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Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure

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ABSTRACT

Background: Emerging findings have increased concern that exposure to fine particulate matter air pollution (aerodynamic diameter ≤ 2.5 µm; $PM_{2.5}$) may be neurotoxic, even at lower levels of exposure. Yet, additional studies are needed to determine if exposure to current $PM_{2.5}$ levels may be linked to hemispheric and regional patterns of brain development in children across the United States.

Objectives: We examined the cross-sectional associations between geocoded measures of concurrent annual average outdoor $PM_{2.5}$ exposure, regional- and hemisphere-specific differences in brain morphometry and cognition in 10,343 9- and 10- year-old children.

Methods: High-resolution structural T1-weighted brain magnetic resonance imaging (MRI) and NIH Toolbox measures of cognition were collected from children at ages 9–10 years. FreeSurfer was used to quantify cortical surface area, cortical thickness, as well as subcortical and cerebellum volumes in each hemisphere. $PM_{2.5}$ concentrations were estimated using an ensemble-based model approach and assigned to each child's primary residential address collected at the study visit. We used mixed-effects models to examine regional- and hemispheric- effects of $PM_{2.5}$ exposure on brain estimates and cognition after considering nesting of participants by familial relationships and study site, adjustment for socio-demographic factors and multiple comparisons.

Results: Annual residential $PM_{2.5}$ exposure (7.63 ± 1.57 µg/m^3) was associated with hemispheric specific differences in gray matter across cortical regions of the frontal, parietal, temporal and occipital lobes as well as subcortical and cerebellum brain regions. There were hemispheric-specific associations between $PM_{2.5}$ exposures and cortical surface area in 9/31 regions; cortical thickness in 22/27 regions; and volumes of the thalamus, pallidum, and nucleus accumbens. We found neither significant associations between $PM_{2.5}$ and task performance on individual measures of neurocognition nor evidence that sex moderated the observed associations.

Discussion: Even at relatively low-levels, current $PM_{2.5}$ exposure across the U.S. may be an important environmental factor influencing patterns of structural brain development in childhood. Prospective follow-up of this cohort will help determine how current levels of $PM_{2.5}$ exposure may affect brain development and subsequent risk for cognitive and emotional problems across adolescence.

1. Introduction

Ambient fine particulate matter (aerodynamic diameter ≤ 2.5 µm; $PM_{2.5}$) is a ubiquitous criteria air pollutant and environmental neurotoxin (Brockmeyer and D'Angiulli, 2016; Cohen et al., 2017). $PM_{2.5}$ particles are small enough to infiltrate the lower respiratory tract, and

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Abbreviations: $PM_{2.5}$, particulate matter with aerodynamic diameter of ≤2.5 µm; ABCD, Adolescent Brain Cognitive Development (ABCD) study; MRI, magnetic resonance imaging

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as shown in experimental studies, cause oxidative stress, systemic inflammation and toxic effects on the nervous system and the brain (Block et al., 2012; Thomson, 2019; Woodward et al., 2017; World Health Organization, 2013). Recent evidence from epidemiological studies also indicates that $PM_{2.5}$ exposure may be especially harmful to children, as the brain continues to develop across childhood and into the third decade of life (Block et al., 2012; Clifford et al., 2016; Costa et al., 2017; de Prado et al., 2018; Sram et al., 2017). Exposure to $PM_{2.5}$ and its constituents have been linked with adverse neurobehavioral effects during childhood and adolescence, including reduced intelligence (IQ) (Chiu et al., 2016; Edwards et al., 2010; Perera et al., 2009; Porta et al., 2016; Wang et al., 2017) and impairment in cognitive function (Chiu et al., 2016; Sunyer et al., 2015, 2017). These adverse behavioral effects suggest $PM_{2.5}$ may impact distinct patterns of brain development, especially given that improvements in cognitive functioning parallel regional and hemispheric cortical and subcortical gray matter neuromaturation across childhood and adolescence (Casey et al., 2005; Giedd et al., 1999; Gogtay et al., 2004; Herting et al., 2018; Shaw et al., 2006; Sowell et al., 2001, 2003, 2004; Tamnes et al., 2017) and functional specialization of brain regions (Gazzaniga, 1995; Gotts et al., 2013; Kong et al., 2018; Mesulam, 1990; Nagel et al., 2013).

Human *in vivo* neuroimaging studies have begun to examine how $PM_{2.5}$ exposure may influence brain development, but the results have been inconsistent and very little attention has been directed to hemispheric and regional specificity in the brain structures potentially affected by air pollution neurotoxicity. Specifically, patterns of brain maturation occur in a posterior-to-anterior and inferior-to-superior fashion, with sensory and motor cortices developing earlier (Giedd et al., 1999; Sowell et al., 2004), while prefrontal and limbic regions (e.g., amygdala, hippocampus) continue to undergo considerable maturation during adolescence (Giedd et al., 1999; Herting et al., 2018). In addition, cortical areas respond to specific stimuli and are involved in distinct mental processes (Afifi and Bergman, 2005). As such, hemispheric specialization exists for a number of cognitive functions that continue to develop across childhood and adolescence, such as language (Purves et al., 2001), working memory (Nagel et al., 2013) and relational reasoning (Vendetti et al., 2015). Because the human brain is comprised of highly specialized components (Kanwisher, 2010), understanding hemispheric and regional specificity of $PM_{2.5}$ exposure may help elucidate the neural circuits most vulnerable to exposure across child and adolescent development. While associations with global brain volumes have not been observed, previous studies provide preliminary evidence for regional and hemispheric specificity of differences in brain development related to $PM_{2.5}$ exposure (Beckwith et al., 2020; Guxens et al., 2018; Mortamais et al., 2017; Peterson et al., 2015; Pujol et al., 2016b, 2016a). For example, higher prenatal $PM_{2.5}$ exposure in Rotterdam, Netherlands was related to reduced cortical thickness in the right prefrontal cortex at ages 6–10 years (N = 783), while no associations were seen for the left hemishere (Guxens et al., 2018). Reduced cortical thickness, with regional and hemispheric differences noted in the posterior frontal and anterior parietal lobes, were also found in 12 year-old children from Cincinnati, Ohio who were exposed to high traffic-related air pollution during their first postnatal year of life (N = 135) (Beckwith et al., 2020). In Barcelona, Spain, increased gray matter density within the basal ganglia in 8–12 year-olds was associated with exposure to $PM_{2.5}$ components (elemental carbon (EC), polycyclic aromatic hydrocarbons (PAHs), copper) at the time of testing (N = 263) (Mortamais et al., 2017; Pujol et al., 2016b, 2016a). Two other studies, however, found no associations of cortical gray matter thickness with either prenatal exposure (N = 40, ages 7–9 years (Peterson et al., 2015)) or recent exposure (N = 263, ages 8–10 (Pujol et al., 2016a)) to $PM_{2.5}$ constituents. However, these studies have had small sample sizes and limited geographical coverage; potentially limiting generalizability of findings to children in cities across the United States.

In the current study, we aimed to examine how annual $PM_{2.5}$ exposure relates to gray matter morphology in 10,343 9 to 10-year-olds enrolled in Adolescent Brain Cognitive Development (ABCD) study™. We utilized a novel hybrid model to estimate residential $PM_{2.5}$ exposure at the time of the study visit and further accounted for geographic, demographic, and socioeconomic diversity at 21 research sites throughout the United States (Compton et al., 2019; Garavan et al., 2018; Jernigan et al., 2018; Volkow et al., 2018). Cortical volume is a composite score that reflects both cortical thickness and surface area, with known differences in the developmental trajectories of cortical volume, thickness, and surface area across various brain regions (Raznahan et al., 2011). Moreover, gray matter morphometric properties are not genetically linked (Rakic, 2009); rather cortical thickness and surface area capture distinct biological processes (Raznahan et al., 2011) and should be considered separately in understanding how $PM_{2.5}$ exposure may impact brain development. Therefore, we hypothesized that higher $PM_{2.5}$ exposure would be associated with widespread differences in gray matter morphology as well as distinct regional- and hemispheric- specificity. We also hypothesized higher $PM_{2.5}$ exposure would be associated with worse cognitive performance, particularly for measures of general intelligence.

2. Methods

2.1. Study population

We obtained baseline data from the 2019 NDA 2.0.1 data release of the ABCD study™, which includes in total 11,875 9–10 year-olds (Garavan et al., 2018; Jernigan et al., 2018; Volkow et al., 2018). Participants were assessed at 21 study sites across the United States. Sample recruitment at these sites and other information about the ACBD study have been reported previously in detail (Bagot et al., 2018; Barch et al., 2018; Casey et al., 2018; Feldstein Ewing et al., 2018; Garavan et al., 2018; Hagler et al., 2019; Luciana et al., 2018; Uban et al., 2018). A schematic overview of the study is available in Supplementary Material (SFig. 1). Briefly, inclusion criteria for the ABCD study were as follows: 1) age 9.00 to 10.99 years at the time of baseline assessment; 2) able to validly and safely complete the baseline visit including MRI; 3) Fluent in English. Child and caregiver participants completed an in-person baseline visit between October 2016 and October 2018 in which residential address and brain scans were collected. Annual average $PM_{2.5}$ exposure levels estimated for 2016 were assigned to each participant's primary residential address at the time of the study visit. Details of exclusionary criteria are presented in Supplementary Material. Centralized institutional review board (IRB) approval was obtained from the University of California, San Diego. Study sites obtained approval from their local IRBs. Written informed consent was provided by each parent or caregiver; each child provided written assent. All ethical regulations were complied with during data collection and analysis.

An identical protocol was utilized for recruitment, neuropsychological assessment, and neuroimaging of all participants in the ABCD study (Auchter et al., 2018). Our analytic sample was limited to participants with 1) an estimate of $PM_{2.5}$ exposure in microgram per m^3 ($\mu g/m^3$) at the 1-km^2 grid assigned to the primary residence address collected at the time of the study visit, 2) complete data on major sociodemographic characteristics, including age, sex, race/ethnicity and family socioeconomic status, and 3) either complete NIH Cognitive Toolbox scores and/or high-quality T1-weighted magnetic resonance imaging (MRI) scan. Missingness in covariates was minimal (N = 183), therefore multiple imputations were not performed, rather these individuals were excluded from the study. A total of 10,343 participants had information of $PM_{2.5}$ exposure, covariates, and at least one outcome of interest. Of them, 10,341 subjects were retained in the MRI analyses and 10,127 were included in the cognitive analyses (SFig. 2).

2.2. MRI acquisition and preprocessing

ABCD MRI methods and assessments have been optimized and harmonized across the 21 sites for 3 Tesla scanners (Siemens Prisma, General Electric 750, Philips) (Casey et al., 2018; Hagler et al., 2019). Cortical surface reconstruction and subcortical segmentation was completed via FreeSurfer (version 5.3), including total gray and white matter as well as subcortical volumes, cortical thickness and cortical surface area estimates for cortical regions using the Desikan-Killiany Atlas (Dale et al., 1999; Hagler et al., 2019). At the central ABCD Data Analysis, Informatics & Resource Center (DAIRC), T1-weighted structural images underwent quality control (QC) across five categories, both prior to and after post-processing to gauge the severity of motion, intensity inhomogeneity, white matter underestimation, pial overestimation, and magnetic susceptibility artifact (Hagler et al., 2019). Only image types passing QC for all categories were included in our analyses (SFig. 2). Subjects lost after MRI QA/QC ($n = 644$) were significantly younger (age in months: 117.7 ± 7.3; $p < 0.0001$) but did not significantly differ by sex (53.6% male; $p = 0.53$) from the rest of the cohort.

2.3. Estimation of fine particulate matter exposure

We used daily estimates from state-of-the-art hybrid spatiotemporal $PM_{2.5}$ models to aggregate annual $PM_{2.5}$ exposure levels with 1-km^2 resolution and to assign them to each participant's home addresses at the time of the baseline visit (Di et al., 2019). Each child's primary residential address was collected from the participant's caregiver during the study visit and geocoded by the DAIRC using the google map API to generate latitude and longitude (Google Maps Platform Documentation, 2019). Daily $PM_{2.5}$ concentrations were obtained for the 2016 calendar year using an ensemble-based model approach (Di et al., 2019) that combines the strengths of satellite-based aerosol optical depth (AOD) models, land-use regression, and chemical transport models (CTM). This spatiotemporal modeling approach also incorporated the input of normalized difference vegetation index (NDVI), surface reflectance, absorbing aerosol index, elevation, road density, emission inventory, population density, percentage urban land, meteorological parameters, and other spatial covariates. To account for complex atmospheric mechanisms, a neural network, a random forest, and gradient boosting were used for their capacity to model nonlinearity and interactions, and then ensemble averaged with a geographically weighted regression. The model for the continental United States from 2000 to 2016 has been trained and tested with left out monitors, with ten-fold cross-validation (CV) for daily predictions showing a high R^2 of 0.86 on the left-out monitors; for annual average exposure, CV R^2 was 0.89. Annual average 2016 calendar year estimates were then aggregated and assigned to the geocoded baseline residential locations of ABCD participants by the DAIRC.

2.4. Covariates

Selection of potential confounders was based on both prior knowledge and empirical data (Weng et al., 2009). A directed acyclic graph (DAG) (Greenland and Brumback, 2002) was used to identify confounders that may predict neurobehavioral development and exposure to ambient air pollutants (SFig. 3). The following covariates were included in the main analysis: child's age, familial relationships, caregiver's report of the child's sex at birth, race/ethnicity, parental higher education (highest of any household member), total combined family income, parental employment status, handedness and the imaging device manufacturer. We also included an average score of three-items assessing parent perspectives of how safe and free from crime their neighborhood is (Mujahid et al., 2007). For subcortical volume analyses, intracranial volumes (ICV) were also included as a covariate. The ABCD Data Exploration and Analysis and Exploration Portal (DEAP) variable definitions were used for race and ethnicity and for parental higher education. Details about the remaining covariate measurements and selection of additional covariates are available in Supplementary Material (STable 1).

$PM_{2.5}$ exposure estimates capture both local and regional sources of air pollution, and the urban built environment is likely to impact $PM_{2.5}$ exposure. In sensitivity analyses we assessed additional confounding effects of population density and distance to road (STable 2), and we explored heterogeneity of $PM_{2.5}$ effects by ABCD site. Specifically, residentially derived United Nations population density was measured as persons per km^2 (based on population counts of the 2010 national census tract adjusted for potential underreporting across the world) (Center for International Earth Science Information Network - CIESIN - Columbia University, 2016) as a proxy for urbanicity. Distance to major roads and highways in meters (U.S. Department of the Interior, 2017) was treated as a categorical variable reflecting those living < 150, 150–300 m, 300–600 m, or > 600 m based on previous studies showing that near-roadway pollutants decay to background levels by approximately 115–570 m (Karner et al., 2010).

2.5. Neurocognitive performance

The ABCD study neurocognitive session at the baseline visit included the NIH Toolbox Cognition Battery (NIHT) (Heaton et al., 2014; Luciana et al., 2018; Weintraub et al., 2014). Each child completed the List Sorting Working Memory Test, Flanker Attention Test, Dimensional Card Sorting Task, Picture Vocabulary Test, Oral Reading Recognition Test, Picture Sequence Memory Test, and Pattern Comparison Processing Speed Test. Using performance on these 7 items, composite scores include a total cognitive score, as well as crystalized and fluid cognitive function score (Gershon et al., 2013). Given our models included demographic variables, unstandardized scores were utilized as the primary dependent variables of cognition.

2.6. Statistical analysis

All analyses were performed using R software (version 3.5.2). We first examined differences in covariate information across $PM_{2.5}$ quintiles using Pearson's Chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables. Next, we implemented multilevel mixed effects modeling to examine the association between annual $PM_{2.5}$ exposure and structural brain or neurocognitive performance outcomes of interest. Based on recent evidence showing regional- and hemisphere- specific differences in surface area and cortical thickness in the general population (Kong et al., 2018) as well as in relation to $PM_{2.5}$ (Guxens et al., 2018; Peterson et al., 2015) we examined the main effect of $PM_{2.5}$ and a cross-product term of $PM_{2.5}$ by hemisphere (i.e. interaction, see Eq. (1)), to determine if the association between $PM_{2.5}$ and brain morphology differed by hemisphere, in 31 regions of surface area and 27 regions of cortical thickness. Previous research has showed subcortical volumes may also be associated with annual $PM_{2.5}$ related exposure during childhood (Pujol et al., 2016b), therefore we also examined 8 subcortical regions including cerebellum volumes. We included a random effect for ABCD site (j) and a nested random effect for family (k) within ABCD site for participant i so as to account for between-site variability and within-family correlations. A nested random intercept for subject (i) was also added to the model to account for the hemisphere related within-subject variability. At the first stage of the analysis we used generalized additive mixed effect models (GAMMs) to explore the shape of the association between $PM_{2.5}$ and outcomes under study. Significant deviations from linearity were not detected, so we proceeded with a linear modeling strategy. Our final modeling equation was:

$$\begin{aligned} Y_{jki} = {} & \beta_0 + \beta_1 \mathrm{PM2.5}_i \times Hemisphere_i + \beta_2 Age_i + \beta_3 Sex_i \\ & + \beta_4 Race/Ethnicity_i + \beta_5 Parental\ \ higher\ \ education_i \\ & + \beta_6 Total\ \ family\ \ income_i + \ \beta_7 Parental\ \ employment\ \ status_i \\ & + \beta_8\ \ Handedness_i + \beta_9\ \ Imaging\ \ device_i \\ & + \beta_{10} Neighborhood\ \ safety_i + \beta_{11} \mathrm{PM2.5}_i + \beta_{12} Hemisphere_i + U_{j\,[ki]} \\ & + \varepsilon_{jki} \end{aligned} \tag{1}$$

Next, we employed a two-level linear mixed-effects model to examine the association of annual residential $\mathrm{PM}_{2.5}$ exposure with whole brain estimates (total surface area, total cortical thickness, total gray and total white matter, cerebrospinal fluid, intracranial volume, and ventricle volumes). We included a random effect for ABCD site (*j*) and a nested random effect for family (*k*) within ABCD site for participant *i*, as presented in the following equation:

$$\begin{aligned} Y_{jki} = {} & \beta_0 + \beta_1 \mathrm{PM2.5}_i + \beta_2 Age_i + \beta_3 Sex_i + \beta_4 Race/Ethnicity_i + \beta_5 \\ & Parental\ \ higher\ \ education_i + \beta_6 Total\ \ family\ \ income_i + \ \ \beta_7 \\ & Parental\ \ employment\ \ status_i + \beta_8 Handedness_i + \beta_9 \\ & Imaging\ \ device_i + \beta_{10} Neighborhood\ \ safety_i + U_{j\,[k]} + \varepsilon_{jki} \end{aligned} \tag{2}$$

In all analyses, we scaled the effect estimates for $\mathrm{PM}_{2.5}$ to 5 µg/m^3. This increment has been widely used in previous research assessing health effects of $\mathrm{PM}_{2.5}$, including brain and cognitive development, thus allowing direct comparability of previous results with ours (Beelen et al., 2014; Guxens et al., 2014, 2018). Regional and hemispheric analyses were corrected for multiple comparisons using a false discovery rate correction and a 0.05 level of significance. To interpret $\mathrm{PM}_{2.5}$ and brain metrics in regions with significant interactions, individual regression models were fit for each hemisphere separately to illustrate the difference in the associations with $\mathrm{PM}_{2.5}$ by hemisphere interactions (Robinson and Schumacker, 2013). Finally, we also employed the two-level linear mixed-effects model presented in Eq. (2) to examine the association of $\mathrm{PM}_{2.5}$ exposure with each of the 7 NIH Cognitive Toolbox outcomes and the 3 composite scores. We also examined the potential effect moderation by sex through stratified analyses, as previous studies have suggested sex-specific effects of $\mathrm{PM}_{2.5}$ (Costa et al., 2017; Kern et al., 2017). In follow-up sensitivity analyses, we adjusted for population density and distance to road, and explored heterogeneity of $\mathrm{PM}_{2.5}$ effects by site by including a random slope of $\mathrm{PM}_{2.5}$ by site.

3. Results

3.1. Study population and exposure distribution

Substantial variability was seen in annual $\mathrm{PM}_{2.5}$ exposures both within and between the 21 ABCD study sites, with median $\mathrm{PM}_{2.5}$ concentrations ranging from 5.1 µg/m^3 (Site 17, min = 2.4 µg/m^3, max = 9.3 µg/m^3) to 10.4 µg/m^3 (Site 01, min = 1.7 µg/m^3, max = 13.2 µg/m^3) and overall distribution ranging from 1.72 – 15.9 µg/m^3 (Fig. 1, Table 1). The distribution of annual $\mathrm{PM}_{2.5}$ exposures was associated with both demographic and social covariates (Table S2). Participants with relatively high exposure in the upper two quintiles (> 8.45 µg/m^3) were more likely to be ethnic minorities (Hispanic or Black), to have parents with a lower level of education, and to come from families earning less than *$49,999* in total family income over the past 12 months (Table S2).

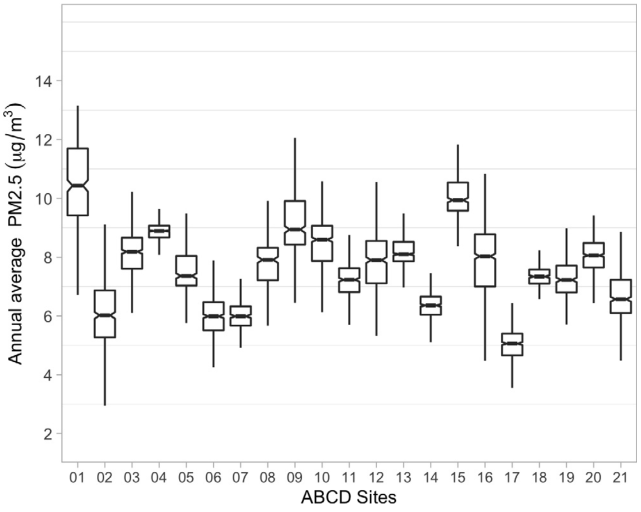

Fig. 1. Distribution of baseline annual $\mathrm{PM}_{2.5}$ average (based on daily estimates at the primary residential location) by study site (N = 10,343) in the ABCD Study. Footnote: The line within the box marks the median; the boundaries of the box indicate the 25th and 75th percentiles; horizontal bars denote the variability outside the upper and lower quartiles (ie, within 1.5 IQR of the lower and upper quartiles).

3.2. Links between residential $\mathrm{PM}_{2.5}$ exposure levels and cortical brain structure

Increased $\mathrm{PM}_{2.5}$ exposure was associated with hemispheric-specific differences in surface area and cortical thickness in regions of the frontal, parietal, temporal, occipital and cingulate lobes (FDR corrected, $p < 0.05$). Specifically, we observed hemispheric differences (i.e. significant $\mathrm{PM}_{2.5}$-by-hemisphere interaction) in the association of $\mathrm{PM}_{2.5}$ with surface area for 9/31 regions (29%) (Fig. 2A) and 22/27 (81%) cortical thickness regions examined (Fig. 3A). Results from regional effect estimates stratified by hemisphere revealed positive associations between $\mathrm{PM}_{2.5}$ in some regions and negative associations in others. For surface area, an increase of 5-µg/m^3 in $\mathrm{PM}_{2.5}$ exposure was associated with 17.5 mm^2 smaller surface area in the left cuneus and 6.5 mm^2 smaller surface area in the right frontal pole. In contrast, an increase of 5-µg/m^3 in $\mathrm{PM}_{2.5}$ exposure was associated with a 34.9 mm^2 increase in right lateral orbital frontal surface area (Fig. 2B, Fig. 4). For cortical thickness, an increase of 5-µg/m^3 in $\mathrm{PM}_{2.5}$ exposure was associated with thinner cortices (0.01–0.02 mm) in the left superior frontal, left orbital frontal, left cingulate cortex (rostral anterior, caudal anterior, posterior, isthmus), right inferior temporal, right parahippocampal, and right insula (Fig. 3B, Fig. 4). In addition, an increase of 5-µg/m^3 in $\mathrm{PM}_{2.5}$ exposure was also found to be associated with increases in cortical thickness (0.01–0.04 mm) in the right lateral orbital frontal, right paracentral, right caudal anterior and posterior cingulate, and the left middle temporal cortex (Fig. 3B, Fig. 4).

3.3. Links between residential $\mathrm{PM}_{2.5}$ exposure levels and brain volumes

Increased $\mathrm{PM}_{2.5}$ exposure was associated with hemispheric-specific differences in subcortical and cerebellum volumes, with the exception of the hippocampus (Fig. 5A). Regional effect estimates stratified by hemisphere revealed an increase of 5-µg/m^3 in exposure was associated with a 112.7 mm^3 increase in right thalamic volumes, 26.3 mm^3 increase in the right pallidum, 7.4 mm^3 in the left accumbens (Fig. 5B, Fig. 6). In contrast, an increase of 5-µg/m^3 was also related to a 65.2 mm^3 decrease in the left putamen and a 20.1 mm^3 decrease in the left pallidum (Fig. 5B, Fig. 6). No significant associations were found between $\mathrm{PM}_{2.5}$ exposure and global measures of whole-brain surface area, cortical thickness, cortical volume or subcortical volumes (Table 2).

3.4. $\mathrm{PM}_{2.5}$ exposure and neurocognitive performance

There were no significant associations between $\mathrm{PM}_{2.5}$ and task performance on individual measures of neurocognition or composites of

Table 1
Baseline characteristics of study sample (N = 10,343) in the ABCD Study.

Characteristics of study sample (N = 10, 343)	
Age (months): mean ± SD (range)	119.1 ± 7.7 (108–131)
Familial relationship	
Single: N (%)	7179 (69.4%)
Sibling: N (%)	1368 (13.2%)
Twin: N (%)	1769 (17.1%)
Triplet: N (%)	27 (0.3%)
Sex	
Female: N (%)	4933 (47.7%)
Male: N (%)	5410 (52.3%)
Race and ethnicity	
Asian: N (%)	212 (2.1%)
Black: N (%)	1461 (14.1%)
Hispanic: N (%)	2111 (20.4%)
Other: N (%)	1025 (9.9%)
White: N (%)	5534 (53.5%)
Parental higher education	
≤HS diploma/GED: N (%)	1426 (13.8%)
Some college: N (%)	2682 (25.9%)
Bachelor: N (%)	2663 (25.7%)
Post Graduate: N (%)	3572 (34.5%)
Total family income	
< $5,000: N (%)	337 (3.3%)
$5,000 - $11,999: N (%)	359 (3.5%)
$12,000 - $15,999: N (%)	237 (2.3%)
$16,000 - $24,999: N (%)	430 (4.2%)
$25,000 - $34,999: N (%)	571 (5.5%)
$35,000 - $49,999: N (%)	803 (7.8%)
$50,000 - $74,999: N (%)	1329 (12.8%)
$75,000 - $99,999: N (%)	1401 (13.5%)
$100,000 - $199,999: N (%)	2942 (28.4%)
> $200,000: N (%)	1094 (10.6%)
Unknown: N (%)	840 (8.1%)
Parental employment status	
Working: N (%)	7187 (69.5%)
Unemployed: N (%)	73 (0.7%)
Temporarily Laid Off: N (%)	71 (0.7%)
Looking for Work: N (%)	411 (4.0%)
Sick Leave: N (%)	17 (0.2%)
Stay at Home Parent: N (%)	1826 (17.7%)
Maternity Leave: N (%)	26 (0.3%)
Retired: N (%)	65 (0.6%)
Student: N (%)	200 (1.9%)
Disabled: N (%)	213 (2.1%)
Other: N (%)	207 (2.0%)
Unknown: N (%)	47 (0.5%)
Handedness	
Left: N (%)	1145 (11.1%)
Right: N (%)	9157 (88.5%)
Both: N (%)	41 (0.4%)
MRI manufacturer	
Ge Medical Systems: N (%)	2415 (23.3%)
Philips Medical Systems: N (%)	1205 (11.7%)
Siemens: N (%)	6723 (65.0%)
Neighborhood quality: mean ± SD (range)	3.9 ± 0.97 (1–5)
Annual average $PM_{2.5}$ (μg/m^3): mean ± SD (range)	7.63 ± 1.57 (1.72–15.9)

total, crystallized or fluid cognition (Table 3).

3.5. Sensitivity and exploratory analysis of sex differences in PM2.5 effects

Because some studies that have found sex differences in $PM_{2.5}$ effects on behavior (Chiu et al., 2016; Sunyer et al., 2015; Wang et al., 2017), we also performed analyses stratified by sex. However, we found no evidence that sex moderated the associations of $PM_{2.5}$ with stratified hemispheric regions of surface area, cortical thickness, subcortical volume, whole brain measures and neurocognitive performance in children ages 9–10 years (STables 4–8). $PM_{2.5}$ exposure levels were similar among subjects living < 150 m from a major roadway (Mean = 7.53, SD = 1.63 ug/m^3), 150–300 m (Mean = 7.79, SD = 1.57 ug/m^3) or 300–600 m (Mean = 7.72, SD = 1.59 ug/m^3). A small, but significant, association was seen between $PM_{2.5}$ exposure levels and population density (β = 0.0001, 95% CI: 0.00008–0.000098, $p < 0.0001$). Adjustment for population density and residential distance to major road did not materially change $PM_{2.5}$ results (STables 9–11). We also explored heterogeneity of the $PM_{2.5}$ exposure effect by site (by including a random slope of $PM_{2.5}$ by site in our models) and did not find significant heterogeneity between $PM_{2.5}$ exposure and any of the outcomes examined.

4. Discussion

This is the largest air pollution-brain MRI study (N = 10,343) to examine effects of exposure to fine particulate matter on morphometric measures of developing brains of children (age 9–10 years) in the United States. In this respect, the sample size provided statistical power to examine the effects of $PM_{2.5}$ by hemisphere in cortical and subcortical brain regions, as well as neurocognitive outcomes. Annual residential $PM_{2.5}$ exposure assigned to the primary address at baseline study enrollment was associated with hemispheric- and region-specific differences in gray matter. However, no associations were found with cognitive function as measured by the NIH Toolbox. The observed brain morphological findings were robust to adjustment for various sociodemographic factors and multiple comparison adjustment.

Our findings are congruent with previous studies suggesting brain regional specificity in neurotoxic effects of air pollution exposure during childhood (Pujol et al., 2016b, 2016a). Children and adolescents may be especially at risk for neurotoxic effects of air pollution because their brain are still growing and they are developing vital learning skills as well as social and interpersonal competencies (Sebastian et al., 2008; Steinberg, 2005). Interestingly, $PM_{2.5}$ exposure was associated with both increases and decreases in gray matter surface area, thickness, and volume. The observed regional- and hemispheric specific patterns of both positive and negative associations between $PM_{2.5}$ and gray matter may reflect the dynamic neurodevelopmental trajectories across early life that vary by brain region. For instance, sensory motor and language functions reach peak volumes in early childhood while the prefrontal, temporal, and basal ganglia continue to mature through the mid-to-late twenties (Crone, 2009; Herting et al., 2018; Lebel and Deoni, 2018; Lebel et al., 2017; Sowell et al., 2003; Tamnes et al., 2017). A hallmark pattern of child and adolescent development is synaptogenesis and peak volume around age 10, followed by pruning of synapses and increases in myelination, which is captured on MRI as a decrease in cortical thickness (Gotts et al., 2013; Herting et al., 2018; Mallya and Deutch, 2018; Sowell et al., 2003). In line with these findings, we found regional specific associations between $PM_{2.5}$ exposure and cortical thickness of the frontal lobe, temporal lobe, and basal ganglia as well as differences in the directionality of associations by hemisphere. Interestingly, hemispheric differences have also been previously noted in typical patterns of cortical thickness, albeit the pattern of asymmetry was found to change between early childhood versus late adolescence (Shaw et al., 2011). Moreover, regional- and hemispheric- differences have also been noted in a number of neurodevelopmental and mental health disorders, including Attention-Deficit/Hyperactivity Disorder (ADHD) (Shaw et al., 2011, 2009), Autism (Eyler et al., 2012), and depression (W. Liu et al., 2016; Yucel et al., 2009). Additional research is needed to understand if environmental exposures, including $PM_{2.5}$, may partially contribute to risk for these types of disorders through effects on hemispheric patterns of brain maturation across childhood and adolescence.

We hypothesize that annual $PM_{2.5}$ exposure could alter the timing of the pruning process, either delaying or accelerating this process, in a regional and hemisphere specific manner. A possible biological mechanism of $PM_{2.5}$ exposure on the pruning process could be through actions on microglia cells. Microglia engulf dendritic spines during synaptic pruning in adolescence (Mallya et al., 2018). Both animal studies and human studies in populations living in highly polluted cities

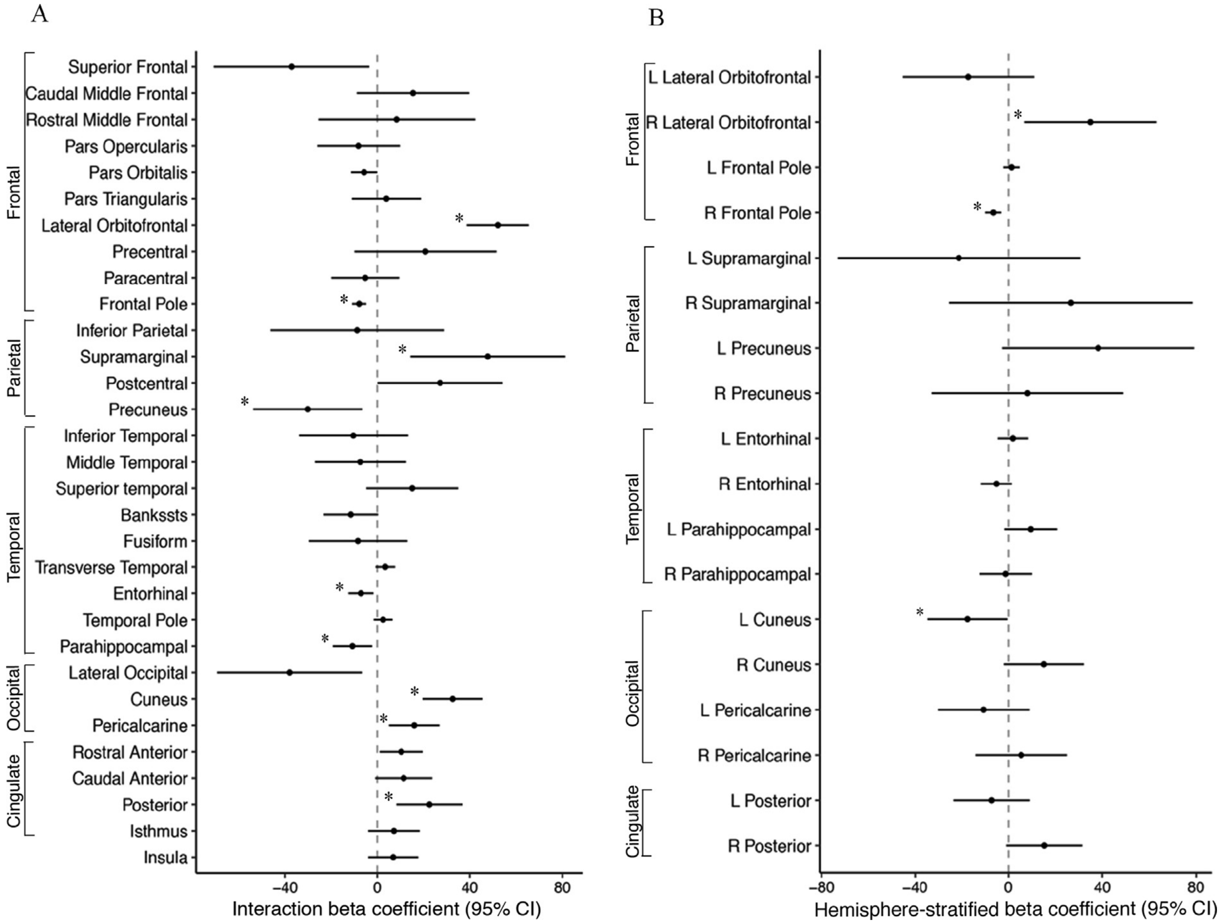

Fig. 2. A) $PM_{2.5}$-by-hemisphere interaction effect estimates; and B) Region-specific $PM_{2.5}$ effect estimates on surface area (mm^2) that differed statistically by hemisphere in the ABCD Study. Footnote: A) Visualization of beta coefficients (95% CI) denoting regions associated with $PM_{2.5}$-by-hemisphere interaction presented with '*' for passed False Discovery Rate correction. B) Visualization of beta coefficients (95% CI) denoting regions associated stratified post-hoc analyses within a given hemisphere derived from significant $PM_{2.5}$-by-hemisphere interactions presented with '*' $p < 0.05$. $PM_{2.5}$ units are 5 μg/m^3.

indicate that PM exposure leads to changes within the brain (Block et al., 2004; Levesque et al., 2011; F. Liu et al., 2015; Ljubimova et al., 2018; Pope et al., 2016), including microglial activation (Calderon-Garciduenas et al., 2008; Ljubimova et al., 2018; Woodward et al., 2017). Additional experimental studies are needed to elucidate the underlying role of microglia and to identify additional plausible neurological consequences of $PM_{2.5}$ exposure during adolescence, such as neuroinflammation, neurovascular damage, altered neurotransmitters, and up-regulation of genes encoding inflammatory cytokine pathways (Calderon-Garciduenas et al., 2008, 2015; Ljubimova et al., 2018; Pope et al., 2016).

The current study strengthens preliminary evidence from previous human studies suggesting that air pollution may exert region-specific neurotoxic effects on the brain (Guxens et al., 2018; Mortamais et al., 2017; Pujol et al., 2016b, 2016a). A few studies have examined associations of prenatal or postnatal exposure to ambient air pollution and brain structure in children. One study found that higher prenatal $PM_{2.5}$ exposure was associated with reduced cortical thickness in the right prefrontal cortex in 6 to 10 year-olds (Guxens et al., 2018). In another study of 7–9 year-old children, PAHs derived from $PM_{2.5}$ exposure were associated with surface reductions largely seen in the left hemisphere, as well as more focal patterns of increases in surface area that were largely driven by white matter (Peterson et al., 2015). Our findings provide additional evidence that the brain is vulnerable to air pollution through postnatal development, as air pollution exposure at ages 9–10 was associated with concurrent brain structure morphology. Given that both the prenatal and childhood windows have been identified as robust periods of neuromaturation, future studies are needed to disentangle specific brain alterations due to prenatal versus postnatal ambient $PM_{2.5}$ exposure.

Structural brain differences associated with ambient $PM_{2.5}$ identified in the current study are of particular concern as exposure levels of ABCD sites (median = 5.1–10.4 μg/m^3; overall range = 1.72–15.9 μg/m^3) were generally below the regulatory standards set by the U.S. Environmental Protection Agency (12 μg/m^3) (U.S. Environmental Protection Agency, 2012) and the World Health Organization (10 μg/m^3) (World Health Organization, 2005). Similarly low $PM_{2.5}$ exposure levels in large, recent studies from the U.S. (N = 4,522,160; mean = 10.1 μg/m^3; range = 4.8–20.1 μg/m^3) (Bowe et al., 2019) and Canada (N = 299,500; mean (SD) = 6.32 (2.54) μg/m^3) (Pinault et al., 2016) were associated with increased mortality risk. Our study adds to emerging evidence that health effects of $PM_{2.5}$ may be seen at concentrations below the national or international standards. While the majority of low to middle income countries do not meet standards of the U.S. EPA or WHO, 49% of high income countries in North America, Europe, and the Western Pacific have low $PM_{2.5}$ exposure levels (World Health Organization, 2018). Thus, our findings of potential brain effects of $PM_{2.5}$ in children may be most generalizable to countries and urban areas that are currently near meeting those worldwide standards. Consequently, our data suggest that current $PM_{2.5}$ exposure across the U.S. may be an important environmental factor influencing patterns of structural brain development in childhood.

We did not observe associations of current childhood $PM_{2.5}$ exposure with assessments of neurocognitive performance. In this respect,

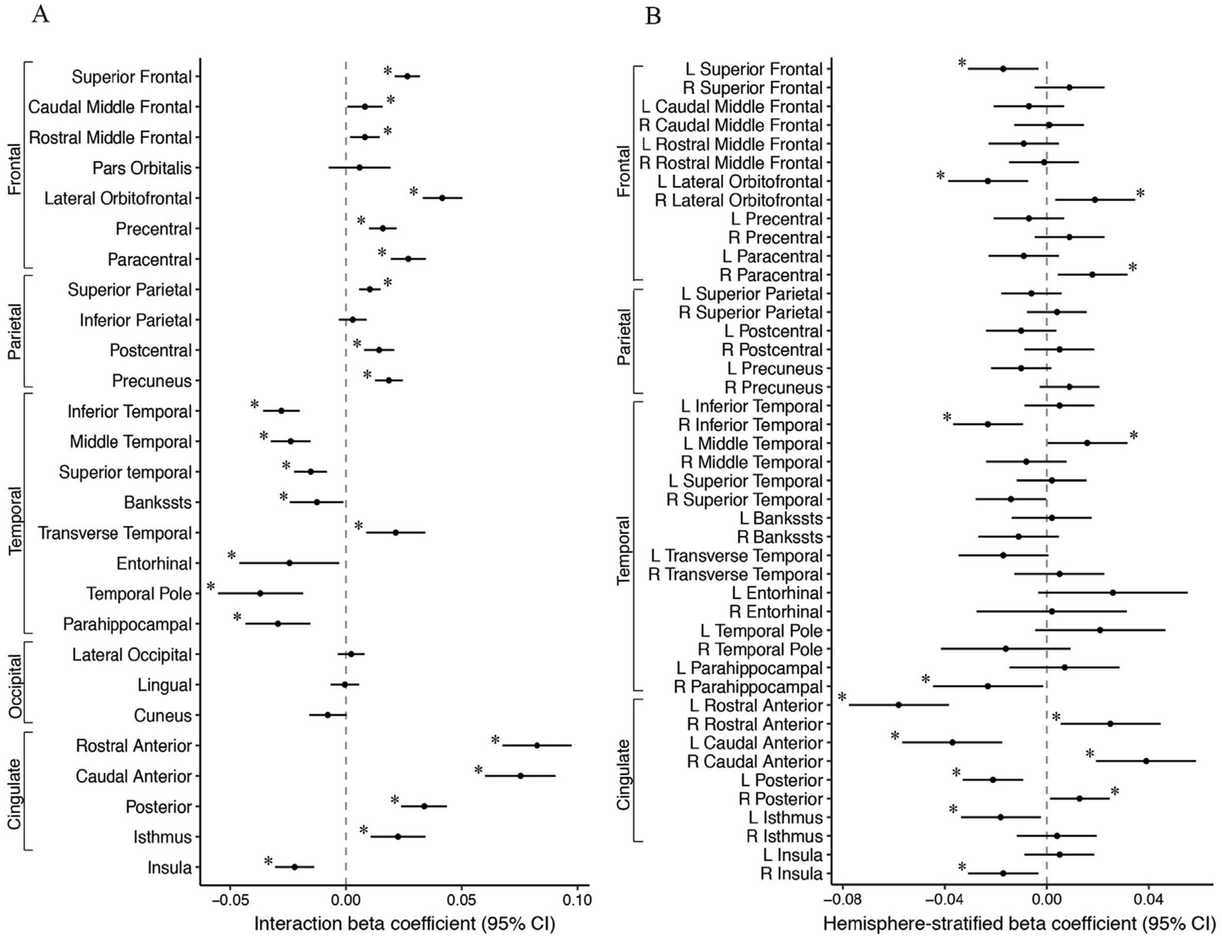

Fig. 3. A) $PM_{2.5}$-by-hemisphere interaction effect estimates; and B) Region-specific $PM_{2.5}$ effect estimates on cortical thickness (mm) that differed statistically by hemisphere in the ABCD Study. Footnote: A) Visualization of beta coefficients (95% CI) denoting regions associated with $PM_{2.5}$-by-hemisphere interaction presented with '*' for passed False Discovery Rate correction. B) Visualization of beta coefficients (95% CI) denoting regions associated stratified post-hoc analyses within a given hemisphere derived from significant $PM_{2.5}$-by-hemisphere interactions presented with '*' $p < 0.05$. $PM_{2.5}$ units are 5 μg/m^3.

our results are not consistent with previous studies showing that residential exposure to fine particulate matter or its constituents is associated with deficits in general intelligence (Chiu et al., 2016; Edwards et al., 2010; Perera et al., 2009; Wang et al., 2017) and poorer cognitive performance (Chiu et al., 2016). These differences between studies may be a function of exposure heterogeneity, type of exposure assessment, geographical location, sensitivity of cognitive tests implemented, or differences in study design. For instance, a number of studies focused on PAHs, a specific component of $PM_{2.5}$ (Edwards et al., 2010; Perera et al., 2009). The two studies assessing childhood $PM_{2.5}$ exposure and cognitive outcomes conducted in the U.S. (Perera et al., 2009; Wang et al., 2017) had small sample size, geographical/spatial coverage

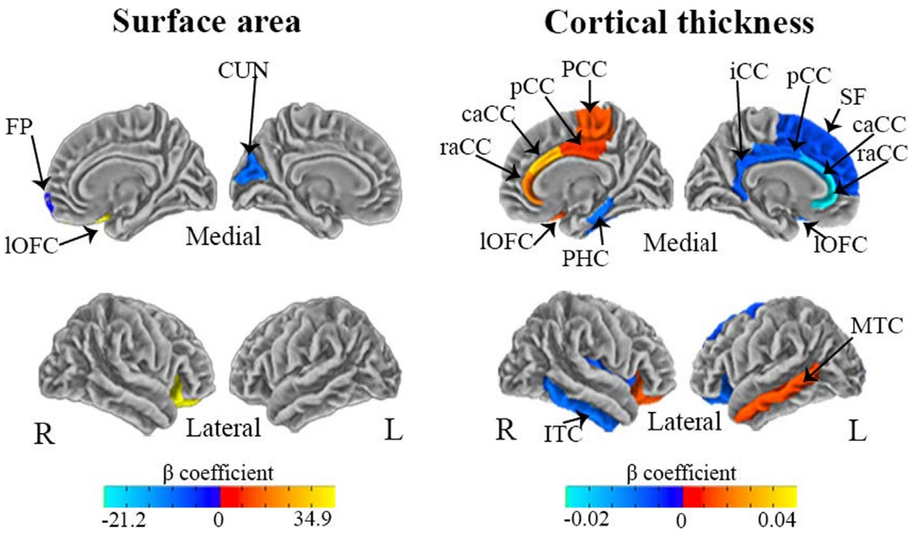

Fig. 4. Hemispheric-specific differences in regional effects of $PM_{2.5}$ exposure on surface area and cortical thickness in the ABCD Study. Visualization of beta coefficients denoting regions significantly associated with $PM_{2.5}$ (using a fixed increment of 5 μg/m^3) within a given hemisphere based on stratified post-hoc analyses (P-values at $p < 0.05$), including CUN: Cuneus; lOFC: Lateral Orbitofrontal; FP: Frontal Pole; SF: Superior Frontal; lOFC: Lateral Orbitofrontal; raCC: Rostral Anterior Cingulate; caCC: Caudal Anterior Cingulate; pCC: Posterior Cingulate; iCC: Isthmus Cingulate; PCC: Paracentral; ITC: Inferior Temporal; MTC: Middle Temporal; PHC: Parahippocampal. Negative associations are presented in dark-light blue and positive associations are presented in red-yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

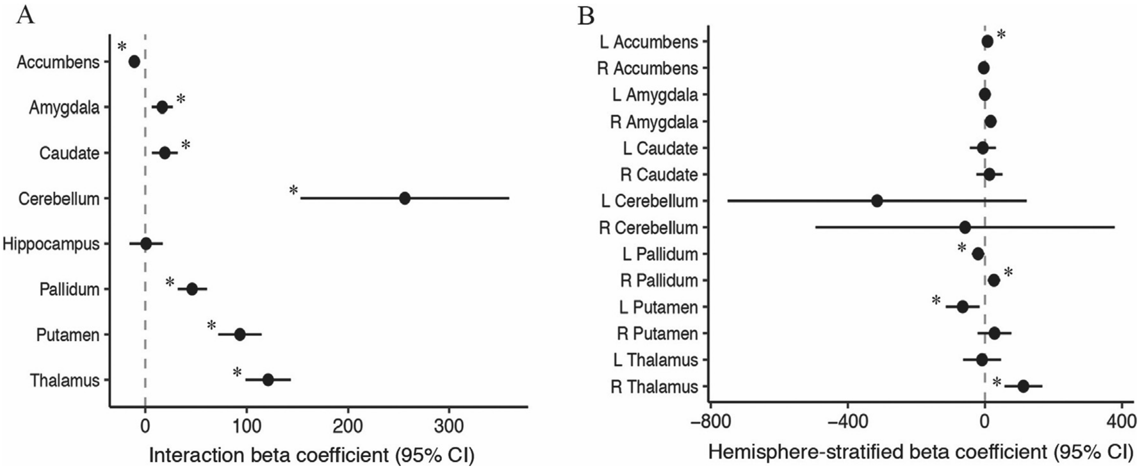

Fig. 5. A) $PM_{2.5}$-by-hemisphere interaction effect estimates and; B) Region-specific $PM_{2.5}$ effect estimates on cerebellum and subcortical volumes (mm^3) that differed statistically by hemisphere in the ABCD Study. Footnote: A) Visualization of beta coefficients (95% CI) denoting regions associated with $PM_{2.5}$-by-hemisphere interaction presented with '*' for passed False Discovery Rate correction. B) Visualization of beta coefficients (95% CI) denoting regions associated stratified post-hoc analyses within a given hemisphere derived from significant $PM_{2.5}$-by-hemisphere interactions presented with '*' $p < 0.05$. $PM_{2.5}$ units are 5 μg/m^3.

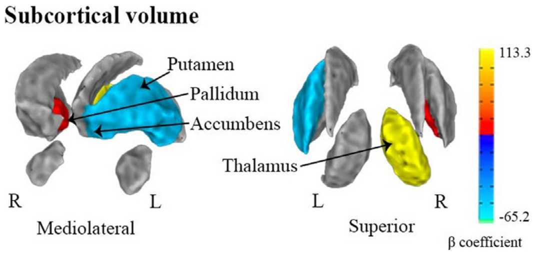

Fig. 6. Hemispheric-specific differences in regional effects of $PM_{2.5}$ exposure on subcortical volumes (mm^3) in the ABCD Study. Visualization of beta coefficients denoting regions of subcortical volumes significantly associated with $PM_{2.5}$ (using a fixed increment of 5 μg/m^3) within a given hemisphere based on stratified post-hoc analyses (P-values at $p < 0.05$). Negative associations are presented in dark-light blue and positive associations are presented in red-yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Annual $PM_{2.5}$ average and global measures of whole brain estimates in the ABCD Study.

ROI	Coefficients	CI (95%)		P-value
Total Cortical Surface area	276.6	−1080.0	1633.1	0.689
Mean Cortical Thickness	−0.004	−0.013	0.006	0.457
Whole Brain Volume	669.5	−3056.5	4395.4	0.725
Subcortical Gray Matter Volume	71.4	−184.0	326.8	0.583
Cerebrospinal Fluid Volume	−2.6	−20.2	15.0	0.771
Intracranial Volume	1676.5	−8846.2	12199.1	0.755
All Ventricles Volume	−192.3	−679.5	294.9	0.439
Lateral Ventricles Volume	−219.9	−686.3	246.5	0.355
Cerebral White Matter Volume	1256.2	−871.1	3383.5	0.247

ROI, Region of Interest; β, Beta coefficient; CI, Confidence Interval.
Note: The models are based on main effects of $PM_{2.5}$. All models were adjusted for age, sex, ethnicity, neighborhood quality, parental higher education, total family income, parental employment status, imaging device manufacturer, handedness and intracranial volume for volumetric measures, including random intercepts for ABCD site and familial relationship (participants belonging to the same family). Models were scaled for $PM_{2.5}$ using a fixed increment of 5 μg/m^3.

limited to cities (New York, Southern California), restricted sociocultural backgrounds (ethnic minorities) and/or higher exposed populations that could possibly explain observed associations attributable to unmeasured or residual confounding. Notwithstanding absence of measureable neuroperformance deficits, the observed alterations in brain structure found in the present study may still have important clinical relevance and public health implications. Specifically, these structural alterations could be early biomarkers of neurocognitive impairments, or other unfavorable neurological outcomes, that may develop over time. Specifically, recent neuroscience has identified the need to understand how individual differences in brain maturation contribute to vulnerability (Foulkes and Blakemore, 2018); trajectories of brain development at either extreme (reduced and/or augmented structural brain development via over or under pruning) may be linked to various cognitive and mental health problems (Gogtay and Thompson, 2010). From childhood to adulthood, individuals typically show a ~1 mm change in gray matter (Tamnes et al., 2017) with about ~0.021 mm/year seen during childhood (Zhou et al., 2015). In the current study an increase of 5-μg/m^3 was associated with differences in cortical thickness on the magnitude ranging from 0.01 to 0.04 mm, suggesting that continual exposure to $PM_{2.5}$ during childhood and adolescence could substantially impact an individual's brain growth trajectories with potentially lifelong consequences.

The study has several strengths, including a large, diverse sample with air pollution estimates at the individual level with high spatiotemporal precision (1-km^2 resolution) (Di et al., 2019), and the ability to adjust for important demographic and socio-economic confounders. This unique sample provided us with complete structural evaluation of MRI measurements of cortical thickness, surface area, and subcortical volume in a regional fashion as well as whole-brain assessments and explored a critical time window of children's brain maturation when dynamic changes accompany cortical development. However, a few limitations should be noted. The cross-sectional design is a limitation to causal inference, especially since brain maturation is an ongoing developmental process. Future research is needed to determine the impact of $PM_{2.5}$ exposure on the subsequent maturation of brain regions during the transition period from early childhood to adolescence, as these prospectively collected data become available through ABCD or other cohorts. As the ABCD dataset does not currently include $PM_{2.5}$ estimates for prenatal and earlier life residential addresses, we were not able to assess the role of prenatal $PM_{2.5}$ exposure in brain structure and function. Once lifetime address history has been collected (which is planned for follow-up visits in the ABCD cohort), it will be a priority to assess early life PM associations with brain health. The ABCD study enrollment process was dynamically monitored to ensure the study met target sex, socioeconomic, ethnic, and racial diversity (Garavan et al., 2018). However, participation was limited to the 21 study sites, which may

Table 3
Annual $PM_{2.5}$ average exposure and neurocognitive performance in the ABCD Study.

NIH Toolbox Score	Coefficients	CI (95%)		P-value
List Sorting Working Memory Test	−0.2	−1.2	0.9	0.76
Flanker Inhibitory Control and Attention Test	0.7	−0.1	1.6	0.09
Dimensional Change Card Sort Test	0.2	−0.6	1.0	0.63
Picture Vocabulary Test	−0.1	−0.8	0.5	0.67
Oral Reading Recognition Test	0.3	−0.3	1.0	0.282
Picture Sequence Memory Test	−0.71	−1.7	0.3	0.175
Pattern Comparison Processing Speed Test	−1.1	−2.4	0.3	0.117
Total Cognition Composite	−0.1	−0.8	0.7	0.85
Crystallized Cognition Composite	0.1	−0.5	0.7	0.66
Fluid Cognition Composite	−0.3	−1.2	0.6	0.55

β, Beta coefficient; CI, Confidence Interval.
Note: The models are based on main effects of $PM_{2.5}$. All models were adjusted for age, sex, ethnicity, neighborhood quality, parental higher education, total family income, parental employment status, including random intercepts for ABCD site and familial relationship (participants belonging to the same family). Models were scaled for $PM_{2.5}$ using a fixed increment of 5 μg/m^3.

contribute to ecological confounding effects. The current study was also limited in exposure assessment as it did not include personal, home, or school-based measures of air pollution using real-time monitors. In addition, the ABCD dataset does not currently contain estimates of other regional pollutants at the 1-km^2 resolution or $PM_{2.5}$ constituents (for example polyaromatic hydrocarbons, elemental carbon, or metals), or the near-roadway PM mixture that may be more toxic than mass alone, and may vary across the participating study sites. However, in sensitivity analyses $PM_{2.5}$ effect estimates did not vary substantially across study site locations. Previous studies have suggested $PM_{2.5}$ findings may be driven by traffic-related pollution (Pujol et al., 2016a; Sunyer et al., 2015, 2017). However, our results remained robust to adjustment for distance to major roadway, as well as for population density. Distance to major roadway is only a proxy for near-roadway exposure. Better indicators of near-roadway air pollution exposure and of exposure to $PM_{2.5}$ constituents are needed to assess their effects.

5. Conclusions

The current study found associations between childhood brain structure and $PM_{2.5}$ exposure, even at levels of exposure below the current standard. While progress has been made in improving air quality, our findings indicate that additional research is needed to understand the long-term consequences of neurodevelopmental effects of air pollution at levels children are currently experiencing across the U.S.

CRediT authorship contribution statement

Dora Cserbik: Formal analysis, Writing - original draft, Validation, Visualization. **Jiu-Chiuan Chen:** Conceptualization, Supervision, Writing - review & editing. **Rob McConnell:** Methodology, Writing - review & editing. **Kiros Berhane:** Methodology, Writing - review & editing. **Elizabeth R. Sowell:** Investigation, Writing - review & editing. **Joel Schwartz:** Methodology, Resources, Writing - review & editing. **Daniel A. Hackman:** Methodology, Writing - review & editing. **Eric Kan:** Data curation. **Chun C. Fan:** Methodology, Data curation. **Megan M. Herting:** Funding acquisition, Conceptualization, Methodology, Supervision, Project administration, Writing - original draft.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105933.

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