NeuroImage: Clinical 13 (2017) 123–129

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

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

ARTICLE INFO

Article history:
Received 21 July 2016
Received in revised form 18 November 2016
Accepted 19 November 2016
Available online 21 November 2016

Keywords:
ADHD
Methylphenidate
Dopamine
Age
Cerebral blood flow
Arterial spin labeling

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).

http://dx.doi.org/10.1016/j.nicl.2016.11.021

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.