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# The age-dependent effects of a single-dose methylphenidate challenge on cerebral perfusion in patients with attention-deficit/hyperactivity disorder

A Schrantee[a,b,*], HJMM Mutsaerts[a,c], C Bouziane[a], HGH Tamminga[a,d], MA Bottelier[e], L Reneman[a,b]

[a]Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[b]Amsterdam Brain and Cognition, University of Amsterdam, Amsterdam, The Netherlands
[c]Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada
[d]Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands
[e]Department of Child- and Adolescent Psychiatry, Triversum, Alkmaar, The Netherlands

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ABSTRACT

Methylphenidate (MPH) is a stimulant drug and an effective treatment for attention-deficit/hyperactivity disorder (ADHD) in both children and adults. Pre-clinical studies suggest that the response to stimulants is dependent on age, which may reflect the ontogeny of the dopamine (DA) system, which continues to develop throughout childhood and adolescence. Therefore, the aim of this study was to investigate the modulating effect of age on the cerebral blood flow (CBF) response to MPH in stimulant treatment-naive children and adults with ADHD.

Ninety-eight stimulant treatment-naive male pediatric (10–12 years) and adult (23–40 years) patients with ADHD were included in this study. The CBF response to an acute challenge with MPH (0.5 mg/kg) was measured using arterial spin labeling (ASL) pharmacological magnetic resonance imaging, as a proxy for DA function. Region-of-interest (ROI) analyses were carried out for the striatum, thalamus and medial prefrontal cortex and in addition voxel-wise analyses were conducted.

An acute challenge with MPH decreased CBF in both children and adults in cortical areas, although to a greater extent in adults. In contrast, ROI analyses showed that MPH decreased thalamic CBF only in children, but not adults.

Our findings highlight the importance of taking the developmental perspective into account when studying the effects of stimulants in ADHD patients.



## 1. Introduction

Pharmacological treatment of attention-deficit hyperactivity disorder (ADHD) is increasing in children, but also in the adult population (McCarthy et al., 2012). Stimulants, such as methylphenidate (MPH), are the main pharmacological treatment in both children and adults. MPH is the most frequently prescribed stimulant and is particularly effective in reducing behavioral symptoms (MTA group, 1999), at least on the short term. Its therapeutic efficacy has largely been ascribed to its ability to prevent reuptake of catecholamines, such as dopamine (DA) and noradrenalin (NA), thereby enhancing DAergic and noradrenergic neurotransmission (Arnsten, 2011). Indeed, neuroimaging studies have suggested major DAergic alterations in the pathogenesis of ADHD and thereby lend further support for the efficacy of stimulants (Castellanos et al., 1996; Larisch et al., 2006; Spencer et al., 2013). Thus, assessment of the functioning of the DA system is key for studying the pathophysiology of ADHD across development.

The DA system develops throughout childhood, but is not fully mature until adulthood (Wahlstrom et al., 2010). Remodeling of pre- and postsynaptic receptors continues during development, resulting in differential functioning and output of the DA system at different developmental stages. For example, preclinical studies have observed a major shift in the ratio of excitatory $D_{1/5}$ and inhibitory $D_{2/3/4}$ receptors (Chen et al., 2010). Also, previous studies have demonstrated anatomical developmental abnormalities in patients with ADHD (Shaw et al., 2014, 2009). In addition, both the structure and function of the DA system may be altered in children and adults with ADHD when compared to healthy controls (Weyandt et al., 2013).

Functional abnormalities in DAergic areas have originally been assessed using perfusion studies with position emission tomography (PET) and single photon emission computed tomography (SPECT), but more recently also with magnetic resonance imaging (MRI). Using these techniques, not only baseline perfusion in DAergic brain areas can be studied, but also the response to stimulant medication such as

* Corresponding author at: Department of Radiology z0-180, Academic Medical Center, P.O. Box 22660, 1105AZ Amsterdam, The Netherlands.
*E-mail address:* a.g.schrantee@amc.uva.nl (A. Schrantee).

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MPH. Although early PET studies in children with ADHD suffered from methodological constraints such as small sample size, they consistently reported decreased perfusion in the striatum compared to controls, which was, in some studies, reversed by a single dose of MPH (Kim et al., 2001; Lee et al., 2005; Lou et al., 1989). In contrast, in adult ADHD patients both increases and decreases in CBF have been reported following MPH administration using PET and MRI (O'Gorman et al., 2008; Schweitzer et al., 2003). Thus, the current evidence suggests that the effects of MPH on CBF and DA function may be modified by age, although this has not been properly studied.

Therefore, to further enhance our understanding of the functioning of the DA system in response to MPH, we set up the current study in which we directly investigated the modulating effect of age on the CBF response to MPH in stimulant treatment-naive boys and men with ADHD. We used arterial spin labeling (ASL) based pharmacological MRI (phMRI) with a MPH challenge to assess changes in cerebral perfusion. PhMRI is based on the principle that neurotransmitter-specific drug challenges evoke changes in neurovascular coupling that result in hemodynamic changes (Jenkins, 2012). Non-invasive phMRI measurements have been shown to be well-correlated with PET and SPECT studies of DA function (Chen et al., 1997; Jenkins et al., 2004). Based on previous studies, we hypothesized that a single oral dose of MPH would increase CBF in the striatum, thalamus and prefrontal cortex (PFC) in children, whereas in adults we expected a decrease in perfusion, as a result of the functional ontogeny of the DA receptors (Chen et al., 2010).

## 2. Methods

### 2.1. Participants

Participants were stimulant-treatment naive boys and men with ADHD; 50 aged between 10 and 12 years and 49 aged between 23 and 40 years. The children were recruited from clinical programs at the Child and Adolescent Psychiatry Center Triversum (Alkmaar) and from the Department of (Child and Adolescent) Psychiatry of the Bascule/AMC (Amsterdam). The adults were recruited from the clinical programs at the PsyQ Mental Health Facility (The Hague) and from the Department of Psychiatry of the AMC (Amsterdam). Patients were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 4th edition) and the diagnosis was subsequently confirmed with a structured interview: Diagnostic Interview Schedule for Children (National Institute of Mental Health Diagnostic Interview Schedule for Children Version IV (NIMH-DISC-IV, authorized Dutch Translation) in children and Diagnostic Interview for ADHD (DIVA) for adults (Kooij, 2012). Participants were excluded when diagnosed with a co-morbid axis I psychiatric disorder requiring pharmacological treatment at study entry; IQ < 80 (estimated with two subscales of the Wechsler Intelligence Scale for Children-Revised (WISC-R); prenatal use of MPH by the mother; clinical treatment with drugs influencing the DA system (for adults before 23 years of age), such as stimulants, neuroleptics, antipsychotics, and D2/3 agonists; MRI contraindications; or MPH contraindications. ADHD symptoms severity was assessed in children using the DBD-RS (Pelham et al., 1992) and in adults using the ADHD-RS (Kooij et al., 2008).

### 2.2. Procedure

The current study reports data from the baseline MRI assessment of a 16-week double blind, randomized, placebo-controlled trial: the ePOD study (Bottelier et al., 2014). After the screening procedure, but before randomization and onset of treatment, participants underwent two MRI scans, one before and one 90 min after administration of 0.5 mg/kg MPH (with a maximum dose of 20 mg for children and 40 mg for adults), at peak plasma levels (Swanson and Volkow, 2003).

### 2.3. MRI

#### 2.3.1. Pharmacological MRI – acquisition

Data were acquired using a 3.0 T Philips Achieva MR Scanner (Philips Medical Systems, Best, The Netherlands). A pseudo continuous arterial spin labeling (pCASL) sequence with a gradient-echo echo-planar imaging readout was used with the following parameters: TR/TE = 4000/14 ms; post-label delay = 1525 ms; label duration = 1650 ms; FOV = 240 × 240 × 119 mm; 75 dynamics; voxel size 3 × 3 × 7 mm, no background suppression, scan time = 10 min. In addition, a high resolution anatomical 3D T1-weighted scan was obtained.

#### 2.3.2. Pharmacological MRI – processing

ASL post-processing was performed with the "ExploreASL" toolbox, an in-house developed toolbox based on SPM (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) (Mutsaerts et al., 2016). First, the T1 images were registered to the MNI template and segmented into gray matter (GM) and white matter (WM) probability maps. Then, for the ASL time series, motion estimation was used to assess large motion artifacts and discard any motion spikes frames, where the spike exclusion threshold was the mean + 3 standard deviations (SD). Participants were removed from the analysis if the mean of the frame-wise displacement vector was >2 mm. With the cleaned dataset, accurate motion estimation was run. Subsequently, the ASL perfusion-weighted images were registered to the GM tissue probability maps of each subject using 6 parameter rigid body registration. After this, label and control images were pair-wise subtracted (ΔM), corrected for slice gradients and averaged. CBF was calculated according to Alsop et al. (2014) using the mean of the control images as M0 image. Following quantification, voxel-based outlier rejection was applied (mean ± 3 SD) and CBF images were averaged. The GM tissue probability maps were then spatially normalized using the Diffeomorphic Anatomical Registration analysis using Exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007), and the transformation fields were applied to the CBF maps as well.

### 2.4. Statistical analysis

Regional changes in the striatum, thalamus and medial PFC (mPFC) were assessed with a region of interest (ROI) analysis. These ROIs were selected because the striatum is rich in DAT (the primary target of MPH). The thalamus and ACC were chosen because animal literature has demonstrated the largest age-dependent effects of MPH in these two important projections from the striatum (Andersen et al., 2008). From the CBF maps, the median CBF was extracted for these ROIs within a subject-specific GM mask. Subsequently, the effect of MPH on ROI values was analyzed in SPSS using a mixed model with head motion as a time-variant covariate. Additionally, explorative voxel-wise changes in CBF were determined non-parametrically using the Randomise toolbox in the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL 4.0, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl) (Winkler et al., 2014). CBF maps were smoothed within the GM mask with a 7 mm FWHM Gaussian kernel for the voxel-based analysis. Permutation inference was used to assess the acute effects of MPH on CBF, thresholded at family-wise error (FWE) corrected $p < 0.05$ using threshold free cluster enhancement (TFCE) (Smith and Nichols, 2009). An independent *t*-test was used to assess baseline CBF differences between children and adults. To assess the effect of MPH in each group, and the interaction effect of MPH and age group, we conducted a paired samples *t*-test and a 2-way mixed effect analysis of variance, respectively. As head motion has been identified as a confounder, particularly in ADHD patient groups, log-transformed head mean motion was added to the model as a nuisance regressor.

## 3. Results

Table 1 summarizes the patient characteristics. From the initial sample of 50 children, six children were excluded because of excessive motion. In addition, one child was excluded because we could not obtain the second phMRI scan after MPH administration (due to technical difficulties) and three children were excluded because the ASL scan was obtained with a different protocol. In addition, from the initial sample of 49 adults, one adult was excluded because of undisclosed prior treatment with stimulants. Thus, 40 children and 48 adults were included in the analysis. Mean motion differed between children and adults ($t = 5.42$, $p < 0.01$) at baseline. In children, motion was significantly reduced after the MPH challenge ($t = 3.93$, $p < 0.01$), whereas in adults this effect was not statistically significant ($t = 1.72$, $p = 0.09$). SNR did not change from pre- to post-MPH challenge for children or adults, nor was there an age * challenge interaction for any of the ROIs (striatum $F = 0.68$ $p = 0.42$; thalamus $F = 0.08$ $p = 0.78$; mPFC $F = 1.17$ $p = 0.28$). As expected, baseline CBF was higher in children than in adults (Fig. 1) in both cortical and subcortical areas, and similar to values that have been reported in the literature for the respective age groups (Biagi et al., 2007). Global gray matter perfusion decreased from pre- to post-MPH both in children (−24%) and adults (−22%) (Fig. 1). Our ROI analyses demonstrate that in children acute MPH significantly decreased CBF in the thalamus ($F = 8.12$ $p < 0.01$) and the mPFC ($F = 5.55$ $p = 0.02$), whereas in adults MPH only decreased CBF in the mPFC ($F = 11.58$ $p < 0.01$). In addition, we found a significant age * MPH challenge interaction in the thalamus ($F = 8.07$ $p < 0.01$) (see Fig. 2), indicating that in this brain region the effects of MPH on CBF differ between children and adults. Our voxel-wise analyses demonstrated a *reduction* in CBF in cortical areas following MPH administration in children and adults (please see Supplementary Table 1 for more details). In the adults mostly cortical regions showed a response, whereas in children mainly the subcortical areas, such as the thalamus, were affected. Although the global maps (Fig. 3c) indicated that the effect of MPH on CBF differed between children and adults, on the voxel-based analysis we did not identify any clusters that showed a significant interaction between age group and MPH administration.

## 4. Discussion

In this study we investigated the modulating effect of age on CBF response to a DA challenge in stimulant treatment-naive children and adults with ADHD. Whole brain analyses showed more widespread reductions in perfusion in the cortex in adults than children, whereas in ROI analyses we found significant reductions in thalamic CBF in children only. A significant age*MPH challenge interaction in the thalamus on our ROI analyses provided further evidence that the effects of MPH in the human brain differ particularly in this brain region.

**Table 1**
Patient characteristics.

| | Children *n = 40* Mean (SD) | Adults *n = 48* Mean (SD) |
|---|---|---|
| Mean age (years) | 11.5 (0.8) | 28.6 (4.6) |
| Estimated IQ[a] | 104.0 (18.3) | 107.9 (7.6) |
| ADHD symptom severity | | |
| DBD-RS Inattention | 22.3 (3.2) | |
| DBD-RS Hyperactivity | 15.9 (5.7) | |
| ADHD-SR | | 31.5 (9.7) |
| ADHD subtype | | |
| Inattentive | 22 | 16 |
| Hyperactive/impulsive | 1 | 0 |
| Combined | 17 | 32 |
| Comorbidity | | |
| History of depressive episode(s)[b] | | 6 |
| History of anxiety disorder[b] | | 1 |
| ODD/CD[c] | 4 | |

[a] For children: WISC, for adults: NART.
[b] For adults: MINI Plus 5.0.
[c] For children: NIMH DISC-IV.

### 4.1. Age-dependent effects of MPH on CBF

To our knowledge, this is the first study to directly compare the effect of a single dose of MPH on CBF between stimulant treatment-naive children and adults with ADHD. Interestingly, in this study the only area in which we find significant differences in the CBF response between children and adults was the thalamus (i.e. reduction in children, no change in adults). Activating inhibitory $D_2$ receptors could induce lower CBF, but the thalamus is not rich $D_2$ receptors, but rather contains more vasodilatory DA $D_5$ receptors on the microvasculature (Choi et al., 2006). Activating those receptors would result in increased CBF rather than decreased CBF (Choi et al., 2006). Therefore, it is more likely that the large changes found in the thalamus are due to downstream inhibitory effects from the $D_2$-rich striatum, as the thalamus is the main output structure of the striatal circuitry. Furthermore, the thalamus is also rich in noradrenergic transporters, a secondary target of stimulants, which provides an alternative explanation for the thalamic CBF difference.

Although we do not find statistically significant differences between children and adults in the cortex, the extent of activation appeared to be larger in adults. In the cortex, the MPH challenge reduced CBF in frontal and parietal areas in children with ADHD. This is in contrast with previous clinical studies that report increased CBF after MPH administration in subcortical and cortical areas, although this was after prolonged treatment rather than a single dose of MPH (as used here) (Kim et al., 2001; Lee et al., 2005; Lou et al., 1989; Teicher et al., 2000). In adults, the MPH-induced CBF reductions in sensory-motor areas, rostral anterior cingulate cortex, temporal cortex and lateral frontal areas are in line with previous studies in ADHD patients. For example, a study in adults with ADHD demonstrated that 3 weeks of MPH treatment resulted in decreased rCBF, as measured by PET, in the striatum and precentral gyri, but increased CBF in the cerebellum, compared to the off-medication condition (Schweitzer et al., 2003). An ASL study, demonstrated higher CBF in adult ADHD patients in the caudate nucleus as well as frontal and parietal areas when compared to controls, which normalized when on medication (O'Gorman et al., 2008). However, these studies are difficult to compare with this study because of prior stimulant exposure and length of MPH treatment in the study.

In contrast, studies administering MPH to healthy volunteers report more mixed results. In a small group of adult healthy volunteers, an intravenous challenge with 0.25 mg/kg MPH decreased absolute CBF, but increased relative CBF measured with $H_2[O^{15}]$ PET in the anterior cingulate, supplementary motor areas and temporal poles, as well as decreased relative CBF in the superior temporal gyri, right medial frontal gyrus, and right inferior parietal cortex (Udo de Haes et al., 2007). In an ASL-based study, decreased CBF was reported following 30 mg oral MPH in lateral frontal, rostral cingulate and sensorimotor areas, amygdala, parahippocampal gyrus and in multiple regions of the occipital and temporal cortices (Marquand et al., 2012). However, they also report increased CBF, particularly in the striatum and thalamus in adult healthy volunteers. The discrepancy with our study might be explained by the difference in populations, i.e. healthy volunteers vs. ADHD patients. It has been shown previously that DA release to a stimulant challenge is altered in adult ADHD patients compared to healthy controls (Cherkasova et al., 2014; Volkow et al., 2007). Recent studies have suggested that neurobiologically, ADHD is characterized by reduced tonic firing of the DA system and subsequent augmented phasic DA release, which can be normalized by means of stimulant treatment (Badgaiyan et al., 2015). This might seem counterintuitive as MPH blocks the reuptake of DA through the pre-synaptic transporter, thereby increasing extracellular DA levels. Yet, this is specifically thought to increase tonic levels of DA, causing increased stimulation of presynaptic autoreceptors

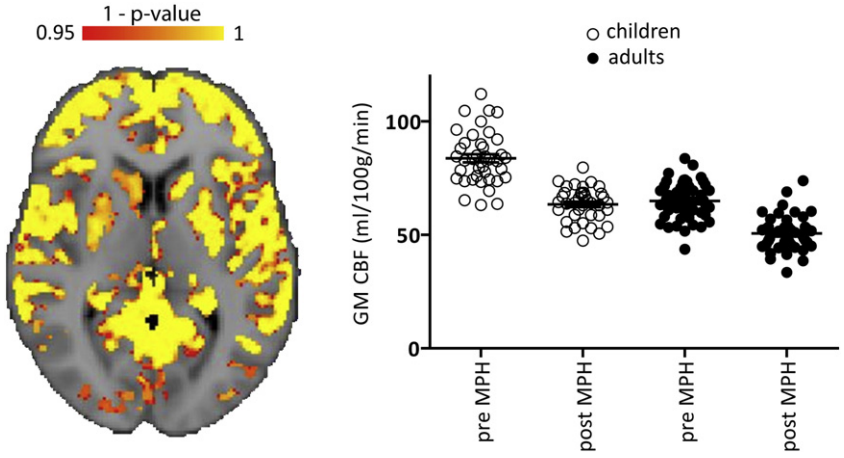


**Fig. 1.** Baseline differences in CBF (mL/100 g/min) (left) Brain regions displaying significant higher CBF in children than adults ($p < 0.05$, FWE corrected). Displayed in radiological convention; coordinates provided in MNI standard space; the color bar represents 1-*p*-value. (right) Gray matter (GM) CBF (mL/100 g/min) in children and adults before and after MPH.

and reduce phasic DA release, which in turn results in lower CBF. Thus, the reductions in CBF we find here are in line with findings on the disturbance of the DA system in ADHD subjects and could therefore explain the discrepancy with studies in healthy volunteers.

Surprisingly, we did not find any changes in striatal CBF in either children or adults, despite the striatum being the area with the highest DAT expression. However, when reviewing the literature, the effects of MPH on the striatum are inconsistent, with both increases in CBF and metabolism, as well as decreases and no change having been reported. This has been attributed to the state of the individual's DA system at baseline resulting in a variable response of the striatum (Ernst et al., 1994; Volkow et al., 1997), or could be a consequence of prior stimulant treatment, which was not taken into account in these previous studies. An additional explanation for the discrepant findings is that particularly the downstream areas, such as the thalamus and frontal cortex, displayed changes in metabolism or perfusion following DA changes in the striatum (Udo de Haes et al., 2007).

### 4.2. Neurobiological correlates of age-dependent CBF response to MPH

We observed age-dependent effects of MPH administration on CBF. Adults showed a more widespread area of decreased perfusion in the cortex than children, whereas subcortically we found significant reductions in thalamic CBF in children only. These findings suggest an age-dependency in the CBF response to MPH, which could reflect different maturational stages of the DA system in children and adults. A preclinical phMRI study has previously demonstrated that MPH reduced subcortical and posterior cingulate rCBV in young rats, whereas it increased rCBV in the striatum and frontal cortex in adult rats (Chen et al., 2010). This was linked to a higher $D_1/D_2$ ratio in adult vs young rats, as it has been shown that post-synaptic activation of $D_1$ receptors typically results in increased excitatory neurotransmission, which increases metabolic demand and subsequently increases CBF, whereas post-synaptic activation of the inhibitory $D_2$ receptors generally results in decreased CBF (Choi et al., 2006). The different patterns of activation between children and adults may also be explained in part by the ratio of $D_1$ and $D_2$ receptors and DAT expression in the developing brain. However, as little is known about the development of DA receptors in humans, most evidence comes from preclinical studies. In humans and non-human primates, $D_1$ and $D_2$ receptor expression appears to peak in childhood and to slowly decline thereafter. In contrast, studies in rodents typically show peak receptor expression in peri-adolescence (Wahlstrom et al., 2010). Functionally, adolescent rats express a pattern of $D_1$ hypo-activation in response to a $D_1$ agonist. This suggests a dominant response of the $D_2$ receptor in adolescence with a concomitant decrease in CBF (Chen et al., 2010). These changes in the DA system parallel other changes in structural and functional development during adolescence, with marked differences between subcortical and cortical brain areas (Andersen, 2003). Most studies focus on the prefrontal cortex, as this is the latest brain region to develop, and demonstrate

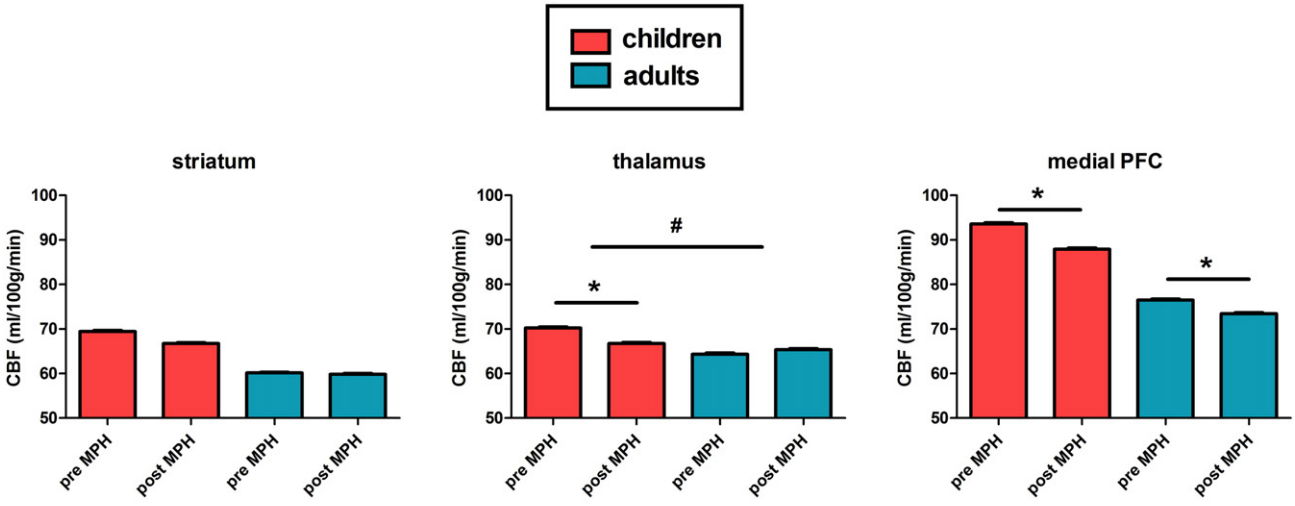


**Fig. 2.** ROI analysis. Effect of an acute challenge on the striatum, thalamus and medial PFC. *paired *t*-test $p < 0.05$, #age * challenge interaction effect $p < 0.05$.

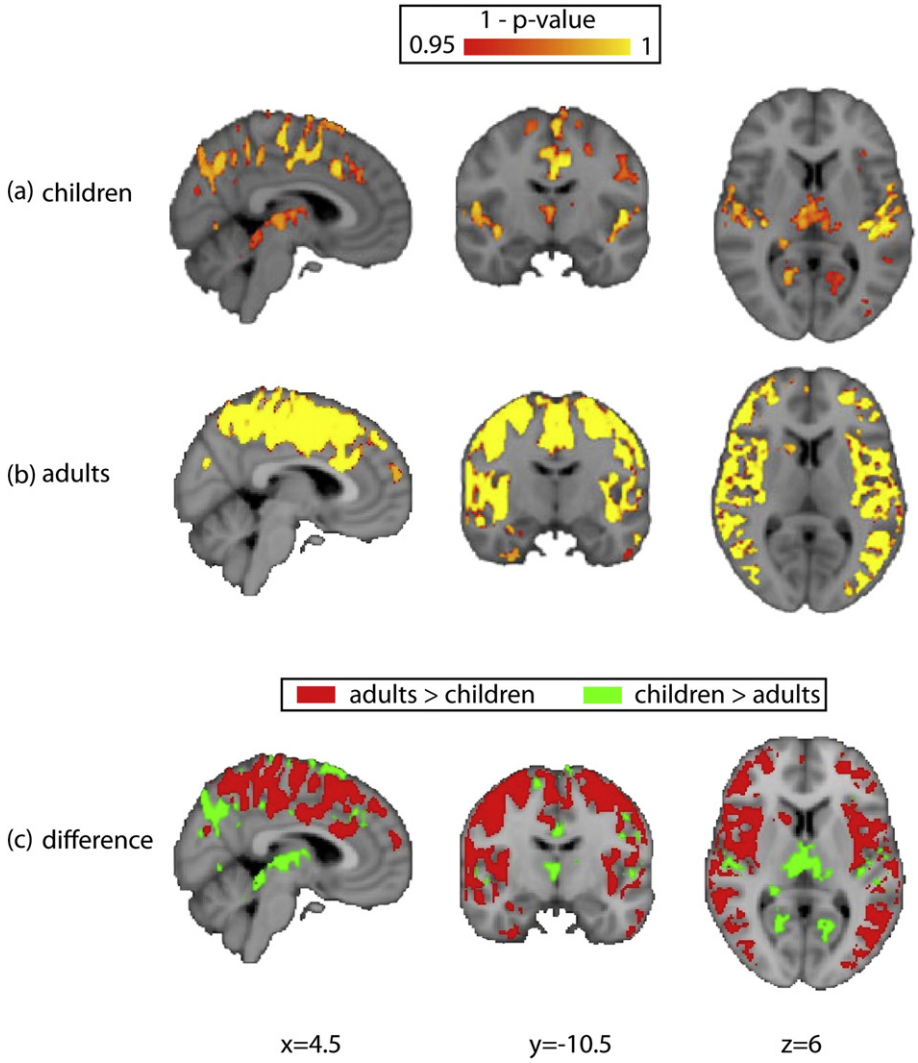


**Fig. 3.** Whole brain analysis. Effect of acute challenge with 0.5 mg/kg MPH on CBF (ml/100 g/min) in (a) children (b) adults ($p < 0.05$, FWE corrected) (c) differences between reductions in CBF in adults and children (non-significant); red = more reduction in CBF in adults than children, green = more reduction in CBF in children than adults. Displayed in radiological convention; coordinates provided in MNI standard space; the color bar represents 1-*p*-value.

continued development of attention, memory and executive function during adolescence (Casey et al., 2000).

### 4.3. Clinical relevance

This is the first study examining perfusion changes in patients with ADHD in a developmental context. We show that, in accordance with preclinical data from separate studies in children and adults, MPH affects the developing brain differently from the adult brain. Nevertheless, current treatment guidelines are based on weight and the assessment of symptom improvement and side-effects, ignoring age as an important determinant of the neurobiological response to stimulants. The adolescent brain is a rapidly developing system with high levels of plasticity. As such, it may be particularly vulnerable to drugs that interfere with these processes or modify the specific transmitter systems involved. Therefore, future long-term studies will have to show what the consequences of stimulant treatment during development are on the DA system, and how they affect the course and outcome of ADHD. Additionally, these results bear relevance for task-based functional MRI studies, as we show here that is important to take into account developmental differences in CBF response, which is one of the major contributors to the BOLD response. Therefore, we suggest future studies should obtain both task-based BOLD fMRI measurements as well as resting state measurements of CBF.

### 4.4. Methodological considerations

Although we can explain the subcortical and cortical effects of MPH on CBF partially through the ontogeny of the DA system, other neurotransmitter systems may also contribute to this response. For example, the noradrenalin transporter is more important for clearing DA in (pre)-frontal areas relative to DAT and, using phMRI, we cannot distinguish between these neurotransmitter systems. In addition, it is important to realize that both DA and noradrenalin have vasoconstrictive properties and we cannot exclude that our results can partially be explained by direct effects of these neurotransmitters on the microvasculature. In addition, although $D_{1,5}$ are excitatory post-synaptic receptors and $D_{2,3,4}$ are inhibitory receptors, it is important to note that those receptors located on GABA-ergic or cholinergic neurons could result in the opposite effect on CBF. Global changes in CBF due to systemic changes can also contribute to the CBF response. It is difficult to correct for these changes, especially if the drug of interest induces widespread neuronal changes, as is the case with MPH. In that case, a large part of the GM CBF is determined by the drug effects and removing this by normalizing the data for

GM or adding GM CBF as covariate will also remove a large part of the true variance. Future studies could benefit from combined BOLD/ASL based methods to obtain additional information, such as cerebral metabolic rate of oxygen, in order to better distinguish vascular and neuronal effects (Bulte et al., 2012; Wise et al., 2013). Although there were differences in motion between children and adults, we accounted for this in the data pre-processing and group-level analysis, and together with a similar SNR between both age-groups, it is unlikely that differences in data quality underlie our results.

It is possible that the effect of MPH on CBF is also influenced by differences in baseline DA release between individuals. Volkow et al. (2001) have shown that there is significant variability among participants in DA release in response to MPH, which could result in different potency of its effects across participants. However, it is still unclear whether baseline DA release changes across the lifespan and this therefore remains to be further investigated.

Here we show lower baseline CBF in children than in adults, comparable to reference values from healthy volunteers in literature (Biagi et al., 2007). However, a well-controlled experimental study has recently demonstrated that small changes in baseline CBF do not alter the absolute response to a neuronal stimulus and there therefore absolute CBF better reflects neuronal activity than relative CBF (Whittaker et al., 2015). This makes us confident that the presently observed changes in CBF after acute MPH administration are not solely due to different baseline CBF levels.

We included both pediatric and adults patients with ADHD. Although some studies use pediatric templates for analysis, this was not feasible here as we directly compared children and adults. Therefore we chose to use a study specific template which included all T1 scans and was therefore unbiased with regard to age group. This approach is supported by the fact that brain weight does not increase much after the age of 10 (Dekaban and Sadowsky, 1978). Moreover, although we ensured that all participants were stimulant treatment naive, some of the adults patients had a history of recreational drug use. However, when comparing those adult subjects with extensive drug use with those with no or low recreational use we do not find differences between the groups (please see Supplementary Table 2 and Supplementary results for more details). Therefore we conclude that recreational drug use likely did not affect our findings. In addition, as this is a cross-sectional study it is possible that our findings are a result of neuronal differences between pediatric and adult ADHD, because the adult group had persistent ADHD, whereas for the children we do not know this yet. Furthermore, we included only male patients to reduce heterogeneity, but this limits to generalizability to female patients.

### 4.5. Conclusion

In sum, we here provide a direct comparison of the CBF response to MPH between children and adults in a large stimulant treatment-naive ADHD sample using ASL phMRI. The cortical response to MPH appears more widespread in adults than in children, whereas subcortical thalamic CBF was reduced following MPH in children, but not adults with ADHD. These findings confirm the age-dependent effects of MPH on CBF, possibly due to differences in the development of the DA system. Our findings thus highlight the importance of taking a developmental perspective into account for the treatment of ADHD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.11.021.

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