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Methylphenidate significantly improves driving performance of adults with attention-deficit hyperactivity disorder: a randomized crossover trial

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Abstract

Although patients with attention-deficit hyperactivity disorder (ADHD) have reported improved driving performance on methylphenidate, limited evidence exists to support an effect of treatment on driving performance and some regions prohibit driving on methylphenidate. A randomized, crossover trial examining the effects of methylphenidate versus placebo on highway driving in 18 adults with ADHD was carried out. After three days of no treatment, patients received either their usual methylphenidate dose (mean: 14.7 mg; range: 10–30 mg) or placebo and then the opposite treatment after a six to seven days washout period. Patients performed a 100 km driving test during normal traffic, 1.5 h after treatment administration. Standard deviation of lateral position (SDLP), the weaving of the car, was the primary outcome measure. Secondary outcome measurements included the standard deviation of speed and patient reports of driving performance. Driving performance was significantly better in the methylphenidate than in the placebo condition, as reflected by the SDLP difference (2.3 cm, 95% CI = 0.8–3.8, $P = 0.004$). Variation in speed was similar on treatment and on placebo (−0.05 km/h, 95% CI = −0.4 to 0.2, $P = 0.70$). Among adults with ADHD, with a history of a positive clinical response to methylphenidate, methylphenidate significantly improves driving performance.

Keywords

driving, methylphenidate, ADHD

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Introduction

Up to 5% of the adult population with a driver's license is estimated to suffer from attention-deficit hyperactivity disorder (ADHD) (Murphy *et al.*, 1996a; Kessler *et al.*, 2005). Attention-deficit hyperactivity disorder comprises symptoms of inattention, hyperactivity/impulsivity or both (combined subtype). The majority of ADHD patients suffer from at least one (87%) or two (56%) co-morbid disorders, most notably anxiety and depression (Kooij *et al.*, 2004; McGough *et al.*, 2005). Treatment with stimulant drugs such as methylphenidate significantly benefits patients with ADHD and greatly improves their quality of life (Kuperman *et al.*, 2001; Dorrego *et al.*, 2002; Bouffard *et al.*, 2003). The annual costs of untreated adult ADHD in terms of work loss and economic burdens on the health-care system are substantial. Effective treatment with methylphenidate significantly reduces these costs (Birnbaum *et al.*, 2005; Matza *et al.*, 2005; Secnik *et al.*, 2005). There is controversy whether it is safe to drive a car for ADHD patients, either with or without successful treatment with methylphenidate. Attention-deficit hyperactivity disorder patients relative to control subjects are more likely to be involved in car crashes (Barkley *et al.*, 1993, 1996; Murphy *et al.*, 1996a), have bodily injuries, be at fault, receive speeding tickets and experience suspension of their driver license (Barkley *et al.*, 1993, 1996). Young unmedicated ADHD adults were further found to exhibit more crashes, scrapes and erratic steering controls than those on a computer-simulated driving test, when compared with healthy controls (Barkley *et al.*, 1996), although this could not be replicated in a subsequent study (Barkley *et al.*, 2002).

Patients often report that driving *improves* when treated with methylphenidate. Results from experimental studies vary, but indicate that methylphenidate improves driving skills, often toward levels measured in healthy controls. For example, a study in a virtual-reality driving simulator showed steering and speed variability to be significantly reduced in ADHD patients after intake of 20 mg, but not after 10 mg of methylphenidate (Barkley *et al.*, 2005). In contrast, another small study found significant improvement in a driving simulator after intake of 10 mg (Cox *et al.*, 2000). Further, driving performance of adolescents with ADHD was more stable during the day after treatment with controlled-release as opposed to immediate-release methylphenidate (Cox *et al.*, 2004a).

In the past, simulator results poorly predicted actual driving, and thus it remains to be determined if driving simulator findings generalize to real life (Volkerts *et al.*, 1992). The absence of other traffic and the knowledge of participants that the driving simulator is an artificial laboratory setting greatly limit their ecological validity. Only one previous study examining 12 adolescent boys with ADHD involved real traffic (Cox *et al.*, 2004b). During a car drive of 16 miles following intake of controlled-release methylphenidate (1 mg/kg or their regular dose) or placebo, an experimenter rated the number of impulsive and inattentive driving errors. Only the number of inattentive errors was significantly reduced after methylphenidate intake. A major limitation of this study is that driving performance was assessed by subjective ratings. These ratings may be inaccurate and poorly predict actual driving performance (Verster, 2002).

To replace inaccurate subjective assessment and artificial simulator environments, a standardized on-the-road driving test was developed (O' Hanlon *et al.*, 1982, 1984).

This article presents results from the first study examining the effects of methylphenidate on driving performance of adult ADHD patients using the standardized on-the-road test. It was hypothesized that, relative to placebo, treatment with methylphenidate significantly improves driving ability of ADHD patients.

Methods

Design overview

The study had a double blind, placebo-controlled, randomized, two-way, counter-balanced crossover design and was performed between February 2003 and February 2006. The Medical Ethical Committee of the University Medical Center, Utrecht approved the protocol. Patients were treated according to guidelines for Good Clinical Practice and the Declaration of Helsinki and its amendments. Patients were informed about the possible risks of the driving test and the adverse effects of treatment cessation. Written informed consent was obtained before inclusion.

Participants

Patients were recruited from two sources, that is referrals to outpatient clinics for adult ADHD (GGZ Delfland/PsyQ, $N = 10$) and via an advertisement ($N = 8$). Patients from the outpatient clinics ($N = 10$) underwent a standardized clinical assessment consisting of a review of prior records and a psychiatric evaluation by experienced psychiatrists using a semi-structured diagnostic interview for the presence of ADHD and co-morbid disorders both current and in childhood. To measure the presence and severity of current ADHD-symptoms during the last six months, we used a Dutch version of the DSM-IV ADHD-rating scale, which is based on the 18 DSM-IV items for ADHD (DuPaul *et al.*, 1998; Kooij *et al.*, 2005). Information from the patient about symptoms of ADHD and associated impairment of functioning was complemented by collateral information from the partner and the parents, and by obtaining school reports about childhood, if available. To fulfill diagnostic criteria, subjects must have (a) met six or more out of nine DSM-IV ADHD criteria of inattention and/or of hyperactivity/impulsivity in childhood; (b) met five or more out of nine DSM-IV ADHD criteria of inattention and/or of hyperactivity/impulsivity in adulthood; (c) described a chronic persisting course of ADHD symptoms from childhood to adulthood and (d) endorsed a moderate to severe level of impairment attributed to the ADHD symptoms. A cutoff point of five of nine criteria was set for adult diagnosis of ADHD based on the literature and epidemiological data using the same DSM-IV ADHD-rating scale (Murphy *et al.*, 1996b; Biederman *et al.*, 2000; Kooij *et al.*, 2005). Earlier diagnosed ADHD patients ($N = 8$) had underwent similar diagnostic procedures at other clinics.

At the start of this study, we confirmed earlier diagnosis by assessing the severity of current ADHD symptoms using the DSM-IV ADHD-rating scale (DuPaul *et al.*, 1998; 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).

Inclusion criteria were being adult (21–55 years old), having a driver's license for at least three years, for women of childbearing potential, a negative urine pregnancy test result and the use of a medically acceptable method of contraception, normal static binocular acuity 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 dependence or drug addiction, a positive alcohol breath test, the use of medication known to affect driving performance, having a psychiatric disease or excessive caffeine consumption (>5 cups/day) and nicotine use (>10 cigarettes/day).

Randomization and interventions

An independent co-worker performed the randomization using random numbers without blocking or stratification. The randomization code (001-030) was stored at the pharmacy. Patients received a number (001-030) when signing the informed consent. This number allocated patients to the randomization code and corresponding medication regimen.

Prior to participation in the study, patients were effectively treated with methylphenidate. To participate in this study, patients were asked to voluntarily stop their treatment, starting three days before the first test day (Session 2) until the second test day (Session 3). Sessions 2 and 3 were separated by six to seven days without treatment. On the first test day, methylphenidate (patients' regular dosage) or placebo was administered. On the second test day, the other treatment was administered. Treatment (capsules of identical shape, size and color) was administered orally with 240 ml tap water, 1.5 h before the start of the driving test. If applicable, a second treatment dose was administered according to the patient's usual interval between the first and the second dose.

The adequacy of blinding was evaluated by a short questionnaire at the end of each test day.

Outcomes and measurements

Before discontinuation of their medication, all patients were trained on the driving test, to become familiar with test procedures. Patients arrived by public transport at the Institute in a fasting condition, and nicotine and caffeine use were not allowed. At the Institute, they consumed a standardized breakfast. To confirm compliance, at all visits, patients were tested for the presence of alcohol (breath alcohol analysis) and drug abuse (urine drug screen, including amphetamines, barbiturates, cannabinoids, benzodiazepines, cocaine and opioids). In addition, female subjects underwent a urine pregnancy test.

Treatments were administrated in the presence of study personnel, 1.5 h before the start of the driving test. Thereafter, patients were transported to the highway circuit and performed the driving test. Thereafter, visual analog scales were completed and patients were transported to the institute. After a medical check, patients traveled home by public transport and were cautioned not to drive their own vehicles or engage in potentially dangerous activities.

Driving test A standardized driving test was performed on a primary highway during normal traffic, on a 100 km track between the cities of Utrecht and Arnhem. A camera, mounted on the roof of the test vehicle, measured the vehicle's lateral position relative to the road delineation. The vehicle's speed and lateral position were continuously recorded. Before treatment unblinding, the data were edited off-line to remove data that were disturbed by extraneous events (e.g., overtaking maneuvers and traffic jam). Patients were instructed to drive with a steady lateral position within the right traffic lane while maintaining a constant speed of 95 km/h (60 mph). Patients were allowed to deviate from the instructions to overtake a slower-moving vehicle in the same traffic lane. A licensed driving instructor who had access to dual controls sat in the right front seat, guarding the subject's safety. Tests could be terminated if the driving instructor or the subject felt it was unsafe to continue. The amount of weaving of the car, measured by the standard deviation of the lateral position (SDLP, cm), is the primary outcome parameter. The standard deviation of speed (km/h) is a secondary parameter. Time-on-task of the driving test was approximately 75 min.

To illustrate the clinical relevance of driving performance, SDLP changes are generally compared with those that were obtained with blood alcohol concentrations (BAC) that correspond to legal limits for driving a car (Louwerens *et al.*, 1987). A clear relationship between SDLP increment, blood alcohol concentration and the risk of becoming involved in a traffic accident has been established (Louwerens *et al.*, 1987; Borkenstein *et al.*, 1964). Generally, an SDLP increment of 2.4 cm or more (found with BAC = 0.05%) is viewed as a clinically relevant effect.

Self-reports on driving ability and driving style Various assessments were made to investigate patients' own perception of their driving skills and driving habits. Patients indicated the perceived quality of their driving performance on a visual analog scale, which ranged from 0 ('I drove exceptionally poorly') to 20 ('I drove exceptionally well') around a midpoint of 'I drove normally'. The level of mental effort they had to invest in performing the task was indicated on a 15 cm equal interval scale.

Patients rated six dimensions of their driving style on 10 cm bipolar visual analog scales (McCormick *et al.*, 1986), including foolish–wise, inconsiderate–considerate, dangerous–safe, tense–relaxed, unpredictable–predictable and irresponsible–responsible. They also compared their own performance with that of the 'average driver' on a 10 cm scale.

Follow-up procedures

After completion of the study, subjects continued their regular treatment regimen, under supervision of their psychiatrist. Patients were not paid for participation, but their travel expenses were

reimbursed. In case of withdrawal or discontinuation, a patient was replaced.

Statistical analysis

Sample size estimation of 30 subjects was based on the primary outcome measure, SDLP. The standard deviation for SDLP was estimated at 3.0 cm from previous studies carried out by the Department of Psychopharmacology. The study was designed to detect a mean difference of 2.0 cm with at least 90% power using a two-sided test at the 0.05% significance level. After three years, 18 patients completed the study and we decided to stop recruiting. Slow enrollment of participants was caused by the fact that the majority of ADHD patients experience co-morbid disorders and a number of other patients were not interested in participating or did not meet other study criteria such as possession of a driver's license.

After we decided to cease enrollment, statistical analyses were performed using the SPSS statistical program (SPSS 12.0, SPSS Inc., Chicago, IL, USA). No interim analyses were performed. Mean, standard deviation (SD) and 95% confidence intervals (CI) were computed for each parameter.

The following statistical analyses were preformed:

(1) In a preliminary analysis, the main effects of gender and period (test day 1 versus test day 2) were tested for significance ($P < 0.05$) using ANOVA for repeated measures. If not significant, these effects were not included in the principal analysis.
(2) In the principal analysis, the within-subject factor treatment (two levels: methylphenidate and placebo group), the between-subject factor treatment order (placebo-> methylphenidate, methylphenidate-> placebo) and their interaction were tested for significance ($P< 0.05$) using ANOVA for repeated measures.
(3) All variables (placebo–methylphenidate difference scores) were examined for normality using the Shapiro–Wilk test, and in case that a normal distribution was not met, non-parametric analyses were applied. To address possible outliers, homogeneity of variance analysis was performed.
(4) Stepwise regression analysis was performed to examine whether patient characteristics (the CAARS ADHD-index score, DSM-IV defined ADHD inattention, hyperactivity/impulsivity and total ADHD scores, STAI anxiety index, CES-D, duration of treatment, regular daily dose, the treatment dose used in this trial, yearly driven kilometers and years of possessing a driver's license) predict the SDLP difference between methylphenidate and placebo.
(5) To determine whether different centers that established the ADHD diagnosis had an effect on any of the outcome measures, ANOVA for repeated measures was applied with treatment as within-subject factor and center as between-subject factor.
(6) To assess the effect of imperfect blinding (those who correctly recognized the administered treatment versus those who guessed wrong) on outcome measures, ANOVA for repeated measures was applied with treatment as within-subject factor and blinding as between-subject factor.

Results

Participants

Seventy-five Patients were assessed for eligibility; of whom 56 were excluded and 19 were included. Eighteen patients completed the study (Figure 1).

One randomized subject voluntarily withdrew his participation after performing the training session, due to a lack of confidence that he could manage a week without methylphenidate treatment. He reported sickness during concurrent methylphenidate and smoking cessation before the study start. No data obtained from this subject were included in any analysis. The other 18 randomized patients (11 men and 7 women) completed the study. There were no missing data from these patients. Mean (SD) age was 38.3 (7.7) years, mean (SD) weight was 79.9 (16.4) kg and mean (SD) height was 1.82 (0.09) m. Patient characteristics are summarized in Table 1. Three patients used concomitant anti-hypertensive mediation (#1, 3 and 12) and another used venlafaxine (#8). None of these drugs has been found to affect driving performance (O' Hanlon *et al.*, 1998).

Driving test

On test days, all patients completed their driving tests. Means and 95% confidence interval of the driving test parameters and results from the statistical analyses are presented in Table 2 and Figure 2.

Preliminary statistical analysis showed no main effects of gender and of period. The principal analysis revealed no significant

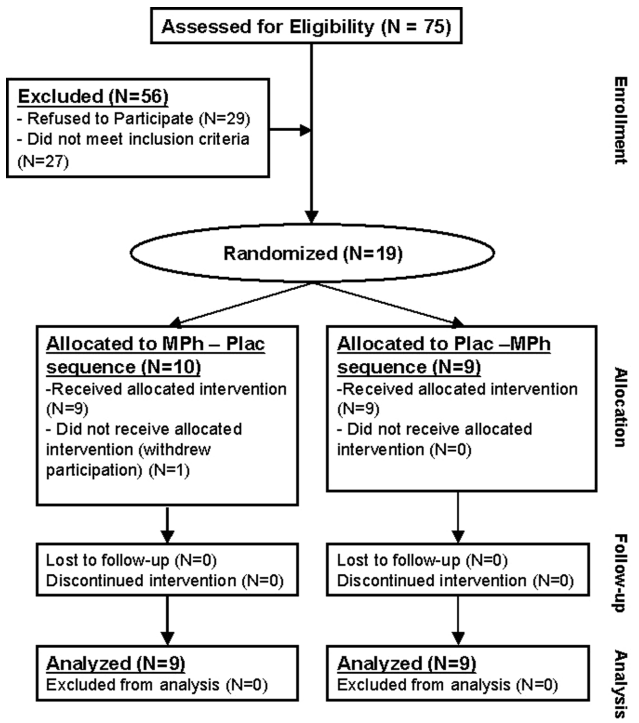

Figure 1 Flow diagram of the trial

Table 1 Descriptives of participants

Patient	Gender	Center	CAARS ADHD-index	DSM-IV attention index	DSM-IV hyperactivity index	DSM-IV ADHD index	STAI	CESD	Daily Divided Dosages (mg)	Time since diagnosis and duration of use of methylphenidate (months)	Study Dose (mg)	Km/year	Years of Driving
1	male	1	70	17	13	30	56	25	10-10-10	6	10	70000	30
2	female	2	65	17	12	29	51	29	10-10-10	26	10	12000	7
3	male	1	43	4	5	9	30	7	20-15-15-10	33	15	15000	17
4	male	1	63	19	17	36	50	14	15-15-15	9	15	5000	8
5	female	1	68	19	14	33	62	22	20-20-10-10	9	20	30000	25
6	female	1	72	18	23	41	45	10	15-15-15-15	7	15	2000	10
7	male	1	66	15	20	35	46	16	30-20-20-10	60	30	5000	27
8	male	1	77	22	18	40	64	33	18-36©	72	20 (10)*	4000	22
9	male	1	56	7	9	16	53	14	20-20-20-20	9	20	12000	12
10	female	1	61	5	16	21	47	10	10-10-10-10	32	10	10000	4
11	male	2	67	16	20	36	47	7	18-36-18©	46	20	12500	22
12	male	2	70	14	17	31	49	21	10-10-10	72	10	12000	20
13	male	2	46	3	6	9	28	5	36-36©	8	10 (10)*	7500	15
14	female	2	72	14	12	26	37	11	10-10-10-10	72	10	17000	22
15	female	2	70	14	18	32	62	14	10-10-10-10-10	13	10	13000	13
16	male	1	64	9	17	26	43	8	15-20-25-15-15-15	20	15	90000	20
17	male	2	67	14	18	32	40	8	10-10-10-10	5	10 (10)*	70000	25
18	female	2	68	21	18	39	55	27	15-15-15-15	13	15	18000	3
	Mean		64.7	13.8	15.2	28.9	48.1	15.6	54.0	28.4	14.7	22500	16.8
	Median		67.0	14.5	17.0	31.5	48.0	14.0	50.0	16.5	15.0	12250	18.5
	Range		43-77	3-22	5-23	9-41	28-64	5-33	30-105	5-72	10-30	2000-90000	3-30

Patient characteristics. Cut-off scores for clinical relevance: Depression (CES-D) ≥ 16; Anxiety (STAI) ≥ 54, ADHD-index (CAARS) ≥ 65. All patients used methylphenidate before participation in the study, except for 3 patients who used slow-release methylphenidate (Concerta, indicated by ©). *A second dosage (between brackets) was administered, 2 – 2.5 hours after the first dose.

Table 2 Results from the driving test

	Mean (95% Confidence Interval)				
	Training	Placebo	Methylphenidate	Placebo-Methylphenidate difference	*P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95% CI)	
SDLP (cm)	18.7 (2.6)	21.1 (4.0)	18.8 (3.5)	2.3 (0.8, 3.8)	$P = 0.004$
Lateral position (cm)	17.7 (15.7)	16.8 (16.8)	15.6 (20.1)	1.2 (1.6, 4.0)	$P = 0.37$
SD speed (km/h)	2.6 (0.8)	2.5 (0.6)	2.6 (0.7)	0.05 (0.4, 0.2)	$P = 0.70$
Mean speed (km/h)	93.8 (1.2)	93.7 (1.2)	94.3 (1.7)	0.5 (1.2, 0.2)	$P = 0.12$

Note: The training session was performed while taking methylphenidate.
SD = standard deviation, SDLP = standard deviation of lateral position, CI = confidence interval.

effect of treatment order and the treatment by treatment order interaction was not significant. Mean SDLP after methylphenidate was statistically significantly lower ($P = 0.004$) than after placebo (placebo-methylphenidate difference = 2.3 cm, 95% CI = 0.8–3.8). Individual SDLPs after placebo were worse than after methylphenidate treatment for 13 participants (72.2%, 95% CI 51.5–92.9%). Mean SDLPs from the training session on which patients used methylphenidate (18.8 cm) match those of the methylphenidate condition during the study (18.7 cm). Mean SD speed did not differ significantly ($P = 0.70$) between the treatment conditions (placebo–methylphenidate difference = −0.05 km/h, 95% CI = −0.4 to 0.2). Also, mean speed and mean lateral position did not differ significantly after methylphenidate and placebo administration.

Performing the same analysis without the patient using venlafaxine or all subjects on concomitant medication yielded similar results on SDLP differences between methylphenidate and placebo: 2.0 cm (95% CI= 0.6–3.5, $P = 0.009$) and 1.8 cm (95% CI= 0.2–, $P = 0.028$), respectively. None of the patient characteristics (summarized in Table 1) was statistically significantly associated with SDLP differences between methylphenidate and placebo.

Self-reports on driving quality and driving style

Relative to placebo, methylphenidate significantly improved subjective driving quality ($P = 0.023$) and mental effort when driving was significantly less ($P = 0.022$).

After methylphenidate, patients reported that their driving style was significantly less unpredictable ($P = 0.004$), less dangerous ($P = 0.043$), less foolish ($P = 0.034$) and less tensed ($P = 0.005$). By self-report, patients were not significantly less inconsiderate ($P = 0.099$) or less irresponsible ($P = 0.067$).

Centers where ADHD was diagnosed

Centers were ADHD was diagnosed had no significant effect on SDLP ($P = 0.58$) or other objective or subjective outcome measure.

Effects of blinding

On 22 of 36 test days (61.1%, 95% CI = 45.2–77.0%) patients correctly guessed which treatment they received, and on 14 of 36 test days the guess was wrong (38.9%, 95% CI = 23.0–54.8%). Patients who correctly identified treatment did not differ significantly from those who did not on SDLP ($P = 0.35$) or driving test parameter. However, imperfect blinding was reflected by significant differences on subjective measures of driving performance. Those who correctly recognized their treatment reported significantly less difference in mental effort to perform the test ($P = 0.005$) between methylphenidate and placebo, and less difference between the treatments in driving safe ($P = 0.046$), being predictable ($P = 0.009$), tensed ($P = 0.001$), inconsiderate ($P = 0.035$) and responsible ($P = 0.010$).

Discussion

This study shows that driving performance of adult ADHD patients significantly improves when taking methylphenidate. Driving improvement was expressed by a significant reduction in weaving of the car (SDLP). Attention-deficit hyperactivity disorder patients confirmed by subjective reporting that driving was significantly improved and less effortful, dangerous and foolish and more relaxed and predictable.

This is the first study in ADHD patients conducted on a regular highway using an objective measure of overall vehicle control, that is weaving of the car (SDLP). Driving was tested over an extensive period of time in the presence of real traffic. These methodological improvements relative to previous research were necessary to enable testing in a naturalistic setting.

Improvement in driving performance after intake of methylphenidate confirms the results found in previous studies using laboratory tests or driving simulators (Barkley *et al.*, 2002, 2005; Cox *et al.*, 2000, 2004a). Also, in a sample of 18 recreational ecstasy users, similar improvement in SDLP relative to placebo

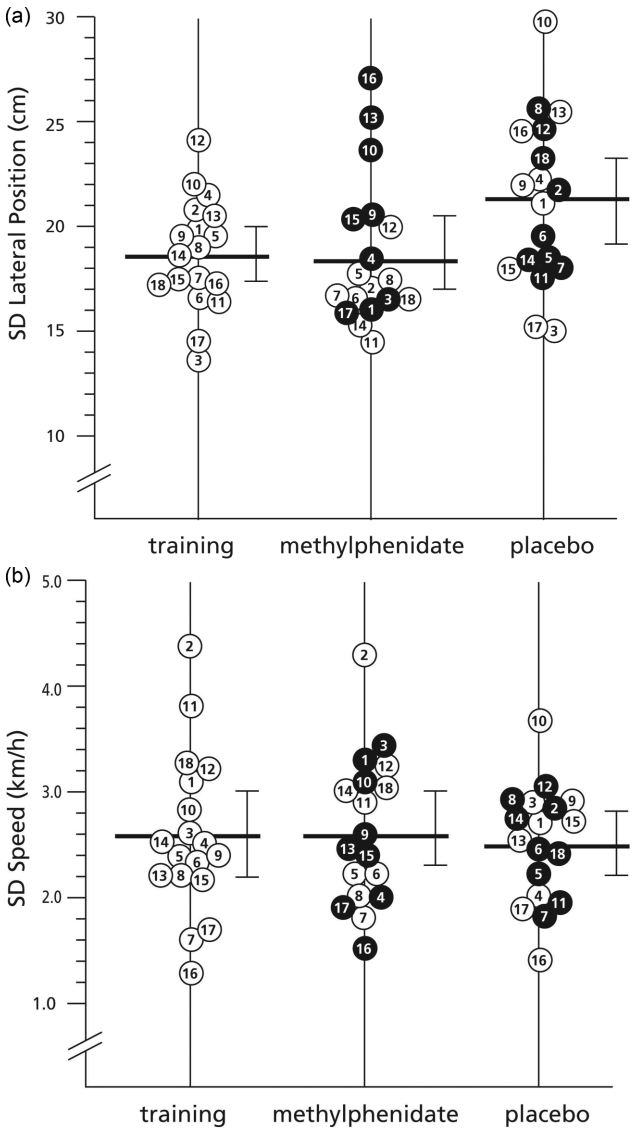

Figure 2 Results on the driving test for the standard deviation of lateral position (a) and standard deviation of speed (b) for the training session and the test days with methylphenidate or placebo. Bars show the group average and 95% confidence interval. All patients are indicated by numbers and participated in all conditions. For the methylphenidate and placebo condition, black circles indicate that the driving test was performed in the first test period and open circles indicate the second test period. Note that the training session was performed while taking methylphenidate.

was reported after intake of 20 mg methylphenidate (Ramaekers *et al.*, 2006).

The most likely explanation for performance improvement is the direct positive effect of methylphenidate on focusing attention and sustaining alertness during the driving test. In fact, this is the rationale for recreational or occupational use of stimulant drugs such as methylphenidate.

A limitation of our study may be the focus on rather basic measures of vehicle control, that is lane keeping (SDLP) and speed maintenance. Driving is, however, an example of complex behavior, and some aspects of driving behavior such as overtaking or behavior at crossings are not assessed by the on-the-road driving test.

Blinding is difficult in placebo-controlled studies in patients who are experienced with a treatment. In this study, imperfect blinding had a significant effect on subjective measures of driving quality and driving style. Therefore, these subjective measures should be interpreted with caution. However, for objective outcomes (i.e. SDLP), no significant differences were observed between patients who correctly identified treatments and those who did not. The fact that patients were diagnosed at different centers is another limitation of this study, but statistical analyses revealed no significant difference on any outcome measure between patients from the adult ADHD outpatient clinics and patients who had been diagnosed elsewhere. Inclusion of ADHD patients who are effectively treated with methylphenidate may limit the generalizability of our findings. The relative small sample size is another issue that deserves attention; however, using the crossover design improves power.

Future driving studies should include larger number of patients. It has to be further investigated whether our findings will be similar for patients new to treatment, with co-morbid conditions, or taking concomitant medication. It is also essential to assess the possible interaction between methylphenidate and treatments that are used for co-morbid conditions. In addition, other driving skills that may be impaired in ADHD patients such as time estimation at crossings and risk-taking behavior deserve further examination.

Taken together, a significant improvement in real-life driving ability of ADHD patients was observed after intake of methylphenidate. The results from this study strengthen the idea that lawmakers should reconsider current regulations that prohibit driving when treated with methylphenidate.

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