Age-Dependent Effects of Methylphenidate on the Human Dopaminergic System in Young vs Adult Patients With Attention-Deficit/Hyperactivity Disorder
A Randomized Clinical Trial

Anouk Schrantee, MSc; Hyke G. H. Tamminga, MSc; Cheima Bouziane, MSc; Marco A. Bottelier, MD;
Esther E. Bron, MSc; Henk-Jan M. M. Mutsaerts, MD, PhD; Aeilko H. Zwinderman, PhD; Inge R. Groote, PhD;
Serge A. R. B. Rombouts, PhD; Ramon J. L. Lindauer, MD, PhD; Stefan Klein, PhD; Wiro J. Niessen, PhD;
Brent C. Opmeer, PhD; Frits Boer, MD, PhD; Paul J. Lucassen, PhD; Susan L. Andersen, PhD; Hilde M. Geurts, PhD;
Liesbeth Reneman, MD, PhD

IMPORTANCE Although numerous children receive methylphenidate hydrochloride for the treatment of attention-deficit/hyperactivity disorder (ADHD), little is known about age-dependent and possibly lasting effects of methylphenidate on the human dopaminergic system.

OBJECTIVES To determine whether the effects of methylphenidate on the dopaminergic system are modified by age and to test the hypothesis that methylphenidate treatment of young but not adult patients with ADHD induces lasting effects on the cerebral blood flow response to dopamine challenge, a noninvasive probe for dopamine function.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled trial (Effects of Psychotropic Drugs on Developing Brain–Methylphenidate) among ADHD referral centers in the greater Amsterdam area in the Netherlands between June 1, 2011, and June 15, 2015. Additional inclusion criteria were male sex, age 10 to 12 years or 23 to 40 years, and stimulant treatment–naive status.

INTERVENTIONS Treatment with either methylphenidate or a matched placebo for 16 weeks.

MAIN OUTCOMES AND MEASURES Change in the cerebral blood flow response to an acute challenge with methylphenidate, noninvasively assessed using pharmacological magnetic resonance imaging, between baseline and 1 week after treatment. Data were analyzed using intent-to-treat analyses.

RESULTS Among 131 individuals screened for eligibility, 99 patients met *DSM-IV* criteria for ADHD, and 50 participants were randomized to receive methylphenidate and 49 to placebo. Sixteen weeks of methylphenidate treatment increased the cerebral blood flow response to methylphenidate within the thalamus (mean difference, 6.5; 95% CI, 0.4-12.6; *P* = .04) of children aged 10 to 12 years old but not in adults or in the placebo group. In the striatum, the methylphenidate condition differed significantly from placebo in children but not in adults (mean difference, 7.7; 95% CI, 0.7-14.8; *P* = .03).

CONCLUSIONS AND RELEVANCE We confirm preclinical data and demonstrate age-dependent effects of methylphenidate treatment on human extracellular dopamine striatal-thalamic circuitry. Given its societal relevance, these data warrant replication in larger groups with longer follow-up.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Liesbeth Reneman, MD, PhD, Department of Radiology Academic Medical Center, University of Amsterdam, Room G1-222, Meiberdgreef 9, 1105 AZ Amsterdam, the Netherlands (l.reneman@amc.uva.nl).

Methylphenidate hydrochloride is the most frequently prescribed medication for the treatment of attention-deficit/hyperactivity disorder (ADHD). It effectively reduces symptoms of inattention, hyperactivity, and impulsivity in up to 80% of children with ADHD.[1] Methylphenidate increases extracellular dopamine (DA) levels in the brain by blocking the DA transporters in the synapse.[2] Its short-term safety has been documented in many studies, and its efficacy is among the highest of all psychiatric medications.[3] However, despite its prevalent use among children and adolescents, little is known about lasting effects of methylphenidate on the developing DAergic system.[3-5]

The adolescent brain is a rapidly developing system that maintains high levels of plasticity. As such, the brain may be particularly vulnerable to drugs that interfere with these processes or modify the specific transmitter systems involved. The effects of methylphenidate on brain development have so far only been studied in healthy male animals,[4,6] with short washout periods.[7] More recent evidence indicates that psychotropic drugs affect the brain in a differential manner that depends on the age at exposure.[5] Whereas long-term stimulant exposure in adult animals results in a temporary adaptation to the drug effects, more lasting (and sometimes permanent) alterations are seen when methylphenidate is administered to juvenile animals, a process referred to as *neurochemical imprinting*.[5]

Safety investigations on the effects of methylphenidate on DA function in the developing brain are scarce in children.[7] Regardless of this alarming paucity of findings, increasingly greater numbers of children and young adolescents are exposed to methylphenidate, many of whom likely do not meet the criteria for ADHD.[8] This heightened use has led to considerable debate and concern (eg, among parents) about the long-term consequences or possible adverse effects of methylphenidate use in children. Such knowledge is urgently needed, as recently emphasized by several entities, including the US Food and Drug Administration[9] and National Institutes of Health[10] and the European Committee for Medicinal Products for Human Use.[11]

The primary aim of the Effects of Psychotropic Drugs on Developing Brain-Methylphenidate study was to assess the effects of long-term methylphenidate treatment on DA function in children and adults with ADHD. We probed DA function using methylphenidate-based pharmacological magnetic resonance imaging (phMRI), a powerful noninvasive technique to investigate DA function in vivo.[12,13] Due to increased DA levels,[14] we hypothesized an increased cerebral blood flow (CBF) response to methylphenidate in children treated with methylphenidate for 4 months (with a 1-week washout) but no such lasting effects in methylphenidate-treated adults.

Methods

Trial Design

The Effects of Psychotropic Drugs on Developing Brain-Methylphenidate[15] study was a 16-week double-blind, randomized, placebo-controlled, multicenter trial of the use

Key Points

Question Are the effects of methylphenidate hydrochloride on the dopaminergic system in patients with attention-deficit/hyperactivity disorder modified by age?

Findings In a randomized clinical trial of 99 male patients with attention-deficit/hyperactivity disorder, 4 months of methylphenidate treatment induced enduring effects in the cerebral blood flow response to an acute challenge with methylphenidate (a noninvasive probe for dopamine function) in children but not in adults.

Meaning Methylphenidate has a different effect on the developing dopaminergic system compared with the matured dopaminergic system.

of methylphenidate and a blinded end point evaluation in stimulant treatment-naive patients with ADHD. The effect of age on the CBF response to a DA challenge and overall clinical outcome was assessed using phMRI in children and adults with ADHD, randomly assigned to either placebo or active treatment with methylphenidate, at baseline and after a 1-week washout (eFigure 1 in Supplement 1). The trial protocol applied the code of medical ethics and was registered by the Central Committee on Research Involving Human Subjects (an independent registry) on March 24, 2011 (identifier NL34509.000.10) and subsequently at The Netherlands National Trial Register (identifier NTR3103), with enrollment of the first patient on October 13, 2011. In addition, the institutional review board of the Academic Medical Center approved the study. The full protocol is available in Supplement 2. The trial ended on June 15, 2015, and was monitored by the Clinical Research Unit of the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

All patients and parents or legal representatives of the children provided written informed consent.

Participants

Participants were 50 stimulant treatment-naive boys (10-12 years old) and 49 stimulant treatment-naive men (23-40 years old) diagnosed as having ADHD and recruited through clinical programs at the Department of Child and Adolescent Psychiatry at Triversum (Alkmaar, the Netherlands), De Bascule Academic Center for Child and Adolescent Psychiatry (Amsterdam), and PsyQ mental health facility (The Hague). All children and adults who were included met strict criteria for ADHD according to the *DSM-IV*[16] and were diagnosed by an experienced psychiatrist (M.A.B.), which was confirmed with the *Diagnostic Interview Schedule for Children* (authorized Dutch translation)[17] and the *Diagnostic Interview for ADHD in Adults*.[18] Patients with comorbid Axis I psychiatric disorders requiring treatment with medication at study entry, a history of major neurological or medical illness, or a history of clinical treatment with drugs influencing the DAergic system (for adults before age 23 years), such as stimulants, neuroleptics, antipsychotics, and dopamine 2 and 3 (D_2 and D_3) agonists, were excluded. More detailed inclusion and exclusion criteria are available in the trial protocol (Supplement 2).

Intervention, Randomization, and Blinding

Patients were randomly assigned to either methylphenidate or placebo treatment (eAppendix in Supplement 1). The treating physicians (C.B. and M.A.B.) prescribed the study medication under double-blind conditions on clinical guidance (ie, reduction in ADHD symptoms) in accord with Dutch treatment guidelines. Adult participants received coaching sessions, and parents of children received psychoeducation. Adherence to the study medication was monitored at each of the 5 control visits (weeks 1, 3, 8, and 12 for children and weeks 1, 2, 4, 8, and 12 for adults).

Outcomes

Primary Outcome Measure of DA Function

We used phMRI to assess the CBF response to the DA challenge with methylphenidate. Pharmacological MRI is based on the principle that neurotransmitter-specific drug challenges evoke changes in neurovascular coupling and resultant changes in brain hemodynamics, such as the CBF.[19] It has been shown to indirectly assess DA dysfunction in a noninvasive manner similar to positron emission tomographic and single-photon emission computed tomographic studies.[12,13,20,21]

The phMRI scan consisted of 2 sessions, one before and one 90 minutes after oral administration of 0.5 mg/kg of methylphenidate hydrochloride (with a maximum dose of 20 mg for children and 40 mg for adults) acquired on a 3.0-T MR imaging system (Philips). Heart rate (HR) was determined using a peripheral pulse unit, and carotid flow was measured using 2-dimensional phase-contrast MRI. Pharmacological MRI assessment took place at baseline (week 0) and posttreatment after a 1-week washout (week 17) to ascertain drug clearance (methylphenidate has a half-life of 2-3 hours[22]). Arterial spin labeling phMRI was used to assess the CBF. The means of the CBF values in the gray matter of 3 a priori selected regions of interest (eFigure 2 in Supplement 1) (ie, striatum, thalamus, and anterior cingulate cortex) were used for statistical analysis. These regions of interest were selected because the striatum is rich in DA transporters (the primary target of methylphenidate) and because animal literature has demonstrated large phMRI effects of early methylphenidate treatment in the thalamus and anterior cingulate cortex.[14] Data acquisition, postprocessing, absolute CBF values, exploratory voxel-based analyses of the CBF maps, HR, and carotid flow are described and shown in detail in the eAppendix and eFigures 3, 4, 5, and 6 in Supplement 1, respectively.

Secondary Outcome Measure of Clinical Assessment

Clinical change was rated using the Clinical Global Impression–Severity and Clinical Global Impression–Improvement[23] scores, both on a 7-point Likert-type scale. Response to treatment was defined as a score of 1 or 2 on the Clinical Global Impression–Improvement (indicating "very much improved" or "much improved") and compared between groups at trial's end.

Statistical Analysis

All primary analyses are intent-to-treat, with the significance level set at $P < .05$ (2-sided). To evaluate the effect of methylphenidate on the development of the DAergic system, paired

t tests were used to assess individual change in acute CBF response after a methylphenidate challenge from baseline to posttreatment (Δi CBF) for all 4 groups separately. The effect of treatment on Δi CBF within both age groups was assessed using independent t tests. To test the interaction between age and treatment on Δi CBF, a 2-way analysis of variance (ANOVA) was performed with age and medication group as factors. Missing values for the CBF (3.6% [14 of 392] due to dropout and 10.7% [42 of 392] in total) and clinical assessments (3.6% [14 of 392] due to dropout and 18.9% [74 of 392] in total) were replaced using nearest neighbor interpolation within age and medication group. For baseline characteristics and clinical outcome, a Fisher exact test was used for the analysis of categorical data, with odds ratio as effect size estimate (Clinical Global Impression-Improvement), and t test and ANOVA were used for continuous variables (Clinical Global Impression–Severity and CBF), with normal distributions and partial eta squared (η_p^2) as effect size estimate. Statistical analyses were conducted with a software program (SPSS, version 22; IBM). Sample size calculations are available in the eAppendix in Supplement 1.

Results

Randomization and Baseline Characteristics

Between June 1, 2011, and February 6, 2015, a total of 99 patients with ADHD in 3 Dutch centers were randomized to methylphenidate or placebo treatment. After randomization, one individual disclosed that he had been treated for ADHD with methylphenidate before and was therefore excluded from the statistical analyses. Fifty children and 48 adults were included in the primary analysis (**Figure 1**), although one individual was included at age 22 years 5 months. Treatment groups did not differ in age, ADHD symptom severity, and clinical impairment (**Table 1**). No serious adverse events were noted in any of the individuals studied.

Treatment Assignment and Details

Treatment allocation and dropout rates are shown in Figure 1. Owing to unforeseen technical changes to the MRI scanner, 8 adults underwent the posttreatment scan at 8 weeks instead of 17 weeks. The mean treatment duration did not differ between treatment groups in adults ($P = .68$) and children ($P = .73$).

Main Outcome of the CBF Response to Methylphenidate Challenge

Paired t tests indicated a significant increase (mean difference, 6.5; 95% CI, 0.4-12.6; $P = .04$) (**Figure 2**) in the CBF change from pretreatment to posttreatment in the thalamus of children treated with methylphenidate and nonsignificant differences in the striatum and anterior cingulate cortex (mean difference, 5.7; 95% CI, −0.4 to 11.8; $P = .07$ and mean difference, 5.5; 95% CI, −0.1 to 11.1; $P = .06$, respectively), presumably reflecting increased DA levels. As hypothesized, treatment of adults with methylphenidate did not induce such an effect, nor did placebo treatment in either age group. Further-

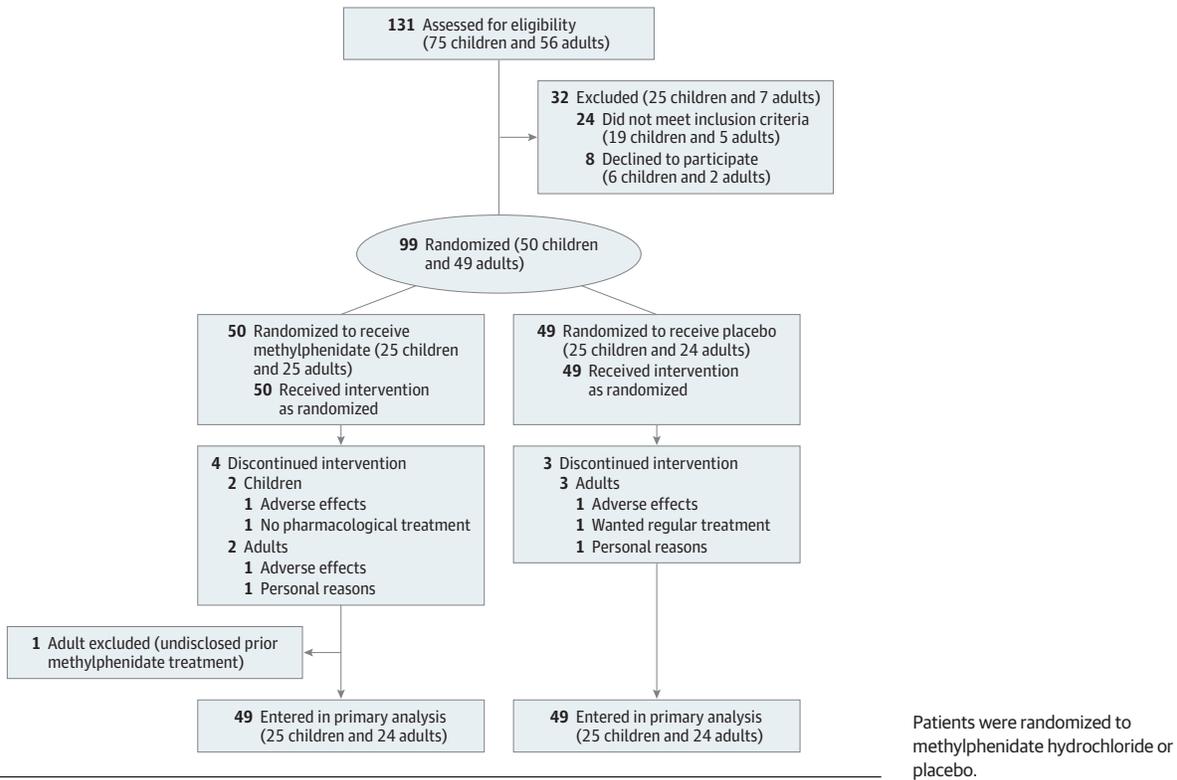Figure 1. Consolidated Standards of Reporting Trials Flow Diagram

131 Assessed for eligibility
(75 children and 56 adults)

32 Excluded (25 children and 7 adults)
 24 Did not meet inclusion criteria
  (19 children and 5 adults)
 8 Declined to participate
  (6 children and 2 adults)

99 Randomized (50 children
and 49 adults)

50 Randomized to receive
methylphenidate (25 children
and 25 adults)
 50 Received intervention
 as randomized

49 Randomized to receive placebo
(25 children and 24 adults)
 49 Received intervention
 as randomized

4 Discontinued intervention
 2 Children
  1 Adverse effects
  1 No pharmacological treatment
 2 Adults
  1 Adverse effects
  1 Personal reasons

3 Discontinued intervention
 3 Adults
  1 Adverse effects
  1 Wanted regular treatment
  1 Personal reasons

1 Adult excluded (undisclosed prior
methylphenidate treatment)

49 Entered in primary analysis
(25 children and 24 adults)

49 Entered in primary analysis
(25 children and 24 adults)

Patients were randomized to
methylphenidate hydrochloride or
placebo.

Table 1. Demographics and Characteristics of the Study Participants

	Children		Adults	
Variable	Methylphenidate Hydrochloride n = 25	Placebo n = 25	Methylphenidate Hydrochloride n = 24	Placebo n = 24
Age, mean (SD), y	11.4 (0.8)	11.3 (0.9)	28.6 (4.6)	29.0 (4.9)
Estimated IQ, mean (SD)[a]	104.8 (21.0)	103.4 (15.1)	107.9 (8.8)	107.9 (6.4)
ADHD subtype, No.				
Inattentive	14	14	11	5
Hyperactive/impulsive	0	1	0	0
Combined	11	10	13	19
ADHD symptom score, mean (SD)				
DBD-RS inattention	21.7 (3.2)	22.8 (3.4)	NA	NA
DBD-RS hyperactivity	15.0 (5.0)	16.4 (6.3)	NA	NA
ADHD-RS self-report	NA	NA	30.6 (10.0)	30.4 (9.3)
Clinical impairment score, mean (SD)	4.0 (0.2)	4.0 (0.3)	3.8 (0.5)	3.8 (0.5)
Adherence, mean (SD), %	84 (15)	80 (18)	90 (8)	86 (8)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder;
ADHD-RS, ADHD Rating Scale; DBD-RS, Disruptive Behavior Disorder Rating
Scale; NA, not applicable.

[a] For children, the Wechsler Intelligence Scale for Children was used. For adults,
the National Adult Reading Test was used.

more, striatal CBF values were also significantly higher (mean difference, 7.7; 95% CI, 0.7-14.8; $P = .03$) in children treated with methylphenidate compared with placebo, whereas no such treatment effect was observed in adults (**Table 2**). Finally, 2-way ANOVA showed a nonsignificant age × treatment interaction in the striatum (8.0; 95% CI, −0.3 to 16.3; $P = .06$) ($\eta_p^2 = 0.04$). The difference in response to methylphenidate or placebo treatment in children can also be observed in the difference maps (eFigure 4 in Supplement 1).

Clinical Assessment

A repeated-measures ANOVA showed a significant time × treatment interaction in children ($P = .01$, $\eta_p^2 = 0.21$) and adults ($P = .02$, $\eta_p^2 = 0.20$) on the Clinical Global Impression–Severity scale (**Figure 3**), with the methylphenidate groups reporting lower global clinical impairment compared with the placebo groups. The methylphenidate group in children showed more improvement than the placebo group at week 3 ($P = .03$, $\eta_p^2 = 0.09$) and week 8 ($P < .01$, $\eta_p^2 = 0.15$), whereas

Figure 2. Treatment Effects on the Cerebral Blood Flow (CBF) Response to Dopamine Challenge
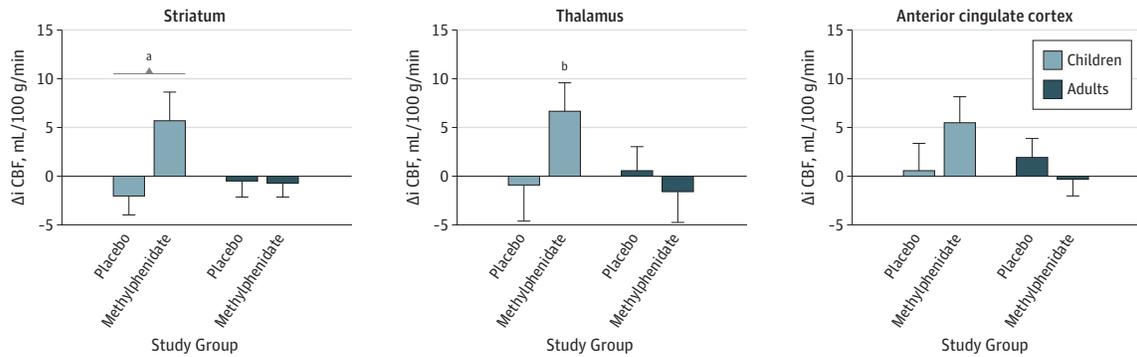
Shown are the means (SEMs) for the individual change in acute CBF response (Δi CBF) in the placebo and methylphenidate hydrochloride groups.

[a] $P < .05$ by independent t test comparing Δi CBF between the 2 treatment groups in the striatum (mean difference, 7.7; 95% CI, 0.7-14.8; $P = 0.03$,

$\eta_p^2 = 0.09$) (see also Table 2).

[b] $P < .05$ by paired t test comparing pretreatment to posttreatment Δi CBF within each group in the thalamus (mean difference, 6.5; 95% CI, 0.4-12.6; $P = 0.04$, $\eta_p^2 = 0.17$).

Table 2. Cerebral Blood Flow (CBF) Response to Dopamine Challenge[a]

	Children			Adults		
Δi CBF	Mean Difference (95% CI), mL/100 g/min (n = 50)	P Value[b]	η_p^2 Value	Mean Difference (95% CI), mL/100 g/min (n = 48)	P Value[b]	η_p^2 Value
Striatum	7.7 (0.7 to 14.8)	.03	0.09	−0.2 (−4.6 to 4.1)	.92	<0.01
Thalamus	7.5 (−2.1 to 17.1)	.12	0.05	−2.1 (−10.2 to 5.9)	.60	<0.01
Anterior cingulate cortex	4.9 (−2.9 to 12.7)	.22	0.03	−2.3 (−7.5 to 3.0)	.39	0.02

[a] Shown are differences between treatment groups in individual CBF response to methylphenidate hydrochloride from pretreatment to posttreatment acute CBF response (Δi CBF).

[b] By independent t test.

Figure 3. Treatment Effects on Global Clinical Impairment in the Methylphenidate and Placebo Groups
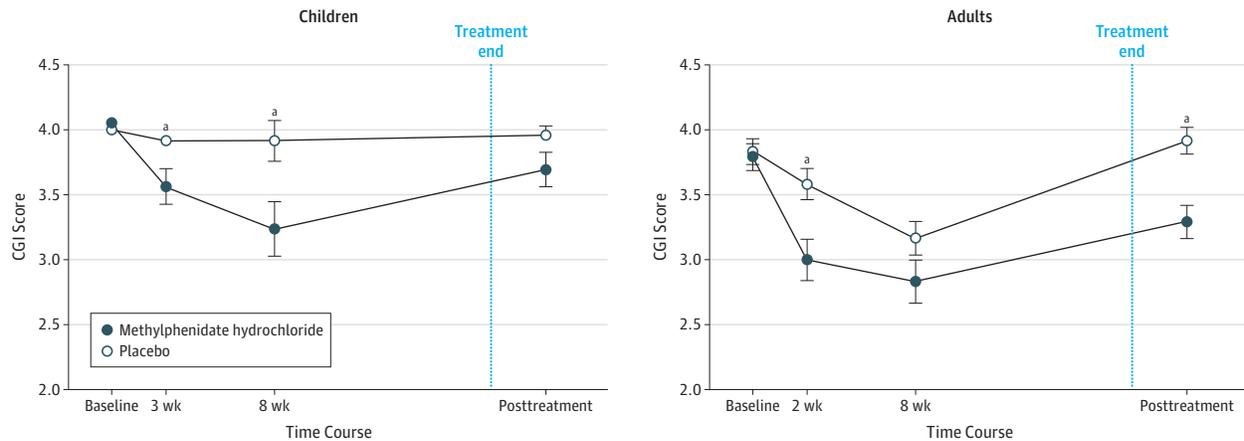
Shown are the means (SEMs) for Clinical Global Impression (CGI) scores at baseline, week 3, week 8, and posttreatment (week 17). In children, we found a significant difference between treatment groups in the change from baseline to week 3 ($P = .03$) and week 8 ($P = .005$) but not at week 17 ($P = .06$). In contrast,

in adults, we found a significant time × treatment interaction at week 3 ($P = .01$) and week 17 ($P = .01$) but not at week 8 ($P = .20$).

[a] $P < .05$ comparing treatment groups on individual time points (by t test).

in adults this difference was only significant at week 3 ($P = .01$, $\eta_p^2 = 0.14$) and week 17 ($P = .01$, $\eta_p^2 = 0.14$). On the Clinical Global Impression-Improvement scale, the proportion of patients who reported feeling "much improved" or "very much improved" (compared with baseline) 1 week after the end of

the trial was significantly higher for the methylphenidate condition relative to the placebo condition in adult patients but not in children. The values in adults were 62.5% (15 of 24) for the methylphenidate group vs 8.3% (2 of 24) for the placebo group (odds ratio, 18.33; $P < .001$). The values in children were

12.0% (3 of 25) for the methylphenidate group vs 0% (0 of 25) for the placebo group (odds ratio, 7.93; $P = .24$).

Discussion

We studied whether age modulates the effects of prolonged methylphenidate treatment on the human DAergic system. After 4 months of methylphenidate treatment, we found significant increases in the CBF response to a DA challenge in the striatum and thalamus 1 week after the end of the trial in treatment-naive children, suggesting lasting changes in the DAergic system. This effect was specific to children because placebo treatment failed to show such an effect in either age group, and active treatment with methylphenidate in adults had no effect either. In contrast, methylphenidate induced persistent clinical improvement in adults but not in children.

Our finding that methylphenidate treatment induces persistent increases in the CBF response to an acute challenge with methylphenidate in children is in line with preclinical phMRI investigations that report long-lasting increases in regional CBF in several DA-rich brain regions in juvenile rats treated with methylphenidate.[14] Similarly, more invasive techniques have demonstrated that long-term methylphenidate treatment with clinically relevant doses causes long-lasting reductions in striatal DA transporters,[24] expression of D_3 receptors in the prefrontal cortex,[14] increased DA levels,[25] and a reduction in prefrontal neuronal excitability and synaptic transmission[6] in juvenile (but not adult) rats. In humans, structural MRI studies[26,27] have shown that stimulant treatment affects brain maturation, such that untreated children with ADHD show more rapid cortical thinning and smaller white matter volumes than children with ADHD receiving stimulant medication. Several positron emission tomographic investigations have compared on-medication and off-medication conditions in children and adults with ADHD. They showed mostly reductions in the CBF when off medication in motor and anterior cingulate cortices,[28] somatosensory cortices,[29] striatum,[29] and parietal areas[30] in children. However, in adults, decreases were seen in precentral gyri and striatum but increased CBF in the vermis.[31] In addition, an arterial spin labeling–based study[32] reported reduced frontal and striatal perfusion in adults receiving ADHD medication. These findings are in line with our exploratory voxelwise analyses that showed reduced CBF after methylphenidate challenge (eFigure 4 in Supplement 1).

Preclinical evidence suggests that our present findings are mediated, in part, by changes in the expression of cortical D_3 receptors. For example, juvenile exposure to methylphenidate induced a long-lasting decrease in D_3 receptor messenger RNA in the medial prefrontal cortex.[33] In rats, D_3 receptor expression is high during early adolescence and then wanes until becoming absent in adulthood. Reduced D_3 receptor autoregulation after early methylphenidate treatment causes DA levels to rise, which subsequently increases activity at other DA receptors. The D_2 and D_3 receptors have the highest affinity for DA. However, as extracellular DA levels increase, more binding to D_1 occurs, inducing increases in the hemodynamic response.[14]

Because ADHD is associated with DA hypofunction,[2] a lasting increase in DA neurotransmission—as evidenced by increased CBF values in response to an acute challenge with methylphenidate (which we found in methylphenidate-treated children only)—will likely result in positive effects on the clinical condition. However, this finding was not the case in the children in our cohort, with the positive effect of methylphenidate on clinical assessment during the trial waning after drug clearance. In contrast, adults in the methylphenidate group showed clinical improvement after washout, but there was no response difference in the placebo group at week 8, which is probably owing to the large placebo response as a result of coaching. Despite limited evidence for cognitive interventions in children,[34] coaching has shown to be beneficial in adult ADHD both with and without additional pharmacological treatment.[35-38] Nevertheless, it cannot be excluded that pharmacological treatment is less robust in adults than in children, and this hypothesis warrants further research.

Because maturation of several brain regions is not complete until adolescence,[39] drugs given during the sensitive early phases of life may affect neurodevelopmental trajectories that can have more profound effects later in life.[24] Indeed, the most comprehensive trial on the long-term effects of ADHD, the Multimodal Treatment Study of Children With ADHD,[1] reported that 6 years after enrollment, medication management was associated with a transient increase in the prevalence of anxiety and depression.[40] This finding is in line with animal studies that reported increased anxiety and depression scores in juvenile methylphenidate-treated rats[41] and memory impairments.[42] In addition, cohort investigations have provided evidence for age-dependent effects. For example, adult ADHD is associated with a high rate of substance abuse,[43] but ADHD stimulant medication use in childhood does not increase this risk[44,45] and may even decrease such vulnerability.[46]

A major strength of the present study is its design, such that the effects of confounders (eg, age and sex) are small. We chose to include only male patients to limit participant variation because girls and boys differ considerably in brain growth patterns[39] and because ADHD is most prevalent in male individuals.[15] The selective inclusion of stimulant treatment-naive patients was also critical for addressing our objective. Ideally, we would have used a longer washout period because the effects of drug exposure on the developing brain are hypothesized to be only fully expressed during early adulthood,[5,24] and the present results indicate that such follow-up studies are warranted. However, for ethical reasons, the time that a child would not receive adequate treatment (placebo condition) dictated the length of this randomized clinical trial because the waiting list for treatment in the Netherlands was typically 4 months.

Our study had limitations. Owing to its complexity, the power of the study was limited, especially because we examined 3 different brain regions, which could have increased the risk of a type I error. Hence, our findings need to be replicated using a larger sample size with more statistical power. In addition, it is likely that the effects of methylphenidate are not

confined to the regions of interest studied but likely affect DAergic projections throughout the brain, including other cortical regions.

Another potential weakness is that—despite its advantages and sensitivity, as discussed above—phMRI remains an indirect measure of DA function. It specifically assesses the hemodynamic response as a proxy of neurotransmission, and physiological effects could affect the hemodynamic response. For example, HRs differ between children and adults.[47] Although acute methylphenidate administration increased HR, it occurred in both children and adults. Moreover, we found no age × treatment interaction at baseline, nor did methylphenidate treatment significantly alter HR in either age group (eFigure 5 in Supplement 1). Therefore, although we did not find evidence for systemic vascular effects (eFigure 6 in Supplement 1), we cannot fully disentangle DA neurotransmission from direct effects of DA on the microvasculature.[48]

Another potential limitation is baseline differences in the CBF between children and adults. However, additional analyses assessing changes in relative CBF provided similar results (eAppendix in Supplement 1). Therefore, it is unlikely that the differences between children and adults are attributable to differences in HR or global CBF. Furthermore, previous studies have shown that time-course changes in the phMRI signal closely parallel microdialysis measurements of striatal DA release[21] and correlate well with positron emission tomographic and single-photon emission computed tomographic measurements of DA transporter availability,[12] DA release,[13] and behavioral measures of DA dysfunction.[12,13] Pharmacological MRI investigations in rats[5] further report data similar to the present findings. This collective evidence indicates that phMRI is ideally suited to noninvasively study methylphenidate effects in children.

Conclusions

In line with extensive preclinical data, we provide the first evidence, to our knowledge, that methylphenidate treatment during a specific period of maturation alters the CBF response, likely reflecting increased DA neurotransmission due to neurochemical imprinting by methylphenidate. In the short term, these alterations do not induce major benefits or harm regarding clinical improvement, but the long-term consequences remain to be established. Therefore, our data stress the need for longer follow-up studies that address possibly progressive disturbances of the DAergic system and associated behavioral abnormalities.

Author Affiliations: Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Schrantee, Tamminga, Bouziane, Bottelier, Mutsaerts, Reneman); Brain Imaging Center, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Schrantee, Bouziane, Mutsaerts, Reneman); Amsterdam Brain and Cognition, University of Amsterdam, Amsterdam, the Netherlands (Schrantee, Reneman); d'Arc (Dutch Autism and Attention-Deficit/Hyperactivity Disorder Research Center), Department of Brain and Cognition, University of Amsterdam, Amsterdam, the Netherlands (Tamminga, Geurts); Department of Child and Adolescent Psychiatry, Triversum, Alkmaar, the Netherlands (Bottelier); Biomedical Imaging Group Rotterdam, Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands (Bron, Klein, Niessen); Biomedical Imaging Group Rotterdam, Department of Radiology, Erasmus MC, Rotterdam, the Netherlands (Bron); Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Zwinderman); Institute of Psychology, Department of Social Sciences, University of Oslo, Oslo, Norway (Groote); Institute of Psychology, Leiden University, Leiden, the Netherlands (Rombouts); Department of Radiology, Leids Universitair Medisch Centrum, Leiden, the Netherlands (Rombouts); Department of Child and Adolescent Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Lindauer, Boer); De Bascule Academic Center for Child and Adolescent Psychiatry, Amsterdam, the Netherlands (Lindauer, Boer); Department of Imaging Physics, Faculty of Applied Sciences, Delft University of Technology, Delft, the Netherlands (Niessen); Clinical Research Unit, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Opmeer); Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam, Amsterdam, the Netherlands (Lucassen); Department of Psychiatry, Harvard Medical School and McLean Hospital, Belmont, Massachusetts (Andersen).

Author Contributions: Ms Schrantee and Dr Reneman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lindauer, Boer, Geurts, Reneman.
Acquisition, analysis, or interpretation of data: Schrantee, Tamminga, Bouziane, Bottelier, Bron, Mutsaerts, Zwinderman, Groote, Rombouts, Klein, Niessen, Opmeer, Lucassen, Andersen.
Drafting of the manuscript: All authors.
Administrative, technical, or material support: All authors.

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