Methylphenidate Effect in Children With ADHD Can Be Measured by an Ecologically Valid Continuous Performance Test Embedded in Virtual Reality

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ABSTRACT

Background: Continuous performance tasks (CPTs) embedded in a virtual reality (VR) classroom environment have been shown to be a sensitive and user-friendly assessment tool to detect cognitive deficits related to attention-deficit/hyperactivity disorder (ADHD). The aim of the current study was to compare the performance of children with ADHD on a VR-CPT while on and off treatment with methylphenidate (MPH) and to compare the VR-CPT to a currently used CPT, Test of Variables of Attention (TOVA).

Methods: Twenty-seven children with ADHD underwent the VR-CPT, the same CPT without VR (no VR-CPT), and the TOVA, 1 hour after the ingestion of either placebo or 0.3 mg/kg MPH, in a double-blind, placebo-controlled, crossover design. Immediately following CPT, subjects described their subjective experiences on the Short Feedback Questionnaire.

Results: MPH reduced omission errors to a greater extent on the VR-CPT compared to the no VR-CPT and the TOVA, and decreased other CPT measures on all types of CPT to a similar degree. Children rated the VR-CPT as more enjoyable compared to the other types of CPT.

Conclusions: It is concluded that the VR-CPT is a sensitive and user-friendly assessment tool in measuring the response to MPH in children with ADHD.

FOCUS POINTS

- The effect of methylphenidate (MPH) can be measured using continuous performance test embedded in virtual reality (VR-CPT).
- The VR-CPT detects the effect of MPH in children with attention deficit/hyperactivity disorder and is comparable to other CPTs in detecting the effect to MPH.
- The VR-CPT is perceived as more enjoyable compared to other CPTs.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) constitutes a major cause of school and behavioral problems, affecting over 5% of school age children.[1] The diagnosis of ADHD is clinical and based on information obtained from parents and teachers. Due to the lack of biological markers for ADHD, continuous performance tasks (CPTs) have been developed to provide objective criteria for the diagnostic process. The basic paradigm of a CPT involves selective attention and vigilance for an infrequently occurring stimulus. CPTs are generally characterized by rapid presentation of continuously changing stimuli among which there is a designated "target" stimulus or "target" pattern. The duration of the task varies, but the task is intended to be of sufficient length to measure sustained attention.[2] The American Academy of Pediatrics currently does not support the use of CPT in the ADHD diagnostic process due to suboptimal sensitivity and specificity.[3] However, the need for an objective measure of ADHD symptoms still exists because reports from parents and teachers tend to be subjective.[4]

CPTs, such as the Test of Variables of Attention (TOVA), are sensitive to the attention deficits of ADHD and methylphenidate (MPH) treatment, the medication of choice in this disorder.[5] However, CPTs are delivered in sterile environments, such as the clinician's office, which do not replicate the school environment, are tedious, and are infamous for the negative reaction evoked in the child (eg, in a recent study from our laboratory[6] the majority of children reported that they did not enjoy the TOVA). A virtual reality (VR) classroom environment has been created specifically to assess ADHD.

VR may be defined as a technology which allows a user to interact with a computer-simulated environment, typically of the real world environment.[7] The rationale for using VR is based on the unique attributes of this technology including the opportunity for experiential, active participation that encourages and motivates subjects; the ability to objectively measure attention and motor behaviors in challenging, safe, and meaningful environments; and maintenance of strict experimental control over stimulus delivery and measurement.[8-10]

Virtual environments (VEs) may be viewed by participants on large screen monitors or via head mounted displays (HMDs). Together with a tracking device, the HMD enables participants to view a VE from a first person viewpoint, and to exercise full and natural control over the required task. Until recently, HMDs were relatively heavy and often caused side effects such as nausea or eyestrain. These were due to a conflict between flat displays and human eye accommodation, convergence factors, delays in display refresh rate, and inconsistencies between sensory modalities.[11] Recently, our group, as well as others,[6,12-13] has demonstrated that a group of children with ADHD exhibited more omission and commission errors than control children, that the VR classroom measures correlated with traditional flatscreen CPT, that the VR-CPT was experienced by the children more positively compared to traditional CPT, and did not elicit side effects or discomfort.

The objective of the current study was to assess the ability of the VR classroom to quantify the effect of pharmacological treatment in ADHD. We used the VR classroom with an embedded CPT (VR-CPT) and compared it to a similar CPT (no VR-CPT) and the TOVA on a flatscreen. Importantly, the VR-CPT and no VR-CPT differ from the TOVA in many ways, including length of tasks and ratio of go/no go stimuli. The comparison between the different types of CPT was meant to examine whether the VR-CPT version can detect attention deficits similarly to a widely used CPT (the TOVA) and whether the addition of the VR component to the CPT affects the ability of the test to detect attention deficits (compared to no VR-CPT). In addition, we examined how the VR-CPT is experienced by the subjects compared to the clinically-used TOVA.

METHODS

Testing was carried out at the Neuropediatric Unit, Shaare Zedek Medical Center. The subjects were 16 boys and 11 girls, 11–17 years of age, with 13.7±1.6 years attending mainstream schools, and consenting to participate. Years of mothers' and fathers' education were 15.7±3.0 and 14.7±3.9, respectively. Clinical diagnosis of ADHD was made by a child neurologist at the Neuropediatric Unit, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria and confirmed by a structured psychiatric interview for the *DSM-IV* axis I disorders.[14] Exclusion criteria were history or current diagnosis of any serious systemic or neurological condition, severe visual impairment,

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pervasive developmental disorder, or psychotic disorders (*DSM-IV* Axis I). Of the 26 participants, 19 were newly diagnosed with ADHD and 7 were already taking MPH at the time of the study. During the day of the experiment these 7 subjects did not take their medication.

The study was approved by the hospital institutional review board for research on human subjects and written consent of the parents and verbal assent from the children was obtained.

Instruments

Questionnaires

The ADHD rating scale (ADHD-RS)[15] assesses each of the 18 individual criteria symptoms of ADHD in *DSM-IV-TR* on a severity grid (0=not present; 3=severe; overall minimum score=0; maximum score=54). Its internal consistency was reported to be .86–.92.

The subjective feedback questionnaire (SFQ) consists of 8 items assessing the participant's subjective feelings during a testing session. All items were administered but questions relevant to this study were (1) feeling of enjoyment, (3) feeling of success, (7) discomfort during the test, and (8) perceived difficulty while performing task. Responses to the items were rated on a scale of 1–5 where 1=not at all and 5=very much, while for item 8 responses were 1=very easy and 5=very difficult. The internal consistency reliability of the SFQ ranged between α=.70 to α=.81.[16]

Types of CPT

The VR-CPT classroom was developed originally by Rizzo and colleagues[9] with Digital MediaWorks (2002) (http://www.dmw.ca/), and modified for Israel by Rizzo and colleagues and Digital MediaWorks (2006). The alterations included digits used instead of letters and instructions in Hebrew. Research participants were fitted with the personal display system eMagin Z800 3DVisor (http://www.3dvisor.com/).

The task required the child to tap the response button when the digit 7 preceded by the digit 3 appeared on the virtual classroom blackboard. The stimuli remained on the screen for 150 milliseconds with a fixed inter-stimulus interval of 1,350 milliseconds. Participants were instructed to press a mouse button as quickly and accurately as possible, using their dominant hand upon detection of a 7 after 3 (correct hit stimulus) and withhold response to any other sequence of digits. The test lasted 10 minutes during which 400 stimuli were presented accompanied by 20 distracters (eg, pure audio [classroom noises], pure visual [paper airplane flying across the visual field], and mixed audiovisual [a car "rumbling" by a window, person walking into classroom with hall sounds when door opened]). Distracters were each displayed for 5 seconds and presented in randomly assigned intervals of 10, 15, or 25 seconds.

In no VR-CPT, the same CPT that was embedded in the VR-CPT was displayed on a standard computer monitor. In addition, the speaker was turned off and only the center of screen, where digits were presented, was visible to the participant.

The TOVA CPT[5] incorporates a standardized 2 second inter-stimulus interval during a 21.6 minute test. The test presents stimuli over a consistent 3.5:1 ratio. There are 2 target paradigms, target infrequent and target frequent. In the first part of the test, a 3.5:1 ratio of non-targets to targets is presented. In the second part, the ratio is reversed. The participant is instructed to press the microswitch as quickly as possible when the target appears on the computer screen. The stimulus is a single square within a square.

Four measures were derived from the administered CPTs: response time, response time variability, omissions (not responding to a target), and commissions (responding to a nontarget). They were automatically calculated by the computer software. Administration of the three CPTs was counter-balanced. Subjects responded to the SFQ after each CPT.

Pharmacological Treatment

A double-blind, placebo-controlled, within subject design was used to assess CPT performance 1 hour following either a placebo or .3 mg/kg MPH. A fixed dosage ration was preferred since the majority of the participants were naïve to MPH and consequently, data regarding optimal dosage was not available. The specific dosage was chosen in accordance with Klorman's suggestions.[17] The order of administration (MPH or placebo) was determined by random assignment. MPH and placebo were prepared in identical colored capsules that were placed in packages marked with either A or B, according to the order of administration. The content of the capsule was unknown both to the participant and to the research assistant who ran the study.

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Data Analysis

Means and standard deviations (M±SD) of CPT parameters (ie, reaction times, variability of reaction time, omissions, and commission) were automatically calculated for each CPT by the computer software. Analysis of variance (ANOVA) with repeated measures was used. Treatment condition and type of CPT were the within subjects' independent variables while the parameters of the CPT were multiple dependent variables. Between treatment effects as well as treatment by type of test interactions were analyzed. Post-hoc analyses were used to determine specific treatment by type of test differences.

RESULTS

Subjects' ratings on the ADHD-RS were 13.8±4.7 and 8.0±6.4 for inattention and hyperactivity/impulsivity, respectively. Scores in the clinical range of the TOVA were obtained by 20 and 8 out of the 27 participants under placebo and MPH, respectively.

Effects of MPH and Type of Test on the Different Measures of the CPT

Table 1 summarizes the performance on the three types of CPT. ANOVAs on the CPT parameters resulted in significant treatment effects on the number of omissions and the variability of reaction time (F(1,19)=12.1 and 20.8, respectively, $P<.01$). In addition, a tendency toward a significant treatment effect was found on reaction time (F(1,19)=3.5, $P=.076$). No significant treatment effect was found on commissions (F(1,19)=1.8, $P=.19$. Partial Eta Squared estimations of the treatment effect size were large for omissions, reaction time, and variability, and moderate for commissions.

Type of test effect was found for number of omissions and commissions, as well as for reaction time (F(2,38)=12.6, 6.2, 57.8, respectively, $P<.01$). A tendency toward significant effect was found on the variability of reaction time (F(2,38)=2.9, $P=.069$). Pairwise comparisons revealed significant differences among each pair of tests on omissions and reaction time, and between the TOVA and both the VR and no VR CPT on commissions. Partial Eta Squared estimations of the treatment effect size were large for omissions, commissions, and reaction time, and moderate for variability.

Treatment by type of test interaction was revealed only on rate of omission errors (F(2,38=5.8, $P<.01$). Post-hoc analyses revealed significant differences between the rates of omissions under MPH versus placebo in the VR-CPT, but not in other CPTs. Partial Eta squared estimations of the treatment by type of test effect size were large for omissions, moderate for commissions and variability, and small for reaction time.

TABLE 1.
Effect of MPH on CPT Parameter

		Treatment	
CPT Parameter	Type of Test	Placebo*	MPH*
Reaction time (ms)	TOVA	412±74	394±78
	No VR-CPT	491±62	501±107
	VR-CPT	551±62	521±53
Variability of reaction time (ms)	TOVA	133±39	107±36
	No VR-CPT	118±31	109±28
	VR-CPT	143±30	116±28
Errors of omission (%)	TOVA	2.38±4.25	1.08±2.06
	No VR-CPT	4.70±6.54	2.55±3.47
	VR-CPT	10.65±11.97	4.65±6.11
Errors of commission (%)	TOVA	3.72±3.61	2.56±2.49
	No VR-CPT	4.50±3.63	5.00±6.56
	VR-CPT	6.65±5.12	4.45±4.48

* The values represent mean±SD. Data was analyzed by ANOVA with repeated measures.

MPH=methylphenidate; CPT=continuous performance task; ms=millisecond; TOVA=test of variables of attention; VR=virtual reality; SD=standard deviation; ANOVA=analysis of variance.

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Effect of MPH and Type of CPT on the SFQ

Mean scores for the four items on the SFQ are shown in Table 2. ANOVA revealed significant feedback differences for the three CPTs on the scales of feeling of enjoyment, discomfort, and perceived difficulty (F(2,52)=20.2, 9.0 and 3.3, $P<.05$, respectively), but not feeling of success (F(2,52)=2.0, $P=.14$). Main effect of medication and an interaction of medication by type of test were not significant. Post hoc comparisons revealed significant differences between each pair of CPT on enjoyment with VR-CPT scored highest, no VR-CPT lower, and the TOVA lowest. In addition, both the VR-CPT and the TOVA were rated as significantly more comfortable than the no VR-CPT. The no VR-CPT was rated as less difficult than the other CPTs. However, this difference failed to reach significance on the post-hoc analyses.

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DISCUSSION

VR-CPT, as well as the TOVA and no VR-CPT, were found to be sensitive to the ameliorative effect of MPH on the rate of omissions and variability of reaction time, reflected by treatment main effect across CPT types. In addition, a tendency toward a significant effect was found on reaction time. These findings are in agreement with the effect of MPH consistently reported in the literature.[18-21] Treatment by CPT type significant interaction followed by post-hoc analysis suggested that the VR-CPT was more sensitive than the TOVA and the no VR-CPT to the effect of MPH on rate of omission errors. The effect of MPH on other CPT parameters was comparable on the three types of CPT. These findings suggest that the VR-CPT, although it lasts only 10 minutes, is at least as sensitive as the TOVA in detecting the effect of MPH on ADHD-associated cognitive deficits.

In terms of subjective experience, VR-CPT was perceived as more enjoyable compared to the TOVA and was not inferior to the TOVA in revealing the cognitive deficits of the ADHD. Both the VR-CPT and the TOVA elicited similar levels of difficulty, success, and discomfort. These findings replicate previous findings with the same system.[6] Notably, the combination of enjoyment and failure on the same test suggests that the tendency of children with ADHD to fail on CPT is not due to difficulty with handling boredom and unrewarding activities. Indeed, by and large, those reinforcement contingencies have a positive impact on task performance for both children with ADHD and unaffected controls.[22]

The finding that the VR-CPT is a user-friendly tool is consistent with the VR literature for children with pathological conditions including ADHD, autism, and intellectual disability.[6,23-25] In all these studies, participant enjoyment of virtual environments has been positive. Moreover, data from the current study demonstrate that the concern that use of head gear would be disturbing or uncomfortable to the participants was unjustified. Indeed, there were no reports of cyber-sickness-like side effects, a finding confirmed in recent studies of children with ADHD who used the same environment.[6,23]

VR environments provide test situations that are ecologically valid, motivating, and dynamic. The VR-CPT allows for controlled performance assessment within a classroom environment.[6,12-13,23] Naturalistic visual and auditory distractors can be easily inserted and used to elicit varied behavioral responses and alter test parameters, such as duration, number, and type of stimuli. Consequently, the VR-CPT has the potential to serve as an efficient tool for conducting attention performance measurement while also allowing for the monitoring and measurement of head and limb movement thus providing an additional behavioral response. The validity of the VR-CPT in the context of ADHD and the positive experience it elicits may prove to be an effective asset for both assessment and intervention purposes.

This study was conducted on adolescents, however many children are diagnosed with ADHD and treated with stimulants in early school age. Consequently, it would be important to verify these findings on a younger age group.

TABLE 2.
Effect of Type of Test on SFQ

		Treatment	
Measure	*Type of Test*	*Placebo**	*MPH**
Enjoyment	TOVA	1.63±0.84	1.93±1.07
	No VR-CPT	2.30±0.87	2.56±1.19
	VR-CPT	3.16±1.10	2.85±1.20
Success	TOVA	3.10±1.08	3.56±1.09
	No VR-CPT	3.63±0.93	3.74±0.86
	VR-CPT	3.37±0.97	3.63±0.88
Discomfort	TOVA	2.15±1.29	1.63±0.84
	No VR-CPT	1.07±0.27	1.11±0.42
	VR-CPT	1.70±0.95	1.59±0.97
Difficulty	TOVA	2.59±0.97	2.15±0.91
	No VR-CPT	2.04±0.90	1.89±0.70
	VR-CPT	2.41±0.97	2.41±0.89

* The values represent mean±SD. Data was analyzed by ANOVA with repeated measures.

SFQ=short feedback questionnaire; MPH=methylphenidate; TOVA=test of variables of attention; VR=virtual reality; CPT=continuous performance task; SD=standard deviation; ANOVA=analysis of variance.

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CONCLUSION

The use of VR as a tool for assessment, therapy, and rehabilitation is expected to grow as the medical and psychological sciences evolve in the digital age. In this study, a VR-CPT was found to be a sensitive assessment tool in measuring the effect of MPH on sustained attention in children

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with ADHD. The VR-CPT was also perceived as more enjoyable compared to a currently used CPT. This study illustrates one area where VR technology can add value over existing traditional methods. ***CNS***

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