A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP5859.

Associations of Air Pollution and Noise with Local Brain Structure in a Cohort of Older Adults

René Nußbaum,[1,2,3] Sarah Lucht,[3,4] Christiane Jockwitz,[2,5] Susanne Moebus,[6] Miriam Engel,[6] Karl-Heinz Jöckel,[7] Svenja Caspers,[1,2,8] and Barbara Hoffmann[3]**

[1]Institute for Anatomy I, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[2]Institute of Neuroscience and Medicine, Research Centre Jülich, Jülich, Germany
[3]Environmental Epidemiology Group, Institute of Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[4]Institute for Medical Statistics, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[5]Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, Rheinisch-Westfälische Technische Hochschule Aachen University, Aachen, Germany
[6]Centre for Urban Epidemiology, Institute of Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany
[7]Institute of Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany
[8]Jülich-Aachen Research Alliance (JARA)-BRAIN, JARA, Jülich, Germany

Background: Despite the importance of understanding associations of air pollution and noise exposure with loss of neurocognitive performance, studies investigating these exposures and local brain structure are limited.

Objective: We estimated associations of residential air pollution and noise exposures with neurocognitive test performance and the local gyrification index (lGI), a marker for local brain atrophy, among older adults.

Methods: For $n = 615$ participants from the population-based 1000BRAINS study, based on the German Heinz Nixdorf Recall study, we assessed residential exposures to particulate matter (PM_{10}, $PM_{2.5}$, $PM_{2.5abs}$), accumulation mode particle number (PN_{AM}), and nitrogen oxides (NO_x, NO_2), using land-use regression and chemistry transport models. Weighted 24-h and nighttime noise were modeled according to the European noise directive. We evaluated associations of air pollution and noise exposure at the participants' 2006–2008 residential addresses with neurocognitive test performance and region-specific lGI values ($n = 590$) from magnetic resonance imaging, both assessed in 2011–2015, using linear regression and adjusting for demographic and personal characteristics.

Results: Air pollution and noise were associated with language and short-term/working memory and with local atrophy of the fronto–parietal network (FPN), a functional resting-state network associated with these cognitive processes. For example, per $2\text{-}\mu g/m^3$ PM_{10}, local brain atrophy was more pronounced in the posterior brain regions of the FPN, with a -0.02 [95% confidence interval (CI): -0.04, 0.00] lower lGI. In contrast, in the anterior regions of the FPN, weighted 24-h and nighttime noise were associated with less local brain atrophy [e.g., 0.02 (95% CI: 0.00, 0.04) for 10 dB(A) 24-h noise].

Conclusions: Air pollution and noise exposures were associated in opposite directions with markers of local atrophy of the FPN in the right brain hemisphere in older adults, suggesting that both chronic air pollution and noise exposure may influence the physiological aging process of the brain. https://doi.org/10.1289/EHP5859

Introduction

Long-term air pollution and noise exposure are known to have various adverse health effects (Clark and Paunovic 2018; van Kempen et al. 2018; Kim and van den Berg 2010; Thurston et al. 2017; WHO Regional Office for Europe 2013), but it is only recently that the impact of long-term air pollution and noise on mental health has come under investigation. Previous literature supports associations between exposure to air pollutants and a higher incidence of Alzheimer's disease, depressive symptoms, and suicide (Bakian et al. 2015; Carey et al. 2018; Lim et al. 2012; Power et al. 2016). Further, air pollution exposure may have an adverse effect on cognitive performance, including tasks related to working and long-term memory, verbal fluency, and pattern recognition (Power et al. 2016; Tzivian et al. 2015, 2016a, 2016b; Xu et al. 2016). The effects of chronic noise exposure on cognitive functions of adults, however, have rarely been investigated (e.g., Hygge et al. 2003; Schapkin et al. 2006; Tzivian et al. 2015, 2016a, 2016b).

Potential and partly overlapping biologic pathways of air pollution and noise action on the brain include the elicitation of systemic inflammation and local inflammatory processes in the brain; vascular effects, including the development and progression of atherosclerosis; sleep disturbances; and stress reactions with endocrinological sequelae. (Block et al. 2012; Münzel et al. 2017). Importantly, the extent to which air pollution and noise exposure may affect the brain's physiological aging process is not yet understood. In an effort to understand whether associations with lower cognitive function for memory, verbal fluency, and pattern recognition (Ailshire and Clarke 2015; Power et al. 2011; Tonne et al. 2014; Tzivian et al. 2015, 2016a, 2016b; Weuve et al. 2012; Xu et al. 2016) could have a morphological substrate in brain structure, several prior studies have investigated the association between air pollution and mostly global measures of brain structure (Casanova et al. 2016; Chen et al. 2015; Kulick et al. 2017; Power et al. 2018; Wilker et al. 2015). Generally, higher exposure to particulate matter (PM) has been associated with adverse effects on brain structure, including lower total brain volume (Wilker et al. 2015), increased odds of covert brain infarctions (Wilker et al. 2015), reduced white matter volume in several brain regions (Casanova et al. 2016; Chen et al. 2015), and reduced cortical and

*These authors contributed equally to this study.

Address correspondence to B. Hoffmann, Environmental Epidemiology Group, Institute of Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Postfach 101007; 40001 Düsseldorf, Germany. Telephone: 49 (0) 211-586729 110. Email: b.hoffmann@uni-duesseldorf.de

Supplemental Material is available online (https://doi.org/10.1289/EHP5859).

The authors declare they have no actual or potential competing financial interests.

Received 8 July 2019; Revised 16 April 2020; Accepted 21 May 2020; Published 15 June 2020.

total deep gray matter volume (Casanova et al. 2016; Power et al. 2018). These volumetric findings imply that air pollution may have serious effects on the structure of the brain during the aging process. Furthermore, the global measures of brain structure neglect the intrinsic organization of the brain into functionally distinct networks that underlie cognitive abilities (Smith et al. 2009). These networks are susceptible to age-related changes and show a high interindividual variability especially during older ages (Marstaller et al. 2015). However, the question of whether air pollution and noise might be related to atrophy in such cognitive brain networks remains open. Therefore, in the population-based 1000BRAINS study, we first investigated whether air pollution and noise exposure were associated with cognitive test performance in men and women 55–85 years of age. Then, for the specific cognitive functions associated with exposures in the initial analysis, we further investigated whether exposures were associated with the underlying functional brain networks characterized by magnetic resonance imaging (MRI). Within these functionally relevant brain regions, we investigated whether exposure to air pollution and noise was associated with differences in local gyrification indices (lGIs), a surface-based measure used for studying atrophy in the physiologically aging brain.

Methods

Study Design

The present study was conducted using data from participants of the 1000BRAINS study (age range: 55–85 y), a population-based study assessing the variability of brain structure and function in the course of normal aging (Caspers et al. 2014). The 1000BRAINS study is based on the Heinz Nixdorf Recall study (HNR study), a population-based cohort study located in three adjacent cities (Bochum, Essen, and Mülheim/Ruhr) in the urban and industrialized German Ruhr Area (Schmermund et al. 2002). In total, 4,814 randomly selected women and men (age range: 45–75 y at baseline) were enrolled into the HNR study between December 2000 and August 2003. The first follow-up examination ($n = 4{,}157$) was performed after 5 y (2006–2008). At the 10-y follow-up (2011–2015; $n = 3{,}089$), HNR study participants were invited to participate in the 1000BRAINS study (see Figure S1). Participants had to be physically able and have no medical contraindications for MRI. In addition, they underwent a neuropsychological assessment, a motor assessment and laboratory, genetic, and epigenetic testing.

The HNR and associated 1000BRAINS studies were approved by the ethics committee of the University Hospital Essen. All participants gave their written informed consent. All study procedures complied with the Declaration of Helsinki (WMA 2013).

Environmental Exposures

All exposure estimates as described below were assigned to the geocoded residential addresses of the participants obtained in 2006–2008 during the first follow-up examination. All exposure assignments were conducted using ArcView 9.2.

Air pollution. The study area included about $600\,\mathrm{km}^2$. Air pollution and noise exposure were derived from several sources and for overlapping time periods (see Figure S2). First, we used the land-use regression model (LUR) according to the European Study of Cohorts for Air Pollution Effects (ESCAPE) standardized procedure (ESCAPE-LUR), which has been described elsewhere (Beelen et al. 2013; Eeftens et al. 2012). Briefly, PM of varying aerodynamic diameter [≤ 10 μm (PM_{10}) and ≤ 2.5 μm ($PM_{2.5}$)] and $PM_{2.5}$ absorbance ($PM_{2.5abs}$), a surrogate for black carbon, were measured at 20 sites. Nitrogen oxide concentrations [nitrogen oxides (NO_x) and nitrogen dioxide (NO_2)] were measured at 40 sites. All exposures were measured in three separate 2-week periods (to cover different seasons) between October 2008 and October 2009 (Beelen et al. 2013). For building the LUR model, we used annual averages of the measured pollutant concentrations from background and traffic-specific monitoring sites as well as predictor variables from Europe-wide and local Geographic Information System databases. This model was then used to estimate exposure concentrations for the participants' residential addresses at the first follow-up examination (2006–2008). In the Ruhr Area, the models explained 88% of the variability in the annual concentrations of $PM_{2.5}$, 69% of that for PM_{10}, 97% of that for $PM_{2.5abs}$, 89% of that for NO_2, and 88% of that for NO_x (Beelen et al. 2013; Eeftens et al. 2012).

Moreover, accumulation mode particle number concentration [PN_{AM}; mean diameter of 0.07 μm, 67% of particles ranged between 0.035 and 0.14 μm in aerodynamic diameter (Nonnemacher et al. 2014)], a measure of quasi-ultrafine particles some of which may translocate into the brain tissue (Oberdörster et al. 2004), was estimated for each participant using the validated, spatio-temporal, three-dimensional (3D) EURopean Air Pollution Dispersion (EURAD) chemistry transport model (Büns et al. 2012; Hass et al. 1993; Memmesheimer et al. 2004). It is a multilayer, multigrid model that projects the transport, chemical transformation, and deposition of tropospheric components (Büns et al. 2012). Input data consists of topographic information from the U.S. Geological Survey database (resolution of ~ 500 m), land use data from the German Tropospheric Research Programme, and both European and local official emission inventories (Memmesheimer et al. 2004). Pearson correlation coefficients between the model estimates and daily measurements of PN_{AM} were 0.57, with highest seasonal correlations during winter and fall. Participants were assigned the 2006–2008 average PN_{AM} concentrations from the 1-km^2 grid cell in which they resided at the time of the first follow-up examination of the HNR study (Hennig et al. 2016; Nonnemacher et al. 2014). This 3-y average was used as a surrogate for long-term exposure.

Noise exposure. Long-term outdoor road traffic noise exposure [dB(A)] was modeled in 2007 according to the 2002/49/EC Directive (EC 2002). Noise modeling was performed on behalf of the local city administrations who supplied source-specific traffic noise values applying the VBUS/RLS-90 method and using the software CadnA (Bundesministerium für Justiz 2006; DataKustik 2019). For the year 2006, averaged weighted day–evening–night (24-h) (L_{den}) and average levels of nighttime noise (L_{night}; 2200–0600 hours) were modeled considering the following factors: small-scale topography of the area (3D city model), building dimensions, noise barriers, street axis, type-specific vehicle traffic density, speed limit, and type of road surface. The immission of noise at participants residences was estimated at a height of 4 ± 0.2 m selecting the highest estimated noise level within a buffer of 10 m of the geocoded address.

Traffic indicators. As an additional indicator for traffic-related exposure, we used the distance (in meters) to the nearest heavily trafficked road ($Dist_{majroad}$), which was defined as a street in the upper quintile of traffic density ($>26{,}000$ vehicles/d). Data on this was obtained from the State Office for Nature, Environment and Consumer Protection of North-Rhine-Westphalia.

Outcome Data

Neuropsychological assessment. All participants took part in an in-depth neuropsychological assessment (paper/pencil-based administration of the tests) that took place on the same day as the MRI session between 2011 and 2015. Tests were administered and explained by trained personnel with continuous quality assurance (Caspers et al. 2014). Due to skewed distributions of test performances, the results of the neuropsychological tests were rank-transformed, mean-centered, and scaled between −1 and 1. Up to three missing test values per subject were replaced by the age- and sex-stratified median scores. Participants with more than three missing values were excluded from further analyses. Of these standard scores, tests were grouped into five cognitive domains (calculated as mean of all rank-transformed and mean-centered test results for each domain): *a*) Attention: selective attention, processing speed; *b*) Executive Functions: problem solving, figural fluency, concept shifting, and susceptibility to interference; *c*) Memory: figural memory and verbal learning; *d*) Short-Term and Working Memory: visual, visual-spatial, and verbal; *e*) Language Functioning: semantic and phonemic verbal fluency and vocabulary (see Table S1). This approach is commonly used in neuropsychological research (e.g., Heaton et al. 2014; Lim et al. 2016) and refers to the composition of discrete cognitive abilities into larger cognitive constructs that are differentially affected during aging and disease.

Magnetic resonance image acquisition. 1000BRAINS brain imaging data were obtained on a 3T Siemens Tim-TRIO MRI scanner with a 32-channel head coil. Surface reconstruction was performed on 3D high-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo anatomical scans [176 slices; slice thickness, 1 mm; repetition time (TR), 2,250 ms; echo time (TE), 3.03 ms; field of view (FoV), $256 \times 256\ \mathrm{mm}^2$; flip angle, 9°; and voxel resolution, $1 \times 1 \times 1\ \mathrm{mm}^3$] (Caspers et al. 2014). As for the functional scans that were used for localization of the fronto–parietal network (FPN), echo planar imaging generated 300 images (36 slices; slice thickness, 3.1 mm; TR, 2,200 ms; TE, 30 ms, FoV, $200 \times 200\ \mathrm{mm}^2$, and voxel resolution, $3.1 \times 3.1 \times 3.1\ \mathrm{mm}^3$) for each participant at rest.

Image processing—definition of the FPN seed regions in resting-state functional MRI data. Based on the identified associations between air pollution and noise with cognitive performance domains (see above), we selected the bihemispheric FPN for further examination. The FPN—composed of the dorsolateral prefrontal cortex (DLPFC), posterior cingulate cortex and precuneus (PCC/PCu), and the inferior parietal lobule (IPL)—has previously been shown to be associated with, among others, working memory and language functions (Smith et al. 2009) (Figure 1). For the present study, the FPN was extracted from resting-state data of the participants using the state-of-the-art processing pipeline implemented in the Functional Magnetic Resonance Imaging of the Brain (FMRIB) software [FMRIB Software Library (version 6.0; Analysis Group, FMRIB, Oxford, UK; Jenkinson et al. 2012)]. This included a preprocessing of the resting-state data of each individual participant (for a detailed description of the methods used, see Jockwitz et al. 2017) and MELODIC multi-session temporal concatenation to identify common spatial patterns across subjects within the resting-state signal using probabilistic independent component analysis decomposition. This approach has been proven to be useful in extracting functional brain networks related to specific cognitive functions (Smith et al. 2009). The FPN in our data was selected via visual inspection to identify the best spatial match to the FPN as published by Smith et al. (2009).

Image processing—surface reconstruction and lGI. Preprocessing of the anatomical images was performed using Statistical Parametric Modeling (SPM8) as well as FreeSurfer 5.3.0 (http://freesurfer.net/; Dale et al. 1999; Fischl et al. 1999). For detailed information see Jockwitz et al. (2017). Afterward, lGIs were calculated (Schaer et al. 2012), defined as the ratio of the total pial surface area (including sulci) to the outer hull surface area (excluding sulci) in a specific region of the brain. The higher the lGI, the stronger the cortical folding, with decreases of this measure indicating local brain atrophy (Zilles and Palomero-Gallagher 2015). For the purpose of the present study, the lGI

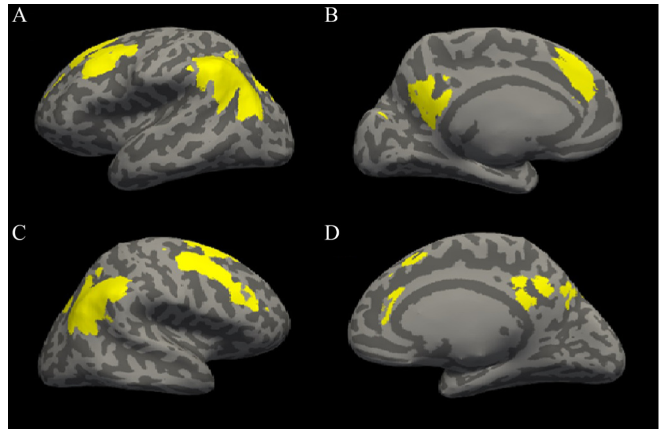

Figure 1. Regions of interest in the fronto–parietal network. (A) left hemisphere from lateral: left dorsolateral prefrontal cortex (DLPFC) and left inferior parietal lobule (IPL). (B) left hemisphere from medial: left posterior cingulate cortex and precuneus (PCC/PCu) and left dorsomedial prefrontal cortex. (C) right hemisphere from lateral: right dorsolateral prefrontal cortex (DLPFC) and right inferior parietal lobule (IPL). (D) right hemisphere from medial: right PCC/PCu and parts of the right dorsomedial cortex.

was extracted for each part of the FPN (left and right: DLPFC, PCC/PCu, and IPL).

Covariate Assessment

Covariate information was collected at the first follow-up examination (2006–2008) of the HNR study (Schmermund et al. 2002) with the exception of education, which was assessed at baseline (2000–2003). Socioeconomic status (SES) was assessed as education level and classified by the International Standard Classification of Education as total years of formal education, combining school and vocational training in four categories: low ($\leq$10 y), medium low (11–13 y), medium high (14–17 y), and high ($\geq$18 y). The neighborhood unemployment rate, a measure of neighborhood SES, was acquired from local census authorities for each participant's neighborhood according to administrative bounds (median population size of 11,263; collected around baseline) (Dragano et al. 2009). Lifestyle variables included alcohol consumption (in five categories: 0, 1–3, 4–6, 7–14, and $\geq$14 drinks per week), smoking status (never, former, current), regular exposure to environmental tobacco smoke (ETS; yes/no), cumulative pack-years at baseline examination (in five categories with the first group being never-smokers and the rest divided by quartiles), and physical activity (in four categories: 0, $\leq$50, $\leq$100, and $>$100 kcal expended per week through exercise). Further covariates used in sensitivity analyses included body mass index [BMI; weight in kilogram divided by squared height in meters ($\mathrm{kg/m^2}$)] and coronary heart disease (CHD; self-reported history of myocardial infarction or coronary intervention at baseline or documented incidence of CHD during follow-up). Type 2 diabetes mellitus was defined as a fasting blood glucose level of $>$125 mg/dL, a blood glucose level of $\geq$200 mg/dL, or reported use of insulin or oral antihyperglycemic medication in the last 7 d before examination. Depressive symptoms were assessed using the German version of the Center for Epidemiologic Studies Depression scale (CES-D) short form (Hautzinger and Bailer 1993).

Statistical Analysis

Multiple linear regression models were conducted for each exposure variable and overall performance in the five cognitive domains as well as each neuropsychological test individually as outcome variables. We first conducted an unadjusted model as well as a discovery model adjusted for age, individual SES, and sex in order to identify potentially affected brain regions for the subsequent lGI analysis. In order to address potential confounding by lifestyle, we further included alcohol consumption, smoking status, ETS, cumulative pack-years, and physical activity in an extended model and additionally adjusted for neighborhood unemployment rate in a separate step. For model fit, we checked the residuals for nonnormality and nonconstant variance of the error terms. Due to nonlinearity, age was modeled using mean-centered quadratic and cubic terms. All air pollution exposures were modeled as continuous variables and model parameters were estimated per interquartile range (IQR) increase in exposure. Noise exposure was modeled with a threshold at 45 dB(A) for L_{night} and at 50 dB(A) for L_{DEN}, with all noise values lower than the defined threshold being set to the threshold value and all values over the threshold being modeled linearly. Model parameters in noise models were estimated per 10-dB(A) increase. $Dist_{majroad}$ was modeled using three categories (<100 m, 100 m ≤ distance <200 m, and ≥200 m as reference).

Similar multiple linear regression models were constructed for all exposure variables using the lGI values of the identified brain regions as outcome variables. We used the covariate sets of the discovery and the full model from the neuropsychological tests analysis to create the base and main models of the lGI analysis, respectively.

In sensitivity analyses, we separately added potential intermediates such as BMI, CHD, depression, and diabetes to the main model. We conducted two-exposure models, adding $PM_{2.5}$ to other exposures and L_{night} to the $PM_{2.5}$ analysis. We checked for robustness to the exclusion of influential observations with Cook's D. All analyses were conducted in R (version 3.4.0; R Development Core Team).

Results

Demographic Characteristics

Of the 3,087 HNR study participants at the second follow-up visit (FU2), 666 completed the first follow-up examination (FU1) and agreed to MRI scanning (see Figure S1). Reasons for nonparticipation in the imaging studies included medical contraindications (e.g., implanted metals) and unwillingness to travel to the imaging center because of, for example, general health status. Complete data on covariates and air pollution and noise exposure at FU1 was available for 630 participants. For our analyses, we included study participants who had complete or almost complete neuropsychological testing results (≤3 missing values; $n = 615$). Of the 615 participants, 39 had one missing value, 13 had two missing values, and 4 had three missing values. In addition, 25 participants were excluded from the lGI analysis owing to methodological problems during image data processing, leaving 590 subjects for MRI analysis (i.e., the lGI group).

Participants were middle-aged to older (mean age of 61.5 y) and of relatively high educational attainment status (Table 1; see also Tables S2–S3). Exposure to PM_{10} and $PM_{2.5}$ was 27.5 and 18.3 $\mu g/m^3$, and mean nighttime noise level was 52.9 dB(A) (Table 2). Air pollution and noise exposures were right skewed and only low-to-moderately correlated (Spearman correlation coefficients ranged from 0.17 to 0.39; see Table S4).

Summary estimates for neurocognitive test results are shown in Tables 3 and S5. Mean lGI values were generally highest in the IPL and lowest in the DLPFC, and the right hemisphere had a wider range of lGI values than the left hemisphere in all three regions (Table 4).

Table 1. Demographic and lifestyle characteristics of the participants of the HNR study at first follow-up examination (2006–2008) included in the analyses ($n = 615$).

Variable	$n = 615$ [mean ± SD or n (%)]
Age (y)	61.5 ± 6.7
Sex (female)	271 (44.1)
Education level (y)	
≤10	29 (4.7)
11–13	316 (51.4)
14–17	161 (26.2)
≥18	109 (17.7)
Smoking status	
Never	266 (43.3)
Former	258 (42.0)
Current	91 (14.8)
Cumulative smoking (pack-years)[a]	22.1 ± 22.3
ETS exposure, yes	162 (26.3)
Alcoholic drinks per week	
0	163 (26.5)
1–3	136 (22.1)
4–6	63 (10.2)
7–14	137 (22.3)
>14	116 (18.9)
Weekly energy expenditure through physical activity (kcal)	
0 (no sports)	205 (33.3)
>0–≤ 50	169 (27.5)
>50–≤ 100	153 (24.9)
>100	88 (14.3)
Neighborhood unemployment (%)	12.0 ± 3.2
BMI (kg/m^2)	28.2 ± 4.4
CHD (yes)	10 (1.6)
Diabetes mellitus (yes)	90 (14.6)
CES-D score	7.0 ± 6.0

Note: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CHD, coronary heart disease diagnosis; ETS, environmental tobacco smoke; HNR, Heinz Nixdorf Recall; SD, standard deviation.
[a]Among current and former smokers only.

Table 2. Summary statistics for residential long-term exposure levels 1 y before the first follow-up of the HNR study (2005–2006) from the EURAD and ESCAPE-LUR exposure models.

Exposure	$n = 615$ Mean ± SD or n (%)	Range	IQR
PM_{10} ($\mu g/m^3$)[a]	27.5 ± 1.8	24.1–34.2	2.0
$PM_{2.5}$ ($\mu g/m^3$)[a]	18.3 ± 1.0	16.1–21.4	1.4
PN_{AM} (n/mL)[b]	3,203.6 ± 358.2	2,447.1–4,431.6	497.0
NO_x ($\mu g/m^3$)[a]	49.3 ± 11.3	24.3–107.7	14.2
NO_2 ($\mu g/m^3$)[a]	29.6 ± 4.7	19.8–62.4	5.3
$PM_{2.5abs}$ (10^{-5}/m)[a]	1.5 ± 0.3	1.0–3.4	0.3
L_{night} [dB(A)][c]	44.0 ± 8.5	25.2–75.3	12.6
L_{DEN} [dB(A)][c]	52.9 ± 8.7	34.3–83.7	12.6
$Dist_{majroad}$ (m)[d]			
Absolute distance	1,098.4 ± 812.0	15.8–4,599.7	1,054.8
<100	23 (3.7)	—	—
≥100–< 200	28 (4.6)	—	—
≥200	564 (91.7)	—	—

Note: —, No data; $Dist_{majroad}$, distance to the nearest major road; ESCAPE-LUR, European Study of Cohorts for Air Pollution Effects–Land-Use Regression; EURAD, European Air Pollution Dispersion; HNR, Heinz Nixdorf Recall; IQR, interquartile Range; LANUV, State Office for Nature, Environment and Consumer Protection of North Rhine-Westphalia; L_{DEN}, 24-h mean noise; L_{night}, nighttime mean noise (2200–0600 hours); NO_x, any nitrogen oxide; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, PM ≤ 2.5 µm in aerodynamic diameter; PM_{abs}, PM absorbance; $PM_{2.5abs}$, $PM_{2.5}$ absorbance; PM_{10}, particulate matter with aerodynamic diameter ≤10 µm; PN_{AM}, accumulation mode particle number; SD, standard deviation.
[a]From ESCAPE-LUR.
[b]In line with EURAD procedures.
[c]Modeled according to European Standards.
[d]From LANUV.

Table 3. Description of neurocognitive test results by domain in the neuropsychological tests group ($n = 615$).

Domain and neurocognitive test	Mean ± SD	Range
Attention (s)		
Selective attention	35.3 ± 11.9	17–136
Processing speed	40.9 ± 17.8	16–300
Executive function		
Problem solving (*n*)	20.2 ± 5.1	5–34
Figural fluency (*n*)	26.0 ± 7.5	4–57
Concept shifting (s)	56.5 ± 40.1	2–372
Susceptibility to interference (s)	44.8 ± 25.7	4–307
Memory (*n*)		
Figural memory	17.3 ± 8.5	1–51
Verbal learning	41.4 ± 10.3	6–66
Verbal learning delayed	10.6 ± 2.7	0–15
Short-term/working memory (*n*)		
Visual pattern	7.6 ± 1.7	4–12
Visual-spatial STM	6.5 ± 1.8	1–12
Visual-spatial WM	4.8 ± 1.8	0–12
Verbal STM	7.7 ± 2.0	2–13
Verbal WM	6.8 ± 1.8	2–18
Language		
Phonemic verbal fluency [words (*n*)]	18.6 ± 6.5	2–39
+ concept shifting [words (*n*)]	18.8 ± 6.2	1–40
Semantic verbal fluency [occupations (*n*)]	23.8 ± 6.9	5–50
+ concept shifting [sports/fruits (*n*)]	19.8 ± 4.8	4–37
Vocabulary (*n*)	30.8 ± 5.2	2–41

Note: STM, short-term memory; WM, working memory (see also Table S1 for test descriptions).

Air Pollution, Noise, and Neuropsychological Tests

Generally, we observed that participants with higher air pollution exposure exhibited lower cognitive function in several, but not all domains. In the discovery models, we observed inverse associations of several air pollutants ($PM_{2.5}$, $PM_{2.5abs}$, NO_x, PN_{AM}) and noise (L_{DEN}, and L_{night}) with cognitive function in the Language Domain (Figure 2; see also Table S6). These inverse associations were similar for all air pollutants and noise across all individual tests in the Language Domain (Figure 3; see also Table S7). Within the Short-Term/Working Memory Domain, air pollution exposure was associated with lower verbal working memory but also, on the other hand, associated with higher visual-spatial working memory. Noise exposure was inversely associated with visual working memory (see Figure S3 and Table S8). No clear pattern of association was observed for the individual neuropsychological tests from the other three cognitive domains (see Figures S4–S6 and Tables S9–S10). In the extended models, all estimates became attenuated, especially upon addition of neighborhood unemployment rate (see Tables S6–S10).

Air Pollution, Noise, and Brain Structure

In the main models, IQR increases in PM_{10}, $PM_{2.5}$, NO_x, and NO_2 were generally associated with lower lGI values in the right PCC/PCu {e.g., −0.02 [95% confidence interval (CI): −0.04, 0.00] per 1.4-$\mu g/m^3$ $PM_{2.5}$} and the right IPL [e.g., −0.01 (95% CI: −0.03, 0.00) per 5.3-$\mu g/m^3$ NO_2; Figure 4 and also Table S11]. In the right DLPFC, air pollutant associations were less clear; however, an IQR increase in PN_{AM} was associated with lower lGI values [−0.02 (95% CI: −0.04, 0.00)]. In contrast, 10-dB(A) increases in L_{night} and in L_{DEN} were associated with higher lGI values in the DLPFC [e.g., 0.03 (95% CI: 0.00, 0.05) for L_{night}; Figure 4 and also Table S11], but not in the other two regions. Participants who lived between 100 m and 200 m from a heavily trafficked road had lower lGI values in the right DLPFC [−0.06 (95% CI: −0.12, −0.01)] and in the PCC/PCu [−0.07 (95% CI: −0.13, 0.00)] than participants who lived ≥200 m from a heavily trafficked road (Figure 4 and also Table S11).

In the left hemisphere, we saw no clear pattern of associations between air pollution or noise exposures and lGI (Figure 5; see also Table S11). A detailed summary of the estimates for all crude, base, and main models of both hemispheres is given in Table S11. Separately adding BMI, CHD, depression, and diabetes to the main model did not change the results of the model (see Figures S7–S8). Results from the two-pollutant models were very stable (see Figures S9–S10): Upon mutual adjustment, the associations of $PM_{2.5}$ and L_{night} did not change. In models including two air pollutants, only estimates for $PM_{2.5abs}$ slightly attenuated and confidence intervals slightly increased. After exclusion of two participants with highly influential observations (both participants with high lGI values and moderate-to-high exposures), the associations became slightly stronger.

Table 4. Description of MRI scan local gyrification index (lGI) results in the lGI analysis group ($n = 590$).

Outcome	Mean ± SD	Range
Right hemisphere		
DLPFC	2.64 ± 0.13	2.28–3.34
PCC/PCu	2.73 ± 0.17	2.19–3.27
IPL	2.93 ± 0.14	2.46–3.40
Left hemisphere		
DLPFC	2.50 ± 0.13	2.10–2.92
PCC/PCu	2.76 ± 0.18	2.27–3.29
IPL	2.98 ± 0.13	2.63–3.40

Note: DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule; MRI, Magnetic Resonance Imaging; PCC/PCu, posterior cingulate cortex and precuneus; SD, standard deviation.

Discussion

In this study, we found some evidence for an association of air pollution and noise with neurocognitive test performance corresponding to the Language Domain and, less consistently, for the Short-Term/Working Memory Domain. Based on this, we focused our structural MRI analyses on the functionally relevant brain regions of the FPN associated with these domains. For the right hemisphere, air pollution exposures were inversely associated with lGI in all three regions of the FPN and noise exposure was directly associated with lGI in one region of the FPN. No associations between environmental exposures and lGI were observed for the left hemisphere.

The main aim of this study was to investigate associations between air pollution and noise exposure and local brain structure, measured via the lGI, a marker of local brain atrophy in the aging brain. Previous work by Casanova et al. (2016), Chen et al. (2015), Power et al. (2018), and Wilker et al. (2015) have considered total, white matter, and gray matter volumes as markers of brain structure and found that $PM_{2.5}$, PM_{10}, and $Dist_{majroad}$ were associated with lower total white and gray matter volumes. Providing evidence for local modification of brain structure, our results strengthen the evidence that an association between air pollution and brain atrophy in the course of the normal aging process may exist but might affect functionally relevant regions locally.

In the present study, air pollution was inversely associated with lGI values in the right hemisphere (DLPFC, PPC/PCu, and IPL) only. These findings could be explained by the right hemi-aging theory (Albert and Moss 1988; Brown and Jaffe 1975; Dolcos et al. 2002; Goldstein and Shelly 1981; Grady et al. 1994), which states that the right brain hemisphere changes more rapidly during the normal aging process than the left hemisphere. Although mainly supported by behavioral data, current research has shown that the theory is also supported by findings in brain structure (e.g., Jockwitz et al. 2017; Kovalev et al. 2003) and functional connectivity (e.g., Lu et al. 2011). Our results suggest that exposure to air pollutants might accelerate the normal aging process of the brain,

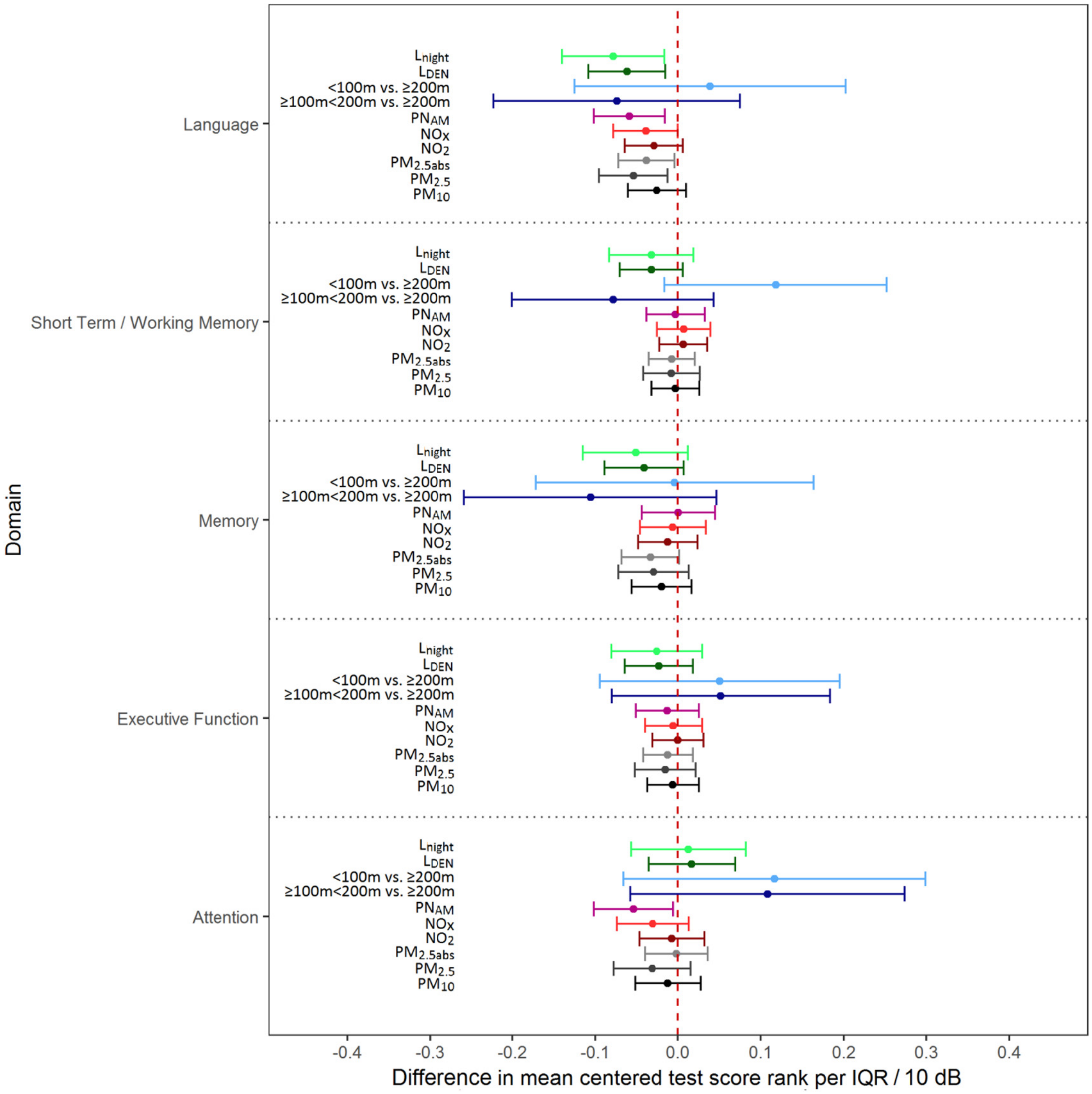

Figure 2. Difference in test score rank and 95% CI for the associations of air pollution and noise exposures with cognitive domain scores. $n = 615$. Linear regression models were adjusted for age, sex, and SES (Discovery Model). IQR-values: PN_{AM}, 497; NO_x, 14.2; NO_2, 5.3; $PM_{2.5abs}$, 0.3; $PM_{2.5}$, 1.4; and PM_{10}, 2.0. See Table S6 for corresponding numeric data. Note: CI, confidence interval; IQR, interquartile range; L_{DEN}, averaged weighted day–evening–night (24-h); L_{night}, average levels of nighttime noise (2200–0600 hours); NO_x, nitrogen oxides; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, PM ≤ 2.5 μm in aerodynamic diameter; $PM_{2.5abs}$, $PM_{2.5}$ absorbance; PM_{10}, PM ≤ 10 μm in aerodynamic diameter; PN_{AM}, accumulation mode particle number; SES, socioeconomic status.

which might also result in a higher vulnerability of right hemispheric brain regions to endogenous or exogenous risk factors, resulting in structural changes.

Overall, air pollutants were more consistently associated with posterior brain regions than with the frontal brain region. The posterior–anterior shift in aging theory (PASA; Davis et al. 2008) could be used to explain the missing association with the frontal brain region. The PASA theory, which was initially observed for brain function, has also recently been substantiated by a counterpart in brain structure (e.g., Jockwitz et al. 2017). The PASA theory states that, in the course of the normal aging process, frontal brain areas take over functions of posterior areas in order to compensate for a loss of function in those areas. This implies that damage to posterior regions could be compensated by activation in frontal areas, possibly leading to more preserved brain structure and even brain plasticity processes in those now more-required areas. Because of this compensatory process, an adverse effect of $PM_{2.5}$, PM_{10}, NO_x, and NO_2 on the prefrontal cortex might not have been observable.

On the other hand, PN_{AM} was associated with lower lGI values in the DLPFC only. For PM, NO_2, and NO_x, it is hypothesized that air pollution exerts direct and indirect effects on the body via inhalation through the lungs (Block et al. 2012). These pollutants may also affect the brain through direct transportation or through indirect initiation of systemic and local inflammation, processes that may reach all of the observed brain areas through the cerebral arteries (Block and Calderón-Garcidueñas 2009; Jayaraj et al. 2017). For PN_{AM}, an additional potential mechanistic pathway may exist, where very small particles or small particle-induced inflammatory processes reach the brain via axonal transport from the olfactory bulb after nasal intake (Elder et al. 2006; Oberdörster et al. 2004). We speculate that higher concentrations of PN_{AM} from direct transport along the olfactory nerve or PN_{AM}-associated inflammation in frontal brain areas might explain the adverse association of PN_{AM} exposure on the right DLPFC.

Higher 24-h mean weighted noise and nighttime noise exposures were associated with higher lGI values in the right DLPFC, but these were not associated with any decreases in lGI values in

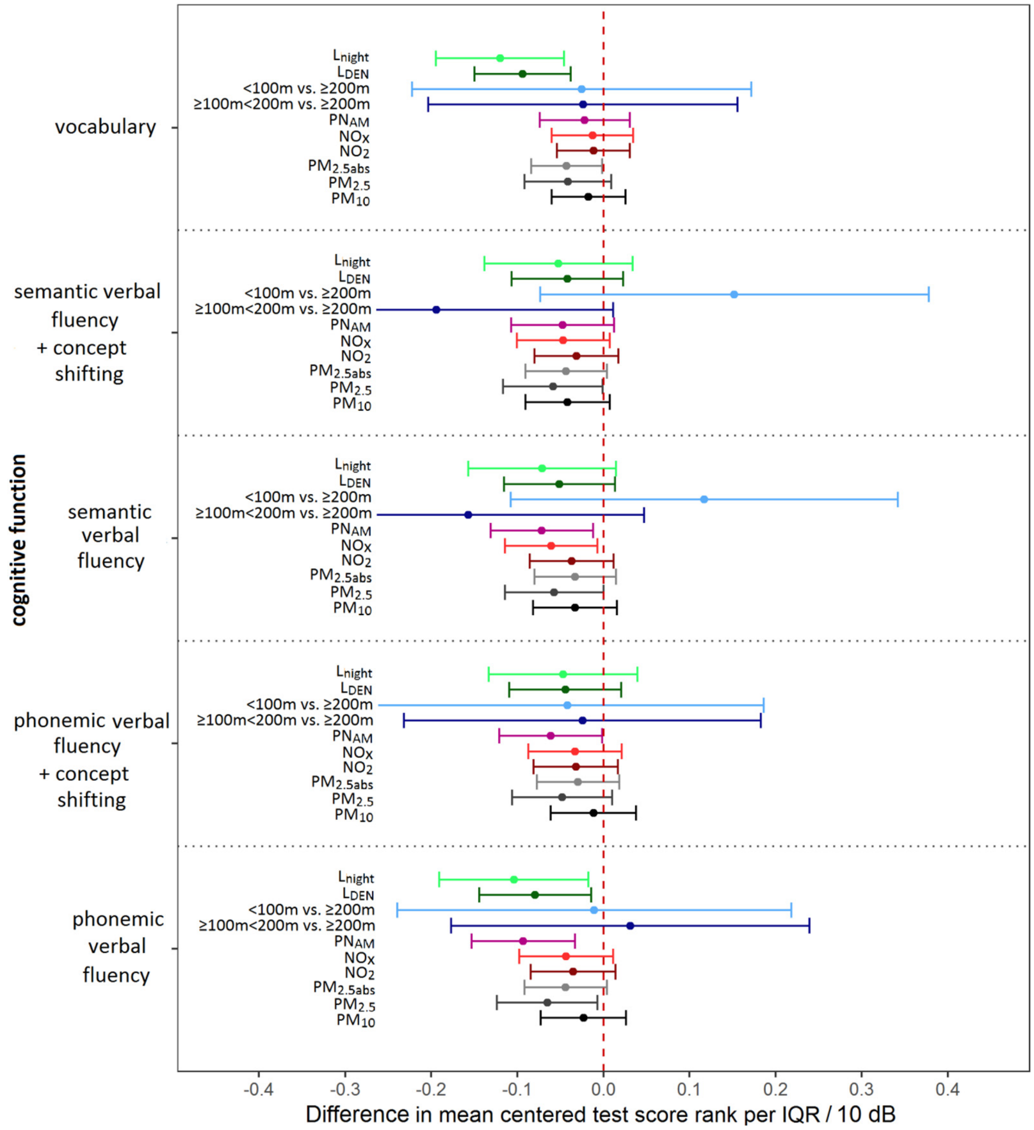

Figure 3. Difference in test score rank and 95% CI for the associations of air pollution and noise exposures with neuropsychological test results from the Language Domain. $n = 615$. Linear regression models were adjusted for age, sex, and SES (Discovery Model). IQR-values: PN_{AM}, 497; NO_x, 14.2; NO_2, 5.3; $PM_{2.5abs}$, 0.3; $PM_{2.5}$, 1.4; and PM_{10}, 2.0. See Table S7 for corresponding numeric data. Note: CI, confidence interval; IQR, interquartile range; L_{DEN}, averaged weighted day–evening–night (24-h); L_{night}, average levels of nighttime noise (2200–0600 hours); NO_x, nitrogen oxides; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, $PM \leq 2.5$ μm in aerodynamic diameter; $PM_{2.5abs}$, $PM_{2.5}$ absorbance; PM_{10}, $PM \leq 10$ μm in aerodynamic diameter; PN_{AM}, accumulation mode particle number; SES, socioeconomic status.

the other tested regions. At first sight, this seems to indicate that noise exposure has no adverse effect, and perhaps even a protective effect, on local gray matter. Next to chance, several explanations could be responsible for this finding. Considering the fact that we used outdoor façade noise values, it is possible that participants exposed to higher levels of noise exhibited more protective behaviors, such as leaving the windows closed more often or installing soundproof windows. An alternative explanation is that frontal brain areas could experience compensatory processes of brain plasticity and, possibly, hypertrophy to make up for diffuse losses of function induced by noise-related stress and annoyance, noise-related reduced sleep quality, or energy-carrying sound waves. The results of the cognitive test analyses support that chronic noise exposure might have a damaging effect on higher cognitive function, with verbal fluency and the vocabulary test performance being most adversely affected. Thus, although we found adverse effects of noise exposure on cognitive function, further studies are warranted to unravel the inverse association between noise exposure and brain atrophy.

In future studies, functional connectivity of the FPN should be looked at in connection to air pollution and noise exposure in order to evaluate whether support for the PASA theory and right hemi-aging theories can also be found based on functional network reorganization. In addition to already existing research on the topic, even more basic experimental research needs to be done with animal and human brain tissue, as well as brain imaging studies on regional differences attributable to air pollution, to further clarify pathways and mechanisms. If we want to better understand the effect air pollutants have on the brain, we need to know which, and in what quantities, particles are able to reach certain brain regions; how pollutants are able to cross or circumvent the blood–brain barrier to directly access the brain; and how other pollutants may exert adverse effects across the blood–brain barrier without directly reaching the brain.

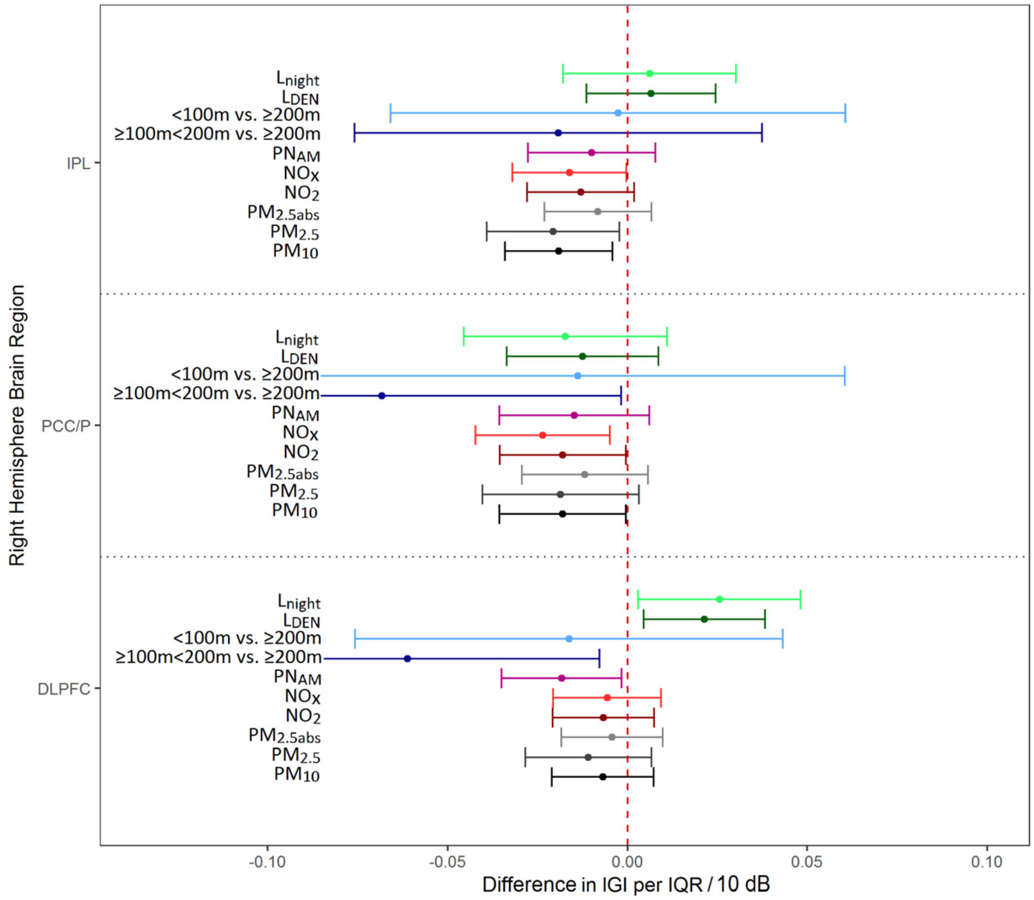

Figure 4. Differences and 95% CI for the associations of air pollution and noise exposures with lGI in the IPL, PCC/PCu, and DLPFC of the right hemisphere. $n = 590$. Linear regression models were adjusted for age, sex, SES, alcohol consumption, smoking status, cumulative pack-years, ETS, physical activity, and neighborhood unemployment rate (Main Model). IQR-values: PN_{AM}, 497.8; NO_x, 14.0; NO_2, 5.3; $PM_{2.5abs}$, 0.3; $PM_{2.5}$, 1.4; and PM_{10}, 2.0. See Table S11 for corresponding numeric data. Note: CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; ETS, environmental tobacco smoke; lGI, local gyrification index; IPL, inferior parietal lobule; IQR, interquartile range; L_{DEN}, averaged weighted day–evening–night (24-h); L_{night}, average levels of nighttime noise (2200–0600 hours); NO_x, nitrogen oxides; NO_2, nitrogen dioxide; PCC/PCu, posterior cingulate cortex and precuneus; PM, particulate matter; $PM_{2.5}$, $PM \leq 2.5$ μm in aerodynamic diameter; $PM_{2.5abs}$, $PM_{2.5}$ absorbance; PM_{10}, $PM \leq 10$ μm in aerodynamic diameter; PN_{AM}, accumulation mode particle number; SES, socioeconomic status.

Pathways by which noise exposure affects the brain have not been previously investigated. It would, therefore, be of interest to explore whether chronic ambient noise exerts an effect on the brain via activation or deactivation of certain brain areas via the auditory system and whether these changes in activation may lead to changes in brain plasticity as well as to changes in structure and function.

Currently, it is highly debated among researchers which structural marker is most suitable to make a statement about structural properties of the aging brain (Storsve et al. 2014, Lemaitre et al. 2012). Given that lGI is more focused on the cortical surface than overall brain volume, lGI is more sensitive to small changes of local brain structure; however, it is not the only marker for brain atrophy (Hutton et al. 2009).

One major limitation of this study is that the number of participants was relatively low in comparison with previous studies on air pollution and brain structure. In addition, the high degree of effort needed for participation in this MRI study resulted in a selection of younger and well-educated men into the study population, potentially leading to selection bias. Another limitation is the lack of a clear temporal order of exposure and effect. Although the exposure assessment was conducted before the measurement of the outcome, we have no information about the timing of the actual change in cognitive function and brain morphology in the follow-up period. This will be the subject of further analyses with forthcoming longitudinal neuropsychological and MRI data. Furthermore, due to the relatively large number of analyses, individual associations can be chance findings. We therefore tried to limit the number of analyses by reducing the investigated local brain regions to those that were associated with specific impaired cognitive functions in the neuropsychological testing. Although the two applied air pollution exposure models are accepted and validated models for application in epidemiological studies, exposure measurement error of long-term ambient exposures is an important issue in environmental epidemiology, specifically for participants who relocate or spend little time of the year at their home address. We did not conduct a detailed analysis of the residential exposure history in this study, but systematic differences in relocations might exist and may have led to a biased estimate. Furthermore, we did not have knowledge about the use of protective measures concerning noise exposure, which could also bias the effect estimates. Small numbers of participants in the distance categories close to major roads resulted in very imprecise estimations, which should not be overinterpreted.

One of the strengths of our study was that we were able to investigate the variability of structural differences (i.e., measured by lGIs) in the aging brain in association with air pollution and noise exposure across a wide range of participant ages (55–85 y at FU1). By this, we particularly covered the period of aging

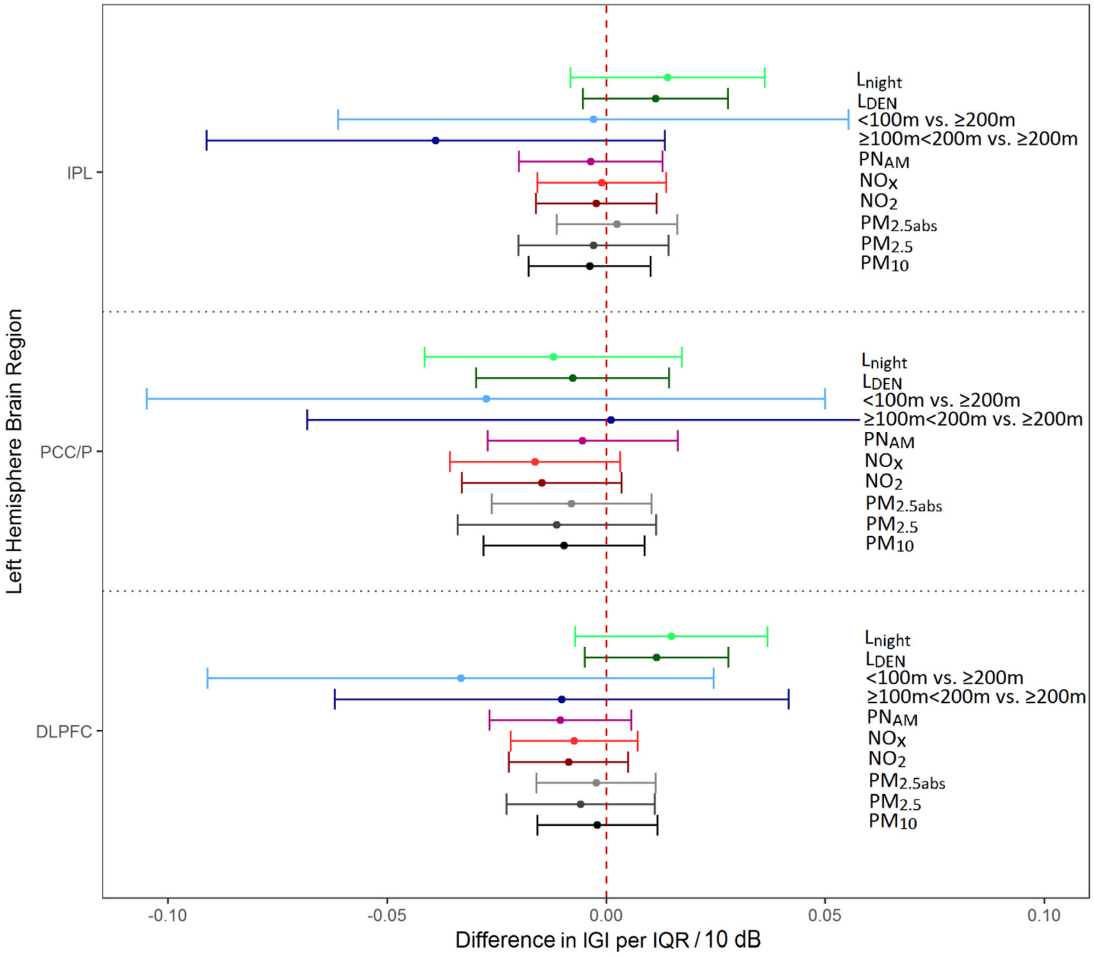

Figure 5. Differences and 95% CI for the associations of air pollution and noise exposures with lGI in the IPL, PCC/PCu, and DLPFC of the left hemisphere. $n = 590$. Linear regression models were adjusted for age, sex, SES, alcohol consumption, smoking status, cumulative pack-years, ETS, physical activity, and neighborhood unemployment rate (Main Model). IQR-values: PN_{AM}, 497.8; NO_x, 14.0; NO_2, 5.3; $PM_{2.5abs}$, 0.3; $PM_{2.5}$, 1.4; and PM_{10}, 2.0. See Table S11 for corresponding numeric data. Note: CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; lGI, local gyrification index; IPL, inferior parietal lobule; IQR, interquartile range; L_{DEN}, averaged weighted day–evening–night (24-h); L_{night}, average levels of nighttime noise (2200–0600 hours); NO_x, nitrogen oxides; NO_2, nitrogen dioxide; PCC/PCu, posterior cingulate cortex and precuneus; PM, particulate matter; $PM_{2.5}$, $PM \leq 2.5$ μm in aerodynamic diameter; $PM_{2.5}$ absorbance; $PM_{2.5abs}$, $PM_{2.5}$ absorbance; PM_{10}, $PM \leq 10$ μm in aerodynamic diameter; PN_{AM}, accumulation mode particle number; SES, socioeconomic status.

after a critical point in the mid 50s of age, where cognitive performance and brain function decline is more pronounced (e.g., Seattle Longitudinal Study: Schaie et al. 2004). In addition, we included both men and women, which has not been the case in the previous female-only works of Casanova et al. (2016) and Chen et al. (2015). We also had comprehensive data on exposures, covariates, and possible confounders because of the extensive individual-level assessment within the HNR and the 1000BRAINS studies. The neuropsychological testing and MRI data within the 1000BRAINS study is particularly noteworthy given that very few cohort studies have test data as well as MRI scans available. In addition, we were able to look at differences in task-specific, fronto–parietal regions rather than at global differences in the brain structure in an analysis that directly links to previous work on cognitive function and air pollution/noise exposure. Although there have been previous studies on air pollution and volumetric measures of the brain, to our knowledge, this is the first study looking at air pollution and lGI, a sensitive marker of local brain atrophy. Moreover, this is the first study to look at noise exposure in the broader context of brain structure, and thus our study is also the first study to look at air pollution and noise exposure simultaneously in this context. Another strength of this study is the extensive sensitivity analyses that revealed robust results to different assumptions.

Conclusion

Air pollution and noise exposures were associated in opposite directions with markers of local atrophy of the right hemispheric FPN in older adults, suggesting that both chronic air pollution and noise exposure may influence the physiological aging process of the brain. Our research delivers further evidence for the existence of structural changes in the brain due to air pollution and noise exposure that accompany cognitive performance losses.

Acknowledgments

We thank the North Rhine-Westphalia State Agency for Nature, Environment and Consumer Protection (LANUV) for providing emission and land use data for North Rhine-Westphalia. We are indebted to the investigative group and the study personnel of the Heinz Nixdorf Recall (HNR) study and the 1000BRAINS study. We also thank the Heinz Nixdorf Foundation for the generous support of this study. The HNR study was supported by grants from the German Research

Council (Deutsche Forschungsgemeinschaft; grants ER 155/6-1, ER 155/6-2, SI 236/8-1, and SI 236/9-1) and the Kulturstiftung Essen, Germany. The exposure assessment was funded through the European Community's Seventh Framework Program (FP7/2007–2011; grant 211250) and by the German Research Council (DFG; HO 3314/4-3). Further, this project was partially funded by the 1000BRAINS-Study of the Institute of Neuroscience and Medicine, Research Centre Jülich, Germany, and has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement no. 785907 (HBP SGA2; S.C.) as well as from the Initiative and Networking Fund of the Helmholtz Association (S.C.).

References

Ailshire JA, Clarke P. 2015. Fine particulate matter air pollution and cognitive function among U.S. older adults. J Gerontol B Psychol Sci Soc Sci 70(2):322–328, PMID: 24906394, https://doi.org/10.1093/geronb/gbu064.

Albert MS, Moss MB. 1988. *Geriatric Neuropsychology.* London, UK: Guilford Press.

Bakian AV, Huber RS, Coon H, Gray D, Wilson P, McMahon WM, et al. 2015. Acute air pollution exposure and risk of suicide completion. Am J Epidemiol 181(5):295–303, PMID: 25673816, https://doi.org/10.1093/aje/kwu341.

Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. 2013. Development of NO_2 and NO_x land use regression models for estimating air pollution exposure in 36 study areas in Europe—the ESCAPE project. Atmos Environ 72:10–23, https://doi.org/10.1016/j.atmosenv.2013.02.037.

Block ML, Calderón-Garcidueñas L. 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci 32(9):506–516, PMID: 19716187, https://doi.org/10.1016/j.tins.2009.05.009.

Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen J-C, et al. 2012. The outdoor air pollution and brain health workshop. Neurotoxicology 33(5):972–984, PMID: 22981845, https://doi.org/10.1016/j.neuro.2012.08.014.

Brown JW, Jaffe J. 1975. Hypothesis on cerebral dominance. Neuropsychologia 13(1):107–110, PMID: 1109452, https://doi.org/10.1016/0028-3932(75)90054-8.

Bundesministerium Für Justiz. 2006. Vorläufige Berechnungsmethode für den Umgebungslärm an StraBen (VBUS). [In German.] Bundesanzeiger 154a:30–49. https://www.bmu.de/fileadmin/bmu-import/files/pdfs/allgemein/application/pdf/bundesanzeiger_154a.pdf [accessed 1 June 2020].

Büns C, Klemm O, Wurzler S, Hebbinghaus H, Steckelbach I, Friesel J, et al. 2012. Comparison of four years of air pollution data with a mesoscale model. Atmos Res 118:404–417, https://doi.org/10.1016/j.atmosres.2012.07.009.

Carey IM, Anderson HR, Atkinson RW, Beevers SD, Cook DG, Strachan DP, et al. 2018. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. BMJ Open 8(9):e022404, PMID: 30206085, https://doi.org/10.1136/bmjopen-2018-022404.

Casanova R, Wang X, Reyes J, Akita Y, Serre ML, Vizuete W, et al. 2016. A voxel-based morphometry study reveals local brain structural alterations associated with ambient fine particles in older women. Front Hum Neurosci 10:495, PMID: 27790103, https://doi.org/10.3389/fnhum.2016.00495.

Caspers S, Moebus S, Lux S, Pundt N, Schütz H, Mühleisen TW, et al. 2014. Studying variability in human brain aging in a population-based German cohort—rationale and design of 1000BRAINS. Front Aging Neurosci 6:149, PMID: 25071558, https://doi.org/10.3389/fnagi.2014.00149.

Chen J-C, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, et al. 2015. Ambient air pollution and neurotoxicity on brain structure: evidence from Women's Health Initiative Memory Study. Ann Neurol 78(3):466–476, PMID: 26075655, https://doi.org/10.1002/ana.24460.

Clark C, Paunovic K. 2018. WHO Environmental noise guidelines for the European region: a systematic review on environmental noise and cognition. Int J Environ Res Public Health 15(2):285, PMID: 29414890, https://doi.org/10.3390/ijerph15020285.

Dale AM, Fischl B, Sereno MI. 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9(2):179–194, PMID: 9931268, https://doi.org/10.1006/nimg.1998.0395.

DataKustik. 2019. CadnaA (computer aided noise abatement). Stand der Technik beim Immissionsschutz. [In German]. https://www.datakustik.com/de/produkte/cadnaa/cadnaa/ [accessed 14 December 2019].

Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. 2008. Qué PASA? The posterior-anterior shift in aging. Cereb Cortex 18(5):1201–1209, PMID: 17925295, https://doi.org/10.1093/cercor/bhm155.

Dolcos F, Rice HJ, Cabeza R. 2002. Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. Neurosci Biobehav Rev 26(7):819–825, PMID: 12470693, https://doi.org/10.1016/s0149-7634(02)00068-4.

Dragano N, Hoffmann B, Stang A, Moebus S, Verde PE, Weyers S, et al. 2009. Subclinical coronary atherosclerosis and neighbourhood deprivation in an urban region. Eur J Epidemiol 24(1):25–35, PMID: 18931923, https://doi.org/10.1007/s10654-008-9292-9.

EC (European Commission). 2002. Directive 2002/49/EC of the European Parliament and of the Council of 25 June 2002 relating to the assessment and management of environmental noise–Declaration by the Commission in the Conciliation Committee on the Directive relating to the assessment and management of environmental noise. Off J L 189:12–26.

Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of land use regression models for $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10} and PM_{coarse} in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46(20):11195–11205, PMID: 22963366, https://doi.org/10.1021/es301948k.

Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, et al. 2006. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect 114(8):1172–1178, PMID: 16882521, https://doi.org/10.1289/ehp.9030.

Fischl B, Sereno MI, Dale AM. 1999. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9(2):195–207, PMID: 9931269, https://doi.org/10.1006/nimg.1998.0396.

Goldstein G, Shelly C. 1981. Does the right hemisphere age more rapidly than the left? J Clin Neuropsychol 3(1):65–78, PMID: 7276197, https://doi.org/10.1080/01688638108403114.

Grady CL, Maisog JM, Horwitz B, Ungerleider LG, Mentis MJ, Salerno JA, et al. 1994. Age-related changes in cortical blood flow activation during visual processing of faces and location. J Neurosci 14(3 pt 2):1450–1462, PMID: 8126548, https://doi.org/10.1523/JNEUROSCI.14-03-01450.1994.

Hass H, Ebel A, Feldmann H, Jakobs HJ, Memmesheimer M. 1993. Evaluation studies with a regional chemical transport model (EURAD) using air quality data from the EMEP monitoring network. Atmos Environ Part Gen Top 27(6):867–887, https://doi.org/10.1016/0960-1686(93)90007-L.

Hautzinger M, Bailer M. 1993. *Allgemeine Depressions Skala: ADS*. [In German]. Weinheim, Germany: Beltz.

Heaton RK, Akshoomoff N, Tulsky D, Mungas D, Weintraub S, Dikmen S, et al. 2014. Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. J Int Neuropsychol Soc 20(6):588–598, PMID: 24960398, https://doi.org/10.1017/S1355617714000241.

Hennig F, Sugiri D, Tzivian L, Fuks K, Moebus S, Jöckel K-H, et al. 2016. Comparison of land-use regression modeling with dispersion and chemistry transport modeling to assign air pollution concentrations within the Ruhr Area. Atmosphere 7(3):48, https://doi.org/10.3390/atmos7030048.

Hutton C, Draganski B, Ashburner J, Weiskopf N. 2009. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. Neuroimage 48(2):371–380, PMID: 19559801, https://doi.org/10.1016/j.neuroimage.2009.06.043.

Hygge S, Boman E, Enmarker I. 2003. The effects of road traffic noise and meaningful irrelevant speech on different memory systems. Scand J Psychol 44(1):13–21, PMID: 12602999, https://doi.org/10.1111/1467-9450.00316.

Jayaraj RL, Rodriguez EA, Wang Y, Block ML. 2017. Outdoor ambient air pollution and neurodegenerative diseases: the neuroinflammation hypothesis. Curr Environ Health Rep 4(2):166–179, PMID: 28444645, https://doi.org/10.1007/s40572-017-0142-3.

Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. 2012. FSL. Neuroimage 62(2):782–790, PMID: 21979382, https://doi.org/10.1016/j.neuroimage.2011.09.015.

Jockwitz C, Caspers S, Lux S, Jütten K, Schleicher A, Eickhoff SB, et al. 2017. Age- and function-related regional changes in cortical folding of the default mode network in older adults. Brain Struct Funct 222(1):83–99, PMID: 26943919, https://doi.org/10.1007/s00429-016-1202-4.

Kim R, van den Berg M. 2010. Summary of night noise guidelines for Europe. Noise Health 12(47):61–63, PMID: 20472950, https://doi.org/10.4103/1463-1741.63204.

Kovalev VA, Kruggel F, von Cramon DY. 2003. Gender and age effects in structural brain asymmetry as measured by MRI texture analysis. Neuroimage 19(3):895–905, PMID: 12880818, https://doi.org/10.1016/S1053-8119(03)00140-X.

Kulick ER, Wellenius GA, Kaufman JD, DeRosa JT, Kinney PL, Cheung YK, et al. 2017. Long-term exposure to ambient air pollution and subclinical cerebrovascular disease in NOMAS (the Northern Manhattan Study). Stroke 48(7):1966–1968, PMID: 28455324, https://doi.org/10.1161/STROKEAHA.117.016672.

Lemaitre H, Goldman AL, Sambataro F, Verchinski BA, Meyer-Lindenberg A, Weinberger DR, et al. 2012. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol Aging 33(3):617.e1–e9, PMID: 20739099, https://doi.org/10.1016/j.neurobiolaging.2010.07.013.

Lim Y-H, Kim H, Kim JH, Bae S, Park HY, Hong Y-C. 2012. Air pollution and symptoms of depression in elderly adults. Environ Health Perspect 120(7):1023–1028, PMID: 22514209, https://doi.org/10.1289/ehp.1104100.

Lim YY, Snyder PJ, Pietrzak RH, Ukiqi A, Villemagne VL, Ames D, et al. 2016. Sensitivity of composite scores to amyloid burden in preclinical Alzheimer's disease: introducing the *Z*-scores of attention, verbal fluency, and episodic memory for nondemented older adults composite score. Alzheimers Dement (Amst) 2:19–26, PMID: 27239532, https://doi.org/10.1016/j.dadm.2015.11.003.

Lu H, Xu F, Rodrigue KM, Kennedy KM, Cheng Y, Flicker B, et al. 2011. Alterations in cerebral metabolic rate and blood supply across the adult lifespan. Cereb Cortex 21(6):1426–1434, PMID: 21051551, https://doi.org/10.1093/cercor/bhq224.

Marstaller L, Williams M, Rich A, Savage G, Burianová H. 2015. Aging and large-scale functional networks: white matter integrity, gray matter volume, and functional connectivity in the resting state. Neuroscience 290:369–378, PMID: 25644420, https://doi.org/10.1016/j.neuroscience.2015.01.049.

Memmesheimer M, Friese E, Ebel A, Jakobs HJ, Feldmann H, Kessler C, et al. 2004. Long-term simulations of particulate matter in Europe on different scales using sequential nesting of a regional model. Int J Environ Pollut 22(1–2):108–132, https://doi.org/10.1504/IJEP.2004.005530.

Münzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. 2017. Impact of oxidative stress on the heart and vasculature: part 2 of a 3-part series. J Am Coll Cardiol 70(2):212–229, PMID: 28683969, https://doi.org/10.1016/j.jacc.2017.05.035.

Nonnemacher M, Jakobs H, Viehmann A, Vanberg I, Kessler C, Moebus S, et al. 2014. Spatio-temporal modelling of residential exposure to particulate matter and gaseous pollutants for the Heinz Nixdorf Recall Cohort. Atmos Environ 91:15–23, https://doi.org/10.1016/j.atmosenv.2014.03.052.

Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, et al. 2004. Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol 16(6–7):437–445, PMID: 15204759, https://doi.org/10.1080/08958370490439597.

Power MC, Adar SD, Yanosky JD, Weuve J. 2016. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: a systematic review of epidemiologic research. Neurotoxicology 56:235–253, PMID: 27328897, https://doi.org/10.1016/j.neuro.2016.06.004.

Power MC, Lamichhane AP, Liao D, Xu X, Jack CR, Gottesman RF, et al. 2018. The association of long-term exposure to particulate matter air pollution with brain MRI findings: the ARIC study. Environ Health Perspect 126(2):027009, PMID: 29467108, https://doi.org/10.1289/EHP2152.

Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A III, Schwartz J. 2011. Traffic-related air pollution and cognitive function in a cohort of older men. Environ Health Perspect 119(5):682–687, PMID: 21172758, https://doi.org/10.1289/ehp.1002767.

Schaer M, Cuadra MB, Schmansky N, Fischl B, Thiran J-P, Eliez S. 2012. How to measure cortical folding from MR images: a step-by-step tutorial to compute local gyrification index. J Vis Exp 59:e3417, PMID: 22230945, https://doi.org/10.3791/3417.

Schaie KW, Willis SL, Caskie GIL. 2004. The Seattle Longitudinal Study: relationship between personality and cognition. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 11(2–3):304–324, PMID: 16755303, https://doi.org/10.1080/13825580490511134.

Schapkin SA, Falkenstein M, Marks A, Griefahn B. 2006. Executive brain functions after exposure to nocturnal traffic noise: effects of task difficulty and sleep quality. Eur J Appl Physiol 96(6):693–702, PMID: 16421758, https://doi.org/10.1007/s00421-005-0049-9.

Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. 2002. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL study. Risk factors, evaluation of coronary calcium and lifestyle. Am Heart J 144(2):212–218, PMID: 12177636, https://doi.org/10.1067/mhj.2002.123579.

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. 2009. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci USA 106(31):13040–13045, PMID: 19620724, https://doi.org/10.1073/pnas.0905267106.

Storsve AB, Fjell AM, Tamnes CK, Westlye LT, Overbye K, Aasland HW, et al. 2014. Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: regions of accelerating and decelerating change. J Neurosci 34(25):8488–8498, PMID: 24948804, https://doi.org/10.1523/JNEUROSCI.0391-14.2014.

Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, et al. 2017. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J 49(1):1600419, PMID: 28077473, https://doi.org/10.1183/13993003.00419-2016.

Tonne C, Elbaz A, Beevers S, Singh-Manoux A. 2014. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology 25(5):674–681, PMID: 25036434, https://doi.org/10.1097/EDE.0000000000000144.

Tzivian L, Dlugaj M, Winkler A, Hennig F, Fuks K, Sugiri D, et al. 2016a. Long-term air pollution and traffic noise exposures and cognitive function: a cross-sectional analysis of the Heinz Nixdorf Recall study. J Toxicol Environ Health A 79(22–23):1057–1069, PMID: 27924705, https://doi.org/10.1080/15287394.2016.1219570.

Tzivian L, Dlugaj M, Winkler A, Weinmayr G, Hennig F, Fuks KB, et al. 2016b. Long-term air pollution and traffic noise exposures and mild cognitive impairment in older adults: a cross-sectional analysis of the Heinz Nixdorf Recall Study. Environ Health Perspect 124(9):1361–1368, PMID: 26863687, https://doi.org/10.1289/ehp.1509824.

Tzivian L, Winkler A, Dlugaj M, Schikowski T, Vossoughi M, Fuks K, et al. 2015. Effect of long-term outdoor air pollution and noise on cognitive and psychological functions in adults. Int J Hyg Environ Health 218(1):1–11, PMID: 25242804, https://doi.org/10.1016/j.ijheh.2014.08.002.

van Kempen E, Casas M, Pershagen G, Foraster M. 2018. WHO environmental noise guidelines for the European Region: a systematic review on environmental noise and cardiovascular and metabolic effects: a summary. Int J Environ Res Public Health 15(2):379, PMID: 29470452, https://doi.org/10.3390/ijerph15020379.

Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. 2012. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med 172(3):219–227, PMID: 22332151, https://doi.org/10.1001/archinternmed.2011.683.

WHO (World Health Organization) Regional Office for Europe. 2013. *Review of Evidence on Health Aspects of Air Pollution—REVIHAAP Project: Technical Report*. Copenhagen, Denmark: WHO Regional Office for Europe. http://www.euro.who.int/__data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report.pdf [accessed 1 June 2020].

WMA (World Medical Association). 2013. World Medical Association Declaration of Helsinki. Ethical principles for medial research involving human subjects. JAMA 201(20):2191–2194, PMID: 24141714, https://doi.org/10.1001/jama.2013.281053.

Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. 2015. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke 46(5):1161–1166, PMID: 25908455, https://doi.org/10.1161/STROKEAHA.114.008348.

Xu X, Ha SU, Basnet R. 2016. A review of epidemiological research on adverse neurological effects of exposure to ambient air pollution. Front Public Health 4:157, PMID: 27547751, https://doi.org/10.3389/fpubh.2016.00157.

Zilles K, Palomero-Gallagher N. 2015. Gyrification in the human brain. In: *Brain Mapping: An Encyclopedic Reference*. Toga AW, ed. San Diego: Elsevier Academic Press, 37–44.