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Exposure to residential air pollution and the development of functional connectivity of brain networks throughout adolescence

Michelle S.W. Kusters [a,b,c], Laura Granés [a,d,e], Sami Petricola [a,b], Henning Tiemeier [c,f], Ryan L. Muetzel [c,g], Mònica Guxens [a,b,c,d,h,*]

[a] ISGlobal, Barcelona, Spain
[b] Universitat Pompeu Fabra, Barcelona, Spain
[c] Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre, Rotterdam, the Netherlands
[d] Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
[e] Department of Psychiatry, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, Barcelona, Spain
[f] Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, USA
[g] Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
[h] ICREA, Barcelona, Spain

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ABSTRACT

Background: A few studies linked air pollution to differences in functional connectivity of resting-state brain networks in children, but how air pollution exposure affects the development of brain networks remains poorly understood. Therefore, we studied the association of air pollution exposure from birth to 3 years and one year before the first imaging assessment with the development of functional connectivity across adolescence.

Methods: We utilized data from 3,626 children of the Generation R Study (The Netherlands). We estimated residential exposure to PM_{10}, $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_X, and NO_2 with land-use regression models. Between- and within-network functional connectivity was calculated for 13 cortical networks, and the amygdala, hippocampus, and caudate nucleus at two assessments (8.6–12.0 and 12.6–17.1 years), resulting in 4,628 scans (2,511 for assessment 1 and 2,117 for assessment 2) from 3,626 individuals. We investigated the association between air pollution and functional connectivity with linear mixed models adjusted for life-style and socioeconomic variables, and corrected for multiple testing.

Results: Higher exposure to $PM_{2.5}$ from birth to 3 years was associated with persistently lower functional connectivity over time between the amygdala and the ventral attention, somatomotor hand, and auditory networks throughout adolescence (e.g. −0.027 functional connectivity [95 % CI −0.040; −0.013] amygdala – ventral attention network per 5 $\mu g/m^3$ higher $PM_{2.5}$). Higher exposure to PM_{10} one year before the first imaging assessment was associated with persistently lower functional connectivity between the salience and medial-parietal networks throughout adolescence. Air pollution was not associated with a faster or slower change in functional connectivity with age.

Conclusions: Air pollution exposure early in life was associated with persistent alterations in connectivity between the amygdala and cortical networks involved in attention, somatomotor, and auditory function. Concurrent exposure was associated with persistent connectivity alterations between networks related to higher cognitive functions (i.e. the salience and medial-parietal networks).

1. Introduction

The majority of the world population remains exposed to air pollution concentrations above recommended limits from the World Health Organization guidelines (Shaddick et al., 2020). Many studies have linked air pollution exposure to a decline in cognitive function and a higher incidence of psychiatric problems in children, although several studies reported null and even protective associations (Donzelli et al., 2019; Kusters et al., 2022; Reuben et al., 2021). Particulate matter is suggested to activate the hypothalamus–pituitary–adrenal axis

* Corresponding author at: ISGlobal, Barcelona, Spain.
E-mail address: monica.guxens@isglobal.org (M. Guxens).

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(Thomson, 2019), as well as to travel to the human brain through the nasal olfactory mucosa and by entering circulation via the lungs (Costa et al., 2017). There it triggers neuroinflammation, microglia activation and oxidative stress, as indicated by lipid peroxidation (Costa et al., 2017). The adverse effects of air pollution are likely more pronounced during childhood and adolescence as compared to adulthood, due to the continuous neurodevelopment taking place combined with less capacity to mitigate the adverse effects of air pollution (Rice and Barone, 2000).

Even in the absence of external stimuli, the brain exhibits activity. This brain activity can be organized in so-called "resting-state networks", which is comprised of different brain regions that exhibit temporally-correlated fluctuations in activity, and have been shown to be reproducible across individuals (Gordon et al., 2016). Resting state functional magnetic resonance imaging (rs-fMRI) allows for the investigation of "functional connectivity" within and between these networks, by detecting levels of increased oxyhaemoglobin (i.e. the blood oxygen level dependent (BOLD) signal). Previous research has linked these networks to the development of major cognitive functions and found changes in functional connectivity within and between networks across multiple psychiatric disorders (Gao et al., 2017; Sha et al., 2019; Zimmermann et al., 2018). The primary organization of many functional networks is largely in place around 2 years of age, but development continues as the brain further matures (Gilmore et al., 2018). During childhood and adolescence, increasing functional connectivity between regions belonging to the same network (i.e., higher within-network connectivity) and decreasing functional connectivity between regions belonging to different networks (i.e., lower between-network connectivity) is generally seen (Grayson and Fair, 2017). Yet, recent evidence suggests that the development of functional connectivity with age varies across networks and can also consist of decreasing within-network connectivity and increasing between-network connectivity (Cotter et al., 2023; Sanders et al., 2023).

Two analyses embedded in the BREATHE Project (Barcelona, Spain) found an association of air pollution exposure at schools in the year of the MRI assessment, with lower functional connectivity between the caudate nucleus and the frontal cortex, lower functional connectivity within the default-mode-network, and higher functional connectivity between the default-mode-network and adjacent regions in 8- to 12-year-olds (Pujol et al., 2016a,b). Cotter et al. (2023) and Zundel et al. (2024) investigated the longitudinal association of outdoor residential exposure to several air pollutants in the year prior to the MRI assessment at age 9–10 years with changes in functional connectivity during a 2-year follow-up period, utilizing data from the ABCD study (United-States). Higher air pollution exposure was associated with both higher and lower functional connectivity, depending on the pollutant and the network. We previously studied the association between outdoor residential exposure to air pollution and functional connectivity in 9- to 12-year-olds of the Generation R Study (Rotterdam, the Netherlands), and found that higher exposure from birth to 3 years was primarily associated with higher functional connectivity between the task positive and task negative networks (Pérez-Crespo et al., 2022).

The availability of a second neuroimaging assessment within the Generation R Study (i.e., at age 12–17 years) allows us to investigate whether the previously found associations remain, attenuate, or worsen throughout adolescence. Furthermore, we aim to investigate how environmental exposure shortly prior to the brain imaging assessment is associated with functional connectivity development. We took an exploratory approach by including within- and between functional connectivity of all resting state networks in our analyses, as there are currently no well-defined hypotheses regarding localized or specific effects. The importance of the current work is highlighted by the limited evidence on air pollution exposure and functional connectivity in children, especially in regards to longitudinal development.

2. Methods and Materials

2.1. Population and study design

This study was carried out within the Generation R Study, which is a population-based birth cohort in Rotterdam, the Netherlands. All pregnant women with a delivery date between April 2002 and January 2006 were eligible for participation. The majority of women were enrolled during pregnancy (8,879 women), some women shortly after delivery (899 women) (Fig. S1). We excluded all non-singleton births for this study (N = 246). Follow-up of parents and their child was continued after delivery and children underwent a neuroimaging assessment at median age 9.9 (range 8.6 – 12.0; rs-fMRI 1) and 13.8 years (range 12.6 – 17.1; rs-fMRI 2). All children were invited for both neuroimaging assessments. In our sample, we had air pollution exposure data available for 9,248 children. Of these children, 4,294 participated in rs-fMRI 1 and/or 2. After exclusion based on the image quality assurance protocol, a total of 3,626 children had data on at least one of the rs-fMRI assessments (2,511 for rs-fMRI 1 and 2,117 for rs-fMRI 2). Written informed consent was obtained and the study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam.

2.2. Exposures

We estimated average exposure to air pollution at the reported residential address for each participant for two exposure periods: (i) birth to 3 years, and (ii) 1 year before rs-fMRI 1 (Methods S1). A detailed description on how exposure was estimated with land-use regression models can also be found in Guxens et al. (2022). We had estimates available for particulate matter (PM) with aerodynamic diameter of less than 10 μm (PM_{10}) and of less than 2.5 μm ($PM_{2.5}$), the absorbance of $PM_{2.5}$ ($PM_{2.5}$ absorbance), nitrogen oxides (NOx), and nitrogen dioxide (NO_2). We used data from 7 routine background monitoring network sites to back- and forward extrapolate air pollution concentrations to the 2 periods of interest. We accounted for the number of days that a participant lived in each address when calculating average exposure concentrations for each of the two exposure periods. For participants with missing data at rs-fMRI 1, we could not define the second exposure period as one year before rs-fMRI 1. Based on the distribution of age at rs-fMRI 1, we estimated air pollution exposure from 8 to 9 years for these participants.

2.3. Magnetic resonance imaging

2.3.1. fMRI image acquisition and preprocessing

We used a 3 Tesla General Electric scanner (MR750W; GE) MRI System in the Erasmus Medical Centre to collect rs-fMRI imaging data. Both neuroimaging assessments took place with the same scanner. The fMRIPrep pipeline version 20.2.7 was used to preprocess the BIDS data (Esteban et al., 2019). A detailed description on fMRI preprocessing and quality assessment can be found in Xu et al. (2024). In short, we performed the following steps: (i) intensity normalization for B1-inhomogeneity and brain extraction, (ii) nonlinear registration to MNI space, (iii) Freesurfer processing, (iv) volume realignment of the rs-fMRI data using MCFLIRT (FSL), (v) slice-time correction with 3dTshift (AFNI) of the BOLD runs, co-registration to the corresponding T1w reference as well as the MNI152 2009c Asym space, and (vi) resampling of the data to the CIFTI grayordinate space. We only included images without major artefacts, with whole-brain coverage, and without excessive motion, and all images were visually inspected for accuracy of co-registration.

2.3.2. Parcellation and whole-brain connectivity estimation

We used Python (version 3.9.0) to compute the functional connectivity matrices for the entire brain. The Gordon parcellation (Gordon et al., 2016) was used for cortical parcels, and Freesurfer was used for the subcortical segmentation (Fischl et al., 2002). This generated a total of 349 parcels, but for the purpose of this study we only used the 333 cortical regions, and the amygdala, hippocampus, and caudate nucleus regions. We selected these 3 subcortical regions based on findings from previous research (Cotter et al., 2023; Pujol et al., 2016). Time series from each parcel was extracted and adjusted for cerebral spinal fluid and white matter signals (and their quadratic terms and temporal derivatives), the ICA AROMA motion regressors, and high-pass temporal filtering parameters. A 333x333 correlation matrix was constructed by computing the Pearson correlation for each pair of time series data, and data were then converted to Z-scores with the Fisher r-to-z transform. The main analyses were performed on data without global signal regression, but we ran sensitivity analyses with data were the global signal was regressed out, due to a lack of consensus on the best approach (Murphy and Fox, 2017). Although regressing out the global signal might be an effective way of reducing noise, it comes with the risk of removing valuable information. Global signal is computed by taking the mean of the voxel time-series within the brain. Therefore, it represents both neural and non-neural fluctuations (e.g., respiratory and cardiac activity). Using the Gordon parcellation, we grouped the 333 cortical regions into the following networks: auditory, cingulo-opercular, default mode network, dorsal attention, fronto-parietal, medial-parietal, parieto-occipital, salience, somatomotor hand, somatomotor mouth, ventral attention, visual and none (Fig. 1) (Gordon et al., 2016). None represents the connectivity of cortical regions that are not included in any of the other cortical networks. Functional connectivity within each of the 13 networks was calculated by averaging the pairwise Fisher z-transformed Pearson correlations between regions within the same network. Between-network functional connectivity was calculated by averaging the pairwise correlation of regions belonging to the first network with regions belonging to the second network. Finally, subcortical-network functional connectivity was calculated by averaging the pairwise correlation between regions belonging to the amygdala, hippocampus or caudate nucleus, with regions belonging to each of the 13 cortical networks.

2.4. Statistical analysis

We used the R package "mice" (version 3.14.0) to impute missing values in the co-variates and generated 25 imputed datasets for the data analysis (Spratt et al., 2010; Sterne et al., 2009) (Table S1-S2). The percentage of missing values was below 30 % for all covariates, with the exception of education of the father (36.5 %) (Table S2). Imputed values were similar to observed values (Table S2). Next, we performed a comparison of the characteristics of participants included in our study and the full population at baseline, with the exclusion of twins (Table S3). Since our study population differed significantly in e.g. several variables related to socioeconomic status, we performed inverse probability weighting to address potential selection bias (Fig. S2). In short, we utilized the R CBPS package (version 0.23) to calculate the inverse of probability of participation for each of our study participants. Weights were truncated at 10. Then we weighted all following analyses accordingly.

For the main analyses we aimed to test the association of exposure to each pollutant during each of the 2 exposure periods with each of the within- and between functional connectivity outcomes, separately, using 2 approaches: (i) an association with a lower or higher functional connectivity aggregated across the 2 timepoints (Model $_{\text{overall associations}}$), and (ii) an association with change in functional connectivity between the 2 timepoints (i.e., faster/slower increase/decrease in functional connectivity with age) (Model $_{\text{interaction associations}}$) (Methods S2). For the first approach, we ran linear mixed models with a random intercept for participant and adjusted for potential confounders based on a direct acyclic graph (Fig. S3) (Guxens et al., 2018). The included confounders were child's sex, age, and season of birth, parental age at enrolment, parental national origin and education level, household income, maternal marital status, maternal parity, parental pre-pregnancy body mass index, maternal alcohol consumption, smoking, and folic acid use during pregnancy, maternal intelligence quotient, socioeconomic status of the neighbourhood, which included mean household income of the neighborhood, and proportion of households with low income, low educational level, and without paid work (NIPHE, 2017), and greenness, estimated with the Normalized Difference Vegetation Index in the surrounding area of 300 m of maternal home addresses. For the second approach we ran the same adjusted linear mixed models, but now included an air pollutant*age interaction term. We centered age at the 5th percentile of age over the 2 timepoints (9.6 years). All assumptions for linear mixed models were fulfilled (i.e., linearity between the

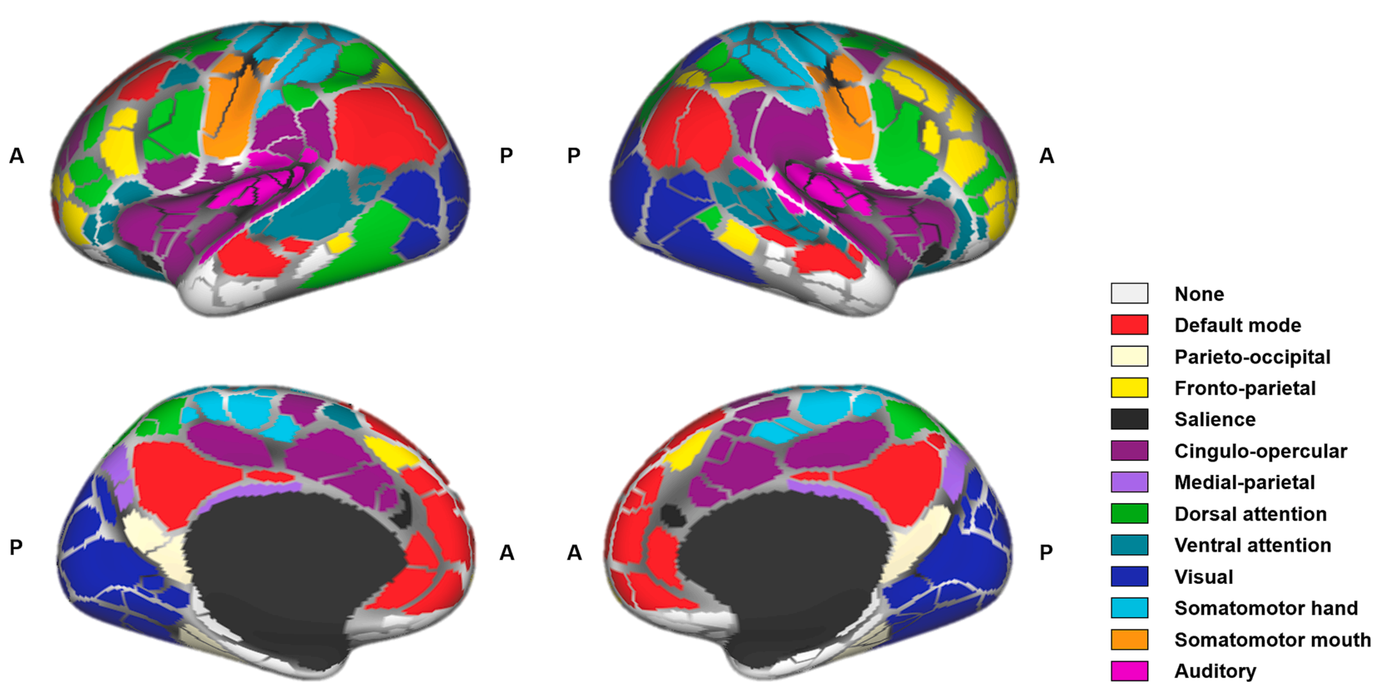

Fig. 1. Gordoń s parcellation schema color-coded by cortical network. Adapted from Gordon et al., 2018.

exposure and outcome, normality of the residuals, homoscedasticity, and no collinearity).

Finally, we corrected all analyses for multiple testing given the different exposures and outcomes, by multiplying the mean effective number of tests over the exposures (2.8) with the mean effective number of tests over the outcomes (58.2), and dividing $p < 0.05$ by this number, following the approach suggested by Galwey (2009). This yielded a new p-value cut-off of 0.0003. Since the majority of pollutants in our study were highly correlated (i.e., ranging from 0.45 to 0.92) (Fig. S4), we opted for this approach instead of a multi-pollutant analysis, like the least absolute shrinkage and selection operator.

As a follow-up analysis, to place our results into perspective of normal development, we investigated the relationship between age and the outcomes for which we found an association after applying multiple testing correction. Next, we performed the following sensitivity analyses: (i) we repeated the main analyses after additionally regressing out the global signal from the original time series data and recomputing the connectivity matrices (N = 3,626 participants and 4,628 scans) (Murphy and Fox, 2017), (ii) we restricted the main analyses to children with available exposure and outcome data on both of the rs-fMRI assessments, to address potential bias following imputation of one of the outcomes by the linear mixed-effects models (N = 1,002 participants and 2,004 scans), and (iii) we restricted the 1 year before rs-fMRI 1 analyses to those children who did not move house address between the rs-fMRI assessments to address potential misclassification of the exposure (N = 3,012 participants and 3,861 scans).

All statistical analyses were carried out using R (version 4.2.1; R Development Core Team).

3. Results

3.1. Descriptive results

Slightly over half of the participants' mothers was of Dutch national origin (57.6 %) and highly educated (51.7 %) (Table 1). Median air pollution exposure from birth to 3 years was 28.6 μg/m^3 for PM_{10}, 17.9 for $PM_{2.5}$, 1.3 * 10^{-5}/m for $PM_{2.5}$ absorbance, 35.1 μg/m^3 for NO_2, and 55.4 μg/m^3 for NO_X (Table 2). Concentrations for exposure 1 year before rs-fMRI 1 were lower: 21.0 μg/m^3 for PM_{10}, 13.4 for $PM_{2.5}$, 1.0 * 10^{-5}/m for $PM_{2.5}$ absorbance, 27.8 μg/m^3 for NO_2, and 40.4 μg/m^3 for NO_X. Mean within- and between-network functional connectivity for rs-fMRI 1 is shown in interactive Fig. 1 (Fig. 2). and for rs-fMRI 2 in interactive Fig. 2 (Fig. 3).

3.2. Overall associations: The aggregated association between air pollution exposure and functional connectivity over time (Model $_{overall\ associations}$)

Higher exposure to all air pollutants from birth to 3 years and in the year before rs-fMRI 1 was associated with primarily lower within- and between-network functional connectivity over the two timepoints (Fig. S5-S6). After correction for multiple testing, higher exposure to $PM_{2.5}$ from birth to 3 years remained associated with lower functional connectivity between the amygdala and the ventral attention, somatomotor hand, and auditory cortical networks (e.g. −0.027 units of functional connectivity [95 % CI −0.040; −0.013] between the amygdala and the ventral attention network per 5 μg/m^3 higher $PM_{2.5}$ exposure during birth to 3 years) (Fig. 4a, Table 3). Higher exposure to PM_{10} in the year before rs-fMRI 1 remained associated with lower functional connectivity between the salience and medial-parietal networks (−0.022 [95 % CI −0.034; −0.010] per 10 μg/m^3 higher PM_{10} exposure in the year before rs-fMRI 1) after correction for multiple testing (Fig. 4b, Table 3).

Table 1
Characteristics of the study participants (N=3,626)

Participant characteristics	Distribution
Maternal age at enrolment (years)	31.1 ± 4.9
Maternal national origin	
Dutch	57.6
Moroccan	4.9
Surinamese	7.6
Turkish	5.9
European, other	7.8
Non-European, other	16.1
Maternal educational level at enrolment	
Higher or above	51.7
Secondary	30.9
Primary or lower	17.4
Household income at enrolment	
>2,200€	63.8
1,600-2200€	14.3
900-1,600€	14.4
<900€	7.6
Maternal marital status at enrolment	
Married	50.0
Living together	38.8
No partner	11.2
Maternal parity	
0 children	57.0
1 child	30.8
≥ 2 children	12.2
Maternal pre-pregnancy BMI (kg/m2)	23.5 ± 4
Maternal alcohol use during pregnancy	
Never	39.4
Until pregnancy known	14.2
Occasional use during pregnancy	36.4
Frequent use during pregnancy	10.0
Maternal smoking during pregnancy	
Never	73.2
Until pregnancy known	8.4
Continued during pregnancy	18.5
Maternal folic acid use during pregnancy	
Start preconceptional	47.9
Start in the first 10 weeks of pregnancy	31.6
None periconceptional	20.5
Maternal intelligence quotient	97.7 ± 14.7
Socioeconomic status neighbourhood	-0.9 ± 1.4
Residential greenness birth - 3 years	0.4 ± 0.1

Values are percentages for categorical variables, mean ± standard deviation for continuous variables.

3.3. Interaction associations: Association between air pollution exposure and the change in functional connectivity with age (Model $_{interaction\ associations}$)

Higher exposure to all air pollutants from birth to 3 years and in the year before rs-fMRI 1 was associated with a change of within- and between functional connectivity between the 2 timepoints with age (Fig. S7-S8). However, after correction for multiple testing none of the associations in the Models $_{interaction\ associations}$ remained.

3.4. Follow-up and sensitivity analyses

Higher age was associated with higher functional connectivity between the amygdala and the ventral attention, somatomotor hand, and auditory networks, and between the salience and medial-parietal networks (e.g. 0.009 functional connectivity [95 % CI 0.008; 0.011] between the amygdala and the ventral attention network per year higher age) (Table S4). When applying global signal regression to the dataset, beta estimates were similar or smaller and all in the same direction as the observed significant associations in the main analyses (N = 3,626 participants and 4,628 scans) (Table S5). Furthermore, we observed similar beta estimates when only analyzing those participants with complete data on both rs-fMRI assessments (N = 1,002 participants and 2,004 scans), and when analyzing only those participants that did not

Table 2
Air pollution exposure concentrations during pregnancy and childhood

	Birth - 3 years			1 year before rs-fMRI 1			Corr
	median	p25	p75	median	p25	p75	
PM_{10} (μg/m^3)	28.6	27.2	30.5	21.0	19.9	23.1	0.52
$PM_{2.5}$ (μg/m^3)	17.9	17.3	18.8	13.4	12.8	14.1	0.52
$PM_{2.5}$ abs (10^{-5m-1})	1.3	1.2	1.5	1.0	0.9	1.2	0.50
NO_2 (μg/m^3)	35.1	31.9	38.6	27.8	24.4	31.2	0.52
NO_X (μg/m^3)	55.4	47.7	72.1	40.4	34.2	51.5	0.49

Abbreviations: Corr, Spearman's correlation; NO_X, nitrogen oxides; NO_2, nitrogen dioxide; PM, particulate matter with different aerodynamic diameters: less than 10 μm (PM_{10}); less than 2.5 μm ($PM_{2.5}$); $PM_{2.5}$ abs, absorbance of $PM_{2.5}$ filters.

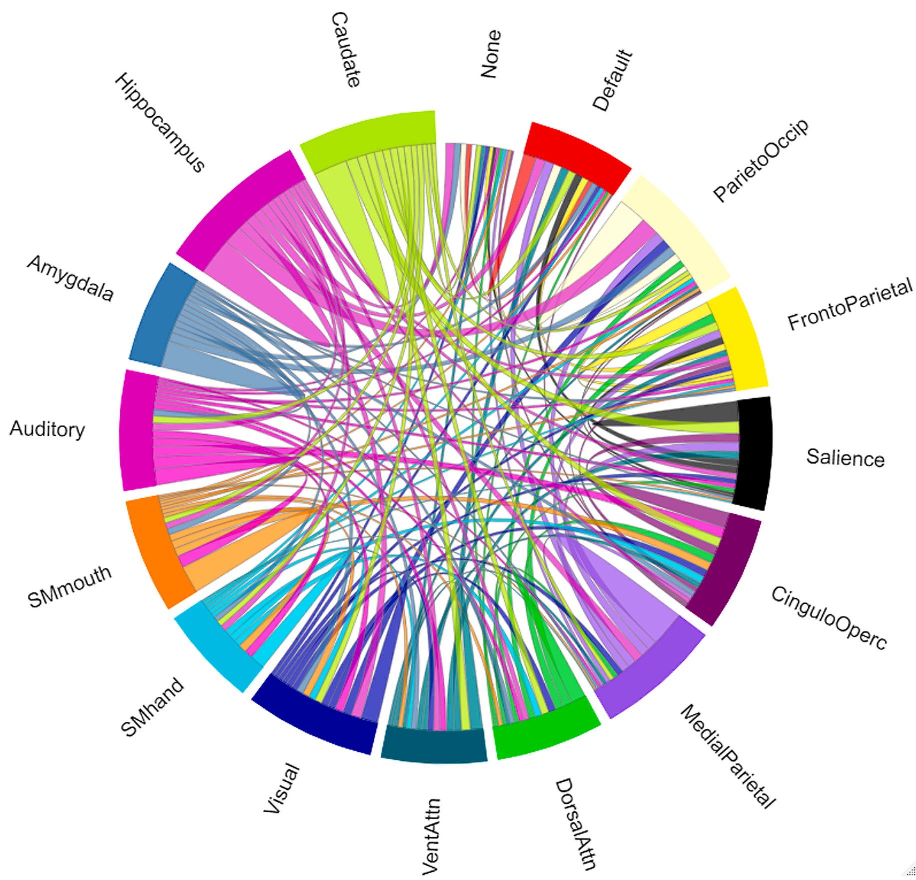

Fig. 2. Mean within- and between-network functional connectivity for rs-fMRI 1. All correlations are positive and the thickness of the lines represent the strength of the connections. Abbreviations: CinguloOperc, cingulo-opercular; Default, default mode network; DorsalAttn, dorsal attention; FrontoParietal, fronto-parietal; ParietoOccip, parieto-occipital; SMhand, somatomotor hand; SMmouth, somatomotor mouth; VentAttn, ventral attention.

move house address between the two rs-fMRI assessments (N = 3,012 participants and 3,861 scans) (Table S6).

4. Discussion

In this large population-based birth cohort, higher exposure to $PM_{2.5}$ from birth to 3 years was associated with persistently lower functional connectivity between the amygdala and the ventral attention, somatomotor hand, and auditory cortical networks throughout adolescence. Higher exposure to PM_{10} in the year before rs-fMRI 1 was associated with persistently lower functional connectivity between the salience and medial-parietal cortical networks throughout adolescence. These results remained after carefully correcting for multiple testing. We did not observe worsening or an attenuation of the effect of air pollution on functional connectivity with age. The results of our study suggest distinct effects of air pollution exposure on brain function, depending on the window of exposure.

Currently available studies on the association between air pollution and functional connectivity in children only include a selection of resting-state networks and none looked at between-network functional connectivity between the amygdala and the ventral attention, somatomotor hand, and auditory networks, and between the medial-parietal and salience networks (Cotter et al., 2023; Pujol et al., 2016a,b; Zundel et al., 2024). This makes comparison with our results difficult. Simultaneously it highlights the importance to consider all cortical networks and relevant subcortical regions in future environmental – resting state functional connectivity studies, as long as clear hypotheses on a localized effect remain absent. Reasons that we were unable to replicate findings from other studies, such as associations between higher air pollution exposure and alterations in the default mode and frontoparietal networks, include the consideration of different pollutants, different pollutant assessments and concentrations, a stronger multiple testing penalty due to the inclusion of more outcomes, and differences in the processing of rs-fMRI data. In our previous work we

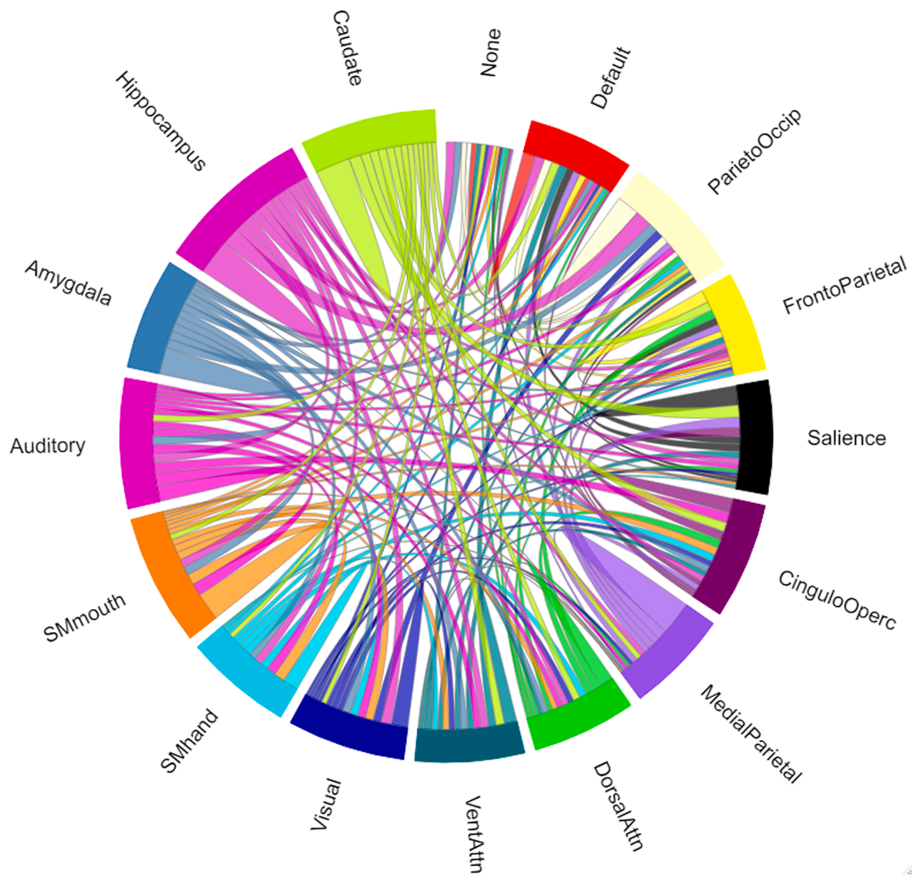

Fig. 3. Mean within- and between-network functional connectivity for rs-fMRI 2. All correlations are positive and the thickness of the lines represent the strength of the connections. Abbreviations: CinguloOperc, cingulo-opercular; Default, default mode network; DorsalAttn, dorsal attention; FrontoParietal, fronto-parietal; ParietoOccip, parieto-occipital; SMhand, somatomotor hand; SMmouth, somatomotor mouth; VentAttn, ventral attention.

found several associations between higher outdoor residential exposure to NO_2, NO_X and $PM_{2.5}$ absorbance, and higher functional brain connectivity in 9– to 12-year-olds of the Generation R study (rs-fMRI 1) (Pérez-Crespo et al., 2022). Although we used the same study population in the current work, we did not observe similar associations due to several methodological choices. We opted for using the Gordon parcellation instead of the previously used Glasser parcellation, since Bryce et al. (2021) showed relatively low correlation of within-network functional connectivity estimates derived from the Glasser parcellation with estimates derived with other commonly used parcellation methods, and since we aimed to harmonize our study with data from the United-States based ABCD Study (Cotter et al., 2023; Zundel et al., 2024). Furthermore, we grouped the regions of interest into networks, instead of looking at each region separately, as done previously, to ease interpretation and reduce the number of performed tests. Finally, the aggregate analyses optimized power of our study by including data from 2 timepoints.

We observed different association patterns for the two exposure periods. Research in neonates and young children indicated that primitive functional resting state networks, including the auditory network, somatomotor hand network, and the amygdala show rapid development in the first years of life (Gilmore et al., 2018). The amygdala, involved in emotional processing and response to emotional stimuli, grows about 105 % in the first year and 15 % in the second year. For attentional function, a shift from bottom-up attentional function (i.e., the ventral attention network) to top-down attentional function (i.e., the dorsal attention network) is seen with increasing age, suggesting that the development of the ventral attention network also takes place early in life (Farrant and Uddin, 2015). This aligns with our findings of birth to 3 years as a susceptible period for air pollution exposure on the amygdala, ventral attention, somatomotor hand, and auditory networks. In contrast, networks linked to higher cognitive functions, such as the salience and medial-parietal network typically develop later in childhood, which likely explains why we only observed an association of exposure to air pollution with between-network connectivity of the salience and medial-parietal network for exposure 1 year before rs-fMRI 1 (Gilmore et al., 2018). The salience network is involved in identifying and responding to internal and external stimuli in order to maintain homeostasis and guide behavior (Seeley, 2019). The medial-parietal network is crucial in self-referential processing (Northoff et al., 2006), perspective-taking and consideration of others (Herold et al., 2016; Pfeifer and Peake, 2012). Furthermore, it is involved in higher cognitive functions like theory of mind (Cavanna and Trimble, 2006; Northoff et al., 2006). Our follow-up analyses showed that increasing age was associated with higher functional connectivity between the amygdala and the ventral attention, somatomotor hand, and auditory networks, and between the salience and medial-parietal networks. Considering the opposite effects of air pollution compared to age on functional connectivity, we suggest that exposure to traffic-related air pollution is associated with deviation from normal brain function development throughout adolescence, especially with regard to emotional processing and higher cognitive functions.

This study is one of the first to investigate the association between exposure to air pollution and resting state functional connectivity in a large population-based birth cohort, using repeated measures of rs-fMRI. We considered 5 pollutants during 2 exposure periods, all 13 cortical networks, and 3 subcortical regions. However, the results of our study should be considered in the context of several limitations. First, we only considered residential air pollution exposure, due to the unavailability of air pollution estimates at schools. This limitation is especially relevant

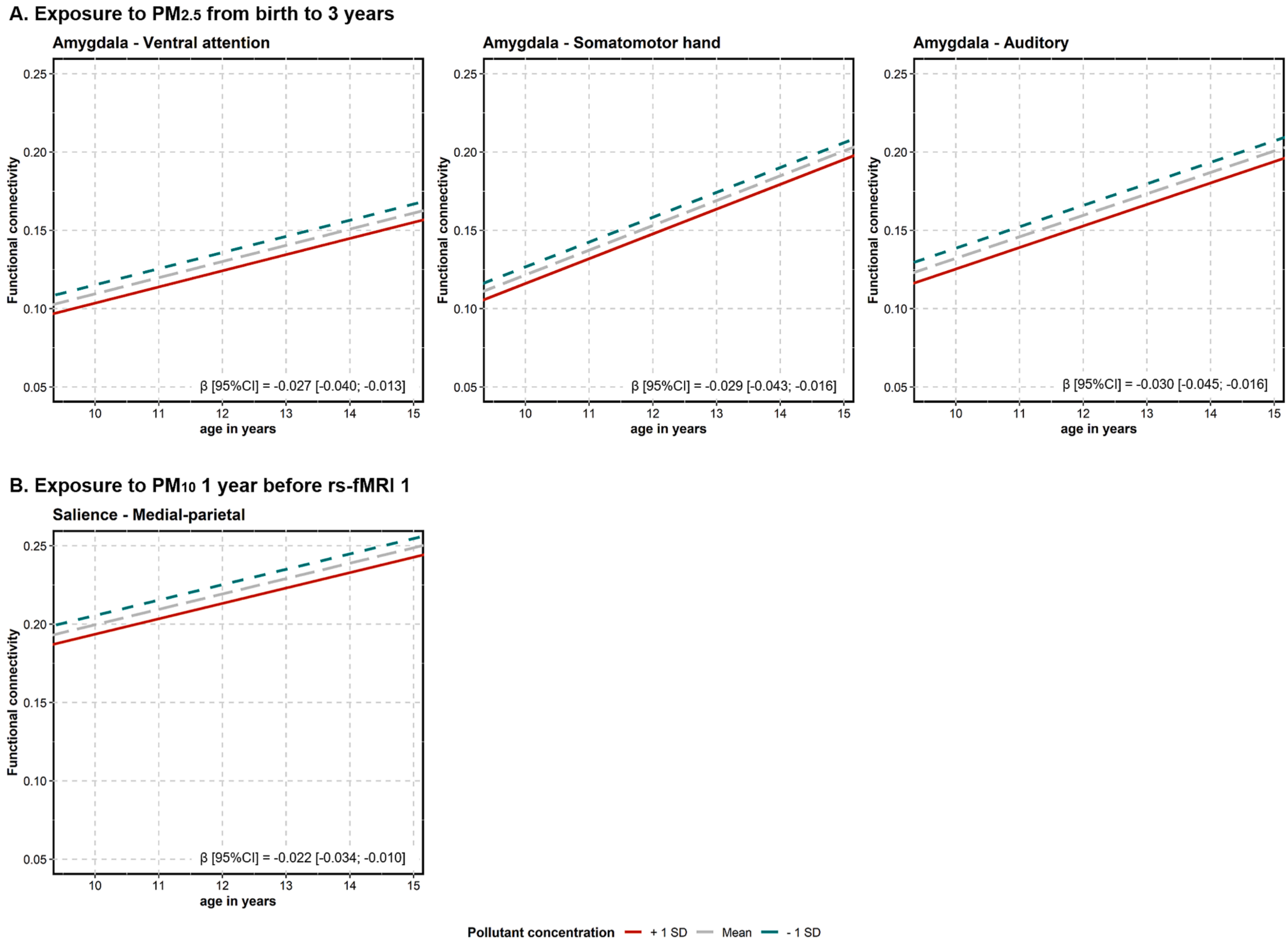

Fig. 4. Model $_{overall\ association}$: Association of low and high $PM_{2.5}$ exposure from birth to 3 years and PM_{10} exposure in the year before rs-fMRI 1 (one standard deviation below and above the mean, respectively) with changes in predicted between-network functional connectivity across adolescence, based on the fully adjusted mixed-effects models (N = 3,626 participants and 4,628 scans). Categorization into low (-1SD), medium (mean), and high (+1SD) air pollutant exposure was performed for depiction purposes only (i.e., metrics were not dichotomized in analyses). The x-axis depicts the 5 percentile – 95 percentile of age. Only associations that remain after multiple testing correction are presented.

Table 3
Model $_{overall\ association}$: Adjusted beta estimates of each air pollutant with functional connectivity for exposure during birth to 3 years and 1 year before rs-fMRI 1. Only associations that remain after multiple testing correction are shown.

	beta [95%CI]	p-value
Exposure to $PM_{2.5}$ (Δ 5 μg/m^3) from birth to 3 years(Δ 5 μg/m		
Amygdala – Ventral-attention	-0.027 [-0.040; -0.013]	0.0001
Amygdala – Somatomotor hand	-0.029 [-0.043; -0.016]	<0.0001
Amygdala – Auditory	-0.030 [-0.045; -0.016]	<0.0001
Exposure to PM_{10} (Δ 10 μg/m^3) 1 year before rs-fMRI 1		
Medial-parietal - Salience	-0.022 [-0.034; -0.010]	0.0003

Abbreviations: PM, particulate matter with different aerodynamic diameters: less than 10 μm (PM_{10}); less than 2.5 μm ($PM_{2.5}$). Beta coefficients and 95% CI from linear mixed models, including a random intercept for participant and adjusted for child's sex, age and season of birth, maternal and paternal age at enrollment, maternal and paternal education level, maternal and paternal national origin, household income, marital status, maternal parity, maternal and paternal pre-pregnancy body mass index, maternal alcohol consumption, smoking and folic acid use during pregnancy, maternal intelligence quotient, socioeconomic status neighborhood, and greenness.

for the 1 year before rs-fMRI 1 exposure period, since children spend a large proportion of the day at school at this stage. We recommend future studies to include both residential and school exposure to air pollution. Second, we did not have repeated measurements available for all children in our study population. Yet, a complete-case analysis for the outcomes indicated robustness of our findings. Third, due to high correlation between the pollutants we were unable to apply a multi-pollutant model. Associations were observed for only some of the investigated pollutants, but our high multiple testing penalty could be underlying the lack of findings for $PM_{2.5}$ absorbance, NO_2 and NO_X, especially since associations were present for all pollutants at $p < 0.05$. Furthermore, all pollutant concentrations included in this study are indicators of traffic. Fourth, we had a relatively short scan duration time of 5 min and 52 s as we aimed to balance minimizing the burden on young participants while maintaining high quality data (Birn et al., 2013). Finally, the parcellation by Gordon et al. that we used to define the cortical resting state networks is derived from research in adults and might thus not be fully applicable to the child brain.

In conclusion, higher air pollution exposure from birth to 3 years was associated with lower functional connectivity between the amygdala and some cortical networks, while higher air pollution exposure in the year before rs-fMRI 1 was associated with lower functional connectivity between two cortical networks (i.e., salience and medial-parietal). Since all associations were persistent across adolescence, our findings might suggest lasting deviations from normal development of brain networks following exposure to air pollution. This potentially impacts emotional processing and higher cognitive functions, but more research is needed to replicate our findings and understand the exact functional implications of the observed disruptions in between-network functional connectivity.

CRediT authorship contribution statement

Michelle S.W. Kusters: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft. **Laura Granés:** Methodology, Validation, Writing – review & editing. **Sami Petricola:** Formal analysis, Methodology, Writing – review & editing. **Henning Tiemeier:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Ryan L. Muetzel:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Mònica Guxens:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109245.

Data availability

Datasets are not publicly available, but may be made available upon request to the Director, Vincent Jaddoe (secretariaat.genr@erasmusmc.nl), in accordance with the national, and EU regulations.

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