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Association between Long-Term Air Pollution, Chronic Traffic Noise, and Resting-State Functional Connectivity in the 1000BRAINS Study

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Background: Older adults show a high variability in cognitive performance that cannot be explained by aging alone. Although research has linked air pollution and noise to cognitive impairment and structural brain alterations, the potential impact of air pollution and noise on functional brain organization is unknown.

Objective: This study examined the associations between long-term air pollution and traffic noise with measures of functional brain organization in older adults. We hypothesize that exposures to high air pollution and noise levels are associated with age-like changes in functional brain organization, shown by less segregated brain networks.

Methods: Data from 574 participants (44.1% female, 56–85 years of age) in the German 1000BRAINS study (2011–2015) were analyzed. Exposure to particulate matter (PM_{10}, $PM_{2.5}$, and $PM_{2.5}$ absorbance), accumulation mode particle number (PN_{AM}), and nitrogen dioxide (NO_2) was estimated applying land-use regression and chemistry transport models. Noise exposures were assessed as weighted 24-h (L_{den}) and nighttime (L_{night}) means. Functional brain organization of seven established brain networks (visual, sensorimotor, dorsal and ventral attention, limbic, frontoparietal and default network) was assessed using resting-state functional brain imaging data. To assess functional brain organization, we determined the degree of segregation between networks by comparing the strength of functional connections within and between networks. We estimated associations between air pollution and noise exposure with network segregation, applying multiple linear regression models adjusted for age, sex, socioeconomic status, and lifestyle variables.

Results: Overall, small associations of high exposures with lesser segregated networks were visible. For the sensorimotor networks, we observed small associations between high air pollution and noise and lower network segregation, which had a similar effect size as a 1-y increase in age [e.g., in sensorimotor network, −0.006 (95% CI: −0.021, 0.009) per 0.3 $\times 10^{-5}$/m increase in $PM_{2.5}$ absorbance and −0.004 (95% CI: −0.006, −0.002) per 1-y age increase].

Conclusion: High exposure to air pollution and noise was associated with less segregated functional brain networks. https://doi.org/10.1289/EHP9737

Introduction

Every day, people are involuntarily exposed to a harmful mixture of gases and particles called air pollution that increases their risk for cardiovascular and respiratory diseases (Thurston et al. 2017). Air pollution may also affect the brain by inducing oxidative stress and chronic neuroinflammation, possibly leading to impaired cognition (as reviewed by Allen et al. 2017) and increasing incidence of neuronal diseases (Casanova et al. 2016; Jung et al. 2015; Peters et al. 2019). These observations lead to the question whether alterations in brain structure might explain the reported impaired cognitive performance. Anatomical neuroimaging studies have shown associations between high air pollution and lower brain volume (Casanova et al. 2016; Chen et al. 2015; Nußbaum et al. 2020; Power et al. 2011; Wilker et al. 2015). Given that cognitive decline and reduced brain volume are also characteristic of normal neuronal aging, it has been suggested that air pollution may accelerate brain aging (Clifford et al. 2016; Fougère et al. 2015).

Chronic ambient noise is another growing environmental health problem, stemming from similar air pollution sources (e.g., traffic, transport, industry) (WHO 2011). Chronic noise can lead to annoyance, sleep disturbance, and stress, arousing the autonomous nervous and endocrine system, thereby leading to adverse health outcomes, most prominently cardiovascular diseases (Basner et al. 2014; WHO 2011). In addition, research has linked chronic noise to impaired cognitive function (Fuks et al. 2019; Jafari et al. 2019; Tzivian et al. 2016) and possible changes in brain structure (Cheng et al. 2019; Nußbaum et al. 2020) in adults. However, the precise mechanisms by which noise may affect the brain remain largely unknown.

Besides morphological changes, neurological studies on the aging brain also showed changes on the level of functional brain organization related to impaired cognitive function (Betzel et al. 2014; Ramanoël et al. 2018; Armstrong et al. 2020; Stumme et al. 2020). Although brain structure and functional organization are different aspects of the brain that require different analytical methods, they are both important to understand how environmental exposures may affect cognitive function. Therefore, to gain a better understanding of the complex relationship between environmental exposures, brain structure, and cognitive function, studies on how air pollution and noise may influence functional brain organization in the whole brain are needed. The brain is a complex system consisting of different brain regions interconnected with each other for information processing (Biswal et al. 2010).

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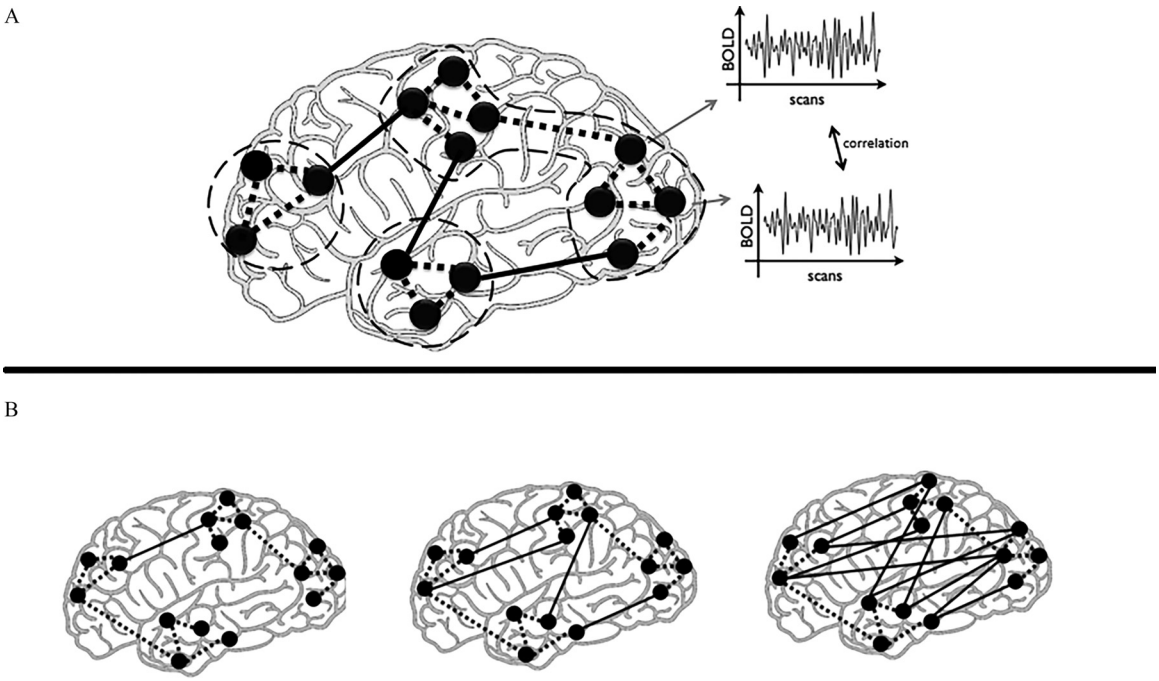

Figure 1. Functional connectivity metrics and segregation vs. integration. (A) Graph representing intra- and internetwork connectivity within the brain. Dashed lines represent brain networks, in which the black dots (nodes) represent brain regions. Two brain regions (dots) are functionally connected if their BOLD-signals are temporally correlated, which is displayed by lines (edges) connecting these two dots. The dotted lines between nodes reflect intra-network connectivity (i.e., links between regions belonging to one network). The solid black lines represent internetwork connectivity (i.e., links connecting regions of one network to regions of other networks. (B) Depiction of brain network segregation and integration. On the left side, segregation of networks is high with low integration (i.e., few links between networks) such that networks are easily distinguishable from each other. On the right side, more connections between networks are built, resulting in more integrated brain networks with less segregation, making networks less distinguishable. Note: BOLD, blood–oxygen level dependent.

Functional connectivity (FC) describes the strength of connectivity between these different brain regions (Friston et al. 1996). Using functional magnetic resonance imaging (fMRI) during a resting state (Biswal et al. 1995), the brain can be grouped into seven functionally specialized networks (i.e., visual, sensorimotor, dorsal and ventral attention, limbic, frontoparietal, default network) (Schaefer et al. 2018). Within each network, brain regions are highly interconnected, whereas there are few connections between brain regions from different networks (Bassett and Bullmore 2006) (Figure 1A). Therefore, functional brain organization is characterized by a balance between densely connected regions within networks together with few long-range connections between more remote regions and networks (Wig 2017).

From childhood to adulthood, the brain undergoes various age-related changes in FC. Although there are many open questions regarding the maturation of functional networks, it is believed that networks are already to some extent established in infants, showing a coarser network structure compared with adults (Grayson and Fair 2017). With age, this network structure is refined with increasing connections between functionally related brain regions and the strengthening of long-range connections between functionally related, but anatomically distant, brain regions (Grayson and Fair 2017). Thereby a pattern of segregation (decrease in connectivity strength) between anatomically close brain regions and integration (increase in connectivity strength) between functionally related brain regions emerges, and an organized, widespread system of networks is formed (Bassett and Bullmore 2006) (Figure 1B).

Neuroimaging studies investigating the association between age and functional brain organization in healthy adults reported decreasing segregation with age in various networks (Betzel et al. 2014; Chan et al. 2014; Geerligs et al. 2015; Malagurski et al. 2020; Stumme et al. 2020). Furthermore, decreasing segregation was also linked to declining cognitive performance in adults, such as poor memory function (Chan et al. 2014), reduced learning rates (Iordan et al. 2018), and low processing speed (Ng et al. 2016), supporting the suggestion that preserving segregated brain networks with age is important for good cognitive functioning.

One study investigated the impact of indoor household incense burning on cognitive functions and brain health in older adults (Wong et al. 2020). They reported associations between regular incense burning with poorer cognitive performance and decreased FC within regions of the default mode network. Other studies exploring the impact of environmental pollutants on functional brain organization have only been conducted in children or adolescents and reported slower functional brain maturation (Pujol et al. 2016) or lower FC strength within brain regions for emotion processing and regulation (de Water et al. 2018), as well as for motor control (de Water et al. 2019). However, the brain is not susceptible to environmental factors only during early brain development, but also in later life when progressive neurocognitive degeneration starts (Park and Reuter-Lorenz 2009; Wig 2017) and compensatory mechanisms begin to falter owing to aging (Grossman 2014). Although average cognitive performance declines with age, this is not the case for all older adults, and there is a large variability among older adults that has yet to be explained (Nelson and Dannefer 1992). To our knowledge, there have been no studies on long-term outdoor air pollution and functional brain organization in older adults.

Related to noise, few studies have investigated the impact of environmental noise on functional organization in the adult brain, and these point to a less segregated network structure for high levels of short-term ambient noise exposure (Zou et al. 2019) and neuronal loss together with reduced neuronal activity under chronic noise and stress (Cheng et al. 2019). Because air pollution and environmental noise often occur at the same time

owing to their common sources (e.g., motorized traffic), it is important to consider both exposures simultaneously, especially if they may have synergistic or antagonistic effects.

In this population-based 1000BRAINS study, we therefore aimed to examine whether long-term exposure to ambient air pollution and road traffic noise are associated with global functional brain organization by creating whole-brain functional networks from resting-state MRI data in a cohort of people 55–85 years of age. Based on our prior work showing associations of air pollution with age-like morphological changes in the brain (Nußbaum et al. 2020), we hypothesized that global functional brain organization shows age-like alterations, namely a decrease in segregation index, under high exposure to air pollution and noise. With this study, we want to contribute to the understanding of how ubiquitous external factors, such as air pollution and noise, act on brain function, possibly mediating the already observed adverse effects on cognition.

Materials and Methods

Study Design

This analysis was conducted using data from participants of the 1000BRAINS study (age range: 56–85 y), a cohort study examining interindividual variability of structure, function, and connectivity in the aging brain in relation to genetic and environmental influencing factors (Caspers et al. 2014). For the 1000BRAINS study, participants from the German Heinz Nixdorf Recall (HNR) study and the HNR MultiGeneration Study were recruited (Figure S1). This analysis includes only participants recruited from the HNR study because air pollution and noise exposure data were not available for participants from the HNR MultiGeneration study. The HNR study is a prospective cohort study of randomly selected men and women living in three adjacent cities (Bochum, Essen, and Mülheim) in the densely populated Ruhr area (Schmermund et al. 2002). Between December 2000 and August 2003, 4,814 people (age range: 45–75 y) attended the baseline examination, where data from self-administered questionnaires, face-to-face interviews along with anthropometric measurements, and laboratory tests were collected. A 5-y follow-up examination was conducted between 2006 and 2008 ($n = 4{,}157$), with repeated assessments of medical condition and risk factor status. HNR participants attending the 10-y follow-up (2011–2015; $n = 3{,}087$) were invited to participate in the 1000BRAINS study. Participants had to be physically able and have no medical contraindications to undergo MRI. Each participant underwent MRI scans along with neuropsychological and motor testing (Caspers et al. 2014). Compliance with prompts during MRI was assessed by post-MRI questionnaires. For this analysis, eligible functional MRI data from 685 participants were available. Both the HNR and 1000BRAINS study were approved by the ethics committee of the University Hospital Essen. Participants gave informed consent and all study procedures complied with the Declaration of Helsinki (WMA 2013).

Air Pollution. To model point-specific residential long-term exposure concentrations of particulate matter (PM) of aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$), $\leq$10 μm (PM_{10}), and soot [$PM_{2.5}$ absorbance ($PM_{2.5abs}$)], as well as nitrogen dioxide (NO_2), we used the European Study of Cohorts for Air Pollution Effects land-use regression (ESCAPE-LUR) model with region-specific land use data. For detailed description of the model, see Beelen et al. (2007). In short, PM was monitored at 20 sites and nitrogen oxides at 40 sites in the Ruhr area in three different 2-wk periods between October 2008 and October 2009 to reflect different seasons (Beelen et al. 2013; Eeftens et al. 2012). The LUR model was created using annual averages of measured pollutant concentrations from background and traffic-related monitoring sites and predictor variables from Europe-wide and local Geographic Information System databases. To model long-term exposure, participants were assigned point-specific exposure concentrations based on their address at HNR baseline examination (2000–2003), $\sim$10 y prior to their 1000BRAINS examination.

In addition, we estimated participants' exposure to accumulation mode particle number concentration (PN_{AM}), a measure of quasi-ultrafine particles, using the validated, spatiotemporal, three-dimensional EURopean Air Pollution Dispersion (EURAD) model (Büns et al. 2012; Hass et al. 1993; Memmesheimer et al. 2004). The multilayer model simulates transport, chemical transformation, and deposition of tropospheric constituents. Ambient air concentrations were assigned to North Rhine-Westphalia and the Ruhr area using a sequential nesting grid of 1 km^2 (Büns et al. 2012). The long-term exposure was calculated as average concentration from 2001 to 2003 and assigned to each participant according to the 1-km^2 grid in which they lived at the time of the HNR baseline.

Traffic Noise. Long-term traffic noise was modeled at façade points according to the European Directive 2002/49/EC (European Commission 2002) as weighted 24-h (L_{den}) and nighttime (2200–0600 hours) mean noise (L_{night}) for the year 2006. Individual residential exposures were assigned using the maximum noise value in a 10-m buffer around each participant's HNR baseline address in 2000–2003. Based on the assumption that mean noise levels have remained mostly constant over time in regard to spatial distribution and exposure level in the HNR study area, these noise exposures reflect long-term exposure. In addition, we examined indoor noise during the daytime (In-L_{den}) and at night (In-L_{night}), derived from outdoor noise levels, and took into account noise-reducing factors, such as room orientation and noise shielding (Foraster et al. 2014; Ohlwein et al. 2019).

Residential Traffic Density. To estimate exposure to traffic on a small spatial scale, we used the distance (in meters) from the HNR baseline home address to the nearest high-traffic roads ($Dist_{trafroad}$), defined as roads with a traffic count of >26,000 vehicles/d, categorized into three groups (<100 m, 100–200 m, >200 m). The necessary data was acquired from the State Office for Nature, Environment and Consumer Protection of North Rhine-Westphalia.

Image Acquisition and Image Preprocessing

Imaging was performed using a 3T Siemens Tim-TRIO magnet resonance scanner with a 32-channel head coil. For resting-state fMRI, 300 functional images were acquired using a gradient–echo planar imaging sequence (36 slices, slice thickness = 3.1 mm, repetition time = 2,200 ms, echo time = 30 ms, field of view = 200 × 200 mm^2, voxel resolution 3.1 × 3.1 × 3.1 mm^3) (Caspers et al. 2014). Resting-state fMRI scans of 11-min duration were performed while eyes were closed, light switched off, and with the instruction to let the mind wander without thinking of anything in particular and not to fall asleep. A post-scan debriefing was performed to verify compliance with these instructions.

In the preprocessing, the first four gradient–echo planar imaging scans were removed for each participant. A two-pass procedure was applied to corrected functional images for head movements [Statistical Parametric Mapping 12 (Friston et al. 2007)]. In the first pass, all scans were aligned to the first image. In the second pass, an average image was estimated using affine registration, and all images were then aligned to the average image as a reference. To normalize all images to the standard Montreal Neurological Institute (MNI) 152 template (Holmes et al. 1998), the unified segmentation approach (Ashburner and Friston 2005) was used. Compared with the often-applied normalization based on T1 weighted images, the unified segmentation approach increases

accuracies of registration (Calhoun et al. 2017; Dohmatob et al. 2018). To minimize the impact of motion artifacts on measurements of FC, recent findings recommend a combined use of independent component analysis (ICA)-based Automatic Removal Of Motion Artifacts (ICA-AROMA) (Pruim et al. 2015) with global signal regression (Burgess et al. 2016; Ciric et al. 2017). Therefore, the present study included both AROMA and global signal regression. Finally, all resting-state fMRI images were bandpass filtered (0.01–0.1 Hz).

Resting-State FC. To explore the brain's global intrinsic functional organization, we used resting-state fMRI data available in the 1000BRAINS study. Because resting-state fMRI allows indirect measurement of neuronal activity at rest (task-negative state), it is possible to analyze and visualize interactions between regions across the whole brain, instead of only specific brain regions as in task-based fMRI. The resting-state fMRI depicts low frequency changes in the blood–oxygen level dependent (BOLD) signals, which arise from changes in blood flow due to an increasing neuronal metabolism resulting from neuronal activity (Fox and Raichle 2007). Functionally related brain regions are synchronously activated and therefore show a contemporaneous increase in neuronal metabolism. This FC between two brain regions can then be measured by the temporal correlation of the BOLD signals of both brain regions (Biswal et al. 1995; Fox and Raichle 2007; Margulies et al. 2007; Smith et al. 2009) (Figure 1A). In general, regions with high values of FC (i.e., high temporal correlations of their BOLD signals) are grouped into large-scale functional networks called resting-state networks (Damoiseaux et al. 2006; Schaefer et al. 2018; Yeo et al. 2011).

To define large-scale brain networks, we used Schaefer's cerebral cortex parcellation with 400 distinct brain regions partitioned into seven large-scale networks: visual, sensorimotor, dorsal and ventral attention, limbic, frontoparietal, and default network (Schaefer et al. 2018). To calculate FC for these large-scale brain networks, we used a graph–theory approach, where functional brain networks are graphically represented by nodes (i.e., brain regions) and edges (i.e., connections between two brain regions; Figure 1A) (Biswal et al. 2010; Bullmore and Sporns 2009, 2012; Rubinov and Sporns 2010), allowing FC within regions belonging to one network and FC between regions of different networks to be assessed.

To estimate FC between all predefined 400 brain regions, for each brain region a BOLD mean time series over 300 time points was extracted from the preprocessed fMRI data for each of the 400 brain regions (i.e., nodes). Next, correlations between these 400 BOLD mean times series were calculated using Pearson's product-moment correlation, resulting in a 400×400 (node-to-node) correlation matrix (Biswal et al. 1995). Then, these correlations were converted into z-values using Fisher's equation (Fisher 1915) to estimate three FC metrics.

To estimate the strength of FC within each network, intra-network FC was calculated as the mean z-transformed FC value between all pairs of nodes belonging to the same network ($\bar{z}_{\text{intra}}$) (Figure 1A, dotted lines) between nodes of one network). Internetwork FC, which quantifies how strongly a network is connected to all other networks, was calculated as the mean z-transformed FC value from one network to all other networks ($\bar{z}_{\text{inter}}$) (Figure 1A, solid lines). To assess the relation between intra- and internetwork FC in one quantity, we calculated a ratio of intra- and internetwork FC called the segregation index (Chan et al. 2014):

$$\text{segregation index} = \frac{\bar{z}_{\text{intra}} - \bar{z}_{\text{inter}}}{\bar{z}_{\text{intra}}}.$$

A segregation index of >0 indicates a more segregated network, with larger connections within the network (high intra-network FC) compared with its connections to all other networks (low internetwork FC). Negative values express higher brain network integration, with connections within the same network being weaker than connections to all other networks (Figure 1B). The maximal value of the segregation index is 1, which displays an isolated network with large connections within and no connections to other networks.

When calculating the mean z-transformed FC value, a distinction between positive and negative correlations must be made, otherwise they cancel out each other. Moreover, interpretation of negative correlations is still unclear (Chai et al. 2012; Fornito et al. 2013; Murphy and Fox 2017). In addition, it is suggested that negative correlations may be strengthened during the preprocessing of functional imaging (Fox et al. 2009; Murphy et al. 2009; Murphy and Fox 2017). Therefore, we only used positive correlations in the main analysis and set negative correlations to zero.

Covariates. Except for age (in years), where age at time of 1000BRAINS examination (2011–2015) was taken, only covariates from the HNR baseline examination (2000–2003) were used in all analyses. Socioeconomic status (SES) and lifestyle variables were assessed by questionnaire. Individual SES was defined based on the International Standard Classification of Education as total years of formal education, combining primary schooling and vocational or professional education (UNESCO 1997) and categorized into four groups ($\leq$10, 11–13, 14–17, and $\geq$18 years of age). To assess neighborhood SES, unemployment rates (units of percentage) between 2001 and 2003 were provided by local census authorities for each residential neighborhood according to administrative boundaries (median size: 11,263 inhabitants) (Dragano et al. 2009). Smoking status was categorized into current, former (>1 y since quitting), and never smoker. Cumulative smoking exposure (pack-years) was assessed for former and current smokers and accounted for periods of nonsmoking. Environmental tobacco smoke exposure (ETS; Yes/No) reflected regular passive exposure to smoke at home, work, or another location. Physical activity (Yes/No) was defined by regular sporting activities at least once a week for a minimum of 30 min. Alcohol intake was obtained and grouped into five categories (0, 1–3, >3–6, >6–14, >14 drinks per week). A dietary pattern index ranging from 0 to 26, with 26 representing an ideal diet (Winkler and Döring 1998), was divided into quantiles (<10, 11–12, 13–15, >15). Anthropometric measurements (height, weight) were conducted according to standard protocols and body mass index (BMI) was calculated as kilograms per meter squared.

Statistical Analyses

We used multiple linear regression models to evaluate the association between long-term air pollution and noise exposure at baseline (2000–2003) with FC metrics at 1000BRAINS examination (2011–2015) for seven brain networks, using each single exposure as an independent variable and the segregation index for each network as the main outcome. We chose a period of $\sim$10 y between exposure and outcome measurement because of the long latency of effects of external exposures on the brain. To improve the understanding of changes in the segregation index, we performed additional regression models with intra- and internetwork FC as dependent variables.

We first conducted an unadjusted model (model 0) for each brain network, where we performed separate crude linear regression models. In model 1, we added to model 0, adjustments for sex and age at time of fMRI scan. Using a directed acyclic graph (DAG; Figure S2) (Textor et al. 2011), we chose the minimal adjustment set, including BMI, smoking status, physical activity, alcohol consumption and diet, which were then included in model

2. In model 3 (main model), we further adjusted model 2 for individual SES and neighborhood SES. In the main model, air pollution exposure models were further adjusted for 24-h outdoor noise whereas noise models were additionally adjusted for $PM_{2.5abs}$. Age and BMI were modeled using restricted cubic splines with three knots. We examined the residuals for nonnormality and nonconstant variance of the error terms for model fit. To reduce the influence of measurement inaccuracies on noise levels at the lower end, we modeled noise as a partially bound continuous variable with a lower cutoff value of 50 dB(A) for L_{den} and 45 dB(A) for L_{night}, with all noise values lower than the defined threshold being set to the threshold value following (Nußbaum et al. 2020). For noise, we estimated model parameters per 10-dB(A) increase in noise level. All air pollution exposures were modeled as continuous variables, and air pollution exposure model parameters were computed per interquartile range (IQR) increase to allow comparable relative increases across exposures.

For comparison, we additionally examined the relationship between age as an independent variable and FC metrics as outcomes for each of the seven networks. The regression models were adjusted for sex, BMI, diet, physical activity, smoking status, cumulative smoking, environmental tobacco smoke exposure, alcohol consumption, and individual and neighborhood SES.

To summarize the results in one graphic, we use an algorithm (see "R-code to Categorize Confidence Limits for Summarization Plot" in the Supplemental Material) that categorized all confidence intervals (CIs) into 10 categories by considering the direction of the effect size and the precision of estimation (width of the CI). For this, the direction of the effect size and the precision of estimation (width of the CI) were considered. First, for each estimate, CIs were divided into 8 equally sized segments. Depending on the location of the zero value in segments, these 8 segments plus 2 categories for confidence limits completely above or below the zero value, formed 10 categories. Then, each category was assigned a color from blue to green displaying possible decrease (CI mostly of <0) to increase (CI mostly of >0). To avoid graphically overestimating effects, confidence limits with effect estimates very close to zero (categories 4–7) were grouped into 1 category (white) (Figure S3).

Sensitivity Analyses

For the noise models, we performed sensitivity analyses using different noise threshold values (45 dB(A) for L_{den} and 35 dB (A) for L_{night}). To account for possible exposure misclassification in noise (e.g., due to house structure, ventilation habits), we also evaluated indoor noise measures with threshold values for indoor L_{den} and L_{night} of 35dB(A) and 10dB(A) following Ohlwein et al. (2019). Because ~10% of values in indoor noise levels were missing, these analyses were performed in a smaller sample of 522 participants. In another sensitivity analysis, we used inverse probability weighting (IPW) to account for selection bias introduced by the recruitment of participants for MRI toward a more male, younger, and better-educated study population compared with the general population. Given that distributional assumptions have to be made for IPW with continuous exposures, we followed recent recommendations and applied a distribution-free method of quantile binning, with 20 distinct bins, using the SAS code from Naimi et al. (2014). Because we hypothesized that potential environmental effects on FC have a long latency period, we used exposure data from the baseline examination (2000–2003) in the main analysis. In a sensitivity analysis, we used exposure data from the 5-y follow-up HNR examination (2006–2008) instead. Because of the yet ambiguous meaning of negative correlations (Chai et al. 2012; Fornito et al. 2013; Fox et al. 2009; Murphy et al. 2009; Murphy and Fox 2017), the main analysis included only positive correlations. Statistical analyses were performed using R (version 3.6.2; R Development Core Team).

Results

Study Population

Of 685 participants of the 1000BRAINS examination (2011–2015) with exposure assessment (2000–2003), fMRI data were available for 592 (Figure S4). Of these, 18 participants were excluded owing to incomplete exposure data ($n=2$) or covariate data ($n=16$), resulting in a final study population of 574 participants (44.1% female) of middle age at HNR baseline examination (mean = 56.1 y) and ~10 y older at 1000BRAINS examination (mean = 67.4 y) (Table 1).

Participants excluded from the analysis were more likely nonsmokers, slightly less highly educated, and were less physically active compared with included participants (Table S1). Compared with HNR participants who did not participate in the 1000BRAINS study, HNR participants who participated in the 1000BRAINS study were on average younger, more likely male, drank more alcohol, and more highly educated (Table S1).

Mean concentrations of $PM_{2.5}$, PM_{10}, and NO_2 were 18.3, 27.5, and 29.5 $\mu g/m^3$ (Table 2). The IQRs for $PM_{2.5}$, PM_{10}, and NO_2 were 1.4, 2.0, and 5.2 $\mu g/m^3$. Mean outdoor noise levels were 53.0 dB(A) for 24-h values and 44.1 dB(A) for nighttime values. Some air pollution and noise exposures had a right-skewed distribution and showed a small correlation (Spearman correlation coefficient = 0.18–0.39) (Table 3).

On average, FC within networks was comparatively larger (higher intra-network FC) than between networks (lower

Table 1. Demographic and lifestyle characteristic of the 1000BRAINS study participants at HNR baseline examination (2000–2003) ($n=574$).

Variable	Mean ± SD or median (IQR) or *n* (%)
Age at HNR baseline (y)	56.1 ± 6.6
Age at fMRI (y)	67.4 ± 6.6
Sex	
Female	253 (44.1)
Male	321 (55.9)
BMI (kg/m^2)	27.1 ± 4.0
Physical activity	
Yes	368 (64.1)
No	206 (35.9)
Nutrition index	12.2 ± 3.1
Environmental tobacco smoke exposure	
Yes	216 (37.6)
No	358 (62.4)
Smoking status	
Never smoker	240 (41.8)
Ex-smoker	220 (38.3)
Current smoker	114 (19.9)
Cumulative smoking (pack-years)	18.0 (24.5)
Alcohol consumption (drinks/wk)	
Never	209 (36.4)
1–3	95 (16.6)
>3–6	85 (14.8)
>6–14	89 (15.5)
>14	96 (16.7)
Education (y)	
≤10	29 (5.1)
11–13	290 (50.5)
14–17	153 (26.7)
≥18	102 (17.8)
Neighborhood unemployment (%)	12.0 ± 3.3

Note: No missing values included. BMI, body mass index; fMRI, functional magnetic resonance imaging; HNR, Heinz Nixdorf Recall; IQR, interquartile range; SD, standard deviation.

Table 2. Description of residential long-term air pollution at HNR baseline examination (2000–2003) and chronic traffic noise exposure levels modeled in 2006 in the study population.

Exposure	Mean ± SD or *n* (%)	Range	IQR
Air pollution			
PM_{10} [$\mu g/m^3$]	27.52 ± 1.81	24.11–34.11	2.04
$PM_{2.5}$ [$\mu g/m^3$]	18.26 ± 1.04	16.09–21.31	1.40
$PM_{2.5abs}$ ($\times 10^{-5}/m$)	1.54 ± 0.32	1.04–4.28	0.34
PN_{AM} (*n*/mL)	3,737.71 ± 437.10	2,774.14–5,087.34	613.03
NO_2 [$\mu g/m^3$]	29.54 ± 4.44	19.81–52.76	5.19
Traffic noise			
L_{den} [dB(A)]	52.98 ± 8.76	34.30–77.63	12.90
L_{night} [dB(A)]	44.07 ± 8.44	25.16–68.54	12.68
$Dist_{trafroad}$ (m)			
<100	18 (3.1%)	—	—
100–200	27 (4.7%)	—	—
>200	530 (92.2%)	—	—

Note: —, not applicable; dB(A), A-weighted decibels; $Dist_{trafroad}$; distance to nearest high-traffic roads; HNR, Heinz Nixdorf Recall; IQR, interquartile range; L_{den}, outdoor 24-h weighted noise; L_{night}, outdoor nighttime noise; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with diameter ≤2.5 μm; $PM_{2.5abs}$, $PM_{2.5}$ absorbance (soot); PM_{10}, particulate matter with diameter ≤10 μm; PN_{AM}, accumulation mode particle number concentration; SD, standard deviation.

Table 3. Spearman correlations between residential long-term air pollution at HNR baseline examination (2000–2003) and chronic traffic noise exposure levels modeled in 2006 in the study population.

Exposure	$PM_{2.5}$	$PM_{2.5abs}$	PN_{AM}	NO_2	L_{den}	L_{night}	$Dist_{trafroad}$
PM_{10}	0.91	0.90	0.49	0.55	0.22	0.23	−0.52
$PM_{2.5}$		0.89	0.73	0.64	0.22	0.23	−0.40
$PM_{2.5abs}$			0.53	0.62	0.39	0.39	−0.55
PN_{AM}				0.56	0.18	0.18	−0.11
NO_2					0.30	0.29	−0.28
L_{den}						0.99	−0.33
L_{night}							−0.36

Note: $Dist_{trafroad}$; distance to nearest high-traffic roads; HNR, Heinz Nixdorf Recall; L_{den}, outdoor 24-h weighted noise; L_{night}, outdoor nighttime noise; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with diameter ≤2.5 μm; $PM_{2.5abs}$, $PM_{2.5}$ absorbance (soot); PM_{10}, particulate matter with diameter ≤10 μm; PN_{AM}, accumulation mode particle number concentration.

internetwork FC) for all networks (Table 4), resulting in a segregation index ranging from −0.17 to 0.93. Across all networks, the mean segregation index took on positive values, reflecting lager connections within networks (higher intra-network FC) compared with smaller connections between networks (lower internetwork FC). We observed the highest mean segregation (0.60) in the visual network, and the lowest mean segregation (0.32) in the frontoparietal network. Although mean internetwork FC was quite constant across networks (ranging from 0.23 to 0.27), mean intra-network FC showed more variation across networks. For instance, regions belonging to the visual network showed large intra-network FC (mean = 0.62), whereas regions of the frontoparietal network showed smaller functional connections (mean = 0.37).

Air Pollution and FC

Only results from the main model (model 3) are described in detail here given that the results for the other models do not differ considerably (Figure S5; Table S2). For several pollutants, a tendency toward a small association of higher air pollution with less segregated networks (a lower segregation index) was observed, with estimates ranging from −0.018 (95% CI: −0.037, 0.001) for a 613 n/mL increase in PN_{AM} in the ventral attention network to 0.013 (95% CI: −0.011, 0.036) per 1.4-$\mu g/m^3$ increase in $PM_{2.5}$ in the visual network (Figures 2 and 3; Table S2). In comparison, changes in the segregation index seen for 1 y of additional age with estimates ranged from −0.004 (95% CI: −0.006, −0.002) to −0.001 (95% CI: −0.003, 0.002) (Table S3). In particular, for an increase of 0.3 $\times 10^{-5}/m$ in $PM_{2.5}$ absorbance, the segregation index decreased by 0.006 (95% CI: −0.021, 0.009) in the sensorimotor network. In comparison, a 1-y increase in age showed a decreasing segregation index by 0.004 (95% CI: −0.006, −0.002) in the same network. Thus, for $PM_{2.5}$ absorbance we observed an effect size comparable to a 1-y increase in age in the sensorimotor network (Table S3).

A pattern of small, but overall positive, associations of higher air pollution with comparatively larger connections between networks (higher internetwork FC) was most noticeable for soot ($PM_{2.5abs}$) [e.g., 0.004 (95% CI: −0.004, 0.012) per 0.3 $\times 10^{-5}/m$ $PM_{2.5}$ absorbance in the ventral attention network] and distance of <100 m to the nearest high-traffic roads [e.g., 0.031 (95% CI: −0.003, 0.065) in the visual network] (Figures 3 and 4; Table S2). On the other hand, no consistent pattern of larger or smaller connections within networks (intra-network FC) was detectable (Figures 3 and 4; Table S2). Although we saw some possible associations between higher pollutants and higher intra-network FC, smaller connections within networks, especially in the ventral attention [e.g., −0.012 (95% CI: −0.026, 0.001) per 2.0 $\mu g/m^3$ PM_{10}] and sensorimotor network [e.g., −0.009 (95% CI: −0.026, 0.008) per 2.0-$\mu g/m^3$ PM_{10}], were also observable. For the default network, only small associations between distance to the nearest high-traffic roads and decreased segregation [e.g., −0.051 (95% CI: −0.127, 0.025) for <100-m vs. >200-m distance to high-traffic roads] were observed, with no clear pattern of increase or decrease in intra- or internetwork FC.

Traffic Noise and FC

For outdoor noise exposures, we observed small associations between high noise exposure and low network segregation (Figures 3 and 4; Table S2). These were most noticeable in the frontoparietal and visual network [−0.020 (95% CI: −0.037, −0.003) and −0.028 (95% CI: −0.049, −0.006) per 10-dB(A) increase in L_{den}, respectively] and slightly smaller in the default

Table 4. Summary statistics for FC metrics at 1000BRAINS examination (2011–2015).

Metric	Min	Max	Mean ± SD
Segregation index			
Visual	−0.02	0.93	0.60 ± 0.18
Sensorimotor	0.05	0.79	0.47 ± 0.15
Dorsal attention	−0.03	0.77	0.37 ± 0.15
Ventral attention	−0.01	0.75	0.39 ± 0.14
Limbic	−0.17	0.86	0.33 ± 0.19
Frontoparietal	−0.01	0.72	0.32 ± 0.14
Default	−0.07	0.77	0.40 ± 0.16
Intra-network FC			
Visual	0.20	1.74	0.62 ± 0.22
Sensorimotor	0.25	1.28	0.51 ± 0.16
Dorsal attention	0.22	1.02	0.44 ± 0.12
Ventral attention	0.23	1.00	0.45 ± 0.12
Limbic	0.17	1.05	0.40 ± 0.15
Frontoparietal	0.22	0.93	0.37 ± 0.10
Default	0.23	0.95	0.38 ± 0.09
Internetwork FC			
Visual	0.11	0.84	0.23 ± 0.07
Sensorimotor	0.15	0.81	0.26 ± 0.07
Dorsal attention	0.16	0.78	0.27 ± 0.07
Ventral attention	0.17	0.79	0.27 ± 0.07
Limbic	0.14	0.75	0.25 ± 0.07
Frontoparietal	0.13	0.79	0.25 ± 0.07
Default	0.11	0.80	0.23 ± 0.08

Note: A segregation index of >0 indicates a more segregated network (theoretical maximal value of 1). A segregation index of <0 indicates higher integration with other networks. FC, functional connectivity; Max, maximum value; Min, minimum value; SD, standard deviation.

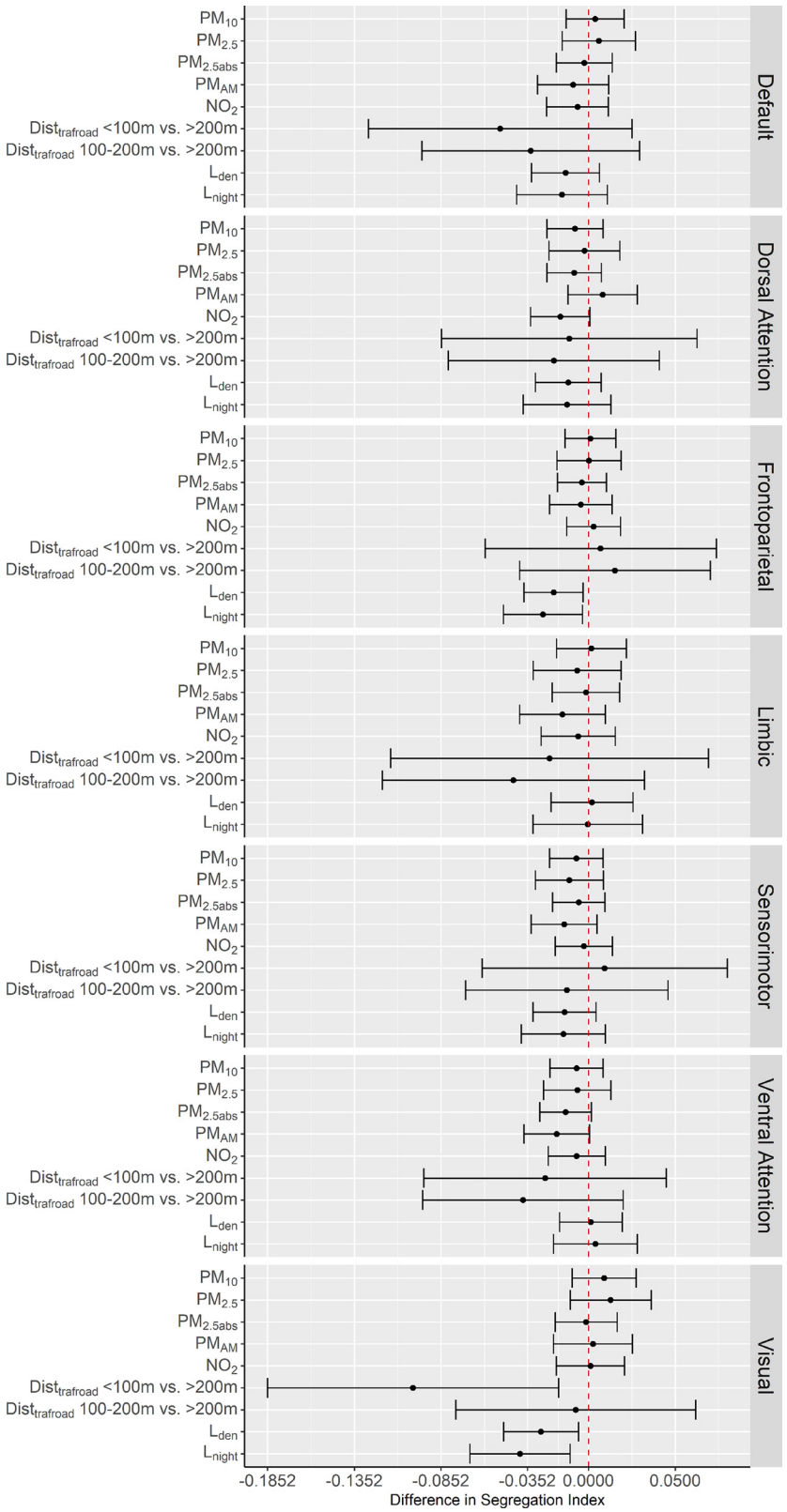

Figure 2. Segregation index. Associations between an IQR increase in mean air pollution exposure or an 10-dB(A) increase in mean noise level and network segregation for seven established brain networks (default, dorsal and ventral attention, frontoparietal, limbic, sensorimotor, and visual). Estimates are for an IQR increase of $2.0\,\mu g/m^3$ for PM_{10}, of $1.4\,\mu g/m^3$ for $PM_{2.5}$, of $0.3\times10^{-5}/m$ for $PM_{2.5abs}$, of $613\,n/mL$ for PM_{AM}, and of $5.2\,\mu g/m^3$ for NO_2. All models were adjusted for age at fMRI scan, sex, BMI, diet, physical activity, smoking status, cumulative smoking, environmental tobacco smoke exposure, alcohol consumption, and individual and neighborhood SES. Air pollution models were further adjusted for 24-h outdoor noise and noise models were adjusted for $PM_{2.5abs}$. Estimates are displayed in Table S2. Note: BMI, body mass index; dB(A), A-weighted decibels; $Dist_{trafroad}$, distance from home address to the nearest high-traffic roads; fMRI, functional magnetic resonance imaging; IQR, interquartile range; L_{den}, outdoor 24-h weighted noise; L_{night}, outdoor nighttime noise; NO_2, nitrogen dioxide; PM_{10}, particulate matter with diameter $\leq$10 μm; $PM_{2.5}$, particulate matter with diameter $\leq$2.5 μm; $PM_{2.5abs}$, $PM_{2.5}$ absorbance (soot); PN_{AM}, accumulation mode particle number concentration; SES, socioeconomic status.

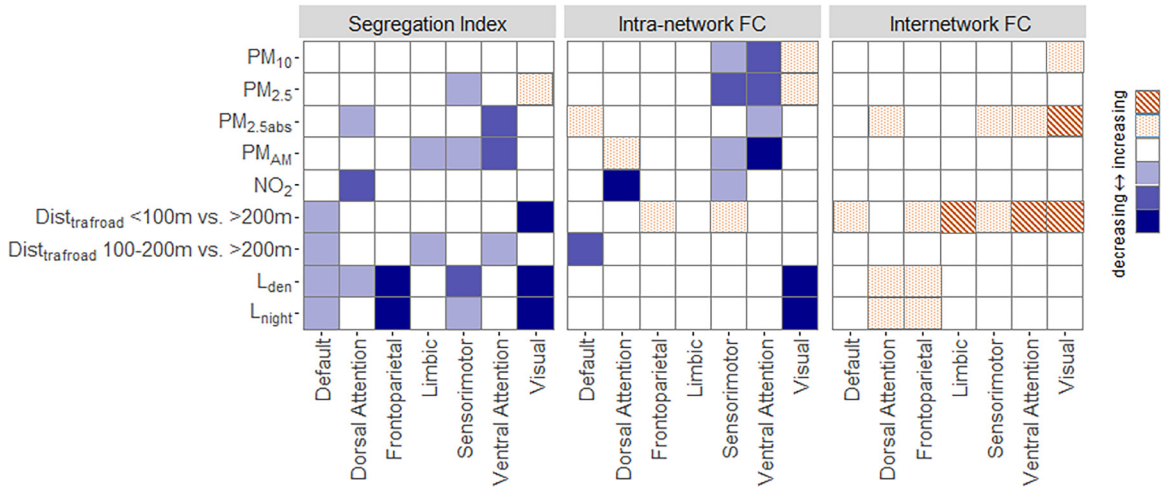

Figure 3. Summarization plot. Graphical summarization of associations between air pollution, noise, and altered network segregation, intra- and internetwork FC in seven established networks (default, dorsal and ventral attention, frontoparietal, limbic, sensorimotor, and visual). Estimates for an IQR increase of 2.0 $\mu g/m^3$ for PM_{10}, of 1.4 $\mu g/m^3$ for $PM_{2.5}$, of 0.3 $\times 10^{-5}/m$ for $PM_{2.5abs}$, of 613 n/mL for PM_{AM}, and of 5.2 $\mu g/m^3$ for NO_2. All models were adjusted for age at fMRI scan, sex, BMI, diet, physical activity, smoking status, cumulative smoking, environmental tobacco smoke exposure, alcohol consumption, and individual and neighborhood SES. Air pollution models were further adjusted for 24-h outdoor noise and noise models were adjusted for $PM_{2.5}$ absorbance. To evaluate the effects and to summarize the results graphically, we defined 10 categories into which we categorized all CIs, depending on the location of the zero value in each CI (see Figure S3). To avoid graphically overestimating effects, CIs with effect estimates very close to zero were grouped into one category (white). Note: BMI, body mass index; CI, confidence interval; dB(A), A-weighted decibels; $Dist_{trafroad}$, distance from home address to the nearest high-traffic roads; FC, functional connectivity; fMRI, functional magnetic resonance imaging; IQR, interquartile range; L_{den}, outdoor 24-h weighted noise; L_{night}, outdoor nighttime noise; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with diameter $\leq$2.5 μm; $PM_{2.5abs}$, $PM_{2.5}$ absorbance (soot); PM_{10}, particulate matter with diameter $\leq$10 μm; PN_{AM}, accumulation mode particle number concentration; SES, socioeconomic status.

and sensorimotor network [−0.013 (95% CI: −0.033, 0.006) and −0.014 (95% CI: −0.032, 0.004) per 10-dB(A) increase in L_{den}, respectively].

Decreased intra-network FC [−0.029 (95% CI: −0.057, −0.002) per 10-dB(A) increase in L_{den} in the visual network] and increased internetwork FC [e.g., 0.005 (95% CI: −0.004, 0.014) per 10-dB(A) increase in L_{den} in the dorsal attention network] were observable for higher noise levels (Figures 3 and 4; Table S2).

Sensitivity Analysis

Our results were robust to different noise thresholds [45 dB(A) for L_{den} and 35 dB(A) for L_{night} (Figure S6; Table S4)]. In line with the main analysis, higher indoor and outdoor noise exposures were associated with smaller segregation in the frontoparietal and visual network in the subsample of 522 participants with indoor noise exposure values (Figure S7; Table S5). Moreover, across all noise variables, smaller connections within regions of the visual network were observable for high outdoor and indoor noise levels. In addition, high indoor noise values showed small associations with more pronounced network segregation of the dorsal attention and possibly limbic networks, whereas this was not apparent for outdoor noise values. No associations between outdoor or indoor noise levels and internetwork FC were visible compared with the main model.

Using IPW, we observed a more pronounced pattern of less network segregation for high particle (PM_{10}, $PM_{2.5}$, $PM_{2.5abs}$, PN_{AM}), and NO_2 concentration than in the main analysis (Figure S8; Table S6). For intra-network FC, we continued to see no clear pattern of increase or decrease, but for high particle concentrations and high noise levels, we observed smaller connections within regions belonging to the ventral attention network and the visual network, respectively.

In another sensitivity analysis using exposure data from 2006 to 2008 (5 y before the fMRI scans), we observed patterns similar to those seen in the main analysis, with associations between higher exposure and mostly higher segregation and lower internetwork FC (Figure S9; Table S7). For intra-network FC, a mixture of higher and lower intra-network FC with high exposure was seen.

Discussion

The present study suggests that long-term exposure to ambient air pollution and road traffic noise is associated with altered global intrinsic functional organization of the brain. Our findings appear to support the hypothesis that exposure to long-term ambient air pollution and road traffic noise may lead to less segregated and more integrated brain networks. Therefore, high air pollution and noise levels might favor an age-like change in functional brain organization.

Functional Organization and Brain Aging

The healthy brain is intrinsically organized into functionally distinct and specialized brain networks that process different types of information (Wig 2017). The resulting structure of segregated networks for specialized functions (e.g., fast processing visual input) alongside integrated networks for higher cognitive functions (e.g., memory function) is characteristic of functional brain organization. The degree of network segregation is used to assess functional network organization (Chan et al. 2014). Neuroimaging studies in adults have reported decreasing segregation with increasing age in various networks (Chan et al. 2014; Iordan et al. 2018; Malagurski et al. 2020; Stumme et al. 2020). These changes were further linked to decreased cognitive function in adults (Chan et al. 2014; Cohen and D'Esposito 2016; Damoiseaux 2017; Marques et al. 2016; Stumme et al. 2020; Wig 2017). In particular, evidence indicates that lower functional segregation (a more integrated network structure) is linked to worse episodic memory (Chan et al. 2014), declines in processing speed (Ng et al. 2016), and slower learning rates (Iordan et al. 2018).

Two aging theories try to link the altered functional brain organization to cognition, and it is suggested that they are not

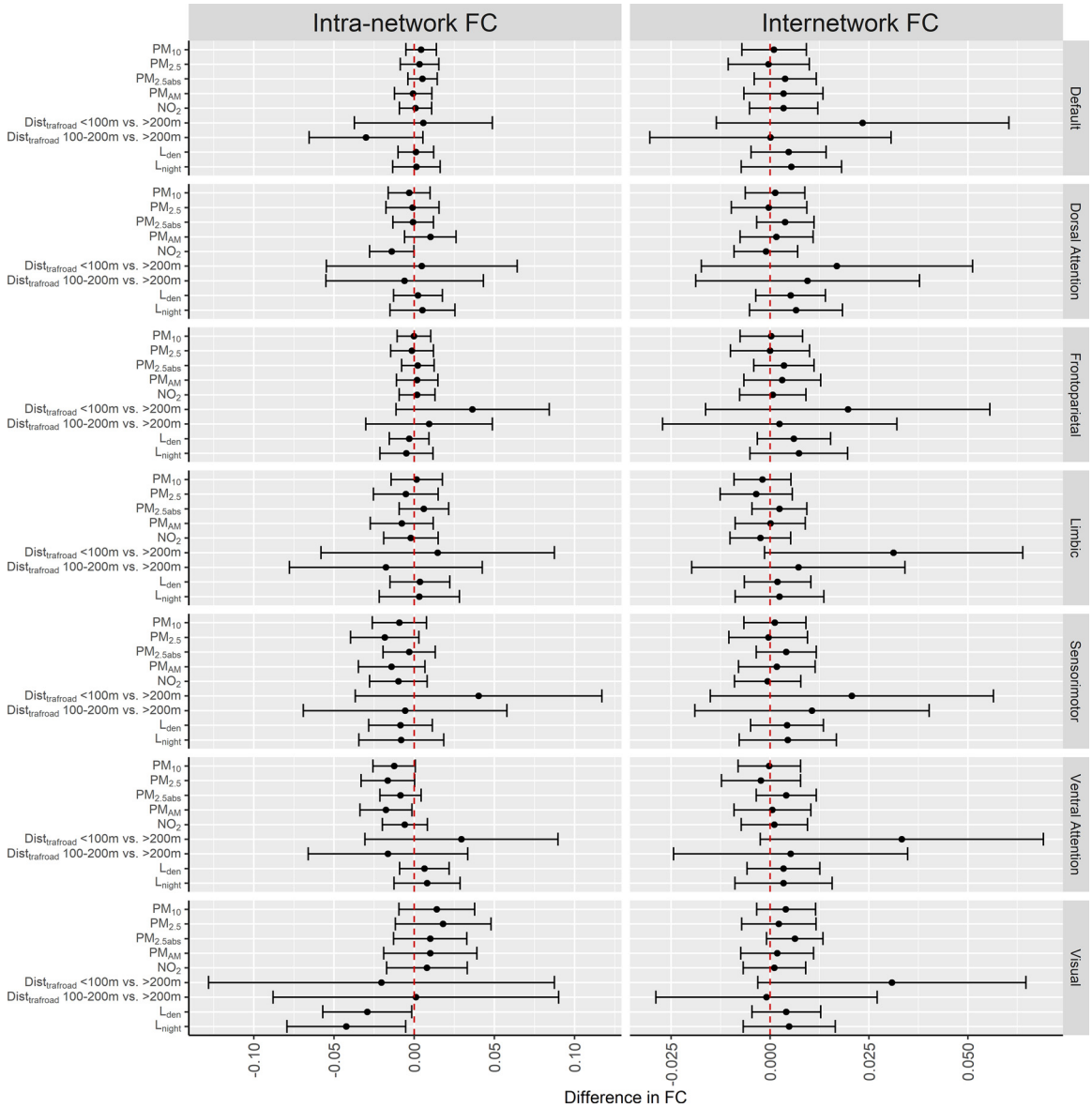

Figure 4. Intra- and internetwork FC. Associations between an IQR increase in mean air pollution exposure or an 10-dB(A) increase in mean noise level and intra- or internetwork FC for seven established brain networks (default, dorsal and ventral attention, frontoparietal, limbic, sensorimotor, and visual). Estimates are shown for an IQR increase of 2.0 $\mu g/m^3$ for PM_{10}, of 1.4 $\mu g/m^3$ for $PM_{2.5}$, of 0.3 $\times 10^{-5}/m$ for $PM_{2.5abs}$, of 613 n/mL for PM_{AM}, and of 5.2 $\mu g/m^3$ for NO_2. All models were adjusted for age at fMRI scan, sex, BMI, diet, physical activity, smoking status, cumulative smoking, environmental tobacco smoke exposure, alcohol consumption, and individual and neighborhood SES. Air pollution models were further adjusted for 24-h outdoor noise and noise models were adjusted for $PM_{2.5}$ absorbance. Note: BMI, body mass index; dB(A), A-weighted decibels; $Dist_{trafroad}$, distance from home address to the nearest high-traffic roads; fMRI, functional magnetic resonance imaging; IQR, interquartile range; L_{den}, outdoor 24-h weighted noise; L_{night}, outdoor nighttime noise; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with diameter $\leq$2.5 μm; $PM_{2.5abs}$, $PM_{2.5}$ absorbance (soot); PM_{10}, particulate matter with diameter $\leq$10 μm; PN_{AM}, accumulation mode particle number concentration; SES, socioeconomic status.

mutually exclusive and may even influence each other (Gazzaley and D'Esposito 2003; Stumme et al. 2020). The compensatory theory suggests that connections between networks increase with age to compensate for age-related decreased FC within networks to maintain cognitive performance (Gazzaley and D'Esposito 2003). The dedifferentiation theory states that a reduced specification of networks leads to increased neuronal noise, reduced processing speed, and increased energy consumption (Gazzaley and D'Esposito 2003). Eventually, this leads to cognitive decline (Geerligs et al. 2015). It is proposed that the reduced specification of networks results from of a series of age-related neurobiological processes, beginning with the reduced concentrations of neurotransmitters (e.g., dopamine), with lower neuronal responsiveness and increased neuronal noise (Li et al. 2001). To maintain performance, brain regions are activated in a nonspecific (random) fashion, which eventually results in diffuse patterns of functional connections (Fornito et al. 2015). Although cognitive ability is maintained at first, the progressive diffusion of networks leads to less distinct activation patterns of different stimuli, such as visual perception (Bennett et al. 2007; Goh et al. 2010; Park et al. 2004) or motor action (Carp et al. 2011), and may subsequently result in impaired cognitive function (Koen and Rugg 2019).

Air Pollution

To date, studies investigating the impact of air pollution on FC are scarce. Only one study examined the impact of indoor air

pollution on cognitive function and brain health in older adults (Wong 2020). They reported associations between regular incense burning with poorer cognitive performance. Although no structural brain alterations were visible for regular incense burning, decreased FC within regions of the default network were observed. The insufficient suppression of the default network has been linked to attention deficit hyperactivity disorder (Mowinckel et al. 2017), autism (Padmanabhan et al. 2017), and cognitive impairment (Lee et al. 2016). Therefore, Wong et al. (2020) suggested that indoor incense burning alters FC, possibly leading to increased vulnerability to future cognitive decline.

Other studies on air pollution and FC have been conducted only in children. In a cohort of children (8–12 years of age), Pujol et al. (2016) found older age was associated with higher functional connection within the default network along with smaller connections to other networks. In contrast, they observed smaller connections within the default network in children with higher exposure to air pollution (elemental carbon and NO_2). Because with increasing age, stronger connections are built between functionally related brain regions in normal brain maturation, they concluded that exposure to higher air pollution may decelerate brain maturation. Similarly, in a pilot study, de Water et al. (2018) found that prenatal exposure to manganese, which is neurotoxic at high levels, was associated with reduced FC within brain regions involved in emotions and regulation processing in childhood (6–7 years of age). In addition, in a group of 14 adolescents (12–18 years of age) they observed associations between early postnatal exposure to manganese and decreased functional connections within brain regions for motor function (de Water et al. 2019). Thus, research indicates that children's functional organization may be altered by environmental exposures, possibly slowing brain maturation. To our knowledge, there have been no prior studies examining the association of outdoor air pollution and FC in adults. Therefore, it is unclear how adult FC may be affected by outdoor air pollution.

In line with several neurological studies on healthy aging and functional organization in adults, overall patterns of slightly lower network segregation with higher air pollution exposure were visible in the present study. This suggests that high air pollution might be associated with altered functional network organization (less segregated and more integrated network structure). Overall, the less segregated and more integrated network structure seems to be related to increasing connectivity between networks rather than decreasing connectivity within networks. In line with de Water et al. (2019), we observed a tendency toward smaller connections with higher air pollution exposure within regions of the sensorimotor network, which is responsible for motor function, and the ventral attention network, which is associated with detecting unexpected stimuli and shifting attention. For other networks, no clear pattern was detectable for intra-network FC. Contrary to the results of other studies, we did not find a general decrease in FC between regions of the default network. We did, however, observe reduced segregation in the default network. Whether this comes from reduced FC within the network or from stronger functional connections to other networks is not clear. Our results were even more pronounced using IPWs, indicating that effects may be stronger in a more general population than those observed in our study population. Moreover, our findings are consistent with previous neurological research on age-related changes in FC and correspond to the dedifferentiation theory (loss of functional specification) in healthy aging (Goh 2011).

Traffic Noise

Up to now, the association between noise and functional brain organization has rarely been studied. In a small experimental study with 30 participants, Zou et al. (2019) reported that short-term noise levels were associated with a less segregated and more integrated brain network structure. A recent study investigated the impact of long-term aircraft noise exposure on various brain outcomes in fighter jet pilots using a matched study design (Cheng et al. 2019). They reported impaired working memory function and neuronal loss, as well as reduced neuronal activity in the hippocampus and other brain regions important for cognition, under exposure to chronic noise and stress.

Similar to our findings for air pollutants, we observed patterns of less segregated and more integrated brain networks with increasing long-term outdoor noise exposure, especially for the visual and frontoparietal network. Although these changes seem to result from lower intra-network FC in the visual network, higher internetwork FC seems to drive the lower segregation in the frontoparietal network.

The associations with outdoor noise seemed to indicate that increasing integration arises from increased connections between distinct networks. Similar to the dedifferentiation theory, higher noise levels were associated with more integrated networks. Although these results were also present for indoor noise values, we additionally observed lager network segregation for the dorsal attention network (associated with orientation of attention) and the limbic network (associated with emotion regulation and social interaction). This may be a result of lager connections between regions within these networks. However, the reduced sample size may have influenced the results. In addition, indoor noise values were calculated based on questionnaire data but were not validated, and thus they might be biased. Nevertheless, these results show that noise may affect the intrinsic organization of the brain and be a vital piece in unraveling how functional organization may be affected by external factors.

Potential Biological Mechanisms

The biological mechanisms through which air pollution is associated with neurocognitive impairments are still not fully understood. It is assumed that particles reach the brain through inhalation either indirectly from the lungs into the bloodstream and crossing the blood–brain barrier or directly from the nose through the olfactory nerve (Geiser et al. 2005; Oberdörster et al. 2004). Accumulated particles can then cause chronic brain inflammation, oxidative stress and microglia activation, which are linked to cognitive impairment and neurodegeneration (Block et al. 2012). With experimental studies showing that microglia activation amplifies dopaminergic neurotoxicity (Block et al. 2004), it is hypothesized that neurotransmitter systems are weakened and that synaptic plasticity, important for learning processes or recovery from brain lesions, is reduced (Allen et al. 2017). At this level, long-term air pollution could adversely affect FC and lead to reorganized functional connections between brain regions, as seen in the age-related dedifferentiation process. These functional changes could, in turn, due to neuronal death, lead to structural changes as reduced brain volume and lead to impaired cognitive function.

Chronic noise is assumed to affect the brain through different, but possibly interrelated, biological mechanisms as air pollution. Noise leads to increased annoyance and stress, thereby arousing the autonomous nervous system/hypothalamus–pituitary–adrenal axis (HPA-axis) (Jafari et al. 2019). Animal studies suggest that chronic activation of the HPA-axis may lead to reduced neurogenesis (production of neurons) and altered synaptic plasticity, followed by functional and structural changes (Cheng et al. 2019). However, it remains to be investigated precisely how noise can affect brain functionality.

Strengths and Limitations

Although the size of the study is relatively large compared with other MRI studies, the power to detect small environmental effects might not be sufficient, and single statistically significant results can occur by chance only. Therefore, further studies with larger sample sizes should follow. Moreover, potential selection bias occurred with younger, better educated, and healthier study participants compared with the general population. Although we performed IPW analysis to compensate for this, residual selection bias could still occur. Because we used functional scans from one time point, we were unable to establish the exposure-related change in FC over time. Although having a relatively small exposure variability compared with other, specifically national studies, this study is based on a contiguous study area that is relatively homogeneous in terms of primary and secondary pollutant sources and living conditions. Thus, there is less random and systematic variation compared with studies covering different parts of a country. Exposure contrast is primarily based on small-scale intra-urban differences, which have been shown to be more important for health effects than between-area variability in many studies (Zemp 1999; Miller 2007; Atkinson 2013).

To our knowledge, this is the first study to investigate the association of long-term air pollution and chronic traffic noise with functional brain organization in older adults. Later in life, the brain is very vulnerable, as progressive neurocognitive degeneration starts (Park and Reuter-Lorenz 2009; Wig 2017) and compensatory mechanisms begin to falter (Grossman 2014). Given the increasing life expectancy, it is important to understand how cognitive function can be preserved (Park and Reuter-Lorenz 2009). Furthermore, air pollution and noise are worldwide issues, and with globally increasing life expectancy, it is of high importance to understand how environmental exposures affect the brain. Because of the age range of the 1000BRAINS study (55–85 y), we were able to investigate effects during this vulnerable period. Moreover, only a limited number of studies on functional brain organization and noise exposure exist to date. Our study contributes new insights into how long-term noise exposures may influence brain function.

Conclusions

Overall, high exposure to air pollution and noise was associated with less segregated functional brain networks. To our knowledge, this is the first study examining associations between exposure to long-term air pollution and chronic traffic noise and FC in older adults. Although we observed only small associations, for high air pollution and noise exposure, we noticed possible trends toward more diffuse patterns of FC, which are also seen in normal brain aging. With continuously increasing global life expectancy, maintaining cognitive function is essential for good quality of life and independence in older age, for individuals and society. As such, it is an important public health issue to understand how modifiable external factors affect the brain and cognition. In this study, we observed associations comparable to a 1-y increase in age. Thus, long-term exposure to air pollution and noise might favor age-like changes in FC, possible mediating adverse effects on cognition. Further studies are needed to understand the complex way in which air pollution and noise may affect the brain.

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