Cognition and comorbidity in ADHD: The role of methylphenidate and development
Tamminga, G.H.

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CHAPTER 5

DIFFERENCES IN PERSISTENT EFFECTS OF METHYLPHENIDATE ON COGNITION IN CHILDREN AND ADULTS?
A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

ABSTRACT

Objective MPH is the first-choice pharmacological treatment for treatment of ADHD across the lifespan. It is important to determine whether stimulant treatment during development has a differential persistent effect on cognition for children and adults with ADHD, as little is known of the effect of MPH on the developing brain.

Method We assessed the age-modulated effects of MPH on cognitive functioning in a randomized, placebo-controlled trial. Boys aged 10 to 12 years and men aged 23 to 40 years with ADHD were randomly assigned to 16 weeks of MPH (boys \( n = 25 \), men \( n = 24 \)) or placebo (boys \( n = 25 \), men \( n = 24 \)). Outcome measures were neuropsychological tests of visuo-spatial working memory, response inhibition, response speed, episodic memory, and delay aversion. Tests performance pre- and post-treatment (following a one-week wash-out) was compared between age and treatment conditions with repeated measures ANOVAs.

Results Regardless of treatment condition, children and adults improved on tests of working memory and episodic memory, but not response inhibition, response speed and delay aversion. While MPH and placebo treated conditions were comparable in change from pre- to post-treatment, exploratory analyses confirmed the acute positive effects of MPH relative to placebo. We observed no interaction between age and treatment group.

Conclusion These findings suggest an absence of either positive or negative persistent effects of 16 weeks of MPH treatment on cognitive functioning in boys and males with ADHD. Hence, while MPH does have a clear acute effect on cognition, these effects seem to be transient in adults as well as children, suggesting no age-related modulation of MPH effects.
INTRODUCTION

ADHD is a neurodevelopmental disorder with an estimated prevalence of approximately 5 to 9% in children (Akinbami, Liu, Pastor, & Reuben, 2011; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and 1 to 7% in adults (Fayyad et al., 2007). Pharmacological treatment with psychostimulants, such as MPH, has positive short-term consequences for children and adults with ADHD, such as improving behavioural symptoms of inattention and/or hyperactivity/impulsivity, as well as cognitive functioning (Castells et al., 2011; Coghill et al., 2013; Faraone & Buitelaar, 2010; Tamminga, Reneman, Huizenga, & Geurts, chapter 3; van der Oord et al., 2008). However, the human brain continues to mature throughout childhood and adolescence (Giedd & Rapoport, 2010), and experience and environmental conditions can affect development positively or negatively (Fox, Levitt, & Nelson, 2010). Thus, chronic use of stimulants might also influence brain development, as is suggested by, for instance, a different rate of cortical thinning in medicated versus stimulant naïve adolescents with ADHD (Shaw et al., 2009).

Several animal studies have shown that the brain reacts to chronic administration of drugs with neuroadaptive processes (Andersen & Navalta, 2004). Also in humans, imaging studies have demonstrated stimulant treatment-associated normalization of brain structure and function (Frodl & Skokauskas, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Wang et al., 2013). However, whereas studies on the potential long-term effects of stimulants have a high clinical relevance, few such studies exist. Moreover, a lack of randomization or an untreated control group within these studies prevents causal inferences. For example, significant improvement in impulsivity or IQ in children with ADHD who were tested off-medication after 12 months of treatment was observed in two studies lacking an untreated control group, hampering the distinction between treatment induced normalization, and test-retest effects or expected development (Aggarwal & Lillystone, 2000; Huang, Wang & Chen, 2012; Tsai et al., 2013). Furthermore, a history of pharmacological treatment for ADHD was associated with higher levels of academic performance in adolescence (Powers, Marks, Miller, Newcorn, & Halperin, 2008) a lower risk of substance use disorders (Mannuzza et al., 2008; Wilens et al., 2003), and a superior occupational outcome (Halmoy, Fasmer, Gillberg, & Haavik, 2009). Regarding cognition, children with a history of medication use revealed superior inhibition and attention relative to stimulant naïve children (Semrud-Clikeman, Pliszka & Liotti, 2008), whereas adults with childhood ADHD performed similar on tests of attention, working memory and learning regardless of treatment history (Stoy et al., 2011). Together, this might imply that the effects of stimulants...
on cognition extend beyond treatment, but dissolve on the long-term. However, due
to the naturalistic study designs, pre-existent between-subject differences might also
account for these findings. In general, limited long-term effects of stimulants on
cognition and behaviour are concluded, as few children remain symptom or deficit free
after extended treatment (Halperin & Healey, 2011; van de Loo-Neus, Rommelse &
Buitelaar, 2011). One randomized trial, however, actually studied the effects of chronic
treatment on behaviour and impairment (MTA study; The MTA Cooperative Group,
1999). After an initial trial of 14 months, participants were free to extend or change
treatment. Directly after treatment (at 14 months) as well as one year later, superior
behavioural effects of the two structured medication conditions over behavioural
treatment or community care were observed. However, at six years, stimulant use
was associated with worse behavioural symptoms and impairment, which could be
due to the self-selection of treatment after the trial, whereas at eight years, no initial
randomization effects were observed anymore (Molina et al., 2009). Unfortunately,
cognitive functioning was not studied in the MTA study. Furthermore, studying off-
treatment functioning and the role of age in the effect modification of persistency was
not the focus of the MTA study. Thus, to date, the question whether the cognitive
effects of stimulants persist beyond treatment, and whether this persistency of effects
differs for children and adults with ADHD, remains unanswered.

In the present study, children and adults with ADHD were assessed with
neuropsychological tests, before randomized treatment with MPH or placebo for 16
weeks, and after treatment, following a wash-out period of one week. We hypothesized
that persistent (off-medication) effects of stimulants would be marked by a larger pre- to
post-treatment difference in the active treatment condition as compared to the placebo
condition. Additionally, larger cognitive improvement due to MPH in children than in
adults would suggest that effects are developmentally driven. We expected persistent
effects of MPH on prepotent response inhibition and response speed, as acute effects of
MPH on these functions are moderate and consistent (Coghill et al., 2013; Tamminga
et al., chapter 3). In addition, a small effect was expected for episodic memory, as
memory functions are mediated by executive functions (Andersen, Egeland, & Oie,
2013), on which MPH is hypothesized to have the largest effect. With this unique
design, the present study provides insight into the effects of stimulant treatment on the
development of cognition in children with ADHD.
METHODS

Participants

The present study is part of a multicentre, randomized, double-blind, placebo-controlled, parallel-group study (ePOD-MPH; for details see Bottelier et al., 2013). The ePOD-MPH study was approved by the CCMO (NL34509.000.10), and subsequently registered at the NTR (NTR3013). All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Inclusion criteria were meeting criteria for an ADHD diagnosis (IT, HI or CT), determined by an experienced clinician based on the DSM-IV-TR (APA, 2000), which was confirmed with a (semi-)structured interview (NIMH DISC-IV [Ferdinand & Van der Ende, 1998] in children and the DIVA [Kooij & Francken, 2010] in adults). At least 6 of 9 symptoms of inattention or hyperactivity/impulsivity needed to be present in children and adults. Participants were not eligible when they had received clinical treatment influencing the DA system (for adults before 23 years of age), 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 23 years of age), such as: MDMA, amphetamine, methamphetamine, cocaine, heroin and LSD. As ADHD is more prevalent in males as compared to females, only males were included to reduce heterogeneity (Boyle et al., 2011; Faraone & Biederman, 2005). Furthermore, exclusion criteria were an estimated IQ < 80 and/or a history of major medical or neurological trauma or illness. IQ was estimated in children with the Block Design and Vocabulary subtests of the WISC-III-R (Kort et al., 2002), and in adults with the DART (Schmand, Lindeboom, & van Harskamp, 1991). Based on these inclusion criteria, finally 50 boys aged 10-12 years and 48 men aged 23-40 years with ADHD were included (for further details see results section).

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, participants aged 12 years or older gave written informed consent, as did caregivers in the case of children. Additionally, children younger than 12 years gave verbal informed consent. In- and exclusion criteria were checked at study entry. At the pre-treatment assessment, participants were randomly assigned to MPH or placebo treatment lasting
16 weeks (participants, caretakers, treating clinician and investigators were all blinded). In week 17, following a wash-out period of one week, participants were re-assessed while off-medication. Assessment with neuropsychological tests occurred in a counterbalanced fashion and lasted one hour.

**Treatment**

Patients were randomly assigned to either MPH or placebo treatment. During pharmacological treatment, adult participants and parents of children received psycho-education and supportive coaching regarding stimulant use. Medication was titrated to an optimal dose (on clinical guidance) under double-blind conditions by the treating physician (MB, CB), in accordance with Dutch treatment guidelines. 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 GMP guidelines (Slotervaart Hospital, Amsterdam, the Netherlands). Labelling was according to European standards, as defined in the guideline Good Manufacturing Practice (2003/94/EG). Compliance to the study medication was monitored at each of 5 control visits (at 1, 2, 3, 5, 8 and 12 weeks after treatment start).

**Materials**

*N-back* – The n-back test of visuo-spatial working memory (van Leeuwen, van den Berg, Hoekstra, & Boomsma, 2007; designed after Gevins & Cutillo, 1993) has three conditions with increasing difficulty. Each condition contained 32 consecutive trials, in which a target (caterpillar) appeared in one of four locations (holes in an apple, see Figure 5.1). Each target (2000 ms) was followed by a beep, which was the probe to indicate where the target was seen one, two or three trials ago, depending on the condition (1-back, 2-back, and 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 sequence was repeated after 3000 ms. Participants practiced each condition, until they clearly understood the task. The number of correct responses for each condition could theoretically range between 0 and 32. The dependent variable was the difference in accuracy between the two highest achieved conditions, with higher scores demonstrating a decline in performance at increasing complexity.

*Go/No-Go test* – An adaptation of the GNG test of psychomotor inhibition (Durston, Thomas, Worden, Yang, & Casey, 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 inter-stimuli-interval (ISI) was 3000 ms. Three blocks of 58 trials each (43 targets
and 15 non-targets) were separated by 30 second breaks, with pseudorandomized order of non-targets. The dependent variable was the number of commission errors, reflecting impulse control.

**SRT** - In this test of simple psychomotor speed designed after the ANT BS (de Sonneville, 1999), participants were asked to respond as quickly as possible with a button press to a target stimulus on the centre of the screen (a friendly looking monster). After a 12 trial practice session, 30 stimuli were presented for each hand consecutively, with variable ISIs 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).

**RAVLT** – The RAVLT (Saan & Deelman, 1986) consists of five acquisition or IR trials, a 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.

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**Figure 5.1** Schematic presentation of the *n*-back test. The sequence of correct responses is depicted from bottom to top.

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Maudsley’s Index of Delay Aversion - The MIDA (Kuntsi, Oosterlaan, & Stevenson, 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). Due to time constraints, test duration was adjusted, so that participants chose between waiting 0.5 s for 1 point (instead of 2 s; smaller sooner (SS) reward), and waiting 19.5 s for 2 points (instead of 30 s; larger later (LL) reward). The next trial started directly after each response. After the test, all participants could choose a small prize. The dependent measure was the percentage of choices for the LL reward.

Data imputation and statistical analyses

We used SPSS version 22.0 (SPSS/IBM 2013) for statistical testing and analysed data intention-to-treat, using last observation carried forward (LOCF) for missing not at random data (MNAR; \( n = 7 \) in total, with \( n = 2 \) children in the MPH condition, \( n = 2 \) adults in the MPH condition, and \( n = 3 \) adults in the placebo condition). After adjusting extreme outliers to the next highest value plus one (Field, 2009; median SRT \( n = 1 \), SD SRT \( n = 1 \), RAVLT DR \( n = 1 \)), 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 task, or when data on both time points was missing, resulting in different sample sizes for the GNG and MIDA. One adult participant was not tested with the RAVLT because of insufficient command of the Dutch language. For neuropsychological tests with normally distributed data, repeated-measures ANOVAs were executed with time (pre- or post-treatment) as within-subjects factor, and treatment condition (MPH or placebo) and age group (boys or men) as between-subjects factors. Seven pre-defined dependent variables were included: RAVLT IR and DR, \( n \)-back difference in accuracy between the two highest achieved conditions, median RT and SDRT on the SRT test, MIDA % LL, and GNG commission errors. \( p \)-values were Bonferroni corrected to account for multiple comparisons and effect sizes were expressed as partial eta squared. Data for which transformation did not yield a near-normal distribution, was analysed with a Kruskall-Wallis test with four groups, with separate post-hoc Mann-Whitney U tests in the case of a significant effect.
RESULTS

Participant characteristics

Pre-treatment neuropsychological performance was described elsewhere (Chapter 2). Ninety-eight participants were randomly assigned to a MPH or placebo condition (received treatment: boys $n = 25$ placebo, $n = 25$ MPH, men $n = 24$ MPH and $n = 24$ placebo). For pre-treatment characteristics of each treatment and age group see Table 5.1. One adult was aged 22 years and 5 months at study entry. Boys in the MPH and placebo condition did not differ with respect to age, estimated IQ, inattentive, hyperactive/impulsive, ODD and CD symptoms, and depressive and anxiety symptoms. Also, male adults in the two treatment conditions did not differ in the descriptive variables. MPH and placebo treated conditions did not differ in neuropsychological performance pre-treatment.

All children were stimulant naïve. Forty-six adults did not receive any stimulant treatment, but two adults had received stimulant treatment after the age of 23. Many adults (65%) did, however, report (a history of) recreational drug use of mainly cannabis, followed by MDMA/XTC (see Appendix 5.1 for the self-reported duration of drug use). In order to evaluate the effects of chronic MPH in stimulant treatment-naïve participants only, we analysed the data both with and without the two previously treated adults.

Study medication

Following optimal titration, at eight weeks after treatment commencement, children in the MPH condition had a mean weight of 39 kg ($SD = 7.2$) and received a mean daily dosage of 31.3 mg ($SD = 7.3$), which was 83.7 kg ($SD = 18.7$) and 51.6 mg ($SD = 9.7$) in adults. At the end of the study, overall compliance in the MPH treated children was 83.6% ($SD = 15.6$), and 90.8% in the MPH treated adults ($SD = 7.8$).

Main study findings: off-medication effects of MPH treatment

Means and standard deviations of age- and treatment groups on neuropsychological tests are reported in Table 5.2. Applying a Bonferroni correction for multiple testing in follow-up tests, we considered $p$-values for tests of between-subjects significant when $\alpha \leq .007$ ($\alpha = .05 / 7$ dependent variables). Separate repeated-measures ANOVA’s yielded main effects of time, indicating general improvement from pre- to post-treatment, on the RAVLT IR ($F(1, 93) = 183.94, p < .001, \eta^2_p = .66$), RAVLT DR ($F(1, 93) = 94.23, p < .001, \eta^2_p = .50$), and n-back ($F(1, 94) = 15.00, p = .001, \eta^2_p = .14$), but not on log-transformed median RT ($F(1, 94) = 1.11, p = .30, \eta^2_p = .01$), log-transformed SDRT ($F(1, 94) = 0.09, p = .76, \eta^2_p < .01$), and GNG commission
Table 5.1 Pre-treatment characteristics

<table>
<thead>
<tr>
<th></th>
<th>MPH</th>
<th>Placebo</th>
<th>Statisticsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>11.35 (0.83) 25</td>
<td>11.24 (0.93) 25</td>
<td>$t(48) = 0.43, p = .67$</td>
</tr>
<tr>
<td>IQ</td>
<td>105.68 (19.98) 25</td>
<td>103.35 (15.05) 23</td>
<td>$U = 286.00, z = -.031, p = .98$</td>
</tr>
<tr>
<td>DISC-P Inatt</td>
<td>7.80 (1.08) 25</td>
<td>7.68 (1.18) 25</td>
<td>$U = 298.00, z = -.29, p = .77$</td>
</tr>
<tr>
<td>DISC-P Hyp/Imp</td>
<td>4.64 (2.16) 25</td>
<td>4.64 (2.23) 25</td>
<td>$t(48) = -.64, p = .53$</td>
</tr>
<tr>
<td>DBD Inatt</td>
<td>21.68 (3.24) 25</td>
<td>22.72 (3.31) 25</td>
<td>$U = 368.50, z = 1.09, p = .27$</td>
</tr>
<tr>
<td>DBD Hyp/Imp</td>
<td>14.96 (4.98) 25</td>
<td>16.00 (6.49) 25</td>
<td>$U = 391.50, z = 0.14, p = .89$</td>
</tr>
<tr>
<td>DBD ODD</td>
<td>6.48 (5.68) 25</td>
<td>7.36 (5.52) 25</td>
<td>$U = 345.50, z = 0.64, p = .52$</td>
</tr>
<tr>
<td>DBD CD</td>
<td>1.28 (1.57) 25</td>
<td>3.20 (4.50) 25</td>
<td>$U = 405.00, z = 1.85, p = .07$</td>
</tr>
<tr>
<td>CDI</td>
<td>8.12 (4.55) 25</td>
<td>7.76 (4.29) 25</td>
<td>$t(48) = .29, p = .78$</td>
</tr>
<tr>
<td>SCARED</td>
<td>26.32 (17.13) 25</td>
<td>29.00 (16.82) 25</td>
<td>$t(48) = -.56, p = .58$</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>28.01 (4.45) 24</td>
<td>28.90 (4.97) 24</td>
<td>$U = 324.50, z = 0.75, p = .45$</td>
</tr>
<tr>
<td>IQ</td>
<td>107.86 (8.75) 22</td>
<td>107.30 (6.81) 23</td>
<td>$t(43) = 0.24, p = .81$</td>
</tr>
<tr>
<td>DIVA Inatt</td>
<td>8.13 (1.14) 23</td>
<td>7.81 (1.12) 21</td>
<td>$U = 196.50, z = -1.12, p = .26$</td>
</tr>
<tr>
<td>DIVA Hyp/Imp</td>
<td>5.22 (2.71) 23</td>
<td>6.67 (2.08) 21</td>
<td>$U = 315.50, z = 1.76, p = .08$</td>
</tr>
<tr>
<td>ADHD-RS</td>
<td>31.75 (9.92) 24</td>
<td>31.13 (9.67) 24</td>
<td>$t(46) = 0.22, p = .83$</td>
</tr>
<tr>
<td>BDI</td>
<td>6.13 (5.30) 24</td>
<td>8.25 (5.97) 24</td>
<td>$U = 356.50, z = 1.42, p = .16$</td>
</tr>
<tr>
<td>BAI</td>
<td>9.08 (6.41) 24</td>
<td>9.00 (7.43) 24</td>
<td>$U = 286.00, z = -0.04, p = .97$</td>
</tr>
</tbody>
</table>

Note: DISC-P=Diagnostic Interview Schedule for Children; DBD=Disruptive Behavior Disorders rating scale; Inatt=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
errors ($F(1, 74) = 5.18, p = .03, \eta_p^2 = .07$). No enduring effects of MPH as compared to placebo treatment were observed, as indicated by a lack of time * treatment interactions (RAVLT IR $p = .11, \eta_p^2 = .03$; RAVLT DR $p = .22, \eta_p^2 = .02$; n-back $p = .64, \eta_p^2 < .01$; GNG $p > .99, \eta_p^2 < .01$, median RT $p = .22, \eta_p^2 = .02$, SDRT $p = .75, \eta_p^2 < .01$). Furthermore, the interaction time * age * treatment was not significant for any neuropsychological measure, thus, children and adults across treatment conditions showed comparable pre-post treatment differences (RAVLT IR $p = .46, \eta_p^2 < .01$; RAVLT DR $p = .59, \eta_p^2 < .01$; n-back $p = .33, \eta_p^2 = .01$; GNG $p = .89, \eta_p^2 < .01$, median RT $p = .26, \eta_p^2 = .01$, SDRT $p = .10, \eta_p^2 = .03$). Also, a Kruskall-Wallis test of pre- and post-treatment differences revealed that change in MIDA performance was not significantly affected by age or treatment group membership ($H(3) = 3.41, p = .33$). Imputing the median of age groups for MNAR, instead of LOCF imputation, or excluding adults with ADHD who reported more than 3 clinical doses of prior stimulant treatment after the age of 23 ($n = 2$) did not alter the findings.

**Exploratory analyses**

One could argue that an absence of persistent effects of MPH on cognition in children is to be expected if treatment did not yield acute effects on cognition. As most of the participants were also assessed 8-weeks into treatment, we explored treatment effects by comparing pre- to peri-treatment performance on the RAVLT ($n = 87$), n-back ($n = 86$), SRT ($n = 88$), and GNG test ($n = 65$). Positive treatment effects of MPH as compared to placebo were observed in both age groups on the RAVLT DR (time * treatment, $p < .05, \eta_p^2 = .05$) and median RT (time * treatment, $p = .01, \eta_p^2 = .07$), whereas the RAVLT IR and GNG but not SDRT merely yielded age and treatment unspecific improvement in performance over time (practice effects). Positive treatment effects of MPH as compared to placebo were observed for children, but not adults, on the n-back test (time * treatment * age, $p = .02, \eta_p^2 = .07$). At baseline, children’s performance declined substantially with increasing test difficulty, whereas room for improvement was smaller in adults. The lack of response to MPH in the adult group seems to follow from this ceiling effect.

Since the acute effects of MPH on cognition are generally smaller than acute effects on behaviour (Faraone & Buitelaar, 2010; Tamminga, Reneman, Huizenga, & Geurts, chapter 3), we explored whether improvement of inattentive and hyperactive/impulsive symptoms was persistent for children on the DBD (Oosterlaan, Scheres, Antrop, Roeyers, & Sergeant, 2000) and for adults on the ADHD-Rating Scale (ADHD-RS; DuPaul, Power, Anastolpoulos, & Reid, 1998; Kooij et al., 2005) by repeated-measures analyses of pre- and post-treatment scores. In children, the MPH
Table 5.2 Means and standard deviations of age- and treatment groups on neuropsychological tests

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
<th></th>
<th>Men</th>
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<tbody>
<tr>
<td></td>
<td>MPH placebo</td>
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<td>MPH placebo</td>
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<td></td>
<td>pre post n</td>
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<td>pre post n</td>
<td>pre post n</td>
</tr>
<tr>
<td>n-back</td>
<td>11.3 (8.8) 4.6 (4.6) 25</td>
<td>10.7 (6.6) 6.8 (6.7) 25</td>
<td>8.7 (5.7) 7.1 (5.9) 24</td>
<td>8.9 (7.7) 6.4 (6.4) 24</td>
<td></td>
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<tr>
<td>GNG</td>
<td>18.3 (4.7) 19.8 (7.0) 18</td>
<td>18.3 (5.5) 20.0 (7.3) 19</td>
<td>29.5 (5.2) 31.1 (7.0) 21</td>
<td>26.2 (6.0) 27.6 (7.0) 20</td>
<td></td>
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</tr>
<tr>
<td>RAVLT IR</td>
<td>42.3 (9.3) 54.6 (8.2) 25</td>
<td>41.4 (7.9) 52.3 (8.7) 25</td>
<td>46.6 (9.0) 58.4 (9.0) 23</td>
<td>46.6 (8.5) 54.7 (9.1) 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT DR</td>
<td>8.7 (2.3) 11.0 (2.0) 25</td>
<td>8.7 (2.0) 10.8 (2.1) 25</td>
<td>9.7 (2.4) 12.3 (1.9) 23</td>
<td>9.6 (2.4) 11.4 (2.1) 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT Med</td>
<td>279 (39) 283 (40) 25</td>
<td>282 (29) 287 (29) 25</td>
<td>262 (33) 257 (28) 24</td>
<td>252 (38) 260 (31) 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT SDRT</td>
<td>89 (41) 89 (36) 25</td>
<td>86 (29) 84 (51) 25</td>
<td>64 (26) 57 (23) 24</td>
<td>59 (32) 68 (41) 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIDA</td>
<td>91 (10) 87 (14) 24</td>
<td>90 (12) 87 (15) 25</td>
<td>94 (11) 90 (15) 20</td>
<td>96 (10) 95 (14) 19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: pre = pre-treatment stimulant naïve assessment; post = post-treatment assessment after 16 weeks of treatment and 1 week wash-out; MPH = methylphenidate; n-back = difference between performance on the two highest achieved conditions; RAVLT = Rey’s Auditory Verbal Learning Test; IR = immediate recall; DR = delayed recall; SRT = Simple Reaction Time test; Med = median; SDRT = standard deviation; MIDA = percentage correct on the Maudsley’s Index of Delay Aversion.
condition demonstrated more off-medication improvement of inattentive but not hyperactive/impulsive symptoms than the placebo group ($p = .02$, $\eta_p^2 = .13$, and $p = .14$, $\eta_p^2 = .05$ respectively). In adults, the MPH group also demonstrated more off-medication improvement of the total number of symptoms than the placebo group ($p = .01$, $\eta_p^2 = .15$).

**DISCUSSION**

In order to determine whether MPH treatment for ADHD has age-modulated persistent effects on cognitive functioning, boys and male adults with ADHD were treated for 16 weeks with MPH or placebo in a randomized, double-blind trial, and were assessed after a wash-out period of one week. Irrespective of treatment condition, both children and adults improved significantly on tests of episodic memory and complex visuospatial working memory. This improvement likely reflects practice effects, which we observed for these specific tests of episodic and working memory, but not for response speed in an earlier study with TD children and adults. In contrast to our hypotheses, we observed no persistent effects of MPH over placebo in children, nor in adults on any of the administered tests. Thus, 16 weeks of MPH treatment does not seem to alter the development of working memory, inhibition, episodic memory, simple response speed or delay aversion in boys with ADHD.

The absence of detrimental persistent MPH effects in children could be reassuring to parents and therapists. The findings are in line with a study revealing similar neuropsychological performance in stimulant naïve and treated adults with childhood ADHD (Stoy et al., 2011). Our observations extend previous findings of a lack of behavioural normalization at 8 year follow-up in the condition originally randomized to 14-months of treatment with medication (Molina et al., 2009). However, using pharmacological MRI, our research group demonstrated developmentally associated adaptations of the DAergic system to MPH treatment, including the same participants as described here (Schrantee et al., submitted). We observed a change in cerebral blood flow in DAergic areas in the MPH treated children in response to an acute challenge with MPH, but not in placebo treated children or adults treated with MPH or placebo. This pattern of response may indicate neuroadaptive processes in the dopaminergic system of MPH treated children with ADHD. Extending this to the present findings, we conclude that this neurobiological adaptation does not seem to directly translate into altered cognition, at least on the short-term. However, our exploratory observations of an age-independent improvement in ADHD symptoms, which may reflect general neuroplasticity, contrasts the age-dependent effects observed
with imaging. As may be expected with subjective measures, several participants and parents reported they could not accurately reflect on one week off-medication, as they had not experienced all situations in this short timeframe. Although speculative, we therefore cannot exclude a carry-over effect of on-medication experiences to the off-medication assessment.

The literature describes acute effects of MPH on both behaviour and cognition (Castells et al., 2011; Coghill et al., 2013; Faraone & Buitelaar, 2010; Tamminga et al., chapter 3; van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). However, cognitive dysfunction is not a diagnostic criterion, is not consistently observed, and effects on cognition are generally smaller than on behaviour. Therefore, we explored whether MPH yielded cognitive improvement during treatment, since an absence of acute effects may explain the lack of persistent (off-medication) effects. Contrasting our expectations, the GNG did not demonstrate acute treatment effects. In addition, ceiling-effects were observed on the delay aversion test, especially in adults, deeming our adaptation of this test inappropriate for the evaluation of treatment effects. However, at 8 weeks of optimally titrated treatment, the MPH conditions demonstrated improved episodic memory, working memory and response speed relative to the placebo conditions, which is in line with beneficial acute effects reported previously (Cubillo et al., 2014b; Dorrego, Canevaro, Kuzis, Sabe, & Starkstein, 2002; Holmes et al., 2010; Spencer et al., 2009). Furthermore, our exploratory analysis revealed that MPH relative to placebo improved ADHD symptoms from pre- to post-treatment, indicating beneficial effects of MPH treatment on behaviour. Thus, in general, MPH treatment has acute enhancing effects over placebo on cognition, in addition to beneficial behavioural effects. Therefore, the lack of persistent effects of MPH on episodic memory, working memory and response speed could not be explained by a general lack of effect of MPH treatment.

An important strength of the present study is its randomized, double-blind, placebo-controlled design. The few studies considering long-term effects of stimulants have a naturalistic nature, whereas randomization is essential to determine causality of effects. It could therefore be that previous results were influenced by pre-existent differences, while the design of the present study accounted for such differences. In addition, none of the authors have medication related conflicts of interest, which is exceptional in medication research, and important since a relationship between industry sponsorship and study outcomes is apparent (Bekelman, Li, & Gross, 2003). A final strength is that MPH was titrated in children and adults until the balance between behavioural symptoms and side-effects was clinically optimal, as is described in international guidelines (Kooij et al., 2010; National Collaborating Centre for Mental Health, 2009; Trimbos-instituut, 2005). Thus, the results following from this
approach can be easily generalized to clinical practice.

However, some might argue that the duration of treatment, which was 16 weeks only, is insufficient to yield cognitive alterations, even though we observed a neurobiological alteration. 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 been ethically challenging. Given our null findings, however, it could be that MPH affects cognitive development when a longer treatment period is considered. A second limitation might be that the present study included males only, while ADHD is also prevalent and disruptive in females (Biederman et al., 2010; Merikangas et al., 2010) and patterns observed in males are not by definition generalisable to females. Replication of our findings in a sample including both sexes, and with extended treatment duration, would underlie the observed lack of age-modulated persistence of MPH.

A point of discussion is the ADHD status and stimulant naivety in adults with ADHD. It was recently argued that the aetiology of adult ADHD is debatable, as the majority of adults with ADHD complaints did not meet diagnostic criteria in childhood, and retrospective reports seem unreliable (Moffitt et al., 2015). In addition, inclusion of stimulant naïve adults with ADHD in a pharmacological study is troublesome. In the present study, the majority of the included adults were stimulant treatment-naïve, however, many reported recreational drug use, which is inherently related to ADHD. Even though these issues could not account for the presently observed absence of persistent MPH effects in children, they offer a challenge in the field of adult ADHD research.

In conclusion, the results from the present randomized, placebo-controlled trial suggest that the effects of MPH on cognitive functioning are limited to the moment of treatment, in both children and adults. Hence, there is no age-modulated persistent effect of MPH treatment on cognitive functioning. As no harmful or positive cognitive effects of 16 weeks of MPH treatment were observed, the results of this study could on the one hand alleviate concerns of parents and therapists of younger and older patients. On the other hand, the results offer no lead for normalization of ADHD related cognitive impairment with MPH use. Given the importance of the subject, it is crucial that the current findings will be replicated.
# APPENDIX CHAPTER 5

## Appendix 5.1 Type and duration of recreational drug use in adults with ADHD ($n = 48$)

<table>
<thead>
<tr>
<th></th>
<th>MDMA/XTC</th>
<th>cocaine</th>
<th>amphetamine</th>
<th>cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (&lt;1 yrs)</td>
<td>31</td>
<td>38</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Short (1-2 yrs)</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Moderate (3-4 yrs)</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Long (≥5 yrs)</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

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