The Relationships among the Stimulus Functions and the Clinical Effects of Methylphenidate in Children Diagnosed with ADHD

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THE RELATIONSHIPS AMONG THE STIMULUS FUNCTIONS AND THE CLINICAL EFFECTS OF METHYLPHENIDATE IN CHILDREN DIAGNOSED WITH ADHD

by

Emily K. MacDonald

A Thesis
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Emily K. MacDonald
Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed childhood psychiatric disorder in the United States. Approximately 90% of children receiving pharmacological treatment for ADHD receive the stimulant methylphenidate (MPH). MPH is associated with positive effects across many behavioral domains, yet the mechanisms through which it exerts clinical effects have not been conclusively determined. MPH produces reinforcing and subjective effects, however it is not understood how these functions relate to clinical effects. The present study examined the relationship among several stimulus functions and the clinical effects of MPH. Participants were 5 children (aged 10-14) diagnosed with ADHD who were currently receiving MPH. The reinforcing effects of MPH were assessed using a double-blind choice procedure. Subjective effects were measured using self-report questionnaires. Clinical effects were measured using direct observations and a behavioral rating form. Results indicated that MPH functioned as a reinforcer in 3 of the 5 participants. Out of 30 total choices across participants (6 choices each), MPH was chosen 18 times (60%), placebo and neither were both selected 6 times (20%). MPH also produced variable patterns of participant-rated effects across subjects.
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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). 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. To address these behavioral problems, approximately 85-95% of individuals diagnosed with ADHD receive psychopharmacological treatment, and approximately 90% of children receiving medication are treated with the stimulant, methylphenidate (Ritalin®; Robison, Sclar, Skaer & Galen, 1999; Zito et al., 2000).

Methylphenidate (MPH) has been shown to have positive effects across a wide range of behavioral domains (for reviews, see DuPaul, Barkley, & Connor, 1998; Greenhill, 1998). These clinical effects are discussed in the following sections.
Clinical Effects of MPH

Inappropriate/Disruptive Behaviors

ADHD is associated with a developmentally inappropriate pattern of disruptive and maladaptive behaviors, and compared to a placebo, methylphenidate has demonstrated short-term efficacy in reducing these problems (for reviews see Greenhill, 1995; Jacobvitz, Srouge, Stewart, & Leffert, 1990). For example, in a study of 40 children diagnosed with ADHD, MPH significantly decreased the percentage of fidgety behavior, motor restlessness, teacher ratings of inattention, overactivity and problem situations (DuPaul, Barkley, & McMurray, 1994).

Treatment with MPH is also associated with reductions in overt aggression (e.g., Gadow, Nolan, Sverd, Sprafkin, & Paolicelli, 1990), covert aggression (e.g., Bukstein & Kolkso, 1998) and displays of covert antisocial behaviors such as stealing and property destruction (e.g., Klein et al. 1997). For example, in a three year study of 83 children, Klein et al. (1997) found that children who received MPH (average dose 41.3 mg/day) versus placebo demonstrated reductions in antisocial behaviors such as obscene language, attacking others, stealing and property destruction as measured by parent, teacher and clinician ratings and direct classroom observations.

Academic Functioning

Children diagnosed with ADHD typically experience school-related difficulties in areas of academic performance and achievement (Barkley, DuPaul, &
McMurray, 1990). Studies have demonstrated that methylphenidate contributes to immediate improvements in arithmetic, spelling and handwriting in children diagnosed with ADHD (for review see DuPaul et al., 1998). For example, Stoner et al. (1994) investigated the utility of curriculum-based measures (CBM) of math and reading for evaluating the effects of MPH (5 mg, 10 mg, 15 mg) on the academic performance of two students diagnosed with ADHD. The results demonstrated that improvements were seen in these areas, with best academic performances at 15 mg for one student and 5 mg for another student (Stoner et al., 1994).

Stimulant-induced improvements in academic productivity, teacher ratings of academic performance and accuracy have also been found in several other studies (e.g., DuPaul, Barkley, & McMurray, 1994; Pelham, & Milich, 1991). In a study of 76 children diagnosed with ADHD, Rapport, Denney, DuPaul, & Gardner (1994) evaluated the effects of MPH (5, 10, 15 and 20 mg) on children’s attention, academic efficiency and teacher ratings of classroom behaviors. Children were observed in their regular classrooms for 20 minutes, 3 days/week across a six-week period. Weekly classroom behaviors were measured by teacher ratings every Friday. Attention was characterized as on-task or off-task during 15-second observation intervals. Percent of problems on a graded assignment completed, and the percent of problems answered correctly were used as objective indices of academic functioning. Rapport et al. (1994) found that attention, double-blind teacher ratings and academic functioning all improved in a linear manner as a function of increasing dose of MPH. Additionally, compared to a group of non-diagnosed peers, 76% of ADHD children demonstrated
significantly improved or “normalized” attention, 94% showed improvements on
teacher ratings of classroom behavior, and 53% demonstrated improved academic
performance as a function of MPH treatment.

Social Functioning

The quality of social interactions between children diagnosed with ADHD and
their parents, peers and teachers is significantly improved by MPH, along with
concurrent reductions in the intensity of these interactions (e.g., Barkley, 1989;
Rapport et al., 1994).

Numerous studies have been conducted demonstrating the effectiveness of
MPH on improving mother-child interactions of children diagnosed with ADHD
(Barkley & Cunningham, 1979; Barkley, Karlsson, Strzelecki, & Murphy, 1984).
These studies have found that MPH increases children’s compliance with parental
commands and enhances their responsiveness in interactions with others. For
example, Barkley et al. (1984) observed the mother-child interactions of 54
hyperactive children, aged 4-9 years, during a double-blind, drug-placebo evaluation
of MPH (0.3 and 1.0 mg/kg) in free play and task situations. Results suggest that
MPH may “normalize” the mother-child interactions of children diagnosed with
ADHD to resemble the interactions of non-diagnosed children and their mothers. In
particular, children were observed to comply with greater frequency to maternal
commands during both free play and task situations. In addition, these children
sustained task compliance for longer time intervals, and exhibited fewer off-task
behaviors following maternal commands as a function of receiving MPH (Barkley et al., 1984).

In addition to affecting parent-child relationships, MPH has also been demonstrated to affect the social interactions of children diagnosed with ADHD and their non-diagnosed peers. In particular, MPH is dose-dependently associated with reductions in noncompliance, verbal and physical aggression, and the negative social behaviors exhibited by children diagnosed with ADHD (e.g., Bukstein & Kolkso, 1998). For example, in a study that examined the effects of 0.3 mg/kg MPH in 34 males, aged 7-14 years, diagnosed with ADHD, MPH decreased a variety of negative social behaviors including interrupting, swearing and teasing (Pelham, Vodde-Hamilton, Murphy, Greenstein, & Vallano, 1991). In addition, positive peer behaviors, such as helping, sharing, saying something nice and ignoring provocation improved as a function of age and MPH.

Mechanisms of Drug Action

Although methylphenidate is associated with a wide range of clinically beneficial effects, the manner in which the drug exerts its effects is not clear. That is, the specific mechanisms by which MPH alters behaviors have not been conclusively determined. A “mechanism of action” of a drug refers to a basic process by which a drug interacts with some variable regulating behavior to produce a change in a particular response (Thompson & Boren, 1977). For example, a stimulant drug like amphetamine may be said to increase productivity if the result of the drug’s
administration is an increase in response rate of some behavior that results in adaptive consequences.

The behavioral mechanism of a drug’s action is likely to vary across individuals, even for the same type of drug, due to the fact that different behavioral processes are involved in maintaining the behavior of different people (Pickens, 1977). The specification of these drug-behavior interactions has defined the field of behavioral pharmacology. There is a range of drug variables (e.g., dosage, time course of drug, etc.) that can interact with a range of behavioral and environmental variables (e.g., antecedent events, response topography, consequence variables, etc.) to produce a drug effect.

For example, a drug can interact with different schedules of reinforcement to produce behavioral effects. Rapport, DuPaul, and Smith (1985) investigated the effects of differing doses of MPH on operant responding under a multiple VR 5 FI 30-second reinforcement schedule in children characterized as hyperactive. The results showed the lower doses (5, 10 mg) increased responding on a schedule that controlled high response rate (VR 5), while having no significant effect on responding to a schedule which controlled a low rate (FI 30). This demonstrates that the same dose of MPH was shown to either increase or have no effect on operant responding, depending on whether the performance was maintained on a VR 5 or a FI 30-second schedule. Thus, the drug effects on behavior may be explained by the interaction between the drug and the schedules of reinforcement under which responding is maintained.
Before understanding how MPH interacts with behavioral and environmental variables to produce behavioral changes, it is necessary to briefly review the pharmacological mechanisms through which MPH is believed to exert its effects. MPH functions pharmacologically by stimulating the release of catecholamines. These effects are stronger in dopaminergic as compared to noradrenergic pathways, which are also significantly affected, and the net result is an overall facilitation of dopaminergic transmission (Kutcher, 1997). There is also a possibility that the effects of psychostimulants, including MPH, may be mediated by serotonergic pathways. Gainetdinov et al. (1999) examined the effects of the psychostimulants MPH, d-amphetamine, and cocaine in mice with genetically altered dopaminergic transport systems (e.g., DAT knockouts), which resulted in behavioral problems such as hyperactivity. Results indicated that psychostimulants (e.g. MPH) that increase serotonergic transmission were observed to reduce hyperactivity in the mice, and that this effect was not a result of dopaminergic activity. However, drug-induced alterations in neurotransmission alone do not reveal how a drug results in behavioral changes.

Despite knowledge of methylphenidate’s pharmacological effects, it is difficult to translate these effects into clinically meaningful events because behavioral events occur at different levels of analysis and are measured in different dimensions. The behavioral effects of drugs could be mediated by alterations in neurotransmission, but this does not imply that all drug effects are reducible to physiological events. This reduction would imply that the laws of physiology, per se,
yield the principles of drug effects on behavior (see Marr, 1990 for a discussion of reductionism). Rather, there are several variables that are said to control the effects of drugs on behavior, such as consequences, context, drug and behavioral history, demonstrating that drugs can be viewed as simply another environmental manipulation, and act as reinforcing, punishing, eliciting or discriminative stimuli (Marr, 1990). Therefore, it is important to conceptualize other factors that interact with the drug to have an effect on the behavior of the individual.

As mentioned previously, MPH produces changes in neurotransmitter activity, which produces changes in central nervous system functioning. This CNS change is associated with changes in behavior that may vary based on an individual organism’s behavioral history and the prevailing environmental conditions. These changes in behavior subsequently exert effects on the environment, thus influencing future drug-behavior interactions (Dykstra, 1992). For example, Chait, & Perry (1992) demonstrated that instructions and previous exposure to a drug could serve as discriminative stimuli thereby affecting behavior. Participants with a history of marijuana use were permitted an opportunity to smoke placebo marijuana. The participants that were informed that placebo marijuana was in fact active marijuana self-administered more placebo marijuana and reported more drug-induced subjective effects than the group told they might receive placebo marijuana. It is evident that nonpharmacological factors participate in drug-environment interactions to determine a behavioral outcome (Thompson & Boren, 1977).
Another example of the interaction between drugs and environmental variables is a study that demonstrated how MPH functions as an establishing operation (EO) when administered to children diagnosed with ADHD (Northup, Fusilier, Swanson, Roane, and Borrero, 1997). In a study of three children diagnosed with ADHD who were receiving MPH treatment, Northup et al. (1997) determined that MPH functioned to change the reinforcing efficacy of at least one reinforcer class. For example, activities functioned as more potent reinforcers following MPH administration as compared to placebo, while edibles were more effective reinforcers when MPH was not administered. Thus, Northup et al. (1997) demonstrated that one of the functions of MPH in producing behavioral changes is to alter the reinforcing efficacy of other stimuli and events in the child’s environment. Thus, it is important to examine other variables that may interact with MPH to regulate behavior.

Some clinical effects are obtained and measured in overt behavioral terms. To explain how MPH influences the clinical effects, we should conceptualize the mechanisms of action that influence behavioral changes of the drug. The following sections will provide a discussion of the discriminative stimulus effects, the participant-rated effects, and the reinforcing effects of MPH and how these mechanisms may influence clinical outcomes.

**Discriminative Stimulus Effects**

Methylphenidate can function as a discriminative stimulus, which sets the occasion for responding that is maintained by other reinforcers. In other words,
humans and nonhumans can be taught to discriminate between methylphenidate and placebo. This function of MPH has been demonstrated in nonhumans (Perkins, Eckerman, & MacPhail, 1991; Wood & Emmett-Oglesby, 1988), adult humans (Rush, Kollins, & Pazzaglia, 1998) and children (Kollins, Shapiro, Newland, & Abramowitz, 1998).

As Kollins et al. (1998, p. 375) pointed out, “Conceptualizing MPH as a stimulus embedded in a pattern of ongoing behavior may offer new insights into the behavioral mechanisms of action underlying the improvements noted with this drug.” To examine whether MPH serves as a discriminative stimulus in a clinical setting, Kollins et al. (1998) attempted to train children (aged 6-16) diagnosed with ADHD, who had a history of stimulant use for behavioral problems, to discriminate their usual dose of MPH (10-20 mg) from placebo. The results indicated that children diagnosed with ADHD could learn to reliably discriminate MPH from placebo. This study is the only demonstration in which drugs were shown to exert discriminative stimulus effects in children and adolescents in a manner similar to adults, suggesting that the mechanisms that mediate drug discrimination may also operate in childhood. Likewise, this is the only study demonstrating that a drug used to treat a clinical disorder can be discriminated by a group of individuals diagnosed with that disorder using traditional drug discrimination procedures. This raises the possibility that there may be a relation between discriminative stimulus effects and clinical effects. Such a hypothesis, however, remains to be empirically verified.
Successful drug discrimination behavior predicts that a drug may produce some subjectively described effects, although discrimination itself is not isomorphic with such effects (Kollins & Rush, 1999; Kollins et al., 1998; Preston & Bigelow, 1991; Rush et al., 1998). Thus, it is important to also consider the participant-rated effects of a drug in order to gain some insight into the subjective drug experience.

Methylphenidate produces significant changes in a number of participant-rated effects when compared to placebo in human adults. Studies examining the participant-rated effects have found that MPH significantly affects scores on several mood scales (Chait, 1994; Heishman & Henningfield, 1991; Martin, Sloan, Sapira, & Jasinski, 1971; Roehrs, Papineau, Rosenthal, & Roth, 1999; Rush et al., 1998; Rush, Essman, Simpson, & Baker, in press; Smith & Davis, 1977). These studies demonstrated that MPH increased ratings on (a) four scales of the Profile of Mood States (POMS): (1) arousal, (2) vigor, (3) tension, (4) anxiety; (b) three scales of the Addiction Research Center Inventory (ARCI): (1) A (amphetamine scale), (2) BG (benzedrine group; empirically-derived amphetamine sensitive scale), and (3) MBG (morphine benzedrine group; a measure of euphoria); (c) visual analog scale ratings of (a) “stimulated,” (b) “high,” (c) “anxious,” (d) “talkative,” (e) “euphoric,” (f) “like drug,” and (g) “like to take again.” In addition, MPH has been demonstrated to reduce scores on the ARCI subscale LSD (lysergic acid diethylamide; a measure of dysphoria) and the POMS Fatigue scale (Chait, 1994; Roehrs et al., 1999).
However, differing results were obtained from a sample of 57 cocaine-dependent patients, in which MPH produced significant increases in (a) anxiety, (b) depression and (c) anger on the POMS; shaky/jittery on a visual analog scale; and dysphoria on the LSD scale of the ARCI (Roache, Grabowski, Schmitz, Creson, & Rhoades, 2000).

Despite these results, few studies have examined the participant-rated effects of methylphenidate in children. In a series of experiments, Kollins et al. (1998) studied the participant-rated effects of MPH in children diagnosed with ADHD using the Subjective Effects Rating Scale (SERS) which was developed for the study. The results demonstrated that MPH did not produce reliable patterns of participant-rated effects in children diagnosed with ADHD, despite the fact that MPH was discriminated by these children. The children’s individual ratings of subjective effects were highly variable. In one experiment, the only participant who exhibited significant changes in subjective effects was also the only participant who had significant changes in behavior as rated by caregivers (Kollins et al., 1998). These authors suggested that this finding may be evidence for a link between clinical effects and subjective effects.

Several variables may account for the lack of reliable participant-rated effects. First of all, Kollins et al. (1998) did not use instruments that are typically used to assess subjective effects, such as the POMS or the ARCI. Items on the SERS were derived from three sources. First, stimulant-appropriate items from the Addiction Research Center Inventory (ARCI: Martin et al., 1971) were selected and changed to
an age-appropriate reading level. Secondly, items were selected from the Side Effects Rating Scale (Barkley, 1991). Lastly, items were selected based on discussions with clinicians experienced in working with children diagnosed with ADHD. Although the items on the SERS may have clinical utility for assessing the effectiveness of stimulant medication in children, the psychometric properties of this instrument are not known.

A second explanation for the lack of participant-rated effects could be that these children lack the verbal repertoire, the reinforcement history for identifying drug effects or a combination of both (Kollins et al., 1998).

In another study assessing the subjective-effects of methylphenidate, Walker, Sprague, Sleator and Ullman (1988) examined the mood reports of children diagnosed with ADHD who were being treated with MPH. Using a version of the POMS modified for use in pediatric populations, they examined the effects of MPH on six factors: (1) tension-anxiety, (2) depression-dejection, (3) anger-hostility, (4) vigor-activity, (5) fatigue-inertia, and (6) confusion-bewilderment. Results indicated a significant reduction in “anger-hostility” related to a 0.7 mg/kg dose of MPH. Changes in scores on the remaining scales did not reach statistical significance.

Walker et al. (1988) noted that although the POMS is considered a reliable measurement of mood effects, the generalization of the results to all children diagnosed with ADHD would be unwarranted for several reasons. First, the children and parents in this study were aware of their need for therapy and were actively seeking outpatient treatment. Again, when studying these subjective effects, it is
important to consider the possibility that children diagnosed with ADHD may lack
the verbal repertoire necessary to accurately describe the drug’s effects.

In a similar line of research Bowen, Fenton and Rappaport (1991) investigated
the general feelings, knowledge and attitudes of 45 children receiving stimulant
medications for ADHD. This study also compared the children’s perceptions
concerning the effects of their medication with those of their parents. Their results
demonstrated that 89% of the children felt that the medication was helpful and would
continue to take the medication if the decision was theirs, and most children (78%)
liked or were indifferent to the medication despite any side effects that were
experienced. The remaining children (11%) who responded that they would stop
taking their medication if they could were more likely to perceive the medication as
unhelpful. Further, Bowen et al. (1991) found that three variables (1) embarrassment
about taking medication, (2) sleeping difficulties, and (3) type of medication were
able to predict whether a child liked or disliked taking their medication.

Reinforcing Effects of Methylphenidate

Most researchers agree that there is a strong relationship between the
participant-rated effects and the reinforcing effects of methylphenidate and other
drugs. Thus, one might predict that drugs which serve as reinforcing stimuli in
animals should produce euphoria in humans (Schuster, Fischman, & Johanson, 1981).
Nonhuman research

Nonhuman self-administration provides an opportunity to assess the reinforcing properties of a drug. In many studies, infrahumans are given an opportunity to emit a response that is followed by drug delivery. If a drug maintains responding it serves as a positive reinforcer. Nonhuman self-administration provides a way of studying the mechanisms controlling behavior including an array of physiological mechanisms and environmental variables, such as reinforcement contingencies and stimulus control (Thompson & Boren, 1977). Thus, the study of drugs as reinforcers offers insight into understanding basic mechanisms controlling behavior.

Methylphenidate produces reinforcing effects as demonstrated by a number of studies in which it is reliably self-administered by nonhumans. For example, Risner, & Jones (1975) demonstrated that dogs would initiate and maintain responding reinforced by MPH. Under conditions in which MPH was freely available, wherein every response produced a drug injection, the subjects began to self-administer MPH within one to six days after it became available. Numerous additional studies have demonstrated that methylphenidate is self-administered at rates above saline in infrahumans, thus it is an effective reinforcer (e.g., Aigner & Balster, 1979; Johanson & Schuster, 1975).
Human Research

Examining methylphenidate self-administration behaviors in nonhumans provides us with a way of studying the mechanisms that control behavior in a laboratory setting. However, it is important to also examine the conditions in which MPH serves as a reinforcer and gains control over human behavior (e.g., Henningfield, Lukas, & Bigelow, 1986; Johanson & deWit, 1989). MPH produces dose-related increases in participant-rated effects in non-drug abusing adult humans on measures such as “euphoria” (Chait, 1994; Martin et al., 1971; Smith & Davis, 1977). However, it is necessary to examine both the reinforcing effects as well as the subjective effects of MPH in human participants in order to improve the understanding of the mechanism of drug action.

One way to assess the reinforcing effects of a substance in humans is through a choice procedure (e.g., deWit & Johanson, 1987) wherein the participants’ preference for one of two substances is measured. During this procedure, participants first experience a sampling phase in which they are exposed to a drug and a placebo, contained in separate color-coded capsules, under double-blind conditions on separate days. In these double-blind conditions, neither the subject nor the experimenter is aware of the contents of the capsules. Participants are typically told they are receiving “Drug A” or “Drug B.” They are instructed to note the color of the capsule and to try to associate any drug effects with that color capsule. Participants are told that the same drug will always be contained in the same color capsule. Following the
sampling phase, the participants are given the opportunity to choose which drug (i.e., which colored capsule) they would like to administer.

There are only three published studies that have directly examined the reinforcing effects of MPH in humans (Chait, 1994; Roehrs et al., 1999; Rush, et al., in press). 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 neither drug. Participants participated in three choice days. The results indicated that out of 105 total choices across participants, MPH was chosen 29 (27.6%) times, placebo was chosen 9 (8.6%) times, and neither substance was chosen in 67 (63.8%) occasions. Conclusions regarding the sources of variability that predict the choice of MPH cannot be drawn based solely on an individual study. Nevertheless, the findings warrant a more comprehensive assessment of the subjective and reinforcing effects of MPH, especially given its widespread clinical use.

In the second study that examined the reinforcing effects of MPH (Roehrs et al., 1999), researchers manipulated the sleep times of six healthy volunteers 21-30 years of age. During four sampling days, participants received 10 mg MPH or placebo following four or eight hours in bed. On four separate choice days, after spending 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 suggest that the enhanced preference for MPH after four hours in bed is consistent with studies showing that the reinforcing effects of a drug relate to current environmental circumstances.

In the final study, Rush et al. (in press) assessed the reinforcing effects of MPH (20-40 mg), d-amphetamine (10-20 mg), and placebo in eight healthy, non-drug-abusing, non-sleep-deprived adults using a modified progressive ratio schedule, which are frequently used to assess the reinforcing effects of commonly abused drugs. In the progressive ratio schedule used, participants had eight opportunities to work on a computer task in order to earn eight capsules. These capsules each contained 12.5% of the dose used in the sampling session. The number of mouse clicks required to earn additional capsules doubled (e.g., 50, 100, 200, 400, 800, 1600, 3200, 6400). The dependent measure used was the break point, which is the last ratio completed. Results indicated that the highest dose of MPH (40 mg) increased the break-point values significantly above placebo, demonstrating that MPH functioned as a reinforcer in these non-drug-abusing, non-sleep-deprived participants.

Through increased understanding of the reinforcing and participant-rated effects of MPH, it may be possible to clarify the behavioral mechanisms of this drug with respect to its clinical effects in children to whom it is prescribed for behavioral difficulties. It is probable that drugs that cannot be differentiated from placebo are less likely to be self-administered again by a subject, while drugs that are identified (discriminated) as a stimulant have a higher chance of being self-administered by the
subject (Foltin & Fischman, 1991). Similarly, it is often assumed that certain subjective effects of drugs are related to their reinforcing effects, however, the exact nature of this relationship may vary across participants and environmental settings. In addition, the clinical effects of MPH may be associated with the subjective and reinforcing effects of the drug as well. This relationship may also vary across participants and environmental settings.

The reinforcing effects of a drug are typically associated with the drug’s abuse liability. However, the present study will explore an alternative to this conceptualization that will result in a better understanding of the stimulus functions of MPH. By examining the relationships among the subjective, reinforcing and clinical effects, we can gain insight into the behavioral mechanisms of MPH in children diagnosed with ADHD. An investigation of the relationship between these functions can extend the present understanding of how a drug works.

Purpose of Present Study

Methylphenidate produces a wide array of clinical effects in children diagnosed with ADHD. Yet, we do not know how these clinical effects are related to the stimulus functions of MPH. It is not known if evidence of the clinical effects of MPH can be used to predict the subjective and reinforcing effects of the drug. Likewise, it is not certain whether information regarding the reinforcing and subjective effects can be used to predict the clinical efficacy of MPH in children diagnosed with ADHD.
Methylphenidate has several stimulus functions, yet we do not know how these functions relate to the behavioral effects seen in children diagnosed with ADHD who are prescribed MPH. The present study examines (a) the extent to which MPH exerts reinforcing effects determined by the reliable choice of active medication versus placebo, (b) the extent to which MPH exerts subjective effects, and (c) the extent to which the subjective and reinforcing effects are associated with one another and with the clinical effects of MPH.
METHODS

Participants

Participants for this study included four males (ages 10-14) and one female (aged 10). Participants were recruited through local physicians and psychologists, recruitment flyers, and word of mouth.

Participants were recruited on the basis of two criteria: (1) an established diagnosis of ADHD, and (2) a history of methylphenidate use for behavior problems associated with ADHD. The subject’s parents, or one parent and another individual with whom the child has significant contact, completed the Child Behavior Checklist (Achenbach & Edelbrock, 1993; inclusionary criterion was an Attentional Problems subscales T score ≥ 65); Conners’ Parent Rating Scale-48 (Conners, 1990; inclusionary criterion was an Impulsive-Hyperactive Scale T score ≥ 65). These inclusionary criteria were used to corroborate the ADHD diagnostic status of participants and to ensure a relatively homogeneous group. (See Table 1 for subject demographics.)

In addition, all participants in the study had a prescription for immediate-release methylphenidate (Ritalin) for the treatment of ADHD. Subject 2 was previously receiving sustained-release MPH due to poor treatment compliance; however, his physician altered his dose to a comparable dosage of MPH-IR for the purposes of this study. Participants each had been receiving MPH treatment for at
<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Time on MPH</th>
<th>Dose</th>
<th>CBCL (Attention Problems)</th>
<th>CPRS-48 (Impulsive-Hyperactive; Hyperactivity Scale)</th>
<th>WISC (Block Design + Vocab.)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>10</td>
<td>4'11&quot;</td>
<td>85 lbs.</td>
<td>36 mos.</td>
<td>10 mg</td>
<td>T = 69</td>
<td>T = 72</td>
<td>IQ = 91</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>14</td>
<td>5'7&quot;</td>
<td>200 lbs.</td>
<td>60 mos.</td>
<td>20 mg</td>
<td>T = 81</td>
<td>T = 72</td>
<td>IQ = 68</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>36 mos.</td>
<td>10 mg</td>
<td>T = 70</td>
<td>T = 76</td>
<td>IQ = 83</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>14</td>
<td>5'2&quot;</td>
<td>100 lbs.</td>
<td>84 mos.</td>
<td>30 mg</td>
<td>T = 78</td>
<td>T = 76</td>
<td>IQ = 126</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>10</td>
<td>5'2&quot;</td>
<td>100 lbs.</td>
<td>12 mos.</td>
<td>10 mg</td>
<td>T = 72</td>
<td>T = 87</td>
<td>IQ = 106</td>
</tr>
</tbody>
</table>
least six months prior to selection for the study, so as to determine the probability of any potential side effects. Due to the inclusion of MPH manipulation, each subject's prescribing physician was contacted and the purpose and procedure of the study was explained. On experimental days, participants experienced only one variation in their typical daily medication regimen. This drug manipulation involved the child's late afternoon dose and occurred in the laboratory setting. The child received his/her usual maintenance dose during morning and noon administrations.

Participants were excluded from the study if (a) they were taking any other type of psychoactive medication, (b) they exhibited any gross neurological, (c) if there was any sensory or motor impairment, (d) they had a history of other significant learning or psychiatric problems, and/or a known family history of diabetes. Nine of the 14 children screened were excluded for various reasons. Three children were excluded because they were receiving psychoactive medications in addition to MPH, two were not currently receiving MPH treatment, one did not meet age requirements, and two could not commit to the length of the present study.

Volunteers were directly compensated in two ways. Participants received $1.00 for each session completed, plus an additional $10 bonus for completing all 13 sessions. In addition, during experimental sessions, participants received assistance with outside homework assignments, and practiced basic academic skills.
Location and Duration

LCABS

Participants reported to the Laboratory for Child and Adolescent Behavioral Studies (LCABS), which is located in 1504 Wood Hall at Western Michigan University. The screening session, medication administration and the completion of self-report forms took place in LCABS. This is also where the subject received compensation for participation.

Project Help

Behavioral observations took place in a classroom operated and staffed by Project Help, a remedial education service project sponsored by the School Psychology program and the Department of Psychology at WMU, located in 1509 Wood Hall. Project Help is an academic skills enrichment program which serves K-12 students who are at-risk of academic failure and who may benefit from instruction in basic skill areas such as reading, math, writing and spelling. This setting included approximately ten students enrolled in Project Help with their respective tutors. Children enrolled in this program receive one-to-one attention from the staff. Participants in this study were not formally enrolled in the tutorial program, thus did not have an individual tutor. However, participants were seated at individual cubicles and had access to a desk and a computer. Participants were engaged in various academic tasks while in the Project Help facility.
Parents/guardians were responsible for arranging transportation to and from LCABS on 13 separate occasions. The screening session lasted approximately one hour. Subsequent experimental sessions were conducted Monday through Thursday beginning at approximately 4:00 p.m. and lasting until approximately 6:00 p.m.

Apparatus/Materials

Capsules

The subject’s maintenance dose of methylphenidate and an inert placebo were each packaged in opaque capsules (size 01) to ensure that the enclosed substance was unknown to the subject and to the researcher. The capsules were placed in separate bottles labeled as “Bottle A” and “Bottle B” with the methylphenidate being 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 thing.

Colored Wristbands

The participants received a wristband that was labeled with the letter of the capsule he/she received that day. This wristband was to remind the participants which letter capsule they received, so that they could associate the effects of that capsule with the appropriate letter.
Cueing Tape

A tape recording that contains cues for the beginning of 30-second intervals was used in direct observations. The tape said, "Begin 1" and then 30-seconds later, "Begin 2." Observers used a tape recorder and headphones when using this tape while recording observations.

Dependent Measures

Drug Choice Behavior

Participants first sampled two capsules containing either methylphenidate or placebo, which were contained in capsules labeled with different letters. In subsequent discrete choice trials, the subjects were presented with the labeled capsules and chose the substance they preferred (i.e., "Pill A", "Pill B" or neither). The use of a "Neither" option was included to replicate prior examinations 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). The number of times one substance was chosen over the other served as an indicator of its relative reinforcing effects (de Wit, 1991). The drug choice was recorded on the subject's daily score sheet. 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 (Johanson & de Wit, 1989; de Wit & Griffiths, 1991; Foltin & Fischman, 1991).
Participant-Rated Effects

In order to assess the participant-rated effects of MPH in children diagnosed with ADHD, the participants completed various self-report measures. Subjective effects are important because of their potential relationship to drug choice (Jasinski & Henningfield, 1989). Children may experience a variety of mood and physiological changes as a result of stimulant medication. The participant-rated effects are important in that they may be useful in predicting reinforcing and clinical efficacy of MPH. The subjective ratings were assessed pre-drug administration, and 1½-2 hours post-drug administration. The following self-report scales were used to evaluate these effects.

How I Feel Questionnaire

This is a 28-item questionnaire adapted from the van Kammen-Murphy Mood Scale (van Kammen & Murphy, 1975). Items are rated on a 4-point scale (0 = Not at all, 1 = A little, 2 = Some, 3 = A lot). This adapted scale has been used with children to measure the subjective effects produced by caffeine (Elkins et al., 1981) and d-amphetamine (Rapoport et al, 1980).

Profile of Mood States (POMS)

A short form of the POMS was used to assess mood and affective state. This version consists of 37-items that are rated on a 5-point scale (0 = Not at all, 1 = A little, 2 = Moderately, 3 = Quite a bit, 4 = Extremely). Compared to the original 65-
item scale (McNair et al., 1971), the shortened version has been shown to have adequate psychometric properties (Shacham, 1983). This scale has been used to assess the effects of stimulants in children (Walker et al., 1988). Six scales are derived from the 37 items: (1) anger/hostility, (2) confusion/bewilderment, (3) depression/dejection, (4) fatigue/inertia, (5) tension/anxiety, and (6) vigor/activity.

Subjective Effects Rating Scale (SERS)

This is a 22-item scale developed by Kollins et al. (1998) to assess the participant-rated effects of methylphenidate and other stimulant medication in children and adolescents. Items from the questionnaire are rated on a 4-point scale (0= Not at all, 1=A little, 2=Some, 3=A lot). Items on the SERS were derived from three sources. First, stimulant-appropriate items from the Addiction Research Center Inventory (ARCI; Martin et al., 1971) were selected and changed to an age-appropriate reading level. Secondly, items were selected from the Side Effects Rating Scale (Barkley, 1991). Lastly, items were selected based on discussions with clinicians experienced in working with children diagnosed with ADHD.

Visual Analog Scale (VAS)

The VAS consisted of ten 100-mm horizontal lines each labeled with a different item. Each scale was presented individually. Participants were instructed to rate each item on the basis of how they felt at the present time. Each VAS scale was anchored with “not at all” at the left-most extreme, and “very much” at the right-most
extreme. Participants were instructed to place a mark on each line indicating how they felt at the moment. The items rated included (a) like drug, (b) energetic, (c) sleepy, (d) friendly, (e) restless, (f) nervous, (g) hungry, (h) excited, (i) happy, and (j) feel like talking.

Direct Behavioral Observations

An independent observer began direct observations 45 minutes after the pill ingestion to ensure peak behavioral drug effects, and observed for three 15-minute intervals. Participants were observed for 15 minutes while they were engaged in academic work. Using the cueing tape, every 30 seconds the observer checked on the coding sheet whether any of the five behavior categories were observed. Once a behavior was checked during an interval, it could not be checked again until the next interval. The first and third observation periods were conducted in Project Help, while the second period was conducted during a break in order to observe the child during social situations.

During the direct observation periods conducted in Project Help, children completed the in-seat academic work assigned by the research assistant. Data were collected using the ADHD Behavior Coding System developed by Barkley (1990). In this system, the child was observed during the performance of independent academic work (the Restricted Academic Situation; RAS). Observers recorded the occurrences of (a) off-task behavior, (b) fidgetiness, (c) vocalizing, (d) playing with objects, and (e) out of seat behavior.
During the social situation observations, observers recorded behavioral observations that occurred during a 15-minute break from academic work. During this break, children were allowed to leave their assigned seat and engage in social activities with other children in the Project Help program. The types of social activities included (a) playing computer games, (b) listening to music, (c) visiting the vending machines, and (d) playing outdoors. Data were collected using the Social Situations Behavior Coding Form (adapted from Pelham, Vodde-Hamilton, Murphy, Greenstein and Vallano, 1991). Observers recorded the occurrences of (a) positive peer interactions, (b) conduct problems, (c) noncompliance, (d) interrupting, and (e) negative verbalizations.

The observers were advanced undergraduate psychology students. The researcher trained the observers using instructions adapted from Barkley (1990), role playing, and by modeling appropriate coding using videotapes of children in school and social situations. Observers were trained using the videotapes until 0.90 agreement was achieved. This training was completed in an average of four sessions lasting one-half hour each. During the present study, observers were situated in the room such that they avoided direct eye contact with, and were distanced from, the target child by approximately two cubicles, while allowing for clear determination of task-related attention. Observers were blind to the contents of the medication capsules.
Interobserver Agreement

A second independent observer collected data using the Restricted Academic Situation and Social Situations behavioral coding forms during a minimum of 25% of the direct observations across participants. Interobserver agreement for all ten categories was calculated by dividing the number of agreements by the number of agreements and disagreements and multiplying by 100. The interobserver agreement was calculated separately for each category used in the behavioral observations.

Teacher Ratings

In-class observations correlate highly with teaching ratings of ADHD symptoms (Barkley, 1990). Therefore to evaluate reliability, the same research assistant completed the Conners’ Teacher Rating Scale-28 (CTRS-28; Conners, 1990) every session, 1.5-2 hours after the subject received his/her capsule. The CTRS-28 is effective in assessing stimulant drug effects and other treatment effects, when the convenience of completion of the scale is paramount (Barkley et al., 1988).

Procedures

Screening Session

The first session was a screening session wherein the child’s parent completed the CBCL (Achenbach & Edelbrock, 1993) and the CPRS-48 (Conners, 1990). Parents were also given an additional copy of these forms to be completed by another
adult with whom the child has significant contact. In the first session the child was administered a short form of the Wechsler Intelligence Scale for Children (3rd ed.: WISC-III; Block Design and Vocabulary subtests; Wechsler, 1991), to screen for intellectual functioning. If the children met criteria for the experiment, parents were asked to provide consent to contact the child’s physician to assure that the protocol was in the best interest of the child and to provide a prescription for MPH and placebos. The placebo used was dextrose, so all participants were screened for diabetes through the parent interview on medical history. The same local pharmacist at Sindecuse Health Center at Western Michigan University filled all prescriptions. The pharmacist encapsulated the active medication and the placebo in capsules that were identical in appearance, which were placed in separate bottles labeled with different letters. All filled prescriptions were paid for and picked up by the researcher at Sindecuse Health Center.

Throughout the remaining 12 sessions, participants arrived at LCABS between 3:45-4:00 p.m. A multiple drug free choice procedure was used to assess the reinforcing effects of MPH. This design consisted of six sampling sessions designed to provide participants with experience with the effects of the two drug conditions, MPH and placebo, on the basis of which they subsequently chose their preferred substance. The choice phase consisted of six choice sessions wherein under double-blind conditions, participants selected MPH, placebo, or neither substance. Details of the sampling and choice sessions are as follows.
Sampling Sessions

There were six sampling sessions, which occurred on Mondays and Tuesdays for three weeks. On the first sampling day, upon arriving at LCABS, participants completed the participant-rated effects questionnaires. After completing the questionnaires, 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 of a different letter. Participants also received a wristband labeled with the same letter as the pill administered to help them remember what capsule they received that day. Participants were instructed to associate the effects of the capsule with the letter. Capsule letter assignments varied across participants. Participants were informed that the same letter capsule would always contain the same thing (e.g., “real” medication or “pretend” medication). The order in which placebo and MPH were scheduled in the sampling sessions was counterbalanced across subjects and within-subjects across weeks. Drug administration was double-blind, and the experimenter and the observers were unaware of the contents of the capsules.

After receiving the capsule, the subject was escorted across the hall to the Project Help facility. While in Project Help, the subject was seated at his/her assigned desk and worked on various academic tasks. Participants received assistance with homework assignments from school, played computer games, and worked on math and spelling worksheets provided by the researcher.
An independent observer began direct behavioral observations 45 minutes after the ingestion of the capsule (approximately 4:45 p.m.). During this time the participant was directed to work on various math sheets and was observed for 15 minutes. Project Help had a scheduled break from 5:00-5:15 p.m. During this time, research participants also took a break, and were encouraged to participate in the break-time activities. During the break, the observer recorded behaviors using the Social Situations Behavioral Coding Form.

Following these direct behavioral observations, between 1½ -2 hours after the ingestion of the capsule, a research assistant completed the CTRS-28 rating form.

Two hours after the ingestion of the capsule (approximately 5:45 p.m.-6:00 p.m.), the subject met with the researcher in the conference room in LCABS to complete the participant-rated effects questionnaires. After the completion of the questionnaires, the subject received monetary compensation from the researcher and was provided with verbal praise for his/her participation.

Choice Sessions

The choice phase provided the primary dependent measure, the number of occasions on which one substance was chosen over another. There were six choice sessions which occurred on Wednesdays and Thursdays for three weeks. In the choice sessions, upon arriving at LCABS, participants completed the participant-rated effects questionnaires. Following the completion of the questionnaires, participants were presented with three cups: one with “Pill A,” one with “Pill B,” and an empty cup
labeled “C.” The participant chose one of three options: (1) to ingest “Pill A,” (2) to ingest “Pill B,” or (3) to take neither capsule. The child was presented with a letter-matched wristband (with “Neither” being labeled “C”). Following the choice procedure, the participant was escorted to Project Help. The procedures for collecting direct behavioral observations, teacher ratings and participant-rated effects were the same as in the sampling sessions.

Integrity of Independent Variable

The independent variable in this experiment involved the pharmacological manipulations of drug type (i.e., MPH or placebo). In order to ensure that the independent variable contacted the participant’s behavior and was consistently administered, there was a data-recording checklist. On this chart, the letter of the pill administered and the time of administration was recorded. In addition, after the behavioral observations were completed, the observer initialied the data-recording sheets. Likewise, when the participant-rated effects were collected, they were checked on the recording form. All of the participant’s data were labeled with his/her identification number and stored in a binder kept in a locked cabinet in LCABS.
RESULTS

Reinforcing Effects

The results of the choice sessions were analyzed by examining the percentage of MPH choices per subject (Figure 1). Overall, out of 30 total choices across participants (six choices each), MPH was chosen 18 times (60%), placebo and neither were each chosen six times (20%).

Figure 1. Reinforcing Effects of MPH Across Participants.

According to the criteria used by Chait (1994), Participants 2, 4 and 5 were classified as “MPH choosers.” Participant 2 chose MPH 4/6 (67%) and Placebo 2/6
Participants 4 and 5 both chose MPH 5/6 times (83%) and Neither one time (16%).

Participants 1 and 3 did not have reliable choice patterns and were classified as “non-choosers.” Participant 1 chose MPH 3/6 times (50%), Placebo 2/6 times (33%) and Neither 1/6 times (16%). Participant 3 chose MPH 1/6 times (16%), Placebo 2/6 times (33%) and Neither 3/6 times (50%) (Figure 2).

![Figure 2. The Choices of MPH, Placebo, and Neither for Each Participant to Demonstrate Relative Reinforcing Effects.](image)

MPH choice was also plotted as a function of dose across participants (Figure 3), wherein the percentage of choices made at Placebo/Neither, 10 mg, 20 mg, and 30 mg were plotted. Out of the 30 choice opportunities in which Placebo and Neither were available, 12 choices (40%) were for Placebo or Neither. Out of the 18 choice opportunities in which 10 mg of MPH was available, MPH was selected nine times
(50%). Out of the six choice opportunities in which 20 mg of MPH was available, MPH was selected four times (66.7%). Out of the six choice opportunities in which 30 mg of MPH was available, MPH was selected five times (83.3%). This indicates that MPH choice increased as a function of dose.

Clinical Effects

Behavioral observations and the number of math problems attempted and correctly completed were examined under MPH and placebo conditions. Initial t-tests
on the categories used for behavioral observations and academic performance yielded no significant results between MPH and the No Drug condition (Placebo/Neither). In addition, there were no significant differences obtained between sampling and choice sessions. The results from the behavioral observations using the Restricted Academic Situations coding form are shown in Table 2.

The results from the Social Situations observations are not presented since the participants did not typically engage in activities that yielded any behaviors that met criteria for the categories used during observations.

Given the lack of significant differences, examining the interactions between the clinical effects, reinforcing effects, and subjective effects of MPH was not possible.

Participant-Rated Effects

Subjective effect questionnaire data were analyzed for each participant. In order to examine the participant rated effects, the change from baseline (post-drug administration scores-pre-drug administration scores) was computed for each item, and the absolute values for the change scores were averaged for each questionnaire. The differences between change scores obtained on MPH days and No Drug (i.e., Placebo or Neither) days were computed. Items that differed from the average by one standard deviation were considered to be meaningful changes.

Table 3 shows the results from the individual-subject analyses. The patterns of responding on the participant-rated effects questionnaires were inconsistent across
Table 2

Percentage of Intervals in Which Target Behaviors Were Observed Using the Restricted Academic Situations Coding Form Averaged Across Sampling and Choice Sessions*

<table>
<thead>
<tr>
<th>Subject</th>
<th>MPH</th>
<th>No Drug</th>
<th>MPH</th>
<th>No Drug</th>
<th>MPH</th>
<th>No Drug</th>
<th>MPH</th>
<th>No Drug</th>
<th>MPH</th>
<th>No Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Of task</td>
<td>36.6</td>
<td>55.5</td>
<td>51.4</td>
<td>49</td>
<td>67.5</td>
<td>78.8</td>
<td>63.8</td>
<td>83.3</td>
<td>48.9</td>
<td>53.3</td>
</tr>
<tr>
<td>Fidgety</td>
<td>65.8</td>
<td>85.2</td>
<td>20.2</td>
<td>18.3</td>
<td>80.5</td>
<td>86.7</td>
<td>77.6</td>
<td>50.0</td>
<td>61.25</td>
<td>60.0</td>
</tr>
<tr>
<td>Vocalizing</td>
<td>2.5</td>
<td>1.7</td>
<td>0</td>
<td>0.3</td>
<td>3.6</td>
<td>23.8</td>
<td>4.8</td>
<td>2.7</td>
<td>8.9</td>
<td>083</td>
</tr>
<tr>
<td>Playing w/objects</td>
<td>3.6</td>
<td>3.8</td>
<td>7.4</td>
<td>9.7</td>
<td>3.9</td>
<td>8.6</td>
<td>19.5</td>
<td>27.2</td>
<td>8.9</td>
<td>21.3</td>
</tr>
<tr>
<td>Out of seat</td>
<td>5.5</td>
<td>5.2</td>
<td>8</td>
<td>4.0</td>
<td>20</td>
<td>15.7</td>
<td>6.9</td>
<td>11.6</td>
<td>4.8</td>
<td>9.6</td>
</tr>
</tbody>
</table>

* No significant differences between the MPH condition and the No Drug (Neither/Placebo) conditions were observed.
Table 3
Participant-Rated Effects

<table>
<thead>
<tr>
<th>POMS Subscales</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension</td>
<td>↓</td>
<td>-</td>
<td>↑</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>Confusion</td>
<td>-</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vigor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↓</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How I Feel Items</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trouble keeping mind on things</td>
<td>↓</td>
<td>-</td>
<td>↓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Restless</td>
<td>↓</td>
<td>-</td>
<td>-</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>“Funny”</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A lot of energy</td>
<td>↓</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tired and slow</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weird, “freaky”</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No one wants to help me</td>
<td>-</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>Unusual thoughts</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unhappy</td>
<td>-</td>
<td>-</td>
<td>↑</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Doing a pretty good job</td>
<td>-</td>
<td>-</td>
<td>↑</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Something good will happen</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Mad</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>Friendly</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Happy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SERS</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feel like talking</td>
<td>↓</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Can concentrate</td>
<td>↑</td>
<td>↓</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Like joking</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
<td>↑</td>
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<tr>
<td>Hungry</td>
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<tr>
<td>Focused on work</td>
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<tr>
<td>Popular</td>
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<td>↓</td>
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<tr>
<td>Get along with others</td>
<td>-</td>
<td>↓</td>
<td>-</td>
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<tr>
<td>Daydreamed</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Heart beating fast</td>
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<td>↓</td>
<td>-</td>
<td>↑</td>
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<tr>
<td>Worked well</td>
<td>-</td>
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<td>↑</td>
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<tr>
<td>Excited</td>
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Table 3—Continued

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<th>Visual Analog Scales</th>
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<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
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</thead>
<tbody>
<tr>
<td>Energetic</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
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<tr>
<td>Excited</td>
<td>-</td>
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<tr>
<td>Like Drug</td>
<td>-</td>
<td>-</td>
<td>↑</td>
<td>↑</td>
<td>-</td>
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<tr>
<td>Sleepy</td>
<td>-</td>
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<tr>
<td>Restless</td>
<td>-</td>
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</tr>
</tbody>
</table>

Note: Questionnaires were averaged across sampling and choice sessions for individual subjects. Arrows indicate a significant deviation from the average change across questionnaires. The direction of the arrows indicates the effect of MPH relative to the “no drug” condition (i.e., placebo or neither). Dashes indicate no significant differences.

Subjects. Table 3 shows differences across participants with respect to the number of items significantly affected.

For example, in the present study, relative to placebo, MPH produced increased ratings of “feel funny,” and “tired/slow” in Participant 1, and decreased ratings of “tension,” “restless,” “energetic,” and “feel like talking”. MPH also increased ratings of “can concentrate” and decreased ratings of “trouble keeping mind on things.”

Participant 2 had a variable pattern of responding in which, relative to placebo, MPH produced decreases in “popular,” “energetic,” and “excited”. MPH was associated with increased ratings of “confusion,” “having unusual thoughts,” and
“no one wants to help me.” MPH also increased ratings of “focused on work,” but decreased ratings of “can concentrate.”

Relative to changes seen with placebo, MPH produced increased ratings of “like drug,” “doing a good job” and “tension” in Participant 3. Yet, MPH produced decreased ratings of “daydreamed,” “popular,” “unhappy,” and “having trouble keeping mind on things.”

MPH produced increased ratings of “like drug,” “excited,” “worked well,” and “something good will happen today” in Participant 4 when compared to placebo. MPH also decreased ratings of “restless” and “vigor.”

When compared to placebo, MPH produced increases in “friendly,” “doing a good job,” “happy,” “feel like talking,” and “heart is beating fast” in Participant 5. MPH decreased ratings of “sleepy,” “restless,” “mad,” “tired/slow,” and “tension.”
DISCUSSION

The present study demonstrated that MPH served as a reinforcer for three out of five participants, and produced idiosyncratic patterns of subjective effects. Before discussing implications, several limitations are warranted.

These limitations include the small sample size, such that only five children were included. The results obtained may not be typical since this small sample may not be a representative population. Previous studies examining the reinforcing effects of MPH in adults used larger sample sizes (N=35, Chait, 1994; N=6, Roehrs, et al., 1999; and N=8 Rush et al., in press). Thus, it would be beneficial to replicate these findings with a larger subject population.

In addition, the choice procedure may not be a valid measure of abuse potential upon considering the possibility of a child who chooses to take medication (e.g., MPH) because the consequences are better academic performance and improved social interactions, yet there is a lack of clear euphorogenic results. However, this substance still has abuse potential in adults, as demonstrated by reinforcing, subjective and discriminative stimulus effects. This may call for an examination of the validity of the choice procedure as a measure of abuse liability. In fact, the strong preference for a drug in an experimental context may not indicate that a particular research participant (or an individual sharing similar qualities) will abuse
that substance given the many environmental factors that contribute to drug use (Johanson & deWit, 1989).

Another weakness of the present study surrounds the collection of subjective effect data. In the present study, the subjective effects were evaluated two hours post-drug administration. Previous studies examining the subjective effects of drugs have collected participant-rated effects pre-ingestion, one, three, and six hours post-ingestion (Chait, 1994; Johanson & Uhlenhuth, 1980). In the present study, collecting participant-rated effects at more than one time period post-drug administration could have been used to determine a time-course function of MPH. In addition to the collection of data, the reading level of the children may have affected the manner in which the subjective effects were evaluated, such that the participants may not have fully understood the items on the questionnaires. Thus, the lack of reading comprehension may have contributed to within-subject variability on the measures of subjective effects.

Lastly, relevant behavior changes were not observed under both drug and placebo conditions. The setting used for the behavioral observations may have caused the lack of clinical effects. In the Project Help facility, enrolled students receive one-to-one attention from their respective tutors. Tutors are instructed to prompt students to attend to their assignment when they are off-task. Students have the opportunity to earn rewards for remaining on task. Participants in the present study did not have these contingencies in place. Thus, it was not possible to compare the behavior of the participants to non-diagnosed peers. In addition, during social situations, the
participants, and the enrolled students, engaged in activities that did not involve interaction with others, (e.g., computer games at their cubicles). Therefore it was not possible to observe the effects of MPH on the social skills of the participants. The prevailing contingencies in the Project Help facility may have masked any behavioral changes. Therefore, the present study should be replicated in a different setting that may yield clinically relevant behavioral changes. However, despite these limitations, given the widespread clinical use of MPH, the present findings appear to warrant a more comprehensive assessment of the subjective and reinforcing effects of MPH, and how these effects are related to the clinical effects.

Our study demonstrates that MPH functioned as a reinforcer in three out of five participants according to the criteria used by Chait (1994). The demonstration of the reinforcing effects of MPH in children diagnosed with ADHD has several important implications. First of all, the present study demonstrates that a drug used to treat a clinical disorder (i.e., ADHD) functions as a reinforcer in a group of individuals diagnosed with that disorder. This has implications for the practice of clinical psychopharmacology. For example, if MPH functions as a reinforcer that sustains self-administration behavior, this could be utilized therapeutically to the extent that the reinforcing efficacy of the drug may predict the degree to which a patient complies with medication treatment (Henningfield et al., 1986). If the stimulus functions are related to the clinical effects of MPH, one might be able to predict whether MPH will be successful in treating ADHD symptomatology.
Although drug self-administration has been used to predict abuse potential, it is possible that the reinforcing effects observed in the present study do not necessarily suggest abuse. Substance abuse is defined as a maladaptive pattern of substance use, which leads to significant impairment arising from social, vocational, legal or family problems (DSM-IV; APA, 1994). The DSM-IV defines substance dependence as a pattern of repeated self-administration leading to clinically significant impairment associated with difficulty controlling the substance-taking behavior, withdrawal and tolerance (APA, 1994). Both substance dependence and abuse are associated with compulsive drug seeking and drug-taking behavior.

The reinforcing effects of a substance describe the relationship between the behavior (i.e., drug taking) and the consequences of that behavior (i.e., drug effect). Drug self-administration is a primary indicator of drug reinforcement—the choice behavior directly produces administration of the drug (deWit & Johanson, 1987). Reinforcement is said to occur when the presentation of the reinforcing stimulus (i.e., drug) increases the probability (or frequency) of the behavior that presentation of the stimulus is contingent upon. This differs from the “abuse liability” of a substance, which refers to the likelihood that its use will result in drug abuse and/or dependence (Bozarth, 1987).

It is within reason to suggest that individuals may “like” a medication perceived as being “helpful” without suggesting that they are abusing it. For example, in the present study participants were asked under double blind conditions to provide reasons for choosing the option they did during the choice sessions (e.g., Pill A, Pill B.
or Neither). Participants were also asked to comment on what they believed the pill to be. Following the completion of the study, once the blind was broken, two-thirds of the MPH-choosers (Participants 2 and 4), and 1 MPH-non-chooser (Participant 1) correctly identified which pill was MPH. The anecdotal subject comments suggested that children chose MPH (e.g., “Pill A” or “Pill B”) when they “needed to calm down” or wanted “to be able to concentrate.” Participant 1 reported that he chose Placebo or Neither when he believed he was “having a good day.” These explanations may not be indicative of “abuse,” yet these patterns of self-administration becomes “abuse” when MPH is ingested improperly (e.g., snorted or injected), administered in amounts that exceed what was prescribed, or is used outside the scope of medical authority by those for whom it is not prescribed.

A recent report by the Drug Enforcement Administration (DEA) suggested that MPH has a high abuse potential, and is associated with diversion and trafficking to an extent similar to other pharmaceutical Schedule II substances (Drug Enforcement Administration, 2000). The diversion of MPH has been identified by drug thefts, illegal sales and prescription forgeries (Drug Enforcement Administration, 2000). However, unlike other Schedule II drugs, MPH is prescribed predominately to children. Thus, information from parents, schools, physicians, adolescent treatment centers, poison control centers, and law enforcement data suggest that adolescents who are using this drug illicitly obtain it from individuals that have been prescribed this drug for the treatment of ADHD (DEA, 2000). For example, one recent survey of children and adolescents who had been prescribed
MPH revealed that nearly one in five had been approached to sell, give away or trade their medication at least once in the past five years (Musser, Ahmann, Mundt, Broste, & Mueller-Rizner, 1998).

Because of the increased availability of MPH, resulting from a 800% increase in MPH production and sales from 1990-1999, it is imperative to continue to examine the behavioral pharmacological profile and abuse potential in children and adolescents.

The variable patterns of responding in the present study make it difficult to determine what accounts for the reinforcing effects of MPH. Choice behavior in this and other contexts in which MPH is used is likely to be influenced by non-pharmacological factors such as differential attention from peers, teachers, etc. Biological, environmental and psychological factors, including drug availability and socio-cultural variables may all influence drug choice behavior. (For review see Altmann et al., 1996). For example, peer relations play a significant role in the initiation and escalation of substance use by increasing access to substances, generating pressure and modeling or reinforcing maladaptive coping efforts (Bates & Labouvie, 1995).

In addition to behavioral, psychological and environmental influences on choice behavior, Volkow and colleagues (1999a, 1999b) have demonstrated that the reinforcing effects of MPH are associated with increases in brain dopamine and occupancy of D2 receptors. Results indicate that there is a significant relationship between increases in brain dopamine in response to MPH and the subjective ratings
of “high” and “rush,” with subjects having the greatest increases in DA being those who perceived the most intense high. Likewise, subjects for whom MPH did not increase dopamine did not perceive a drug related high. Thus, the differences between subjects in the rate of DA release contributes to the intersubject variability in response to MPH and may influence drug choice behavior.

There are several participant characteristics that may explain the intersubject variability with respect to choice. First, the age of the participants may have affected the reinforcing effects of MPH. Of the three MPH-choosers, two (Participants 2 and 4) were aged 14, while two of the non-choosers (Participants 1 and 3) were both aged 10. Participant 5, who was classified as a MPH-chooser, was also 10 years old, yet she was the only female participant. This raises the possibility of gender related differences in the reinforcing effects of MPH.

Another possible explanation for the variable pattern of reinforcing effects surrounds the length of time on medication. Participants classified as MPH-choosers had been exposed to MPH treatment for an average of 52 months as compared to the non-choosers who had been receiving MPH for an average of 36 months. The two male MPH choosers had a longer treatment history than the other participants (60 months and 84 months, respectively). Thus, the amount of exposure to MPH may have contributed to the reinforcing effects of MPH.

The dose of MPH may have also contributed to the reinforcing effects. Two of the MPH-choosers were also receiving the highest doses of MPH. Participant 2, who chose MPH four out of six times, was receiving 20 mg of MPH. Participant 4, who
selected MPH five out of six times, was receiving 30 mg of MPH. Thus, the reinforcing effects of MPH may increase in a dose-related manner.

There are several possible explanations for the variable choice patterns seen across participants in the present study, thus it is difficult to determine the factors that account for the reinforcing effects of MPH. Nevertheless, the results of the present study with respect to the reliable selection of a drug that has been demonstrated to have abuse potential, along with reports from the DEA should underscore the need for additional research that assesses the reinforcing effects of MPH in humans.

In addition to investigating the reinforcing effects of MPH, the present study examined responses on a series of participant rated effects questionnaires. The patterns of responding obtained from the children in this study were inconsistent with the patterns of responding in adult humans. In normal adult humans, MPH produces increases in ratings on items such as (a) “arousal,” (b) “vigor,” (c) “stimulated,” (d) “high,” (e) “talkative,” and (f) “euphoric,” while reducing ratings on items of “depression” and “fatigue” (e.g., Rush et al., 1998). In a sample of cocaine-dependent adults, MPH increased subjective ratings of a “dysphoric” nature, such as (a) “anxiety,” (b) “depression,” (c) “anger,” and (d) “dysphoria” (Roache et al., 2000). Yet, the responses on the participant-rated effects questionnaires among the children in the present study were idiosyncratic. This pattern of idiosyncratic responding may provide additional evidence for a developmental difference in the ability to subjectively report drug effects.
For example, previous studies examining the effects of caffeine and d-amphetamine have demonstrated discrepancies in the subjective ratings of adults and children (see Rapoport, 1982/1983 for review). In a series of studies examining the effects of caffeine in grade school children, subjective reports of side effects or mood alterations were more drug-sensitive for adults as compared to the children (Elkins et al., 1981; Rapoport, et al., 1981). Whether the children actually experienced fewer subjective effects, or simply were poor reporters is unknown. A similar age difference was found in a comparison of d-amphetamine effects between children and adults, wherein subjective ratings were more sensitive in detecting stimulant placebo differences for adults while objective measures were more successful for children (Rapoport et al., 1980).

There are several explanations for the variable patterns of responding on the participant-rated effects questionnaires. First of all, the children may lack the verbal repertoire necessary to accurately describe drug effects. In addition, children may not have the reinforcement history or training in identifying subjective drug effects. Also, the variable response patterns may be a result of the combination of the inability to accurately verbalize subjective experiences and the lack of reinforcement history for providing verbal labels for these subjective effects. Thus, research on the developmental pathways of the participant-rated effects of drugs is needed.

Despite the rates of MPH use in children, only a few studies have assessed children’s perceptions of the effects of stimulant medications and how children feel about receiving such treatment (Baxley, Turner, & Greenwold, 1978; Henker &
Whalen, 1980; Cohen & Thompson, 1982). In general, these studies have demonstrated that children are generally knowledgeable about the perceived function of their medication, but are uncertain of their feelings surrounding taking the medication. Many students report disliking their stimulant medication, although they state that it is beneficial. Because a child’s dissatisfaction with stimulant medication may have significant implications for compliance (e.g., Brown, Borden, & Clingerman, 1985; Brown, Borden, Wynne & Spunt, 1987) it seems important to assess the general feelings, knowledge and attitudes of children diagnosed with ADHD who are being treated with stimulant medication.

The literature in customer satisfaction and treatment efficacy is rather limited, thus, although the patterns of responding on the participant-rated effects questionnaires in the present study were inconsistent, these subjective effects can provide valuable information in the monitoring of MPH effects in children for whom it is prescribed. The participant-rated effects can provide information regarding the child’s attitudes, moods and feelings associated with the drug. If a child has negative attitudes, moods and feelings surrounding the administration of MPH, he/she may be less likely to comply with taking medication. Thus, assessing the subjective effects of MPH may provide valuable information regarding a child’s adherence to stimulant treatment.

The present study began to address the extent to which MPH exerts reinforcing effects and participant-rated effects in children diagnosed with ADHD, as well as the extent to which the participant-rated effects and the reinforcing effects are
associated with one another and with the clinical effects of MPH. Further examination of the relationships among these stimulus functions and the clinical effects of MPH may provide valuable information regarding the behavioral pharmacological profile of this drug. This information may be used to not only assess the abuse potential of MPH, but perhaps more importantly to determine the likelihood of treatment compliance and treatment satisfaction.
Appendix A

Protocol Clearance From the Human Subjects
Institutional Review Board
Date: 30 July 1999

To: Scott Kollins, Principal Investigator
Emily MacDonald, Student Investigator for thesis

From: Sylvia Culp, Chair

Re: HSIRB Project Number 99-06-01

This letter will serve as confirmation that your research project entitled “Relationship Among Stimulus Functions and Clinical Effects of Methylphenidate in Children Diagnosed with 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: 30 July 2000
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