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Effects of Prenatal Exposure to Air Pollutants (Polycyclic Aromatic Hydrocarbons) on Development of Brain White Matter, Cognition, and Behavior in Later Childhood

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Abstract

Importance—Polycyclic aromatic hydrocarbons (PAH) are ubiquitous and neurotoxic environmental contaminants. Prenatal PAH exposure is associated with subsequent cognitive and behavioral disturbances in childhood.

Objective—To identify the effects of prenatal PAH exposure on brain structure, and to assess the cognitive and behavioral correlates of those abnormalities, in school-age children.

Design—Cross-sectional imaging study in a representative, community-based cohort followed prospectively from the fetal period to 7–9 years of age.

Setting—Urban community residences and an academic imaging center

Participants—A community-based sample of 40 minority urban youth born to Latina (Dominican) or African-America women and followed prospectively from gestation to early school age.

Main Outcome Measures—Morphological measures that index local volumes of the surface of the brain and of the white matter surface after cortical gray matter was removed

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Results—We detected a powerful dose-response relationship between increased prenatal PAH exposure (measured in the 3rd trimester, but thought to index exposure for all of gestation) and reductions of the white matter surface in later childhood that were confined almost exclusively to the left hemisphere of the brain, and that involved nearly its entire surface. Reduced left hemisphere white matter was associated with slower information processing speed during intelligence testing and more severe externalizing behavioral problems, including ADHD symptoms and conduct disorder problems. The magnitude of left hemisphere white matter disturbances mediated the significant association of PAH exposure with slower processing speed. Measures of postnatal PAH exposure correlated with white matter surface measures in dorsal prefrontal regions bilaterally while controlling for prenatal PAH exposure.

Conclusions and Relevance—Our findings suggest that prenatal exposure to PAH air pollutants contributes to slower processing speed, ADHD symptoms, and externalizing problems in urban youth by disrupting development of left hemisphere white matter, whereas postnatal PAH exposure contributes to additional disturbances in development of white matter in dorsal prefrontal regions.

Keywords

Magnetic resonance imaging; toxicology; air pollution; cognition

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAH) are a class of ubiquitous and toxic environmental contaminants generated by the incomplete combustion of organic materials. Sources outdoors include diesel and gasoline-powered vehicles, waste incineration, and oil and coal burning for heat and electricity, and indoors include cooking, tobacco smoke, and space heaters.[1,2] PAH are neurotoxicants that readily cross the placenta and damage the fetal brain,[3,4] likely by inducing inflammation, oxidative stress,[5] and vascular injury.[6] Animal models have shown that prenatal PAH exposure impairs subsequent development of behavior, learning, and memory, in part by disrupting glutamate signaling,[4,5,7,8] activating glial cells that then become neurotoxic,[9] and reducing neural plasticity.[4]

The frequent differential siting of outdoor pollution sources in low-income, urban, and minority communities produces disproportionate exposure of their residents to air pollutants.[10–15] The substantial penetration of outdoor-generated PAH compounds into indoor residential environments[16,17] also translates to disparities in exposure to pollutants indoors. We initiated in 1997 a study of mother-newborn pairs from minority communities in New York City to evaluate the effects of prenatal exposures to ambient and indoor pollutants on birth outcomes and neurocognitive development.[18] We recruited 720 non-smoking women, aged 18–35 years, self-identified as African American or Dominican, and registered at the local prenatal clinics. During the third trimester of pregnancy, 665 mothers completed questionnaires and carried personal backpack monitors for 48 hours to estimate the level of eight common PAH in the breathing zone.[18]

We previously reported in this cohort that exposure during gestation to airborne PAH was associated with multiple neurodevelopmental disturbances, including developmental delay at

age 3 years,[19] reduced full-scale and verbal IQ at age 5 years,[20] symptoms of anxiety, depression, inattention on the CBCL at age 7 years,[21] and slower processing speed index on the WISC-IV at age 7 years, consistent with the cognitive and behavioral effects reported in prior animal models of PAH exposure.[8,22]

We undertook a magnetic resonance imaging (MRI) study of a representative sample (N=40) of this urban community cohort to assess the effects of airborne PAH on brain structure in school-age children with minimal exposure to other common environmental toxicants, including tobacco smoke, chlorpyrifos, and lead. We hypothesized that we would identify regional abnormalities in brain morphology associated with prenatal PAH exposure, and that the magnitude of those brain abnormalities would mediate the effects of PAH on information processing speed and the severity of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms.

METHODS

Details of PAH exposure measures, MRI pulse sequences, and image processing methods are in the Online-Only Materials.

Sample Ascertainment

African-American and Dominican women residing in Washington Heights, Harlem, or the South Bronx in New York City were recruited between 1998 and 2006 through the local prenatal care clinics.[19] To reduce potential confounding, enrollment was restricted to women 18–35 years old who were not cigarette smokers or users of other tobacco products or illicit drugs, who were free of diabetes, hypertension, and known HIV, and who initiated prenatal care by the 20th week of pregnancy. The retention rate to age 10–12 years was 79%.

Of 727 mother-newborn pairs enrolled, 665 completed prenatal PAH monitoring and prenatal questionnaires. To minimize confounding by exposure to other ambient chemicals, we identified 255 of these 665 children with (i) a full range of prenatal PAH exposure levels (ii) no or very low prenatal exposure to environmental tobacco smoke, classified by maternal report validated by cotinine levels <15 ng/mL in umbilical cord blood; and (iii) low chlorpyrifos insecticide exposure, defined as below the upper tertile of the distribution (≥4.39 pg/g). Of these 255 children, 40 were selected for neuroimaging using proportional stratified sampling, such that 20 were randomly selected from those above the median PAH level and 20 from those below the median, to ensure an adequate distribution and representativeness of PAH exposure levels. By design, prenatal levels of cotinine, chlorpyrifos, and lead were low in those who were scanned, and significantly less than in the overall cohort from which they were drawn (Table 1). All participants were right-handed. We obtained written informed consent from parents and signed assent from children. The Institutional Review Boards at the New York State Psychiatric Institute and Columbia University approved the study.

Neurodevelopmental Outcomes

We administered the Child Behavior Checklist (CBCL) and the Wechsler Scales of Intelligence for Children (WISC-IV) between the ages of 7 and 9 years.

Surface Maps

The detailed procedures used to analyze surface morphologies, and related validation studies, are provided elsewhere[23] and in eMethods. Briefly, we flipped the images randomly in the left-right direction prior to processing and reversed after processing in order to eliminate any possible influence of left-right human perceptual bias on morphological measures. We isolated the brains from non-brain tissue using semi-automated methods with detailed manual editing (eMethods). We coregistered each brain to an appropriately selected template brain using a similarity transformation followed by a high-dimensional, nonrigid warping algorithm based on the dynamics of fluid-flow. This 2-stage coregistration transformed each brain to match the template precisely in size and shape, permitting identification of points on the surfaces of each brain in the dataset that corresponded precisely with those of the template brain. We then reversed the high-dimensional, non-rigid warping to bring each brain into the position of the similarity transformation with the template brain, while carrying along with each brain the point correspondences established during the non-rigid, high-dimensional warping.

Surface Morphology—We measured the signed Euclidean distance of each point on the surface of the brain of each participant from the corresponding point on the surface of the template brain. These distances were positive for an outward deformation and negative for an inward deformation of the surface of participant brain relative to the template surface. To assess similar measures at the surface of the white matter rather than the surface of the brain, we removed the gray matter of the cortical mantle from the images, transferring the point correspondences determined in our co-registration procedures to the nearest point on the underlying white matter surface, and then assessed the correlation of surface distances with total PAH exposure at each point. These distances from the corresponding point of the surface of the template brain provide a continuous measure that assesses the degree of indentation or protrusion at that point on the surface relative to the template brain and that can be considered an index of local volume at that point.

Statistical Analysis

The associations of PAH measures with CBCL and WISC-IV scores were assessed using Pearson correlation coefficients calculated in IBM SPSS Statistics-v21. For statistical analyses of imaging measures, we used general linear modeling at each point on the surface of the template brain, to correlate PAH exposure, CBCL scores, or processing speed indices with morphological measures (distances of the cerebral or white matter surfaces from the corresponding surface of the template brain, and cortical thickness), while covarying for age and sex. P-values for voxel-wise analyses across the cerebral surface were corrected for multiple comparisons using a False Discovery Rate with $p<0.05$.[24] The p-value for the correlation coefficient at voxels that survived FDR correction was color-coded and plotted at each point on the cerebral surface.

RESULTS

Participating children were representative of the cohort from which they were drawn (Table 1), except for having significantly lower lead levels, and lower levels of environmental tobacco smoke and chlorpyrifos by design. One boy had a total PAH level that was an outlier in the sample (36.5 ng/m^3, >5 standard deviations from the sample mean); we report results excluding that child, although including his data yielded the same findings.

PAH Correlations with Surface Morphological Measures

Prenatal exposure to PAH correlated significantly and inversely with our morphological measure (distance from the template surface, an index of local volume) at each voxel on the cerebral surface in childhood (mean age 8.0±1.3 years) in most of the frontal, superior temporal, and parietal lobes, as well as the entire rostrocaudal extent of the mesial surface, in the left but not the right hemisphere of the brain (Fig. 1, upper panel). This index of local volume can derive from underlying cortical gray matter, white matter, or both. Therefore, we independently explored these two tissue types for their associations with PAH exposure levels. PAH exposure did not correlate significantly with measures of cortical thickness anywhere across the cerebrum, suggesting that the surface abnormalities were likely determined primarily by abnormalities in underlying white matter. Therefore, we removed the cortical mantle from each brain to assess the effects of prenatal PAH exposure on the underlying white matter. These analyses confirmed that the modest PAH-related effects at the cerebral surface derived from spatially much larger and statistically stronger effects of PAH on the underlying white matter, extending throughout the entire lateral, mesial, dorsal, and ventral surfaces of the left hemisphere (Fig. 1, lower panel). Much less prominent inverse correlations in the right hemisphere were localized primarily to sensorimotor white matter regions (Fig. 1). These correlations were unchanged when covarying for prenatal cotinine levels, measures of postnatal PAH exposure at age 5 years, or a standard measure of handedness.[25] Surface maps constructed using the nonparametric Spearman's rank-order correlation yielded the same findings as those constructed using parametric linear regression (eFig. 1). Scatterplots confirmed that correlations of white matter surface measures extended across the entire range of PAH, cognitive, and behavioral values (Fig. 2).

Measures of PAH exposure at age 5 years did not correlate significantly with prenatal PAH exposure or measures of the cerebral surface or cortical thickness, but did correlate significantly with white matter measures in dorsal prefrontal regions bilaterally, especially along the superior frontal gyrus, even when covarying for prenatal PAH exposure (Fig. 2, eFig. 3). Including PAH exposure at age 5 years as a covariate in our original model did not change the correlation of prenatal PAH levels with white matter surface measures.

Behavioral Measures

Significant behavioral correlates of PAH exposure included Processing Speed Index on the WISC-IV at age 7 years ($r=-0.32$, $p<0.05$) (Table 1), similar to the correlation detected in the larger cohort from which our sample was drawn.

Processing speed on the WISC-IV and numerous CBCL measures, including externalizing problems and DSM ADHD symptoms, correlated significantly and inversely with white matter surface measures, more strongly in the left than in the right hemisphere (Figs.3–4, eFigs.3–5), and in spatial patterns nearly identical to those for prenatal PAH exposure (Fig. 1). The direction of correlations and the associated scatterplots indicated that progressively more prominent white matter reductions accompanied progressively greater impairments in processing speed and more severe behavioral problems (Fig. 4). Because CBCL subscales were intercorrelated (eTable), we present findings for externalizing problems, as they subsume problems in the other subscales of the CBCL, and specifically for DSM-ADHD symptoms because our a priori hypotheses included these measures based on prior findings in our larger cohort. Correlations between white matter measures and selected CBCL scores are shown in eFigs.3–5. White matter correlations with externalizing problems persisted when controlling for DSM-ADHD symptom scores (eFig. 6).

We next applied the Sobel test[26] at each point on the surface of the white matter (eMethods) to test our hypothesis that the effects of prenatal PAH exposure on brain structure partially mediated the effects of prenatal PAH exposure on processing speed in later childhood. Plotting the p-value of the mediation pathway at each voxel on the surface of the template brain, we confirmed throughout the entire surface of the left hemisphere that white matter measures mediated the effects of prenatal PAH exposure on measures of processing speed (Fig. 3, lower panel). Mediation effects were not significant for DSM-ADHD symptom scores because PAH exposure in our sample did not correlate significantly with the severity of these measures, as it did in the larger cohort.

Exploratory analyses suggested that the associations of prenatal PAH exposure with white matter measures, though present in both sexes separately, may have been stronger in girls than in boys. Scatterplots indicated that the effects were driven by relatively few participants, however (eFig. 7).

DISCUSSION

This is the largest MRI study thus far of the brain effects of prenatal exposure to air pollutants (PAH specifically), and the first to report effects from prenatal exposure. In our community-based sample of minority urban youth followed from gestation to school age, we detected a powerful dose-response relationship between prenatal PAH exposure and subsequent reductions of the white matter surface in childhood. The effects of PAH exposure on white matter were confined almost exclusively to the left hemisphere of the brain and involved nearly its entire surface, including the frontal, parietal, temporal, and occipital lobes. Reduced white matter measures of the left hemisphere were associated significantly with higher scores for the externalizing problems subscale of the CBCL, as well as with externalizing symptoms that included ADHD symptoms and conduct disorder problems. Higher prenatal PAH exposure was associated significantly with reduced processing speed during intelligence testing, consistent with the association detected in the larger study population from which our sample was drawn. The magnitude of white matter disturbances in the left hemisphere mediated the association of processing speed with PAH exposure. These findings suggest that PAH air pollutants are important contributors to

slower processing speed, ADHD symptoms, and externalizing problems in urban youth via the disruptive effects of prenatal PAH exposure on development of left hemisphere white matter, particularly in the frontal, parietal, and temporal lobes, which subserve attention and impulse control.

Additional effects of postnatal PAH exposure, measured at age 5 years, were detected bilaterally in dorsal prefrontal white matter, while covarying for prenatal PAH exposure. These effects of postnatal PAH exposure were spatially distinct from and statistically independent of those for prenatal PAH exposure. Their locations in the dorsal prefrontal cortices are consistent with the timing of exposure and the protracted postnatal development of the prefrontal cortex in humans, which continues through late childhood and adolescence. Although our data do not indicate what consequences these postnatal effects on prefrontal white matter may have on cognition or behavior, the location of the effects would be expected to exacerbate difficulties with processing speed, attention, and impulse control, functions supported by the prefrontal cortices.[27]

Our imaging findings are consistent with those of a prior pilot study that reported a higher rate of white matter hyperintensities in children living in a highly polluted urban environment (13 of 23,56.5%) compared with a rate in children living in a less polluted urban environment (1 of 13,7.7%).[28] In addition, reduced white matter volumes measured using automated computer algorithms were detected bilaterally in a subset of 20 children from the highly polluted environment compared with a subset of 10 from the less polluted environment.[29] The levels of exposure to specific air pollutants such as PAH, however, were not measured.

Previous anatomical imaging studies of youth with ADHD using deformation-based measures of the cerebral surface, similar to the measures employed here, reported bilaterally reduced volumes of inferior frontal and anterior temporal lobes,[30] likely as a consequence of delayed maturation relative to healthy comparison youth.[31] The morphological features associated with ADHD symptoms detected in our community sample differed from those reported previously in ADHD youth in clinical samples, suggesting that exposure to high levels of air pollutants (PAH) may produce a specific morphological subtype of ADHD.

Our findings that left hemisphere white matter reductions mediated the effects of PAH exposure on processing speed, and that white matter reductions were also associated with attention problems and ADHD, are consistent with reports from animal studies that prenatal exposure to high PAH levels reduces long-term potentiation[7] and impairs various cognitive abilities, including spatial learning, short-term memory,[32–34] and novel object discrimination.[35,36] Animal studies of PAH-induced neurotoxicity have focused primarily on brain gray matter, but our findings suggest that they should investigate PAH effects on white matter as well.

Our findings indicate that the left hemisphere compared with the right is more susceptible to the effects of PAH in the relatively low exposure range experienced in our study population; higher exposure levels might have produced more prominent right hemisphere effects. A greater left hemisphere susceptibility could derive from several possible sources, including a

greater sensitivity to PAH in the molecular pathways that control prenatal development of hemispheric asymmetries in brain structure, which are present by week 10 of gestation.[37] The genetic and molecular determinants of anatomical asymmetries in humans are still unknown, though in other species several have been identified, such as Nodal, FGF8, and ion channel-related gene products,[38] at least some of which regulate development of white matter pathways.[39–41] PAH could also influence expression of regulatory genes that have been reported to differ across the left and right hemispheres during early fetal development.[42] PAH could also alter levels of monoaminergic neurotransmitters[33,43] or their receptors[44] that regulate early brain development and lateralization. Serotonin, for example, regulates the early patterning of the left-right body axis in animals via its effects on asymmetrically expressed genes that control brain development, such as Sonic hedgehog.[45,46] Our findings could also derive from the known cytotoxic effects of PAH, but these effects would have to operate unilaterally on white matter at some time during development if they were to explain our lateralized findings. The neurotoxic effects of PAH are thought to occur indirectly via microglial activation: the PAH benzo[a]pyrene (B[a]P) increases reactive oxygen species within microglia, thereby reducing levels of antioxidant proteins and increasing expression of nitric oxide synthase; these in turn increase production of nitric oxide and proinflammatory cytokines in microglia, leading to both the bystander death of neurons and astrogliosis.[9] Finally, the effects of PAH on microglia could also in some way alter their production of myelin,[47] specifically in the left hemisphere, to reduce white matter in direct proportion to the degree of PAH exposure.

Our study has several limitations. First, we assessed the effects of PAH only at the cerebral and white matter surfaces, not deep within the brain's parenchyma. Second, our sample size was limited. We are imaging a much larger number of children in our study population to confirm these findings, and to assess the interactive effects of PAH with other environmental contaminants on brain structure and function. Third, prenatal PAH monitoring was limited to a short window during the third trimester, and the earlier stages of pregnancy may be more vulnerable to its effects. Nevertheless, estimates of prenatal PAH exposure based on individual 48-hour personal air monitoring correlated significantly with estimates based on the mean of consecutive 2-week integrated indoor air monitoring periods, indicating that PAH exposure is chronic and relatively constant.[48] Fourth, the urinary metabolite concentrations measured at age 5 years represent different sources of PAH exposure besides air, including dietary and dermal. They also represent metabolites of different parent PAH compounds. Fifth, we cannot entirely exclude the possibility that our findings could have been caused by other co-occurring exposures,[49] including non-PAH air pollutants, that we did not measure. Nevertheless, we were careful to select children for MRI scanning from our overall cohort who had minimal prenatal exposure to environmental tobacco smoke, the insecticide chlorpyrifos, and lead. Finally, our findings were identified in a minority population with a high level of poverty, low educational attainment, low English language proficiency, and below average maternal IQ, within a specific population of New York City. Our findings therefore do not necessarily generalize to other populations.

Despite these limitations, our findings raise important concerns about the deleterious effects of air pollutants, and PAH in particular, on brain development in children, and the consequences of those brain effects on cognition and behavior. The linear dose-response

relationship for the effects of PAH exposure on brain morphology suggests that every unit reduction in exposure to PAH during gestation and early postnatal life should yield a proportionate reduction in white matter disturbance and its associated cognitive and behavioral effects. If confirmed, our findings have important public health implications, given the ubiquity of PAH in air pollutants in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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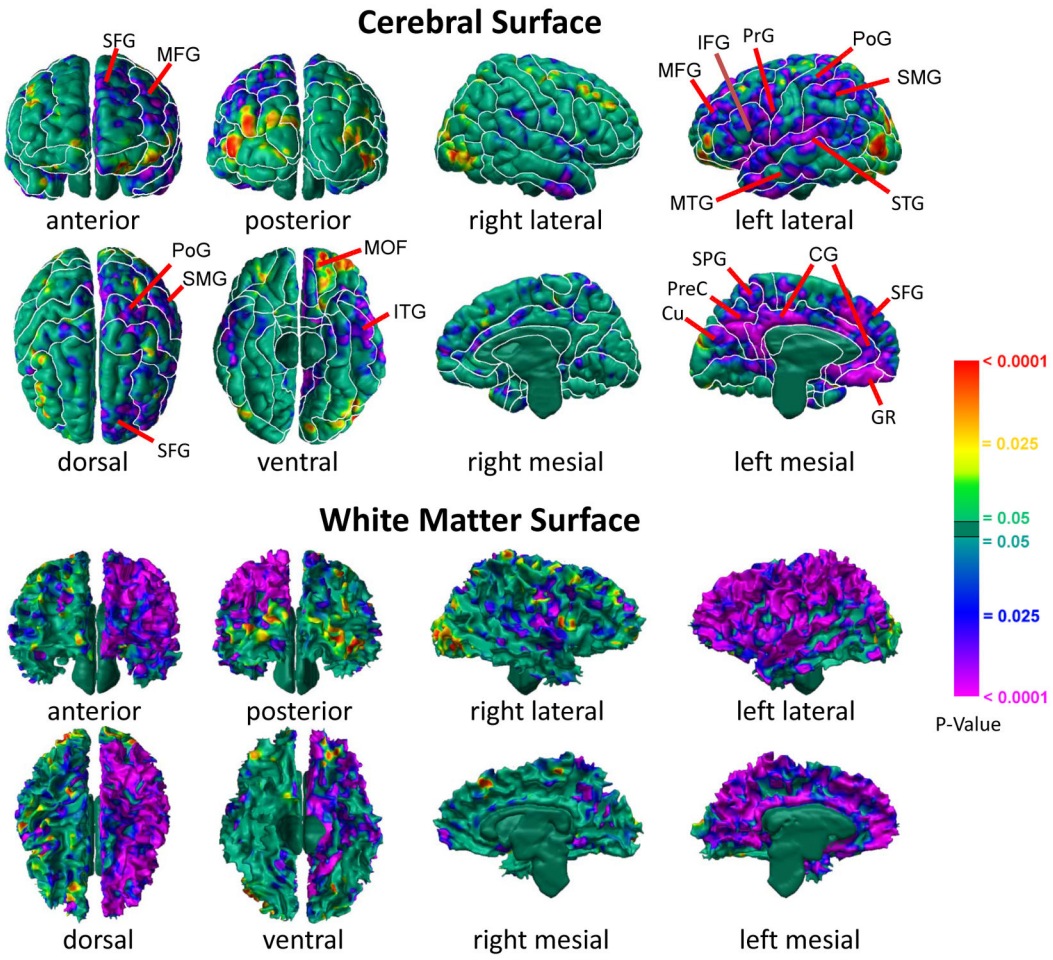

Figure 1. Correlations of Prenatal PAH levels with Cerebral Surface Measures

At each point on the cerebral surface is shown the statistical significance (probability values) for the correlations of total prenatal PAH levels with measures of the cerebral surface, either cortical thickness or distance from the surface of the template brain (see Online Only materials for detailed descriptions of each of these measures). The distance at each point of the cerebral surface in each participant from the corresponding point of the surface of the template brain provides a continuous measure that, when strictly defined, assesses the degree of indentation or protrusion at that point on the surface relative to the template brain, but that can be more loosely considered an index of local volume at that point. This index of local volume can derive from either underlying cortical gray matter, white matter, or both. Both cortical thickness and distance measures were rescaled for overall brain size, and the statistical models accounted for the age and sex of all children. The color bar indicates the color-coding of p-values for testing of statistical significance at each point on the surface. P-values were thresholded at $p<0.05$ after correction for multiple comparisons using the False Discovery Rate. Warm colors (yellow, orange, and red) represent significant positive correlations and cool colors (blue and purple) representing inverse correlations. Sea- green indicates correlations that are not statistically significant. The boundaries of major gyri are outlined in white.

Upper panel: Correlations are shown for total prenatal PAH levels with distances of the cerebral surface of each participant brain from the corresponding point on the template surface. Correlations are much more statistically significant and more spatially extensive in the left hemisphere than in the right. The gyri containing statistically significant correlations are labeled.

Lower panel: These are correlations of total prenatal PAH levels with distances of the white matter surface of each participant from the corresponding point on the surface of white matter in the template brain. Regions with statistically significant correlations are much more extensive than those in the upper panel, covering nearly the entire extent of the white matter surface in the left hemisphere. Correlations with cortical thickness were not statistically significant (not shown). Together these findings suggest that the correlations detected at the cerebral surface in the upper panel derived primarily from the underlying white matter.

CG: cingulate gyrus
Cu: cuneus
GR: gyrus rectus
IFG: inferior frontal gyrus
ITG: inferior temporal gyrus
MFG: middle frontal gyrus
MTG: middle temporal gyrus
MOF: medial orbitofrontal gyrus
PoG: post-central gyrus
PreC: precuneus
PrG: pre-central gyrus
SFG: superior frontal gyrus
SMG: supramarginal gyrus
SPG: superior parietal gyrus
STG: superior temporal gyrus

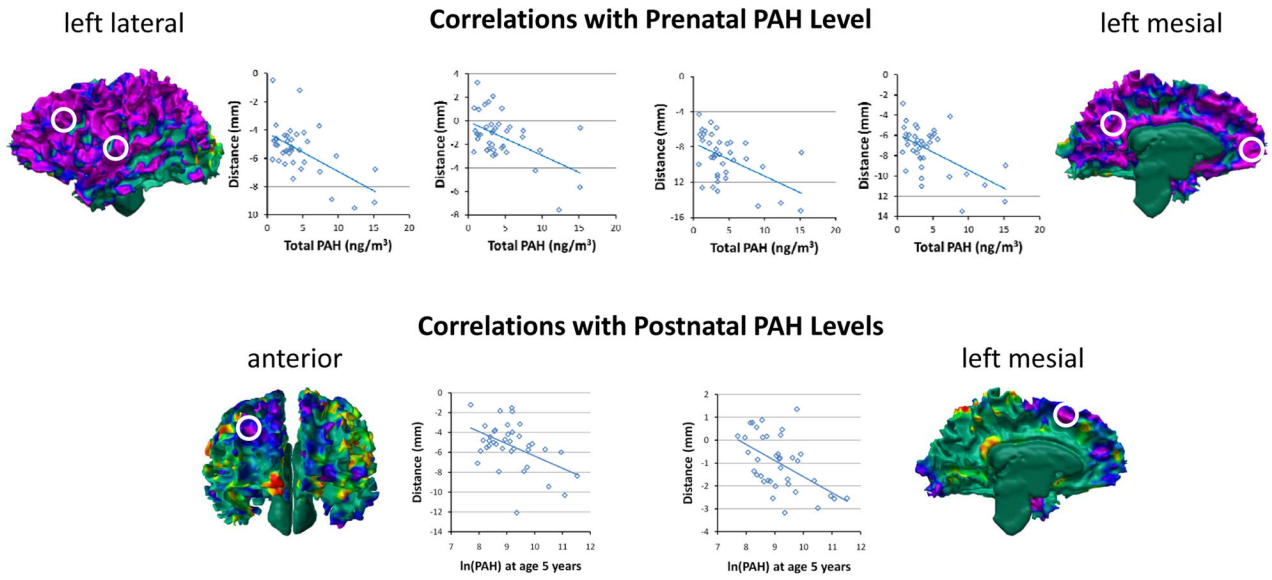

Figure 2. Correlations of PAH levels with White Matter Surface Measures

Scatterplots show that the significant correlations derive from the entire range of prenatal and postnatal PAH values, and are not driven by outliers. White matter measures are adjusted for age and sex of each participant

Upper panel: Maps for these correlations are as described for Figure 1. The white circles indicate where in the brain the dataset was sampled to generate the scatters. The Pearson correlation coefficients and associated 95% confidence intervals from left to right are: –0.57 (–0.75, –0.304), –0.51 (–0.71, –0.23), –0.50 (–0.71, –0.22), and –0.56 (–0.75, –0.30).

Lower panel: Maps for these correlations are as described for Figure 1, except the regressions are for postnatal PAH exposure levels measured at age 5. The analyses covaried for age, sex, and prenatal PAH levels. The values for postnatal PAH metabolite levels have been natural log-transformed. The Pearson correlation coefficients and associated 95% confidence intervals from left to right are: –0.47 (–0.69, –0.18) and –0.52 (–0.72, –0.25).

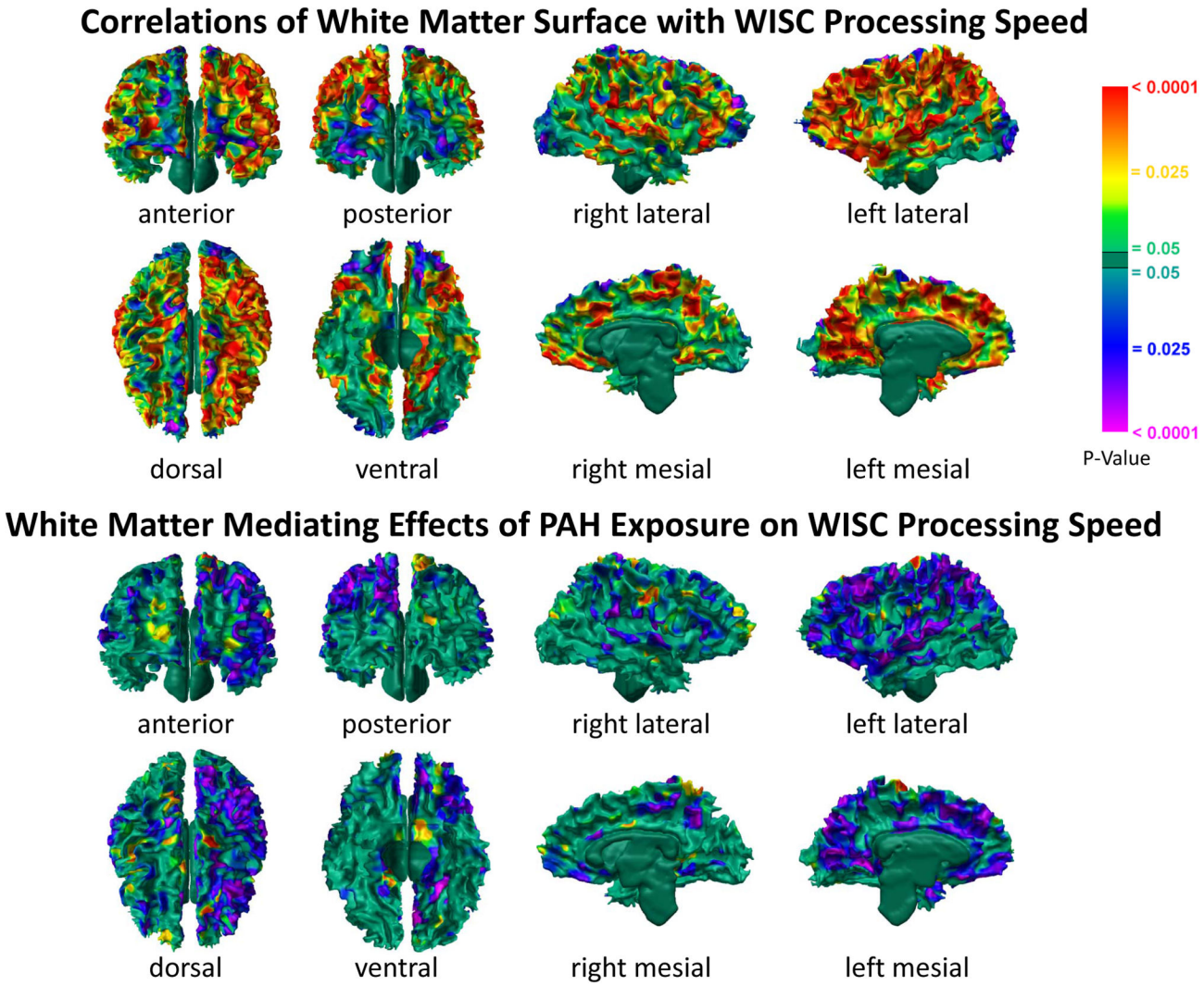

Figure 3. Prenatal PAH Effects on Processing Speed

Upper panel: P-values that are FDR-corrected for multiple comparisons are plotted for partial correlations of processing speed with distances at each point on the white matter surface from the corresponding point on the white matter surface of the template brain while covarying for age and sex. Warm colors (yellow, orange, and red) represent significant positive correlations in which white matter reductions associate with lower indices for processing speed. A sea-green color indicates correlations that are not statistically significant.

Lower panel: P-values are plotted for regression models that test whether white matter surface distances mediate the association of prenatal PAH levels with the processing speed index from the WISC-IV assessed at age 7–9 years. We tested the significance of the mediation effect at each voxel on the surface of white matter using a Sobel test z-score, which were very large, typically over a value of 90. We then plotted the associated P-values for this mediation pathway on the template brain, corrected them for multiple statistical comparisons using False Discovery Rate, and color-coded the corrected p-values, to identify

voxels where partial mediation was statistically significant. These voxels were detected throughout all lobes on the white surfaces of the left hemisphere.

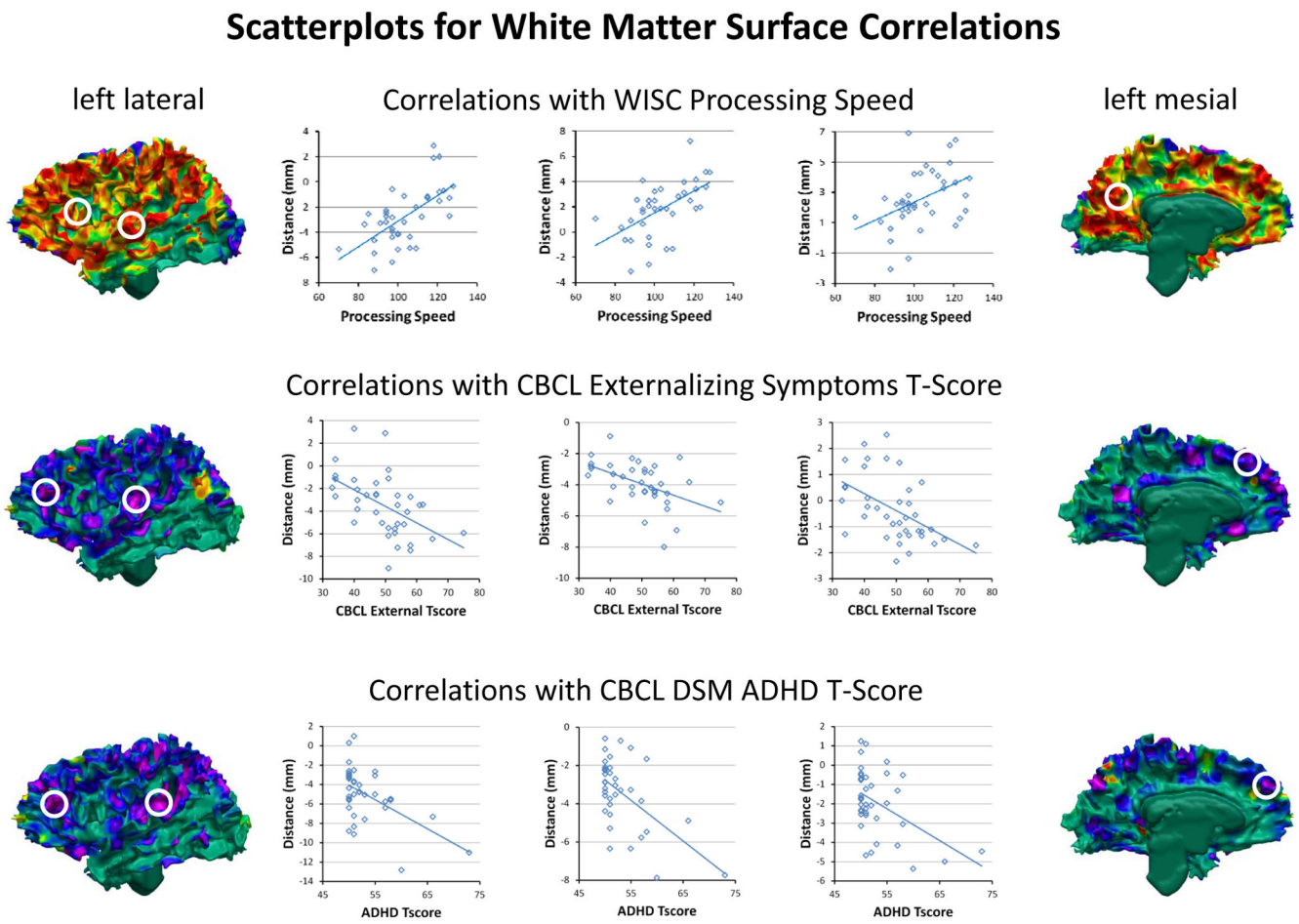

Figure 4. Scatterplots for Correlations of White Matter Surface Measures with Processing Speed, CBCL Externalizing Problems, and CBCL ADHD-DSM Symptoms

The maps were sampled at the locations indicated by white circles. The y-axis shows distances at those points for the white matter surface of each participant from the corresponding point on the white matter surface of the template brain, adjusted for age and sex of each participant. The scatterplots show that the significant findings were not driven by outliers. The externalizing composite scale included only the rule-breaking behavior and aggressive behavior subscales. The Pearson correlation coefficients and associated 95% confidence intervals from left to right are: Processing Speed 0.62 (0.39, 0.79), 0.56 (0.29, 0.74), and 0.43 (0.13, 0.66); Externalizing Symptoms –0.52 (–0.72, –0.24), –0.49 (–0.70, –0.20), and –0.50 (–0.71, –0.21); DSM ADHD –0.53 (–0.72, –0.25), –0.57 (–0.75, –0.31), and –0.48 (–0.69, –0.18).

Table 1

Participant characteristics[1]

Characteristic	MRI Sample (n=40)	Full Cohort (n=625)	P-value
Income			
< $20,000	67.6%	74.3%	p=0.39
≥ $20,000	32.4%	25.7%	
Maternal education (yrs)	12.1 ± 2.0	12.0 ± 4.1	p=0.76
Maternal non-verbal IQ[2]	85.6 ± 15.0	85.4 ± 13.1	p=0.93
Maternal Race/Ethnicity			
Dominican	72.5%	63.7%	p=0.26
African American	27.5%	36.3%	
Child Sex			
Male	42.5%	49.4%	p=0.39
Female	57.5%	50.6%	
Gestational age (weeks)	39.2 ± 1.4	39.3 ± 1.4	p=0.55
Birth weight (gm)	3394.8 ± 468.8	3368.4 ± 476.7	p=0.75
Child age at MRI (yrs)[3]	8.0 ± 1.3	NA	
Mean prenatal PAH air sample (ng/m^3)[4]	5.13 ± 6.2	3.21 ± 6.3	p=0.07
Above median (n=20)	8.20 ± 7.64		
Below median (n=20)	2.06 ± 0.91		
Mean postnatal PAH metabolites (ng/L)[5]	14999.4 ± 19795.8	13638.5 ± 21029.8	p=0.70
Above median (n=20)	16171.35 ± 22383.7		
Below median (n=20)	13827.53 ± 17366.3		
Mean prenatal cotinine (ng/ml)[6]	.008 ± .237	1.85 ± 12.84	p=0.009
Mean prenatal chlorpyrifos (pg/g)[7]	1.34 ± 1.41	3.18 ± 5.79	p<0.001
Cord blood lead (μg/dl)[8]	0.87 ± 0.49	1.19 ± 0.88	p<0.003
Child WISC-IV full scale IQ[9]	99.7 ± 10.3	98.4 ± 13.2	p=0.55
Child WISC-IV processing speed[9]	103.6 ± 13.8	101.4 ± 15.5	p=0.39
CBCL Total Raw Score[9]	21.5 ± 16.3	22.6 ± 19.2	p=0.75
CBCL DSM-ADHD Raw Score[9]	2.9 ± 2.7	3.3 ± 2.9	p=0.49
CBCL Attention Raw Score[9]	3.0 ± 2.8	3.3 ± 3.4	p=0.56
CBCL Anxious/Depressed Raw Score[9]	2.8 ± 2.9	2.6 ± 3.0	p=0.70
CBCL Externalizing Score[9]	5.9 ± 6.2	6.1 ± 5.9	p= 0.88

[1] Demographic characteristics were assessed in the third trimester of pregnancy

[2] Test of Non-Verbal Intelligence-Third Edition (TONI-3)

[3] The children in the full cohort were born between 1998 and 2006. Therefore, the ages of the non-participants for MRI covered the full range from 0 to approximately 12 years during the period in which these scans were conducted.

[4]Total prenatal air PAH is the sum of benzo[a]anthracene, chrysene/iso-chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, indeno[1,2,3-c,d]pyrene, dibenzo[a,h]anthracene, and benzo[g,h,i]perylene concentrations; measured by personal air monitoring in the third trimester of pregnancy

[5]Child postnatal urinary PAH metabolites were measured at age 5 years; samples were available for N=38 in MRI sample; N=368 in full cohort

[6]Cord cotinine or estimated cord cotinine value based on maternal cotinine if missing cord blood (see Online-Only methods)

[7]Cord chlorpyrifos or estimated cord value based on maternal chlorpyrifos if missing; N=472 in full cohort

[8]Child umbilical cord blood lead samples were available for N=30 in MRI sample; N=294 in full cohort

[9]WISC-IV and Child Behavior Checklist outcome measures were administered at child age 7 years. WISC and CBCL data were available for 39 of the 40 children.

NA: not applicable