Ambient Pollution Components and Sources Associated with Hippocampal Architecture and Memory in Pre-Adolescents

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Abstract

Background: Ambient air pollution poses significant risks to brain health. Hippocampal structure and function are particularly vulnerable, yet the extent to which they are associated with air pollution in children remains unclear. We therefore conducted multi-pollutant mixture analyses to examine how air pollution influences hippocampal architecture and memory performance in late childhood.

Methods: We used partial least squares correlation to explore cross-sectional associations between fifteen $PM_{2.5}$ components, six $PM_{2.5}$ source factors, NO_2, and ozone exposures, and measures of hippocampal microstructure and volume in children aged 9-11 years (n = 7,940) We adjusted for demographic, socioeconomic, and neuroimaging confounds. We also tested whether air pollutants were associated with hippocampal-dependent list-learning memory performance to examine functional implications of air pollution exposure. Shared variance refers to the proportion of total covariance between variable sets captured by each latent dimension in the multivariate relationship.

Findings: In the first latent dimension, greater exposure to organic carbon and ozone was associated with differential hippocampal diffusion (72% of shared variance), whereas the second latent dimension linked elemental carbon and iron to hippocampal diffusion (24% of shared variance). Source-based analyses identified biomass burning and traffic pollution as key contributors (61% and 32% variance, respectively). Volumetric analyses revealed higher copper and zinc exposure correlated with smaller hippocampal subregion volumes (left head, right body, tail; 77% variance), whereas lower nickel levels correlated with smaller right head volume (12% variance). Higher industrial and traffic pollutants were also associated with smaller hippocampal volumes (75% variance). We found two latent dimensions (67% and 23% variance, respectively) showing poorer learning, immediate recall, and mnemonic interference performance linked to higher calcium, elemental carbon, and zinc, and organic carbon, alongside lower copper exposure. Finally, hippocampal diffusion (higher free water/lower hindered extracellular diffusion; 83% variance) and smaller tail volumes (96% variance) were linked to poorer RAVLT recall.

Interpretation: These results underscore the complex relationship between air pollution exposure and hippocampal architecture and cautions that such structural changes may either presage or reflect subtle differences in neurocomputational mechanisms associated with learning and memory performance in children.

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Keywords: hippocampus, learning and memory, air pollution, neurotoxicants, longitudinal axis

Research in Context

Evidence before this study

Using PubMed, we conducted a MeSH and text keyword search for air pollution (e.g., “Air Pollution” OR “Air Pollutant” OR “Air Pollutants” OR “Particulate Matter”) and structural MRI (“magnetic resonance image” OR “magnetic resonance images” OR “magnetic resonance imaging” OR “MRI”) among children and adolescents (<24 years-old), published until January 15, 2025, without language restrictions. Existing studies primarily focused on single pollutants or total hippocampal volume across various populations (children, adults, animals), leaving significant knowledge gaps regarding the specific impacts of $PM_{2.5}$ components and their sources on hippocampal structure during childhood. Previous research on hippocampal structure also generally lacked detailed exploration of hippocampal subregions and rarely employed advanced neuroimaging sensitive to microstructural changes. Existing evidence was inconsistent due to methodological differences and variations in pollutant types and exposure periods.

Added value of this study

This study significantly advances our understanding by explicitly linking specific $PM_{2.5}$ components and their source-specific mixtures to detailed hippocampal architecture differences in late childhood. Using advanced neuroimaging (restriction spectrum imaging and volumetric analyses), we identified precise microstructural and volumetric changes associated with exposure to organic carbon, metals, ozone, and pollutant sources such as biomass burning, traffic, industrial emissions, and agricultural pollution. Importantly, our findings also showed associations between $PM_{2.5}$ components and episodic memory performance, highlighting the neurodevelopmental impacts of complex air pollutant mixtures for the life course. This evidence underscores the necessity of targeting source-specific air pollution (e.g., biomass burning, traffic, and industrial emissions) during critical developmental windows to safeguard lifelong cognitive health.

Implications of all the available evidence

Factors in childhood profoundly shape the trajectory of neurocognitive aging, including risks for dementia and other age-related diseases. Our results support the concept that early-life environmental exposures significantly influence brain health, including cognitive function, and emphasize that preventive strategies must begin early. Future longitudinal studies should therefore address how childhood air pollution exposures, with particular focus on which sources, influence subsequent cognitive trajectories, neurodegeneration, and overall brain health in adulthood and older age. This approach will provide critical insights for targeted interventions and policymaking aimed at reducing early-life environmental exposures and promoting healthy aging from childhood into adulthood.

Introduction

Ambient air pollution is a pressing challenge to human health, with neurotoxic effects that pose significant risks across the lifespan (1–3). Particulate matter with an aerodynamic diameter of 2.5μm or less ($PM_{2.5}$) consists of a complex mixture of tiny particles and liquid droplets composed of organic compounds, metals, nitrates, and sulfates. Additionally, major contributors to $PM_{2.5}$ include sources such as biomass burning, which is responsible for approximately 20% of air pollution exposure in the United States (U.S.)(4). $PM_{2.5}$ and other regulated pollutants, including nitrogen dioxide and ozone, have been linked to structural and functional changes in the brain and are associated with an increased risk of cognitive decline and dementia later in life(5). Identifying how air pollution is related to the development of key neural structures critical for memory and cognition, like the hippocampus(6) in childhood is thus essential for understanding the foundations of cognitive health across the lifespan(7). Moreover, studying how air pollution may impact hippocampal architecture and cognition early in life may present a key opportunity to focus public health strategies toward the prevention of age-related cognitive disorders(8).

The hippocampus is highly susceptible to environmental insults, including air pollution. In rodents, exposure to ultrafine particles (UFP) and $PM_{2.5}$ impairs hippocampal neurogenesis, increased microglial responsivity, compromised CA1 blood-brain barrier permeability, and induced deficits in hippocampal-dependent learning and memory(9,10). In humans, the detrimental effects of air pollution on the hippocampus during adulthood are increasingly recognized(7); however, air pollution's impact during childhood and adolescence remains unclear. Prenatal exposure to air pollution was found to be associated with smaller hippocampal volumes in late childhood(11) and with delayed hippocampal growth from 4-10-years-old(12). Concurrent prenatal exposures to decreased NO_2 and increased PM_{10} were also found to be associated with smaller hippocampal volume in infancy(13). Using a single-pollutant model, our previous work showed that $PM_{2.5}$ exposure was not related to hippocampal volume(14). These discrepant findings may be due to timing or the heterogeneous nature of PM, highlighting the urgent need to determine how specific PM components and sources affect hippocampal architecture. Additionally, there is a critical gap in our understanding of how air pollution exposure affects hippocampal-dependent learning and memory in childhood. By moving beyond single exposure to multi-pollutant and source-specific mixture models(15), we can better capture complex relationships and more accurately determine the aggregate versus individual impacts of air pollution on hippocampal architecture and behavior. The specific impacts of an admixture of $PM_{2.5}$ components or their sources on hippocampal microstructure thus remain largely unexplored. This gap underscores the need for more granular approaches to understand how environmental exposures shape the hippocampus.

In this study, we assessed associations between hippocampal structure and $PM_{2.5}$ constituent components and sources alongside NO_2 and O_3, in a large cohort of 9-10-year-olds from the U.S. Adolescent Brain Cognitive Development^{SM} (ABCD) Study. In investigating the hippocampus, we implement two complementary imaging approaches that allow us to disentangle the effects of air pollution on hippocampal macro- and microstructure. Specifically, we examine hippocampus volume among its multiple subregions with distinct functions that are organized, anterior to posterior, along its long (head, body, tail) axis(16). In addition, we leverage the advanced diffusion-weighted imaging technique known as restriction spectrum imaging (RSI). This approach offers enhanced resolution in exploring iso- vs. anisotropic water diffusion within tissue compartments(17) and is sensitive to cellular features such as size, density, and the organization of axons and dendrites(18). We hypothesized that higher air pollution exposure would be associated with distinct hippocampal microstructure patterns (e.g., lower cellularity or cell density)

and smaller subregional volumes. We used partial least squares correlation (PLSC) to test how annual exposure to fifteen $PM_{2.5}$ criterion components, NO_2, and O_3 were associated with hippocampal structure. Moreover, given that these components stem from 6 sources (e.g., traffic)(19), we conducted a secondary PLSC analysis to identify whether we could attribute these components to specific $PM_{2.5}$ sources and relate them to hippocampus structure. We next assessed the relationships between air pollution and hippocampal-dependent memory. Finally, we examined how hippocampal macro- and microstructure was associated with learning and memory performance. By leveraging a multi-pollutant, source-specific framework, we aimed to capture the complex environmental burden of air pollution and its impact on the hippocampus in late childhood.

Methods

We analyzed cross-sectional data from children aged 9-10 years old, collected across 21 study sites from the U.S. ABCD Study®(20) using the 5.1 release (2023) (doi:10.15154/8873-zj65, NDA Study; n = 11,868). ABCD Study exclusion criteria included: lacking English proficiency, having severe sensory, neurological, medical, or intellectual limitations, or being unable to complete an MRI scan(18). The Institutional Review Board (IRB) and Human Research Protections Programs (HRRP) at the University of California, San Diego (UCSD) which oversees all experimental and consent procedures, and local IRB board at each ABCD site, provided approval. Written assent and consent was provided by each participant and legal guardian, respectively(20,21). All analyses described below, excluding the hippocampal long-axis volumes, were pre-processed and tabulated by the Data Analysis, Informatics, and Resource Center at UCSD. We analyzed a subset of the ABCD Study, applying additional exclusion criteria including only one child per family, available variables of interest, and MRI quality (e.g., lower motion, no incidental findings). This resulted in a final sample of 7,940 participants for the RSI and 6,795 for subregion analyses (Table 1; Supplemental Figure 1). This discrepancy was related to additional quality control for hippocampal subregions.

Ambient Air Pollution Estimates and $PM_{2.5}$ Sources

We assigned 2016 annual average air pollution exposure—$PM_{2.5}$ (μg/m³), NO_2 (ppb), and 8-hour maximum ground-level O_3 (ppb)—to each child's primary residence during the initial ABCD Study visits (2016-2018)(22). Hybrid spatiotemporal models combining land-use regression, satellite-based aerosol optical depth, and chemical transport were used to derive estimates at a 1-km² resolution(23–25). Monthly estimates of $PM_{2.5}$ constituent components were calculated at a spatial resolution of 50m² using similar spatiotemporal models. This includes ammonium (NH_4^+), bromine (Br), calcium (Ca), copper (Cu), elemental carbon (EC), iron (Fe), lead (Pb), nickel (Ni), nitrate (NO_3^-), organic carbon (OC), potassium (K), silicon (Si), sulfate (SO_4^{2-}), vanadium (V), and zinc (Zn)(26,27). As previously published, six $PM_{2.5}$ source factors were derived from positive matrix factorization (PMF) with PM sources being primarily driven by the following: crustal materials (V, Si, Ca), secondary ammonium sulfates (SO_4^{2-}, NH_4^+, V), biomass burning (Br, K, OC), traffic emissions (Fe, Cu, EC), secondary ammonium nitrates (NH_4^+, NO_3^-, SO_4^{2-}), and industrial fuel burning (Pb, Zn, Ni) (Figure 1A)(19). Supplemental figures 2 and 3 provide correlograms of components, sources, NO_2, and O_3.

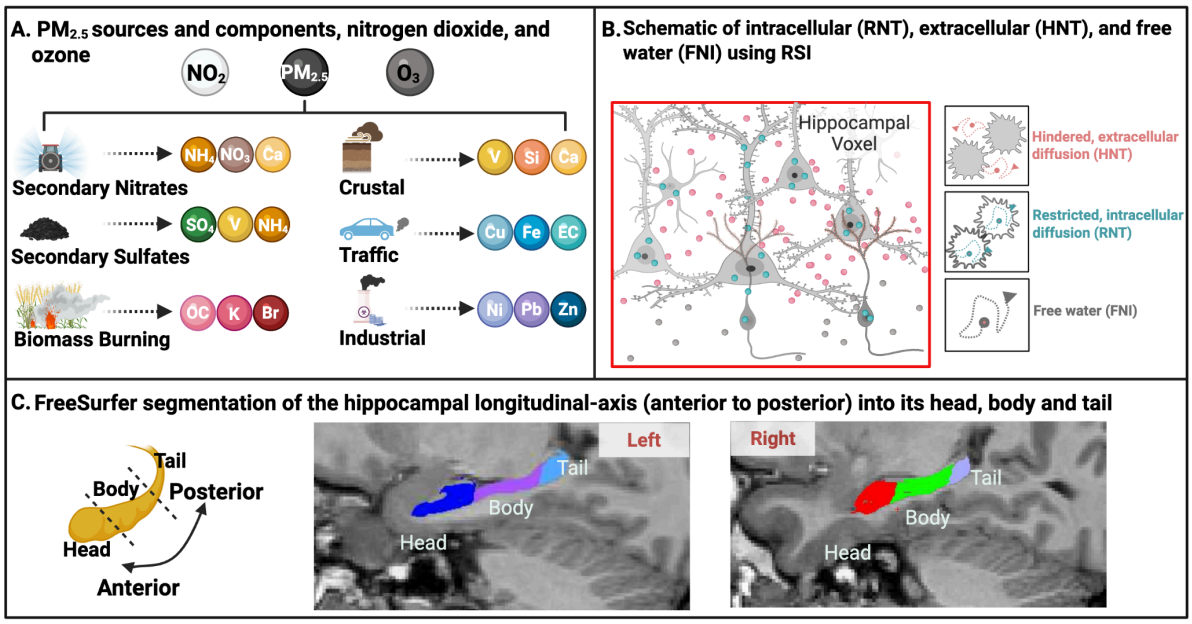
Diffusion Weighted Imaging (DWI): MRI Acquisition and Processing

The DWI acquisition protocols for the ABCD Study have been extensively described(28,29). Each acquisition included a fieldmap scan for B0 distortion correction, included a voxel size of 1.7mm isotropic and employed echo planar imaging(30,31). A multi-shell diffusion acquisition protocol included 7 b=0 frames and 96 total diffusion directions at 4 b-values, and underwent distortion correction, bias field correction, motion correction, and manual and automated quality control(29). RSI–a multicompartmental, biophysical modeling technique–was implemented using all 96 DWI directions collected, providing detailed information about the intracellular and extracellular compartments of the brain(17). RSI model outputs include normalized measures, all of which are unitless on a scale of 0 to 1 including (restricted normalized total signal fraction (RNT; intracellular compartment); hindered normalized total signal fraction (HNT; extracellular compartment; and free normalized isotropic signal fraction (FNI) which represents free water movement and cerebrospinal fluid)(18). Together, these measures let us infer how densely cells are packed and how freely fluid moves in the hippocampus, offering clues about its health and function. Left and right RNT, HNT, and FNI were used in our analyses (Figure 1B).

Hippocampal Subfields: Acquisition and Processing

A harmonized protocol was used across sites with either a Siemens, Phillips, or GE 3T MRI scanner for MRI acquisition(28,29), including motion compliance and real-time motion correction. T1-weighted and T2-weighted images were acquired using a magnetization-prepared rapid acquisition gradient echo and fast spin echo sequence with variable flip angle, respectively(28). Segmentation of hippocampal subregions was completed using T1 and T2 images by co-author J.G.P. with Freesurfer v7.0's automated hippocampal segmentation tool(32,33). A subset of these data have been previously used to determine hippocampal genetic correlates along its long-axis(34). Here, we examine left and right hippocampal head, body, and tail volumes (mm^3) (Figure 1C).

Figure 1. Schematic of primary exposures and outcomes for air pollution and hippocampal analyses. **A.** $PM_{2.5}$ components and their sources, NO_2, and O_3 represent our primary exposures. **B.** Hippocampal microstructure as measured by restriction spectrum imaging (RSI), including voxel level estimates of total hindered extracellular diffusion (HNT), total restricted intracellular diffusion (RNT), and free water (FNI) **C.** Visual reference of hippocampal segmentation into head, body and tail along the hippocampal long-axis using FreeSurfer. Abbreviations: Br: bromine, Ca: calcium, Cu: copper, EC: elemental carbon, Fe: iron, K: potassium, NH_4: ammonium, Ni: nickel, NO_2: nitrogen dioxide, NO_3: nitrate, O_3: ozone, OC: organic carbon, Pb: lead, $PM_{2.5}$: particulate matter, Si: silicon, SO_4^{2-}: sulfate, V: vanadium, Zn: zinc



Rey Auditory Verbal Learning Test (RAVLT)

Learning and memory was measured using the Rey Auditory Verbal Learning Test (RAVLT)(35). The RAVLT evaluates verbal memory by presenting a list of 15 unrelated words (List A) over five learning trials, with participants recalling as many words as possible after each trial. Following these trials, a second list of 15 words (List B) is introduced as a proactive mnemonic interference task, after which participants immediately recall List A. Delayed recall of List A was then assessed 20–30 minutes later. Our primary outcomes included: learning (the difference in words recalled between Trial 5 and Trial 1), proactive mnemonic interference (total words recalled from List B), immediate recall (total words recalled from List A immediately after interference), and delayed recall (total words recalled from List A after the delay).

Statistical Analyses

We conducted all statistical analyses using R(v.4.4.0) and used the ExPosition and TExPosition packages(36). We examined the relationships between air pollution exposure and hippocampal metrics using a series of Partial Least Squares Correlations (PLSC)(37,38). PLSC is a multivariate technique that identifies latent patterns of covariance between interrelated pollutants and measures of hippocampal structure. This method is particularly well-suited for our study, given the high intercorrelations among both our exposure, brain, and cognitive variables of interest (Supplementary Figures 2-3). PLSC analyses require complete-case data, thus we removed missing data before conducting multiple linear regression analyses to obtain residualized hippocampal, air pollution, and learning and memory variables using the *residuals()* function in *R*. To account for the higher pollution levels often found among structurally disadvantaged groups(39), we accounted for race/ethnicity, total household income in USD, highest household education, proximity to major roadways, and neighborhood safety (Table 1). We also controlled for individual differences by including each child's parent-reported sex at birth, handedness, and age. We further controlled for framewise displacement and intracranial volume for RSI and volume analyses, respectively. To mitigate variability introduced by imaging equipment and study sites, we included MRI scanner serial number (n = 29) and urbanicity. Next, we conducted 8 PLSC models using both hippocampal, air pollution, and cognitive residuals. Using bilateral RNT, HNT, FNI as a proxy for cellular density, we aimed to identify which pollutants are most strongly associated with differences in hippocampal microstructure. By examining hippocampal long-axis volumes we investigated subregion volumetric effects associated with air pollution exposure. Finally, to assess functional relevance, we examined the association between air pollution exposure and RAVLT performance and hippocampal volume and microstructure with RAVLT exposure. The component-based analyses helped to pinpoint the chemical constituents driving these associations, whereas the source-based analyses revealed the origins of $PM_{2.5}$ exposure. From PLSC, we identified significant latent dimensions capturing relationships (total shared variance) between the two matrices (e.g., air pollutants and hippocampus outcomes). Shared variance refers to the proportion of total covariation between variable sets captured by a latent dimension, not the percent of the outcome explained as in univariate regression. Thus, the shared variance refers to the latent dimension summarizing the shared relationship between sets of variables.

We assessed the stability and significance of the identified PLSC loadings through permutation testing (10,000 times without replacement) which helped to identify the significant latent dimensions and determined the percentage of variance explained. Bootstrapping (10,000 iterations using *Boot4PLSC()*) was conducted to resample the data and recalculate the PLSC components, generating bootstrap ratios for each variable. PLSC does not allow for standard multiple comparison correction, however, bootstrapping reduces the chance of false positives. Bootstrapping and permutation testing rigorously evaluate the overall importance of each latent dimension and stability of individual variable contributions(38). Variables with bootstrap ratios

exceeding a threshold of ±2.5 (equivalent to $p < .01$) were considered significant contributors to the latent dimensions.

Results

The characteristics of the participant sample (n = 7,940 for microstructure and n = 6,795 for long axis volume) are detailed in Table 1. A comparison between our analytic sample and the broader ABCD Study cohort is provided in Supplemental Table 1. Participants are similar in terms of age, sex, race/ethnicity, and parental education and income. The descriptive statistics of the hippocampal microstructure and volume estimates are reported in Supplemental Table 2, whereas the $PM_{2.5}$ components, sources, NO_2, and O_3 are reported in Supplemental Table 3.

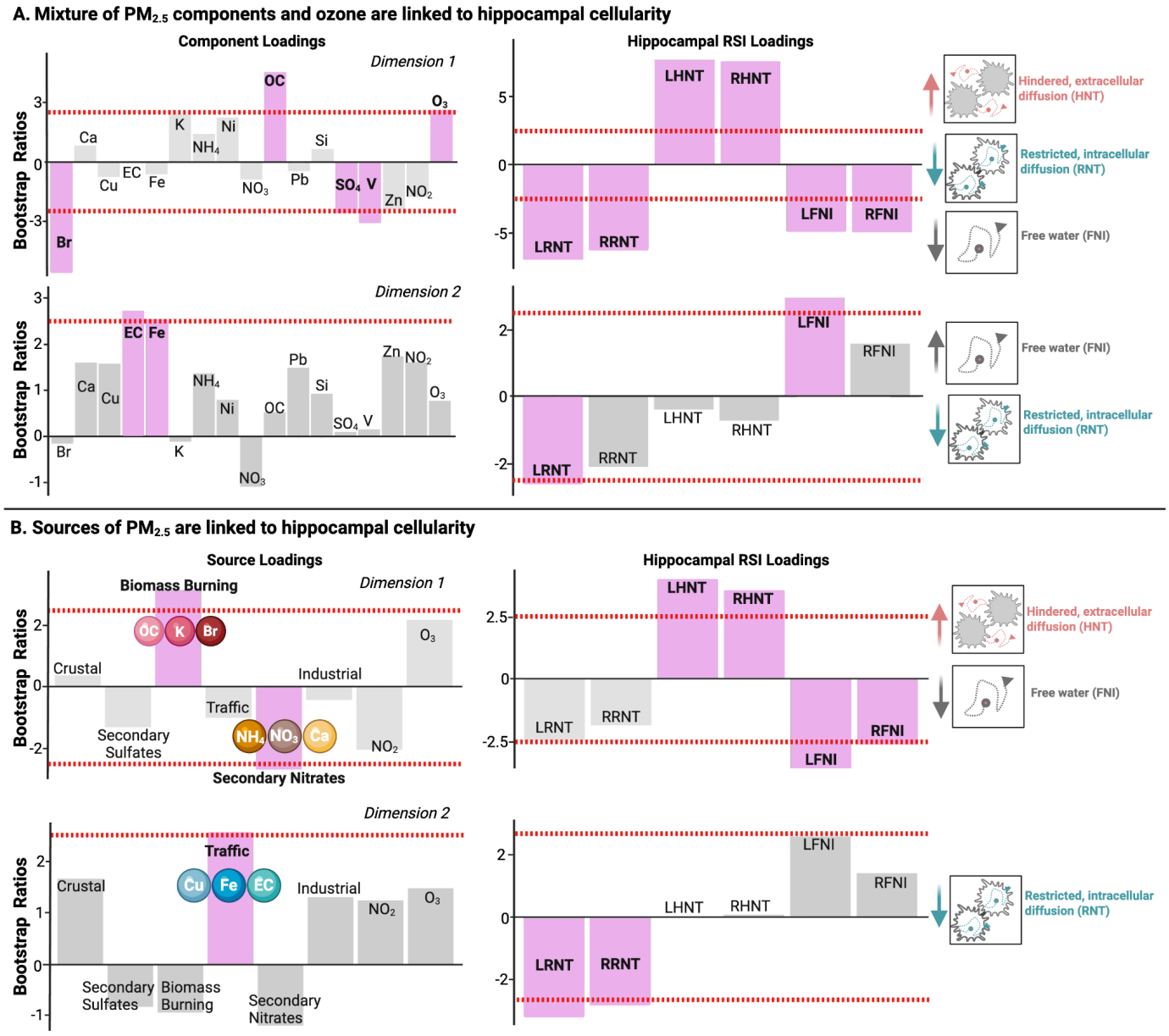
Table 1. Demographics and participant characteristics.

	Diffusion (N=7940)	**Head, Body, and Tail Volume (N=6795)**
Age (months)		
Mean (SD)	120 (± 7.4)	120 (± 7.4)
Assigned Sex at Birth		
Female	4114 (52 %)	3512 (52 %)
Male	3826 (48 %)	3283 (48 %)
Race & Ethnicity		
non-Hispanic white	4162 (52 %)	3719 (55 %)
non-Hispanic Black	1110 (14 %)	882 (13 %)
Hispanic	1676 (21 %)	1362 (20 %)
Asian/Other	992 (12 %)	832 (12 %)
Overall Income		
[<50K]	2108 (27 %)	1739 (26 %)
[≥50K and <100K]	2065 (26 %)	1826 (27 %)
[≥100K]	3103 (39 %)	2680 (39 %)
Don't know/Refuse to answer	664 (8 %)	550 (8 %)
Parental Highest Education		
< HS Diploma	382 (5 %)	272 (4 %)
HS Diploma/GED	729 (9 %)	574 (8 %)
Some College	2041 (26 %)	1762 (26 %)
Bachelor’s Degree	1999 (25 %)	1755 (26 %)
Post Graduate Degree	2781 (35 %)	2425 (36 %)
Missing/Refused	8 (0 %)	7 (0 %)
MRI Manufacturer	nc	
GE Medical Systems	1870 (24 %)	1465 (22 %)
Philips Medical Systems	891 (11 %)	679 (10 %)
SIEMENS	5179 (65 %)	4651 (68 %)
Urban vs Rural		
Urbanized Area	7036 (89 %)	5978 (88 %)
Urban Clusters	242 (3 %)	221 (3 %)
Rural	662 (8 %)	596 (9 %)
Neighborhood Safety		
Mean (SD)	3.9 (± 0.97)	3.9 (± 0.95)

Association between air pollution and hippocampal microstructure

PLSC analysis investigating the relationship between a mixture of $PM_{2.5}$ components and sources, NO_2, and O_3 (Figure 1A) and their association with hippocampal microstructure (left and right RNT, HNT, and FNI) (Figure 1B) revealed two significant latent dimensions explaining 72% and 24% of the shared variance (Supplemental Figure 4), respectively. The first latent dimension showed that exposures to relatively higher concentrations of OC and O_3 co-occurring with relatively lower levels of Br, SO_4, and V were associated with greater bilateral extracellular diffusion (i.e., RNT) but less bilateral intracellular and free water diffusion (i.e., RNT, FNI) (Figure 2A). In the second latent dimension, higher exposure to EC and Fe was associated with lower left hemisphere intracellular diffusion (i.e., RNT) and higher left hemisphere free water (i.e., FNI). We found a similar pattern of covariation between $PM_{2.5}$ sources with hippocampal microstructure with two significant latent dimensions accounting for 61% and 32% of the shared variance (Supplemental Figure 5). Co-exposure to higher levels of biomass burning (OC, Br, K) alongside lower levels of secondary nitrates (NH_4, NO_3, Ca) was associated with higher extracellular diffusion (i.e., RNT) but lower free water (i.e., FNI) in both hemispheres, whereas higher levels of traffic (Cu, Fe, EC) were associated with lower intracellular diffusion (i.e., RNT) (Figure 2B).

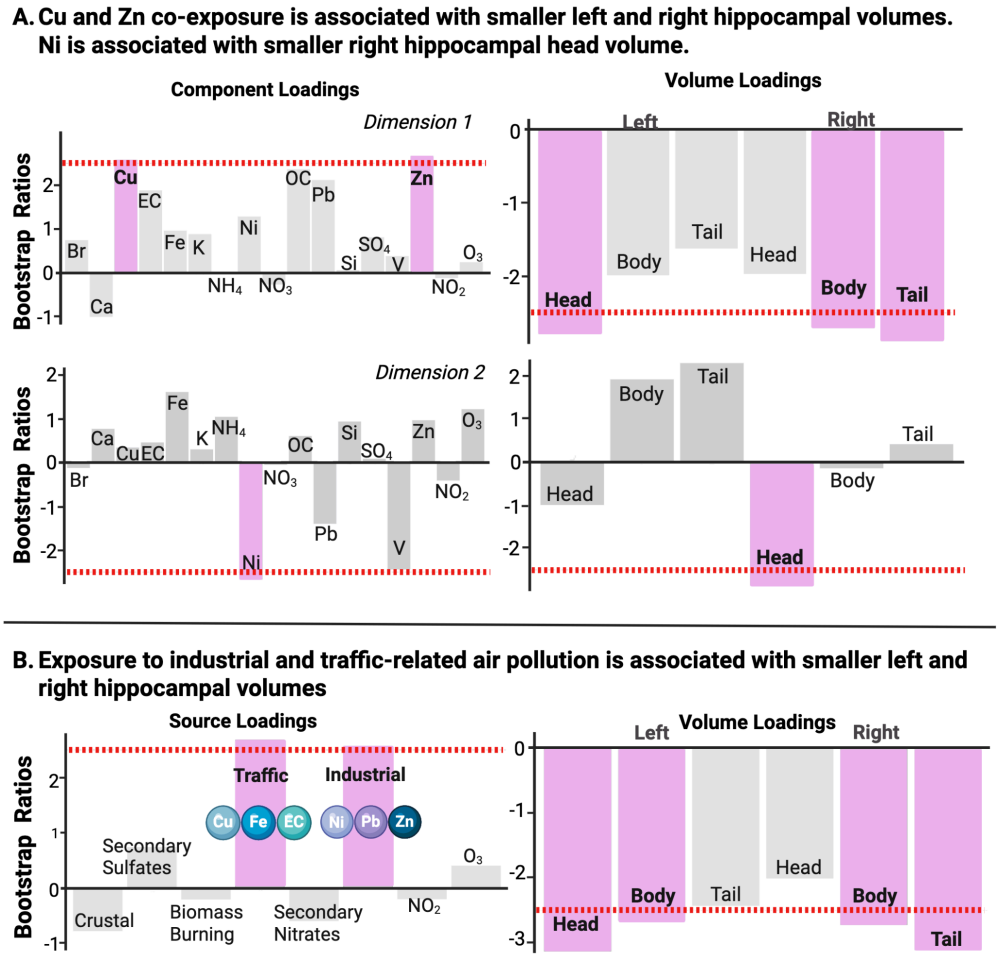
Figure 2. Associations between hippocampal microstructure and air pollution exposure in children ages 9-11 years (n = 7940). A. $PM_{2.5}$ components based analyses revealed greater OC and O_3 alongside lower Br, S, and V, and greater EC and Fe exposure is associated with greater extracellular diffusion (HNT) and decreases in free water and intracellular (RNT) diffusion. **B.** Source based analyses showed greater biomass burning alongside lower secondary nitrate exposure and greater traffic-related exposure in the first and second latent dimensions was associated with increased HNT and decreases in FNI as well as decreases in RNT. Dashed red lines at ±2.5 indicate the bootstrapped thresholds for significance at $p < .01$. Abbreviations: Br: bromine, Ca: calcium, Cu: copper, EC: elemental carbon, Fe: iron, K: potassium, NH_4: ammonium, Ni: nickel, NO_2: nitrogen dioxide, NO_3: nitrate, O_3: ozone, OC: organic carbon, Pb: lead, $PM_{2.5}$: particulate matter, Si: silicon, SO_4^{2-}: sulfate, V: vanadium, Zn: zinc, RSI: restriction spectrum imaging; LRNT: left restricted normalized total fraction, RRNT: right restricted normalized total fraction, LHNT: left hindered normalized total fraction, RHNT: right hindered normalized total fraction, LFNI: left free normalized isotropic fraction, RFNI: right free normalized isotropic fraction.



Association between air pollution and volumes of the hippocampal head, body, and tail

There were two significant latent dimensions accounting for 75% and 14% of shared variance in the relationship between hippocampal volume and $PM_{2.5}$ components (Figure 3A; Supplemental Figure 6). In the first latent dimension, higher exposure Cu and Zn was associated with smaller volumes of left hippocampal head and right body and tail. In the second latent dimension, lower Ni exposure was associated with smaller right hippocampal head volume. The association between $PM_{2.5}$ sources and hippocampal volume revealed one significant latent dimension accounting for 77% of shared variance (Supplemental Figure 7). Exposure to higher levels of industrial and traffic-related air pollution was associated with smaller left hippocampal head and body and right hippocampal body and tail volume (Figure 3B).

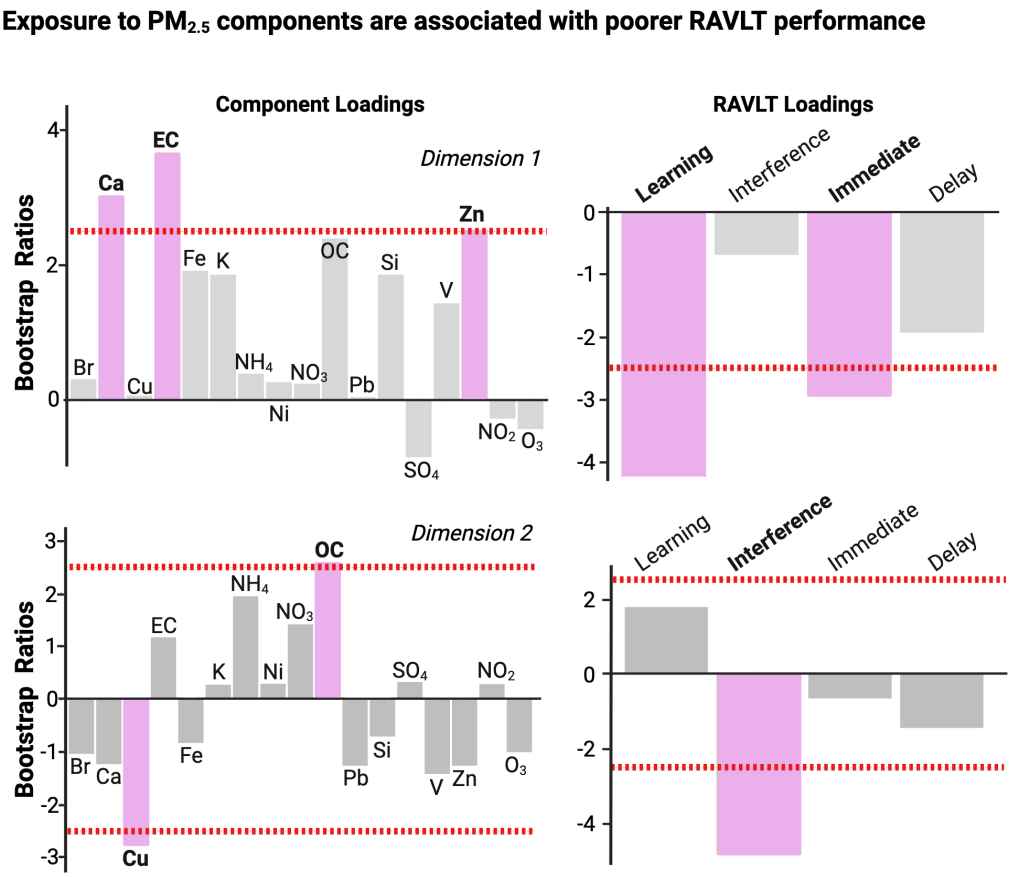
Figure 3. Associations between hippocampal long-axis volume and air pollution exposure in children ages 9-11 years (n = 6,795). **A.** In the first latent dimension, higher Cu and Zn exposure is associated with smaller left hippocampal head and right hippocampal tail. Lower Ni exposure is associated with smaller right hippocampal head. **B.** Exposure to industrial and traffic-related air pollution is associated with smaller left hippocampal head and body and right hipppocampal body and tail volume. Dashed red lines at ±2.5 indicate the bootstrapped thresholds for significance at $p < .01$. Abbreviations: Br: bromine, Ca: calcium, Cu: copper, EC: elemental carbon, Fe: iron, K: potassium, NH_4: ammonium, Ni: nickel, NO_2: nitrogen dioxide, NO_3: nitrate, O_3: ozone, OC: organic carbon, Pb: lead, $PM_{2.5}$: particulate matter, Si: silicon, SO4: sulfate, V: vanadium, Zn: zinc, RSI: restriction spectrum imaging; LRNT: left restricted normalized total fraction, RRNT: right restricted normalized total fraction, LHNT: left hindered normalized total fraction, RHNT: right hindered normalized total fraction, LFNI: left free normalized isotropic fraction, RFNI: right free normalized isotropic fraction



Exposure to $PM_{2.5}$ components are associated with poorer learning and memory performance.

There were two significant latent dimensions accounting for the shared variance (67% and 23 % variance) between $PM_{2.5}$ component exposure and RAVLT performance (Supplemental Figure 8). Specifically, in the first latent dimension higher Ca, EC, and Zn exposure was associated with poorer learning and immediate recall performance. In the second latent dimension higher organic carbon, alongside lower copper was associated with poorer proactive interference trial performance, indicating fewer recalled words (Figure 4). Additionally, source-based analyses identified two significant latent dimensions whereby air pollution exposure from sources was associated with poorer learning and memory (latent dimension one) and biomass burning was broadly associated with overall RAVLT performance (omnibus test $p = .004$); however bootstrap estimates indicated limited reliability of individual variable contributions to the overall model (Supplemental Fig 9).

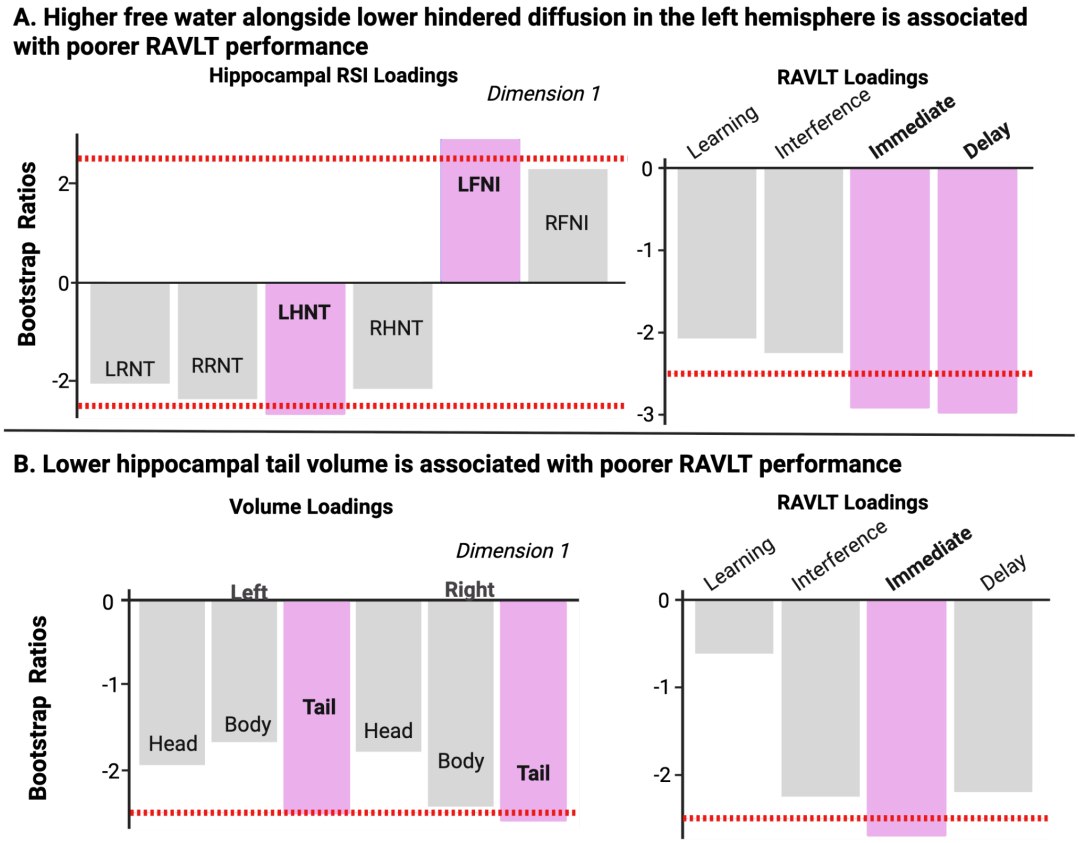
Figure 4. Associations between air pollution exposure and learning and memory performance in children ages 9-11 years (n = 7,699). **A.** In the first latent dimension, higher Ca, EC, and Zn exposure is associated with poorer learning and immediate recall performance. Higher OC, alongside lower Cu, is associated with poorer proactive mnemonic interference (RAVLT List B) performance (fewer List B words recalled after Trial 5). Dashed red lines at ±2.5 indicate the bootstrapped thresholds for significance at $p < .01$. Abbreviations: Br: bromine, Ca: calcium, Cu: copper, EC: elemental carbon, Fe: iron, K: potassium, NH_4: ammonium, Ni: nickel, NO_2: nitrogen dioxide, NO_3: nitrate, O_3: ozone, OC: organic carbon, Pb: lead, $PM_{2.5}$: particulate matter, Si: silicon, SO4: sulfate, V: vanadium, Zn: zinc, RAVLT: Rey Auditory Verbal Learning Test.



Hippocampal architecture is linked to learning and memory performance.

PLSC analysis showed one significant latent dimension explaining 83% of the shared variance between hippocampal diffusion and RAVLT performance (Supplemental Figure 10; Figure 5A). Higher free water alongside lower hindered extracellular diffusion in the left hemisphere was associated with poorer immediate and delayed recall performance. Additionally, there was one significant latent dimension that explained 96% of the shared variance between smaller left and right hippocampal tail volume and poor immediate recall performance (Supplemental Figure 11; Figure 5B).

Figure 5. Associations between hippocampal architecture and learning and memory performance in children ages 9-11 years (n = 7,699; 6,589). **A.** Higher free water alongside lower hindered water diffusion is linked to poorer immediate recall performance. **B.** Lower left and right hippocampal tail volume is linked to poorer immediate and delayed memory performance. Dashed red lines at ±2.5 indicate the bootstrapped thresholds for significance at $p < .01$. Abbreviations: RSI: restriction spectrum imaging; LRNT: left restricted normalized total fraction, RRNT: right restricted normalized total fraction, LHNT: left hindered normalized total fraction, RHNT: right hindered normalized total fraction, LFNI: left free normalized isotropic fraction, RFNI: right free normalized isotropic fraction, RAVLT: Rey Auditory Verbal Learning Test.



Discussion

This study investigated how individual $PM_{2.5}$ components and their sources are related to hippocampal structure and late-childhood learning and memory. We found that pollutants from biomass burning, secondary nitrates, industrial emissions, and traffic, as well as individual components, are distinctly related to hippocampal architecture and cognitive performance. OC consistently emerged as a key predictor of microstructural differences, with source analyses suggesting OC effects may stem from biomass burning exposure. Hippocampal volumes were particularly sensitive to metal exposures associated with metal-heavy industrial burning and traffic emissions. Additionally, we found that multiple $PM_{2.5}$ components were associated with poorer learning and memory performance, corresponding with structural analyses. Finally, differences in hippocampal architecture were associated with poorer RAVLT performance.

Our results underscore that relying solely on total $PM_{2.5}$ obscures unique links of specific pollutants and their sources to hippocampal health and learning and memory. Biomass burning, secondary nitrates, and traffic-related exposure was related to increased extracellular diffusion but reduced intracellular and free water diffusion, indicative of differences in cellular environments potentially involving dynamic processes such as neurogenesis, gliosis, or apoptosis(40,41) or indicate reduced neuron density. A recent study in male mice found that exposure to traffic-related UFPs was associated with decreased cell density(42) and $PM_{2.5}$ exposure induced reduced neurite density(9). Hippocampal neuronal atrophy and reduced neurite density, potentially driven by PM-induced inflammation, may decrease intracellular water movement and increase free-water movement, while responsive microglia and reactive astrocytes may generate extracellular changes that hinder diffusion. Within this study, metals, largely originating from industrial and traffic emissions, appear to exert pronounced effects on hippocampal architecture. Similarly, in our behavioral analyses, Cu and Zn were associated with hippocampal-dependent memory performance, albeit in separate latent dimensions. Emerging evidence suggests $PM_{2.5}$ metals can infiltrate the brain through multiple pathways—including direct translocation along the olfactory and trigeminal nerves(43), as well as systemic circulation via alveolar-capillary transfer in the lungs(44). These findings highlight the pervasive influence of air pollution on the hippocampus and raise questions regarding implications for lifespan hippocampal integrity.

Given the hippocampus's fixture in neurodegenerative diseases(45,46), it is crucial to take a life course approach by investigating early-life factors that may contribute to neurodegeneration. In adulthood, a meta-analysis has identified $PM_{2.5}$ as an environmental determinant of dementia including Alzheimer's disease(5) and linked pollution exposure to cognitive decline(47). Additionally, disruptions in the homeostasis of essential transition metals (e.g., copper, zinc) have been implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's(48), with copper dyshomeostasis, in particular, playing a central role(49). Mirroring our current findings on source-specific exposure, recent research in older adulthood has shown that biomass burning and agricultural emissions (secondary nitrates) show the strongest links with incident dementia(50). In conjunction to our current findings in verbal episodic memory, exposure to ammonium nitrates was associated with poorer visual episodic memory performance(19) suggesting a broad impact on hippocampal-dependent function.

Strengths & Limitations

Our approach provides a comprehensive view of hippocampal architecture by investigating hippocampal micro- and macro-structure. This nuanced analysis offers valuable insights into the impact of air pollution, even at lower levels, on hippocampal neurodevelopment and presages its potential role into older adulthood. However, some limitations warrant consideration. First, we did not examine diffusion properties within specific hippocampal subregions; however, emerging pre-printed neuroimaging techniques(51) will enable future studies to explore these finer-scale

distinctions. Second, the cross-sectional design limits our ability to draw causal inferences and track developmental trajectories. Although we were able to show that relationships exist between air pollution, hippocampal architecture, and learning and memory ability, future studies that employ multivariate mediation analyses are needed to disentangle the complex pathways linking air pollution exposure to cognition. Finally, longitudinal studies with more sensitive task-based neurocognitive assessments and additional physiological markers are needed to fully understand how air pollution impacts hippocampal integrity and, ultimately, cognitive function across the lifespan.

Conclusions

The impact of air pollution on hippocampal structure is nuanced, with different pollutants exerting distinct effects on microstructural integrity and volume. Given the hippocampus's role in memory and its unique vulnerability to environmental exposures, further research is needed to determine whether these structural changes confer resilience or predispose individuals to cognitive decline later in life, and at what levels ongoing exposure translates into cognitive impairments. Additionally, as air pollution transcends national and international borders(52), efforts to mitigate exposure, particularly by targeting specific harmful sources, are critical to preserving brain health and supporting cognitive well-being across the lifespan.

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The ABCD data repository grows and changes over time. The ABCD data used in this report came from [doi:10.15154/8873-zj65]. DOIs can be found at [https://nda.nih.gov/study.html?id=2147].

Competing Interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Megan Herting, Katherine Bottenhorn, Michael Rosario, Carlos Cardenas-Iniguez, Rima Habre, Joel Schwartz, Daniel Hackman, and JC Chen reports financial support was provided by National Institutes of Health. Megan Herting reports a relationship with Health Effects Institute that includes: funding grants. If there are other authors, they declare that they have no competing interests.

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