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Traffic pollution exposure is associated with altered brain connectivity in school children

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ABSTRACT

Children are more vulnerable to the effects of environmental elements due to their active developmental processes. Exposure to urban air pollution has been associated with poorer cognitive performance, which is thought to be a result of direct interference with brain maturation. We aimed to assess the extent of such potential effects of urban pollution on child brain maturation using general indicators of vehicle exhaust measured in the school environment and a comprehensive imaging evaluation. A group of 263 children, aged 8 to 12 years, underwent MRI to quantify regional brain volumes, tissue composition, myelination, cortical thickness, neural tract architecture, membrane metabolites, functional connectivity in major neural networks and activation/deactivation dynamics during a sensory task. A combined measurement of elemental carbon and NO_2 was used as a putative marker of vehicle exhaust. Air pollution exposure was associated with brain changes of a functional nature, with no evident effect on brain anatomy, structure or membrane metabolites. Specifically, a higher content of pollutants was associated with lower functional integration and segregation in key brain networks relevant to both inner mental processes (the default mode network) and stimulus-driven mental operations. Age and performance (motor response speed) both showed the opposite effect to that of pollution, thus indicating that higher exposure is associated with slower brain maturation. In conclusion, urban air pollution appears to adversely affect brain maturation in a critical age with changes specifically concerning the functional domain.

Introduction

Common to living beings, the brain development cycle is characterized by primary growth and subsequent maturation. Maturation changes implicate structure and function with anatomical shaping, progressive myelination of neural tracks and fine-tuning of functional brain networks (Menon, 2013; Pujol et al., 2006; Toga et al., 2006). The highest-order events procure the integration of brain areas into functional systems and the segregation of distinct but interconnected large-scale networks (Uddin et al., 2010; Vogel et al., 2010: Dwyer et al., 2014; Di Martino et al., 2014).

Developing children are at risk due to the potentially hazardous effects of environmental factors (Paus, 2010). Long-term exposure to traffic-related air pollution has been associated with alterations in children's cognition (Perera et al., 2009; Suglia et al., 2008; Wang et al., 2009). We have recently identified a significant association between general markers of road traffic pollution and slower cognitive growth in a large group of children (Sunyer et al., 2015).

Epidemiological studies, therefore, indicate that high levels of urban air pollution may be dangerous to children, as they presumably interfere with brain maturation processes. This hypothesis is largely supported by a set of studies in both animals and humans showing significant associations of pollutant exposure with

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inflammatory and degenerative brain pathology (Block and Calderón-Garcidueñas, 2009; Calderón-Garcidueñas, 2012). However, such an interference effect on brain development has not been thoroughly investigated. We aimed to assess the extent of potential repercussions of traffic pollution exposure on child brain maturation using a variety of imaging measurements ranging from basic anatomy to high-order functional integration. A group of 263 children, aged 8 to 12 years, recruited from a large study assessing the impact of long-term exposure to urban pollution in Barcelona city school environments (Sunyer et al., 2015) completed the protocol.

Our hypothesis was that the potential brain effects of air pollution will be more evident on the more detectable anatomical and functional maturation processes. Whereas developmental changes in gray matter volume are less evident in this age period, active myelination implicates increases of relative white matter volumes, elevated choline compounds and water diffusion changes within white matter tracts (Blüml et al., 2013; Toga et al., 2006; Yoshida et al., 2013). At the functional domain, preadolescence is critical to the optimal assembling of large-scale functional networks (Menon, 2013). Accordingly, the imaging protocol included a high resolution 3D anatomical acquisition to measure regional volumes, brain tissue composition, myelination levels and cortical thickness. Diffusion tensor imaging (DTI) measurements of fractional anisotropy served to explore white matter tract architecture. In vivo spectroscopy was used to grossly estimate precursors of membrane components in white matter. Finally, functional MRI was used to test the integrity of relevant networks using both resting-state functional connectivity and a task activation/deactivation paradigm.

Selected cognitive assessment was also conducted to determine to what extent potential repercussions were also detectable on children's performance in the current study sample.

Table 1
Characteristics of the study sample ($n = 263$).

Gender	48.3% girls 51.7% boys
Age, years, mean ± SD (range)	9.7 ± 0.9 (8.0–12.1)
Overall school achievement—5-point scale	3.7 ± 1.0 (1–5)
Difficulties Score (SDQ), range 0–40	8.8 ± 5.3 (0–25)
Obesity: normal	71.4%
Overweight, BMI 85–94	18.4%
Obesity, BMI >94	10.2%
Mother education (5-point scale. 5 = university)	4.5 ± 0.8 (1–5)
Father education (5-point scale. 5 = university)	4.4 ± 0.8 (1–5)
Vulnerability index[a]—home	0.43 ± 0.21 (0.06–0.90)
Vulnerability index[a]—school	0.43 ± 0.22 (0.13–0.84)
Public/non-public school	43% *vs* 57%
Task performance, N-back	
Working memory, 2-back (detectability)	2.5 ± 1.3 (−0.6–3.9)
Working memory, 3-back (detectability)	1.5 ± 1.1 (−1.4–3.9)
Task performance, attentional network test	
Reaction time (ms)	650.6 ± 119.9 (431–1091)
Reaction time standard deviation (ms)	222.9 ± 91.2 (77.5–571.6)
Commission errors (number)	4.3 (3.4%) ± 5.0 (0–49)
Omission errors (number)	1.6 (1.3%) ± 3.9 (0–44)
Alerting (ms)	53.1 ± 55.5 (−138–270)
Orienting (ms)	24.4 ± 56.8 (−204–191)
Interference (ms)	39.4 ± 35.5 (−91–170)
Air pollution measurements[b]	
Outdoor elemental carbon (EC) year average (μg/m^3)	1.4 ± 0.6 (0.6–3.99)
Outdoor NO_2 year average (μg/m^3)	46.8 ± 12.0 (25.9–84.6)
Indoor elemental carbon (EC) year average (μg/m^3)	1.2 ± 0.5 (0.4–2.7)
Indoor NO_2 year average (μg/m^3)	29.4 ± 11.7 (11.5–65.6)
Overall air pollution indicator (EC + NO_2 weighted average)	0.92 ± 0.30 (0.42–1.92)

BMI, body mass index. SDQ, Strengths and Difficulties Questionnaire.
[a] Neighborhood socioeconomic status vulnerability index based on level of education, unemployment, and occupation at the census tract (Atlas de vulnerabilidad urbana de España, 2012).
[b] After excluding 3 children with outlier measurements.

Methods

Participant selection

This study was developed in the context of the BREATHE project (The European Commission: FP7-ERC-2010-AdG, ID 268479). The general project design is fully described in Sunyer et al. (2015). A total of 1564 families, from 39 schools in the city of Barcelona, were invited to participate in the MRI study via post, email or telephone, and 810 of them gave an initial positive response. The study sample was consecutively recruited from this group with the aim of including children from all participating schools. Parents of 491 children were directly 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. The finally selected study group included 278 cases. A total of 263 children completed the imaging protocol (mean age of 9.7 years, SD 0.9 and range, 8.0 to 12.1 years). Table 1 reports the characteristics of these participants. Additional cases were excluded on the basis of image quality criteria in each specific MRI analysis (see further).

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).

Pollutant exposure

Each school was measured twice during one-week periods separated by 6 months, in the warm (year 2012) and cold (year 2012/2013) seasons. Indoor air in a single classroom and outdoor air in the playground were measured simultaneously. Pollutants were measured during class-time using methods previously described (Amato et al., 2014; Rivas et al., 2014; Sunyer et al., 2015).

Elemental carbon was measured during 8 h (09:00 to 17:00 h) in particulate matter with an aerodynamic diameter < 2.5 μm (PM2.5) collected on filters with High-Volume samplers (MCV SA, Spain) using a Thermo Optical Transmission method (Sunset Laboratories Inc.). We carefully followed the EUSAAR-2 protocol, TOT Sunset Laboratories measurements, with a detection limit of 0.1 μg/m^3 and an uncertainty of ±5%. The air cleaning effect of High-Volume samplers may underestimate absolute measurements of elemental carbon in poorly ventilated indoors. In our study, however, elemental carbon penetration was almost 1(indoor/outdoor ratio 94.1% [95% CI 85.7%–102.4%]), which suggests a permanent ventilation of the measured classrooms. Elemental carbon was additionally measured in each classroom using the MicroAeth AE51 (AethLabs). The correlation between elemental carbon measured through High-Volume samplers and with the aethalometer was 0.95, supporting that High-Volume sampler measurements may be adequate estimations of classroom elemental carbon.

Nitrogen dioxide (NO_2) was measured with passive dosimeters (Gradko). The dosimeter was exposed during a period of 96 h (4 days) from Monday to Thursday in each school in both the warm and cold campaigns. Weekly data from both seasons were averaged to obtain a single measurement. Prior to the campaigns, we tested Gradko NO_2 passive dosimeters in our urban background monitoring station Palau Reial (with relatively low NO_2 concentrations) by measuring during 4 days and comparing the results with simultaneous chemiluminescence NO_2 online data. The results showed that sampling periods of 4 days were enough for ensuring a good precision. Also, during the whole sampling campaign, NO_2 was measured each week (from Monday to Thursday) with both the Gradko passive dosimeter and conventional chemiluminiscence analyzers in this reference station. We obtained a correlation of Gradko =