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REVIEW ARTICLE

Effects of methylphenidate on executive functioning in attention-deficit/hyperactivity disorder across the lifespan: a meta-regression analysis

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Attention-deficit/hyperactivity disorder (ADHD) in childhood and adulthood is often treated with the psychostimulant methylphenidate (MPH). However, it is unknown whether cognitive effects of MPH depend on age in individuals with ADHD, while animal studies have suggested age-related effects. In this meta-analysis, we first determined the effects of MPH on response inhibition, working memory and sustained attention, but our main goal was to examine whether these effects are moderated by age. A systematic literature search using PubMed, PsycINFO, Web of Science and MEDLINE for double-blind, placebo-controlled studies with MPH resulted in 25 studies on response inhibition ($n = 775$), 13 studies on working memory ($n = 559$) and 29 studies on sustained attention ($n = 956$) (mean age range 4.8–50.1 years). The effects of MPH on response inhibition [effect size (ES) = 0.40, $p < 0.0001$, 95% confidence interval (CI) 0.22–0.58], working memory ($ES = 0.24$, $p = 0.053$, 95% CI 0.00–0.48) and sustained attention ($ES = 0.42$, $p < 0.0001$, 95% CI 26–0.59) were small to moderate. No linear or quadratic age-dependencies were observed, indicating that effects of MPH on executive functions are independent of age in children and adults with ADHD. However, adolescent studies are lacking and needed to conclude a lack of an age-dependency across the lifespan.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with defining characteristics of inattention and/or hyperactivity–impulsivity, and symptom onset before the age of 12 years [Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5); American Psychiatric Association, 2013]. Persistence of ADHD symptoms into adulthood has been frequently described (Gittelman *et al.* 1985; Barkley *et al.* 2002; Faraone & Biederman, 2006; Simon *et al.* 2009) and ADHD symptoms have profound implications for academic achievement, social functioning, self-esteem and mental health across the lifespan (Manuzza *et al.* 1991; Barkley *et al.* 2002; Faraone & Biederman, 2006). These consequences endorse the need for effective interventions for ADHD from childhood into adulthood.

Methylphenidate (MPH) is a psychostimulant frequently prescribed in the treatment of ADHD. It increases the availability of extracellular dopamine (DA) and noradrenaline (NA) by blocking the DA transporter and the NA transporter in striatal and prefrontal areas (Koda *et al.* 2010; Volkow *et al.* 2012). These areas are volumetrically smaller and functionally less activated in people with ADHD (Durston *et al.* 2003; Nakao *et al.* 2011; Cortese *et al.* 2012; Frodl & Skokauskas, 2012; Hart *et al.* 2013). In typically developing individuals, maturation of specific brain areas, particularly the prefrontal cortex and frontal–temporal connections, continues well into adulthood (Giedd, 2004; Shaw *et al.* 2008; Westlye *et al.* 2010; Lebel *et al.* 2012). Although the temporal sequence of development of different brain areas in ADHD is comparable with that in typically developing children, peak thickness of the prefrontal, temporal and occipital cortices is attained at a later age in children with ADHD (Shaw *et al.* 2007). As neurotransmitter systems change drastically from early postnatal time to early adulthood, with a peak of synaptogenesis and pruning in the prefrontal cortex around adolescence (Blakemore & Choudhury, 2006), it could be argued that sensitivity to MPH is age-dependent.

In line with this hypothesis, animal studies have shown different behavioral responses, reflecting

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cognitive processes, to stimulant administration in juvenile as compared with adult animals. Some studies have reported a reduced sensitivity in young animals following stimulant administration. For example, peri-adolescent rats exposed to a single challenge of amphetamine responded with less locomotion activity, or subsensitivity, in comparison with adult rats (Bolanos *et al*. 1998), and young mice exposed to a single challenge of MPH responded with less locomotion activity than peri-adolescent and adult mice (Niculescu *et al.* 2005). Other studies, however, suggest a higher sensitivity for juvenile as compared with adult animals. For example, a single dose of MPH has been shown to ameliorate an inhibition deficit in juvenile, but not in adult, spontaneously hypertensive rats (SHR; an animal model of ADHD) (Bizot *et al.* 2007). Together, these animal studies demonstrate that treatment effects of MPH may depend on the maturational level of the brain. However, it is currently unknown whether this holds true for the human brain.

In humans, the primary measure to determine whether MPH works adequately is change in ADHD symptomatology (American Academy of Pediatrics, 2001). When focusing on this specific outcome measure there seems to be no age-dependency in the MPH effect, as similar effect sizes have been reported in a meta-analysis including pediatric studies (effect size 0.79; Faraone & Buitelaar, 2010) and in a meta-analysis including adult studies (effect size 0.96; Faraone & Glatt, 2010). However, while cognitive processes are more closely related to brain maturation, hardly any human study has focused on the age-dependency of MPH effects on cognitive responses, or has summarized MPH effects in adults with ADHD. A study focusing on attention reported enhanced positive effects of MPH on a wide range of attentional functions in preschool children when compared with grade-school children (Hanisch *et al.* 2004). Seven (meta-analytic) reviews have systematically tested or described the influence of MPH on executive functions in ADHD (Kavale, 1982; Solanto, 1984; Losier *et al.* 1996; Riccio *et al.* 2001; Pietrzak *et al.* 2006; Chamberlain *et al.* 2011; Coghill *et al.* 2013), with only one (now dated) review summarizing beneficial effects of MPH on a broader range of cognitive functions in children as compared with adults with ADHD (Solanto, 1984). While a recent meta-analysis studied the effects of MPH on reaction time (variability), response inhibition, and (non-) executive memory (Coghill *et al.* 2013), this study included pediatric studies only. Since the possible age-dependency of MPH effects has not recently been addressed, the current study will test whether the effect of MPH on executive functioning in humans with ADHD is different across developmental stages.

In conclusion, it is unclear whether the magnitude of MPH effects on cognition depends on the maturational level of the human brain. In the current study, we will, therefore, focus on those functions that are known to be often compromised in ADHD and have been sufficiently studied in the context of MPH effects to conduct a meta-regression analysis. While a plethora of articles on the effects of MPH on executive functions of response inhibition, working memory and sustained attention (see also Coghill *et al.* 2013) have been published, there are hardly any studies focusing on MPH effects on, for example, motivation, reward sensitivity and timing (e.g. Shiels *et al.* 2009; Luman *et al.* 2015). Hence, we will focus on the aforementioned executive functions. Fortunately, within the field of executive functions, the same neuropsychological tests are often used in ADHD research with children and adults, creating the opportunity for quantitative evaluation of a potential age effect. Thus, we conducted a meta-regression analysis, to test the hypotheses that the effects of MPH on response inhibition, working memory and sustained attention are moderated by age. Although not previously addressed in meta-analyses regarding the effects of MPH on executive functioning, previous research has shown that medication naivety (Schwartz & Correll, 2014), dosage (Tannock *et al.* 1995; Konrad *et al.* 2004, 2005) and MPH formulation (Punja *et al.* 2013) are additional potential moderators of the effects of stimulants. Therefore, we also included an explorative analysis of these moderators.

Method

Identification of studies

A comprehensive search of the literature was undertaken using search engines PubMed, PsycINFO, Web of Science and MEDLINE. Search terms used were 'ADHD', 'ADD', 'HD' or 'hyperkinetic disorder' AND 'methylphenidate' or 'stimulants' AND 'neuropsychology', 'neuropsychological (test/task)', 'cognition', '(response) inhibition', '(working/verbal/declarative/spatial) memory', '(sustained) attention (span)', 'vigilance', 'reaction time', 'variability', 'intra-individual variability', 'IIV', 'executive functions', '(verbal) learning', '(processing/psychomotor) speed', 'reaction time', 'Nback', 'SART', 'Continuous Performance', 'Stop Signal' or 'Go-NoGo'. In addition, meta-analyses, reviews and references were checked in search of relevant studies.

Studies that met the following criteria were included: (*a*) designs were double-blind, placebo-controlled medication trials with MPH [immediate release (IR) or osmotic release oral system (OROS)] with a parallel-groups or crossover design; (*b*) dependent variables were measures

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of pre-potent response inhibition, sustained attention or working memory (see section 'Selection of dependent variables'); (*c*) population under study was diagnosed with ADHD according to DSM-III, DSM-III-TR, DSM-IV, DSM-IV-R, International Classification of Diseases-10 criteria, or scored above the cut-off on clinical rating scales of ADHD and qualified for pharmacological treatment; (*d*) studies reported sufficient data to allow for the calculation of effect sizes, or contact information of authors could be retraced in order to request sufficient data; (*e*) published articles should be presented in peer-reviewed journals between 1970 and March 2015, and should be written in English, German or Dutch; (*f*) articles should present original data. Studies assessing cognition in an imaging setting (e.g. functional magnetic resonance imaging, electroencephalography, functional near-infrared spectroscopy) were not excluded (see also the footnotes of Table 1).

See Fig. 1 for a flow diagram of the search results. Authors not reporting sufficient data for the calculation of effect sizes were contacted and requested to provide the missing data, as well as any unpublished data on the subject. After the initial search by the first author (H.G.H.T.), the extracted data and inclusion criteria were checked independently by a research assistant.

Selection of dependent variables

The majority of collected studies presented more than one dependent variable for each task. For each task, we selected the variable that best reflected the cognitive function of interest. If this variable was not reported, we selected the next variable. We planned to reduce heterogeneity by selecting the variable most frequently reported in other collected articles, if two or more dependent variables were considered to reflect a cognitive function equally well; however, this was never the case.

Moreover, as some articles presented data from multiple designs, settings, dosages or inter-stimulus intervals, we only included the data with the largest effect size in these cases, assuming that the study design in which these largest effects were obtained was optimal for detection of MPH effects in this specific population. Some data were acquired in a paradigm with conditions with and without incentives. On the grounds of consistency over studies, we used the without-incentives condition to measure the effect of MPH alone. For a more detailed description of this selection process, please see online Supplementary Appendix S1.

Calculation of effect sizes and analysis

In the present analysis, effect sizes reflect the difference between MPH and placebo conditions. For each clinical study, standardized mean differences and variances were calculated. When only the standard error of the mean (S.E.M.) was reported, the standard deviation (S.D.) was obtained by multiplying S.E.M. by the square root of the sample size. When only the median and range were reported, we estimated the mean and S.D. (Hozo *et al.* 2005). We calculated effect sizes based on the Hedges' *g*′ index; however, in order to combine results from different research designs, design-specific equations were applied (Morris & DeShon, 2002; see online Supplementary Appendix S2 for details).

Seven studies presented two tests of the same cognitive construct (Coghill *et al.* 2007; McInnes *et al.* 2007; Bedard & Tannock, 2008; Blum *et al.* 2011; Epstein *et al.* 2011; Murray *et al.* 2011; Wigal *et al.* 2011; Agay *et al.* 2014). To prevent an undesired increase of the relative weight of these studies, which is induced when including both tests, we aggregated two effects sizes within one study into one aggregated effect size (Borenstein *et al.* 2009) and assumed an inter-test correlation of 0.6. To determine the overall effect of MPH on executive functioning, a random-effects meta-regression analysis was executed, weighting effect sizes with their S.D., and accounting for between-study variation. Heterogeneity between studies was determined with the *Q* statistic (Lipsey & Wilson, 2001). The random-effects meta-regression was performed with the metafor package (Viechtbauer, 2010). We tested the effects of each moderator separately.

Results

Population and study characteristics

In all, 50 studies with a total number of 1611 participants were included in the analysis (see Table 1 and online Supplementary Appendix S3 for characteristics of the included studies). Mean age ranged from 4.8 to 50.1 years, with a median of 10.8 years. Of the studies, 33 were conducted with pediatric samples (mean age ⩽12 years), five†[1] with adolescents (mean age 13–18 years), and 12 with adult samples (mean age >18 years). From these 50 studies, 67 data points were obtained, of which 25 were on response inhibition ($n = 787$), 13 on working memory ($n = 559$) and 29 on sustained attention ($n = 956$). The number of times that we had to select the dosage yielding the largest effect size, when multiple dosages were presented in a single study, was comparable between cognitive domains (response inhibition 40%, working memory 38%, and sustained attention 45% of data points, respectively). Most studies that reported a time interval

† The notes appear after the main text.

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Table 1. *Characteristics of included studies*

Study	Subjects (% male)	Mean age, years (S.D.)/range	% Co-morbid ODD	% Stimulant naive	Type of task	Measure	Effect size (variance)	Dosage protocol	Mean challenge dosage
Agay *et al.* (2010)[a]	26 (42)	32.5 (–)/–	–	–	TOVA WISC digit span	Omissions Backwards span	−0.21 (0.29) 1.22 (0.29)	Fixed[b] Single challenge	IR, 15 mg
Agay *et al.* (2014)	20 (45)	30.3 (–)/20–40	–	40	TOVA WISC digit span and CANTAB spatial working memory[c]	Attentiveness (*d′*) Backwards span	0.11 (.22) −0.06 (0.22)	Fixed Single challenge	IR, 0.28 mg/kg
Aron *et al.* (2003)[d]	13 (77)	26.2 (6.9)/18–41	–	–	SST	Omissions	0.57 (0.27)	Fixed Single challenge	IR, 30 mg
Barkley *et al.* (1988)	23 (74)	8.5 (2.3)/5–12	–	–	GDS vigilance GDS delay	Omissions Efficiency ratio	0.52 (0.21) 0.27 (0.21)	Fixed[e] 2 d.d. 1 week/ condition	IR, 0.5 mg/kg
Barkley *et al.* (2005)	54 (77)	31.3 (11.3)/–	–	–	CPT	Omissions	0.13 (0.17)	Fixed[e] Single challenge	IR, 20 mg
Bedard & Tannock (2008)	130 (85)[f]	9 (1.46)/–[g]	20	70	WISC digit span and WRAML finger windows[c]	Backwards span	0.24 (0.16)	Fixed[e] Single challenge	IR, 0.45 mg/kg
Bedard *et al.* (2003)	28 (93)	8.9 (1.4)/6.4–12.0	50	–	SST	SSRT	0.54 (0.20)	Fixed[b,e] Single challenge	IR, 5/10 mg (mg/kg: mean = 0.29, S.D. = 0.08)
Biederman *et al.* (2011)[a]	87 (65)	33.9 (8.2)/19–60[h]	–	–	SST	SSRT	0.08 (0.16)	Optimal 6 weeks/condition	OROS, mean = 1.04 mg/kg
Blum *et al.* (2011)	30 (80)	8.6 (1.9)/6.4–12.5	40	–	WISC digit span and WRAML finger windows[c] CPT TEA-Ch walk don't walk	Backwards span Omissions Total correct	−0.01 (0.19)[i] 0.31 (0.19)[i] 0.24 (0.19)[i]	Optimal 1 week/condition	OROS, mean = 35.4 mg
Boonstra *et al.* (2005)	43 (51)	38.4 (10.1)/20–55	–	100	Change task CPT	SSRT Attentiveness (*d′*)	0.33 (0.18) 0.33 (0.18)	Optimal 4–5 d.d. 3 weeks/ condition	IR, mean = 70.6 mg/ d.d
Bouffard *et al.* (2003)	30 (80)	34 (–)/17–51	–	–	SST CPT	SSRT % Omissions	0.54 (0.19) 0.42 (0.19)	Fixed[e] 3 d.d. 2 weeks/ condition	IR, 15 mg

Bron *et al.* (2014)	22 (77)	30.5 (7.4)/18–55	–	100	CPT and TOVA[c]	Omissions	0.06 (0.21)	Fixed 2 weeks/condition	OROS, 72 mg
Coghill *et al.* (2007)	63 (100)[j]	10.85 (2.46)/7–15[k]	41[l]	100	CANTAB: spatial span and spatial working memory[c] GNG	Span and between-search errors Commissions	0.03 (0.17) 0.33 (0.17)	Fixed[e] 2 d.d. 4 weeks/ condition	IR, 0.6 mg/kg
Coons *et al.* (1987)	19 (84)	14.8 (1.91)/12–19[m]	–	32	CPT[n]	% Omissions	1.04 (0.22)	Fixed 3 d.d. 3 weeks/ condition	IR, 15 mg Mean = 0.25 mg/kg
Cubillo *et al.* (2012)[o,p]	19 (100)	13.1 (2.5)/10–17	10[q]	100	SST	SSRT	0.33 (0.22)	Fixed[b] Single challenge	IR, 0.3 mg/kg
Cubillo *et al.* (2013)	20 (100)	13.1 (2.5)/10–17	10[q]	100	*n*-back	% Accuracy	0.23 (0.22)	Fixed[b] Single challenge	IR, 0.3 mg/kg
DeVito *et al.* (2009)	21 (100)	10 (2.04)/7–13	67	0	SST	SSRT	1.41 (0.22)	Fixed[b] Single challenge	IR, 0.5 mg/kg
DuPaul *et al.* (1994)[r]	40 (90)	8.6 (1.3)/6–12	–	–	CPT	Total correct	0.52 (0.18)	Fixed 2 d.d. 1 week/ condition	IR, 15 mg
Epstein *et al.* (2007)[o,s]	15 (33)	50.1 (8.1)/–	–	>87	GNG	Commissions	0.19 (0.25)	Fixed[b] Single challenge	IR, 0.3 mg/kg
Epstein *et al.* (2011)	93 (73)[t]	8.11 (1.22)/7–11	37	100	SST and GNG[c] *n*-back	% Accuracy % Accuracy	0.07 (0.17)[u] 0.32 (0.16)[u]	Optimal 1 week/condition	OROS, mean = 1.13 mg/kg
Gruber *et al.* (2007)	37 (84)	9.2 (1.8)/6–12	30	–	CPT	% Omissions	0.10 (0.18)	Fixed[b] 2 d.d. 1 week/ condition	IR, 0.5 mg/kg
Günther *et al.* (2010)	25 (20)[v]	11.5 (1.6)/8–12[h]	31[q,w]	–	ANT	Omissions	0.65 (0.20)	Fixed[e] Single challenge	IR, 0.5 mg/kg
Konrad *et al.* (2004)	60 (73)	10.8 (1.6)/8–12	10	100	SST ANT	SSRT Hit RT SD	0.59 (0.17) 0.38 (0.17)	Fixed[e] Single challenge	IR, 0.25 mg/kg 0.5 mg/kg
Konrad *et al.* (2005)	44 (84)	10.3 (1.9)/8–12	–	–	SST ANT	SSRT Total errors	0.74 (0.18) 0.86 (0.18)	Fixed[e] Single challenge	IR, 0.5 mg/kg 0.25 mg/kg

Table 1 (*cont.*)

Study	Subjects (% male)	Mean age, years (S.D.)/range	% Co-morbid ODD	% Stimulant naive	Type of task	Measure	Effect size (variance)	Dosage protocol	Mean challenge dosage
Kuperman *et al.* (2001)[a,o,x]	18 (74)	31.9 (8.7)/18–60[h]	–	–	CPT	Attentiveness (*d'*)	0.40 (0.37)	Optimal 3 d.d. 7 weeks/ condition	IR, maximum 0.9 mg/kg/d.d.
McInnes *et al.* (2007)	16 (75)	9.2 (1.7)/7–12	18	80	WISC digit span and WRAML finger windows[c]	Backwards span	−0.06 (0.24)	Fixed[e] Single challenge	IR, mean = 0.55 mg/ kg
Mehta *et al.* (2004)	14 (100)	10.9 (1.19)/9–14	0	0	CANTAB spatial working memory	Between-search errors	0.32 (0.26)	Fixed[b] Single challenge	IR, 0.5 mg/kg
Milich *et al.* (1989)	26 (100)	8.8 (1.3)/7.1–11.8	77	–	CPT	Omissions	0.61 (0.20)	Fixed[b] Single challenge	IR, 0.3 mg/kg
Monden *et al.* (2012)[y]	16 (75)	8.8 (2.2)/6–13	–	44	GNG	% Omissions	0.35 (0.24)	Optimal Single challenge	OROS, mean = 21.94 mg
Monteiro Musten *et al.* (1997)[z]	31 (84)	4.8 (0.54)/4–5.8	84	94	GDS vigilance GDS delay	Total correct Efficiency ratio	0.47 (0.19) −0.26 (0.19)	Fixed[e] 2 d.d. >1 week/ condition	IR, 0.5 mg/kg 0.3 mg/kg
Murray *et al.* (2011)[aa]	68 (66)	10.3 (−)/9–12	–	0	WISC digit span and WRAML finger windows[c] TOVA	Backwards span SSRT	0.15 (0.17)[u] 0.38 (0.17)[u]	Optimal Single challenge	OROS, mean = 47.65 mg
Overtoom *et al.* (2003)[aa,bb]	16 (100)	10.4 (1.4)/7–12	38	0	SST	SSRT	0.09 (0.24)	Fixed Single challenge	IR, mean = 0.43 mg/ kg
Overtoom *et al.* (2009)[cc,dd]	12 (50)	35.9 (9.8)/23–52	–	100	SST	SSRT	0.60 (0.28)	Fixed[e] Single challenge	IR, 0.6 mg/kg
Pliszka *et al.* (2007)[dd]	12 (67)	12.3 (1.7)/9–15	42	–	SST	SSRT	0.19 (0.28)	Optimal Single challenge	IR, mean = 13.7 mg
Ramtvedt *et al.* (2013)[ee]	36 (81)	11.4 (1.4)/9–14	55	100	CPT[ff]	Inattention composite[gg]	0.28 (0.19)	Fixed 3 d.d. 2 weeks/ condition	IR, 15 mg
Rubia *et al.* (2009)[o]	13 (100)	12.5 (1.3)/10–15	8	100	CPT	Omissions	−0.28 (0.27)	Fixed Single challenge	IR, 0.3 mg/kg
Rubia *et al.* (2011)[o]	12 (100)	13 (1)/10–15	8	100	SST	SSRT	−0.11 (0.28)	Fixed Single challenge	IR, 0.3 mg/kg

Schachar *et al.* (2008)[aa]	17 (88)	11.3 (2.2)/6.8–15.3	–	–	SST CPT	SSRT Omissions	0.80 (0.24) 0.70 (0.24)	Fixed[b] 1 week/condition	MLR, 1.2 mg/kg
Scheres *et al.* (2003)	23 (100)	8.7 (1.7)/6–12	43	100	Follow task	SSRT	0.68 (0.21)	Fixed[e] 2 d.d. 1 week/condition	IR, 10 mg
Solanto *et al.* (2009)	25 (44)	8.8 (1.5)/7–12[h]	16	96	CPT	Omissions[hh]	1.02 (0.20)	Fixed[b,e] 3 d.d. 1 week/condition	IR, 20 mg Mean = 0.59 mg/kg
Stein *et al.* (1996)	25 (100)	8.0 (1.8)/6–12	28	44	TOVA	Omissions[hh]	0.29 (0.20)	Fixed[e] 2 d.d. 1 week/condition	IR, mean = 0.3 mg/kg
Sunohara *et al.* (1999)[dd]	20 (80)	10.5 (1.9)/10–12	20	0	CPT	Hit RT S.D.	0.61 (0.22)	Fixed[e] Single challenge	IR, 0.56 mg/kg
Szobot *et al.* (2004)[a]	36 (100)	11.6 (2.5)/8–17[h]	59[q]	–	CPT	Omissions (relative ratio)	0.19 (0.24)[i]	Fixed[b] 2 d.d. 4 days/condition	IR, 0.36 mg/kg
Tamm & Carlson (2007)[ii]	19 (89)	9.1 (1.6)/7–12	42	0	Ice cream stop task	SSRT	0.62 (0.22)	Regularly prescribed dose Single challenge	IR, mean = 16.05 mg (expressed in MPH)
Tannock *et al.* (1995)	28 (89)	8.9 (1.2)/–	35[q]	80	Change task	SSRT	0.66 (0.20)	Fixed[e] Single challenge	IR, 0.6 mg/kg
Tucha *et al.* (2006)[jj]	58 (84)	10.81 (2.3)/7–14	–	0	Vigilance test	Omissions	0.57 (0.17)[u]	Optimal Single challenge	IR, 19 mg d.d.
Turner *et al.* (2005)[d]	18 (–)	28.4 (8.4)/5–12[h]	–	61	CANTAB spatial working memory Rapid visual information processing	Between-search errors Target sensitivity	0.77 (0.23)[u] 0.38 (0.23)	Fixed Single challenge	IR, 30 mg
Wigal *et al.* (2011)	71 (70)	10.1 (1.08)/9–12	–	–	WISC digit span and WRAML finger windows[c] TOVA	Backwards span Omissions[hh]	0.12 (0.17)[u] 0.36 (0.17)[u]	Optimal Single challenge	OROS, mean = 36.7 mg
Wilson *et al.* (2006)[aa,kk]	35 (54)	17.5 (–)/16–19	6	0	GNG	Commissions	0.30 (0.19)	Fixed 17 days/condition	OROS, 72 mg

Table 1 (*cont.*)

Study	Subjects (% male)	Mean age, years (S.D.)/range	% Co-morbid ODD	% Stimulant naive	Type of task	Measure	Effect size (variance)	Dosage protocol	Mean challenge dosage
Zeiner (1999)	21 (100)	8.8 (1.1)/7–12	62	0	CPT PASAT	Omissions Part A	0.64 (0.22) 0.22 (0.22)	Optimal 2–3 d.d. 3 weeks/ condition	IR, mean = 22.4 mg d.d.

Note that a positive effect size indicates better performance in the MPH condition as compared with the placebo condition.

S.D., Standard deviation; ODD, oppositional defiant disorder; TOVA, Test of Variables of Attention; WISC, Wechsler Intelligence Scale for Children; IR, immediate release; CANTAB, Cambridge Neuropsychological Test Automated Battery; SST, Stop Signal Task; GDS, Gordon Diagnostic System; d.d., *de die* (daily); CPT, continuous performance task; WRAML, Wide Range Assessment of Memory and Learning; SSRT, stop signal reaction time; OROS, osmotic release oral system; TEA-Ch, Test of Everyday Attention for Children; GNG, Go/No-Go; ANT, Amsterdam Neuropsychological Tasks; RT, reaction time; MPH, methylphenidate; MLR, multilayer-release; PASAT, Paced Auditory Serial Addition Test; ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; S.E.M., standard error of the mean.

[a] Parallel-group design: demographic data of the treatment and placebo condition combined.

[b] Participants with a body weight within the normal range received a fixed dose, but dose was adjusted to a fixed high or low dose for participants with high or low body weight dosage.

[c] Effect sizes for two separate tests of the same functions were merged to reduce population bias. Merged data are reported here.

[d] Some participants met criteria for ADHD in remission or subthreshold ADHD.

[e] Trial with multiple fixed dosages: dosage with highest effect size selected and reported here.

[f] Number of participants assessed with the WISC [WRAML Finger Windows $n = 59$ (83%)].

[g] Data based on a larger number of participants than completed assessment.

[h] Demographic data reported for two groups separately were merged for the present analysis. Merged data are reported here.

[i] Effect size calculated with mean and S.D. obtained from median and range, see Hozo *et al.* (2005).

[j] Number of participants assessed with the GNG and CANTAB spatial working memory between search errors [CANTAB Spatial Span $n = 59$ (100%)].

[k] Described in Rhodes *et al.* (2004). [l] Based on a larger number of participants ($n = 75$).

[m] Described in Klorman *et al.* (1987). [n] Rewarded CPT. [o]Assessment during magnetic resonance imaging.

[p] Trial comparing MPH with atomoxetine. [q] Percentage also includes participants with CD. [r] Previous adverse response as exclusion criterion.

[s] Only parents selected from trial with parents and children.

[t] Number of participants in total sample (*n*-back $n = 75$, SST $n = 90$, GNG $n = 85$).

[u] S.D. deducted from S.E.M.; see Higgins & Green (2011).

[v] Part of the total sample of $n = 54$ was already described in another included article (Konrad *et al.* 2004), data of the remaining $n = 25$ were included here.

[w] Based on a larger number of participants ($n = 54$).

[x] Study comparing MPH with bupropion.

[y] Assessment during functional near-infrared spectroscopy.

[z] Attentional dysfunction on neuropsychological tests as inclusion criterion.

[aa] Study included responders.

[bb] Trial comparing MPH with L-dopa and desipramine.

[cc] Trial comparing MPH with paroxetine.

[dd] Assessment during electroencephalography.

[ee] Trial comparing MPH with dex-MPH.

[ff] Assessment during motion-tracking.

[gg] Weighted combination of RT, variability, omission and commission errors.

[hh] Standard score.

[ii] Data from dex-MPH and MPH condition combined.

[jj] Study with a withdrawal condition being administration of placebo during usual treatment.

[kk] Trial comparing MPH with Adderall.

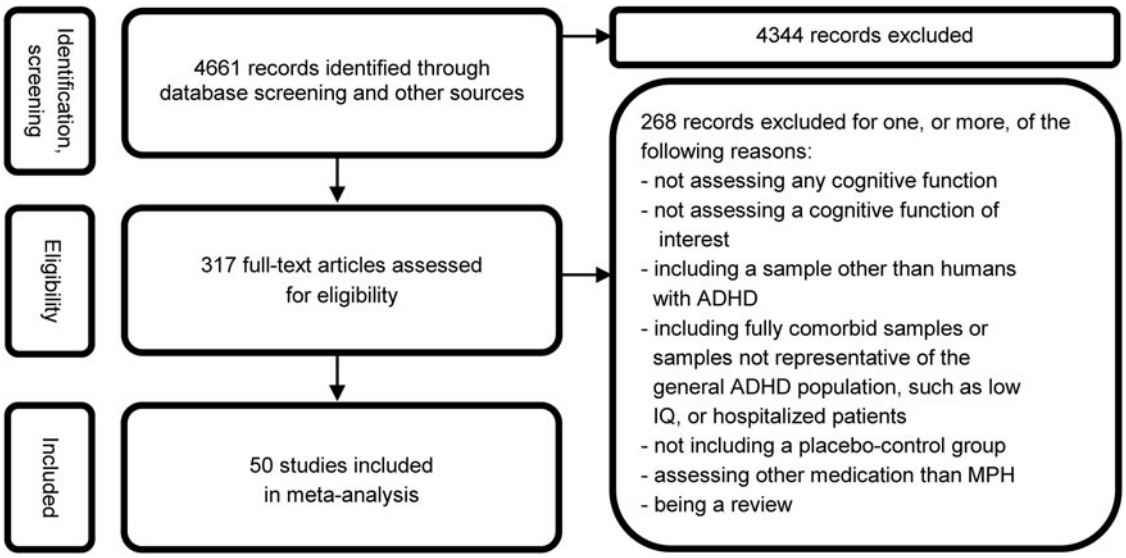

Fig. 1. Flow diagram of search results. ADHD, Attention-deficit/hyperactivity disorder; IQ, intelligence quotient; MPH, methylphenidate.

assessed the MPH effect within 60–180 min after ingestion of MPH.

Overall effect of MPH on cognition

In Fig. 2, effect sizes and 95% confidence intervals (CIs) are presented for all 67 data points, i.e. for response inhibition, working memory and sustained attention. For all data points together, a mean effect size of 0.38 (95% CI 0.27–0.49) was found, which proved significant ($p < 0.0001$), reflecting a medium and positive overall effect of MPH on executive functioning, with non-significant heterogeneity between data points [$Q = 32.51$, degrees of freedom (df) = 66, $p > 0.99$].

Effect of MPH on response inhibition, working memory and sustained attention

The mean effect sizes of 0.40 for response inhibition (95% CI 0.22–0.58) and 0.42 for sustained attention (95% CI 0.26–0.59) were significant (both $p < 0.0001$). The mean effect size of 0.24 for working memory (95% CI 0.00–0.48) failed to reach significance ($p = 0.053$). Mean effect sizes did not differ significantly when compared with each other (sustained attention *v.* response inhibition $\beta = 0.022$, $p = 0.86$; response inhibition *v.* working memory $\beta = 0.160$, $p = 0.230$; sustained attention *v.* working memory $\beta = 0.182$, $p = 0.23$). For each function separately, no significant heterogeneity was observed (response inhibition $Q = 12.87$, df = 24, $p = 0.98$; working memory $Q = 6.11$, df = 12, $p = 0.91$; sustained attention $Q = 11.96$, df = 28, $p > 0.99$).

Age-related effects

We centered the predictor variable around the adolescent age of 14 years, the age around which total brain volume peaks in males (Giedd, 2004). Age-related effects are depicted in Fig. 3. Overall, we found no support for a linear ($\beta = -0.002$, $p = 0.65$) association between age and MPH effect; the quadratic predictor was also not significant ($\beta = -0.0002$, $p = 0.55$)[2]. Visual inspection of scatter plots for cognitive functions separately only suggested a relationship between age and the effect on working memory. However, for working memory, neither a model with a linear predictor ($\beta = 0.02$, $p = 0.16$), nor a model with a quadratic predictor ($\beta = 0.002$, $p = 0.14$) was significant. We also tested the age-relationship for response inhibition and sustained attention separately. No significant linear, quadratic, or combined linear and quadratic relationships were observed.

Exploratory moderator analysis: medication naivety, dosage, MPH formulation, and interactions with age

As we explored three moderators, we corrected for multiple testing with a Bonferroni correction, p values therefore are interpreted as significant if they are below 0.05/3 = 0.017. The relationship between medication naivety and MPH effects was assessed with IR single-dose studies (instead of longer treatment regimens) in which the population was either described as 100% naive ($k = 7$) or as 0% naive ($k = 8$). Naive and non-naive studies were equally represented by cognitive domains. The mean effect size of studies with a treated population (effect size = 0.47, 95% CI 0.15–0.80) was

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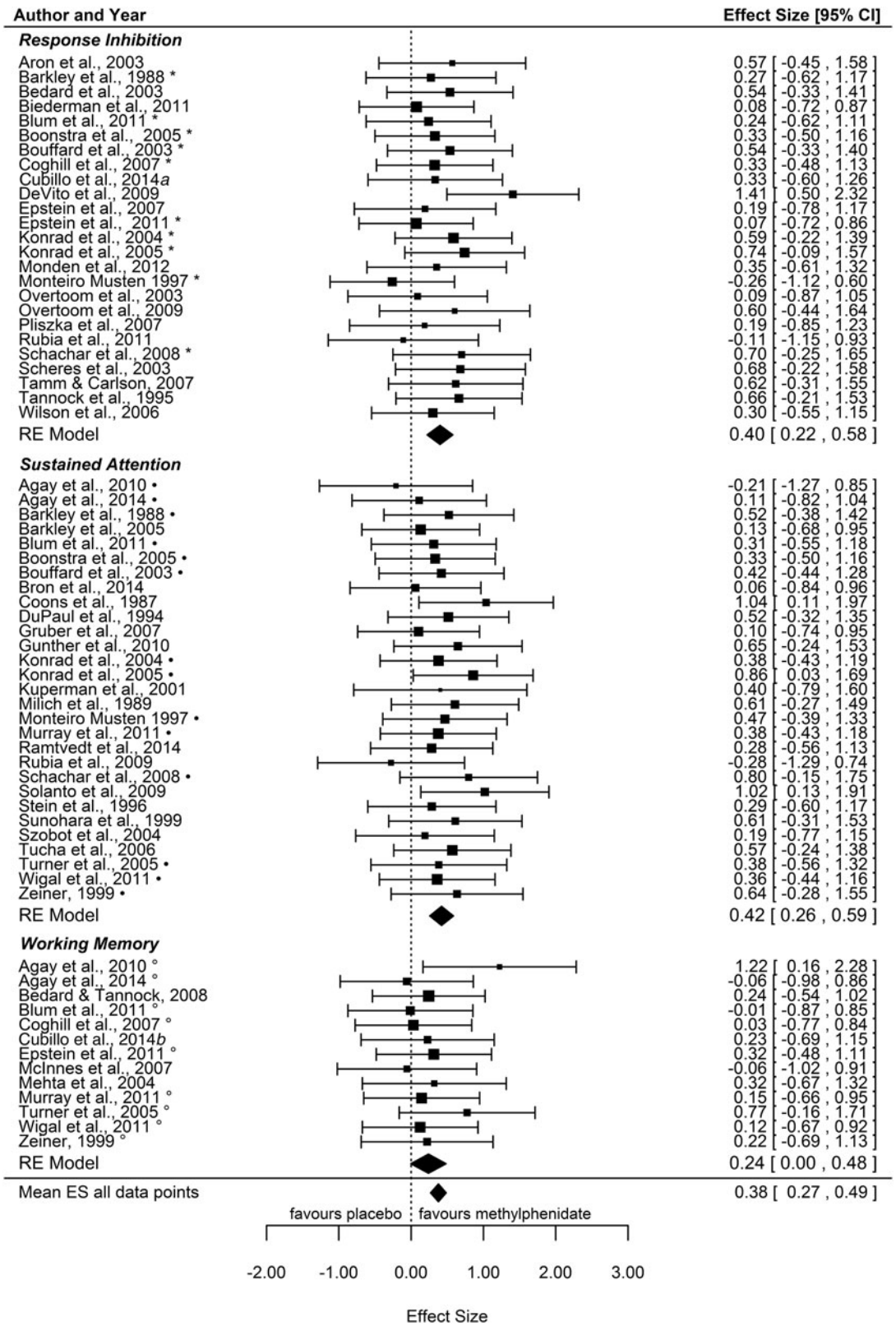

Fig. 2. Forest plot of the effect of methylphenidate on response inhibition, working memory and sustained attention. *, Response inhibition study with >1 variables included in the analysis; ○, working memory study with >1 variables included in the analysis; ●, sustained attention study with >1 variables included in the analysis; CI, confidence interval; RE, random effects; ES, effect size.

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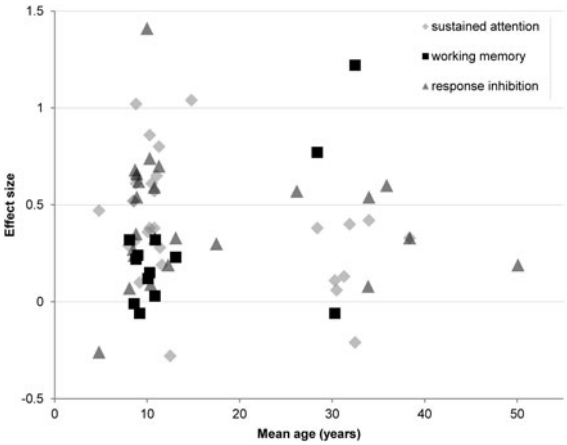

Fig. 3. Overall age–response relationship.

significant, whereas the effect of MPH on studies with stimulant-naive participants was not significant (effect size = 0.28, 95% CI −0.06 to 0.63). However, medication naivety was not a significant moderator ($\beta = 0.19$, $p = 0.44$).

As mentioned, we selected the dosage yielding the largest effect size in approximately 40% of data points. Consequently, mean dosages of studies with MPH IR ranged between 0.21 and 0.60 mg/kg, with a median dosage of 0.50 mg/kg in studies of sustained attention and working memory and of 0.30 mg/kg in studies of response inhibition. No linear effect of dosage was identified ($\beta = 0.49$, $p = 0.39$)[3]. When centering the predictor variable dosage around 0.6 mg/kg (see Tannock *et al.* 1995), a quadratic model yielded no significant results ($\beta = -0.67$, $p = 0.65$)[4]. We inspected the dose–response relationship for each function separately. Visual inspection of the scatter plots suggested a dose–response pattern for working memory only. However, the working memory analysis comprised only six studies, and, as for response inhibition and sustained attention, both the linear and (centered) quadratic dose–response relationships were non-significant ($\beta = -0.11$, $p = 0.94$ and $\beta = -0.31$, $p = 0.95$, respectively)[5].

All studies reported which type of MPH formulation was tested. MPH formulation was not associated with the effect on response inhibition ($\beta = 0.18$, $p = 0.38$), working memory ($\beta = 0.194$, $p = 0.59$) or sustained attention ($\beta = 0.06$, $p = 0.78$). Linear interactions between age and medication naivety, age and dosage, and age and MPH formulation were all non-significant ($\beta = 0.04$, $p = 0.16$; $\beta = 0.05$, $p = 0.58$; $\beta = 0.005$, $p = 0.75$, respectively).

Publication bias

Regression tests for funnel plot asymmetry were not significant (overall $z = 0.40$, $p = 0.69$; response inhibition $z = 0.21$, $p = 0.83$; working memory $z = 1.19$, $p = 0.23$; sustained attention $z = -0.59$, $p = 0.55$), indicating that no publication bias was present. Duval and Tweedie's trim-and-fill method (Duval & Tweedie, 2000) demonstrated six hypothetically missing studies on the right side of the overall funnel plot (see Fig. 4). Inclusion of these hypothetical studies would increase the overall mean effect size from 0.38 to 0.42 (95% CI 0.32–0.53). Applying the trim-and-fill method to the sustained attention and working memory data yielded one and three hypothetically missing studies, respectively, and none for response inhibition. Inclusion of hypothetical studies would increase the mean effect size for sustained attention from 0.42 to 0.44 (95% CI 0.28–0.60) and for working memory from 0.24 to 0.32 (95% CI 0.09–0.54), which indicates a potential negative effects bias. Robustness of the significant effects was demonstrated with Rosenthal's fail-safe n calculation (Rosenthal, 1979), showing a high number of null findings needed to nullify the effects (overall $n = 1091$, $p < 0.0001$; response inhibition $n = 153$, $p < 0.0001$; sustained attention $n = 235$, $p < 0.0001$).

Conclusions

The major goal of the current study was to test whether the effects of MPH on executive functioning are age-dependent. The present meta-analysis shows moderate and consistent effects of MPH on overall test performance in individuals with ADHD, despite the wide age range of the studied population and diversity in neuropsychological tests, dependent variables and medication protocols. However, no age-dependency was observed when analysing response inhibition, working memory and sustained attention separately. Thus, MPH improves executive functioning, irrespective of age.

The first main finding, regarding the effect of MPH on executive functioning, is that the mean effect size of working memory studies was small and, although the magnitude of the MPH effect did not differ significantly between cognitive domains, failed to reach statistical significance when tested separately. This indicates that working memory is the least sensitive to MPH effects of the executive functions we studied. Interestingly, one out of two asymmetry tests suggested an underestimation of the MPH effect on working memory, although this should be interpreted with care as studies on working memory were scarce. Nonetheless, the finding that inhibition and attention, but not working memory, are enhanced by MPH is in line with a lack of MPH-induced normalization in the dorsolateral prefrontal cortex (DLPFC) during working memory tasks, and with the MPH-induced normalization of activation in the inferior frontal cortex

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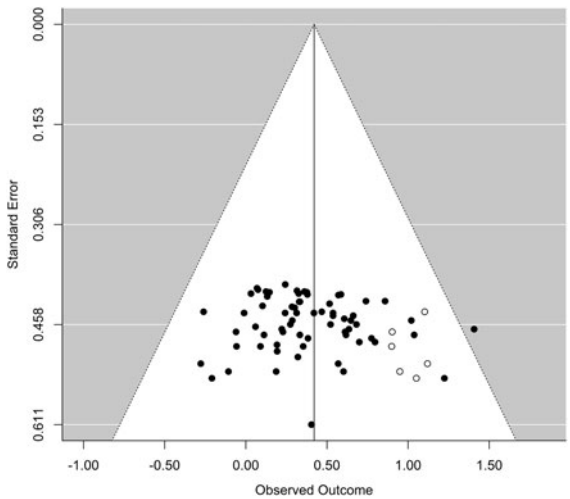

Fig. 4. Trim-and-fill funnel plot with symmetrical distribution and five estimated missing studies indicating that the present meta-regression analysis did not suffer from positive results bias.

(IFC) during inhibition and timing tasks (Rubia *et al.* 2014). It is also in line with a study revealing normalization of DLPFC underactivation by atomoxetine, a NA reuptake inhibitor, but not by MPH (Cubillo *et al.* 2014*b*). As part of the ventral attention system, the IFC plays a crucial role in attention and cognitive control. Thus, MPH seems to improve attentional and inhibitory control by increasing IFC function, but not working memory organization by increasing DLPFC function. Furthermore, the observed effect sizes for inhibition and working memory across the lifespan are in line with the reported effect sizes in a recent meta-analysis comprising pediatric studies only (Coghill *et al.* 2013; 0.42 and 0.24, respectively), even though we included in the current meta-analysis also adult studies and a series of additional pediatric studies (an increase of nine inhibition studies and six working memory studies), and incorporated design-specific effect sizes as a methodological improvement. Moreover, our focus on omissions in sustained attention yielded a similar effect size as reported for reaction time variability in the Coghill meta-analysis. The fact that two meta-analyses with different statistical approaches and inclusion criteria reached similar conclusions increases the validity of the conclusions drawn.

The second main finding is that, when focusing on the age-dependency findings, we did not observe a linear or quadratic relationship between age and the effect of MPH on overall executive functioning, nor on the specific executive functions. Hence, in humans, the cognitive response to MPH did not seem to depend on age. While some human studies have suggested an age-dependency of MPH effects when comparing young children with older children and adolescents (Hanisch *et al.* 2004; Faraone & Buitelaar, 2010; Chamberlain *et al.* 2011), the age-dependency across the life span (i.e. including adulthood) is more apparent from animal studies (Andersen, 2005) and has been hardly studied in humans. The translation from animal research – often with equivocal conclusions – to human findings remains complex, as many differences between these types of research exist. For example, not all animal studies used an ADHD model such as the SHR, the administration method can be oral, intravenous or intraperitoneal, and drug dosages are not directly translatable to those used in humans (Kuczenski & Segal, 2002). Our hypotheses were informed by human studies, but also on animal studies assessing the locomotor response to stimulants. However, this locomotor response is considered to be more representative of reward sensitivity and addiction than of executive function. Given the scarcity of studies on the effect of MPH on reward, as well as on timing, we did not include these domains in the present analysis. Still, given the relevance of these domains in ADHD, it would be pertinent to run meta-regression analyses as soon as a sufficient number of MPH trials focusing on these cognitive domains have been conducted, to determine whether the effects of MPH on reward and timing are age-related.

With respect to the age-dependency results, it is important to note that especially the number of adult working memory studies was low. Put differently, the paucity of adult studies focusing on working memory is hampering the interpretation of the lack of an age-dependency of the effects of MPH on this specific cognitive domain. It is therefore that we also included all three cognitive domains in a single analysis, to determine a general age-dependency of cognitive effects of MPH. However, a general age-dependency was absent. Moreover, given that exposure to stimulants at a young age has been described to decrease sensitivity to stimulants, while exposure at an adult age increases sensitivity to stimulants in animals (Andersen, 2005), prior stimulant use may affect MPH response in humans. Therefore, one could argue that in the present study a potential age-relationship was masked by prior stimulant use. Since most studies do not report all factors potentially affecting the relationship between prior stimulant use and response to MPH (such as the onset and discontinuation of prior treatment), the exact role of prior stimulant use in our findings could not be determined. However, we did compare studies with either a fully treated or a fully naive sample in order to explore the relationship between prior stimulant use and the cognitive effects of MPH. Interestingly, the results of these analyses suggests that stimulant naivety was not a significant moderator of MPH effects

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and no interaction was present between age and medication naivety. Yet, the effect of MPH in fully treated samples was moderate and significant, whereas it was small and non-significant in stimulant-naive samples. Although, due to the scarcity of adult studies, these exploratory findings predominantly apply to the pediatric population, the pattern of findings does not suggest a differential effect of MPH on executive functioning across the lifespan; however, future research is warranted to determine the exact role of prior medication use.

As mentioned, the main goal of our analysis was to determine the age-dependency of the effect of MPH, if any, on executive functions. Therefore, we selected the dosage yielding the largest effect from studies reporting results of multiple dosages. This resulted in a mean dosage of 0.5 mg/kg for sustained attention and working memory and a slightly lower dosage of 0.3 mg/kg for response inhibition. While selecting the optimal effect is likely to induce a bias towards positive effects, which might result in an overestimate of effect sizes, the selected dosages are in line with the optimal effects in studies reporting linear dose–response relationships for working memory and attention, and an inverted U-shaped dose–response relationship for inhibition (Tannock *et al*. 1995; Konrad *et al*. 2004, 2005). Our exploratory analysis, however, did not reveal a significant association between effect size and dosage for any of the executive functions. This does not imply a general absence of a dose–response relationship, but implies that the optimal dose across studies induces comparable effect sizes.

In conclusion, while replicating the general effect of MPH on cognition, the present study shows no age-dependency of MPH effects on overall executive function, response inhibition, working memory and sustained attention. The major challenge for the future is to further unravel the relationship between the onset and duration of stimulant exposure and the cognitive sensitivity to MPH in humans, as there is a lack of knowledge on this subject. This could be done by including stimulant-naive participants in future studies. In addition, more studies with adolescent populations are needed to clarify the cognitive effects of MPH during this highly important developmental period. Moreover, it is of interest to determine how these cognitive effects relate to behavioral improvement (i.e. ADHD symptomatology), which is the primary target of MPH treatment. Some MPH studies, mostly with small samples, suggest minimal association between these two (Konrad *et al.* 2004; Loo *et al.* 2004; McInnes *et al.* 2007; Biederman *et al.* 2011), which is in line with the notion that cognitive (performance-based) measures and clinical rating scales in ADHD seem to tap different aspects of daily functioning (Toplak *et al.* 2013). Since cognitive dysfunction in ADHD is apparent in many individuals with ADHD, and predicts clinical response to MPH (Scheres *et al.* 2006; Coghill *et al.* 2007; van der Oord *et al.* 2012), additional work is needed to clarify the role of cognitive dysfunction in clinical functioning in order to further determine the clinical relevance of cognitive enhancement by MPH. Hence, better insight in the neurocognitive effects of MPH will, hopefully, ultimately result in improved ADHD treatment across the lifespan.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291716000350

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Declaration of Interest

None.

Notes

[1] Cubillo *et al*. (2014*a*, *b*) reported data on different cognitive domains collected in the same adolescent participants. These were reflected once in the total count of 1599 participants. Four studies were conducted with adolescent samples, but only three unique samples of adolescent participants were present.

[2] A model incorporating both a linear and quadratic component also yielded no significant effect.

[3] Note that these analyses reflect dose–response relationships in the data selected for the main age-dependency analysis. They do not comprise all data points from studies presenting the effects of multiple dosages.

[4] A model incorporating both a linear and quadratic component also yielded no significant effect.

[5] A model incorporating both a linear and quadratic component also yielded no significant effect.

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