

Treatment Effects of Methylphenidate on Cognitive Functioning in Children With Mental Retardation and ADHD

DEBORAH A. PEARSON, Ph.D., CYNTHIA W. SANTOS, M.D., CHARLES D. CASAT, M.D., DAVID M. LANE, Ph.D., SUSAN W. JERGER, Ph.D., JOHN D. ROACHE, Ph.D., KATHERINE A. LOVELAND, Ph.D., DAVID LACHAR, Ph.D., LAURA P. FARIA, M.A., CHRISTA D. PAYNE, B.A., AND LYNNE A. CLEVELAND

ABSTRACT

Objective: Cognitive effects of stimulant medication were investigated in children with mental retardation (MR) and attention-deficit/hyperactivity disorder (ADHD). **Method:** Performance on tasks tapping sustained attention, visual and auditory selective attention, inhibition, and immediate memory was assessed for 24 children (mean age 10.9 years) during a placebo-controlled, double-blind, crossover treatment trial with 0.15, 0.30, and 0.60 mg/kg b.i.d. dosages of methylphenidate (MPH). **Results:** Successively higher MPH doses were associated with consistent gains in cognitive task performance, with optimal performance noted at the highest dose. Analysis of dose-response curves revealed significant linear components of trend on measures tapping sustained attention, visual selective attention, auditory selective attention, as well as two tasks tapping inhibition/impulsivity: delay of gratification and match-to-sample. No evidence of a curvilinear dose-response relationship emerged for any measure. **Conclusions:** Inattention and disinhibition/impulsivity decline with MPH treatment in children with ADHD/MR, and consistent with the Multimodal Treatment Study of ADHD, higher MPH doses are most effective. These findings also suggest that cognitive testing, together with behavioral and medical assessment, can be an effective tool in assessing stimulant response in children with ADHD/MR. *J. Am. Acad. Child Adolesc. Psychiatry*, 2004;43(6):677–685. **Key Words:** methylphenidate, mental retardation, attention-deficit/hyperactivity disorder, cognition, children.

Attention-deficit/hyperactivity disorder (ADHD: *DSM-III-R*, *DSM-IV*: 314.01; APA, 1987, 1994) is

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From the Department of Psychiatry and Behavioral Sciences, University of Texas Medical School at Houston (Pearson, Santos, Loveland, Lachar, Faria, Payne, and Cleveland); UT-Dallas School of Behavioral and Brain Sciences (Jerger); Rice University Department of Psychology (Lane); UT San Antonio Department of Psychiatry and Behavioral Sciences (Roache), and Carolinas HealthCare System, Charlotte, NC (Casat). Drs. Pearson, Santos, and Lachar are also with the UT Harris County Psychiatric Center; Drs. Pearson and Loveland are also with the UT Graduate School of Biomedical Sciences, as is Ms. Payne.

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Correspondence to Dr. Pearson, Department of Psychiatry, University of Texas Medical School at Houston, 1300 Moursund, Houston, TX 77030-3497; e-mail: Deborah.A.Pearson@uth.tmc.edu.

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characterized by inattention, hyperactivity, and impulsivity; these symptoms are often successfully treated with psychostimulant medication. The Multimodal Treatment Study of ADHD (MTA) results suggest that higher and more frequent stimulant dosing produces greater reductions in ADHD symptoms than lower and less frequent doses (Jensen et al., 2001). Rapport and colleagues have also noted steady declines in ADHD symptoms at successively higher doses of stimulant medications, with the important caveat that the response of any one child is highly individual (Rapport and Kelly, 1993; Rapport et al., 1994). Although these findings suggest linear improvements in cognitive and behavioral functioning at successively higher stimulant doses, others (Gan and Cantwell, 1982; Sprague and Sleator, 1977) have found a curvilinear response to stimulants, such that lower doses of stimulants produced initial improvements relative to placebo, followed by declines at higher doses.

Although the prevalence of ADHD in children with mental retardation (MR) is higher than in the general school-age population, subaverage IQ has often been an exclusion factor in studies of ADHD (Gadow and Poling, 1988). However, more recently, studies examining ADHD in MR have emerged (Pearson et al., 1997). These studies suggest that although children with ADHD/MR can be treated successfully with stimulants, their response is often more variable or idiosyncratic than that of children with ADHD in the general school-age population (Aman et al., 1991b, 1993; Handen et al., 1990). This is especially true for children with ADHD/MR who are lower-functioning (Aman et al., 1993; Handen et al., 1991) or who have genetic syndromes (fragile X: Hagerman et al., 1988; Williams syndrome: Power et al., 1997). Of considerable concern are the findings of a significant increase in serious side effects (e.g., social withdrawal) of methylphenidate (MPH) in children with MR (Handen et al., 1991). Given that children with MR are often heavily medicated (Gadow, 1985), the risk for overmedication in children with ADHD/MR is considerable.

The behavioral findings of this project have recently been reported in this *Journal* (Pearson et al., 2003); these findings suggested that higher doses of MPH produced optimal parent and teacher behavioral ratings and that these gains were not associated with an increase in serious side effects. Here we report the cognitive response of the same sample of children with ADHD/MR to placebo and to 0.15, 0.30, and 0.60 mg/kg b.i.d. of MPH. In light of the increased risks associated with stimulant treatment in children with ADHD/MR, the purpose of this study was to determine whether cognitive gains could be noted using low doses of MPH. A second aim of this study was to assess whether medication treatment response followed a linear pattern (i.e., successively higher doses producing increasingly better behavior) or a curvilinear pattern (i.e., initial improvement at lower doses, followed by declines at higher doses). We hypothesized that attention, inhibition, and immediate memory would improve in a linear fashion with ascending MPH doses.

METHOD

Participants

The sample was identical with that reported in the article by Pearson and colleagues (2003). Briefly, 24 children with

ADHD/MR (18 boys and 6 girls) participated in this study. The mean chronological age of these children was 10.9 years (SD = 2.4), the mean IQ (Stanford-Binet, 4th edition; Thorndike et al., 1986) was 56.5 (SD = 10.24), and the mean mental age (estimated using the Stanford-Binet) was 5.7 years (SD = 1.2). Seventeen children had mild (50+) MR; seven had moderate MR. The ethnic breakdown of these children was 9 white, 14 African American, and 1 Hispanic. The mean Hollingshead four-factor social class for this sample was 3.39 (SD = 1.16; Hollingshead, 1975). The mean education level was 12.35 (SD = 2.6) years for mothers and 12.24 (SD = 2.7) years for fathers. Psychiatric interview (Diagnostic Interview for Children and Adolescents-Revised) (Reich et al., 1991) established that all participants met *DSM-III-R* criteria for ADHD. As detailed in the article by Pearson and colleagues (2003), additional information collected allowed us to determine that 22 participants met *DSM-IV* criteria for ADHD, combined type, and two for ADHD, predominantly inattentive type. Severity of ADHD symptomatology was assessed using Parent and Teacher versions of the Conners Abbreviated Symptom Questionnaire (CASQ), sometimes called the Hyperactivity Index (Conners, 1989). The mean Parent CASQ score for this group was 20.9 (mean *T* score = 84.3), and the mean Teacher CASQ score for this group was 20.0 (mean *T* score = 77.0).

All children had familial mental retardation; no other etiologies of MR (e.g., Down syndrome, fragile X) were identified on the basis of medical and school records, parent interview, or physician assessment of phenotype during physical examination. All lived at home and were recruited from special education classrooms of a large metropolitan public school district. Exclusion criteria included psychosis, autistic behaviors, and mood disorders (conditions ruled out by psychiatric interview). No children were taking any psychotropic medication at study entry; however, four had taken MPH, one had taken pemoline, and one had taken dextroamphetamine prior to study entry. Previous medication was discontinued at least 1 week prior to entry into the medication trial.

Design

The cognitive effects of four dosages of MPH (placebo, 0.15, 0.30, 0.60 mg/kg b.i.d.) in children with ADHD/MR were investigated using a within-subject, crossover, placebo-controlled design. Dose order was counterbalanced across subjects using a diagram-balanced Latin Squares procedure. Prior to starting the drug trial, all children received a single-blind week of placebo, during which time the pill-taking regimen was established both at home and at school. During the actual medication trial period, each child received 1 week of each dose; medication was given at breakfast and lunchtime. MPH was prepared by crushing and blending white generic MPH tablets with cornstarch and filling two opaque size 1 gelatin capsules. The study director, physician, research assistants, teachers, parents, and children were all blind with respect to dosages given during the drug trial; the study pharmacologist (J.D.R.)—who had no patient contact—ran the double-blind.

Procedure

Potential participants were identified after a clinical assessment that included the psychological testing (including the Stanford-Binet), a psychiatric and developmental interview with the parent, a hearing test, and a physical examination by the study physician (C.W.S.) to confirm medical eligibility to take MPH. The cognitive tasks were performed at the end of each week of the drug trial. Medication was administered at the clinic upon arrival; cognitive

testing started approximately 60 minutes later. Cognitive task order was randomized between subjects, and this order was held constant across all 4 weeks of the drug trial for each individual child.

All the computerized tasks were presented on a Macintosh IIvx computer. Before each task, the children were given practice trials, during which time they were given feedback on their performance. With the exception of the Matching Familiar Figures Test (MFFT), no feedback was given during the actual test trials, but the child was redirected to task if he or she looked away or spoke. Each weekly test session lasted approximately 90 minutes, including short breaks. Tasks were selected on the basis of their ability to discriminate children with and without ADHD, their sensitivity to MPH treatment, and their appropriateness for the cognitive developmental level of the children.

Instruments

Sustained Attention. A modified version of the Continuous Performance Test (CPT) (Rosvold et al., 1956) was used to examine sustained attention. Participants monitored a series of familiar pictures that were presented one at a time (stimuli: cat, bicycle, duck, tree, cow, banana, zebra, truck, fish, house, and a witch). They were instructed to press the response key when they saw the witch (i.e., the target). There were four blocks of 100 stimuli (including 10 targets); each picture was presented for 200 milliseconds, and the interstimulus interval was 1.5 seconds. CPT performance was assessed by the number of errors (omissions and commissions) and reaction time. The CPT differentiates children of normal IQ, with and without ADHD (Hooks et al., 1994), as well as children with and without ADHD who have MR (Pearson et al., 1996). It is also sensitive to MPH in children with ADHD of normal intelligence (Riccio et al., 2001) and in children with ADHD/MR (Aman et al., 1991b; 1993).

Selective Attention. The Speeded Classification Task (SCT) (Strutt et al., 1975) is a visual selective attention task in which children sort stimuli on the basis of a binary dimension. The dimension could be a shape (a circle or a square), a line (horizontal or vertical), or a star (presented above or below the figure). The relevant dimension could appear by itself (e.g., just a circle) or with one or two distracting dimensions (e.g., a circle with a horizontal line drawn through it and a star above it). The test stimulus appeared at the center of the computer screen; children matched this stimulus with one of the two sample stimuli at the bottom corners of the screen (e.g., a circle in one corner, and a square in the other). Children responded by touching the matching sample stimulus, using a computer touch screen (TouchWindow for Macintosh Computers; Edmark Corporation, Redmond, WA). SCT performance was assessed by examining sorting errors and response time. The SCT discriminates children with and without ADHD of normal intelligence (Hooks et al., 1994), as well as children with and without ADHD who have MR (Pearson et al., 1996).

The stimuli used for the Selective Listening Task (SLT) were taken from the competing sentences subtest of the Pediatric Speech Intelligibility Test (PSI) (Jerger, 1987) and were presented over earphones. In the nondistracting condition, a sentence (e.g., "The bear is brushing his hair") was presented by itself to one ear. In the distraction condition, the target message was presented on one ear, and a competing sentence was presented to the other ear. Children were told to touch one of five pictures on a card that matched the target sentence. Performance was measured by correct target identifications, and intrusion errors (messages reported from the irrelevant ear). Prior to doing the SLT each week, the children received

a hearing screen to ensure that they could hear the stimuli adequately. Selective listening tasks differentiate children with and without ADHD of normal intelligence (Pearson et al., 1991; Prior et al., 1985) but to our knowledge have not previously been used with children with ADHD/MR.

Impulsivity/Inhibition. The delay of gratification (DOG) task, adapted from the preschool delay task of the Gordon Diagnostic System (Gordon, 1983), measures the ability to suppress or delay impulsive behavioral responses. Children were told that a star would appear on the computer screen if they waited "long enough" to press a response key. If a child responded sooner than 4 seconds after his or her previous response, he or she did not earn a star, and the 4-second counter restarted. Children performed one block as practice, and then four 92-second blocks during the actual test. Performance was measured by the number of correct responses and the efficiency ratio (number of correct responses/total number of responses). The DOG differentiates children with and without ADHD of normal intelligence (Mayes et al., 2002) and is sensitive to MPH treatment in these children (Hall and Kataria, 1992).

Stimuli from Kagan and colleagues' (1964) original MFFT task were presented at the top of the computer screen and six alternatives (one of which matched the test stimulus) were presented below it. Children were told to touch the picture below that matched the test stimulus exactly. There were 2 practice sets (purse, ruler), followed by 12 test sets: a house, scissors, telephone, teddy bear, tree, leaf, cat, coat, giraffe-chicken, lamp, boat, cowboy. Correct responses resulted in a synthesized voice saying, "that's right"; incorrect responses produced a "try again" response. Performance was measured by matching errors and reaction time. Various versions of the MFFT discriminate children with and without ADHD of normal intelligence (Rapport et al., 2000) and have been found to be sensitive to MPH use in these children (Barrickman et al., 1995) and in children with ADHD/MR (Aman et al., 1991b).

Immediate Memory. The Delayed Match to Sample (DMTS) task was adapted from the version used by Aman and colleagues (1991b). Children initially saw a colored circle (red, yellow, or blue) that appeared at the top of the computer screen. This circle stayed on until the child touched it. This sample then disappeared, and 1 second later, three circles (red, yellow, and blue) appeared on the bottom half of the screen. The child was told to touch the color he or she had just observed. Each time three consecutive correct responses were made, 1 second was added to the delay between the sample and the comparison stimuli. Each incorrect response resulted in a 1-second reduction to the delay, until a minimum interval of 1 second was reached. There were a total of 36 trials, with a possible maximum delay of up to 12 seconds. Performance was measured by the proportion of correct matches, reaction time, and the maximum delay. The DMTS has been found to be sensitive to MPH treatment in children with ADHD/MR (Aman et al., 1991b).

RESULTS

Data were analyzed using SPSS-PC repeated measures one-way analysis of variance (ANOVA), with MPH dose as a within-subjects variable. Because preliminary analyses revealed no significant effects of gender or dose order, these factors were dropped from subsequent analyses. The effects of MPH dosage on task performance are shown in Table 1. As has been

TABLE 1
Summary of Methylphenidate Effects on Cognitive Tasks

Task/Variable	Transformation Used	Placebo (SD)	0.15 mg/kg Low (SD)	0.30 mg/kg Medium (SD)	0.60 mg/kg High (SD)	<i>F</i>	<i>p</i> ^a	Source of Significance	Significance of Linear Trend ^a
Continuous Performance Test (<i>n</i> = 24)									
Omissions	log (<i>x</i> + 1)	2.98 (2.44)	2.66 (2.27)	2.69 (2.68)	2.30 (2.45)	2.14	.103		.029
Commissions	-1/sqrt (<i>x</i> + 1)	4.79 (7.83)	2.07 (3.69)	1.99 (3.23)	1.44 (2.17)	3.58	.018	P:H	.015
Response time	log (<i>x</i>)	797 (163)	788 (183)	738 (160)	729 (135)	2.70	.054		.028
Speeded Classification Task (<i>n</i> = 22)									
Sorting errors	log (<i>x</i> + 1)	3.4 (2.8)	3.1 (2.7)	2.3 (1.8)	2.0 (1.6)	5.35	.002	P:M, P:H, L:M, L:H	.005
Response time	log (<i>x</i>)	1,456 (788)	1,418 (638)	1,511 (881)	1,421 (537)	0.37	.778		.436
Selective Listening Task (<i>n</i> = 16)									
Correct Identifications (%)	<i>x</i> ²	89.61 (10.96)	91.72 (9.10)	93.67 (5.37)	96.48 (4.57)	7.19	<.001	P:H, L:H, M:H	<.001
Intrusions	log (<i>x</i> + 1)	3.09 (3.01)	2.22 (2.47)	2.03 (1.94)	1.03 (1.38)	7.67	<.001	P:H, L:H, M:H	<.001
Delay of Gratification (<i>n</i> = 24)									
Correct responses	NA	9.94 (2.83)	9.92 (2.28)	11.08 (2.94)	11.18 (3.08)	5.18	.003	P:M, P:H, L:M, L:H	.002
Efficiency ratio	NA	63.8 (23.2)	62.8 (22.1)	61.6 (23.6)	70.4 (21.2)	2.33	.082		.067
Matching Familiar Figures Test (<i>n</i> = 24)									
Matching errors (no.)	sqrt (<i>x</i>)	29.0 (17.5)	25.4 (10.8)	24.8 (9.8)	21.2 (10.4)	3.46	.021	P:L, P:M, P:H, L:M, M:H	.008
Response time (sec)	log (<i>x</i>)	4.99 (3.96)	6.04 (4.64)	5.62 (3.57)	6.88 (4.80)	3.45	.021	P:L, L:M, L:H	.049
Delayed Match to Sample (<i>n</i> = 24)									
Correct matches (%)	<i>x</i> ³	72.4 (14.4)	75.2 (13.1)	76.4 (14.3)	72.7 (18.8)	1.45	.236		.390
Response time (msec)	log (<i>x</i>)	1,743 (1,127)	1,902 (1,759)	1,592 (1,100)	1,600 (1,104)	0.54	.656		.232
Longest delay	log (<i>x</i>)	4.00 (1.84)	4.42 (2.24)	4.71 (2.51)	4.72 (3.17)	0.89	.45		.446

Note: P = placebo; L = low; M = medium; H = high; NA = not applicable.

^a Values in boldface type are significant.

found previously (Aman et al., 1991b), a number of our cognitive task variables had very nonnormal distributions. To increase the power and validity of ANOVA, variables were transformed to produce approximately normal distributions, using the Tukey ladder of transformations (Winer, 1971); specific transformations for variables with nonnormal distributions (i.e., all task variables except DOG variables) are reported in Table 1. Inferential statistics are all reported on the transformed variables, but for ease of interpretation, the untransformed means and standard deviations are reported. The linear component of trend was tested to assess whether there was a general improvement in performance with increasing MPH dosage. As described below, the linear component of trend was significant for 9 of the 14 measures. Deviations from linearity were tested to assess whether an initial improvement at lower doses was followed by less improvement or even a decline at higher doses (i.e., a curvilinear dose response). Deviations from linearity did not approach significance ($p > .10$) for any of the measures. Student-Newman-Keuls tests were performed to determine which doses were significantly different from one another.

Sustained Attention

Significant declines in CPT commission errors were noted at higher MPH doses ($p = .018$). Overall, the children slowed down as time on task lengthened ($F_{3,60} = 5.85, p = .001$), but this effect was dose-related ($F_{9,180} = 2.17, p = .026$). As can be seen in Table 2, an

analysis of simple effects revealed that response time slowed significantly as time on task lengthened in the placebo ($p = .009$) and low-dose ($p = .003$) conditions. However, children showed no deterioration in response latency over time on task when taking the medium ($p = .775$) or high MPH dose ($p = .287$). Thus, at the higher doses, children were able to maintain the same response latencies throughout the task.

Selective Attention (Visual and Auditory)

Children made fewer sorting errors on the SCT at higher doses ($p = .002$). Although complete SLT data were available for only 16 subjects (primarily due to equipment failure and examiner error), significant MPH effects emerged. Children made fewer intrusions at higher MPH doses ($p < .001$) and correctly identified more target messages ($p < .001$). Children made fewer correct responses when a distracting message was played to the other ear ($F_{1,15} = 22.02, p < .001$), but they became progressively less susceptible to distractors as MPH dose increased ($F_{3,45} = 6.64, p = .001$).

Impulsivity/Disinhibition

Higher MPH doses were associated with more correct responses ($p = .003$) on the DOG task; they also tended to be more efficient ($p = .082$). Similarly, children made fewer matching errors on the MFFT ($p = .008$) and responded more slowly ($p = .021$) at higher doses, suggesting that they were responding more reflectively (i.e., thinking before responding) at these higher doses.

TABLE 2

Deterioration in CPT Response Latency as a Function of Time on Task: Simple Effect of Block at Each Methylphenidate Dose

MPH Dose ^a	Block 1	Block 2	Block 3	Block 4	Simple Effect of Block	Significance
					at Each MPH dose	of Simple Effect
					<i>F</i>	<i>p</i> ^b
Placebo	717 (142)	764 (182)	787 (191)	850 (209)	4.22	.009
0.15 mg/kg	719 (161)	726 (137)	793 (198)	823 (246)	5.32	.003
0.30 mg/kg	732 (170)	731 (172)	729 (172)	710 (135)	0.37	.775
0.60 mg/kg	730 (208)	703 (136)	715 (129)	756 (147)	1.29	.287

Note: CPT = Continuous Performance Test; MPH = methylphenidate.

^a $n = 21$.

^b Values in boldface type are significant. Significant values represent significant declines in performance over successive blocks (i.e., time on task).

Immediate Memory

No significant MPH effects were found on the DMTS task.

Dose Response

As can be seen in Table 1, post hoc Student-Newman-Keuls analyses revealed that without exception, for variables showing significant MPH effects, optimal cognitive performance occurred at the highest MPH dose. The significant linear trends noted in Table 1 suggest that performance consistently improved at successively higher MPH doses for variables on all tasks except the DMST. Thus our findings suggest strongly that children with ADHD/MR show a linear improvement in cognition with successively higher doses of MPH. These linear trends suggest that even though the difference between placebo and the low dose may not have reached statistical significance in the ANOVAs, even low doses of MPH produce a small (albeit statistically insignificant) improvement relative to placebo. Finally, the absence of any statistically significant quadratic effects suggests that there was no curvilinear response to MPH in cognitive performance across the range of doses studied in this investigation.

DISCUSSION

Our findings suggest that performance on tasks tapping sustained attention, selective attention, and inhibition/impulsivity improves significantly with MPH treatment in children with ADHD/MR. Furthermore, these improvements show steady gains with successively higher doses of MPH. These linear gains in performance are consistent with the MTA study results and are inconsistent with previous studies suggesting a curvilinear response to MPH—although it should be noted that the latter studies used higher MPH doses than we did. Our findings extend the previous literature on stimulant treatment in ADHD/MR by being the only study of which we are aware that assessed stimulant dose-response using three MPH doses in addition to placebo, the only study assessing MPH effects on auditory selective attention, and by confirming the relative inefficacy of the 0.15-mg/kg dose.

It is interesting that, although MPH consistently reduced error rates across a variety of tasks, there

seemed to be less consistency with regard to response latency. For instance, on the CPT, higher MPH doses prevented the sharp deterioration in response latency over time on task that was seen in the placebo and low-dose conditions. In contrast, on the MFFT, higher doses were actually associated with longer response times. On the CPT, optimal performance is obtained by responding quickly without making mistakes; on the MFFT, optimal performance is obtained by taking sufficient time to carefully scan all alternatives before selecting a match. These seemingly divergent patterns in response latency may actually reflect a MPH treatment effect of enhancing the ability of children with ADHD/MR to allocate their attention in better accordance with task demands.

Although these findings are consistent with those of some previous investigations (Aman et al., 1991b; Handen et al., 1990), they are inconsistent with others (Hagerman et al., 1988; Handen et al., 1992), perhaps because of the greater statistical power associated with having more participants ($n = 24$) than these previous studies (Hagerman et al., 1988: $n = 15$; Handen et al., 1992: $n = 14$). This difference may also reflect the fact that our sample was higher-functioning than some others (Hagerman et al., 1988). Given that higher-functioning children have been found to be better MPH responders (Aman et al., 1991a; Buitelaar et al., 1995), our sample may have been more receptive to MPH treatment.

Still another possibility is that our tasks were better adapted to the level of cognitive development of school-age children with MR and hence may have been more sensitive to the sometimes subtle changes in cognition associated with stimulant treatment. In developing our battery, we deliberately selected (or adapted) our tasks from the literature of cognitive development in preschool/early elementary children of normal IQ, whose mental ages would be similar to those of our sample. Specifically, we selected tasks designed to be within the range of ability of these children, but to also be “effortful” for them. More evidence for specific task characteristics having a bearing on our findings is suggested by Handen and colleagues (1992), who suggested that longer CPT’s are more likely to be sensitive to drug effects. Interestingly, our CPT lasted 11.5 minutes, in contrast to the 4.5-minute CPT used by Handen and colleagues (1992), for which effects of MPH were not significant—although they had found

significant MPH effects using the same CPT earlier (Handen et al., 1990).

Of particular interest is the fact that the results of this cognitive study paralleled those that we found in our behavioral study (Pearson et al., 2003), suggesting that parent and teacher ratings of decreased ADHD symptomatology (e.g., inattention) with higher MPH doses are paralleled in improved cognitive performance in these children. Although a discontinuity between behavioral ratings and cognitive task performance has been noted in children with ADHD of normal IQ (Rapport et al., 2000), we did not find this to be the case in our group of children with ADHD/MR. Most important, these findings suggest that improvements in behavior with higher doses of MPH (Pearson et al., 2003) are *not* accompanied by declines in cognition in children with ADHD/MR.

Limitations

As previously discussed in detail (Pearson et al., 2003), due to the protracted (nearly 7 years) recruitment period spanning *DSM-III-R* and *DSM-IV* (during which 1,328 were screened for this study, to find children without comorbid psychiatric diagnoses), our psychiatric interview (Diagnostic Interview for Children and Adolescents-Revised) (Reich et al., 1991) was designed for the *DSM-III-R* criteria. However, we collected sufficient information to allow for *DSM-IV* diagnoses to be determined (with 100% interrater reliability) during a review of the files by two licensed psychologists (D.A.P., K.A.L.) and one child and adolescent psychiatrist (C.W.S.). Given that Biederman and colleagues (1997) have found considerable diagnostic continuity between *DSM-III-R* and *DSM-IV*, and the fact that the *DSM-IV* criteria actually identify *more* children as having ADHD than did the *DSM-III-R* criteria, we feel confident that our sample meets *DSM-IV* criteria for ADHD.

Another potential limitation is that our sample was only 75% stimulant-naïve; that is, the presence of children who had previously taken stimulants may have unduly affected our results. As we did in our earlier study (Pearson et al., 2003), we re-ran our analyses after removing data from the six children who had previously taken stimulants. Even with the reduced statistical power associated with a smaller sample ($n = 18$), the results were very similar: all previously significant

variables remained significant, with the exception of CPT commissions ($p = .067$) and MFFT matching errors ($p = .09$). This finding argues against the previously treated children driving our results. These results were also not due to the use of transformed scores: we re-ran our analyses using the raw, untransformed data, and despite the resulting reduction in statistical power associated with using highly skewed data, the raw score analyses produced identical results to the transformed score analyses, with the exception that the significance of MFFT response time went from .021 (transformed) to .097 (untransformed).

We also recognize that the experimental rigor associated with recruiting "ADHD simplex" children may also be a limitation. Although we purposely recruited children without comorbid psychiatric conditions to avoid possible confounding effects of these comorbidities on MPH treatment, ADHD is often accompanied by comorbid conditions. Given that the MTA study findings suggested that comorbid conditions may influence optimal ADHD treatment choices (Jensen et al., 2001), it will be important for future studies to systematically assess stimulant effects in children with ADHD/MR who have comorbid conditions (e.g., anxiety).

Finally, it is important to note the limitations of cognitive tasks in general. Although they are important research tools (Greenhill et al., 2001), treatment-related changes on cognitive tasks often have only a modest ability to predict treatment-related changes in the classroom and other natural settings, as reported on parent and teacher behavioral ratings and interviews (Aman and Turbott, 1991; DuPaul et al., 1992). Similarly, although cognitive tasks such as the CPT have demonstrated *group* differences between children with and without ADHD, they do not have the sensitivity or specificity to diagnose any *individual* child with ADHD (McGee et al., 2000; Riccio et al., 2002). Thus, given their limited ecological validity, it would be inappropriate to use cognitive tests (e.g., the CPT) to either diagnose ADHD or to determine optimal stimulant treatment dose. However, given that developmentally sensitive cognitive tasks such as those used in this study have shown stimulant dose-related changes in attention and inhibition in children with ADHD/MR, they appear to provide useful adjunctive information for monitoring stimulant treatment in these children.

Clinical Implications

The implications of our findings for clinical treatment are that children with ADHD who also have mild to moderate MR can benefit from MPH treatment, and that a moderate dose of 0.6 mg/kg is associated with significant gains in cognitive performance, relative to placebo. For patients who cannot tolerate this dose (e.g., appetite suppression, insomnia), significant gains were also noted at the 0.3-mg/kg dose. Thus, the behavioral improvements (i.e., declines in hyperactivity, conduct problems, and asocial behavior, as well as improved attention) associated with higher doses of MPH in children with ADHD/MR (Pearson et al., 2003) are accompanied by steady gains in cognitive performance. Furthermore, our results suggest that these behavioral and cognitive gains are *not* associated with a higher side effect risk (Pearson et al., 2003). Specifically, as noted in our earlier report of the behavioral response of these children to MPH, there were only two significant side effects: four children (17%) had insomnia at the high dose, relative to none at placebo ($p \leq .05$), and seven (29%) had loss of appetite at the 0.60-mg/kg dose, relative to one at placebo ($p \leq .05$). There was also no evidence of increased anxiety with MPH treatment in this group. Finally, our findings suggest that in conjunction with appropriate behavioral and medical assessment, cognitive testing may be an effective tool in monitoring medication response in children with ADHD/MR.

Although these findings contribute to the small but growing literature on stimulant treatment effects in ADHD/MR, much remains to be explored. In addition to examining the role of comorbid psychiatric symptomatology in these children, it will be important to examine stimulant effects in subgroups of children with ADHD/MR who have genetic syndromes (e.g., Down syndrome). Given that dose-response curves differ between different domains (Rapport and Kelly, 1993), future studies should examine additional facets of cognitive performance, as well as academic performance. Given that optimal performance occurred at our 0.6-mg/kg dose, future studies might (cautiously) examine the effects of higher MPH doses. Other obvious avenues for future studies include examining the effects of the longer-acting stimulants, as well as the effects of longer-term stimulant treatment. Given that children with ADHD/MR are at high risk for poorer psychiatric, educational, and legal outcomes (Aman et al.,

1996), further investigation into effective treatments for these children is clearly needed.

REFERENCES

- Aman MG, Kern RA, McGhee DE, Arnold LE (1993), Fenfluramine and methylphenidate in children with mental retardation and attention deficit hyperactivity disorder: laboratory effects. *J Autism Dev Disord* 23:491–506
- Aman MG, Marks RE, Turbott SH, Wilsher CP, Merry SN (1991a), Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. *J Am Acad Child Adolesc Psychiatry* 30:246–256
- Aman MG, Marks RE, Turbott SH, Wilsher CP, Merry SN (1991b), Methylphenidate and thioridazine in the treatment of intellectually subaverage children: effects on cognitive-motor performance. *J Am Acad Child Adolesc Psychiatry* 30:816–824
- Aman MG, Turbott SH (1991), Prediction of clinical response in children taking methylphenidate. *J Autism Dev Disord* 21:211–228
- Aman MG, Pejeau C, Osborne P, Rojahn J, Handen B (1996), Four-year follow-up of children with low intelligence and ADHD. *Res Dev Disabil* 17:417–432
- American Psychiatric Association (1987), *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition-revised (DSM-III-R)*. Washington, DC: American Psychiatric Association
- American Psychiatric Association (1994), *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*. Washington, DC: American Psychiatric Association
- Barrickman LL, Perry PJ, Allen AJ et al. (1995), Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 34:649–657
- Biederman J, Faraone SV, Weber W, Russell RL, Rater M, Park K (1997), Correspondence between *DSM-III-R* and *DSM-IV* attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 36:1682–1687
- Buitelaar JK, Van der Gaag RJ, Swaab-Barneveld H, Kuiper M (1995), Prediction of clinical response to methylphenidate in children with attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 34:1025–1032
- Conners CK (1989), *Conners' Rating Scales Manual*. North Tonawanda, NY: Multi-Health Systems
- DuPaul GJ, Anastopoulos AD, Shelton TL, Guevremont DC, Metevia L (1992), Multimethod assessment of attention-deficit hyperactivity disorder: the diagnostic utility of clinic-based tests. *J Clin Child Psychol* 21:394–402
- Gadow KD (1985), Prevalence and efficacy of stimulant drug use with mentally retarded children and youth. *Psychopharmacol Bull* 21:291–303
- Gadow KD, Poling AG (1988), *Pharmacotherapy and Mental Retardation*. Boston: Little Brown
- Gan J, Cantwell DP (1982), Dosage effects of methylphenidate on paired associate learning: positive/negative placebo responders. *J Am Acad Child Psychiatry* 21:237–242
- Gordon M (1983), *The Gordon Diagnostic System*. DeWitt, NY: Gordon Systems
- Greenhill LL, Pliszka S, Dulcan MK, and the Work Group on Quality Issues (2001), Summary of the practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 40:1352–1355
- Hagerman RJ, Murphy MA, Wittenberger MD (1988), A controlled trial of stimulant medication in children with the fragile X syndrome. *Am J Med Genet* 30:377–393
- Hall CW, Kataria S (1992), Effects of two treatment techniques on delay and vigilance tasks with attention deficit hyperactive disorder (ADHD) children. *J Psychol* 126:17–25
- Handen BL, Breaux AM, Gosling A, Ploof DL, Feldman H (1990), Efficacy of methylphenidate among mentally retarded children with attention deficit hyperactivity disorder. *Pediatrics* 86:922–930

- Handen BL, Breaux AM, Janosky J, McAuliffe S, Feldman H, Gosling A (1992), Effects and noneffects of methylphenidate in children with mental retardation and ADHD. *J Am Acad Child Adolesc Psychiatry* 31:455-461
- Handen BL, Feldman H, Gosling A, Breaux AM, McAuliffe S (1991), Adverse side effects of methylphenidate among mentally retarded children with ADHD. *J Am Acad Child Adolesc Psychiatry* 30:241-245
- Hollingshead AB (1975), *Four Factor Index of Social Status*. New Haven, CT: Yale University
- Hooks K, Milich R, Lorch EP (1994), Sustained and selective attention in boys with attention deficit hyperactivity disorder. *J Clin Psychol* 23:69-77
- Jensen PS, Hinshaw SP, Kraemer HC et al. (2001), ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. *J Am Acad Child Adolesc Psychiatry* 40:147-158
- Jerger S (1987), Validation of the pediatric speech intelligibility test in children with central nervous system lesions. *Audiology* 26:298-311
- Kagan J, Rosman B, Day D, Albert J, Phillips W (1964), Information processing in the child: significance of analytic and reflective attitudes. *Psychol Monogr* 78:Whole No. 578
- Mayes SD, Calhoun SL, Crowell EW (2002), The Gordon Diagnostic System and WISC-III Freedom from Distractibility index: validity in identifying clinic-referred children with and without ADHD. *Psychol Rep* 91:575-587
- McGee RA, Clark SE, Symons DK (2000), Does the Conners Continuous Performance Test aid in ADHD diagnosis? *J Abnorm Child Psychol* 28:415-424
- Pearson DA, Lane DM, Swanson JM (1991), Auditory attention switching in children with attention deficit hyperactivity disorder. *J Abnorm Child Psychol* 19:477-490
- Pearson DA, Norton AM, Farwell EC (1997), ADHD in mental retardation: nature and treatment of attention deficits. In: *Attention, Development, and Psychopathology*, Enns JT, Burack J, eds. New York: Guilford, pp 205-229
- Pearson DA, Santos CW, Roache JD et al. (2003), Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. *J Am Acad Child Adolesc Psychiatry* 42:209-216
- Pearson DA, Yaffee LS, Loveland KA, Lewis KR (1996), A comparison of sustained and selective attention in children who have mental retardation with and without attention deficit hyperactivity disorder. *Am J Ment Retard* 100:592-607
- Power TJ, Blum NJ, Jones SM, Kaplan PE (1997), Brief report: response of methylphenidate in two children with Williams syndrome. *J Autism Dev Disord* 27:79-87
- Prior M, Samson A, Freethy C, Geffen G (1985), Auditory and attentional abilities in hyperactive children. *J Child Psychol Psychiatry* 26:289-304
- Rapport MD, Kyong-Mee C, Shore G, Denney CB, Issacs P (2000), Upgrading the science and technology of assessment and diagnosis: laboratory and clinic-based assessment of children with ADHD. *J Clin Child Psychol* 29:555-568
- Rapport MD, Denney C, DuPaul GJ, Gardner MJ (1994), Attention deficit disorder and methylphenidate: normalization rates, clinical effectiveness, and response prediction in 76 children. *J Am Acad Child Adolesc Psychiatry* 33:882-893
- Rapport MD, Kelly KL (1993), Psychostimulant effects on learning and cognitive function. In: *Handbook of Hyperactivity in Children*, Matson JL, ed. Needham Heights, MA: Allyn & Bacon, pp 97-136
- Reich W, Welner Z, Herjanic B (1991), *Diagnostic Interview for Children and Adolescents-Revised*. North Tonawanda, NY: Multi-Health Systems
- Riccio CA, Reynolds CR, Lowe P, Moore JJ (2002), The continuous performance test: a window on the neural substrates for attention? *Arch Clin Neuropsychol* 17:235-272
- Riccio CA, Waldrop JM, Reynolds CR, Lowe P (2001), Effects of stimulants on the continuous performance test (CPT): implications for CPT use and interpretation. *J Neuropsychiatry Clin Neurosci* 13:326-335
- Rosvold HE, Mirsky AF, Sarason I, Bransome SD, Beck LH (1956), A continuous performance test of brain damage. *J Consult Clin Psychol* 20:343-350
- Sprague RL, Sletor EK (1977), Methylphenidate in hyperkinetic children: differences in dose effects in learning in social behavior. *Science* 198:1274-1276
- Strutt GF, Anderson DR, Well AD (1975), A developmental study of the effects of irrelevant information on speeded classification. *J Exp Child Psychol* 20:127-135
- Thorndike RL, Hagen EP, Sattler JM (1986), *Guide for Administering and Scoring the Stanford-Binet Intelligence Scale*, 4th ed. Chicago: Riverside Publishing
- Winer BJ (1971), *Statistical Principles in Experimental Design*, 2nd ed. New York: McGraw Hill