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Impact of Long-Term Use of Methylphenidate on Visual Memory of Drug-Naïve Children with Attention Deficit Disorder

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Abstract

Background: Diverse cognitive functions and behaviors have been monitored in the two sub-types of attention deficit/hyperactivity disorder (ADHD) including the combined type and the inattentive type.
Objectives: Previous studies have shown that ADHD children have problems in visual memory, and short and long-term use of methylphenidate (MPH) improves these functions, but fewer studies have been done on the inattentive subgroup, namely attention deficit disorder (ADD). Due to the different cognitive functions in these two ADHD subgroups, this study was done to investigate the long-term use of MPH on the visual memory of ADD children.
Methods: A 4-week experimental clinical trial using MPH (1 mg/kg/dose) was conducted. Participants were 20 children aged 6 - 11 years with ADD that came to the Rouzbeh Clinic in Tehran in 2010. Cambridge neuropsychological test automated battery (CANTAB) tests of visual memory were used for assessment.
Results: The long-term use of MPH improved 12 aspects of paired associated learning (PAL) such as first-trial memory score, the number of mean mistakes to success and mean efforts to success ($P < 0.05$). However, MPH did not improve the stages completed in the first trial, the total errors, and the total errors adjusted in the three-shape step of PAL ($P > 0.05$). MPH also improved all aspects of pattern recognition memory (PRM) ($P < 0.05$) and the mean correct latency of spatial recognition memory (SRM) ($P < 0.05$). However, MPH had no effect on delayed matching to sample (DMS) ($P > 0.05$).
Conclusions: MPH improved performance on the PAL, PRM, and SRM visual evaluating tests of ADD patients. Nevertheless, the patients did not show any improvement in the DMS test. In comparison with previous studies, our results would suggest that MPH has similar effects on the visual memory of ADD and ADHD patients.

Keywords: Attention Deficit Disorder, Drug Therapy, Methylphenidate, Visual Memory

1. Background

The two sub-types of attention deficit/hyperactivity disorder, including combined inattentive and hyperactivity disorder or ADHD and the permanently inattentive disorder or ADD, have different cognitive functions (1-4).

Individuals with ADHD show defects in inhibitory control and planning whereas problems in set-shifting, vigilance, and interference control can be more related to ADD (5). Underactivity and apathy are associated more with ADD patients than with ADHD patients (6). ADD patients are commonly recognized by sluggish cognitive tempo, but ADHD individuals are more hyperactive.

Different parts of the brain are affected in ADHD and ADD individuals. In ADHD patients, the frontostriatal region is affected. The defect in the striatal part of the brain results in hyperactivity (1, 7). In ADD patients, the frontoparietal circuit is affected. This causes weakness in language learning, mathematics, working memory, and reactions to stimuli (1, 8).

Stimulant therapy by methylphenidate (MPH) is the common medication of ADHD. It prevents the reuptake of dopamine and norepinephrine transporters in the presynaptic areas of this neurotransmitter (9). It not only improves the concentration and decreases the hyperactivity behavior of the patients, but also improves their cognitive function. Functional neuroimaging gives rise to this proposition that MPH regulates the function of the brain by arising frontal and reducing striatal stimulation in normal individuals (10).

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Visual memory is necessary for having good working memory and learning. Children with a deficit in visual working memory have some problems with recalling the visual appearance of words and letters, so having difficulty with reading and writing.

ADHD patients have shown difficulty in CANTAB tests of visual memory, such as paired associated learning (PAL), pattern recognition memory (PRM), spatial recognition memory (SRM), and delayed matching to sample (DMS) (11-14). Coghill et al. and Rhodes et al. have shown that the chronic use of MPH improves ADHD patients' performance in these tests (12, 15). The effect of acute MPH on visual memory tests is controversy as some studies showed improvements on DMS, PRM, and SRM tests (10-12, 16) and a few showed no improvement on PRM and SRM (17).

MPH is also used in ADD patients. Nevertheless, ADD patients are presented with different symptoms in comparison with ADHD individuals. Thus, little effort has been made to show the effect of MPH on different aspects of these patients' behavior.

This paper studied the effect of MPH on the visual memory of ADD patients. As we will show, our empirical results suggest that MPH improves the visual memory of individuals with ADD.

2. Objectives

Previous studies have shown that ADHD children have problems in visual memory, and short and long-term use of MPH improves these functions, but fewer studies have been done on the inattentive subgroup, namely ADD. Due to the different cognitive functions in these two ADHD subgroups, this study was done to investigate the long-term use of MPH on the visual memory of ADD children.

3. Materials and Methods

This study obtained an ethical approval. All participants, parents, or guardians provided their written informed consent. Cambridge neuropsychological test automated battery (CANTAB) visual memory tests were taken from ADD patients.

3.1. Instrument

3.1.1. Cambridge Neuropsychological Test Automated Battery

The best-available computerized test battery for the visual memory is CANTAB (14). It benefits from an extensive bibliography of over 1600 peer-reviewed papers, more than in any other computerized cognitive tests, ensuring the most validated measurement available. The high levels of construct validity increase the likelihood that CANTAB outcomes are clinically meaningful. All CANTAB tests have satisfactory levels of test-retest reliability, with some outcome measures reaching test-retest correlations of around 0.9 (18). CANTAB has four main visual memory tests: PAL, PRM, SRM, and DMS.

3.1.2. Paired Associates Learning

In the PAL test, pattern-based boxes are randomly opened on the screen. The participants must find and palpate the box in the site in which the pattern originally was located. For the test to become gradually more challenging, the number of patterns increases from one to eight. This test evaluates the visual memory and the new learning ability of the participants.

PAL result scales cover the errors made by the participant, the number of efforts, the memory points, and the completed stages.

3.1.3. Delayed Matching to Sample

In DMS, visual patterns are displayed on the screen for a few seconds and after a short pause, four similar patterns will appear. Participants need to recognize and select the most similar models to the original one. This test evaluates the short-term visual memory of the patient. DMS is particularly useful for recognizing defects in the medial temporal lobe area. The outcome measures of the test cover the number of correct and wrong attempts.

3.1.4. Pattern Recognition Memory

In the PRM test, a series of 12 visual patterns are presented to the participants first. In the recognition phase, a two-alternative forced choice is presented. The choices are shown in the opposite order of original patterns. The participants are asked to select the pattern they have already seen. This test evaluates the visual model recognition memory of the patients in a double-alternative forced choice model. The outcome measures of the test include the number of correct efforts and the latent time (the speed of participants to respond).

3.1.5. Spatial Recognition Memory

In SRM, a white square is shown at five diverse sites on the screen. In the recognition step, the participants are asked to locate the square presented in the presentation phase among a series of five pairs of squares. As with the PRM test, the location of the squares is presented in the reverse order of the presentation. PRM and SRM comprise different parts of PAL and all evaluate the visual memory.

This test has three outcome points, including the number and the percentage of correct efforts, and the latent time.

3.2. Participants

In this study, we evaluated 20 children (aged 6 to 11), who were referred from the Rouzbeh Clinic in Tehran in 2010 to the Institute for Cognitive Science Studies (ICSS). Exclusion criteria were having a learning disorder or mental retardation (IQ less than 80), having a chronic bodily illness, sensory or motor deficiency, current or previous taking of stimulant drug, using any illegal drugs, the existence of popular comorbid conditions, neurological deficiency, oppositional defiant disorder, conduct disorder, and anxiety disorder.

Eligible children had DSM-IV criteria for ADD and had an interview with an expert child and adolescent psychiatrist (Dr. Tehranidoust). Guardians answered the ADD rating scale and the Conners' parent rating scale and completed a demographic form. Then, the IQ of the children was evaluated by the WISC-V test.

3.3. Design

The participants were first evaluated by taking the CANTAB and Conners tests. Then, they were treated with MPH 0.5 mg/kg twice a day for 4 weeks. After finishing the treatment process, the participants were re-evaluated by taking the CANTAB and Conners tests. The CANTAB test results were gathered for further evaluation.

3.4. Statistical Analysis

SPSS (SPSS Inc., Chicago, Illinois) program was used to analyze the data. Paired *t*-test was used to evaluate the effect of MPH.

4. Results

4.1. Clinical Response to MPH Using Connors and ADHD Rating Scale Tests

According to Table 1 that illustrates the results of the Conners and ADHD Rating Scale tests, ADD children had significant improvements in inattention, hyperactivity, and ADHD indices of the Conners Rating Scale, after receiving MPH for a month. However, the oppositional index had an insignificant improvement.

ADD children also showed significant improvements in the inattention aspect and the total score of the ADHD Rating Scale but they did not have meaningful improvements in terms of hyperactivity.

Table 1. The Effect of Long-Term Use of MPH on Connors-RS and ADHD-RS[a]

Tests		Week 0	Week 4	P Value
CPRS				
	Oppositional index	56.80 (9.0)	58.05 (8.6)	0.46
	Inattention index	67.45 (9.4)	62.55 (11.0)	0.03*
	Hyperactivity index	59.30 (9.4)	55.10 (7.7)	0.02*
	ADHD index	64.85 (8.9)	59.80 (9.4)	0.008*
ADHD RS				
	Inattention	86.20 (19.1)	79.30 (21.1)	0.02*
	Hyperactivity	76.35 (12.4)	69.40 (22.3)	0.21
	Total score	83.95 (16.6)	76.10 (21.2)	0.02*

[a]Values are expressed as mean (SD).

4.2. The Results of the CANTAB Test

4.2.1. Paired Associates Learning

The chronic use of MPH significantly improved the performance of ADD patients in the first trial memory score, mean errors to success, mean efforts to success, total errors, total errors adjusted, total errors with six shapes, total errors with eight shapes, total errors with six shapes adjusted, total errors with eight shapes adjusted, total trials, and total trials adjusted. However, it did not improve the performance of ADD patients in the number of stages completed in the first trial, total errors with three shapes, and total errors with three shapes adjusted.

4.2.2. Pattern Recognition Memory

The ADD patients showed significant improvements in the mean correct latency, the number and percentage of correct efforts as the indices of PRM tests, after a chronic use of MPH.

4.2.3. Spatial Recognition Memory

MPH only improved the performance of the ADD patients in the mean correct latency index of SRM tests. The patients had no significant improvements in the number and percentage of correct efforts.

4.2.4. Delayed Matching to Sample

MPH had no significant effect on the indices of DMS tests such as DMS A, DMS B, the mean correct latent time, the mean correct latent time all delays, the mean accuracy simultaneously, the mean correct latency (0, 4000 and 12000 msec), the percentage of corrects, the percentage of corrects all delays, the percentage of corrects simultaneously, the percentage of corrects (0, 4000 and 12000

Table 2. Effect of the Long-Term Use of MPH on PAL, PRM, and SRM Test Results[a]

Tests	Week 0	Week 4	T	P Value
PAL				
First trial memory score	11.75 (3.3)	15.40 (2.9)	-5.87	< 0.001*
Mean errors to success	4.37 (3.3)	2.26 (2.2)	3.94	0.001*
Mean trials to success	2.30 (0.78)	1.87 (0.63)	3.03	0.007*
Stages completed	5.00 (0.00)	5.00 (0.00)		
Stages completed in the first trial	2.50 (0.82)	3.00 (0.97)	-2.51	0.02*
Total errors	21.8 (16.6)	11.30 (11.0)	3.94	0.001*
Total errors adjusted	21.8 (16.6)	11.30 (11.0)	3.94	0.001*
Total errors three shapes	1.35 (2.2)	0.50 (0.88)	1.54	0.138
Total errors six shapes	7.25 (11.2)	2.90 (5.4)	2.10	0.04*
Total errors eight shapes	12.45 (7.8)	7.45 (5.6)	3.21	0.005*
Total errors three shapes adjusted	1.35 (2.2)	0.50 (0.88)	1.54	0.138
Total errors six shapes adjusted	7.25 (11.2)	2.90 (5.4)	2.10	0.048*
Total errors eight shapes adjusted	12.45 (7.8)	7.45 (5.6)	3.03	0.005*
Total trials	11.5 (3.9)	9.35 (3.1)	3.03	0.007*
Total trials adjusted	11.50 (3.9)	9.35 (3.1)	3.21	0.007*
PRM				
Mean correct latency	3145.92 (1018.1)	2266.21 (468.3)	5.21	< 0.001*
Number of correct efforts	19.50 (3.4)	21.70 (2.2)	-4.26	< 0.001*
Percentage of correct efforts	81.24 (14.5)	90.41 (9.5)	-4.26	< 0.001*
SRM				
Mean correct latency	3198.58 (778.3)	2791.78 (651.9)	2.29	0.03*
Number of correct efforts	13.15 (2.2)	13.65 (2.4)	-1.12	0.27
Percentage of correct efforts	65.75 (11.3)	68.25 (12.3)	-1.12	0.27

[a]Values are expressed as mean (SD).

msec), prob error given correct, prob error given error, total corrects, total corrects all delays, total corrects simultaneously, and total corrects (0, 4000 and 12000 msec) (Table 3).

5. Discussion

The goal of this research was to assess the influence of MPH on the visual memory of ADD patients. Four main CANTAB tests (PAL, SRM, PRM, and DMS) were used.

Our experimental results illustrated that MPH significantly enhanced the performance of the ADD patients in PAL, SRM, and PRM tests. However, the patients did not have significant improvements in DMS tests.

ADD patients suffer from learning problems. MPH is used for the treatment of both subtypes, but a few studies have been done to show its effect on ADD patients. Different characteristics are seen in these two subtypes as ADHD individuals are known more hyperactive and ADD patients more inattentive and underactive. We believe that MPH shows different effects on brain functions of these two subtypes, and it may even have negative effects on some performances. We conducted this study to evidence more on the underlying cause of learning defects in ADD individuals, and show how MPH affects it.

Visual memory is the core need for learning and writing. The center of the brain involved in the recalling visual memory is the posterior parietal region. Studies have proven that ADHD patients have visual memory problems (11-14). Nevertheless, the part of the brain that is defected in these individuals is the frontostriatal regions, rather than the posterior-parietal. This could lead to the result that ADHD patient's problems in visual memory are due to their lack of inhibitory control than a defect in the visual memory region. MPH by regulating the work of the striatal re-

Table 3. Effect of Long-Term Use of MPH on DMS Test[a]

DMS Test	Week 0	Week 4	T	P Value
DMS A	41 (0.31)	0.44 (0.10)	-2.14	0.16
DMS B	-0.63 (0.46)	-0.59 (0.42)	-0.36	0.71
Mean correct latency	4344.69 (1006.3)	4717.65 (1126.6)	-1.34	0.19
Mean correct latency all delays	4354.60 (1165.4)	4695.01 (1536.3)	-0.80	0.43
Mean corrects simultaneously	4525.62 (1208.9)	4522.20 (1130.0)	0.01	0.98
Mean correct latency 0 sec	3693.25 (1178.7)	4274.50 (1687.2)	-1.25	0.22
Mean correct latency 4 sec	4108.82 (1391.5)	4359.68 (1644.5)	-0.49	0.62
Mean correct latency 12 sec	4979.06 (1400.8)	5788.41 (2629.0)	-1.29	0.21
Percent of corrects	76.00 (13.1)	77.25 (14.1)	-0.31	0.75
Percent of corrects all delays	68.96 (16.3)	72.33 (18.8)	-0.75	0.46
Percent of corrects simultaneously	97.00 (7.3)	92.00 (16.4)	1.15	0.26
Percent corrects 0 sec	63.00 (24.5)	70.00 (23.8)	-1.37	0.18
Percent corrects 4 sec	73.00 (22.7)	76.00 (27.2)	-0.42	0.67
Percent corrects 12 sec	71.00 (22.9)	71.00 (22.9)	0.00	1.0
Prob error given correct	0.27 (0.16)	0.25 (0.15)	0.38	0.70
Prob error given error	0.14 (0.18)	0.14 (0.17)	-0.26	0.79
Total corrects	15.20 (2.6)	15.45 (2.8)	-0.31	0.75
Total corrects all delays	10.35 (2.4)	10.83 (2.8)	-0.74	0.46
Total corrects simultaneously	4.85 (.36)	4.60 (0.82)	1.15	0.26
Total corrects 0 sec	3.15 (1.2)	3.50 (1.1)	0.00	0.18
Total corrects 4 sec	3.65 (1.1)	3.80 (1.3)	-0.42	0.67
Total corrects 12 sec	3.55 (1.1)	3.55 (1.1)	-1.37	1.0

[a] Values are expressed as mean (SD).

gion improves their control on visual memory tests (12, 15).

MPH improves visual memory in ADD patients not by modulating the striatal region but by acting on the visual memory center in the parietal region. ADD patients have defects in the parietal-frontal circuit, and MPH enhances the activity of this region.

A limitation of our study was finding ADD children between six and eleven years old, without previous medication. Another limitation of this research was the side effects of MPH such as palpitation and anorexia that made some patients to stop the medication or to change the prescribed doses. More research should be conducted on ADD patients to evaluate the visual memory of these patients.

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Footnotes

Authors' Contribution: This research was done as part of a thesis for acquiring an M.D. degree by Roheila Seyedtabaei. Roheila Seyedtabaei and Mehdi Tehranidust designed and conducted the study. Reza Seyedtabaei conducted data entry and analyzed the data. Seyed Davood Mohammadi contributed to data collection and manuscript writing. All authors approved the content of the manuscript.

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