Message from the Editor:

In this issue, two original studies are presented, each demonstrating the ability of Mindstreams™ to assess cognitive function and treatment effects in a unique clinical population. The first describes a study of children with attention-deficit hyperactivity disorder (ADHD), highly prevalent but difficult to diagnose with conventional methods. The second presents preliminary data on individuals with Gaucher Disease, an inherited disorder common in individuals of eastern European ancestry.

Ely Simon, MD

In this issue:

Research Letters

Mindstreams™ Identifies Cognitive Deficit in Attention-Deficit Hyperactivity Disorder (ADHD)

R Barak, MD1,2; Y Leitner, MD1,2; N Giladi, MD1,2; GM Doniger, PhD3; ES Simon, MD3; JM Hausdorff, PhD1,2,4

ABSTRACT

Objective: To assess cognitive function in children with attention deficit hyperactivity disorder (ADHD) and to evaluate the effects of methylphenidate (Ritalin®) upon performance.

Background: Robust measures are needed to augment the detection and monitoring of ADHD in children. Recently, Mindstreams™ (NeuroTrax Corp., NY), a set of novel web-enabled computerized cognitive tests, was shown to be valid in identifying elderly with mild cognitive impairment (MCI) and mild Alzheimer’s disease. It was anticipated that these tests might be similarly valid in identifying children with ADHD.

Methods: Participants were 15 children (mean age: 11.8 years) with ADHD and 15 age-, education-, and gender-matched controls. Mindstreams™ performance was compared in ADHD children off methylphenidate and controls. Off-methylphenidate performance in ADHD children was compared with performance on methylphenidate and on placebo (with drug and placebo administered in a double-blind randomized fashion). Cognitive function was assessed with Mindstreams index scores summarizing performance in six cognitive domains (memory, executive function, visual spatial perception, verbal function, attention, and motor skills) and a Global Cognitive Score (GCS), which summarizes overall performance. Individual outcome parameters comprising the index scores were also analyzed.

Results: Performance of ADHD participants was significantly (p<0.05) poorer than controls for memory, visual spatial, verbal, and attention index scores and for the GCS; between-group differences for executive function and motor skills index scores approached significance. ADHD participants on methylphenidate performed significantly better than off methylphenidate (p<0.05) for memory, executive function, visual spatial, and verbal index scores and for the GCS; no significant methylphenidate effect was found for the attention index score, but the difference for the motor skills index score approached significance. No improvement in performance was found for any index score or the GCS for ADHD participants on placebo relative to baseline.

Conclusions: Impairment in ADHD was evident across multiple cognitive domains, and significant improvement was found with administration of methylphenidate. Thus Mindstreams™ appears a useful tool for characterizing impairment and treatment effects in ADHD.
Attention Deficit Hyperactivity Disorder (ADHD) is the most common behavioral disorder in school-age children, affecting ~8 to 10% of this population (American Academy of Pediatrics, 2000). Major symptoms of ADHD include inattention, hyperactivity, and impulsivity (Reiff et al., 1993; Barkley, 1996). Children with ADHD may also have marked functional difficulties, including academic underachievement (Zentall, 1993), problematic interpersonal relationships, and poor self-esteem. Diagnosis of ADHD is typically in childhood, but symptoms may persist into adolescence and adulthood. Early identification of ADHD is critical as it can lead to redirection of the educational and psychosocial development of most children with ADHD.

Computerized tasks have been developed to assist in ADHD diagnosis, but expressly in the domains of attention and executive function. These continuous performance tests (CPTs; e.g., Intermediate Visual and Auditory [IVA] CPT; Test of Variables of Attention [TOVA]) are important to ADHD diagnosis, but little effort has been made to understand the impact of ADHD upon other cognitive domains. Further, CPTs have shown low discriminability in studies differentiating children with ADHD from normal controls (Green et al., 1999; Faraone et al., 1996; Seidel and Joschko, 1991; Dykman and Ackerman, 1991). Therefore the American Academy of Pediatrics (AAP) does not currently recommend any of these tests in ADHD diagnosis. The AAP recommendations do, however, state “it is imperative to develop and assess better measurements of impairment that can be applied practically in the primary care setting.”

Indeed practical, robust, and comprehensive measures are needed to augment the detection and monitoring of ADHD in children. Mindstreams™ (NeuroTrax Corp., NY) computerized cognitive tests designed to detect mild impairment. The NeuroTrax system has been described elsewhere (Dwolatzky et al., 2003). In brief, Mindstreams consists of custom software installed on the local testing computer that serves as a platform for interactive cognitive tests that produce accuracy and reaction time (millisecond timescale) data. 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.

Mindstreams tests sample a variety of cognitive domains, including memory (verbal and non-verbal), executive function, visual spatial skills, verbal fluency, attention, and motor skills (Dwolatzky et al., 2003). Tests were always run in the same fixed order. Following are brief descriptions of the Mindstreams tests administered in the current study (testing time: approximately 40 minutes):

Methylphenidate (Ritalin®, Novartis Pharmaceuticals Corp.) is the standard treatment for ADHD. In fact, a National Institutes of Mental Health (NIMH) review of ADHD studies revealed that methylphenidate alone is more effective that in combination with behavioral therapy or behavioral therapy alone (The MTA Cooperative Group, 1999). Hence a secondary goal of the present study was to determine whether cognitive enhancement due to methylphenidate treatment would be evident on Mindstreams tests.

**Methods**

**Participants**

Participants were 15 children (3 female; mean age: 11.8±1.9 years; mean years of education: 5.7±1.7 years) diagnosed with attention deficit hyperactivity disorder (ADHD) according to Diagnostic and Statistical Manual, 4th ed. (DSM-IV) criteria. A control group consisted of 15 healthy children comparable to the ADHD group in age (U=79.5, p=0.171), years of education (U=84.0, p=0.226), and gender (χ²[1, N=30]=0.186, p=0.666). All ADHD participants were taking methylphenidate (Ritalin®, Novartis Pharmaceuticals Corporation) on a routine basis prior to the study. Institutional Review Board approval was obtained for the study, and informed consent was obtained from all participants.

**Procedure**

All participants completed Mindstreams™ (NeuroTrax Corp., NY) computerized cognitive tests designed to detect mild impairment. The NeuroTrax system has been described elsewhere (Dwolatzky et al., 2003). In brief, Mindstreams consists of custom software installed on the local testing computer that serves as a platform for interactive cognitive tests that produce accuracy and reaction time (millisecond timescale) data. 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.
**Verbal Memory:** Ten pairs of words (the study set) are presented, followed by a recognition test in which one member (the target) of a previously presented pair appears together with a list of four candidates for the other member of the pair. There are four immediate repetitions and one delayed repetition after 10 minutes.

**Non-Verbal Memory:** Eight pictures of simple geometric objects (the study set) are presented, followed by a recognition test in which four versions of each object are presented, each oriented in a different direction. There are four immediate repetitions and one delayed repetition after 10 minutes.

**Go-NoGo test:** Timed continuous performance test (CPT) during which responses are made to large colored stimuli that are any color but red.

**Problem Solving:** Puzzle completion test that increases in difficulty; the best geometric form to complete a pattern must be identified.

**Mindstreams Stroop test:** Timed test of response inhibition and set shifting modified from the well established paper-based test (MacLeod, 1991). 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 Imagery:** 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 requiring hand-eye coordination and rapid responses that requires participants to “catch” a “falling object” by moving a “paddle” horizontally so that it can be positioned directly in the path of the falling object.

**Outcome Parameters and Index Scores**

*Mindstreams* data were uploaded to the NeuroTrax central server, where data processing occurred, during which aggregate outcome parameters were computed from raw single-trial data (Dwolatzky et al., 2003). Outcome parameters were calculated using custom software blind to diagnosis or testing site. To permit averaging performance across different types of outcome parameters (e.g., accuracy, RT), each parameter was normalized and fit to an IQ-style scale (mean: 100, SD: 15). The reference sample consisted of test data for 57 children with a diagnosis of cognitively healthy in controlled research studies at three 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 or fewer years of age and had 12 or fewer years of education. Missing outcome parameter data due to a failed *Mindstreams* practice session was assigned a value of 2.5 standard deviations below the appropriate reference sample mean. To handle outliers, performance poorer than 2 standard deviations below the reference sample mean was replaced with a value 2 standard deviations below the mean. Normalized subsets of outcome parameters were averaged to produce six index scores as follows:

**MEMORY:** mean accuracies for learning and delayed recognition phases of Verbal and Non-Verbal Memory tests

**EXECUTIVE FUNCTION:** performance indices for Stroop test and Go-NoGo test, mean weighted accuracy for Catch game

**VISUAL-SPATIAL:** mean accuracy for Visual Spatial Perception test

**VERBAL:** weighted accuracy for verbal rhyming test (part of Verbal Function test)

**ATTENTION:** mean reaction times for the Go-NoGo test and the No Interference (Meaning) phase of the Stroop test, mean reaction time for a low-load stage of Staged Information Processing test, mean accuracy for a medium-load stage of Information Processing test
MOTOR SKILLS: mean time until first move for Catch game, mean right and left inter-tap intervals for Finger Tapping test.

A Global Cognitive Score (GCS) was computed as the average of the six index scores to summarize performance on the entire battery.

ADHD participants were tested with Mindstreams three times: after discontinuation of methylphenidate administration for 72 hours (baseline), after administration of a placebo, and after administration of methylphenidate. Order of placebo and methylphenidate sessions was randomized, and administration was in a double-blind fashion. Control participants were tested once with Mindstreams.

**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 baseline and methylphenidate were made using the Wilcoxon signed ranks test. Two-tailed statistics were used throughout, and $p<0.05$ was considered significant. All statistics were computed with SPSS statistical software (SPSS, Chicago, IL).

**Results**

ADHD participants at baseline performed more poorly than control participants across all cognitive domains. Indeed performance of ADHD participants was significantly poorer ($p<0.05$) for memory, visual spatial, verbal, and attention index scores and for the GCS; between-group differences for executive function and motor skills index scores approached significance (Table 1). Significantly poorer performance in ADHD was found for all individual outcome parameters from both Verbal and Non-Verbal Memory tests. The pattern of results on these tests suggests that the ADHD children were most impaired at initial learning, but this deficit shrank with learning so that both ADHD and control participants were at or near ceiling after four repetitions of the study set (Figure 1). 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. A selective ADHD deficit was found for timed as compared to accuracy outcome parameters from the Stroop test. Both groups showed reduced accuracy, extended reaction time, and larger standard deviation of reaction time (RT) with interference. However, while accuracy was comparable across ADHD and control groups, reaction time (RT) was significantly longer for the ADHD group for all phases (Figure 2). Standard deviation of RT for the ADHD group was significantly larger than for controls in the No Interference (Meaning) phase but not in the No Interference (Color) phase or the Interference phase. Significant impairment in ADHD was also found for accuracy on the Problem Solving test ($U=57.0$, $p=0.033$), direction changes per trial on the Catch Game ($U=45.0$, $p=0.004$), rhyming ($U=64.5$, $p=0.045$) and naming ($U=38.5$, $p=0.002$) accuracy on the Verbal Function test, and for accuracy on the Visual Spatial test ($U=22.5$, $p=0.001$; Figure 3). As rhyming accuracy on the Verbal Function test is the only constituent outcome parameter contributing to the verbal index score, and accuracy on the Visual Spatial test the only parameter contributing to the visual spatial index score, the results for these outcome parameters are presented as mean (standard deviation).

Table 1. Mindstreams summary score performance in children with attention-deficit hyperactivity disorder (ADHD): descriptive statistics and group differences (Mann-Whitney U test).

<table>
<thead>
<tr>
<th>Summary Score</th>
<th>ADHD N=15</th>
<th>Controls N=15</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>84.2 (13.8)</td>
<td>101.2 (9.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Executive Function</td>
<td>88.4 (10.6)</td>
<td>99.4 (13.5)</td>
<td>0.051</td>
</tr>
<tr>
<td>Visual Spatial</td>
<td>79.6 (14.2)</td>
<td>103.6 (14.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Verbal</td>
<td>84.5 (17.0)</td>
<td>99.1 (16.3)</td>
<td>0.045</td>
</tr>
<tr>
<td>Attention</td>
<td>85.0 (15.0)</td>
<td>99.9 (11.9)</td>
<td>0.011</td>
</tr>
<tr>
<td>Motor Skills</td>
<td>92.6 (9.8)</td>
<td>100.8 (13.9)</td>
<td>0.071</td>
</tr>
<tr>
<td>Global Cognitive Score</td>
<td>85.6 (11.0)</td>
<td>100.4 (10.3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Descriptive statistics presented as mean (standard deviation).
Table 2. *Mindstreams* summary score performance in children with attention-deficit hyperactivity disorder (ADHD; N=15) after taking methylphenidate: descriptive statistics and comparison to baseline (Wilcoxon signed ranks test)

<table>
<thead>
<tr>
<th>Summary Score</th>
<th>Methylphenidate</th>
<th>p-value</th>
<th>Methylphenidate vs. baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>92.5 (13.4)</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Executive Function</td>
<td>94.9 (11.6)</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>Visual Spatial</td>
<td>94.0 (21.5)</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>96.4 (21.0)</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>91.4 (10.4)</td>
<td>0.124</td>
<td></td>
</tr>
<tr>
<td>Motor Skills</td>
<td>94.7 (8.7)</td>
<td>0.071</td>
<td></td>
</tr>
<tr>
<td>Global Cognitive Score</td>
<td>94.8 (10.5)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Descriptive statistics presented as mean (standard deviation).

parameters correspond to those presented in Table 1. No significant differences were found for outcome parameters from the Go-NoGo test or the Finger Tapping test.

Performance of ADHD participants on methylphenidate was significantly better than at baseline (p<0.05) for memory, executive function, visual spatial, and verbal index scores and for the GCS; no significant methylphenidate effect was found for the attention index score, but the difference for the motor skills index score approached significance (Table 2). No improvement in performance was found for any index score or the GCS for ADHD participants on placebo relative to baseline. Significant improvement relative to baseline with administration of methylphenidate but not placebo was found for rhyming accuracy on the Verbal Function test (methylphenidate vs. baseline: W=-2.26, p=0.024) and for accuracy on the Visual Spatial test (methylphenidate vs. baseline: W=-2.30, p=0.022; Figure 3). Note that these outcome parameter results correspond to those presented for the Verbal and Visual Spatial index scores in Table 2. No other outcome parameters evidenced a significant methylphenidate effect in the absence of a placebo effect; however, a significant effect of both methylphenidate (W=-2.32, p=0.020) and placebo (W=-2.11, p=0.035) was found for the first repetition trial of the Non-Verbal Memory test.

Conclusions

The present study substantiates the use of *Mindstreams* tests to differentiate children with ADHD from normal children. Further, the results suggest a broad pattern of cognitive impairment in ADHD, affecting cognitive domains beyond those typically tested. Finally, specific and potentially characteristic patterns of impairment were evident.

Children with ADHD were most impaired at learning new material, but were able to benefit from repetition and approached a normal level of performance after as few as four repetitions. Unfortunately the benefit accrued by immediate repetitions disappeared following a brief delay, suggesting only a transitory benefit of repetition.

During a timed test of moderate difficulty (e.g., Stroop), children with ADHD showed a differential deficit such that they required longer to respond but were not impaired in accuracy. This finding suggests that cognitive impairment in ADHD is not simply an attentional deficit, and this may partially explain the poor discriminability found with existing tests for ADHD (e.g., CPTs).
Lack of impairment in the timed Go-NoGo and Finger-Tapping tests in the present sample indicates that ADHD children are not impaired in simple motor tasks. Rather, more complex motor tasks that also tax cognitive load may more readily show a deficit.

Consistent with a wide body of prior literature and the review conducted by the NIMH (The MTA Cooperative Group, 1999), methylphenidate improved performance across a range of cognitive domains whereas placebo did not. Specific improvement was observed for measures of verbal rhyming and visual spatial skills. If borne out by additional studies, these results may have implications for treatment management.

It is important to note that while the present results are encouraging, they constitute only preliminary findings. Further work with larger sample sizes and analyses by particular symptom clusters are required before the validity and utility of Mindstreams in ADHD detection can be fully established.

Computerized Cognitive Testing in Patients with Type I Gaucher Disease: Effects of Enzyme Replacement and Substrate Reduction

D Elstein, PhD; GM Doniger PhD; ES Simon, MD; J Guedalia PhD; P Rosenberg, MD; Y Finkelstein; D Attias; A Zimran, MD

ABSTRACT (Presented at the WORLD Symposium, 2004)

During the course of clinical trials using substrate reduction therapy (N-butyldeoxyxojirimycin; OGT 918; ZAVESCA®) for adults with type I Gaucher disease, the question of decreased cognitive function was raised. A battery of specific neuropsychological tests were employed to assess the extent of this observation. For the purpose of long-term surveillance, Mindstreams™ (NeuroTrax Corp., New York, NY), a computerized system enorporating comparable subtests as in the original battery, was used. Patients with type I Gaucher disease (N=69; mean age: 47.8±13.4; mean years of education: 14.5±2.4) were compared with a group of age-, education-, and gender-matched controls (N=140). Data from patients with Gaucher disease was normalized according to this control group and fit to an IQ-style scale (mean: 100, SD: 15). Normalized Mindstreams measures were averaged to produce ‘index scores’ that summarize performance by cognitive domain and a Global Cognitive Score computed as the average of the index scores. These summary measures appear on a clinical assessment report produced by the Mindstreams system used to track longitudinal performance. Performance in untreated patients (N=18) was compared with that of patients receiving enzyme replacement (N=15) and with that of those receiving Zavesca (N=36). A consistent drop in performance was observed for patients receiving enzyme (Figure 1). Conversely, patients receiving Zavesca performed consistently better than those who were untreated, with significantly improved performance in Visual Spatial function (p<0.05; Figure 1). These preliminary findings should allay the fears of cognitive dysfunction due to substrate reduction therapy, and may have ramifications for future indications for Zavesca.

Note: Error bars in all figures reflect standard error of the mean.

1 Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel
2 Dept. of Clinical Science, NeuroTrax Corporation, New York, NY USA

© NeuroTrax Corporation 2004