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ORIGINAL INVESTIGATION

Methylphenidate significantly improves declarative memory functioning of adults with ADHD

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Abstract
Background Declarative memory deficits are common in untreated adults with attention-deficit hyperactivity disorder (ADHD), but limited evidence exists to support improvement after treatment with methylphenidate. The objective of this study was to examine the effects of methylphenidate on memory functioning of adults with ADHD.
Methods Eighteen adults with ADHD who were clinical responders to methylphenidate participated in this randomized crossover trial. After 3 days of no treatment, patients received in random order either their usual methylphenidate dose (mean: 14.7 mg; range: 10–30 mg) or placebo, separated by a 6–7-day washout period. Patients performed an immediate word recall test 1 h after treatment administration. Three hours after intake, patients performed the second part of the memory test (delayed word recall and a recognition test).
Results Delayed recognition and immediate recall was similar on treatment and on placebo. Delayed word recall was significantly better in the methylphenidate than in the placebo condition ($F_{1,\ 17}$=7.0, p<0.017). A significant correlation was found between prestudy CES-D depression scores and difference scores on delayed recall (r=0.602, p<0.008).
Conclusion Methylphenidate improves declarative memory functioning in patients with ADHD. New studies should further examine whether subclinical depressive symptoms mediate the effect of methylphenidate on declarative memory.

Keywords Memory · Methylphenidate · ADHD · Adult

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Introduction

Working memory deficits in adult patients with attention-deficit hyperactivity disorder (ADHD) are well documented. Working memory is significantly impaired in untreated adults with ADHD (Ross et al. 2000) and significantly improves once treated with methylphenidate (Cooper et al. 2005, Turner et al. 2005, Mehta et al. 2000a, Mehta et al. 2000b) and in healthy adult volunteers (Elliott et al. 1997). In contrast, much less research has been devoted to declarative memory functioning.

Declarative memory is the ability to store and retrieve facts, plans, or ideas from memory. Declarative memory skills are important in daily life and social interaction (e.g., Kordon et al. 2006). The lives of ADHD patients are often characterized by forgetting appointments, things to do, or even taking their medication on time.

Results on the effects of methylphenidate on declarative memory functioning are inconclusive. Whereas Camp-Bruno and Herting (1994) reported significant memory improvement in 48 healthy volunteers after administration of methylphenidate, Unrug et al. (1997) found no significant effect of methylphenidate (20 mg) on memory functioning measured using a word learning test in 12 healthy volunteers. In patients with ADHD, Riordan et al. (1999) reported significant memory improvement when treated with methylphenidate.

Memory improvement was equal in patients with and without comorbid depression.

Given the limited number of studies, their inconclusive results, and the significant impact of declarative memory deficits on daily life of ADHD patients, the purpose of the present study was to examine declarative memory functioning in adult ADHD patients treated with methylphenidate or placebo. A standardized validated and reliable word learning test was used (Van Loon-Vervoorn 1985, 1986) to test the hypothesis that methylphenidate will significantly improve declarative memory functioning.

Methods and materials

The study was conducted according to a double blind, placebo-controlled, randomized, crossover design.

A detailed description of the diagnosis of patients can be read elsewhere (Verster et al. 2008). Patients underwent a standardized psychiatric evaluation using a semi-structured diagnostic interview for the presence of ADHD and co-morbid disorders both current and in childhood. Presence and severity of current ADHD symptoms during the last 6 months were scored using the Dutch version of the DSM-IV ADHD-rating scale (Kooij et al. 2005), complemented with information from partner, parents, and childhood school reports. A cutoff point of five of nine criteria was set for adult diagnosis of ADHD (Biederman et al. 2000; Kooij et al. 2005). At the start of this study, the diagnosis was confirmed by assessing the severity of current ADHD symptoms using the DSM-IV ADHD-rating scale (Kooij et al. 2005) and the CAARS ADHD rating scale (Conners et al. 1999). Severity of symptoms of anxiety and depression was measured by the Spielberger State Trait Anxiety Inventory (STAI) and the Center for Epidemiological Studies Depression Scale (CES-D) (Spielberger 1983; Beekman et al. 1997). Most important inclusion criteria were having ADHD, being adult (21–55 years old), and being considered as reliable and mentally capable of adhering to the protocol. Exclusion criteria included insensitivity to methylphenidate treatment, a history or presence of alcohol or drug abuse, comorbid anxiety or depression (determined by treating physician), and the use of psychoactive medication known to affect cognitive performance.

Eighteen patients diagnosed with ADHD (combined type) participated in the study. Prior to participation in the study, patients were stable and effectively treated with methylphenidate. Patients were considered as effectively treated if they used a stable daily dose of methylphenidate, did not experience adverse effects from the treatment, and were considered to be a clinical responder by the treating. To participate in this study, patients were asked to voluntarily stop their treatment, starting 3 days before the first test day (session 2) until the second test day (session 3). Session 2 and session 3 were separated by 6 to 7 days without treatment. On the first test day, immediate release methylphenidate (patients' regular dosage) or placebo was administered. On the second test day, the other treatment was administered.

Treatment was administered orally with 240 ml tap water, 1 h before performing the first part of the memory test (learning and immediate word recall). Thereafter, patients performed an on-the-road driving test; results are discussed elsewhere (Verster et al. 2008). After the driving test, i.e., 3 h after treatment intake, patients performed the second part of the memory test (delayed word recall and recognition). If applicable, a second treatment dose was administered according to the patient's usual interval between the first and second doses. This was done to mimic the naturalistic situation in which some patients take a second dose of methylphenidate, for example, 2 h after their first dose. All treatments were capsules of identical shape, size, and color, to allow double blind administration. After completion of the study, subjects continued their regular treatment regimen under supervision of their psychiatrists. Patients were not paid for participation, but their travel expenses were reimbursed. In case of withdrawal or discontinuation, a patient was replaced. The Medical Ethical Committee of the University Medical Center Utrecht approved the study protocol. Written informed consent was obtained before their inclusion in the study.

Word learning test

Before discontinuation of their medication, all patients were trained on the memory test to become familiar with test procedures. The word learning test (Dutch language version) is a computerized and standardized test with high internal consistency. Test–retest reliability for immediate and delayed recall were 0.80 and 0.83, respectively (Van Loon-Vervoorn 1986). The test consists of 12 parallel lists of 15 monosyllabic meaningful nouns (immediate and delayed recall), complemented with 15 distracter words in the recognition test. During training and each test day, different validated word lists were used (versions A and B on test days). Correlation between versions A and B of the word learning test was 0.72 (Van Loon-Vervoorn 1986). All were frequently used Dutch words, with high imageability (Van Loon-Vervoorn 1985), and having low association with each other. Fifteen words were presented five times on a computer display. After each presentation, patients had to write down as many words as they could remember. The highest trial score was a measure of immediate recall. Thereafter, patients performed a driving test on a Dutch highway (Verster et al. 2008). Two hours after immediate recall, delayed recall was recorded. Patients had to write down in 1 min all words they remembered. Finally, the original list along with 15 distracter words was presented.

Patients had to indicate by button press whether a presented word was a member of the original list or not. Recognition was expressed in recognition time (ms) and recognition score (number of correct recognized words).

Statistical analysis

Statistical analyses were performed using the SPSS. Mean and standard deviation (SD) were computed for each parameter. The factor treatment (two levels: methylphendate and placebo group) was tested for significance ($p<0.05$) by using ANOVA for repeated measures. Period (test day 1, test day 2), treatment order (placebo->methylphenidate, methylphenidate->placebo) were tested separately by using ANOVA for repeated measures. The Pearson r correlation coefficient was computed for baseline demographics and difference scores (methylphenidate–placebo) for each memory test parameter. In case of significance ($p<0.05$), the variable was included as covariate in the statistical analysis.

Sample size

Sample size estimation of 30 subjects was based on the primary outcome of the driving test in order to obtain a power of at least 90%. Slow enrollment caused an early study termination after 18 patients were completed (Verster et al. 2008).

Results

The effects of period and treatment order were not significant and, therefore, were omitted in the presented statistical analyses. Eighteen patients (11 men and seven women) completed the study. Mean (SD) age was 38.3 (7.7) years old. All patients had combined-type ADHD. Patient characteristics are summarized in Table 1.

Patients did not differ on immediate word recall, recognition time, and recognition score when treated with methylphenidate or placebo (see Fig. 1). However, delayed word recall was significantly improved when treated with methylphenidate relative to placebo ($F_{1,\ 17}=7.0$, $p<0.017$, observed power 0.706). Performance on the memory test did not significantly differ on any outcome when comparing results from the test day of methylphenidate with the training session results (on that day, patients were on their regular methylphenidate regimen).

None of the baseline measures correlated significantly with drug response, except for the CES-D depression score, which showed a significant correlation with difference scores on delayed recall ($r=0.602$, $p<0.008$). Although depression was not diagnosed or treated, in six patients, screening scores on the CES-D exceeded the cut-off score of 16. When introducing CES-D scores as covariate in the statistical analysis, a significant interaction between CES-D and difference scores on delayed recall was found ($F_{1,\ 16}=11.6$, $p<0.004$). The difference in delayed recall between methylphenidate and placebo was no longer significant ($F_{1,\ 16}=2.0$, $p<0.174$).

Discussion

This study shows that delayed word recall is significantly affected in untreated patients with ADHD. When taking methylphenidate, scores on the delayed word recall test significantly improve to levels comparable of healthy subjects. In contrast, immediate recall and delayed recognition are not impaired in untreated ADHD patients. This suggests that encoding and consolidation of memory is unaffected. Delayed word recall requires patients to write down all words they remember on a piece of paper. In contrast, the recognition test shows all words on a computer screen, mixed with distracting words that were not learned during immediate recall. The recognition test is therefore much easier than delayed word recall. In sum, retrieval without priming as in the recognition test is impaired in untreated patients with ADHD.

Interpretation of the relationship between the baseline depression score and treatment effect on delayed recall is difficult, in particular because some items scored with the CES-D also apply for ADHD. CES-D scores were obtained during screening when patients were all treated with methylphenidate. It should be taken into account that the CES-D is a screening instrument that is not sufficient to diagnose patients. Patients who participated in the current trial were not diagnosed or treated for comorbid depression. The positive correlation between the methylphenidate–placebo difference and CES-D score seems to suggest that methylphenidate is more effective in ADHD patients who report more depression-like symptoms. However, there is mixed scientific evidence on whether methylphenidate has a positive effect on comorbid depression and its effects on memory functioning or not (Riordan et al. 1999; Barrickman et al. 1995; Wilens et al. 1995, 1996; Jones et al. 2008). To answer this question, comorbid depression scores of the current sample were of insufficient clinical concern to draw firm conclusions, as only six patients exceeded the cut-off score of the CES-D. Therefore, future studies should focus on the impact of comorbid disorders such as depression, anxiety, and substance abuse. These comorbid disorders are common and, as evident from this study, may have a clear influence on the efficacy of ADHD treatment and its behavioral correlates.

A limitation of our study may be the focus on declarative memory only, using a single word learning test rather than

Table 1 Patient characteristics

	CAARS ADHD index	DSM attention index	DSM hyperactivity index	DSM ADHD index	STAI	CESD	Total daily dose (mg)	Diagnosed and use of methylphenidate (months)	Study dose (mg)
Mean	64.7	13.8	15.2	28.9	48.1	15.6	54.0	28.4	14.7
SD	8.7	5.8	4.8	9.6	10.1	8.5	20.4	25.0	6.3
Median	67.0	14.5	17.0	31.5	48.0	14.0	50.0	16.5	15.0
Range	43–47	3–22	5–23	9–41	28–64	5–33	30–105	5–72	10–30

A detailed overview of individual patient characteristics is published elsewhere (Verster et al. 2008)

CAARS Connor Adult ADHD Rating Scales, *ADHD* attention-deficit hyperactivity disorder, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *STAI* Spielberger State Trait Anxiety Inventory, *CES-D* Center for Epidemiological Studies Depression Scale, *SD* standard deviation

performing a battery of memory tests that also include other memory functions such as working memory or digit span. Future studies should confirm our findings in a larger sample size, including different treatments such as atomoxetine, and including patients with clinical relevant comorbid disorders such as anxiety and depression.

Studies in untreated adult ADHD patients confirm our findings by showing that declarative memory functioning is significantly worse when compared to healthy controls. For example, Holdnack et al. (1995) compared neuropsychological performance of 25 untreated adult ADHD patients with 30 healthy controls. Verbal learning was significantly worse in patients with ADHD. Seidman et al. (1998) compared performance of 64 untreated adult ADHD patients with healthy controls. Relative to control subjects, patients with ADHD performed significantly worse on the California Verbal Learning test. Impairment on the memory test was significant on immediate word recall and delayed word recall after 20 min. Johnson et al. (2001) compared memory functioning of 56 untreated patients with ADHD with 38 healthy controls. Patients with ADHD demonstrated significant verbal and nonverbal memory deficits. Both immediate recall and delayed recall (after 30 min) were significantly impaired when compared to control subjects. Dige and Wik (2005) examined memory functioning in 48 untreated adult ADHD patients. Compared to healthy controls, ADHD patients scored significantly worse on the auditory Consonant trigram test (verbal dual-task memory), the Benton Visual Retention test (short-term memory), the Rey Auditory Verbal Learning test (immediate and delayed recall, recognition), and the modified *Diagnosticum für Cerebralschädigung* (visual learning and long-term memory).

A possible explanation may be that methylphenidate enhances the release of dopamine. In the brain, the ventrolateral prefrontal cortex and hippocampal formation are involved in encoding and retrieval (Buckner et al. 1995, Schacter and Wagner 1999). Dopamine regulates activity in these brain structures, as well as the communication between them (Schacter and Wagner 1999, Li et al. 2003). Hence, depletion of dopamine in untreated patients with ADHD could result in retrieval problems by dysfunctioning of the circuitry between the hippocampal formation and ventrolateral prefrontal cortex (Bertolino et al. 2006). Histamine plays a key role in learning and memory processes as well. It has therefore also been hypothesized that methylphenidate increases histamine levels in the brain, activated by dopaminergic mechanisms (Horner et al. 2007).

Although the mechanism behind these effects requires further study, the current study showed a significant improvement in declarative memory functioning after administration of methylphenidate.

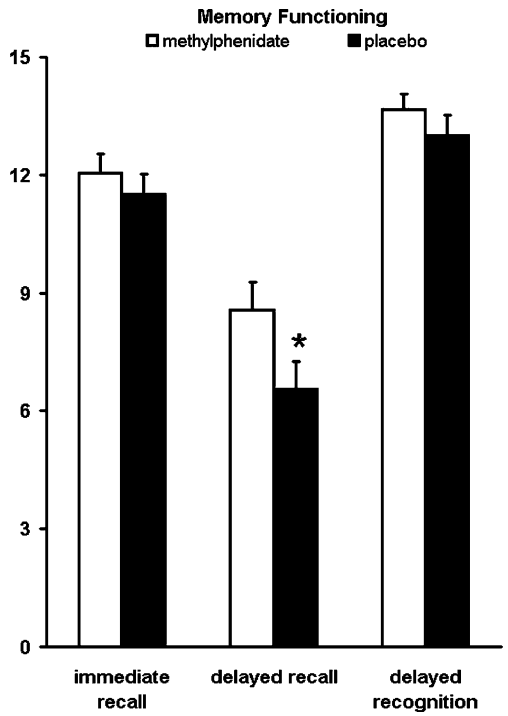

Fig. 1 Results of the Word Learning Test (WLT) Mean (SE) group score after intake of methylphenidate and placebo for immediate word recall, delayed word recall and recognition. *=$p<0.05$

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