessions were designed to allow participants to experience the effects of the two drug conditions (MPH and Placebo) on the basis of which they would subsequently make their drug choice.

On the first sampling day, upon arriving at the laboratory participants were given a standard light snack (juice and breakfast bar). Participants then completed the participant-rated effects scale. During the first sampling session, after completing the participant-rated effects questionnaire, participants received either placebo or MPH in a

capsule labeled “Pill A” or “Pill B.” In the second sampling session, participants received the other substance in a capsule labeled with the other letter. Participants also received a card labeled with the same letter as the pill administered as a reminder of which capsule they received that day. Participants were instructed to associate the effects of the capsule with its letter label. Capsule letter assignments varied across participants, and the order in which placebo and MPH were scheduled in the sampling sessions was counterbalanced across subjects and within-subjects across weeks. As noted previously, the actual letter codes used were varied across participants and they were instructed that capsules with the same letter always contained the same substance. The third and fourth sampling sessions followed the same capsule administration order.

After receiving the capsule, the participants were free to leave the laboratory and resume daily activities. They were given two questionnaire packets and were instructed to complete one packet 1.5 and 4 hours following capsule ingestion. Because these participants had demanding class and work schedules, in addition to being diagnosed with ADHD, they were asked to complete questionnaires only twice post-drug administration so as to minimize interference with their daily functioning. Participants were required to return their packets to the laboratory by 5:00 p.m., at which time they received their ticket for the weekly drawings.

### Choice Sessions

The remaining eight sessions were choice sessions. In the choice sessions, following the completion of questionnaires, participants were presented three cups for the drug choice administration: one labeled “Pill A” (or whatever letter corresponded to

MPH), one labeled “Pill B” (or whatever letter corresponded to placebo), and an empty cup labeled “C.” The participant chose either to ingest “Pill A,” to ingest “Pill B” or to take neither capsule. The use of a “Neither” option was included to replicate prior studies of the reinforcing effects of MPH (Chait, 1994) and to provide a more reliable measure of the reinforcing efficacy of the chosen substance (Spiga & Roache, 1997). This choice procedure is a technique that has been used to measure the reinforcing effects of a number of different drugs, in a range of contexts and with various subject populations (e.g., deWit & Griffiths, 1991; Foltin & Fischman, 1991; Johanson & deWit, 1989). Following each choice, the participant was presented with the appropriate letter-matched card. After capsule administration, the participant was free to leave the laboratory and resume daily activities. The procedures for collecting participant-rated effect questionnaires were identical to those used in the sampling sessions.

## DATA ANALYSIS

### Reinforcing Effects

The number of times MPH, Placebo and Neither were chosen were taken as indicators of their positive reinforcing properties (deWit, Uhlhuth & Johanson, 1984). The reinforcing effects of MPH were assessed by calculating the total number of choices of MPH, placebo, and neither across participants and examining the proportion of choices with a chi-square analysis. “Choosers” were defined as individuals who selected MPH on at least 5 out of 8 occasions.

## Participant-Rated Effects

The participant-rated effects were analyzed by transforming the 25-item questionnaire into three composite scores: (1) ADHD composite (10 items), (2) Mood composite (12 items), and (3) Stimulant composite (3 items) (Appendix C). The composite scores were averaged across “MPH,” “Placebo,” and “Neither” sessions for each subject at each of the three time periods (pre, 1.5 hour, and 4 hour) for both sampling and choice sessions. The change from baseline ([post-drug administration scores]-[pre-drug administration scores]) was also computed using raw scores for each composite for MPH sessions, Placebo sessions and Neither sessions for sampling and choice sessions. The effect size (d) was calculated by dividing the raw score difference by the standard deviation of the measure (Cohen, 1977). The effect size scores obtained for the ADHD symptom composite, the Mood composite and the Stimulant Effects composite for MPH choosers were compared to the effect scores obtained for the non-MPH choosers (i.e., placebo and non-choosers) across sampling sessions.

Data from the sampling sessions were analyzed to in a two-way analysis of variance (Time x Choice) to compare the participant-rated effects obtained by MPH-choosers and non-choosers. In addition, a two-way analysis of variance (Drug x Group) was used to compare the participant-rated effects obtained by MPH-choosers and non-choosers under MPH and Placebo conditions. During choice sessions, participants determined whether they ingested MPH, Placebo or neither. Thus, because participants were not exposed to the same number of MPH, Placebo and no-drug days, data from the choice days were not analyzed statistically.

The End of Day Questionnaire ratings were analyzed using paired t-tests to compare ratings on each item following MPH and Placebo across all sessions and separately across sampling and choice sessions.

## RESULTS

### Reinforcing Effects

The results of the choice sessions were analyzed by examining the percentage of MPH choices per subject (See Figure 1). Out of 80 total choices across all participants (eight choices each), MPH was chosen 40 times (50%), placebo was chosen 26 times (32.5%), and neither was chosen 14 times (17.5%). A chi-square analysis found that the number of choices of MPH, Placebo and Neither differed significantly ( $\chi^2=52.484$ ,  $p<0.001$ ).

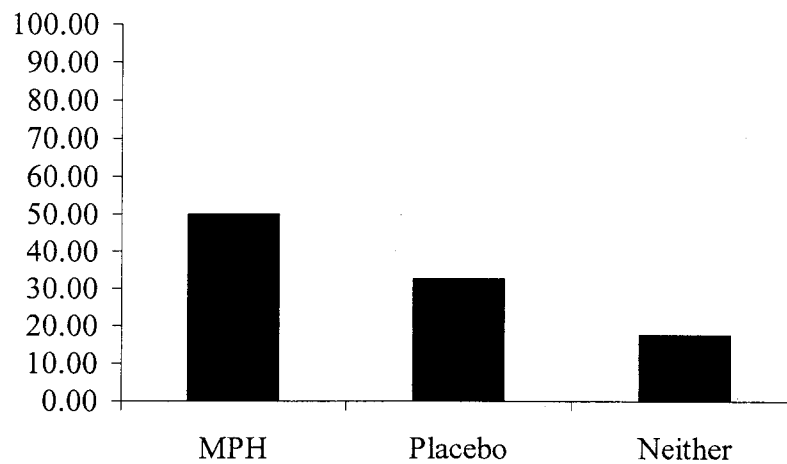


Figure 1. The Percentage of Choices across Participants.

According to the criteria used by Chait (1994), Participants 1, 3, 6, 7 and 10 were classified as “MPH choosers.” The remaining participants were classified as “Non-choosers.” Specifically, Participants 2, 5 and 8 chose placebo more often than MPH, and Participants 4 and 9 did not demonstrate reliable choice patterns (See Table 2). When examining the number of MPH, Placebo and Neither choices among MPH-choosers and non-choosers, MPH-choosers selected MPH significantly more often than non-choosers (77.5% vs. 22.5%;  $F_{1,8}=24.82, p<0.001$ ). In addition, MPH-choosers chose Placebo significantly less often than non-choosers (7.5% vs. 57.5%;  $F_{1,8}=13.11, p<0.01$ ). There were no significant differences with respect to Neither choices (See Figure 2).

Table 2

Participant Choice Patterns

Participant	MPH	Placebo	Neither
1	6	0	2
2	0	5	3
3	8	0	0
4	4	1	3
5	1	7	0
6	7	1	0
7	5	2	1
8	2	6	0
9	2	4	2
10	5	0	3



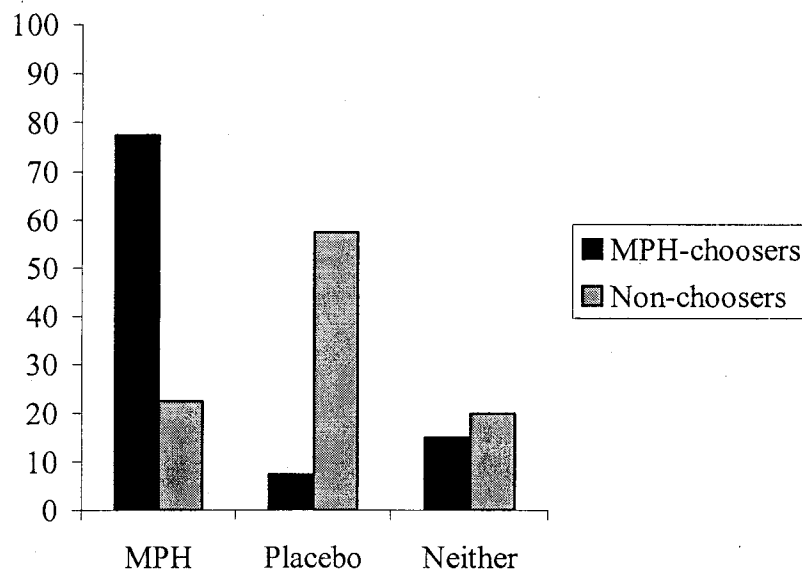


Figure 2. The Percentage of Choices for MPH-Choosers and Non-Choosers.

#### Participant-Rated Effects

Effect size scores indicated that participants who subsequently were MPH-choosers differed significantly from participants who were non-choosers with respect to participant-rated effects obtained during sampling sessions. Specifically, subsequent MPH-choosers exhibited greater reduction in ADHD symptoms ( $d = -0.93$ ), negative mood ( $d = -0.92$ ) and a decrease in stimulant effects ( $d = 1.09$ ) at 1.5 hours post drug administration than the non-choosers. Baseline score differences indicate that MPH-choosers reported higher levels of ADHD symptoms than non-choosers ( $d = 0.76$ ), but did not differ significantly on other composite scores. These large effect sizes indicate that subsequent MPH-choosers and non-choosers differed significantly with respect to their responses to MPH and Placebo. Specifically, participants who experienced a significant reduction in ADHD symptoms and negative mood during sampling sessions were more likely to select MPH during choice sessions.

Results from the two-way ANOVA indicate that relative to placebo, MPH was associated with a significant decrease in ADHD symptoms among MPH-choosers ( $F_{1,56} = 8.01, p < 0.01$ ). The two-way interaction (Drug x Group) was also significant ( $F_{1,56} = 3.50, p < 0.06$ ). Moreover, when compared to non-choosers, MPH-choosers reported a significant decrease in stimulant effects ( $F_{1,56} = 8.68, p < 0.01$ ). This suggests that participants who reliably chose MPH reported a significant decrease in ADHD symptoms and in stimulant drug effects during sampling sessions, while non-choosers did not report reliable changes across sampling sessions. There were no statistically significant differences with respect to time, although visual inspection of the data suggests that the effects were greatest 1.5 hours after MPH ingestion (See Figure 3).

Results of the pairwise *t*-tests examining the items on the End of Day questionnaire indicated that, across participants, when compared to placebo MPH was associated with higher ratings of “Drug Strength” ( $t(9) = 3.59, p < 0.01$ ) and “Good Effects” ( $t(9) = 2.61, p < 0.05$ ) (See Figure 4). There were no significant differences among MPH-choosers and non-choosers, or with respect to dose.

Although statistical analyses suggests that group differences between MPH-choosers and non-choosers exist, visual inspection of individual participant-rated effects suggests that there are variable drug effects across participants with respect to ADHD, Mood and Stimulant Effects associated with MPH, Placebo and Neither days. In addition, there is variability with respect to the drug effects observed during sampling and choice sessions. Figures 5–10 present the ADHD, Mood and Stimulant Effects composites for each individual participant across drug and no-drug conditions for both sampling and choice sessions.

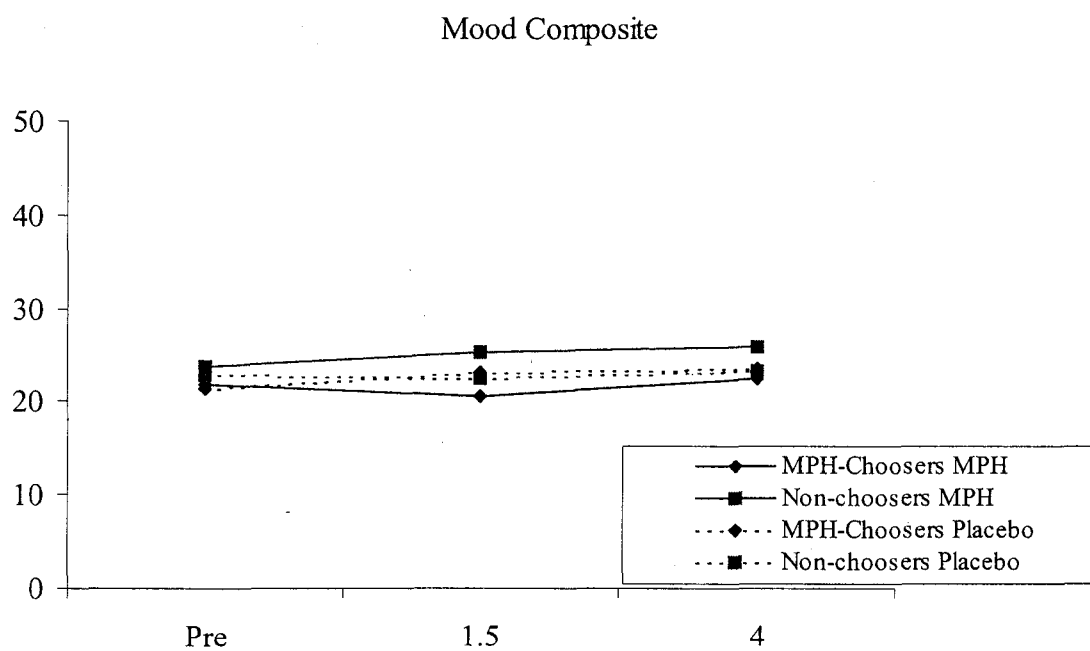
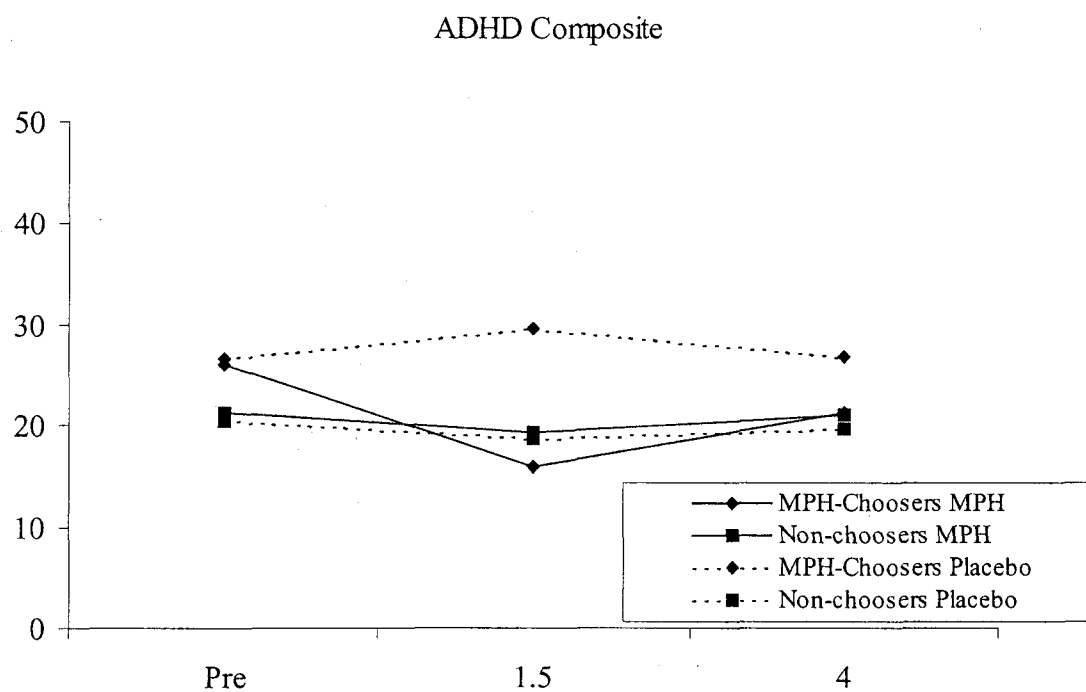


Figure 3. Participant-related Effects across Participants.

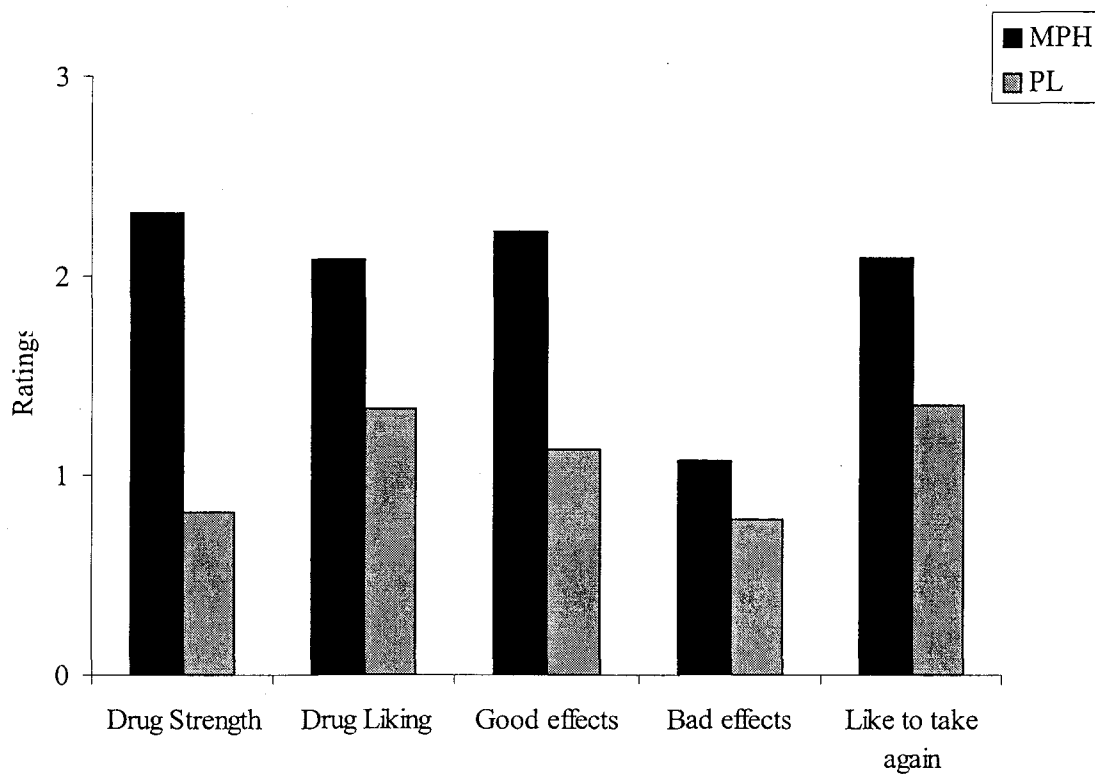


Figure 4. End-of-Day Ratings across Participants.

With respect to the ADHD Composite, MPH-choosers tended to exhibit larger discrepancies between MPH and Placebo sessions (Figures 5). Specifically, Participants 1, 6, 7 and 10 evidenced large discrepancies between ratings obtained following MPH and Placebo during sampling sessions, which may have contributed to subsequent MPH choices. Although a MPH-chooser, Participant 3 did not evidence significant discrepancies between ratings obtained under MPH and Placebo conditions, suggesting that the participant-rated effects did not influence Participant 3's MPH choices. Participants 2, 4, 5, 8 and 9, who were non-choosers, did not evidence any significant differences between ratings obtained following MPH and Placebo sessions (Figure 6).

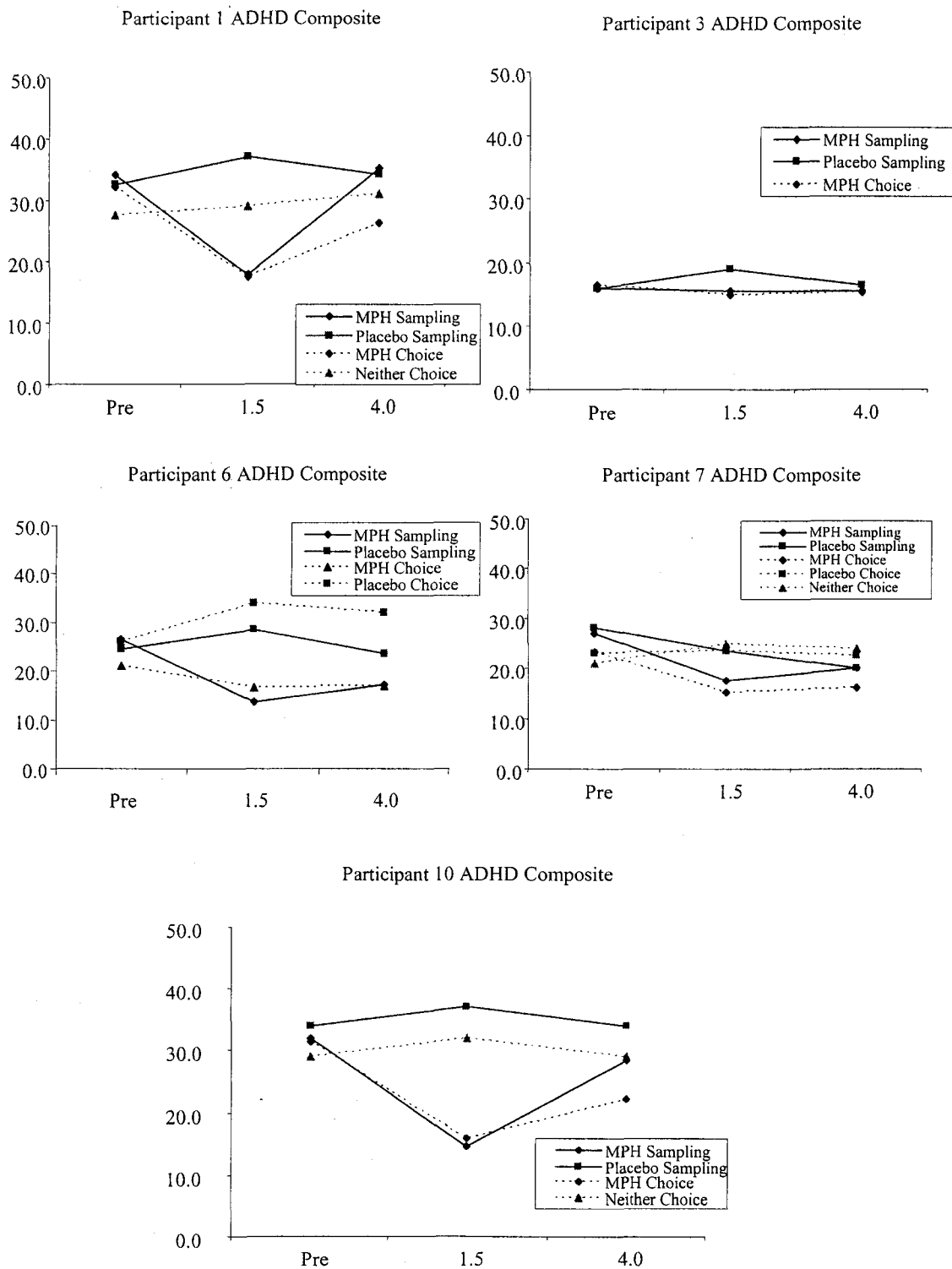


Figure 5. ADHD Composites for MPH-Choosers.

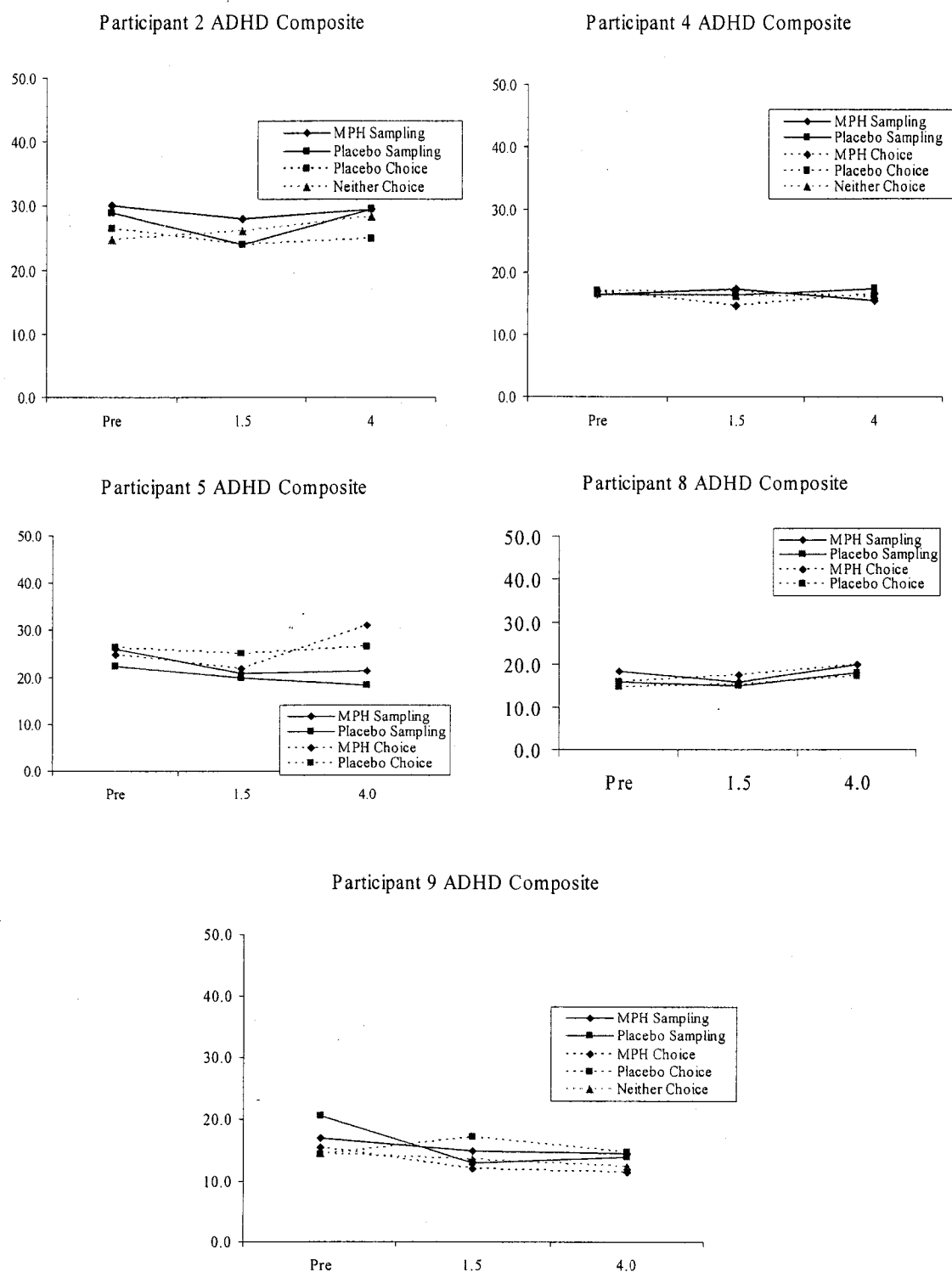


Figure 6. ADHD Composites for Non-Choosers.

With respect to the Mood Composite, there was considerable variability across participants. Based on visual inspection of data, Mood ratings of MPH-choosers do not appear to be reliable predictors of MPH choice (Figure 7). Specifically, Participant 1 demonstrated a significant difference with respect to MPH and Placebo, with MPH being associated with a decrease in negative mood. Participant 3 did not evidence any significant discrepancies between MPH and Placebo. Participant 6 exhibited significant differences with respect to MPH and Placebo at the 4-hour rating, but ratings at pre-drug and 1.5 hours post-drug administration were comparable for MPH and Placebo sessions. Participants 7 and 10 demonstrated differences in MPH and Placebo ratings during choice sessions, yet sampling session ratings were comparable.

The Mood Composites of non-choosers suggest that MPH is associated with negative mood ratings (Figure 8). Specifically, Participant 2, 5 and 9 demonstrated significant discrepancies between MPH and Placebo during sampling sessions, such that MPH was associated with higher negative mood ratings. Participants 4 and 8 did not exhibit significant differences between MPH and Placebo during sampling sessions; however, Participant 8 exhibited significantly higher negative mood following MPH choice sessions.

Similar to Mood ratings, the Stimulant Effects Composites were variable across participants. Specifically, among the MPH-choosers (Figure 9), Participants 6 and 10 reported significant discrepancies between MPH and Placebo such that MPH was associated with a decrease in Stimulant ratings, while Placebo increased Stimulant Ratings. Participant 3 reported higher baseline Stimulant ratings on Placebo sampling days, but when compared to MPH, the magnitude of change was similar. Participant 7

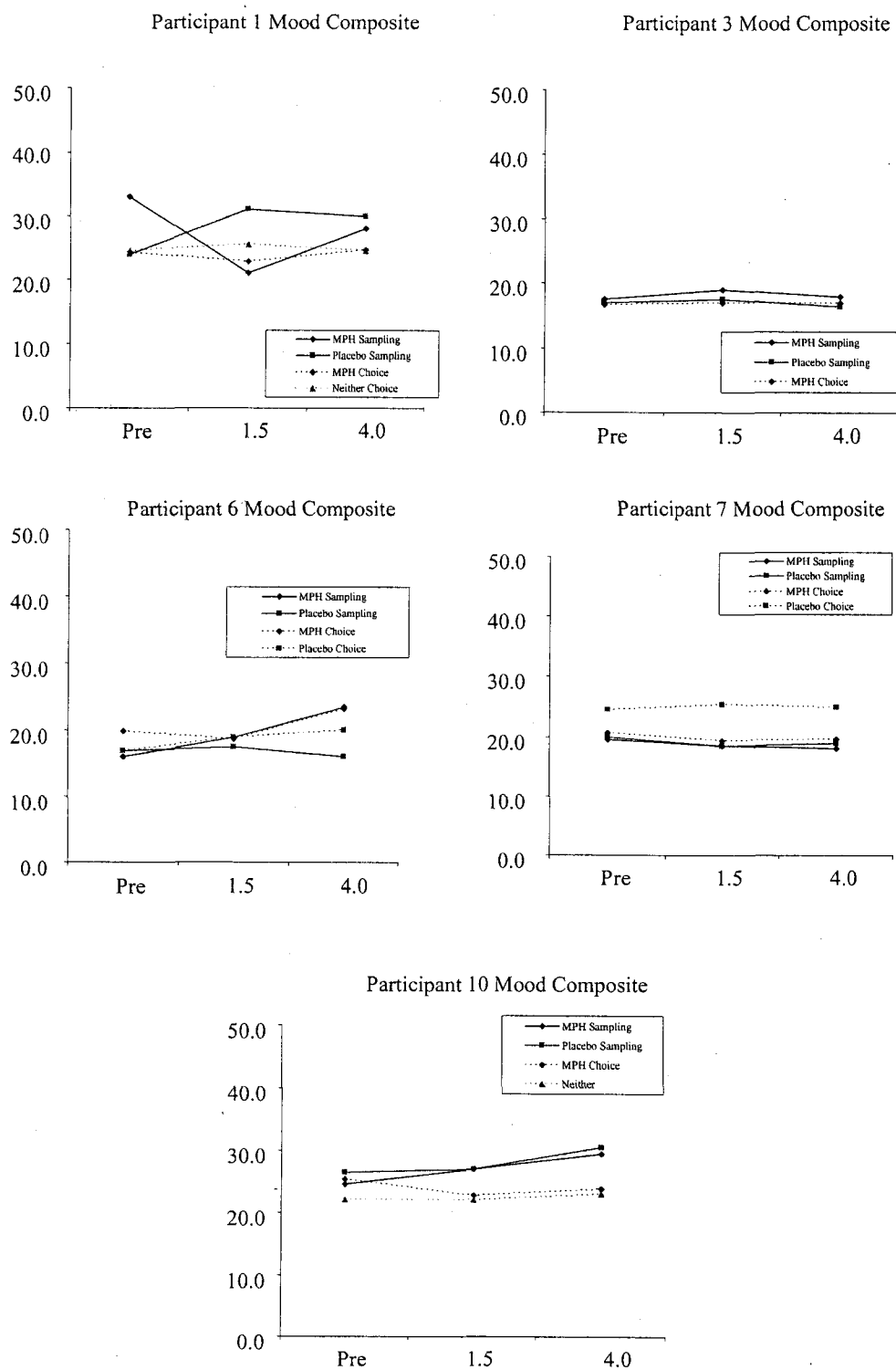


Figure 7. Mood Composites for MPH-Choosers.



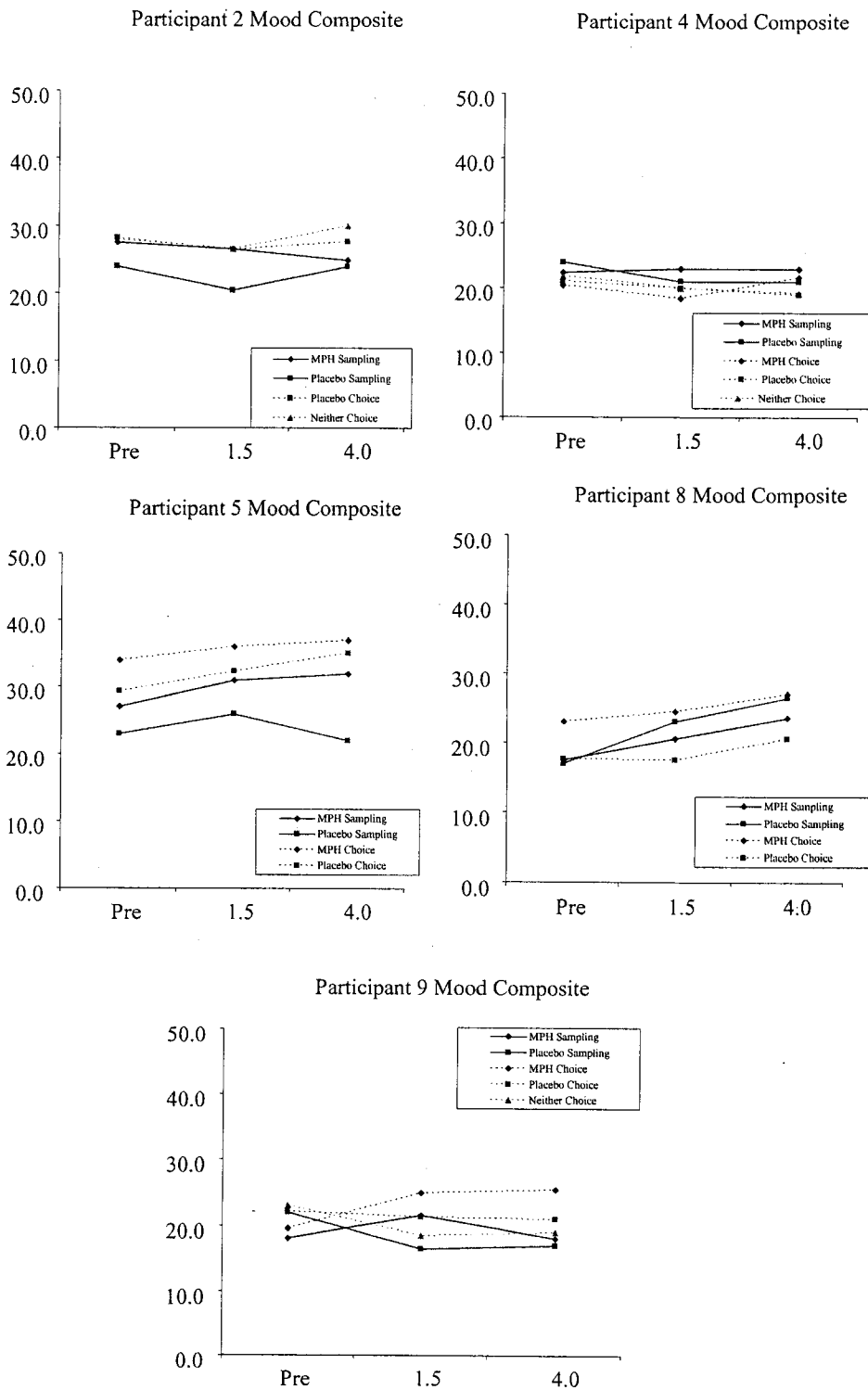


Figure 8. Mood Composites for Non-Choosers.

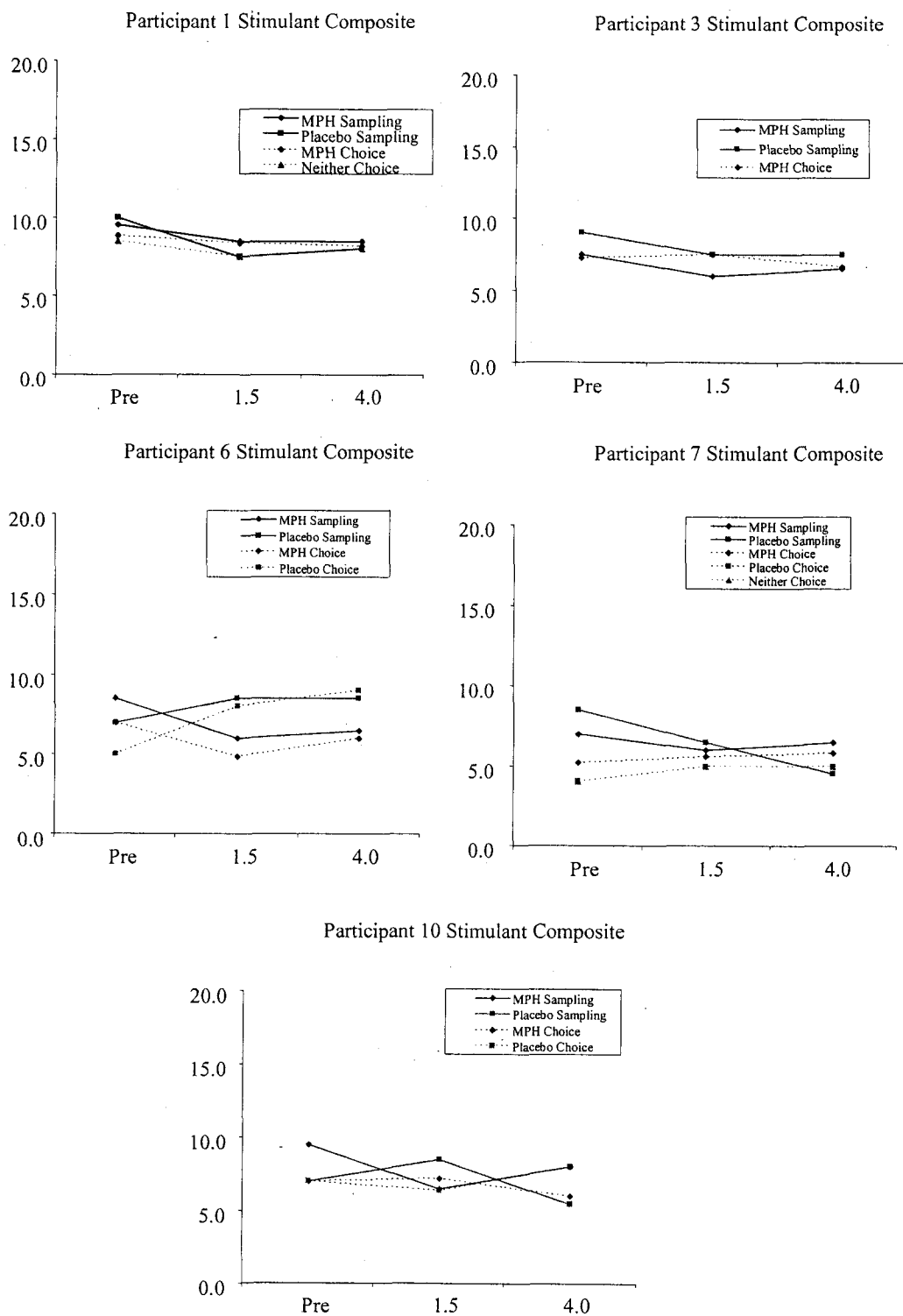


Figure 9. Stimulant Effects Composites for MPH-Choosers.

also demonstrated higher baseline Stimulant ratings on Placebo sampling days, but reported a greater decrease in ratings following Placebo as compared to MPH.

With respect to the Stimulant ratings of non-choosers (Figure 10), Participants 2, 4 and 5 did not exhibit significant differences between MPH and Placebo. Participant 8 and 9 exhibited higher baseline Stimulant ratings on MPH days, and reported significant decreases in ratings following MPH administration. In addition, Participant 9 reported a significant increase in Stimulant ratings following placebo.

## DISCUSSION

Results demonstrate that the differences between the number of MPH, Placebo and Neither choices across subjects was statistically significant, and MPH was chosen more frequently than placebo or no capsules by 5/10 participants. Moreover, MPH was chosen 77.5% of the time by MPH-choosers, as compared to being chosen 22.5% of the time by non-choosers. These findings are commensurate to the results obtained in previous studies examining reinforcing effects in healthy adults and children diagnosed with ADHD.

This study has several important implications. First, it adds to a sparse literature on the reinforcing effects of MPH in humans and is the first to study these effects in a sample of individuals receiving the drug for clinical purposes. To date, the literature is inconclusive with respect to whether methylphenidate exerts reinforcing effects in humans. One study failed to report consistent reinforcing effects (Chait, 1994); one study reported reinforcing effects under specific conditions of sleep deprivation (Roehrs et al.,

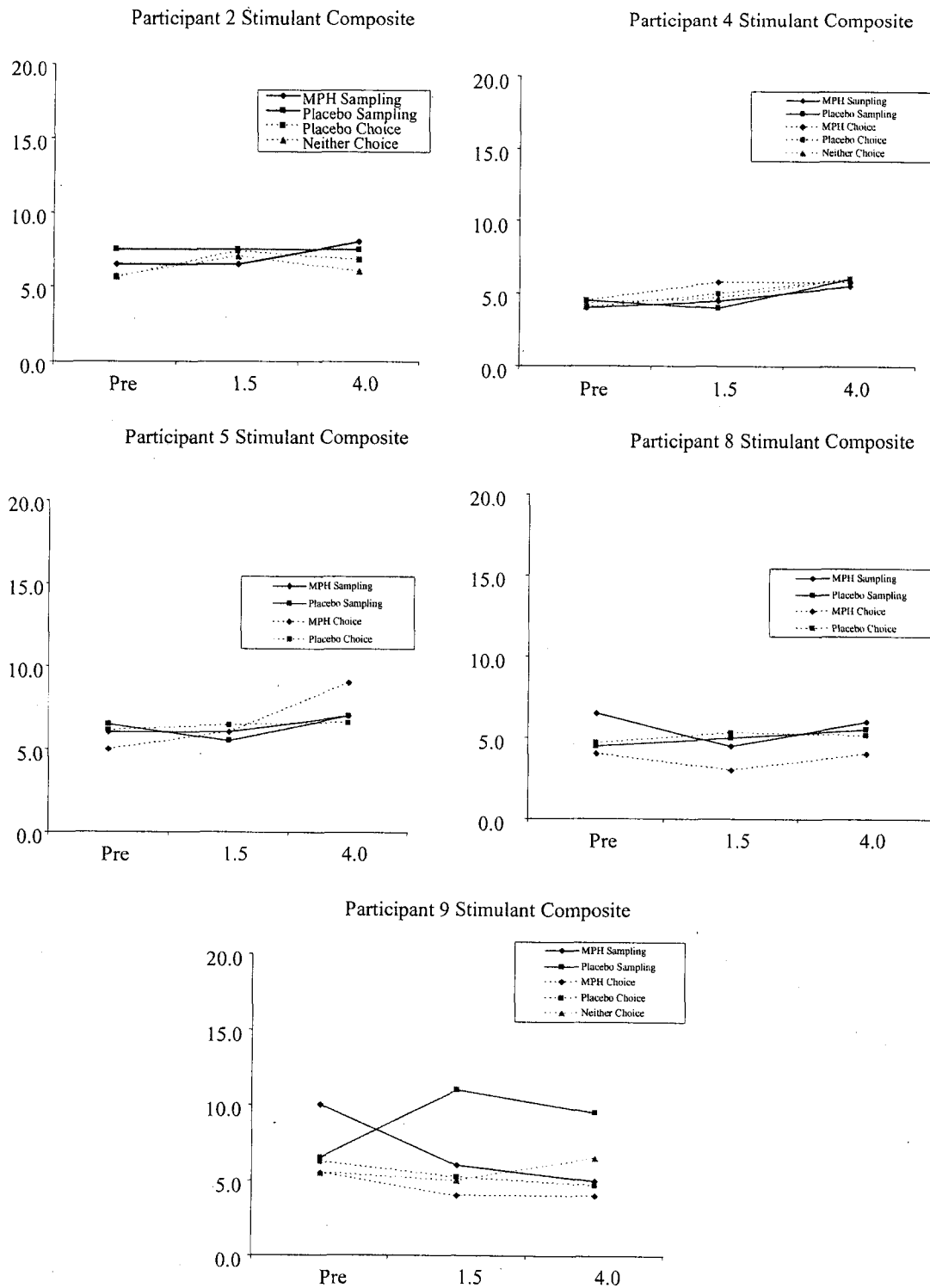


Figure 10. Stimulant Effects Composites for Non-Choosers.

1999); and one study reported significant reinforcing effects compared to placebo using a progressive-ratio procedure (Rush et al., 2001).

The present study may be most similar to Roehrs et al. (1999) such that the reinforcing effects of MPH are context-specific. As such, effect size scores suggest that during sampling sessions MPH-choosers had higher baseline ADHD symptoms, demonstrated greater improvement in mood and a greater reduction in ADHD symptoms upon receiving MPH. Although, the non-choosers reported a reduction in ADHD symptoms following MPH and Placebo during sampling sessions, MPH-choosers reported significantly greater ADHD symptom reduction following MPH administration, and a slight increase in ADHD symptoms following placebo. This suggests that perhaps the reinforcing effects of MPH are related to the clinical efficacy of MPH, such that the more efficacious MPH was in reducing ADHD symptoms, the more likely it was chosen over placebo.

Results of the current study, in addition to previous findings (e.g., Roehrs et al., 1999; MacDonald & Kollins, 2000) suggest that perhaps the reinforcing effects of MPH are expressed only under a particular set of environmental conditions. For example, in the current study, anecdotal subject comments suggested that their drug choice was influenced by the extent of the demands to be placed on them following drug administration. Specifically, participants reported choosing MPH when they needed to study or had class. Moreover, participants reported not choosing MPH when they “wanted to take a nap” or “had nothing to do.” These reports are similar to the work completed by Silverman and colleagues (Silverman, Kirby, & Griffiths, 1994, & Silverman, Mumford, & Griffiths, 1994), which demonstrated that the behavioral

requirements following drug administration (i.e., vigilance or relaxation activities) could alter the self-administration of stimulants (i.e., caffeine and d-amphetamine) and sedatives (i.e., triazolam). Based on these findings, the authors suggested that drug self-administration is related to the changes in environmental conditions. Thus, conditions of sleep deprivation, inattention and distractibility may function as establishing operations that increase the reinforcing efficacy of MPH. Likewise, the behavioral demands to be placed on an individual may also influence the reinforcing efficacy of this stimulant drug.

Continued research examining the conditions associated with the reinforcing effects of MPH may also be important from the standpoint of assessing the abuse potential of MPH. The reinforcing effects and subjective effects of a substance are typically used to assess the abuse potential of that drug. Results of the present study suggest that it may be necessary to reconceptualize indices used to measure the abuse potential of a substance. Most research asserts that if a drug functions as a reinforcer, it is considered to have considerable abuse liability (Fischman & Mello, 1989). Yet, as discussed by Roache and colleagues (1997), drug reinforcement in clinical populations is not always indicative of abuse potential in the same manner as drug reinforcement in drug abusers or other non-clinical (or nonhuman) samples. Drug abuse refers to a repeated pattern of self-administration that results in functional impairment for the individual taking the drugs (APA, 1994).

The reinforcing effects of clinically used agents may necessitate a different conceptualization of such drug-taking behavior. Specifically, the reinforcing effects of a clinically used agent may reflect therapeutic efficacy, rather than abuse potential. In these situations, the choice of drug over placebo may be reinforced by the consequences

of eliminating aversive stimuli (e.g., anxiety; Roache et al., 1997) or by more positive consequences, such as being able to work more efficiently, receiving greater praise from teachers and peers, or getting better grades (as may be the case with ADHD).

In the present experiment, the reinforcing effects of MPH were associated with a reduction in seemingly aversive symptoms (e.g., inattention, anxiety, sadness) and an increase in positive symptoms (e.g., “good effects”). This suggests that choosing to ingest MPH is associated with clinical efficacy, thus perhaps MPH is not producing significant clinical effects in non-choosers. Also of note in this experiment is the pattern of subjective effects associated with MPH. A number of previous studies have demonstrated that orally-administered MPH as low as 20-mg results in significant changes in ratings of “High,” and other effects associated with abuse potential (e.g., Heil et al., 2002; Kollins, Rush, Pazzaglia, & Ali, 1998; Rush et al., 1998). However, in spite of the reinforcing effects reported in the present study, the participant-rated effects of MPH were not consistent with previous studies. This suggests that perhaps the participant-rated effects may contribute to a differential profile of abuse potential of MPH in individuals diagnosed with ADHD. Moreover, this also suggests that the reinforcing effects and participant-rated effects of MPH are not isomorphic, which is consistent with other studies examining the reinforcing effects and participant-rated effects of drugs of abuse (e.g., Roache et al., 1995; Rush et al., 2001).

In addition, research suggests that neuropharmacological differences may contribute to differential abuse potential in individuals diagnosed with ADHD as compared to non-diagnosed individuals. Evidence supports the idea that neuropharmacological differences exist between diagnosed and non-diagnosed

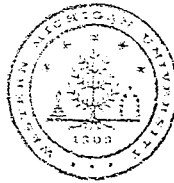
individuals with respect to dopamine functioning. Specifically, individuals diagnosed with ADHD differ from non-diagnosed controls with respect to dopamine transporter (DAT) density, such that DAT was significantly elevated in subjects diagnosed with ADHD (e.g., Dougherty et al., 1999). These differences in DAT density may contribute to the expression of ADHD symptoms and the efficacy of MPH treatment. It is possible that differences in dopamine functioning may influence the abuse potential of MPH such that MPH may not exert the same level of abuse potential in individuals diagnosed with ADHD as compared to non-diagnosed controls (e.g., Volkow et al., 1999, 2002).

Future studies that examine MPH in a context where there are measurable clinical changes will be important to help clarify the functional role of the reinforcing effects of the drug in this and other samples. Specifically, it is suggested that future work examine the reinforcing effects of MPH and concomitant participant-rated effects in diagnosed and non-diagnosed populations to further explore the role of clinical effects in the reinforcing effects of this stimulant drug.



## Appendix A

### Human Subjects Institutional Review Board (HSIRB) Approval Letter



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## WESTERN MICHIGAN UNIVERSITY

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Date: September 18, 2001

To: Galen Alessi, Principal Investigator  
Emily MacDonald, Student Investigator for dissertation

From: Mary Lagerwey, Chair

A handwritten signature in cursive script, reading "Mary Lagerwey".

Re: HSIRB Project Number 01-08-02

This letter will serve as confirmation that your research project entitled "An Evaluation of Methylphenidate Preference in Adults Diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD)" has been **approved** under the **full** category of review by the Human Subjects Institutional Review Board. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

Please note that you may **only** conduct this research exactly in the form it was approved. You must seek specific board approval for any changes in this project. You must also seek reapproval if the project extends beyond the termination date noted below. In addition if there are any unanticipated adverse reactions or unanticipated events associated with the conduct of this research, you should immediately suspend the project and contact the Chair of the HSIRB for consultation.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: August 15, 2002

Appendix B

Participant-Rated Effects Scale

Please place an "X" in the appropriate column to indicate how the following words or phrases describe you **AT THIS MOMENT**

		Not at All (1)	A little Bit (2)	Moderately (3)	Quite a Bit (4)	Extremely (5)
1	Happy					
2	Anxious					
3	Tense					
4	Angry					
5	Sad					
6	Fatigued					
7	Unable to concentrate					
8	Hungry					
9	Energetic					
10	Annoyed					
11	Focused					
12	Forgetful					
13	Cheerful					
14	Nervous					
15	Talkative					
16	Fidgety					
17	Distracted					
18	Restless					
19	Impulsive					
20	Overactive					
21	Inattentive					
22	Excited					
23	Agitated					
24	Irritable					
25	Frustrated					

Appendix C

Participant-Rated Effects Composites

ADHD	Composites	
	Mood	Stimulant Effects
Unable to Concentrate	Happy*	Hungry
Focused*	Anxious	Energetic
Forgetful	Tense	Excited
Talkative	Angry	
Fidgety	Sad	
Distracted	Fatigued	
Restless	Annoyed	
Impulsive	Cheerful*	
Overactive	Nervous	
Inattentive	Agitated	
	Irritable	
	Frustrated	

Note: All items were rated on a 5-point scale as follows: 1= *not at all*, 2= *a little bit*, 3 = *moderately*, 4= *quite a bit*, 5= *extremely*.

\*Reverse-scored

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