Journal of Child Neurology
http://jcn.sagepub.com

A Novel Multidomain Computerized Cognitive Assessment for Attention-Deficit Hyperactivity Disorder: Evidence for Widespread and Circumscribed Cognitive Deficits

Yael Leitner, Glen M. Doniger, Ran Barak, Ely S. Simon and Jeffrey M. Hausdorff

J Child Neurol 2007; 22; 264
DOI: 10.1177/0883073807299859

Original Article

Journal of Child Neurology
Volume 22 Number 3
March 2007 264-276
© 2007 Sage Publications
10.1177/0883073807299859
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

A Novel Multidomain Computerized Cognitive Assessment for Attention-Deficit Hyperactivity Disorder: Evidence for Widespread and Circumscribed Cognitive Deficits

Yael Leitner, MD, Glen M. Doniger, PhD, Ran Barak, MD, Ely S. Simon, MD, and Jeffrey M. Hausdorff, PhD

Multidomain assessment may enhance the diagnosis of cognitive impairment in children with attention-deficit hyperactivity disorder (ADHD). A set of novel Web-enabled computerized tests has recently been shown to be valid for identifying mild cognitive impairment and characterizing the cognitive profile associated with various disorders. It was anticipated that these tests would be well suited for use in children with ADHD. The authors tested this idea in a pilot study of 15 children (12 males, 3 females; mean age, 11 years 10 months; range, 9-15 years) with ADHD and 15 age-, education-, and gender-matched controls. The profile of cognitive impairment in ADHD children off methylphenidate across 6 cognitive domains (memory, executive function, visual-spatial skills, verbal function, attention, and motor skills) was described relative to controls. The effect of treatment with methylphenidate was examined by comparing the ADHD children on methylphenidate and on placebo (administered in a double-blind randomized fashion) relative to controls and by comparing the ADHD children on methylphenidate relative to placebo. Significant impairment in ADHD was evident in memory, visual-spatial, verbal, and attention domains, and near-significant impairment was observed in executive function and motor skills. On methylphenidate but not placebo, performance was comparable to controls in immediate verbal memory, psychomotor accuracy, visual-spatial, verbal rhyming, and overall battery performance. Significant improvement with administration of methylphenidate relative to placebo was evident for psychomotor accuracy, verbal rhyming, and overall battery performance. Hence, on the limited basis of this pilot study, the set of computerized tests studied appears to be useful for measuring cognitive function in ADHD; however, additional studies are needed to confirm this.

Keywords: cognitive function; ADHD

Attention-deficit hyperactivity disorder (ADHD), a behavioral disorder affecting both children and adults, is estimated to have an incidence of 3% to 5% in the United States.[1] The disorder is characterized by inattention and hyperactivity/impulsivity resulting in aberrant social interactions and academic underachievement. According to a leading model, the hyperactive/impulsive symptoms of ADHD are driven by a core deficit in behavioral inhibition contributing to a disruption of working memory, sustained attention, motor control, and affect regulation.[2] This model is supported by converging evidence for behavioral impairment on neuropsychological tests of executive function[3] and imaging evidence for hypoactivation of prefrontal cortex[4] and the anterior cingulate,[5] brain areas that subserve higher-order control processes. However, a number of studies have found additional cognitive deficits in attention, memory, visual-spatial skills, verbal function, and processing speed,[6-11] and it appears that executive function deficit alone cannot fully explain the disorder.[12,13]

Given the potential for wide-ranging cognitive deficits in ADHD[7,14] and the need to rule out comorbidities associated with cognitive dysfunction,[15] sensitivity and specificity of the

Received October 8, 2005. Received revised May 1, 2006. Accepted for publication May 19, 2006.

From the Paediatric Neurology Unit and Child Development Center, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel (YL, RB); the Department of Pediatrics, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel (YL); the Department of Clinical Science, NeuroTrax Corporation, New York, New York (GMD, ESS); Movement Disorders Unit, Department of Neurology, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel (JMH); Division on Aging, Harvard Medical School, Boston, Massachusetts (JMH); and the Department of Physical Therapy, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel (JMH).

Address correspondence to: Jeffrey M. Hausdorff, PhD, Laboratory for Gait and Neurodynamics, Tel-Aviv Sourasky Medical Center, 6 Weizmann Street, Tel-Aviv 64239, Israel; e-mail: jhausdor@bidmc.harvard.edu.

Leitner Y, Doniger GM, Barak R, Simon ES, Hausdorff JM. A novel multidomain computerized cognitive assessment for attention-deficit hyperactivity disorder: evidence for widespread and circumscribed cognitive deficits. *J Child Neurol*. 2007;22:264-276.

ADHD diagnosis may be enhanced by broad cognitive testing. Indeed, in some individuals, results from a detailed cognitive assessment may give a better picture of the patient's status than a psychiatric diagnostic interview or continuous performance test alone when combined with other clinical information. Multidomain assessment both generates a profile of cognitive function across multiple domains and permits aggregation across measures to increase robustness.[7] In addition to breadth, standardized and objective cognitive assessment facilitates meaningful interpretation and exchange of results. Finally, cognitive assessment sensitive to shifts in performance due to medication provides an objective measure helpful in cases in which treatment effects are difficult to gauge on the basis of subjective reports.[16] Methylphenidate, the most commonly prescribed treatment for hyperactive/impulsive symptoms in ADHD, facilitates the ability to inhibit and thereby improves executive function,[10,17] but evidence of improvement due to methylphenidate has also been found in other cognitive domains.[11,18,19] Effective assessment should be able to detect such effects.

Recently, a multidomain battery of computerized cognitive tests has been validated relative to traditional neuropsychological tests in comparable cognitive domains for detection and characterization of mild cognitive deficits and treatment effects.[20-24] Notably, 1 validation study in adult ADHD showed good discriminant and construct validity relative to the Conners Continuous Performance Test II.[25] The tests are relatively brief and sample cognitive domains including memory, executive function, visual-spatial skills, verbal function, attention, and motor skills and include precise response time measurements. Hence, they seem well suited for the type of standardized, broad assessment that may facilitate ADHD diagnosis and clinical management and the evaluations recommended for ADHD research.[13] The present pilot study sought to explore the cognitive profile of impairment in a small ADHD cohort using a battery of these computerized tests as a detailed and objective measure of performance. A secondary goal was to show the ability of methylphenidate to improve cognitive performance on these tests in a double-blind, placebo-controlled manipulation. If favorable, the results of the present pilot study might lead to larger, more definitive trials.

Materials and Methods

Participants

Participants were 15 children (12 males, 3 females; mean age = 11 years 10 months, range = 9-15 years; mean years of education = 5 years 8 months, range = 3-10 years) diagnosed with ADHD according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*).[1] Participants were not selected on the basis of subtype. Eleven participants met *DSM-IV* criteria for the inattentive subtype, and 4 participants met criteria for the combined hyperactive-impulsive/inattentive subtype. A control group consisted of 15 cognitively healthy children (11 males, 4 females; mean age = 12 years 7 months, range = 8-16 years; mean years of education = 6 years 8 months, range = 3-11 years) comparable to the ADHD group in age ($U = 79.5$, $P = .171$), years of education ($U = 84.0$, $P = .226$), and gender ($\chi^2[1, N = 30] = 0.186$, $P = .666$). A diagnosis was made following a complete neurodevelopmental evaluation by an experienced pediatric neurology team, including a pediatric neurologist (Y.L.) and a neuropsychologist in the Pediatric Neurology Unit at the Tel-Aviv Sourasky Medical Center. The initial diagnoses of ADHD were made at least 1 year prior to the study, based on interviews with the parents, teachers, and children as well as by clinical examination and Conners parent/teacher questionnaires. Based on chart review and history, ADHD children were invited to participate only if they did not report or carry a formal diagnosis of any other (even minor) learning disabilities or neurological, orthopedic, or psychiatric diagnoses according to *DSM-IV* criteria. ADHD children were invited to participate only if they were taking methylphenidate (Ritalin; Novartis Pharmaceuticals, Basel, Switzerland) on a daily basis for at least 1 month prior to the study. Dosing (limited to 5-10 mg of short-acting methylphenidate) was optimized for each ADHD participant, as per standard clinical practice, and each participant exhibited good clinical response to the medication. Controls from the community were invited to participate if they both met these exclusion criteria and were not diagnosed with ADHD. Both ADHD participants and controls were enrolled in age-appropriate grades in mainstream schools, suggesting a similar level of academic aptitude among the groups. Institutional Review Board approval and informed written consent were obtained for this study.

Procedures

All participants completed Mindstreams (NeuroTrax, New York, NY) computerized cognitive tests designed to detect mild impairment. The NeuroTrax system has been described elsewhere and has shown good discriminant validity and construct validity relative to traditional neuropsychological tests in the detection and assessment of cognitive impairment in elderly individuals and young adults with ADHD.[20,25] In brief, Mindstreams consists of custom software installed on the local testing computer that serves as a platform for interactive cognitive tests measuring accuracy and response time (millisecond time scale). Practice sessions prior to the individual tests train participants in the types of responses required for the test. Web-based administrative features allow for secure entry and storage of patient demographic data. Once tests are run on the local computer, data are uploaded to a central sever, where automatic calculation of outcome parameters from raw single-trial data and report generation occur.

ADHD participants were tested 3 times: (a) after discontinuation of methylphenidate for at least 72 hours (baseline), (b) 2 hours after administration of a placebo, and (c) 2 hours after administration of methylphenidate. As part of their clinical care, most ADHD participants were receiving 5 to 10 mg of short-acting methylphenidate, and this was the dose that they received. To reduce the heterogeneity of the drug dosing, the few subjects who were taking long-acting or 15 mg of methylphenidate received 10 mg of methylphenidate. Methylphenidate and placebo tablets were identical in appearance and smell. The order of placebo and methylphenidate administration was randomized in a double-blind fashion. The first 2 sessions were on the same day, and the third session was within 2 weeks of the first 2. Control participants were tested once.

The computerized tests sample multiple cognitive domains, including memory (verbal and nonverbal), executive function, visual-spatial skills, verbal function, attention, and motor skills.[20] Tests were always administered in the same fixed order. The following are brief descriptions of tests administered in the current study (testing time = approximately 40 minutes).

Verbal memory. Ten pairs of words (the study set) are presented visually, followed by a recognition test in which 1 member (the target) of a previously presented pair appears together with a list of 4 candidates for the other member of the pair. There are 4 immediate repetitions and 1 delayed repetition after 10 minutes.

Nonverbal memory. Eight pictures of simple geometric objects (the study set) are presented, followed by a recognition test in which 4 versions of each object are presented, each oriented in a different direction. There are 4 immediate repetitions and 1 delayed repetition after 10 minutes.

Go-NoGo test. This is a timed continuous performance test during which responses are made to large colored stimuli that are any color but red.

Stroop test. This is a timed test of response inhibition and set shifting modified from the well-established paper-based test. In the first (no interference [color]) phase, participants choose the letter color of a general word. In the next (no interference [meaning]) phase, the task is to choose the color named by a word presented in white letter color. In the final (interference) phase, participants choose the letter color of a word that names a different color.

Verbal function. In the rhyming portion, participants must choose the word that rhymes with a picture shown on the screen; in the naming portion, the word that names the picture must be selected.

Visual-spatial processing. Computer-generated scenes containing a red pillar are presented. Participants must select the view of the scene from the vantage point of the red pillar.

Finger tapping. Participants must tap on the mouse button with their dominant hand.

Catch Game. A novel test of motor planning involving hand-eye coordination and rapid responses that requires participants to catch a falling object on the computer screen by moving a paddle horizontally so that it can be positioned directly in the path of the falling object.

Outcome Parameters and Index Scores

Test data were uploaded to a central server, where data processing occurred, during which aggregate outcome parameters were computed from raw single-trial data.[20] Outcome parameters were calculated using custom software blind to diagnosis or testing condition (eg, placebo or methylphenidate). Given the speed-accuracy tradeoff,[26] a performance index (computed as [accuracy/response time] × 100) was computed for timed tests in an attempt to capture performance both in terms of accuracy and response time. To permit averaging performance across different types of outcome parameters (eg, accuracy, response time), each parameter was normalized and fit to a standard score scale (mean, 100; SD, 15). The reference sample consisted of test data for 57 children with a diagnosis of being cognitively healthy in controlled research studies at 3 clinical sites; the 15 control group participants of the current study were included in the reference sample. All individuals in the reference sample were 18 years of age or younger and had 12 or fewer years of education. Normalized subsets of outcome parameters were averaged to produce 6 index scores.[27] Outcome parameters contributing to each index score were as follows.

Memory: mean accuracies for learning and delayed recognition phases of verbal and nonverbal memory tests.
Executive function: performance indices for the Stroop test and Go-NoGo test, mean weighted accuracy for Catch Game.
Visual-spatial: mean accuracy for the visual-spatial processing test.
Verbal: weighted accuracy for verbal rhyming test (part of the verbal function test).
Attention: mean response times for the Go-NoGo test and the no interference (meaning) phase of the Stroop test and mean standard deviation of response time for the Go-NoGo test.
Motor skills: mean time until first move for Catch Game and mean intertap interval and standard deviation of intertap interval for the finger-tapping test.

A global cognitive score was computed as the average of the 6 index scores to summarize performance on the entire battery. The index scores and global cognitive score served as primary dependent variables; individual outcome parameters were secondary dependent measures.

Table 1. Summary Score Performance in Children With Attention-Deficit Hyperactivity Disorder (ADHD) and Healthy Controls

Summary Score	Controls (n = 15)	ADHD (n = 15)		
		Baseline	Placebo	Methylphenidate
Memory	101.2 (9.8)	84.2 (13.8)	91.1 (16.5)	92.5 (13.4)
Executive function	99.4 (13.5)	88.4 (10.6)	89.7 (11.3)	94.9 (11.6)
Visual-spatial	104.8 (14.3)	77.5 (13.0)	86.4 (16.9)	95.6 (21.1)
Verbal function	99.1 (16.3)	84.5 (17.0)	79.5 (15.8)	96.4 (21.0)
Attention	100.8 (14.4)	86.3 (16.7)	85.5 (13.9)	89.0 (14.2)
Motor skills	100.8 (13.9)	92.6 (9.8)	95.0 (9.5)	100.2 (13.5)
Global cognitive score	100.6 (10.9)	85.8 (11.1)	87.3 (11.1)	94.3 (11.0)

NOTE: Values are presented as mean (SD).

Statistical Analyses

Mindstreams performance of ADHD participants at baseline was compared with that of control participants using the Mann-Whitney *U* test. Comparisons between ADHD participants at baseline and on placebo and between participants at baseline and on methylphenidate were made using the Wilcoxon signed-ranks test. Two-tailed statistics were used throughout, and $P < .05$ was considered significant. All statistics were computed with SPSS statistical software (SPSS, Chicago, Ill).

Results

Across cognitive domains, ADHD participants at baseline scored more poorly than controls did, while scores on methylphenidate were highest relative to baseline or placebo (Table 1). Indeed, while most cognitive domains evidenced significant impairment relative to controls at baseline, fewer showed impairment on placebo, and only the attention domain evidenced impairment relative to controls on methylphenidate (Table 2). Methylphenidate performance of ADHD participants was significantly better than baseline for most cognitive domains, while performance on placebo was not significantly better than baseline for all domains. Methylphenidate performance of ADHD participants was significantly better than placebo performance for verbal function and overall battery performance (Table 3; Figure 1).

Results for each cognitive domain are reported below, first for ADHD participants in each treatment condition relative to controls (ADHD vs controls) and then between pairs of treatment conditions within ADHD participants (within-ADHD treatment effects).

Memory

ADHD versus controls. Memory performance of ADHD participants at baseline was significantly poorer than that of controls ($P = .001$) (Figure 2); performance on placebo ($P = .186$) was not significantly different from controls, but the difference on methylphenidate ($P = .057$) approached significance (Tables 1 and 2). Results for individual outcome parameters show that whereas ADHD participants

Table 2. Summary Score Performance in Children With Attention-Deficit Hyperactivity Disorder (ADHD; n = 15) and Healthy Controls (n = 15): *P* Values for Tests of Between-Group Differences (Mann-Whitney *U* Test)

Summary Score	ADHD Versus Controls		
	Baseline	Placebo	Methylphenidate
Memory	**.001**	.186	.057
Executive function	.050	.065	.331
Visual-spatial	**<.001**	**.007**	.470
Verbal function	**.045**	**.006**	.949
Attention	**.013**	**.007**	**.026**
Motor skills	.075	.102	.747
Global cognitive score	**.001**	**.006**	.085

NOTE: Differences significant at $P < .05$ appear in bold and reflect poorer performance in the ADHD group. *P* values reflect exact significance level.

Table 3. Summary Score Performance in Children With Attention-Deficit Hyperactivity Disorder (ADHD; n = 15) After Taking Methylphenidate or Placebo: *P* Values for Tests of Within-Group Differences (Wilcoxon Signed-Ranks Test)

Summary Measure	Placebo vs Baseline	Methylphenidate vs Baseline	Methylphenidate vs Placebo
Memory	.158	**.033**	.875
Executive function	.834	**.026**	.152
Visual-spatial	.141	**.012**	.065
Verbal function	**.024**[a]	**.041**	**.012**
Attention	.929	.363	.345
Motor skills	.477	.071	.173
Global cognitive score	.778	**.002**	**.011**

NOTE: Differences significant at $P < .05$ appear in bold; unless otherwise noted, all differences are in the expected direction, with better performance on methylphenidate versus baseline or placebo and better performance on placebo versus baseline.

a. Significant decline relative to baseline.

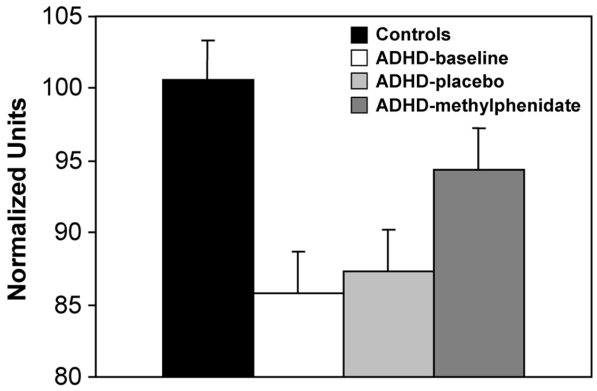

Figure 1. Results for the global cognitive score. Mean score (±SE) for the control group and for attention-deficit hyperactivity disorder (ADHD) participants at baseline (off methylphenidate), on placebo, and on methylphenidate.

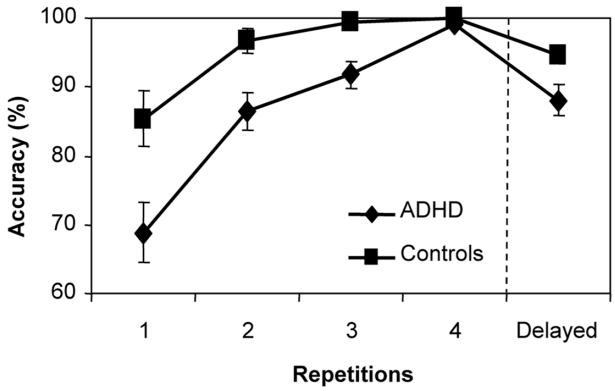

Figure 2. Results for the verbal memory test. Mean accuracy (±SE) for each of the 4 immediate repetitions and the delayed repetition of the recognition test for attention-deficit hyperactivity disorder (ADHD) participants (diamonds) at baseline and the control group (squares).

on both placebo and methylphenidate performed comparably to controls on the immediate portion of the nonverbal memory test, only ADHD participants on methylphenidate performed comparably to controls on the immediate portion of the verbal memory test (although the total accuracy for ADHD participants on methylphenidate was still poorer than controls) (Tables A1 and A2 in the appendix). On the delayed portion of both verbal and nonverbal memory tests, ADHD participants on placebo and methylphenidate performed similarly to controls (although the performance difference between ADHD participants at baseline and controls for delayed verbal memory did not reach significance) (Tables A1 and A2).

The pattern of memory test outcome parameter results for ADHD participants at baseline relative to controls suggests that impairment was greatest for recognition following initial exposure, but this deficit shrank with learning so that both ADHD and control participants were at or near ceiling after 4 repetitions of the study set (Figure 2; Table A1). With repetition of the study set following a 10-minute delay, performance in both groups dropped, and the ADHD deficit returned to a mid–learning level.

Within-ADHD treatment effects. Memory performance of ADHD participants on methylphenidate ($P = .033$) but not placebo ($P = .158$) was significantly better than performance at baseline; performance of ADHD participants on methylphenidate was not significantly different from placebo ($P = .875$) (Tables 1 and 3). Results for individual outcome parameters show that aside from accuracy for the first (immediate) repetition of the nonverbal memory test (performance better than baseline on both methylphenidate [$P = .020$] and placebo [$P = .035$]), no individual outcome parameter showed within-group differences depending on treatment condition (Tables A1 and A3).

Executive Function

ADHD versus controls. Poorer executive function performance of ADHD participants at baseline ($P = .050$) and on placebo ($P = .065$) relative to controls approached significance; performance on methylphenidate ($P = .331$) was comparable to controls (Tables 1 and 2). Results for individual outcome parameters show no between-group differences for Go-NoGo or Stroop interference-level performance indices (Tables A1 and A2). However, for Stroop interference-level response time, ADHD participants at baseline performed more poorly than controls did ($P = .012$) (Figure 3), and the difference approached significance on placebo ($P = .085$) but not on methylphenidate ($P = .150$). For Catch Game individual outcome parameters related to accuracy, ADHD participants on placebo but not methylphenidate performed more poorly than controls did on total score (placebo: $P = .033$; methylphenidate: $P = .847$) and average error for missed catches (placebo: $P = .023$; methylphenidate: $P = .949$); for average direction changes per trial, ADHD participants performed more poorly than controls did at baseline ($P = .004$) and on placebo ($P = .018$) but not on methylphenidate ($P = .217$).

Within-ADHD treatment effects. Executive function performance of ADHD participants on methylphenidate ($P = .026$) but not placebo ($P = .834$) was significantly better than performance at baseline; performance of ADHD participants on methylphenidate was not significantly different from placebo ($P = .152$) (Tables 1 and 3). Results for individual outcome parameters show no within-group differences dependent on treatment condition for Go-NoGo or Stroop interference-level performance indices (Tables A1 and A3). For Catch Game individual outcome parameters related to accuracy, the average error for missed catches for ADHD participants on methylphenidate

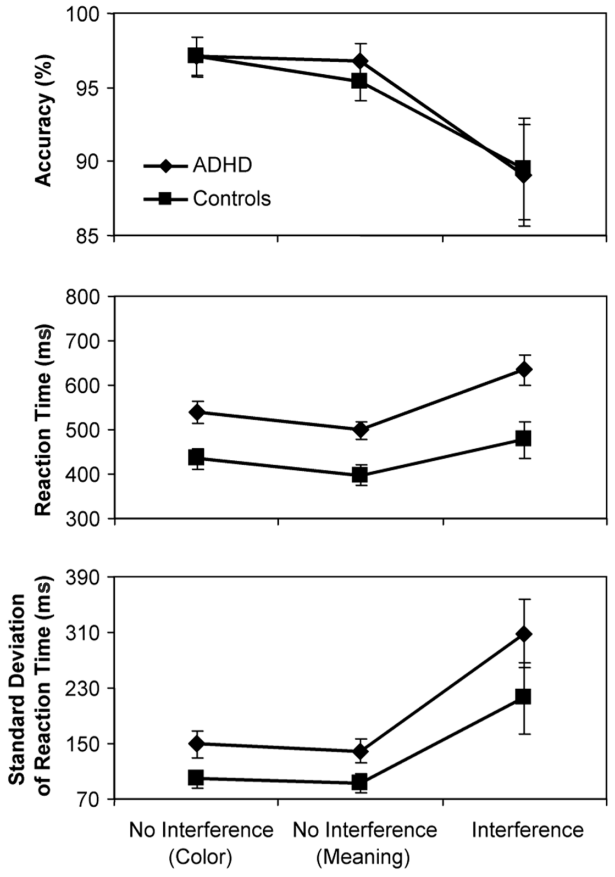

Figure 3. Results for the computerized Stroop test. Mean accuracy (±SE), response time for correct responses, and standard deviation of response time for correct responses for attention-deficit hyperactivity disorder (ADHD) participants (diamonds) at baseline and the control group (squares). Data are shown for no interference (color), no interference (meaning), and interference phases.

(P = .048) but not placebo (P = .589) was significantly better (ie, smaller) than performance at baseline; ADHD participants on methylphenidate performed better than those on placebo (P = .013). The Catch Game total score for ADHD participants was significantly better on methylphenidate relative to placebo (P = .031) but not relative to baseline (P = .136).

Visual-Spatial

ADHD versus controls. Visual-spatial performance of ADHD participants at baseline (P < .001) and on placebo (P = .007) was significantly poorer than controls, but performance on methylphenidate (P = .470) was comparable to controls (Tables 1 and 2; Tables A1 and A2).

Within-ADHD treatment effects. Visual-spatial performance of ADHD participants on methylphenidate (P = .012) but not placebo (P = .141) was significantly better than performance at baseline; the benefit of methylphenidate over placebo approached significance (index score: P = .065; outcome parameter: P = .075) (Tables 1 and 3; Tables A1 and A3).

Verbal Function

ADHD versus controls. Verbal function performance of ADHD participants at baseline (P = .045) and on placebo (index score: P = .006; rhyming outcome parameter: P = .007) was significantly poorer than controls, but performance on methylphenidate (P = .949) was similar to controls (Tables 1 and 2; Tables A1 and A2). Results for the naming outcome parameter were similar, although the between-group difference on methylphenidate approached significance (ADHD at baseline vs controls: P = .001; ADHD on placebo vs controls: P = .012; ADHD on methylphenidate vs controls: P = .077).

Within-ADHD treatment effects. Verbal function performance of ADHD participants on methylphenidate was significantly better (P = .041), and performance on placebo was significantly poorer (P = .024) than performance at baseline; there was a significant benefit of methylphenidate over placebo (index score: P = .012; rhyming outcome parameter: P = .011) (Tables 1 and 3; Tables A1 and A3). There were no within-group differences for the naming outcome parameter (Tables A1 and A3).

Attention

ADHD versus controls. Attention performance of ADHD participants at baseline (P = .013), on placebo (P = .007), and on methylphenidate (P = .026) was significantly poorer than controls (Tables 1 and 2). Results for individual outcome parameters show no between-group difference for Go-NoGo response time, but for standard deviation of response time, ADHD participants on placebo performed more poorly than controls did (P = .006), and the difference at baseline approached significance (P = .081), but there was no significant difference on methylphenidate (P = .102) (Tables A1 and A2). As with the attention index score, Stroop no interference (word meaning) response time for ADHD participants at baseline (P = .003) (Figure 3), on placebo (P = .004), and on methylphenidate (P = .005) was significantly poorer than controls, indicating that this outcome parameter is likely driving the results obtained for the index score (Tables 1 and 2). The same pattern was found for Stroop no interference (meaning) standard deviation of response time (baseline: P = .029; placebo: P = .002; methylphenidate: P = .014) (Figure 3) and performance index, driven by the response time results and not accuracy, for which no between-group differences were found (Tables A1 and A2). Interestingly, for Stroop no interference (letter color) response time, ADHD participants at

baseline performed more poorly than controls did (P = .011) (Figure 3), but differences on placebo (P = .072) and methylphenidate (P = .077) did not reach significance.

The pattern of results on the Stroop test for ADHD participants at baseline relative to controls suggests a selective deficit for timed as compared to accuracy outcome parameters (Tables A1 and A2; Figure 3). Both groups showed reduced accuracy, extended response time, and larger standard deviation of response time with interference. However, while accuracy was comparable across ADHD and control groups, response time was significantly longer for the ADHD group for all phases (Figure 3), and the standard deviation of response time was significantly larger than for controls in the no-interference (meaning) phase (Tables A1 and A2; Figure 3).

Within-ADHD treatment effects. Attention performance of ADHD participants on methylphenidate (P = .929) or placebo (P = .363) was not significantly different from performance at baseline; the performance of ADHD participants on methylphenidate was not significantly different from placebo (P = .345) (Tables 1 and 3). Results for individual outcome parameters show no within-group differences in treatment condition for Go-NoGo response time and standard deviation of response time or Stroop no interference (word meaning) response time (Tables A1 and A3). For Stroop no interference (letter color) response time, the difference between ADHD participants on methylphenidate and those at baseline approached significance (P = .062), while performance on placebo was comparable to baseline (P = .386). There was no added benefit of methylphenidate over placebo (P = .575). A similar pattern was found for the Stroop no interference (letter color) performance index (methylphenidate vs baseline: P = .050; placebo vs baseline: P = .386; methylphenidate vs placebo: P = .328).

Motor Skills

ADHD versus controls. Poorer motor skills performance of ADHD participants at baseline relative to controls approached significance (P = .075); performance on placebo (P = .102) and on methylphenidate (P = .747) was comparable to controls (Tables 1 and 2). Results for individual outcome parameters show no between-group differences for the finger-tapping outcome parameters, although the difference in intertap interval between ADHD participants at baseline and controls approached significance (P = .083) (Tables A1 and A2). For Catch Game time to make the first move, the difference between ADHD participants at baseline (P = .061) and on placebo (P = .070) relative to controls approached significance, but ADHD participants on methylphenidate performed comparably to controls (P = .400). A similar pattern was found for Catch Game standard deviation of time to first move (ADHD at baseline vs controls: P = .089; ADHD on placebo vs controls: P = .102; ADHD on methylphenidate vs controls: P = .847).

Within-ADHD treatment effects. Improved motor skills performance of ADHD participants on methylphenidate relative to baseline approached significance (P = .071); performance of ADHD participants on placebo was comparable to baseline (P = .477) and not significantly different from methylphenidate (P = .173) (Tables 1 and 3). Results for individual outcome parameters show no within-group differences depending on treatment condition for finger-tapping intertap interval or standard deviation of intertap interval (Tables A1 and A3). For Catch Game time to first move, improved performance of ADHD participants on methylphenidate relative to baseline approached significance (P = .055); performance on placebo was comparable to baseline (P = .937), and there was no added benefit of methylphenidate over placebo (P = .255).

Global Cognitive Score

ADHD versus controls. Across cognitive domains, performance of ADHD at baseline (P = .001) and on placebo (P = .006) was significantly poorer than controls, but performance on methylphenidate (P = .085) was more similar to controls (Tables 1 and 2; Figure 3).

Within-ADHD treatment effects. Across cognitive domains, ADHD participants on methylphenidate performed significantly better (P = .002) than at baseline, while performance on placebo was comparable to baseline (P = .778); there was a significant benefit of methylphenidate over placebo (P = .011) (Tables 1 and 3; Figure 3).

Discussion

The present pilot study described the profile of cognitive impairment in a small cohort of children with ADHD and effects of treatment with methylphenidate versus placebo using a relatively broad battery of computerized tests. Significant impairment was found in memory, visual-spatial, verbal function, attention, and overall battery performance; near-significant deficits were found in executive function and motor skills. ADHD participants on methylphenidate but not placebo performed similarly to control participants in immediate verbal memory, psychomotor accuracy, visual-spatial, verbal rhyming, and overall battery performance. Significant improvement on methylphenidate relative to placebo was found for psychomotor accuracy, verbal rhyming, and overall battery performance.

In a meta-analysis of more than 100 studies using traditional neuropsychological measures to distinguish among ADHD and cognitively healthy individuals, Frazier and colleagues[7] found overall cognitive ability to be significantly

lower among persons with ADHD but found varying patterns of cognitive impairment. The authors concluded that the pattern of results is consistent with mild global inefficiencies or multiple specific deficits affecting several cognitive abilities, a conclusion supported by the present findings of global, domain-specific, and outcome parameter–specific impairment. Rapport and colleagues[28] reviewed 142 studies published between 1980 and 1999 using traditional neuropsychological tasks to identify ADHD and characterized the most reliable tests as those that (1) rely on recognition, recall, or some combination of the 2; (2) involve more speeded processing; (3) place special demands on working memory; (4) do not have a response stimulus present throughout each test trial; and (5) are not participant paced. The computerized tests used in the present study meet these criteria, and the pattern of specific outcome parameter results reported appears consistent with them.

In keeping with the first criterion of Rapport and colleagues,[28] a large ADHD deficit was found both in the memory index score and for specific memory outcome parameters. Children with ADHD were most impaired at remembering new material but were able to benefit from repetition and approached a normal level of performance after as few as 4 repetitions. Notably, impairment in ADHD children returned following a brief delay, reflecting a retention deficit relative to controls (Figure 2). Consistent with the present results, other studies have differentiated among ADHD boys and controls with paper-based memory tests.[9,29] Moreover, in his handbook for diagnosis and treatment of ADHD, Barkley[30] counted decreased nonverbal and verbal working memory among impairments likely to be associated with ADHD.

The second criterion of Rapport and colleagues[28] for a reliable test (ie, more speeded processing) is consistent with the pattern of results on the Stroop test. While ADHD and control participants performed comparably in accuracy, response times were both longer and more variable for ADHD participants (Figure 3). The third and fourth design criteria of Rapport and colleagues[28] for a reliable test (demands on working memory and absence of response stimulus during test trial) are inherent in the task demands of the Stroop test. Indeed, the test taxes working memory, requiring the participant to hold the word stimulus in memory until the response stimulus, absent during test stimulus presentation, appears.

The present Stroop results are consistent with those of many other studies showing that the paper-based Stroop Color and Word Test can differentiate ADHD from controls.[9] Indeed, a meta-analysis of 33 studies using various versions of the Stroop test found impairment in ADHD to be reflected in most studies with moderate effect sizes.[31] Notably, unlike the computerized Stroop test, performance on the paper-based Stroop is typically measured by such outcomes as number of trials completed or time to complete the task,[7] and response time measurements are often made to a verbal response.[31] Hence the computerized Stroop test may be more sensitive than similar paper-based tests.

The specific pattern of computerized Stroop results is indicative of an interference effect in both ADHD and control participants but overall slower and more variable processing in ADHD participants. This finding is consistent with the Stroop finding by Lawrence and colleagues,[32] of no executive function difference between ADHD boys and controls but slower processing speed, and that of Rubia and colleagues,[3] showing that responses in ADHD individuals were more variable and erratic than normal controls on a "Stop task." Notably, Barkley[30] counted greater variability in responding among the task performance impairments likely associated with ADHD. The current pattern of Stroop results may also be analogous to the findings of Bush and colleagues[5] using a counting Stroop task. These authors found a behavioral interference effect in both ADHD and control participants but hypoactivation of the anterior cingulate, a brain structure involved in complex cognitive and motor control, in the ADHD participants. Consistently slower response times in the present study may be related to this hypoactivation.

The visual-spatial deficit in ADHD and improvement with methylphenidate administration but not placebo was among the most salient results of the present study. In support, a study by Garcia-Sanchez and colleagues[33] found a visual-spatial deficit in ADHD with a wide-ranging battery of paper-based tests of visuospatial, visuoperceptive, and visuoconstructive functions, and Aman and colleagues[11] found that medicated ADHD boys perform better on paper-based visual-spatial tasks than when nonmedicated. Another notable result of the present study is the absence of a methylphenidate effect on the attention index score. Given that attention is a core domain affected in ADHD and the present results trended toward improvement in attention on methylphenidate, lack of significance may be attributable to severity of impairment[34] coupled with small sample size. Thus, a larger study is necessary before definitive conclusions can be drawn. A further interesting result was the lack of a finger-tapping deficit in the present study. This is consistent with the results of Seidman and colleagues[9] and Berlin and colleagues,[35] who found deficits in executive function measures but not in measures of finger tapping.

ADHD participants in the present cohort were mainly of the inattentive subtype, which is consistent with the large deficit in attention and borderline impairment in executive function. Notably, a recent study found cognitive performance in ADHD children of both combined and inattentive subtypes to be related to inattention rather than impulsivity, supporting the use of a single cohort composed of both inattentive and combined subtypes in the present pilot study.[36]

The present preliminary findings agree with recent reports of broad cognitive impairment in ADHD[6-11] and suggest that testing of multiple cognitive domains with a computerized tool[13] may enhance clinical management of ADHD by providing a detailed and objective profile of deficit in ADHD that is sensitive to pharmacologic intervention. As nonsignificant findings may be due to low statistical power,

additional studies with larger sample sizes are necessary. Follow-up studies are also necessary to examine the clinical utility of computerized assessments such as that used in the present investigation, particularly in ruling out comorbidities affecting cognition and screening for children requiring a comprehensive psychoeducational assessment. Although education level was similar between ADHD and control participants in the current study, future studies should adjust for the level of general intelligence (but see Schuck and Crinella[37]) and focus on devising a targeted battery with differentially weighted measures to optimize identification of ADHD and characterization of the cognitive deficits observed in ADHD. Future work should also explore differential cognitive profiles for ADHD subtypes and examine discriminant validity in distinguishing ADHD from comorbid learning disability and emotional disturbance.

Acknowledgments

We thank the participants and their parents for their time and effort. This work was supported in part by National Institutes of Health grants AG-14100, RR-13622, HD-39838, and AG-08812.

This work was performed in the Paediatric Neurology Unit and in the Movement Disorders Unit at the Tel-Aviv Sourasky Medical Center. Glen M. Doniger and Ely S. Simon are employees of NeuroTrax. Yael Leitner, Ran Barak, and Jeffrey M. Hausdorff contributed to the study design and oversaw data collection. Data analysis was performed by Glen M. Doniger, guided by input from Jeffrey M. Hausdorff and Ely S. Simon. Yael Leitner drafted an initial version of the article. Revised versions were handled by Glen M. Doniger, with contributions from all authors. All authors read and approved the final article.

Appendix

Table A1. Mean (SD) Individual Outcome Parameter Performance in Children With Attention-Deficit Hyperactivity Disorder (ADHD) and Healthy Controls

			ADHD (n = 15)		
Test	Outcome Parameter	Controls (n = 15)	Baseline	Placebo	Methylphenidate
Verbal memory	Immediate recognition				
	Accuracy, repetition 1	85.3 (15.5)	68.8 (17.1)	68.7 (21.7)	73.3 (17.3)
	Accuracy, repetition 2	96.7 (7.24)	86.4 (10.3)	88.2 (10.5)	92.1 (9.7)
	Accuracy, repetition 3	99.3 (2.6)	91.7 (7.3)	92.4 (7.1)	94.9 (7.3)
	Accuracy, repetition 4	100.0 (0.0)	99.2 (1.4)	98.8 (1.5)	99.2 (1.4)
	Accuracy, repetitions 1-4[ME]	95.6 (5.5)	85.9 (8.4)	86.5 (9.8)	90.1 (8.2)
	Delayed recognition				
	Accuracy[ME]	94.7 (5.2)	88.1 (9.06)	92.5 (9.8)	93.3 (9.0)
Nonverbal memory	Immediate recognition				
	Accuracy, repetition 1	70.7 (21.0)	50.4 (13.2)	68.4 (21.4)	69.4 (21.3)
	Accuracy, repetition 2	91.6 (12.3)	81.1 (16.2)	84.3 (14.5)	84.9 (11.3)
	Accuracy, repetition 3	95.5 (9.0)	87.4 (11.0)	92.6 (10.0)	90.7 (9.5)
	Accuracy, repetition 4	98.6 (3.5)	94.6 (5.3)	97.8 (4.2)	95.6 (5.0)
	Accuracy, repetitions 1-4[ME]	89.4 (10.1)	80.2 (9.3)	85.9 (10.4)	85.0 (10.6)
	Delayed recognition				
	Accuracy[ME]	93.1 (8.7)	85.9 (9.4)	90.5 (9.6)	89.2 (8.2)
Go-NoGo	Accuracy	89.4 (7.6)	88.5 (8.2)	89.0 (7.5)	89.0 (6.8)
	Average response time[AT]	409.5 (77.8)	464.1 (98.9)	462.0 (78.9)	421.3 (66.9)
	Performance index[EX]	22.5 (4.8)	19.7 (5.7)	19.7 (4.4)	20.7 (4.9)
	Response time SD[AT]	87.7 (41.9)	114.5 (45.7)	125.6 (37.3)	118.2 (47.7)
	Errors of commission (maximum: 12)	2.6 (1.6)	2.8 (1.8)	2.7 (1.6)	2.4 (1.4)
	Errors of omission (maximum: 18)	0.7 (1.1)	1.1 (1.3)	0.78 (1.2)	0.87 (1.0)
	Response time for errors of commission	330.3 (81.9)	377.8 (89.2)	416.0 (73.4)	344.2 (71.6)
Stroop	No interference: letter color (1)				
	Accuracy	97.1 (4.9)	97.1 (5.0)	97.7 (4.4)	97.9 (4.3)
	Average response time	434.8 (87.2)	539.1 (101.4)	519.4 (116.3)	499.4 (96.3)
	Performance index	22.6 (4.8)	17.8 (5.2)	18.9 (6.0)	20.0 (4.9)
	Response time SD	99.2 (48.9)	149.7 (74.7)	155.5 (70.0)	136.2 (75.3)
	No interference: word meaning (2)				
	Accuracy	95.4 (4.9)	96.8 (4.3)	95.7 (4.6)	98.5 (3.0)
	Average response time[AT]	398.0 (86.2)	499.3 (75.1)	489.9 (79.7)	496.7 (80.5)
	Performance index	24.6 (5.5)	19.0 (4.8)	19.1 (4.7)	19.8 (5.1)
	Response time SD	92.9 (52.6)	139.4 (63.3)	159.9 (51.4)	148.7 (48.2)

(*continued*)

Table A1. (continued)

Test	Outcome Parameter	Controls (n = 15)	ADHD (n = 15) Baseline	ADHD (n = 15) Placebo	ADHD (n = 15) Methylphenidate
	Interference: letter color vs word meaning (3)				
	Accuracy	89.5 (13.4)	89.1 (13.4)	88.5 (11.1)	88.2 (13.1)
	Average response time	477.2 (154.7)	634.4 (130.0)	587.1 (154.5)	555.6 (151.7)
	Performance index[EX]	18.6 (9.4)	12.1 (6.1)	15.2 (8.1)	15.5 (7.6)
	Response time SD	215.3 (191.1)	308.8 (193.9)	312.1 (175.8)	266.5 (174.1)
Verbal function	Rhyming				
	Accuracy, high and low familiarity[VE]	90.3 (6.3)	84.6 (6.6)	82.7 (6.1)	89.2 (8.1)
	Naming				
	Accuracy, high and low familiarity	97.0 (4.4)	91.8 (3.9)	92.4 (4.7)	93.8 (4.7)
Visual-spatial processing	Accuracy[VI]	82.8 (13.4)	57.1 (12.2)	65.6 (15.9)	74.2 (19.8)
Finger tapping	Intertap interval[MO]	198.7 (26.1)	215.9 (19.5)	210.2 (27.8)	203.8 (24.9)
	Tap interval SD[MO]	41.6 (21.7)	42.0 (25.5)	41.7 (19.3)	34.4 (20.6)
Catch Game	Time to make first move[MO]	468.1 (80.6)	533.9 (78.5)	514.9 (54.2)	487.3 (84.8)
	Time to make first move SD	123.5 (35.5)	143.7 (37.6)	147.5 (34.6)	126.3 (40.9)
	Average direction changes per trial	0.12 (0.07)	0.21 (0.09)	0.23 (0.13)	0.21 (0.16)
	Average error for missed catches	0.11 (0.12)	0.20 (0.19)	0.23 (0.15)	0.09 (0.06)
	Total score (maximum: 1000)[EX]	892.6 (104.3)	823.8 (142.9)	786.6 (123.4)	891.4 (80.7)

NOTE: Accuracy is given as percentage correct. Response time and response time standard deviation are given as milliseconds for correct responses. The performance index is given as (accuracy/response time) × 100. Definition of superscripts: ME = constituent of memory index score; EX = consitutent of executive function index score; VI = constituent of visual-spatial index score; VE = consitutent of verbal function index score; AT = constituent of attention index score; MO = constituent of motor skills index score.

Table A2. Individual Outcome Parameter Performance in Children With Attention-Deficit Hyperactivity Disorder (ADHD; n = 15) and Healthy Controls (n = 15): *P* Values for Tests of Between-Group Differences (Mann-Whitney *U* Test)

Test	Outcome Parameter	ADHD vs Controls Baseline	ADHD vs Controls Placebo	ADHD vs Controls Methylphenidate
Verbal memory	Immediate recognition			
	Accuracy, repetition 1	**.015**	**.037**	.063
	Accuracy, repetition 2	**.005**	**.023**	.172
	Accuracy, repetition 3	**.008**	**.014**	.158
	Accuracy, repetition 4	.217	.051	.201
	Accuracy, repetitions 1-4[ME]	**.001**	**.026**	**.041**
	Delayed recognition			
	Accuracy[ME]	.056	.847	.983
Nonverbal memory	Immediate recognition			
	Accuracy, repetition 1	**.008**	.830	.867
	Accuracy, repetition 2	.063	.155	.128
	Accuracy, repetition 3	.070	.519	.239
	Accuracy, repetition 4	.063	.720	.169
	Accuracy, repetitions 1-4[ME]	**.009**	.519	.375
	Delayed recognition			
	Accuracy[ME]	**.046**	.488	.280
Go-NoGo	Accuracy	.683	.821	.780
	Average response time[AT]	.116	.065	.451
	Performance index[EX]	.137	.142	.270
	Response time SD[AT]	.081	**.006**	.102
	Errors of commission (maximum: 12)	.683	.856	.880
	Errors of omission (maximum: 18)	.539	1.000	.683
	Response time for errors of commission	.150	**.013**	.550
Stroop	No interference: letter color (1)			
	Accuracy	.935	.717	.683
	Average response time	**.011**	.072	.077
	Performance index	**.016**	.130	.134
	Response time SD	.137	.065	.303

(*continued*)

Table A2. (continued)

Test	Outcome Parameter	ADHD vs Controls		
		Baseline	Placebo	Methylphenidate
	No interference: word meaning (2)			
	Accuracy	.486	.928	.112
	Average response time[AT]	**.003**	**.004**	**.005**
	Performance index	**.006**	**.019**	**.014**
	Response time SD	**.029**	**.002**	**.014**
	Interference: letter color vs word meaning (3)			
	Accuracy	.935	.786	.847
	Average response time	**.012**	.085	.150
	Performance index[EX]	.081	.413	.533
	Response time SD	.290	.116	.427
Verbal function	Rhyming			
	Accuracy, high and low familiarity[VE]	**.045**	**.007**	.949
	Naming			
	Accuracy, high and low familiarity	**.001**	**.012**	.077
Visual-spatial processing	Accuracy[VI]	**<.001**	**.007**	.470
Finger tapping	Intertap interval[MO]	.083	.310	.621
	Tap interval SD[MO]	.829	.949	.290
Catch Game	Time to make first move[MO]	.061	.070	.400
	Time to make first move SD	.089	.102	.847
	Average direction changes per trial	**.004**	**.018**	.217
	Average error for missed catches	.233	**.023**	.949
	Total score (maximum: 1000)[EX]	.233	**.033**	.847

NOTE: Accuracy is computed as the percentage correct. Response time and response time standard deviation are computed as milliseconds for correct responses. The performance index is computed as (accuracy/response time) × 100. Differences significant at $P < .05$ appear in bold and reflect poorer performance in the ADHD group. *P* values reflect exact significance level. Definition of superscripts: ME = constituent of memory index score; EX = consitutent of executive function index score; VI = constituent of visual-spatial index score; VE = consitutent of verbal function index score; AT = constituent of attention index score; MO = constituent of motor skills index score.

Table A3. Individual Outcome Parameter Performance in Children With Attention-Deficit Hyperactivity Disorder (ADHD; n = 15) After Taking Methylphenidate or Placebo: *P* Values for Tests of Within-Group Differences (Wilcoxon Signed-Ranks Test)

Test	Outcome Parameter	Placebo vs Baseline	Methylphenidate vs Baseline	Methylphenidate vs Placebo
Verbal memory	Immediate recognition			
	Accuracy, repetition 1	.959	.573	.561
	Accuracy, repetition 2	.357	.066	.196
	Accuracy, repetition 3	.593	.167	.196
	Accuracy, repetition 4	.396	.564	.276
	Accuracy, repetitions 1-4[ME]	.726	.107	.305
	Delayed recognition			
	Accuracy[ME]	.228	.084	.863
Nonverbal memory	Immediate recognition			
	Accuracy, repetition 1	**.035**	**.020**	.573
	Accuracy, repetition 2	.719	.720	.878
	Accuracy, repetition 3	.245	.622	.267
	Accuracy, repetition 4	.129	.680	.102
	Accuracy, repetitions 1-4[ME]	.265	.285	.508
	Delayed recognition			
	Accuracy[ME]	.194	.607	.720
Go-NoGo	Accuracy	.767	.783	.563
	Average response time[AT]	1.000	.300	.221
	Performance index[EX]	.929	.330	.552
	Response time SD[AT]	.657	.593	.875
	Errors of commission (maximum: 12)	.720	.592	.893
	Errors of omission (maximum: 18)	.343	.553	.596
	Response time for errors of commission	.374	.410	**.023**

(*continued*)

Table A3. (continued)

Test	Outcome Parameter	Placebo vs Baseline	Methylphenidate vs Baseline	Methylphenidate vs Placebo
Stroop	No interference: letter color (1)			
	Accuracy	.335	.335	1.000
	Average response time	.594	.062	.575
	Performance index	.386	**.050**	.328
	Response time SD	.445	.594	.333
	No interference: word meaning (2)			
	Accuracy	.493	.317	.096
	Average response time[AT]	.779	.859	.866
	Performance index	.779	.477	.646
	Response time SD	.173	.433	.484
	Interference: letter color vs word meaning (3)			
	Accuracy	.734	.888	.837
	Average response time	.674	.093	.263
	Performance index[EX]	.424	.221	.807
	Response time SD	.534	.889	.209
Verbal function	Rhyming			
	Accuracy, high and low familiarity[VE]	**.024**[a]	**.041**	**.011**
	Naming			
	Accuracy, high and low familiarity	.723	.238	.571
Visual-spatial processing	Accuracy[VI]	.141	**.012**	.075
Finger tapping	Intertap interval[MO]	.213	.065	.363
	Tap interval SD[MO]	.838	.414	.374
Catch Game	Time to make first move[MO]	.451	.055	.133
	Time to make first move SD	.937	.133	.255
	Average direction changes per trial	.621	.916	.919
	Average error for missed catches	.589	**.048**	**.013**
	Total score (maximum: 1000)[EX]	.372	.136	**.031**

NOTE: Accuracy is computed as the percentage correct. Response time and response time standard deviation are computed as milliseconds for correct responses. Performance index is computed as (accuracy/response time) × 100. Differences significant at $P < .05$ appear in bold; unless otherwise noted, all differences are in the expected direction, with better performance on methylphenidate vs baseline or placebo and better performance on placebo vs baseline. Definitions of superscripts: ME = constituent of memory index score; EX = consitutent of executive function index score; VI = constituent of visual-spatial index score; VE = consitutent of verbal function index score; AT = constituent of attention index score; MO = constituent of motor skills index score.
a. Significant decline relative to baseline.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
2. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull*. 1997;121:65-94.
3. Rubia K, Oosterlaan J, Sergeant JA, et al. Inhibitory dysfunction in hyperactive boys. *Behav Brain Res*. 1998;94:25-32.
4. Rubia K, Overmeyer S, Taylor E, et al. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am J Psychiatry*. 1999;156:891-896.
5. Bush G, Frazier JA, Rauch SL, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. *Biol Psychiatry*. 1999;45:1542-1552.
6. Shafritz KM, Marchione KE, Gore JC, et al. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *Am J Psychiatry*. 2004;161:1990-1997.
7. Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology*. 2004;18:543-555.
8. Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol*. 2004;19:151-180.
9. Seidman LJ, Biederman J, Monuteaux MC, et al. Learning disabilities and executive dysfunction in boys with attention-deficit/hyperactivity disorder. *Neuropsychology*. 2001;15:544-556.
10. Westby C, Watson S. Perspectives on attention deficit hyperactivity disorder: executive functions, working memory, and language disabilities. *Semin Speech Lang*. 2004;25:241-254.
11. Aman CJ, Roberts RJ Jr, Pennington BF. A neuropsychological examination of the underlying deficit in attention deficit hyperactivity disorder: frontal lobe versus right parietal lobe theories. *Dev Psychol*. 1998;34:956-969.
12. Wilcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry*. 2005;57:1336-1346.
13. Castellanos FX, Sonuga-Barke EJS, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. *Trends Cogn Sci*. 2006;10:117-123.

14. Roth RM, Saykin AJ. Executive dysfunction in attention-deficit/hyperactivity disorder: cognitive and neuroimaging findings. *Psychiatr Clin North Am*. 2004;27:83-96.
15. Preston AS, Fennell EB, Bussing R. Utility of a CPT in diagnosing ADHD among a representative sample of high-risk children: a cautionary study. *Neuropsychol Dev Cogn C Child Neuropsychol*. 2005;11:459-469.
16. Foy JM, Earls MF. A process for developing community consensus regarding the diagnosis and management of attention-deficit/hyperactivity disorder. *Pediatrics*. 2005;115:e97-104.
17. Kramer JR, Loney J, Ponto LB, et al. Predictors of adult height and weight in boys treated with methylphenidate for childhood behavior problems. *J Am Acad Child Adolesc Psychiatry*. 2000; 39:517-524.
18. Mehta MA, Goodyer IM, Sahakian BJ. Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity. *J Child Psychol Psychiatry*. 2004;45:293-305.
19. Pearson DA, Santos CW, Casat CD, et al. Treatment effects of methylphenidate on cognitive functioning in children with mental retardation and ADHD. *J Am Acad Child Adolesc Psychiatry*. 2004;43:677-685.
20. Dwolatzky T, Whitehead V, Doniger GM, et al. Validity of a novel computerized cognitive battery for mild cognitive impairment. *BMC Geriatr*. 2003;3:4.
21. Elstein D, Doniger GM, Guedalia J, et al. Computerized cognitive testing in patients with type I Gaucher disease: effects of enzyme replacement and substrate reduction. *Genet Med*. 2005;7:124-130.
22. Hausdorff JM, Yogev G, Springer S, et al. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res*. 2005;164:541-548.
23. Yogev G, Giladi N, Peretz C, et al. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci*. 2005;22:1248-1256.
24. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patient with Parkinson's disease: a pilot study. *Clin Neuropharmacol*. 2006; 29:15-17.
25. Schweiger A, Abramovitch A, Doniger GM, Simon ES. A clinical construct validity study of a novel computerized battery for the diagnosis of ADHD in young adults. *J Clin Exp Neuropsychol*. 2007;29:100-111.
26. Cauraugh JH. Speed-accuracy tradeoff during response preparation. *Res Q Exerc Sport*. 1990;61:331-337.
27. Schweiger A, Doniger GM, Dwolatzky T, et al. Reliability of a novel computerized neuropsychological battery for mild cognitive impairment. *Acta Neuropsychol*. 2003;1:407-413.
28. Rapport MD, Chung KM, Shore G, et al. Upgrading the science and technology of assessment and diagnosis: laboratory and clinic-based assessment of children with ADHD. *J Clin Child Psychol*. 2000;29:555-568.
29. August GJ, Garfinkel BD. Comorbidity of ADHD and reading disability among clinic-referred children. *J Abnorm Child Psychol*. 1990;18:29-45.
30. Barkley RA. *Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment*. 2nd ed. New York, NY: Guilford; 1998.
31. Homack S, Riccio CA. A meta-analysis of the sensitivity and specificity of the Stroop Color and Word Test with children. *Arch Clin Neuropsychol*. 2004;19:725-743.
32. Lawrence V, Houghton S, Douglas G, et al. Executive function and ADHD: a comparison of children's performance during neuropsychological testing and real-world activities. *J Atten Disord*. 2004;7:137-149.
33. Garcia-Sanchez C, Estevez-Gonzalez A, Suarez-Romero E, Junque C. Right hemisphere dysfunction in subjects with attention-deficit disorder with and without hyperactivity. *J Child Neurol*. 1997;12:107-115.
34. American Academy of Pediatrics, Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics*. 2001;108:1033-1044.
35. Berlin L, Bohlin G, Nyberg L, Janols LO. How well do measures of inhibition and other executive functions discriminate between children with ADHD and controls? *Neuropsychol Dev Cogn Sect C Child Neuropsychol*. 2004;10:1-13.
36. Chhabildas N, Pennington BF, Willcutt EG. A comparison of the neuropsychological profiles of the DSM-IV subtypes of ADHD. *J Abnorm Child Psychol*. 2001;29:529-540.
37. Schuck SE, Crinella FM. Why children with ADHD do not have low IQs. *J Learn Disabil*. 2005;38:262-280.