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Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary school children

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ABSTRACT

Background: Polycyclic aromatic hydrocarbons (PAHs) have been proposed as environmental risk factors for attention deficit hyperactivity disorder (ADHD). The effects of these pollutants on brain structures potentially involved in the pathophysiology of ADHD are unknown.

Objective: The aim of this study was to investigate the effects of PAHs on basal ganglia volumes and ADHD symptoms in school children.

Methods: We conducted an imaging study in 242 children aged 8–12 years, recruited through a set of representative schools of the city of Barcelona, Spain. Indoor and outdoor PAHs and benzo[*a*]pyrene (BPA) levels were assessed in the school environment, one year before the MRI assessment. Whole-brain volumes and basal ganglia volumes (caudate nucleus, globus pallidus, putamen) were derived from structural MRI scans using automated tissue segmentation. ADHD symptoms (ADHD/DSM-IV Scales, American Psychiatric Association 2002) were reported by teachers, and inattentiveness was evaluated with standard error of hit reaction time in the attention network computer-based test.

Results: Total PAHs and BPA were associated with caudate nucleus volume (CNV) (i.e., an interquartile range increase in BPA outdoor level (67 pg/m^3) and indoor level (76 pg/m^3) was significantly linked to a decrease in CNV (mm^3) ($\beta = -150.6$, 95% CI [−259.1, −42.1], $p = 0.007$, and $\beta = -122.4$, 95% CI [−232.9, −11.8], $p = 0.030$ respectively) independently of intracranial volume, age, sex, maternal education and socioeconomic vulnerability index at home). ADHD symptoms and inattentiveness increased in children with higher exposure to BPA, but these associations were not statistically significant.

Conclusions: Exposure to PAHs, and in particular to BPA, is associated with subclinical changes on the caudate nucleus, even below the legislated annual target levels established in the European Union. The behavioral consequences of this induced brain change were not identified in this study, but given the caudate nucleus involvement in many crucial cognitive and behavior processes, this volume reduction is concerning for the children's neurodevelopment.

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1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is among the most frequently diagnosed childhood neurodevelopmental disorders. Symptoms are characterized by an inability to focus on tasks, impulsive hyperactive behavior, or lethargic inattention, and frequently lead to functional impairment in academic, family, and social settings (Barkley, 2002). ADHD affects approximately 5–7.1% of children and adolescents worldwide (Polanczyk et al., 2007; Willcutt, 2012), and persists into adulthood in 65% of cases (Faraone et al., 2006). Although considered to be a familial disorder, ADHD heritability estimated at 60% to 80% highlights the considerable role of environmental factors in disorder susceptibility (Nigg, 2009).

Influence of air pollutants on the ADHD prevalence has been poorly investigated while there is growing evidence of their detrimental effect on the central nervous system (Block et al., 2012). Among the different air pollutants, of particular concern are the polycyclic aromatic hydrocarbons (PAHs), mainly emitted into the air from anthropogenic combustion sources. PAHs are a group of ubiquitous environmental contaminants formed during the incomplete combustion of organic material and found in diverse media including cigarette smoke, charcoal-broiled food and emissions from combustion of fossil and biomass fuels (World Health Organization, 2001). Experimental studies have indeed reported that administration of benzo[*a*]pyrene (BAP) induced spontaneous motor hyperactivity in rodents (Das et al., 2016; Grova et al., 2007; Maciel et al., 2014). Moreover, prenatal exposure to PAHs was associated with attention and ADHD behavior problems in childhood in a birth cohort (Perera et al., 2011, 2012, 2014). Owing to their lipophilicity, PAHs can cross the blood-brain barrier (Yan et al., 2010) and cause pathophysiological changes such as loss of neuronal activity and synaptic plasticity (Chepelev et al., 2015), and neuronal death (Dutta et al., 2010). However, their effects on brain structures remain unknown. To date, only one magnetic resonance imaging (MRI) study, conducted in the same birth cohort reporting the association between prenatal PAHs exposure and ADHD symptoms, has investigated the changes in surface of the brain. This study has highlighted a dose-response relationship between prenatal PAHs exposure and subsequent reductions of the white matter surface (Peterson et al., 2015). In addition to changes in white matter or prefrontal cortex, reductions in basal ganglia (BG) are reported as the most consistently brain abnormalities findings in many MRI meta-analysis in ADHD children (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011; Valera et al., 2007). The BG thalamocortical circuits are indeed involved in processes such as motor control, reward processing, and cognitive and attentional control that are impaired in ADHD (Ring and Serra-Mestres, 2002). Therefore, BG should also be investigated as a potential mediator in the relationship between PAHs exposure and ADHD symptoms.

The main aim of this study was to investigate the effects of PAHs exposure in indoor and outdoor school environments on white matter, gray matter and BG (putamen, caudate nucleus and globus pallidus) in children from the general population. We hypothesized that higher PAHs exposure would be associated with reduced BG volumes and increased risk of ADHD symptoms.

2. Methods

2.1. Schoolchildren

This study was developed in the context of the Brain Development and Air Pollution Ultrafine Particles in School Children (BREATHE) project (Sunyer et al., 2015). Forty schools in Barcelona (Catalonia, Spain) were selected based on modeled traffic-related nitrogen dioxide (NO_2) values (Wang et al., 2013). Low- and high-NO_2 schools were paired by socioeconomic vulnerability index and type of school (i.e., public/private). A total of 39 representative schools of the city of Barcelona and 2897 children agreed to participate in the whole survey. The participating children were in grades 2 through 4 (7–10 years of age), an appropriate school age for the investigation of attention functions (Anderson, 2002; Rueda et al., 2004).

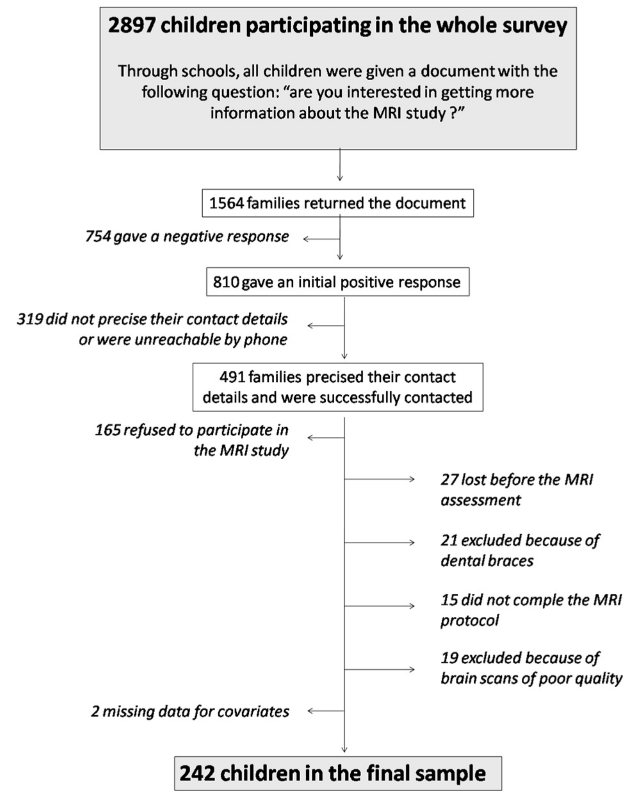

Fig. 1. Flow chart.

Through the schools, all the participating children were given a document asking whether they were interested in further information about the MRI study. From the initial sample, 1564 families returned the document and among them, 810 gave an initial positive response. Parents of 491 children were successfully contacted. Consent to participate was finally not obtained in 165 cases, 27 children were lost before the assessment and 21 children were not eligible because of dental braces. This group was further reduced in excluding 15 children who did not complete the imaging protocol, 19 children with brain scans of poor quality, and 2 with missing data for covariates (Fig. 1). The final MRI sample included 242 children from 35 schools (49% of girls, median age at MRI of 9.7 years). The median time spent in the school before the beginning of the study was 6.5 years.

All parents or tutors signed the informed consent form approved by the Research Ethical Committee (No. 2010/41221/I) of the IMIM-Parc de Salut Mar., Barcelona, Spain and the FP7-ERC-2010-AdG Ethics Review Committee (268479-22022011).

2.2. PAHs exposure

Air pollution measurements were taken in each the 35 schools during two one-week periods separated by 6 months (sampling campaign 1: January to June 2012; sampling campaign 2: September 2012 to February 2013). Indoor air in a single classroom and outdoor air in the courtyard were measured simultaneously. Ambient particulate Matter < 2.5 µm ($PM_{2.5}$) was collected on pre-heated quartz filters (Pall, 2500Q, 15 mm) during 8-h (school time, from 09:00 to 17:00 h) using a High-Volume sampler (MCV SA, Spain). Air samples were collected at a height of around 1.3 m above floor level, which is the height at which the pupils aged 7–9 would usually inhale. A quarter of each $PM_{2.5}$ filter was used for organic analysis using organic solvent

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