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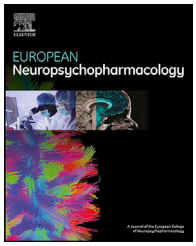

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Do effects of methylphenidate on cognitive performance last beyond treatment? A randomized placebo-controlled trial in boys and men with ADHD

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Abstract
Methylphenidate (MPH) is the first-choice pharmacological treatment for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) across the lifespan. However, it is unclear whether MPH affects cognitive development, while recent (pre-) clinical studies suggest effects on the developing brain. The present randomized, placebo-controlled trial aims to determine whether MPH has short-term, age-dependent effects on cognitive performance in ADHD after a 1-week washout. Effects of 16 weeks MPH treatment were assessed after a one-week washout on cognitive functioning. Boys (age=10–12) and men (age=23–40) with ADHD were assigned to MPH treatment (boys *n*=25, men *n*=24) or placebo (boys *n*=25, men *n*=24). Outcome measures were working memory, response inhibition, response speed, episodic memory, and delay aversion. Differences in task performances over time (pre-, mid-, and post-treatment, following a 1-week wash-out) were compared between age and treatment conditions with mixed ANOVAs.

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MPH improved working memory and response speed, but only during treatment. No lasting age*treatment effects were observed post intervention. Overall, the results from the present randomized, placebo-controlled trial show that the effects of MPH on cognition do not extend past treatment in children or adults. While treatment with MPH improves cognition during treatment, these effects appear transient after 16-weeks of treatment.
(Title trial: "Effects of methylphenidate on the developing brain"; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3103)

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adults is typically associated with executive dysfunctions (e.g., inhibitory control and working memory), timing difficulties, and the sensitivity to (the delay of) reward (Alderson et al., 2013, 2010; de Zeeuw et al., 2012; Martinussen et al., 2005; Sonuga-Barke et al., 2010). Pharmacological treatment with psychostimulants, such as methylphenidate (MPH), has positive short-term acute effects for children and adults with ADHD on behavioral symptoms, as well as cognitive functioning (Coghill et al., 2014; Tamminga et al., 2016; Van der Oord et al., 2008). Acute effects of MPH include improved executive and non-executive aspects of memory, reaction time, reaction time variability, and response inhibition (Coghill et al., 2014). MPH increases the availability of dopamine (DA) and norepinephrine (NE) in striatal and prefrontal brain areas by blocking the reuptake of DA and NE by transporters (Koda et al., 2010; Volkow et al., 2012), hypothetically facilitating neurotransmission in these areas. The human brain, in particular the prefrontal cortex, continues to mature throughout childhood and adolescence (Giedd and Rapoport, 2010), and experiences and environmental conditions can affect development positively or negatively (Fox et al., 2010). In line with this, (sub)chronic use of stimulants might influence brain development and thus cognitive functioning in the long-term.

An interaction between brain development and MPH treatment is suggested by several pre-clinical and clinical studies. The 'neuronal imprinting theory' (Andersen, 2005) suggests a differential effect of MPH exposure, dependent on sensitive periods in brain development, in that treatment in childhood can have different, frequent opposite, effects on the brain and its function than in adulthood. Pre-clinical studies have shown that the juvenile brain reacts with neuroadaptive processes to chronic administration of MPH, such as a reduced density of striatal DA transporters (Moll et al., 2001), reduced expression of D_3 receptors in the frontal cortex (Andersen et al., 2008), and downregulation of basal DA levels (Jezierski et al., 2007) in (sub)chronic MPH-exposed juvenile but not adult rats. In humans no studies directly comparing the differential effects on brain structure between exposure in childhood versus adulthood have been performed. Naturalistic imaging studies suggested stimulant treatment-associated normalization after treatment in childhood in gray matter and/or subcortical structures (Nakao et al., 2011; Shaw et al., 2009; Sobel et al., 2010) and enhanced orbitofrontal-striatal white matter connectivity (Schweren et al., 2016), but these studies investigate relatively long term effects, and in most cases children were already medicated at baseline. Our research group showed, reporting on different outcomes of the current RCT, a long-lasting (one-week beyond treatment) age-dependent decrease in symptoms in stimulant medication-naïve boys but not men. Moreover, this study demonstrated a long-lasting (one- week beyond treatment end) increased blood flow in the striatum and thalamus in response to a dopamine challenge in medication naïve ADHD children randomized to 16 weeks MPH, but not placebo or in ADHD adults (Schrantee et al., 2016). In addition, we found long-lasting age-dependent effects of MPH on gray (Walhovd et al., 2020) and white-matter structure (Bouziane et al., 2019) and sleep efficiency in children (Solleveld et al., 2020), but not adults, randomized to MPH. Taken together, our RCT shows long-lasting age-dependent effects of short-term MPH treatment on the human brain, and here we want to investigate whether stimulant treatment during development is (also) associated with underlying altered cognitive functioning beyond the transient effects of ongoing treatment.

Whereas controlled clinical studies on the potential lasting effects of stimulants after washout on behavioral and cognitive functioning have a high clinical relevance, because MPH is prescribed frequently, few such studies exist. In naturalistic follow-up studies, stimulant treatment is associated with improvements in impulsivity (Aggarwal and Lillystone, 2000; Huang et al., 2012), increased academic performance in adolescence (Powers et al., 2008), lower risk of substance use disorders (Groenman et al., 2019; Mannuzza et al., 2008), and a superior occupational outcome (Halmøy et al., 2009), but also higher persistence rates (Biederman et al., 2012; van Lieshout et al., 2016), underlining the possibility of confounding-by-indication. In these naturalistic studies, the lack of an untreated control group, randomization, confounding-by-indication, self-selection of treatment, and other factors endogenous to being stimulant treated, hampers the distinction between treatment induced normalization, test-retest effects, and expected development history.

Regarding cognition, naturalistic studies have shown inconsistent results. Superior inhibition and attention in children with a history of medication use relative to stimulant naïve children have been described (Semrud-Clikeman et al., 2008), but no effects were found in adolescents on motor control, timing or working memory (Schweren et al., 2019). Adults with childhood ADHD performed similar on tests of attention, working memory and learning regardless of treatment history (Stoy et al., 2011).

Together, these findings might imply that the effects of stimulants on cognition extend beyond treatment, but diminish in the longer-term. However, pre-existing between-subject differences could also account for these findings. Thus, to date, the question of whether stimulant treatment affects cognitive functioning beyond treatment, and whether these off-medication effects differ between children and adults with ADHD, remains unanswered.

In order to determine whether there are age-related, lasting, beyond treatment, effects of MPH on cognitive functioning, the present study is the first RCT that assessed whether 16 weeks of randomized treatment with MPH or placebo alters cognitive performance in children and adults with ADHD in non-medicated state after a one-week washout period. Previous studies considering lasting (short- to longer-term) effects of MPH have a naturalistic nature, whereas randomization is essential to determine causality of effects. Participants were assessed before randomization, at 8 weeks, and after 16 week of treatment with MPH or matching placebo following a one-week wash-out period. Given the research literature and the neurobiological findings of this study (Bouziane et al., 2019; Schrantee et al., 2016) we hypothesize lasting cognitive effects of MPH in children, marked by larger pre- to post-treatment difference in the active MPH condition compared to the placebo condition, but we expect this effect to be absent in adults, suggesting that effects are developmentally driven.

We assessed several cognitive functions, including those considered as “core” deficits in ADHD such as executive dysfunctions (e.g. inhibitory control and working memory), timing, and the sensitivity to (the delay of) reward (Alderson et al., 2013, 2010; de Zeeuw et al., 2012; Martinussen et al., 2005; Sonuga-Barke et al., 2010). In addition, we also focused on domains that are less markedly discussed in the ADHD literature, but which also tend to be compromised in ADHD and improved by acute MPH, such as response speed and episodic memory (Biederman et al., 2008; Coghill et al., 2014; Muir-Broaddus et al., 2002; Schoechlin and Engel, 2005; Swanson et al., 2011). Hence, by focusing on a broad range of cognitive domains we could fully grasp the potentially widespread effects of MPH. For our main hypothesis (i.e. pre- vs post-treatment effects larger in children and absent in adults) we only examined those functions that were affected by MPH during treatment at eight weeks, as we do not expect changes in functions that are not affected by MPH during treatment. Our study on lasting effects of MPH treatment on brain development is unique in assessing cognitive functioning after a one-week washout period and in comparing children to adults.

2. Experimental procedures

2.1. Participants

The present study is part of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (effects of Psychotropic drugs On the Developing brain [ePOD-MPH]; for details see Bottelier et al., 2014). Boys aged 10–12 years and men aged 23–40 years were included. Inclusion criteria were meeting criteria for a diagnosis of, and requiring treatment with medication for ADHD (Inattentive, Hyperactive/Impulsive or Combined subtype). The diagnosis was determined by an experienced clinician based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994), which was confirmed with a (semi-)structured interview (Ferdinand and Van der Ende, 1998) in children; Diagnostic Interview for Adult ADHD (DIVA; Kooij and Francken, 2010). The DSM-IV requirement of at least 6 symptoms of inattention or hyperactivity/impulsivity was applied to both children and adults. Participants were not eligible when they had received clinical treatment influencing the DA system (for adults before age 23), such as: stimulants, neuroleptics, antipsychotics, D2/D3 agonists, or when they had a current or previous dependency of drugs that influence the DA system (for adults before age 23). Other exclusion criteria were an estimated IQ $<$ 80 (Block Design and Vocabulary subtests of the WISC-III-R (Kort et al., 2002), Dutch Adult Reading Test (Schmand et al., 1992), and/or a history of major medical or neurological trauma or illness (see Figure 1 for a CONSORT flow diagram).

The ePOD-MPH study was approved by the Central Committee on Human Research in the Netherlands (CCMO; NL34509.000.10), and subsequently registered at the Netherlands Trial Register (NTR3103; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3103). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. After trial commencement, no significant changes were introduced to the study protocol, other than that the age-range of the adult participants was expanded from 23–30 years to 23–40 years due to inadequate inclusion rate in this age group in March 2014.

2.2. Procedure

Boys were recruited from clinical programs at the Child and Adolescent Psychiatry centre Triversum (Alkmaar) and from the department of (Child and Adolescent) Psychiatry at the Bascule/AMC (Amsterdam). Adult patients were recruited from clinical programs at the PsyQ mental health facility (The Hague) and from the department of Psychiatry of the AMC (Amsterdam). Before entering the study, all participants aged 12 years or older gave written informed consent, as did all caregivers of participating children. Additionally, all children younger than 12 years gave verbal informed consent. In- and exclusion criteria were checked at study entry. Pre-treatment assessment took place within two weeks after study entry. After the pre-treatment assessment, participants were randomly assigned to MPH or placebo treatment (ratio 1:1) lasting 16 weeks, using a permuted block randomization scheme generated by the local Clinical Research Unit. Cognition was re-assessed in week eight (on-medication state), and again in week 17, after 16 weeks of treatment and following a one-week wash-out period (in off-medication state). Please see for the other measures administered within e-Pod the original research protocol (Bottelier et al., 2014). Compliance to the study medication was monitored at each of five control visits (at 1, 2, 3, 5, 8 and 12 weeks after treatment start). During treatment, adult participants and parents of children received psycho-education and supportive coaching regarding stimulant use. Participants, caretakers, treating clinician and investigators were all blinded until study-end. We aimed to test participant on similar times during the day. On all test occasions, feedback was provided during practice sessions, but not during the actual test. Tests sessions occurred in a counterbalanced fashion without breaks and assessment lasted one hour.

2.3. Treatment

Study medication was titrated by the treating physician (MB, CB) to an optimal dose on clinical guidance (e.g., reduction in ADHD symptoms) in accordance with Dutch treatment guidelines (ADHD bij volwassenen, 2015; Multidisciplinaire richtlijn ADHD bij kinderen

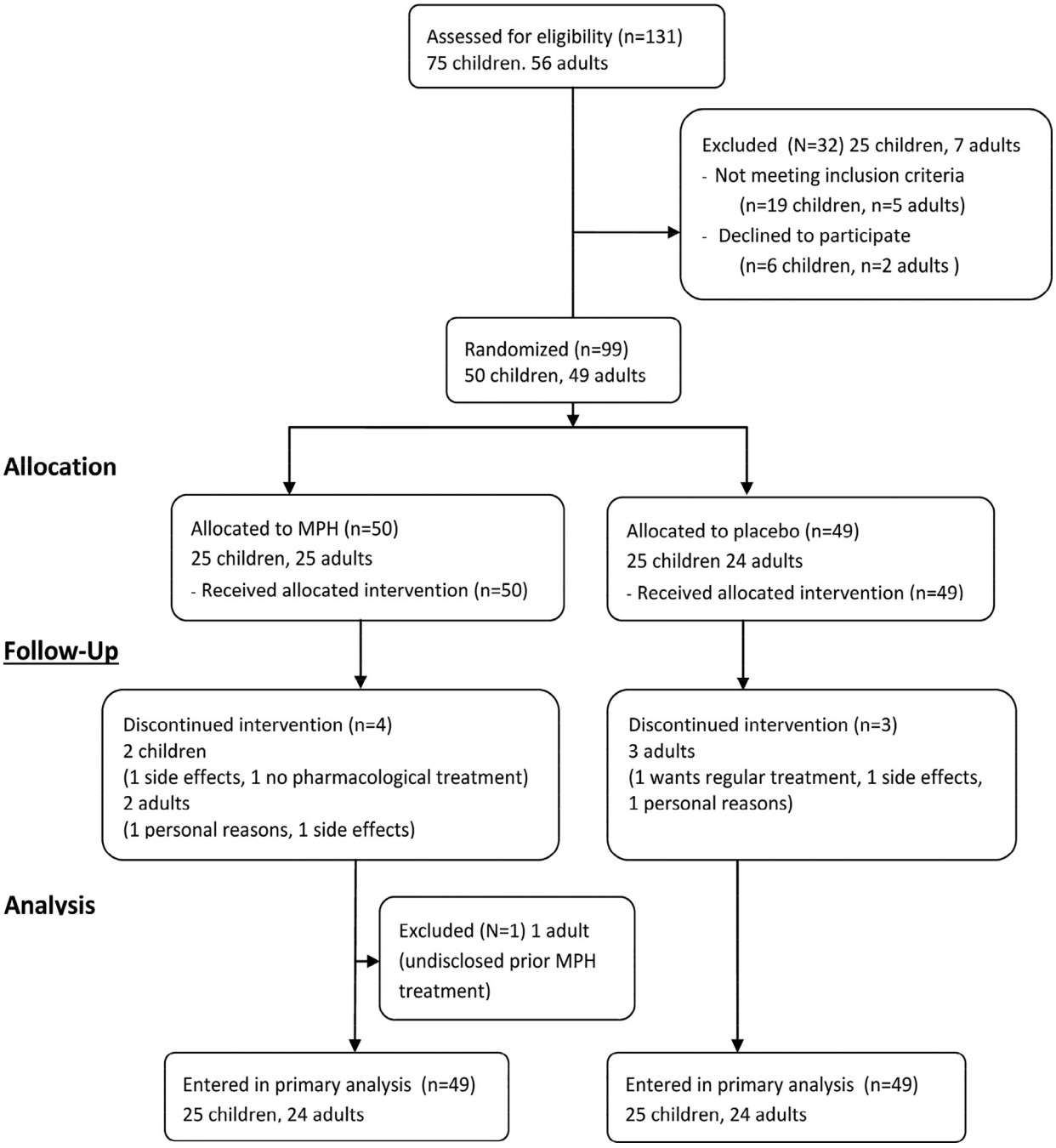

Figure 1 Flow diagram.

en jeugdigen, 2005 (GGZ, 2005)), under double-blind conditions. The maximum daily dose was 40 mg for children and 60 mg for adults. Placebo tablets and MPH tablets had a similar appearance and were manufactured according to Good Manufacturing Practice (GMP) guidelines (Slotervaart Hospital, Amsterdam, the Netherlands). Labeling was according to European standards, as defined in the guideline GMP (2003/94/EG), and containers were numbered sequentially.

2.4. Materials

2.4.1. N-back test

The *n*-back test of visuo-spatial working memory (van Leeuwen et al., 2007; designed after Gevins & Cutillo, 1993) had three conditions with increasing difficulty (1-back, 2-back, and 3-back). Each condition contained 32 consecutive trials. In each trial, a target (caterpillar) appeared in one of four locations (holes in an apple). Each target (2000 ms) was followed by a beep, which was the probe to indicate where the target was seen one trial ago (1-back), two trials ago (2-back) or three trials ago (3-back). A response was made by pressing the corresponding button (digits 1, 3, 7, and 9) on a keyboard with the thumb and index finger of both hands. The following trial started after 3000 ms. Participants practiced each condition until they clearly understood the test, and were instructed to start over in case they lost track of the sequence. The number of correct responses for each condition could theoretically range between 0 and 32. The difference in accuracy between the two highest achieved conditions was selected as the dependent vari-

able, with higher scores demonstrating a decline in performance at increasing complexity.

2.4.2. Go/No-Go (GNG) test

An adaptation of the GNG test of psychomotor inhibition (Durston et al., 2002) was administered during MRI-scanning. Participants were required to press a button with the right index finger each time a target stimulus (Pokemon cartoon character) was presented (the Go-trial), except when the stimulus was the non-target (the No-Go-trial). Stimulus duration was 500 ms and the ISI was 3000 ms. Three runs of 57 trials each (43 targets and 14 non-targets) were separated by 30 second breaks, with pseudo-randomized order of non-targets. The dependent variable was the number of commission errors, reflecting impulse control.

2.4.3. Simple reaction time (RT) test

In this test of simple psychomotor speed designed after the basic reaction speed test of the Amsterdam Neuropsychological Tasks (ANT) battery (De Sonneville, 1999), participants were asked to respond as quickly as possible with a button press to a target stimulus on the center of the screen (a friendly looking monster). After a 12-trial practice session, 30 stimuli were presented for each hand consecutively, with variable inter-stimuli-intervals (ISI) between 500 and 1500 ms. The stimulus disappeared after a button press or after 1500 ms. Hand-order was counterbalanced, but only performance with the dominant hand was included in the present analysis. Dependent variables were median and standard deviation (SD) of the reaction time (RT).

2.4.4. Rey's auditory verbal learning test (RAVLT)

The RAVLT of verbal memory (RAVLT; Rey 1964; Dutch version; Saan and Deelman, 1986) consists of five acquisition or immediate free recall (IR) trials, a delayed free recall (DR) trial, and a recognition trial. During IR, a list of 15 unrelated nouns was read out loud five times. After each trial, the participant was asked to reproduce as many words as possible, resulting in a sum score of correct recalled items (IR: theoretical range of scores 0–75). Recall was repeated after a 20-minute delay (DR: theoretical range of scores 0–15). After DR 15 target and 15 non-target words were presented in a recognition trial (theoretical range of scores 0–30). Dependent variables were IR and DR.

2.4.5. Maudsley's index of delay aversion (MIDA)

The MIDA (Kuntsi et al., 2001) is a test of delay aversion. Participants were told they could win a small prize if they reached a high score. Although the target score was not defined, participants received information about the number of trials (20) and the number of possible points (1 or 2 for each trial). The original test duration was adjusted due to time constraints. Participants chose between waiting 0.5 s for 1-point (smaller sooner (SS) reward; instead of 2 s), and waiting 19.5 s for 2 points (larger later (LL) reward; instead of 30 s). The next trial started directly after responding. After the test, children could choose a small toy as a reward, adults could choose from candy and care products. The dependent measure was the percentage of choices for the LL reward. Because of time constraints, and leaving out this test was the longest it could not be administered during treatment (8weeks) and thus it is only assessed at pre and post measurement.

2.5. Statistical analyses

Our analyses focused on pre- to post-treatment performance in off-medicated state for those tasks that were affected by MPH treatment versus placebo at week 8. We used SPSS version 25.0 (SPSS/IBM 2013) for statistical testing and analyzed data intention-to-treat, using last observation carried forward (LOCF) for missing not at random data (MNAR). Extreme outliers were adjusted to the next extreme value plus one (Field, 2009), and data points missing at random (MAR) were imputed through regression imputation with the other neuropsychological variables, as well as treatment and age group as predictors. MAR data was not imputed when over ten percent of values was missing on a single test. For neuropsychological tests with normally distributed data, $2 \times 2 \times 2$ mixed factorial ANOVAs were executed with time as within-subjects factor, and treatment condition and age group as between-subject factors. First, we checked whether the MPH condition affected cognition (at week 8), for all tasks except the MIDA as this task was not administered at week 8. For this pre- to mid- comparison, we used α=0.05. Second, for the tasks that showed a treatment effect, and the MIDA, we assessed whether this effect outlasted MPH treatment (pre- vs post-treatment). Sensitivity analyses were run to assess the effect of prior treatment (also see Fig. 1) on our outcomes. Applying a Bonferroni correction for multiple testing in follow-up tests, we considered *p*-values for tests of between-subjects significant when $\alpha = 0.05$ divided by the number of relevant outcomes based on pre- to mid- comparisons. Additionally, Bayes factors for the mixed ANOVA were calculated using JASP with default priors. BF_{10} expresses the probability of the data given H1 (a difference between groups) relative to H0 (no difference between groups) BF_{01} expresses the probability of the data given H0 relative to H1 (please note that $BF_{01} = 1/BF_{10}$). Bayes factors larger than 3 can be interpreted as substantial or stronger evidence for either hypothesis (Lee and Wagenmakers, 2014). Data that was not normally distribution was analyzed with a Kruskall-Wallis test with four groups, with separate post-hoc Mann-Whitney U tests in the case of a significant effect.

3. Results

3.1. Participant characteristics

After randomization, one adult disclosed that he had been treated for ADHD with MPH before the age of 23. He was, therefore, excluded from the statistical analyses. One adult was included at age 22 years and 5 months at study entry. In total, the analyses included 98 participants who were randomly assigned to an MPH or placebo condition between June 1 2011, and February 6 2015, (boys $n = 25$ placebo and $n = 25$ MPH, men $n = 24$ placebo and $n = 24$ MPH) (Fig. 1). Two out of 48 adults had received treatment after the age of 23. All children were stimulant naive, and all but two adults were stimulant treatment naïve. These two adults received their first treatment after age 23. Boys and males assigned to the MPH and placebo condition did not differ with respect to age, estimated IQ, ADHD subtype, and symptoms of inattention, hyperactivity/impulsivity, oppositional defiant and conduct behavior, depression and anxiety (see Table 2 for pre-treatment characteristics). Furthermore, in boys and males, pre-treatment neuropsychological performance did not differ between treatment conditions.

A majority of males (65%) reported (a history of) recreational drug use of mainly cannabis, followed by MDMA/XTC (see Table 1), of whom 27% reported use for more than 5 years.

3.2. Study medication

Following optimal titration, at eight weeks after treatment commencement, children in the MPH condition had a mean

Table 1 Pre-treatment characteristics of boys and men randomized to MPH or placebo.

	MPH		Placebo		
Boys	*M (SD)*	*n*	*M (SD)*	*n*	Statistics[b]
Age	11.35 (0.83)	25	11.24 (0.93)	25	t (48) = 0.43, p = .67
IQ	105.68 (19.98)	25	103.35 (15.05)	23	U = 286.00, z = −0.031, p = .98
DBD					
Inatt[a]	21.68 (3.24)	25	22.72 (3.31)	25	U = 368.50, z = 1.09, p = .27
Hyp/Imp[a]	14.96 (4.98)	25	16.00 (6.49)	25	U = 391.50, z = 0.14, p = .89
ODD[a]	6.48 (5.68)	25	7.36 (5.52)	25	U = 345.50, z = 0.64, p = .52
CD[a]	1.28 (1.57)	25	3.20 (4.50)	25	U = 405.00, z = 1.85, p = .07
CDI	8.12 (4.55)	25	7.76 (4.29)	25	t (48) = 0.29, p = .78
SCARED	26.32 (17.13)	25	29.00 (16.82)	25	t (48) = −0.56, p = .58
DISK-P symptoms					
Inatt	7.80 (1.08)	25	7.68 (1.18)	25	*U = 298.00, z = −0.29, p = .77*
Hyp/Imp	4.64 (2.16)	25	4.64 (2.23)	25	*t (48) = −0.64, p = .53*
DISK-P subtype					
Inatt		14		14	
Hyp/Imp		0		1	
Combined		11		10	χ^2 (2, n = 50) = 1.05, p = .59
Men					
Age	28.01 (4.45)	24	28.90 (4.97)	24	U = 324.50, z = 0.75, p = .45
IQ	107.86 (8.75)	22	107.30 (6.81)	23	t (43) = 0.24, p = .81
ADHD-RS	30.60 (10.0)	24	30.40 (9.30)	24	t (46) = 0.07, p = .94
BDI	6.13 (5.30)	24	8.25 (5.97)	24	U = 356.50, z = 1.42, p = .16
BAI	9.08 (6.41)	24	9.00 (7.43)	24	U = 286.00, z = −0.04, p = .97
DIVA symptoms					
Inatt	8.13 (1.14)	23	7.81 (1.12)	21	*U = 196.50, z = −1.12, p = .26*
Hyp/Imp	5.22 (2.71)	23	6.67 (2.08)	21	*U = 315.50, z = 1.76, p = .08*
DIVA subtype					
Inatt		11		5	
Hyp/Imp		0		0	
Combined		13		19	χ^2 (1, n = 48) = 3.38, p = .07

Note: DISK-*P*=Diagnostic Interview Schedule for Children; DBD=Disruptive Behavior Disorders rating scale; Inattt=inattention; Hyp/Imp=hyperactive/impulsive; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder, CDI=Children's Depression Inventory Total Score; SCARED=Screen for Child Anxiety Related Emotional Disorders Total Score; DIVA= Diagnostic Interview for Adult ADHD; ADHD-RS=ADHD-Rating Scale; BDI=Beck Depression Inventory; BAI=Beck Anxiety Inventory.

[a] raw score

[b] independent samples *t*-test or Mann-Whitney test.

Table 2 Type and duration of recreational drug use in adults with ADHD (n = 48).

	MDMA/XTC	cocaine	amphetamine	cannabis
	n	*n*	*n*	*n*
No (<1 yrs)	31	38	38	22
Short (1-2 yrs)	6	2	4	3
Moderate (3-4 yrs)	4	2	3	10
Long (≥5 yrs)	7	6	3	13

Note: classification of duration following Young et al. (2015).

weight of 39 kg (SD = 7.2) and received a mean daily dosage of 31.3 mg (SD = 7.3), which was 83.9 kg (SD = 18.4) and 51.1 mg (SD = 9.8) in adults. At the end of the study, overall compliance in the MPH treated children was 84% (SD = 15), and 90% in the MPH treated adults (SD = 8). No serious (life threatening or requiring hospitalization) adverse events occurred in any of the subjects

3.3. Effects of MPH treatment in medicated state

Means and standard deviations of pre-treatment to on-medication performance are reported in Table 3. We compared pre-treatment performance to on-medication performance in week eight (RAVLT n = 87; n-back n = 86; simple RT n = 88; GNG n = 65) using mixed ANOVA to determine

Table 3 Means and standard deviations and results of pre-treatment to on-medication performance.

	Boys				Male adults			
	MPH		Placebo		MPH		Placebo	
	pre *M (SD)*	during *M (SD)*	pre *M (SD)*	during *M (SD)*	pre *M (SD)*	during *M (SD)*	pre *M (SD)*	during *M (SD)*
n-back difference score	11.32 (8.78)	5.36 (5.74)	10.72 (6.61)	11.20 (6.28)	8.71 (5.66)	9.88 (8.14)	8.92 (7.73)	7.17 (6.69)
Go/No-Go commission errors	18.33 (4.72)	21.12 (8.37)	18.32 (5.51)	22.94 (7.69)	29.48 (5.18)	33.21 (5.73)	26.20 (6.03)	32.18 (5.70)
Simple RT test median RT	279.26 (39.45)	257.26 (25.36)	282.48 (29.14)	290.88 (42.48)	262.17 (32.57)	261.35 (30.59)	251.81 (37.51)	247.54 (29.68)
Simple RT test SDRT	88.52 (40.64)	64.64 (22.83)	86.09 (29.49)	100.05 (49.40)	64.18 (26.06)	63.53 (27.73)	58.52 (31.99)	70.64 (60.16)
Short-term episodic memory	42.28 (9.31)	49.80 (6.73)	41.36 (7.85)	47.08 (8.38)	46.57 (9.08)	53.39 (9.62)	46.62 (8.47)	51.04 (9.29)
Delayed episodic memory	8.68 (2.25)	10.72 (1.72)	8.68 (1.99)	10.12 (2.05)	9.65 (2.42)	11.96 (2.16)	9.58 (2.38)	10.92 (2.08)

Results mixed ANOVAs

	Time		time * treatment		time * treatment * age	
	F	η_p^2	*F*	η_p^2	*F*	η_p^2
n-back difference score	F (1, 94) = 2.26	0.23	F (1, 94) = 0.76	0.01	**F (1, 94) = 5.39***	**0.05**
Go/No-Go commission errors	**F (1, 74) = 20.52*****	**0.25**	F (1, 74) = 1.28	0.02	F (1, 74) = 0.12	0
Simple RT test median RT	F (1, 94) = 2.2	0.02	F (1, 94) = 4.60*	0.05	**F (1, 94) = 7.27****	**0.07**
Simple RT test SDRT	F (1, 94) = 0.007	0	**F (1, 94) = 8.00****	**0.08**	F (1, 94) = 1.96	0.02
Short-term episodic memory	**F (1, 93) = 68.19*****	**.42**	F (1, 93) = 2.02	.02	F (1, 93) = 0.42	0
Delayed episodic memory	**F (1, 93) = 85.08 *****	**0.48**	F (1, 93) = 4.15*	0.04	F (1, 93) = 0.23	0

Results Bayes mixed ANOVA

	time		time*treatment		time*treatment*age	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}
n-back difference score	0.54	1.86	0.32	3.13	**6**	0.17
Go/No-Go commission errors	**404.26**	0.002	0.32	3.14	0.29	3.5
Simple RT test median RT	0.40	2.52	1.73	0.58	**5.71**	0.18
Simple RT test SDRT	0.15	6.67	**8.01**	0.13	0.70	1.44
Short-term episodic memory	**7.48E+09**	1.34E-10	0.48	2.07	0.33	3
Delayed episodic memory	**4.28E+11**	2.34E-12	1.30	0.77	0.29	3.5

Note: SDRT=standard deviation of reaction times, LL= larger later reward.

*$p < .05$ ** $p < .01$ *** $p < .001$, BF_{10} expresses the probability of the data given H1 relative to H0, BF_{01} expresses the probability of the data given H0 relative to H1. NB due to time constraints the MIDA was not administered at the 8-week assessment.

the acute effects of MPH on cognitive functions (for results see Table 3). There was a main effect of medication treatment in that MPH treatment improved performance on median and SD RT on the simple RT task. In addition, a group*treatment effect was found, MPH improved performance of children, but not adults, on the *n*-back test and median RT of the simple RT task. Analysis of the RAVLT IR and GNG tests merely yielded treatment unspecific improvement in performance over sessions (practice effects). Bayes analyses confirm frequentist results (See Table 3). Therefore, subsequent analyses on post treatment performance will be performed on median and SD RT of the simple RT task and accuracy on the *n*-back test.

3.4. Effects of MPH treatment in off-medicated state

Means and standard deviations of pre- and post- treatment performance are reported in Table 4. MIDA data did not follow a normal distribution, therefore a Kruskall-Wallis test was performed. MNAR data was imputed for $n = 2$ children in the MPH condition, $n = 2$ adults in the MPH condition, and $n = 3$ adults in the placebo condition. Seven extreme outliers were adjusted (median RT $n = 1$, SDRT $n = 1$, *n*-back $n = 5$). Following technical difficulties or missing data on both time points, MAR data was not imputed for the MIDA, resulting in different sample sizes for these tests (MIDA boys MPH $n = 24$, placebo $n = 25$, and adults MPH $n = 20$, placebo $n = 19$).

Separate mixed ANOVA's (reported in Table 4) yielded main effects of time, indicating significant improvement from pre- to post-treatment in working memory (*n*-back) performance, but not in reaction time (log-transformed median RT and SDRT). Bayes factors (also see Table 4) support these results. No significant time*treatment or time*age*treatment interactions were observed for any of the outcomes. Bayes factors for RT SD and median do not give clear evidence for either H1 or H0 for working memory The BF_{01} shows strong evidence that our data are more likely to be observed under the null hypothesis (BF_{01}=15.12). Thus, children and adults across treatment conditions showed comparable pre-post treatment differences, indicating no age independent and age-related lasting effects of MPH treatment. A Kruskall-Wallis test showed that age or treatment group membership also did not affect pre- to post-treatment differences on the MIDA ($H(3) = 3.41$, $p = .33$).

Sensitivity analyses showed that imputing the age groups' median scores for MNAR, instead of LOCF imputation, yielded comparable results. In addition, excluding adults with ADHD who reported prior stimulant treatment after the age of 23 ($n = 2$) did not alter the findings.

4. Discussion

In order to determine whether MPH for ADHD has age-modulated lasting effects on cognitive functioning, boys and male adults with ADHD were randomized to 16 weeks of treatment with MPH or placebo in a randomized, double-blind trial. Participants were stimulant treatment naïve before treatment. MPH shortened RT, made RT less variable and improved working memory performance in week 8 on medication. In contrast to our hypotheses, we found no lasting effects after 16 weeks of MPH treatment over placebo on any of the administered tests in boys or men. Bayes factors show that our data concerning treatment and age effects are more likely to occur under the null hypothesis, i.e., we found substantial to decisive evidence pointing to no difference between placebo or MPH treatment, and no differential effect in boys vs. males. Thus, this RCT shows that 16 weeks of clinical MPH treatment temporarily improved RT and working memory, but this effect did not last beyond MPH treatment in boys and males with ADHD.

Studies reporting long-term effects of MPH on cognition (e.g. Rubio Morell and Hernandez Exposito, 2017) are often performed with subjects on-medication, making it difficult to distinguish between lasting effects or transient effects of MPH treatment. Previously, naturalistic studies already indicated the transient nature of MPH on cognition (Schweren et al., 2019), but we are the first RCT study showing these effects are indeed directly transient in nature. Although previous studies have indicated lasting effects of MPH on brain structure (Nakao et al., 2011; Schweren et al., 2016; Shaw et al., 2009; Sobel et al., 2010), these naturalistic studies looked at longer term effects (i.e., naturalistic treatment is often longer than treatment under trial conditions) of MPH. Also our analysis on brain and sleep outcomes in the same participants, showed lasting and age-dependent (developmental) effects on blood flow in the striatum and thalamus after a dopamine challenge (Schrantee et al., 2016), white matter structure (Bouziane et al., 2019), and sleep (Solleveld et al., 2020). Surprisingly, however, we do not find any lasting effects on cognition, while in traditional models of neuropsychological functioning, cognition is hypothesized to be intermediate between brain and behavior. Possibly, although we chose well validated tasks that were sensitive to detecting cognitive deviations in ADHD, the tasks used might not be sensitive enough to detect these changes in brain activation (as reported in (Schrantee et al., 2016)& (Bouziane et al., 2019)), or other cognitive functions than assessed in the current study are underlying changes in behavior. Moreover, possibly changes in brain activation take time to fully be expressed in brain function, as suggested by the neuronal imprinting theory (Andersen, 2005; Andersen and Navalta, 2004). This theory predicts that early drug exposure (during brain development) is only fully expressed in early adulthood. This could indicate that a longer follow-up of the current sample could reveal long term effects of MPH on cognition.

The observed lack of lasting effects of a short MPH treatment should be interpreted with care. Firstly, we suspect a ceiling effect in our measure (MIDA) of delay aversion, leaving very little room for improvement in both boys and males. This could be due to our shortening of the delay time (i.e., from 30 to 19.5 s) making waiting for a larger reward less tedious, although a previous study, using the original waiting period, also reported ceiling effects in this test (Marco et al., 2009). Furthermore, MPH medication was titrated on clinical guidance, increasing the dosage up to the point when behavioral improvement comes to a halt, or adverse effects occur. The average dosage for boys and men in the present study falls within the range of dosages

Table 4 Means and standard deviations and results of pre-treatment to post-treatment performance.

	Boys				Male adults			
	MPH		Placebo		MPH		Placebo	
	pre *M (SD)*	post *M (SD)*	pre *M (SD)*	post *M (SD)*	pre *M (SD)*	post *M (SD)*	pre *M (SD)*	post *M (SD)*
n-back difference score	11.32 (8.78)	4.60 (4.56)	10.72 (6.61)	6.76 (6.72)	8.71 (5.66)	7.13 (5.88)	8.92 (7.73)	6.38 (6.39)
Simple RT test median RT	279.26 (39.45)	283.36 (40.48)	282.48 (29.14)	287.06 (28.85)	262.17 (32.57)	257.00 (28.27)	251.81 (37.51)	259.56 (30.53)
Simple RT test SDRT	88.52 (40.64)	88.77 (36.42)	86.09 (29.49)	84.05 (51.35)	64.18 (26.06)	57.18 (23.01)	58.52 (31.99)	67.55 (41.22)
Maudsley's Index of Delay Aversion% LL	91.23 (9.91)	87.29 (13.48)	90.01 (11.63)	87.24 (14.95)	93.50 (10.53)	89.93 (15.08)	95.92 (9.69)	94.63 (13.55)

Results mixed ANOVAs

	Time		time * treatment		time * treatment * age	
	F	η_p^2	*F*	η_p^2	*F*	η_p^2
n-back difference score	$F(1, 94) = 15.00^{**}$	0.14	$F(1, 94) = 0.22$	0.01	$F(1, 94) = 0.95$	0.01
Simple RT test median	$F(1, 94) = 1.11$	0.01	$F(1, 94) = 1.52$	0.02	$F(1, 94) = 1.28$	0.01
Simple RT test SD	$F(1, 94) = 0.09$	0.01	$F(1, 94) = 0.26$	0.01	$F(1, 94) = 2.81$	0.03

Results Bayes mixed ANOVA

	time		time*treatment		time*treatment*age	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}
n-back difference score	469.89	0.002	0.24	4.24	0.07	15.12
Simple RT test median RT	0.25	3.94	0.44	2.28	0.36	2.76
Simple RT test SD	0.17	6.06	0.29	3.44	1.38	0.72

Results Kruskall-Wallis test

	age * treatment group	
	H	*p*
Maudsley's Index of Delay Aversion% LL	(3) = 3.41	.33

Note: SD=standard deviation of reaction times, LL= larger later reward.

$^{*}p < .05$ (non-significant after bonferoni correction); $^{**}p < .01$ (significant after correction), $^{***}p < .001$ (significant after correction), BF10 expresses the probability of the data given H1 relative to H0, BF_{01} expresses the probability of the data given H0 relative to H1.

in previous clinical RCTs with MPH (for an overview see Castells et al., 2011; Tamminga et al., 2016). However, some cognitive functions (e.g., inhibition) show optimal improvement after moderate dosage and detrimental effects at a high dosage (an inverted-U shape), while others (e.g., working memory and attention) seem to be characterized by a linear dose-response relationship (Konrad et al., 2004, 2005; Tannock et al., 1995). In the current study, the average daily dose in children was moderate. Indeed, we observed acute treatment effects on working memory and response speed, but not on inhibition or episodic memory. Therefore, our results are generalizable to dosages applied in clinical practice, but do not rule out that with higher dosages, that are not often given in clinical practice, lasting effects could occur. Summarizing, observed lack of lasting effects on reward sensitivity could be due to ceiling effects, whereas the lack of effect on impulsivity may follow from clinical titration procedures.

The study has three major strengths. The first is its randomized, double-blind, placebo-controlled design. The few studies considering lasting (short- to longer-term) effects of stimulants have a naturalistic nature, whereas randomization is essential to determine causality of effects. Also, our analyses of brain and sleep outcomes in the same participants (Schrantee et al., 2016; Solleveld et al., 2020), suggest that our 'manipulation' was sufficient/ did have the potential to induce off-medication changes. The present study, therefore, adds to previous work on the potentially lasting effects of MPH on the brain, showing that the effects of MPH on working memory, and response speed are limited to the moment of treatment. Furthermore, Bayesian statistics provided us with the opportunity to draw conclusions about the probability of the null hypothesis that the frequentist analyses could not, and showed that there was indeed evidence for the null hypothesis. Third strength is that MPH was titrated in children and adults until the balance between behavioral symptoms and side-effects was clinically optimal, as is described in international guidelines (Kooij et al., 2010; National Collaborating Centre for Mental Health 2009) and compliance was high. Thus, the results following from this approach can be easily generalized to clinical practice.

Next to strengths, our results should be interpreted in the light of some limitations. One might argue that treatment duration, 16 weeks, is insufficient to yield cognitive alterations. Sixteen weeks was the typical waiting time for treatment in the Netherlands at the start of the study, and withholding treatment in a placebo condition for a longer period of time would have evidently been unethical. Second, only males with normal intellectual ability (IQ>80) were included, lowering the generalizability of our results. Furthermore, due to time- as well as burden constraints, we did not have the opportunity to test all potentially relevant cognitive domains. However, our careful selection of cognitive domains should have grasped the potentially widespread effects of MPH. A general point of discussion is the stimulant medication naivety in adults with ADHD, i.e., inclusion of stimulant medication naïve adults with ADHD in research is troublesome. In the present study, all but two of the adults were stimulant medication naïve, however, many had used recreational drugs, which is inherently related to ADHD (Groenman et al., 2017). Recreational drug use did not change during treatment. Furthermore, the proportion of lifetime recreational stimulant use (Cocaine, MDMA, XTC) did not differ between the placebo and treatment groups. Additionally, we did not we did not note any changes in the dopamine reactivity of the adults, while this is commonly seen in recreational stimulant users (for example see (Schrantee et al., 2015)). Therefore, we feel that recreational drug use did not affect our main pattern results. Eventhough these issues which concern the adult subjects only, could not account for the presently observed absence of lasting MPH effects in children, they offer a general challenge in the field of adult ADHD research.

Overall, the results from the present randomized, placebo-controlled trial show that the effects of MPH on working memory, and response speed are limited to the moment of treatment, in both boys and men. As no deterioration or enhancing cognitive effects of 16 weeks of MPH treatment, prescribed following clinical guidelines, were observed, the results of this study could be reassuring to parents and therapists of patients.

Contributors

	HGHT	LR	AS	MAB	CB	HMG	APG
Study design		x		x		x	
Collecting data	x		x		x		
Drafting first version manuscript	x						
Drafting subsequent versions manuscript							x
Data analysis	x						x
Funding		x				x	
Input on the manuscript and reviewing its intellectual content	x	x	x	x	x	x	x
Final approval of the manuscript	x	x	x	x	x	x	x

Conflicts of Interest

None.

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