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# Exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity in preadolescents

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ABSTRACT

*Background:* The amount of people affected by traffic-related air pollution and noise is continuously increasing, but limited research has been conducted on the association between these environmental exposures and functional brain connectivity in children.

*Objective:* This exploratory study aimed to analyze the associations between the exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity amongst a wide-swath of brain areas in preadolescents from 9 to 12 years of age.

*Methods:* We used data of 2,197 children from the Generation R Study. Land use regression models were applied to estimate nitrogen oxides and particulate matter levels at participant's homes for several time periods: pregnancy, birth to 3 years, 3 to 6 years, and 6 years of age to the age at magnetic resonance imaging (MRI) assessment. Existing noise maps were used to estimate road traffic noise exposure at participant's homes for the same time periods. Resting-state functional MRI was obtained at 9–12 years of age. Pair-wise correlation coefficients of the blood-oxygen-level-dependent signals between 380 brain areas were calculated. Linear regressions were run and corrected for multiple testing.

*Results:* Preadolescents exposed to higher levels of $NO_2$, $NO_x$, and $PM_{2.5}$ absorbance, from birth to 3 years, and from 3 to 6 years of age showed higher correlation coefficients among several brain regions (e.g. from 0.16 to 0.19 higher correlation coefficient related to $PM_{2.5}$ absorbance exposure, depending on the brain connection). Overall, most identified associations were between brain regions of the task positive and task negative networks, and were mainly inter-network (20 of 26). Slightly more than half of the connections were intra-hemispheric (14 of 26), predominantly in the right hemisphere. Road traffic noise was not associated with functional brain connectivity.

*Conclusions:* This exploratory study found that exposure to traffic-related air pollution during the first years of life was related to higher functional brain connectivity predominantly in brain areas located in the task positive and task negative networks, in preadolescents from 9 to 12 years of age. These results could be an indicator of differential functional connectivity in children exposed to higher levels of air pollution.

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## 1. Introduction

The world's population is continuously growing and urbanization is rapidly increasing. Although urbanization is related to improved human health and wellbeing, it could also worsen air and noise quality (Wang, 2018). In urban areas, traffic is the most important source of both air pollution and noise. The health effects of air pollution have been widely investigated, and the central nervous system has been demonstrated as a target organ negatively affected by air pollutants (Block et al., 2012). Air pollution exposure has been linked to neuronal death, synaptic toxicity, and altered gene expression in the brain (Thomson, 2019; U.S. EPA, 2019). Also, the exposure to both noise and air pollution could be a stressor affecting the hypothalamic–pituitary-adrenal (HPA) axis, increasing the levels of stress hormones, affecting the brain (Jafari et al., 2017; Thomson, 2019). Air pollution and noise can affect the brain at any age, but the developing brain is particularly vulnerable because of its immature metabolic system and because many crucial neurodevelopmental processes take place during fetal life and childhood (Stiles & Jernigan, 2010).

Previous epidemiological studies have suggested that exposure to air pollution and noise may be related to impaired cognitive function and neurodevelopmental disorders, although evidence is still inconsistent across studies (Clark & Paunovic, 2018; Costa et al., 2020; Stansfeld & Matheson, 2003; Stansfeld & Clark, 2015; Volk et al., 2021). During the last years, magnetic resonance imaging (MRI) has opened up new possibilities in epidemiological research for investigating the structure and the functioning of the brain. Blood oxygenation level dependent (BOLD) imaging is the standard technique to generate images in functional MRI studies and measures inhomogeneities in the magnetic field due to the difference in magnetic properties between oxygenated and deoxygenated blood (Gauthier & Fan, 2019). BOLD signals can result from spontaneous processes, i.e. not induced by an external stimulus and conscious mentation (Glover, 2011). Spontaneous brain activity is organized in resting state networks defined by their spatiotemporal configuration and functional roles (Biswal et al., 1995; Fox & Raichle, 2007). Biswal et al. were the first to show that this spontaneous brain activity was consistent in regions belonging to the somato/sensory motor network (Biswal et al., 1995). Their results were confirmed later and extended to other networks such as the visual, auditory, and language processing networks (Hampson et al., 2002; van de Ven et al., 2004). Task negative (also known as Default Mode Network) and task positive networks are the strongest anticorrelated resting state networks in the brain (i.e. when one is active, the other one is in its inactive state) (Fox et al., 2005). Additionally, functional connectivity studies have reported a number of other neural networks that are strongly functionally connected during rest (Thomas Yeo et al., 2011).

Only a limited number of studies have used brain MRI to assess its association with air pollution exposure in children, most of them investigating the brain structure (Burnor et al., 2021; Calderón-Garcidueñas et al., 2008, 2011; Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2020, 2021; Mortamais et al., 2017, 2019; Peterson et al., 2015; Pujol et al., 2016a; Pujol et al., 2016b), and only one investigating functional brain connectivity (Pujol et al., 2016b). Regarding air pollution exposure and brain functional connectivity, Pujol et al. found that exposure at school was associated with lower functional integration and segregation in key brain networks relevant to both inner mental processes and stimulus-driven responses in children from 8 to 12 years of age. They used a focused seed-voxel based approach instead of exploring connectivity across all functional networks. The best of our knowledge, no studies have assessed noise in relation to brain MRI.

Using the Generation R Study, previous studies found an association between traffic-related air pollution and several brain structure alterations, including altered brain volumes, reduced cortical thickness, increased surface area, and lower fractional anisotropy and higher mean diffusivity in white matter microstructure (Guxens et al., 2018; Lubczyńska et al., 2020, 2021). Thus we hypothesized that higher exposure to air pollution could also be associated with altered functional brain connectivity in resting-state networks. Furthermore, previous evidence indicated that environmental noise exposure is related to impairment in cognitive functions in children, but there is no evidence of brain alterations that underlie this association. Also, the single study on functional brain connectivity of Pujol et al. explored the exposure in childhood, not being able to identify specific windows of susceptibility. The pregnancy period and first years of life would be critical to the optimal foundation and assembling of large-scale brain functional networks, and we hypothesized that they could be especially more affected by the exposure of traffic-related air pollution and noise compared to other exposure periods. Therefore, the aim of this exploratory study was to investigate the association between the exposure to traffic-related air pollution and noise during different specific windows of susceptibility in pregnancy and childhood periods, and functional brain connectivity in preadolescents from 9 to 12 years of age. We used a multimodal atlas to explore the functional connectivity amongst a wide-swath of brain areas.

## 2. Methods

### 2.1. Population and study design

This study was embedded in the Generation R Study, a population-based birth cohort from fetal life onwards in the city of Rotterdam, the Netherlands (Kooijman et al., 2016). Pregnant women with an expected delivery date between April 2002 and January 2006 were eligible for participation in the study. We included only singleton pregnancies, resulting in 9,610 pregnant women recruited for the study. Children still enrolled in the study at the age of 9 to 12 years, were invited to participate in an MRI scanning session. The written informed consent was obtained from 3,992 mothers and their children, of which 3,439 received a rs-fMRI scan (White et al., 2018). From this total, 2,197 children had good quality imaging scans as well as data on traffic-related air pollution and noise, and hence were included in this analysis. Ethical approval was obtained from the Medical Ethical Committee of Erasmus MC, University Medical Centre Rotterdam, in accordance with Dutch law.

### 2.2. Traffic-related air pollution exposure

Air pollution exposure levels were estimated at all reported home addresses of each participant from conception until children's age at MRI assessment, following a standard procedure that is detailed in previous literature (Beelen et al., 2013; Eeftens et al., 2012a). In brief, within the ESCAPE (European Study of Cohorts for Air Pollution Effects) project, air pollution monitoring campaigns were performed in the Netherlands and Belgium in the warm, cold, and intermediate seasons between February 2009 and February 2010 (Cyrys et al., 2012; Eeftens et al., 2012b). Nitrogen oxides ($NO_x$) and nitrogen dioxide ($NO_2$) were measured in three two-week periods within one year in 80 sites (Cyrys et al., 2012). In addition, measurements of particulate matter (PM) with aerodynamic diameter of less than 10 μm ($PM_{10}$) and of less than 2.5 μm ($PM_{2.5}$) were also carried out three times during two-week periods in 40 sites (Eeftens et al., 2012b). From the $PM_{2.5}$ measurements, we used the filters to measure the absorbance of $PM_{2.5}$ ($PM_{2.5}$ absorbance), as a marker for black carbon. For each pollutant, the levels of the three two-week measurements were averaged, resulting in one annual mean concentration for each pollutant.

Next, land use regression models were developed for each pollutant

based on the measurements of the monitoring campaigns, and on a variety of potential land use predictors (e.g. proximity to the nearest road, traffic intensity on the nearest road, and population density) (Beelen et al., 2013; Eeftens et al., 2012a). To estimate the levels of each air pollutant at each of the participant addresses, these models were applied to each geocoded address where the participants had lived at during the period of interest (i.e. since conception until the date of MRI assessment). If more than one address was collected during the period of interest, we took into account the number of days that the participant had lived at each address and weighted the air pollution levels accordingly (8.9% of children had moved during pregnancy, 44.6% from birth to 3 years, 24.5% from 3 to 6 years, and 19.7% from 6 years of age to the MRI assessment). To back- and forward- extrapolate the concentrations during each period of interest, daily data from seven available routine background monitoring network sites were used where data was collected on daily basis covering the entire period of interest of each participant, i.e. from conception until the age at MRI assessment (Supplementary Material Methods S1) (Brunekreef, 2012). This resulted in a single, time-adjusted mean concentration of each pollutant for each participant for several time periods: i) for the pregnancy period, ii) from birth until 3 years old, iii) from the day after 3 years until 6 years old (hereafter from 3 years until 6 years old), and iv) from the day after 6 years old until the age at MRI assessment (hereafter from 6 years old until the age at MRI assessment). These study periods are based on the prenatal development, infancy and toddlerhood, early childhood, and middle childhood developmental periods (Centers for Disease Control and Prevention, 2022).

### 2.3. Road traffic noise exposure

To estimate the annual average exposure to noise at all reported home addresses of each participant during pregnancy and childhood, we used existing EU noise maps developed in 2012 for the municipalities of Rotterdam (including Maassluis, Rozenburg, Schiedam, and Vlaardingen) (European Environmental Noise Directive, 2002). Noise maps are created every 5 years. However, we did not use the noise maps created in 2007 because the methodology was different and the estimations not comparable. The maps used in the present study were developed following the requirements of the European Environmental Noise Directive, and for different noise sources including residential road traffic, railway, aircraft, and industry noise. However, for this study, only noise levels from residential road traffic were included, since only a smaller proportion of children had levels above 40 deciBels (dB), considered as the minimum reliable value, for the other noise sources (52.6% for railway noise, 19.2% for aircraft noise, and 19.6% for industry noise).

We used the day-evening-night level noise indicator ($L_{den}$). It was the A-weighted average sound level over 24-hours, with a penalty of 10 dB for night time noise ($L_{night}$) and an additional penalty of 5 dB for evening noise ($L_{evening}$) due to higher nuisance perception and greater health impacts during those hours (World Health Organization, 2018). $L_{den}$ was constructed by the following formula:

$$Lden = 10lg\frac{1}{24}\left(12\times 10\frac{Lday}{10}+4\times 10\frac{Levening+5}{10}+8\times 10\frac{Lnight+10}{10}\right)$$

$L_{day}$, $L_{evening}$, and $L_{night}$ were the A-weighted equivalent continuous sound pressure level when the reference time interval is the day (from 7:00 to 19:00), the evening (from 19:00 to 23:00), and the night (from 23:00 to 7:00), respectively (European Environmental Noise Directive, 2002). Levels of $L_{den}$ were assigned to each geocoded home address where the participants had lived during the study period. If more than one address was collected during the period of interest, we took into account the number of days that the participant spent at each address and weighted the noise levels accordingly (percentages detailed in the Traffic-related air pollution exposure section). We calculated the mean levels of $L_{den}$ for each participant for the same time periods as above: i) for the pregnancy period, ii) from birth until 3 years old, iii) from 3 until 6 years old), and iv) from 6 years old until the age at MRI assessment. When a child spent 50% of the time or more living outside of the municipality of Rotterdam for a study time period, we considered the noise exposure of that time period as missing (4.6% in pregnancy, 8.9% in birth to 3 years, 22.3% in 3 to 6 years, and 25.2% in 6 years of age to the MRI assessment).

### 2.4. Resting-state functional MRI acquisition

Prior to the MRI scanning session, all children were first familiarized with the MRI scanning environment during a 30-minute mock scanning session to reduce the possibility of failure to complete the scanning session (White et al., 2018). During the rs-fMRI session, children were instructed to stay awake and with their eyes closed. MRI imaging data were acquired on a study-dedicated 3 Tesla GE Discovery MR750w MRI System (General Electric, Milwaukee, WI, USA) scanner using a standard 8-channel head coil. Structural T1-weighted images were obtained using a 3D coronal inversion recovery fast spoiled gradient recalled (IR-FSPGR, BRAVO) sequence using ARC acceleration (TR = 8.77 ms, TE = 3.4 ms, TI = 600 ms, flip angle = 10°, matrix = 220 × 220, field of view (FOV) = 220 × 220 mm, slice thickness = 1 mm). A total of 200 volumes of rs-fMRI data were obtained using an interleaved axial gradient recalled echo planar imaging sequence sensitive to BOLD contrast. The scan parameters for functional imaging data were as follows: repetition time = 1760 msec, echo time = 30 msec, flip angle = 85°, acquisition matrix = 64 × 64, field of view = 230 × 230 mm, number of slices = 36, slice thickness = 4 mm, in-plane resolution = 3.4 · 3.4 mm. The total duration of the scan was 5 min and 52 s (White et al., 2018). Imaging scans with excessive motion were defined based on whether they had at least one of the following motion parameters criteria: maximum absolute motion higher than 3 mm, mean relative translation higher than 0.5 mm, and root mean square relative motion higher than 0.5 mm. Scans were also visually inspected and screened for major artifacts (e.g. from dental retainers) as well as whole-brain coverage (e.g. missing from field of view). Children with scans considered as being of poor quality following the above criteria were excluded for the analyses. Participants with air pollution data and high quality scans included in the present study had similar characteristics compared with those of children with air pollution data but with poor quality scans not included in these analyses (Supplementary Material Table S1). The rs-fMRI data was subsequently preprocessed using the standardized fMRIPrep software (Esteban et al., 2019). After pre-processing the data, de-spiking was applied, and the cerebrospinal fluid, white matter and global signals, as well as motion parameters (and their quadratic terms and temporal derivatives) were regressed out of the data (Satterthwaite et al., 2013). Next, the Human Connectome Project (HCP) multimodal parcellation was applied to the data for functional connectivity analysis in grayordinate space (Glasser et al., 2016) as well as the FreeSurfer subcortical segmentation included in fMRIPrep software (Esteban et al., 2019). It has been reported that in subjects under resting state conditions, time series of voxels within functionally connected regions of the brain have high cross-correlation coefficients (Cordes et al., 2001). Pair-wise correlation coefficients of residualized time series amongst the 382 brain areas in the parcellation were computed and subsequently transformed using Fisher transformation to Z scores to reach a normal distribution. Given overlap issues with the HCP parcellation and FreeSurfer regions of interest (ROIs), two of the brain areas in the parcellation related to the

**Table 1**
Population characteristics of the subjects included and not included in the analyses of the study.

| Participant characteristics | Distribution | | |
|---|---|---|---|
| | Included (n = 2,197) | Non-included (n = 7,413) | p-value[1] |
| Maternal education level | | | <0.001 |
| Low | 5.9 | 13.0 | |
| Medium | 39.7 | 48.1 | |
| High | 54.4 | 38.9 | |
| Paternal education level | | | <0.001 |
| Low | 5.2 | 9.4 | |
| Medium | 37.2 | 42.7 | |
| High | 57.6 | 47.9 | |
| Monthly household income during pregnancy (€) | | | <0.001 |
| < 900 | 6.7 | 14.6 | |
| 900–1600 | 13.1 | 20.1 | |
| 1600–2200 | 14.4 | 15.2 | |
| > 2200 | 65.8 | 50.1 | |
| Maternal Country of birth | | | <0.001 |
| Dutch | 59.1 | 47.2 | |
| Other Western | 9.1 | 8.3 | |
| Non-western | 31.8 | 44.5 | |
| Paternal Country of birth | | | <0.001 |
| Dutch | 69.8 | 58.4 | |
| Other Western | 6.2 | 7.1 | |
| Non-western | 24.0 | 34.5 | |
| Family status | | | <0.001 |
| Married | 52.3 | 49.1 | |
| Living together | 37.5 | 35.2 | |
| No partner | 10.2 | 15.7 | |
| Maternal parity (nulli vs. multiparous) | 56.4 | 54.8 | 0.001 |
| Maternal smoking use during pregnancy | | | <0.001 |
| Never | 78.8 | 71.8 | |
| Smoking use until pregnancy known | 9.2 | 8.2 | |
| Continued smoking use during pregnancy | 12.0 | 20.0 | |
| Maternal alcohol consumption during pregnancy | | | <0.001 |
| Never | 41.0 | 52.5 | |
| Alcohol consumption until pregnancy known | 14.5 | 13.2 | |
| Continued alcohol consumption during pregnancy | 44.5 | 34.3 | |
| Maternal age at intake (years) | 31.3 (4.8) | 29.5 (5.5) | <0.001 |
| Paternal age at intake (years) | 33.6 (5.4) | 32.4 (5.8) | <0.001 |
| Maternal height (cm) | 168.2 (7.4) | 166.8 (7.4) | <0.001 |
| Paternal height (cm) | 182.8 (7.6) | 181.2 (8.0) | <0.001 |
| Pre-pregnancy maternal body mass index (kg/m$^2$) | 23.4 (20.8; 25.1) | 23.7 (20.7; 25.6) | 0.212 |
| Pre-pregnancy paternal body mass index (kg/m$^2$) | 25.2 (22.9; 27.2) | 25.3 (22.9; 27.4) | 0.291 |
| Maternal psychological distress during pregnancy[2] | 0.2 (0.1; 0.3) | 0.3 (0.1; 0.4) | <0.001 |
| Paternal psychological distress during pregnancy[2] | 0.1 (0.0; 0.2) | 0.2 (0.0; 0.2) | 0.005 |
| Maternal intelligence quotient score | 98.4 (90.0; 107.0) | 94.4 (84.0; 107.0) | <0.001 |
| Child's sex (boy vs. girl) | 51.0 | 48.9 | 0.086 |
| Child's age at scanning session (years) | 10.2 (0.6) | 10.1 (0.6) | <0.001 |

Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (25th percentile; 75th percentile) for body mass index and psychopathological distress. [1] Chi-square tests for categorical variables, two-sample *t*-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables. [2] Score range from 0 to 4.

HCP hippocampus complex were excluded in these analyses. Therefore, the included pair-wise correlation coefficients amongst 380 brain areas resulted in a correlation matrix with 144,400 connectivity scores that indicated the strength and the direction of the functional connectivity amongst the different brain areas, resulting in a total of 71,820 unique connectivity scores between brain areas. We grouped the brain areas into 31 regions based on location and common properties (e.g. architecture, task-fMRI profiles, or functional connectivity) (Glasser et al., 2016) (Supplementary Material Table S2). Next, we grouped those 31 regions into 5 different brain functional networks: auditory, somatosensory/motor, visual, task positive, and task negative (Glasser et al., 2016), and a 6th group comprising subcortical structures and the cerebellum (Supplementary Material Table S2).

### 2.5. Covariates

Covariates were defined a priori using a direct acyclic graph (Hernan, 2002) based on up-to-date knowledge of the scientific literature, and on data availability within the Generation R cohort. We included the following characteristics variables collected by questionnaires during pregnancy: parental ages at enrollment in the cohort (in years), parental education levels (low: primary education or lower, medium: secondary education, high: university degree or higher), parental countries of birth (Dutch, other Western, or non-Western), maternal smoking during pregnancy (never, smoking use until pregnancy known, continued smoking use during pregnancy), maternal alcohol consumption during pregnancy (never, alcohol consumption until pregnancy known, continued alcohol consumption during pregnancy), maternal parity (nulliparous, one child, two or more children), marital status (married, living together, no partner), and monthly household income (< €900, €900 – 1600, €1600 – 2220 or > €2200). Since previous studies showed an association between prenatal parental psychological distress and child brain functional connectivity, as well as between air pollution exposure and parental psychological distress (Sass et al., 2017), we also included parental psychological distress assessed with the Brief Symptom Inventory (Derogatis, 2011) as a covariate. We also included the parental weights and heights (in kilograms and centimeters, respectively) measured or self-reported at the first trimester of

pregnancy and thereafter used to calculate the pre-pregnancy body mass index (in kg/m$^2$). Maternal intelligence was also assessed using the Ravens Advanced Progressive Matrices Test, set I (Raven, 1962). Child's sex (boy or girl) was obtained from hospital records at birth, and child's age (in years) at the scanning session was also collected. Additionally, as motion has been shown to be a major concern in rs-fMRI research (Power et al., 2012), we have extracted framewise displacement values from the fMRIPrep output.

### 2.6. Statistical analyses

The study population was limited to children with available data on traffic-related air pollution and noise exposure and good quality resting state imaging scans (n = 2,197). We first performed multiple imputation of missing values of potential confounding variables using chained equations to generate 25 complete datasets (Spratt et al., 2010) (Supplementary Material Table S3). The percentage of missing values for the confounding variables was below 30%, except for paternal education level and paternal psychological distress during pregnancy, which were 34.7% and 37.4%, respectively. Distributions in imputed datasets were very similar to those observed (Supplementary Material Table S4).

Children included in the analysis (n = 2,197) were more likely to have Dutch parents, with a higher education level, and from a higher household income compared with children who were not included (n = 7,413) (Table 1). To correct for the losses to follow-up we used the inverse probability weighting. This technique allows accounting for selection bias that potentially arises when only participants with available exposure and outcome data are included as compared to a full initial cohort recruited at pregnancy (Weuve et al., 2012). The variables used to create the weights can be found summarized in Supplementary Material Table S5.

After confirming that the assumptions of the linear regression models (i.e. normality of the residuals, linearity between exposure and outcomes, homoscedasticity, no collinearity between covariates) were fulfilled, we performed linear regression models to assess the association between the exposure to each traffic-related air pollutant and noise exposure variable and each brain area pair correlation, adjusting for all potential confounding variables described previously (Supplementary Material Methods S2). Models were performed separately for each air pollutant and the road traffic noise variable. Models were also performed for each exposure period separately. Several sensitivity analyses were performed: i) we evaluated the association between air pollution and functional brain connectivity excluding those children with exposure estimates above or below of 4 standard deviations of the mean, ii) we evaluated the potential effect modification of sex by adding a product interaction between each air pollutant and the road traffic noise variable separately and sex. In the case of interaction terms statistically significant ($p < 0.05$), we would quantify the potential differences by performing stratified analysis by sex. Due to the high correlation between the air pollutants that were associated with functional brain connectivity, multi-pollutant analyses were not carried out.

All analysis were corrected for multiple testing using false discovery rate at $p < 0.05$ level (Benjamini & Hochberg, 1995). Statistical analyses were carried out using STATA (version 14.0; Stata Corporation, College Station, TX) and R (version 3.4.2; R Core Team (2017)).

## 3. Results

### 3.1. Descriptive results

Participant characteristics of the study population are shown in Table 1. Mean $NO_2$ and $PM_{2.5}$ exposure levels during pregnancy were 39.7 μg/m$^3$, ranging from 24.2 μg/m$^3$ and 90.8 μg/m$^3$, and 19.5 μg/m$^3$, ranging from 15.4 μg/m$^3$ and 31.0 μg/m$^3$, respectively (Fig. 1 and Supplementary Material Table S6). Mean road traffic noise exposure levels during pregnancy were 54.7 dB, ranging from 40 dB and 73 dB (Fig. 1 and Supplementary Material Table S6). The individual traffic-related air pollutants and noise exposure levels between the different time periods were low to highly correlated, ranging from 0.26 for $NO_2$ between pregnancy and childhood period from 6 years to the age at MRI assessment, to 0.90 for road traffic noise between the childhood periods from 3 to 6 years and from 6 years of age to the age at MRI assessment (Supplementary Material Table S7). Correlations between the concentrations of traffic-related air pollutants also varied depending on the pollutant and the period of interest (e.g. correlations between $NO_x$ and $PM_{2.5}$ during pregnancy and between $NO_2$ and $PM_{2.5}$ absorbance during pregnancy were 0.39 and 0.86, respectively) (Supplementary Material Figure S1). Noise exposure levels were low to moderately correlated with the concentrations of traffic-related air pollutants (e.g. correlation between road traffic noise and $PM_{10}$ was 0.17 during pregnancy (Supplementary Material Fig. S1). The mean of the correlations between brain areas was 0.12, ranging from −0.49 to 1.68 after Fisher transformation, and 24.1% of the correlations were negative (data not shown).

### 3.2. Air pollution exposure and functional brain connectivity

Higher exposures to $NO_2$ and $PM_{2.5}$ absorbance from birth to 3 years of age, and to $NO_x$ from 3 to 6 years of age were associated with higher functional brain connectivity (Fig. 2 and Supplementary Material Table S8). In contrast, exposure to $PM_{10}$ and $PM_{2.5}$ were not associated with functional brain connectivity.

#### 3.2.1. $NO_2$ exposure and functional brain connectivity

Higher exposure to $NO_2$ from birth to 3 years of age was associated with 2 higher correlation coefficients between brain areas (Fig. 2 and Supplementary Material Table S8). For these associations, we observed 0.11 higher correlation coefficient per 10 μg/m$^3$ increase in $NO_2$ (Supplementary Material Table S8). The mean values of these correlation coefficients were positive, therefore, the exposure to $NO_2$ increased the positive correlation. Both connections were inter-network: regions belonging to the visual and auditory networks were connected with regions belonging to the task positive network, respectively (Fig. 2 and Supplementary Material Table S8). Additionally, one of the connections was inter-hemispheric while the other was intra-hemispheric (Supplementary Material Fig. 2 and Table S8). No associations were found between higher exposure to $NO_2$ during pregnancy, from 3 to 6 years, and 6 years of age to the age at MRI assessment, and any correlation coefficients between brain areas.

#### 3.2.2. $No_x$ exposure and functional brain connectivity

Higher exposure to $NO_x$ from 3 to 6 years of age was associated with 2 higher correlation coefficients between brain areas (Fig. 2 and Supplementary Material Table S8). For these associations, we observed 0.07 higher correlation coefficient per 20 μg/m$^3$ increase in $NO_x$ (Supplementary Material Table S8). The pattern on how the functional connectivity increased was similar to that of $NO_2$, as the mean values of these correlation coefficients were positive, which means that exposure to $NO_x$ increased the positive correlation. Both connections were inter-network (visual with task positive network) and intra-hemispheric (Supplementary Material Fig. 2 and Table S8). No associations were found between exposure to $NO_x$ during pregnancy, from birth to 3 years, and from 6 years of age to the age at MRI assessment, and any correlation coefficients between brain areas.

#### 3.2.3. $PM_{2.5}$ absorbance exposure and functional brain connectivity

Higher exposure to $PM_{2.5}$ absorbance from birth to 3 years of age was related to 22 higher correlation coefficients between brain areas (Fig. 2 and Supplementary Material Table S8). For these associations, we observed between 0.16 and 0.19 higher correlation coefficients per $10^{-5}m^{-1}$ increase of $PM_{2.5}$ absorbance (Supplementary Material Table S8). Almost all the mean values of these correlation coefficients were

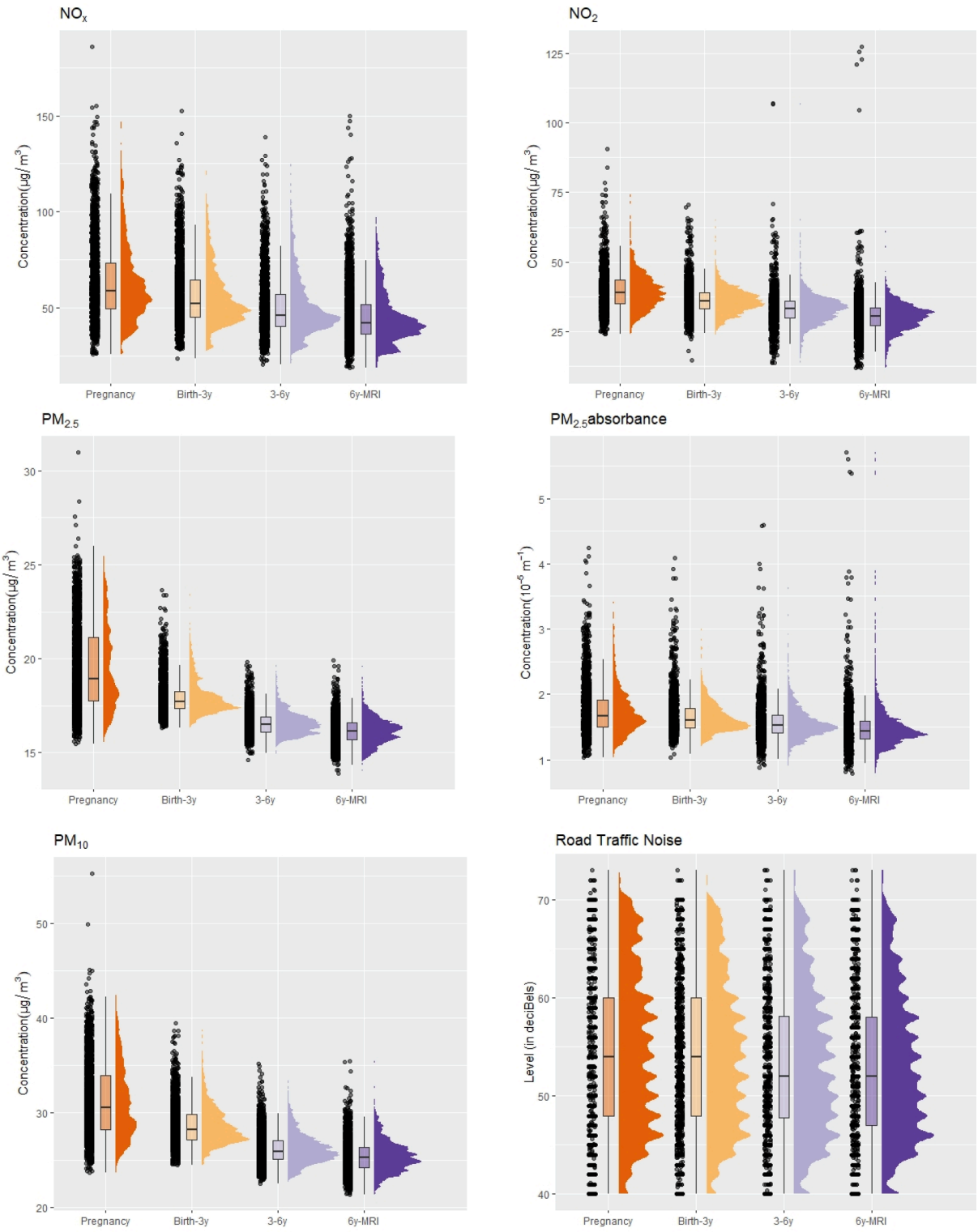


**Fig. 1.** Traffic-related air pollution and road traffic noise exposure levels during pregnancy and childhood periods from birth to 3 years, from 3 to 6 years, and from 6 years to the age at MRI assessment. Abbreviations: $NO_2$, nitrogen dioxide in µg/m$^3$; $NO_X$, nitrogen oxides in µg/m$^3$; PM, particulate matter with different aerodynamic diameters: <10 µm ($PM_{10}$) in µg/m$^3$; <2.5 µm ($PM_{2.5}$) in µg/m$^3$; absorbance of $PM_{2.5}$ filters ($PM_{2.5}$absorbance) in $10^{-5}m^{-1}$.

positive, meaning more exposure to $PM_{2.5}$ absorbance was related to stronger positive correlations between regions, except for three connections which had negative mean correlation coefficients (right lateral occipital (area 1) with left lateral intraparietal dorsal area, left parieto-occipital sulcus (area 2) with the right superior parietal cortex (area 7PC), and right frontal opercular cortex (area 4) with the right lateral temporal cortex (TE1 posterior area)), and thus connectivity shifted from negative to positive with increasing $PM_{2.5}$ absorbance. The brain areas of these three connections belong to regions of the visual, task positive, and task negative networks. Most of the connections related with the exposure to $PM_{2.5}$ absorbance were inter-network (16 of 22) between brain regions predominantly belonging to the task positive and

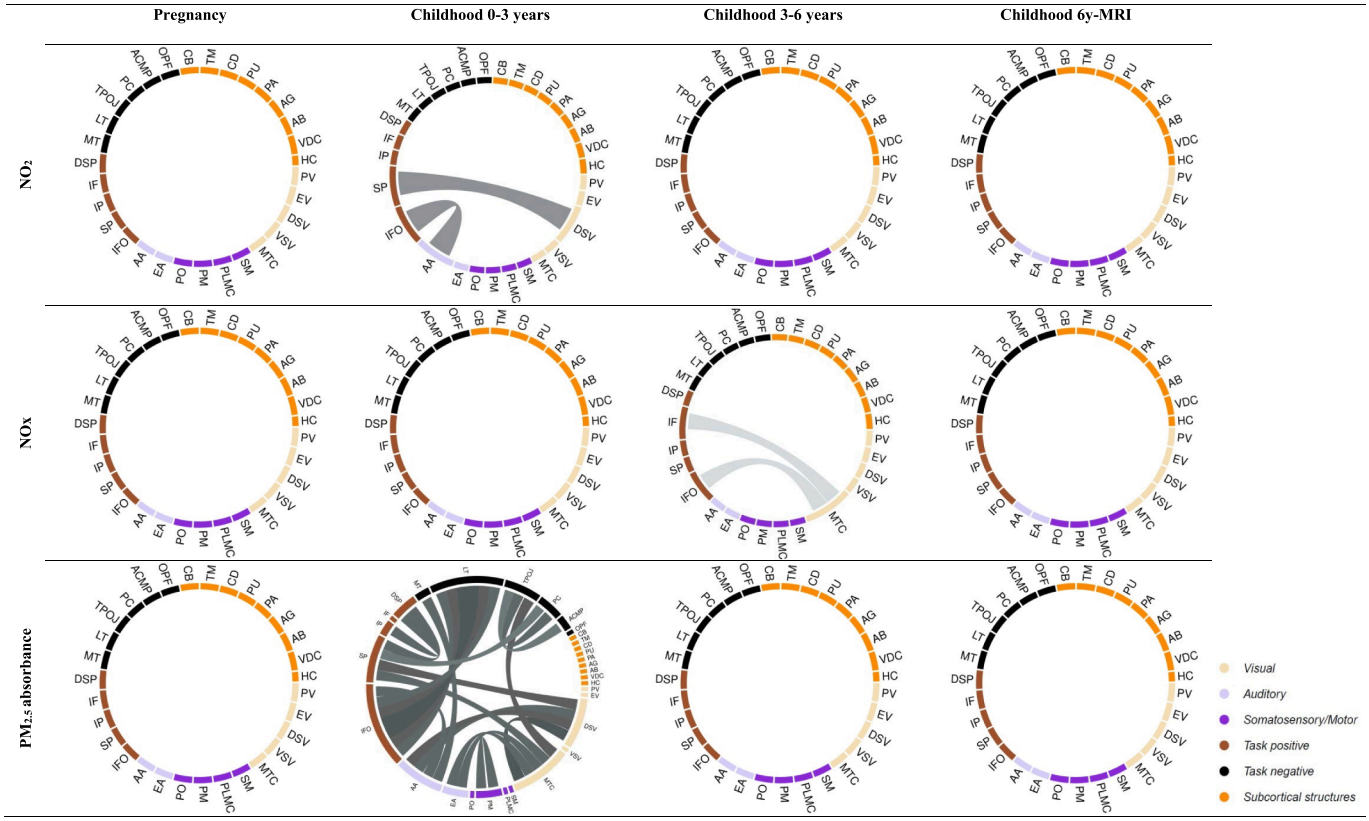


**Fig. 2.** Adjusted associations between exposure to air pollution at each time period and functional brain connectivity in preadolescents. Brain areas were grouped into 31 brain regions (described below) and into 5 different brain functional networks: visual, auditory, somatosensory/motor, task positive, task negative (also known as Default Mode Network (DMN)), and a 6th group with the subcortical structures and the cerebellum: AA, Auditory Association Cortex; AB, Nucleaus Accumbens; ACMP, Anterior Cingulate and Medial Prefrontal Cortex; AG, Amygdala; CB, Cerebellum; CD, Caudate; DSP, DorsoLateral Prefrontal Cortex; DSV, Dorsal Stream Visual Cortex; EA, Early Auditory Cortex; EV, Early Visual Cortex; HC, Hippocampus; IF, Inferior Frontal Cortex; IFO, Insular and Frontal Opercular Cortex; IP, Inferior Parietal Cortex; LT, Lateral Temporal Cortex; MT, Medial Temporal Cortex; MTC, MT + Complex and Neighboring Visual Areas; NOx, nitrogen oxides; NO2, nitrogen dioxide; OPF, Orbital and Polar Frontal Cortex; PA, Pallidum; PC, Posterior Cingulate Cortex; PLMC, Paracentral Lobular and Mid Cingulate Cortex; PM, Premotor Cortex; PM2.5absorbance, absorbance of PM2.5 filters; PO, Posterior Opercular Cortex; PU, Putamen; PV, Primary Visual Cortex; SM, Somatosensory and Motor Cortex; SP, Superior Parietal Cortex; TPOJ, Temporo-Parieto-Occipital Junction; TM, Thalamus; VDC, Ventral Diencephalon; VSV, Ventral Stream Visual Cortex. Associations from linear regression models adjusted for maternal and paternal education, ethnicity, age, body mass index, and psychological distress during pregnancy, maternal smoking and alcohol use during pregnancy, parity, and intelligence quotient, family status, household income, child's gender and age at the scanning session, and mean framewise displacement that survived correction for multiple testing using false discovery rating. All associations showed positive coefficients and the color of the connection represents the strengths of the association (the darkness of the color indicates a larger beta coefficient). Linear regression models were performed separately for each air pollutant.

task negative networks, and half of them were inter-hemispheric (Supplementary Material Fig. 2 and Table S8). No associations were found between higher exposure to $PM_{2.5}$ absorbance during pregnancy, from 3 to 6 years, and from 6 years of age to the age at MRI assessment, and any correlation coefficients between brain areas.

### 3.3. Road traffic noise and functional brain connectivity

Exposure to road traffic noise was not associated with functional brain connectivity (Supplementary Material Table S9).

### 3.4. Sensitivity analyses

Excluding children with air pollution exposure estimates above or below of 4 standard deviations of the mean showed similar results (data not shown). Sensitivity analyses assessing the interaction of each air pollutant and road traffic noise separately with sex yielded to non-significant results (data not shown).

## 4. Discussion

In this study, we found that higher exposures to $NO_2$ and $PM_{2.5}$ absorbance from birth to 3 years, and to $NO_x$ from 3 to 6 years of age were associated with higher functional brain connectivity among several brain regions in preadolescents from 9 to 12 years of age. $PM_{2.5}$ absorbance showed a higher number of associations with functional brain connectivity. Also, the childhood period from birth to 3 years was the period with the highest susceptibility to air pollution. Most associations were found with functional brain connections between brain regions that are part of the task positive and the task negative networks. Also, slightly more than half of the identified connections were intra-hemispheric. We found no evidence of associations between $PM_{10}$, $PM_{2.5}$, or road traffic noise during pregnancy or childhood, and brain functional connectivity.

To our knowledge, this is the first study exploring the associations of the exposures to traffic-related air pollution and noise during pregnancy and childhood, and whole-brain functional connectivity. Previous evidence of such associations is limited to a single study (Pujol et al.,

2016b) where higher exposure to $NO_2$ and elemental carbon at schools in children from 8 to 12 years of age were associated with lower integration and segregation in key brain networks. Our findings indicated that most of the functional connections associated with exposure to air pollution were between brain regions belonging to different networks (20 of 26), which would suggest an indicator of lower segregation.

In our study, we investigated functional connectivity during resting conditions. Under these conditions, the brain is engaged in spontaneous, intrinsic activity (i.e. not attributable to specific inputs or intended to generate specific outputs) (Hausman et al., 2020). Brain areas with higher connectivity in relation to exposure to air pollution were located in most of the networks explored but mainly in brain regions that are part of the task negative and task positive networks. Increased connectivity within the task negative network during rest could be interpreted as a sign of increased self-referential thoughts, and less activity in cognitive-control networks such as attention and inhibitory control (Whitfield-Gabrieli & Ford, 2012). Consistent with these findings, some previous studies also found an association of exposure to air pollution with impaired attentional function and inhibitory control, measured using neuropsychological tests (Basagaña et al., 2016; Chiu et al., 2013; Guxens et al., 2018; Pujol et al., 2016a; Sentís et al., 2017; Sunyer et al., 2015, 2017). Additionally, previous evidence found an association between the exposure to air pollution and thinner cortex as well as alterations in cortical surface in regions belonging to the task negative network (Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2021). While Guxens et al. reported that children exposed to higher levels of air pollution during pregnancy had thinner cortex in several regions of both hemispheres, Cserbik et al. reported hemispheric-specific differences in the associations between air pollution exposure during childhood and cortical thickness and surface area. We also found higher functional connectivity in brain areas belonging to the task positive network during resting conditions. For optimal cognitive processing, the task positive and task negative networks should have an opposite relationship, i.e., the activation of one network would inhibit the other, to avoid the other's interference in the coordination of a neural process (Cheng et al., 2020). Task negative tend to be activated during resting conditions while task positive tend to be activated during attention-demanding tasks and includes our conscious attention towards the external environment. Therefore, increased connectivity of the task positive network during resting conditions, in addition to the activation of both networks at the same time, could be an indicator of functional brain connectivity impairment. Previous evidence also described thinner cortex and a decrease in cortical surface in regions that are part of the task positive network in relation to the exposure to air pollution (Guxens et al., 2018; Lubczyńska et al., 2021).

The specific windows of exposure of air pollution on functional brain connectivity have not been previously explored. We have identified the first years of life as sensitive periods of exposure. Consistent findings of both fetal and neonatal rs-fMRI studies have hypothesized that the foundations of resting-state networks are already laid before 37 weeks of gestation, with rapid neural growth in the last trimester of pregnancy (Doria et al., 2010). However, some networks appear to be more developed than others (e.g., visual and auditory networks). Additionally, changes in network size, represented by a percentage of brain volume, have been observed during first years of life, and several resting state networks also showed a significant increase in functional connectivity during first years of life (Lin et al., 2008). The development of connectivity networks during first years of life could be the explanation of why the exposure to air pollution from birth to 3 years of age was related to more changes in brain functional connectivity than the exposure to air pollution during the other periods of interest in our study. From the age of 2 years onwards, neurodevelopment is characterized by a gain in higher-order cognitive abilities, such as attention and memory (de Bie et al., 2012), and functional networks continue in development between childhood and adulthood. It has been described that the structure of these functional networks differed between children and adults, shifting from a local anatomical architecture in children (i.e., correlations between brain regions close in space) to a more distributed architecture in adults (i.e., correlations between brain regions more distant in space) (Fair et al., 2009). In addition, synaptic pruning and myelination take place until late the second decade of life (Williamson & Lyons, 2018). During synaptic pruning, the brain eliminates extra connections that are no longer needed. Both neurodevelopmental events result in an increased signal propagation that allows for a more efficient communication between distant regions, allowing for a more effective response to any processing demand. Finally, functional neuroimaging investigations have shown that inter-hemispheric connectivity appears at birth and slowly shifts during development to a predominant intra-hemispheric connectivity in the adult, as a result of the process of brain's lateralization (Tzourio-Mazoyer, 2016). In the results of this study, we found that half of the connections associated with air pollution in the exposure period from birth to 3 years of age were intra-hemispheric while the connections we found in the exposure period from 3 to 6 years of age were all intra-hemispheric, although these last results should be interpreted with caution due to the small number of connections identified.

In the present study, we identified $NO_2$, $NO_x$, and $PM_{2.5}$ absorbance as the traffic-related pollutants associated with functional brain connectivity. The same pollutants were identified in the previous study on air pollution exposure at school and functional brain connectivity (Pujol et al., 2016b). In Europe, $NO_x$ and $NO_2$ gasses in the air are predominantly produced by an incomplete combustion of hydrocarbons, mainly originating from diesel fuel (European Environment Agency, 2019). The absorbance of $PM_{2.5}$ is considered as a measure of exposure to black carbon particles. Black carbon refers to the sooty black material emitted during incomplete combustion. Diesel-powered vehicles intensively used in urban areas are an important source, though not the unique source (European Environment Agency, 2019).

Regarding the association between exposure to road traffic noise and functional brain connectivity, we did not find any association in pre-adolescents exposed to higher road traffic noise during pregnancy or childhood in our study. Nevertheless, some studies have shown that noise exposure could act as a stressor that affects the HPA axis leading to an increased level of stress hormones (Jafari et al., 2017; Lautarescu et al., 2020). During pregnancy, these hormones could cross the fetal-placental barrier and influence brain development (Lautarescu et al., 2020), while in children, they could alter the size and neuronal architecture of some brain areas (Smith & Pollak, 2020). Such early life stress could be also related to disturbances in functional brain connectivity (De Asis-Cruz et al., 2020; Hermans et al., 2011; van Marle et al., 2010). Additionally, it has been demonstrated that noise exposure might have negative effects on children's cognition, mainly on memory and reading outcomes (Clark & Paunovic, 2018; S. Stansfeld & Clark, 2015). However, the evidence on the effect of noise exposure on children's cognition remains inconsistent and further studies are warranted. There is no previous evidence evaluating the effect of the exposure to road traffic noise in brain's structure and function. Our null results could be due to the fact that we evaluated long-term exposure to noise instead of acute exposure. Previous studies found an association between the acute exposure to noise generated by MRI and altered functional brain connectivity (Andoh et al., 2017; Pellegrino et al., 2022).

Our study has several strengths: i) the large sample size of study participants with resting state functional imaging data; ii) the longitudinal exposure assessment and prospective nature of the study; iii) the use of multiple imputation and inverse probability weighting to reduce the selection bias in the study; iv) the availability for a large number of socioeconomic and lifestyle factors to control for confounding; v) the standardized and validated traffic-related air pollution and road traffic noise measurement assessments across different time periods to assess sensitive windows of exposure. However, some limitations should also be considered. One of our main limitations related to the exposure assessment is the possibility of measurement error in the air pollution

estimates. Air pollution monitor campaigns were performed between 2009 and 2010 and we used back- and forward- extrapolated concentration levels for the periods of interest of our study, which have been shown to remain spatially stable over time for periods up to 8 or 18 years (Eeftens et al., 2011; Gulliver et al., 2013), however, we cannot discard the introduction of measurement error. Exposure to air pollution and road traffic noise was assessed at the residential home addresses of the study participants, while pregnant women could have spent a large amount of time at work, and children older than 6 years also possibly spent many hours in school settings in the hours that road traffic was higher. This fact could have introduced measurement error on the exposure estimations, and lead to non-differential misclassification, which in turn could have led to underestimation of the effect estimates. Misclassification could also occur if participants changed home addresses and this change was not documented. We used air pollution and noise average levels for the entire pregnancy and for different periods during childhood. Although it has been reported that some neurodevelopmental outcomes are related to a specific exposure window, we did not use statistical methods with higher temporal resolution due to computational reasons. Therefore, the effects could be underestimated. Another limitation that should be addressed is that although we used multiple imputation for missing data, some variables have more than 30% of participants with missing data (e.g. paternal education level and paternal psychological distress during pregnancy). However, the distributions in the imputed datasets were very similar to those observed. Furthermore, we cannot discard the possibility of residual confounding due to the unavailability of other, potentially relevant, confounding variables such as parental social class or genetic and family factors related to both air pollution and brain development. Also, information on some effect modifiers, such as noise sensitivity, location of the child's bedroom, and other noise sources should be included to more accurately estimate the effects of noise exposure and reduce the measurement error in the noise pollution estimates.

## 5. Conclusions

In conclusion, we observed associations of exposure to $NO_2$, $NO_x$, and $PM_{2.5}$ absorbance from birth to 3 years, and from 3 to 6 years of age, with higher functional brain connectivity in preadolescents from 9 to 12 years of age. $NO_x$ and $NO_2$ gasses as well as the absorbance of $PM_{2.5}$ are mainly produced by diesel-powered vehicles in urban areas. $PM_{2.5}$ absorbance was the traffic-related air pollutant most frequently associated with functional brain connectivity, and the period from birth to 3 years of age was the time window most susceptible to the effects of air pollution. The associations found in our study are in brain areas predominantly located in the task positive and task negative networks. An increased connectivity in these networks during resting conditions could be an indicator of differential functional connectivity in children exposed to higher levels of air pollution. No association was observed between exposure to road traffic noise and brain functional connectivity. Future longitudinal studies with repeated brain functional connectivity measures, and including multipollutant approaches, are warranted to better understand the associations found in this study.

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### *CRediT authorship contribution statement*

**Laura Pérez-Crespo:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Visualization. **Michelle S.W. Kusters:** Formal analysis, Writing – review & editing. **Mónica López-Vicente:** Methodology, Writing – review & editing. **Małgorzata J. Lubczyńska:** Writing – review & editing. **Maria Foraster:** Writing – review & editing. **Tonya White:** Conceptualization, Writing – review & editing. **Gerard Hoek:** Writing – review & editing. **Henning Tiemeier:** Conceptualization, Writing – review & editing, Funding acquisition. **Ryan L. Muetzel:** Conceptualization, Methodology, Writing – review & editing. **Mònica Guxens:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107275.

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