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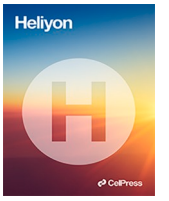

Neuroanatomical differences in Latinx children from rural farmworker families and urban non-farmworker families and related associations with pesticide exposure

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A R T I C L E I N F O

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A B S T R A C T

Exposure to pesticides in humans may lead to changes in brain structure and function and increase the likelihood of experiencing neurodevelopmental disorders. Despite the potential risks, there is limited neuroimaging research on the effects of pesticide exposure on children, particularly during the critical period of brain development. Here we used voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) from magnetic resonance images (MRI) to investigate neuroanatomical differences between Latinx children (n = 71) from rural, farmworker families (FW; n = 48) and urban, non-farmworker families (NFW; n = 23). Data presented here serves as a baseline for our ongoing study examining the longitudinal effects of living in a rural environment on neurodevelopment and cognition in children. The VBM analysis revealed that NFW children had higher volume in several distinct regions of white matter compared to FW children. Tract-based spatial statistics (TBSS) of DTI data also indicated NFW children had higher fractional anisotropy (FA) in several key white matter tracts. Although the difference was not as pronounced as white matter, the VBM analysis also found higher gray matter volume in selected regions of the frontal lobe in NFW children. Notably, white matter and gray matter findings demonstrated a high degree of overlap in the medial frontal lobe, a brain region predominantly linked to decision-making, error processing, and attention functions. To gain further insights into the underlying causes of the observed differences in brain structure between the two groups, we examined the association of organochlorine (OC) and organophosphate (OP) exposure collected from passive dosimeter wristbands with brain structure. Based on our previous findings within this data set, demonstrating higher OC exposure in children from non-farmworker families, we hypothesized OC might play a critical role in structural differences between NFW and FW children. We discovered a significant positive correlation between the number of types of OC exposure and the

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structure of white matter. The regions with significant association with OC exposure were in agreement with the findings from the FW-NFW groups comparison analysis. In contrast, OPs did not have a statistically significant association with brain structure. This study is among the first multimodal neuroimaging studies examining the brain structure of children exposed to agricultural pesticides, specifically OC. These findings suggest OC pesticide exposure may disrupt normal brain development in children, highlighting the need for further neuroimaging studies within this vulnerable population.

1. Introduction

Over the past two decades, studies on the neurological effects of pesticides have gained increasing attention, as many individuals in agricultural communities and urban areas continue to have exposure to these chemicals [1–3]. Farmworker families residing in rural areas are exposed to pesticides through multiple sources, including environmental exposure through drift from adjacent fields, para-occupational routes such as carrying the substances home on clothing, and residential exposure through the use of pesticides for home pest control [4]. Pesticides can also contaminate the urban environment and affect urban families in various ways, including diet [5], household use, emissions from industrial facilities, and water contamination [6]. Pesticides have been shown to be harmful through a variety of mechanisms. OCs can impact the nervous system by acting on sodium-gated channels and receptors, as well as causing apoptotic cell death through mitochondrial dysfunction. On the other hand, OPs mainly act through the inhibition of acetylcholinesterase (AChE) [7]. Children are especially vulnerable to pesticides [8], given their immature metabolism and increased hand-to-mouth activities [9,10], and of particular concern, their developing nervous system [11].

Multiple studies have established the effects of pre and postnatal pesticide exposure on children's cognitive abilities, particularly in children at risk for exposure to agricultural pesticides. Prenatal exposure to pesticides has been associated with pervasive neurodevelopmental disorders [12–14], motor impairments [15], lower processing speed [16], delayed development of language comprehension [17], and behavioral issues such as disrupted social development [18] and attention deficit hyperactive disorder [19–22]. Most notably and consistently reported is that prenatal pesticide exposure results in a reduction in intelligence quotient (IQ) scores [23,24]. Findings from postnatal pesticide exposure studies have less convergence [20], with some reporting pesticide metabolites to be associated with adverse effects on both behavior and cognition [21,25–29], and some reporting no association with IQ [19] and developmental quotients [30] in children. Largely though, evidence indicates pesticide exposure may impact the neurobehavior of children.

Structural neuroimaging studies on the effects of pesticide exposure on brain development, particularly in children, remain limited, and those performed have reported varied and disparate results. To the best of our knowledge, there are only two studies that directly examine neuroanatomical changes in relation to pesticide exposure and both are limited to only OP pesticides. Most notably, in a structural MRI study, Rauh et al. [32] investigated the association between IQ and cortical thickness and size of the cerebral surface of children with organophosphate (OP) exposure. They reported enlargement in cortical surface and decreased cortical thickness in several parts of the temporal, parietal, and frontal lobes of children exposed to OPs. They also concluded that the enlargement in the cortical surface is due to enlargement in the white matter surface [31]. An additional report investigating the effects of agricultural pesticide exposure on white matter in children identified prenatal exposure to OPs to have a negative correlation with fractional anisotropy (FA), a positive correlation with mean diffusivity (MD), and no association with cortical thickness [32]. However, the varying reported findings and the narrow focus on OP exposure highlight the necessity for further neuroanatomical research on the effects of pesticide exposure during childhood when the brain undergoes its most significant developmental changes.

Normal brain development is complex during childhood. While there is a general consensus on the inverted U-shaped trajectory of gray matter development from early life to adulthood, there is significant variation in the findings concerning the age at which gray matter volume peaks. Initial reports suggest that gray matter development trajectory plateaus in late childhood and early adolescence (age 8–15) [33,34]. However, more recent studies have reported that the peak of gray matter volume occurs prior to late childhood (before age 8), with drops in gray matter occurring later [35–37]. The decrease in gray matter volume has been associated with the pruning or refining of anatomical connections in the brain [38]. In contrast to gray matter, white matter has a more established developmental trajectory across literature. White matter volume increases from early childhood to middle adulthood and then starts to decrease [39–41]. The dramatic outgrowth of white matter [42,43] is attributed to increased innervation that refines communications between brain areas. Although there is some variation in the trajectories of specific tracts, diffusion tensor imaging (DTI) studies have also reported the same trajectory for the white matter integrity overall [44–47]. While studies have shown continuous maturation of white matter from early life to adulthood, infancy and early childhood are critical periods where rapid neurodevelopment and particularly maturation of the white matter take place. Taken together, given the ongoing dramatic changes in brain development during the first eight years of life, young children may be exceptionally predisposed to altered neurodevelopment, which could subsequently impact cognitive function.

The objective of the present study was to use magnetic resonance imaging (MRI) data to compare the brain structure of children from farmworker families (FW children) and children from non-farmworker families (NFW children) by utilizing voxel-based morphometry (VBM) to assess gross morphological changes in various brain regions and DTI to evaluate the white matter structure. Additionally, to gain further insight into the possible disparities between the two groups, the association between brain structure and pesticide exposure, including OC and OP pesticides, was examined. Building upon our prior investigation of this dataset, which

identified lower cognitive scores in NFW children that may be associated with OC exposure [48], we hypothesize that structural brain differences between FW and NFW children are related to OC exposure.

2. Material and methods

All data were from the ongoing Preventing Agricultural Chemical Exposure (PACE5) study designed to identify and compare the effects of pesticide exposure on cognitive and brain development in Latinx children from FW and NFW families. PACE5 is a longitudinal community-based participatory research (CBPR) project undertaken as a partnership between Wake Forest University School of Medicine and North Carolina Farmworkers Project (Benson, NC; http://ncfwp.org). Each PACE5 protocol and procedure was approved by the Wake Forest University School of Medicine Institutional Review Board.

2.1. Participant recruitment

All children in this study must have been 8 years of age and have completed the first grade in the US at the time of enrollment. Participants were from self-identified Latinx families with a household income below 200 % of the US federal poverty line. Participants in the FW group must have had at least one adult in the household who had been working on non-organic farms for the past three years. NFW participants could not have had any adults living in the home with routine exposure to pesticides through employment or lived adjacent to agricultural fields within the previous three years. Children were excluded from the study if they had a life-threatening illness, history of neurological, physical, or developmental disorder that would interfere with their completion of the brain scans or cognitive testing.

Based on a community-based participant research (CBPR) design, participant recruitment was predominantly performed by local community members in Winston-Salem/Forsyth County and through our partnership with the North Carolina Farmworkers Project based in Benson. Recruiting took place from March 2018 to December 2019. A list of families with an 8-year-old child was created by local recruiters within these groups for rural farmworkers and urban non-farmworker families. Families from the lists were contacted by bilingual study recruiters, informed of the study design, and screened for inclusion if interested in participation. Parents/guardians provided signed informed consent, and assent was provided by the children. Additional potential families were approached at community events in both the rural and urban communities. A total of 76 children were recruited from farmworker families from eastern North Carolina and 65 from non-farmworker families located in central North Carolina.

Given that recruitment worked through community partners, the number of potential participants and the related number of families who may have refused participation is not known. The methods implemented in this study did not allow for an investigation of potential selection biases with recruitment. While this is a convenience sampling method, it is expected to be representative of respective groups (farmworker and non-farmworker families) of the Latinx population living within the sampled areas.

Assessment of individual exposure to pesticides was performed through passive dosimeter silicon wristbands. These were given to participants after interviews were conducted and were worn by the children for one week to assess their individual exposures. The full details of laboratory analysis of wristband data, in addition to specific exposure details of the individuals assessed in this report have been described previously in Arcury et al. [49]. Briefly, wristbands were stored in Teflon bags on completion of the seven-day exposure monitoring period and remained stored in these bags until laboratory analysis was performed. They were then retrieved from participants by study interviewers and shipped to the laboratory, performing the exposure analysis. This laboratory used validating procedures to analyze the pesticides through dual micro-electron detector gas chromatography [49–52].

While wristbands only detect environmental chemical exposure [49,53] and not the pesticides absorbed directly into the body, they are suitable for this study as all the pesticides being investigated are absorbed through skin contact or, consequently, through ingestion (hand-to-mouth). Moreover, multiple studies have demonstrated a significant association between the chemical concentrations detected in wristbands and the corresponding biological concentrations in urine and serum [54–56]. Therefore, we used the obtained data from the wristbands to investigate the association between exposure to OP and OC pesticides and brain structure.

A subset of that cohort (n = 85 children (8–9 y/o)) was willing and able to participate in an MRI scan. Due to incomplete scanning (5 NFW participants) and excessive head motion, nine participants (5 FW, 4 NFW) were removed (see below). Therefore, a sample of 71 participants was included in the examination of group differences between FW and NFW children (n = 48 FW and n = 23 NFW), and 70 participants were included in the study of the association between brain structure and pesticide exposure, as one participant had missing exposure data. We considered OP as a binary variable (either exposed or not exposed) since the majority of children were exposed to only one type of OP (Chlorpyrifos). Thus, we divided the study participants into two groups: an exposed group comprising 43 participants and a non-exposed group consisting of 27 participants. However, OC exposure data collected through wristbands span over 23 different types of OCs [49], and each had a different scaling. Therefore, as averaging the exposure levels was not feasible in this case, we opted to count the number of exposures to different OC types and examine their association with the brain structure. On average, participants were exposed to a mean (SD, range) of 1.96 (1.52, 0–5) types of OCs.

From the broad set of demographic information, age, gender [33], and handedness [57] were used as covariates for this study as they have been linked to brain structure. One participant had a missing value for handedness but instead of excluding the participant from the analysis, we considered the participant right-handed based on the fact that the majority of the sample was right-handed.

2.2. Imaging details

The brain MRI scans were performed in the MRI center of the Wake Forest University School of Medicine. To help optimize image

quality and improve the overall scanning experience, a training session was held for the children using a mock MRI scanner prior to imaging to train them to not move their head while they were in the scanner. The MRI scans were acquired using a research dedicated 3-T Siemens Skyra scanner with a 32-channel head coil. Acquisition of high-resolution (1.0 mm × 1.0 mm × 1.0 mm) T1-weighted structural scans was performed using a single-shot 3D MPRAGE GRAPPA2 sequence. Total acquisition time was 5 min and 30 s, TR = 2.3 s, TE = 2.99 ms, for 192 slices. DTI was performed with the following parameters, TR = 8500 ms, TE = 82.0 ms, voxel size = 2.2 × 2.2 × 3.0 mm, number of slices = 60, FOV = 246 mm, b value = 1000 s/mm^2, number of weighted directions = 30, number of b0 images = 1, parallel acquisition mode = GRAPPA with factor = 2, and the acquisition time = 4 min 49s.

2.3. Voxel-based morphometry (VBM)

2.3.1. Image processing

Data were analyzed at the Laboratory for Brain Complex Network (LCBN), Wake Forest School of Medicine. VBM was implemented using standard procedures with CAT12 (Computational Anatomy Toolbox, http://dbm.neuro.uni-jena.de/cat/) [58] and SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) [59] using procedures described in the CAT12 manual and default settings (http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). The only change we applied to the standard VBM analysis was creating a subject-specific customized Dartel template according to the CAT12 manual, as our participants were children. All images were first quality controlled, as children are prone to movement in the scanner. Next, T1-weighted scans from each participant were independently coregistered to MNI space using an affine transformation. T1-weighted scans were then segmented into probability maps of gray matter, white matter, and cerebrospinal fluid. An average template was created by implementing SPM DARTEL across the entire cohort. This method iteratively aligns each participant's gray and white matter images as the average template is refined. Once completed, the segmented images from each participant were aligned with the final average template. The magnitude of tissue deformation necessary was captured in the Jacobian determinates from the deformation fields. The Jacobian determinates were used to scale the segmented images, producing modulated images to quantify the volume of tissue in each voxel. The study template was then normalized to MNI space, and these warping parameters were applied to the participant images. All images were smoothed using an 8 mm^3 Gaussian smoothing kernel and used for statistical assessments.

2.3.2. Statistical analysis

Voxel-wise group comparisons and regression analyses were performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Voxel-wise unpaired two sample t-tests were used to compare GM and WM volume between FW and NFW as well as OP exposed and not exposed groups. Regression analysis was conducted on the entire sample to find the association between GM and WM volume and the number of OC types detected in the wristbands. In all analyses, total intracranial volume (TIV), age, gender, and handedness were included as covariates. We used implicit and absolute threshold masking with a threshold of 0.1. Statistical significance for these comparisons was set at $p < 0.005$ and corrected for multiple comparisons at $p \leq 0.05$ using a cluster extent correction [60].

2.4. Diffuse tensor imaging (DTI)

2.4.1. Image processing

Data analyses were carried out with the FSL toolbox (FMRIB Software Library v6.0) [61]. In the first step, the data were pre-processed by applying the motion and eddy current correction. Motion correction was done by affine registration of DWI images to the b0 image, and nine children were removed from subsequent analyses due to excessive head motion (motion greater than the size of a voxel in any direction).

To investigate the white matter differences between the two groups, Tract-Based Spatial Statistics (TBSS) were used [62]. To apply TBSS, first, the tensor model was separately fitted to every voxel of each participant's diffusion data, and Eigenvalues and Eigenvectors of the tensor model were estimated. The Fractional Anisotropy (FA) maps were then extracted from the Eigenvalues maps. FA is an index of diffusion asymmetry within a voxel and has a value between 0 and 1. For isotropic diffusion, this value is 0, and for total anisotropic diffusion, the value is 1. Next, FA images of all participants were registered to standard brain space (1 × 1 × 1 MNI-152). Instead of using the standard adult template, the most representative FA image was used as the standard template for this study of children. The most representative FA image was selected by performing registration between all pairs of participants' FA images and choosing the image with the minimum required deformation to register to all other participants' FA images. The registration of FA images to the study specific standard template, was done using a three-step registration procedure: (1) the FA maps were registered to the image of the most representative participant, selected based on the lowest cost function after registering all participants' FA images to that image; (2) the representative image was warped to the standard space; and (3) the FA images from all participants were warped to standard space using the transformation from the representative image.

Following registration of FA maps into the standard space, the mean FA of all images was computed by averaging FA maps in the standard space and thinned to extract the fiber tracts skeleton. Thinning refers to a morphological operation for extracting the thin version, skeleton, of an object in an image. The mean FA skeleton was then thresholded at 0.2. Next, each participant's FA map was projected onto the FA skeleton by finding maximum FA's perpendicular to the skeleton. This step provided the projection of each participant's FA map on the mean skeleton, which were later used in the voxel-wise cross-subject analysis. In addition to FA, which is the normalized variance of the three eigenvalues, we also extracted the following maps: axial diffusivity (AD), which is the principal eigenvalue in the direction of highest diffusion, radial diffusivity (RD), which is the mean of the second and third eigenvalue, and mean diffusivity (MD), which is the mean of the three eigenvalues. The derived nonlinear warping for FA was also used to project MD, AD,

and RD on the FA derived mean skeleton.

2.4.2. Statistical analysis

To identify group differences, voxel-wise unpaired two sample t-tests were applied to the projected maps (FA, AD, MD, RD) on the mean FA skeleton using the "randomize" tool within FSL with 500 permutations to control for the family-wise error rate. Instead of using a parametric null distribution, randomize uses the data to create the null distribution based on non-parametric permutation [63]. We used the threshold-free cluster enhancement (TFCE) option with a p-value of 0.05. Regression analysis was conducted utilizing the same tool, with FA as the dependent variable and OC exposure as the main independent variable. Age, gender, and handedness were included as covariates for all analyses.

3. Results

3.1. Farmworker vs non-farm worker brain structure difference

The demographics, including age, gender, handedness, and total intracranial volume (TIV) for the two study populations, are reported in Table 1. For categorical variables (gender and handedness), the chi-squared test, and for the continuous variable (age), a two-sample *t*-test was used to compare the two studied groups. No between-group differences were significant.

3.2. Voxel-based morphometry (VBM)

Differences in white matter and gray matter volume between FW and NFW children were observed while we were controlling for gender, age, handedness, and TIV. Fig. 1-A displays the differences identified in gray matter between FW and NFW children. Gray matter was found to be greater in NFW children than FW in the prefrontal cortex. Specifically, higher gray matter volume was identified in the medial prefrontal, superior prefrontal, and gyrus rectus of the frontal pole. The difference in white matter was discovered in distinct brain regions, with the white matter volume also greater in NFW children than in FW (Fig. 1-B). These differences were observed bilaterally in the genu, splenium, and posterior thalamic radiation and superior longitudinal fasciculus tracts regions as well as the left part of forceps minor, right cingulate gyrus, and right body of corpus callosum. The details of the cluster size, significance, and location of the voxels with the highest values for gray and white matter differences are reported in Table 2. Our examination of inverse contrast revealed no significant differences in white or gray matter volume in FW children.

3.3. Diffuse tensor imaging (DTI)

TBSS voxel-wise analysis showed significantly higher fractional anisotropy (FA) in white matter tracts of NFW children than FW children, controlling for age, gender, and handedness. Fig. 2 illustrates the comparison of the FA between the two groups. The location of the peak voxels and associated p-values can be found in Table 1 of the Supplementary material. While the results exhibit significantly higher fractional anisotropy in several bilaterally distributed parts of the NFW's white matter, no part of the FW children's white matter showed higher FA than the NFW. For Rd, MD and AD, no significant results were observed.

The higher FA in NFW children's brain was distributed in several parts of the white matter. Specifically, the lower FA was observed bilaterally in the genu of the corpus callosum, external capsule (EC), posterior limb of internal capsule (PLIC), anterior limb of internal capsule (ALIC), posterior thalamic radiation (PTR), forceps minor (FM), fornix (FX) and laterally in right anterior corona radiata (ACR), superior corona radiata (SCR), posterior thalamic radiation (PTR), and superior longitudinal fasciculus (SLF).

3.4. Combined modalities

To explore multimodal findings, we overlapped results from the VBM analysis with TBSS results. Fig. 3 demonstrates the overlap of the results where the brain structure measures are higher in NFW children than in FW. The background is the mean FA image. The

Table 1
Participant demographics.

Variables		Children From Farmworker Families (n = 48)	Children From Non-Farmworker Families (n = 23)
Age	Years	8.36 ± 0.31	8.41 ± 0.32
Gender	Male, Female	23, 25	9, 14
Handedness	Right, Left, Undefined	45, 3, 0	20, 2, 1
Grade	1, 2, 3,4	6, 28, 14, 0	0, 10, 12, 1
Race	White, Mixed/ Mestizo, Other, Undefined	31, 17, 0, 0	10, 1, 11, 1
Highest Level of Mother Education	–	7.85 ± 3.64	9.57 ± 3.22
Total Intracranial Volume (TIV)	ml	1392.54 ± 108.07	1410.93 ± 137.817

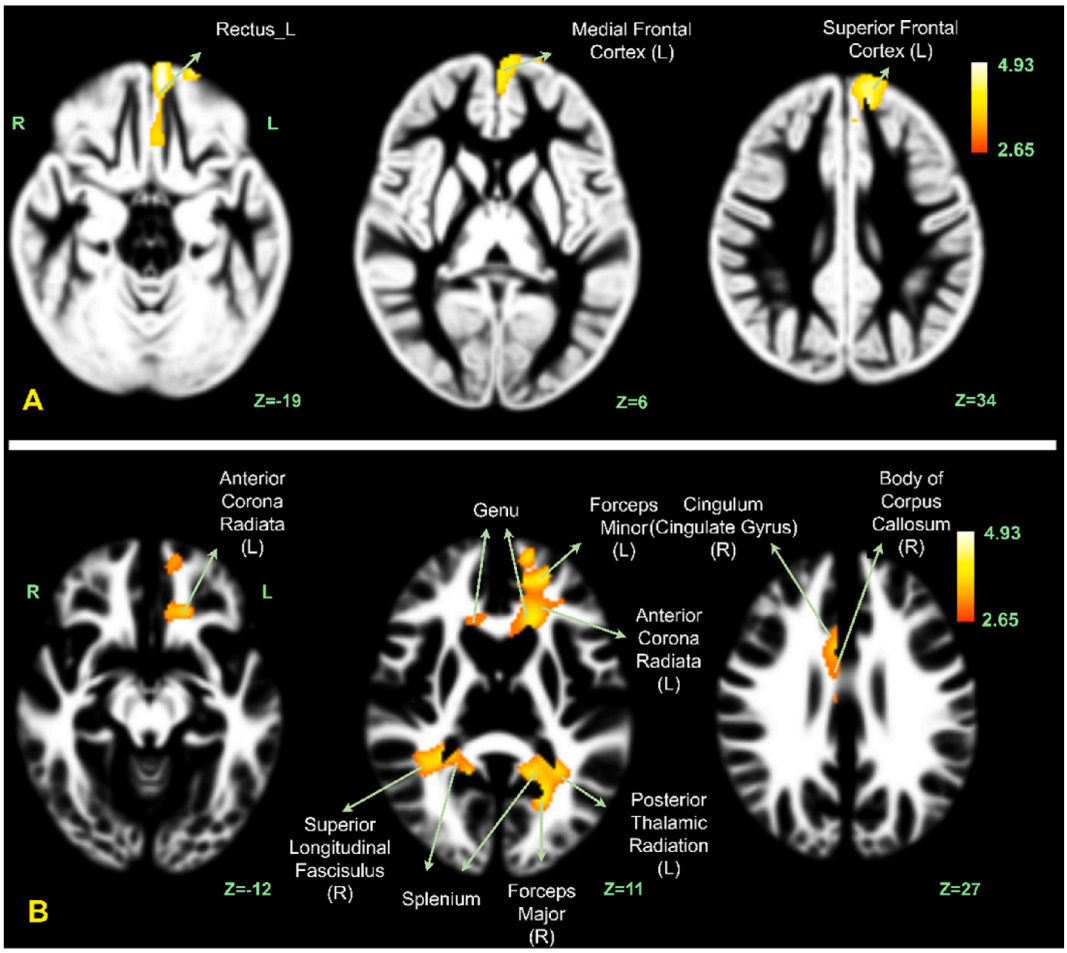

Fig. 1. A. Gray matter volume differences between NFW and FW children. The highlighted regions represent areas of higher gray matter volume in NFW children compared to FW children, including the medial frontal cortex, as well as the left superior frontal cortex and gyrus rectus. All regions shown are significant at $p < 0.05$ after correction for multiple comparisons. B. White matter volume differences between NFW and FW children. The areas shown represent areas of higher white matter volume in NFW children as compared to FW children. These include bilaterally in the genu and splenium of the corpus callosum, as well as posterior thalamic radiation and superior longitudinal fasciculus tracts regions. Furthermore, lateral differences were observed in left forceps major and minor, anterior corona radiata plus right body of corpus callosum, and cingulum. All shown regions are significant at $p < 0.05$ after correction for multiple comparisons.

Table 2
The regions with the most significant volume differences between the children from NFW and FW families.

	Region	Size	p-value	z score	Peak voxel coordinates
Gray Matter					
	Frontal Pole (Rectus L)	2004	0.003	3.74	2,64,15
	Frontal Pole (Medial Frontal Cortex L)	858	0.037	3.79	−4,58,-18
White Matter					
	Posterior Thalamic Radiation L	1574	0.006	4.52	−28,-52,-4
	Anterior Corona Radiata L	3042	<0.001	3.86	−14, 45, 8
	Posterior Thalamic Radiation R	1186	0.015	3.56	28, −42, 12
	Cingulum (Cingulate Gyrus) L	977	0.026	3.27	6, 12, 27

white matter skeleton is white, and the FA difference is marked with yellow. White matter volume differences are in green, and red represents the difference in gray matter volume. The two modalities demonstrated overlap in observed differences within the medial frontal lobe, where higher gray matter is accompanied by a higher white matter volume of the genu and higher FA of forceps minor in NFW children. Furthermore, the white matter volume and FA difference of both groups exhibited overlaps in the genu, right posterior thalamic radiation, and right anterior corona radiata.

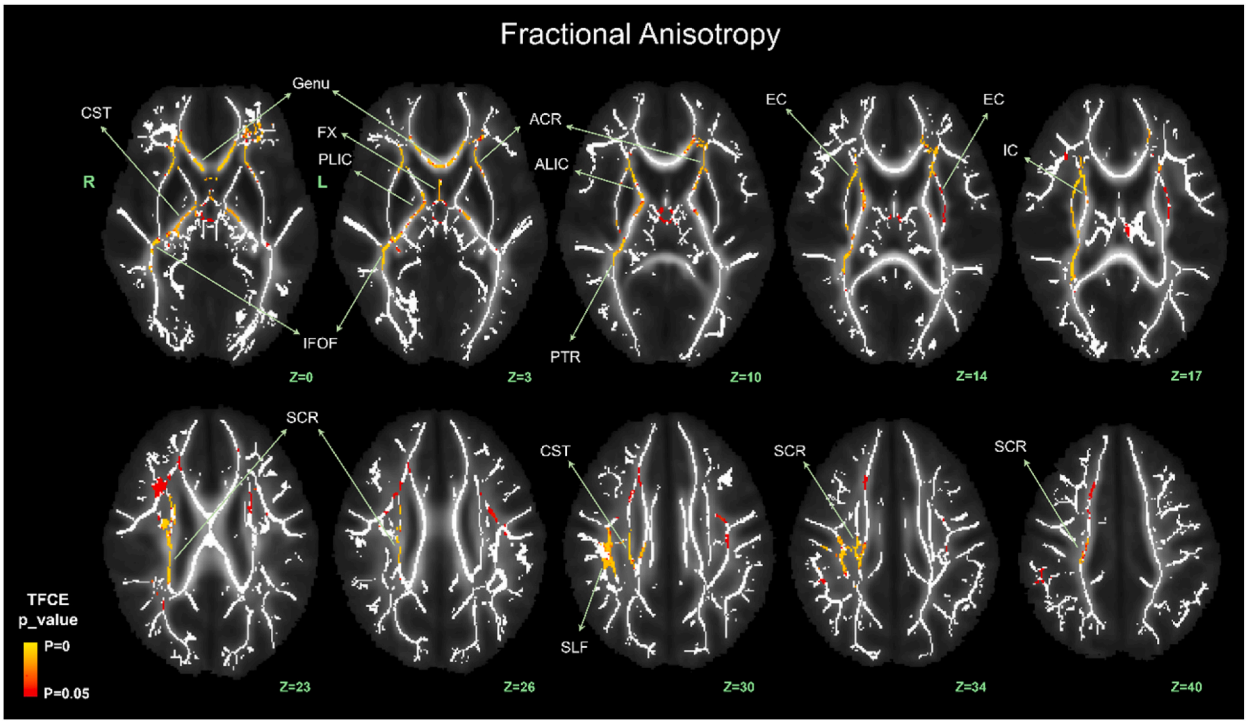

Fig. 2. TBSS showed higher local FA in the white matter of children from NFW families compared to children from FW families. Ten coronal slices through the brain are shown starting at z = 0 and moving superiorly to z = 40. The gray background is the mean FA image. The mean FA skeleton is shown in white. The red regions illustrate significant group differences where FA in the control group is higher than in the farmworker children group (TFCE p-value<0.05). Observed differences were identified in the genu of the corpus callosum, internal capsule (IC), external capsule (EC), fornix (FX), posterior limb of the internal capsule (PLIC), anterior limb of the internal capsule (ALIC), posterior thalamic radiation (PTR), superior corona radiata (SCR), superior longitudinal fasciculus (SLF), Inferior Fronto-Occipital fascicle (IFOF), forceps minor (FM), anterior corona radiata (ACR) and corticospinal tracts (CST). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

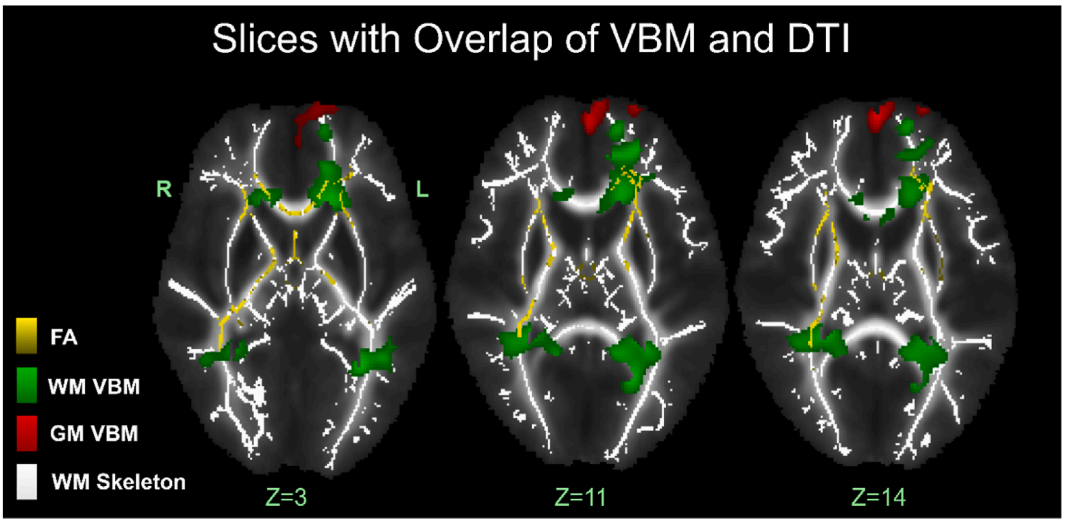

Fig. 3. The overlap of VBM and DTI findings on the mean FA image. Three coronal slices through the brain are shown starting at z = 3 and moving superiorly to z = 14. All results presented are associated with higher brain structure measures in NFW as compared to FW. White: White matter skeleton, Yellow: Fractional anisotropy difference between the two groups. Green: white matter difference between the two groups. Red: gray matter difference between the two groups. The overlap of gray matter and white matter findings was observed in the medial frontal lobe. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.5. Pesticides association with brain structure

We investigated the correlation between brain structure and exposure to pesticides, specifically OP and OC, using data collected from the wristbands. For OP, we divided the study participants into two groups: exposed and non-exposed. TBSS and VBM analyses did not reveal any significant group differences. As mentioned, OC exposure data collected through wristbands was treated as a continuous variable. This allowed us to perform a regression analysis to examine the relationship between the number of types of OC exposure in each participant and brain structure. The analysis of white matter revealed statistically significant results and several overlapping regions with previously observed differences between NFW and FW groups. Fig. 4 demonstrates the positive associations between OC exposure with white matter volume (A) and FA (C). In addition, a single connected region displayed a positive association between gray matter volume and OC exposure (Fig. 4B). The location of the peak voxels and associated p-values can be found in Table 2 of the Supplementary material. No negative correlation was observed for any of the three analyses.

4. Discussion

4.1. Summary

The present study sought to identify anatomical differences in Latinx children from rural FW families and urban NFW families. We investigated the morphological difference in the gray and white matter as well as the integrity of white matter tracts and found NFW children exhibited higher white matter volume and FA in several brain regions than FW children. Although only located in the prefrontal cortex, selected regions of gray matter were identified with higher volume in NFW children. We observed a good overlap between gray and white matter findings in the medial frontal lobe. Additionally, our analysis of the association between pesticide exposure (OC and OP) and brain structure revealed a positive correlation between OC exposure and the identified white and gray matter differences. Observed white matter differences were consistent with the group comparisons indicating higher volume and FA was present in the group with higher OC exposure. Given the higher levels of OC exposure found in NFW children in our previous study

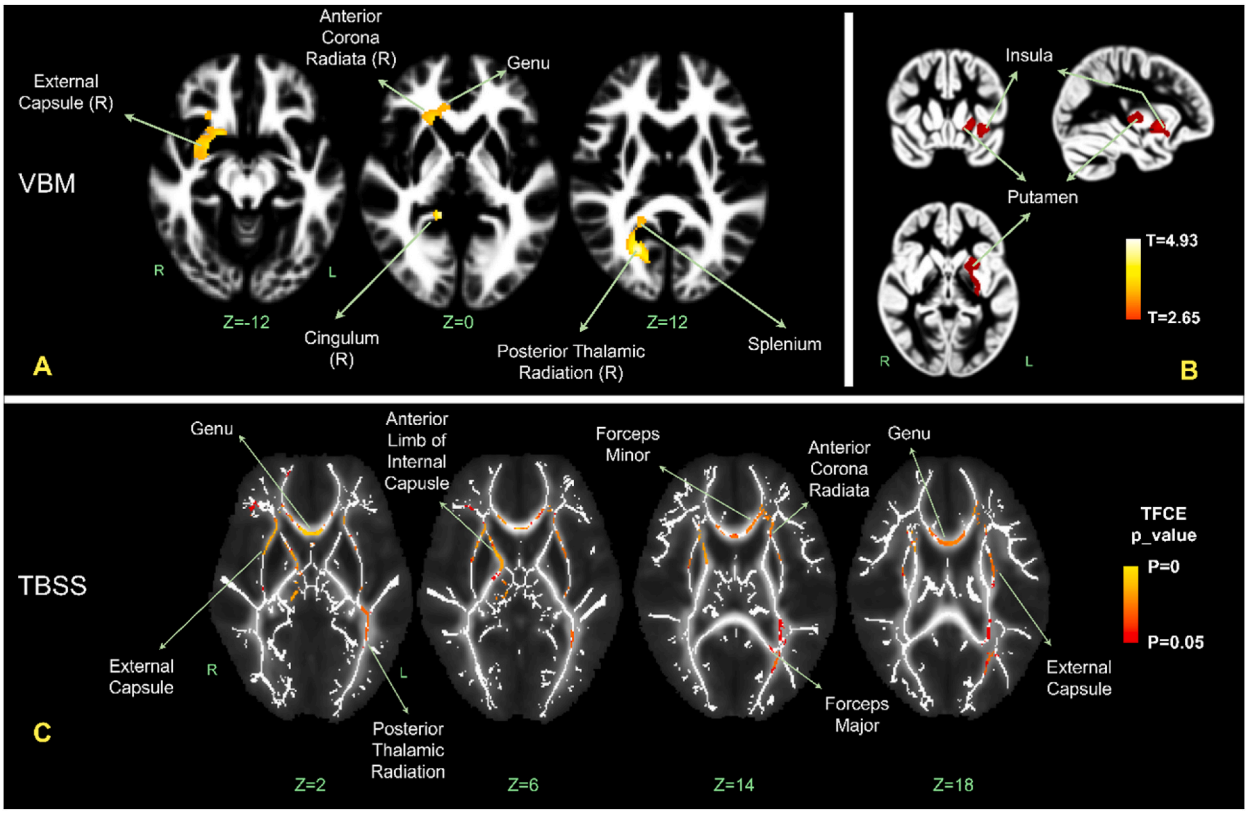

Fig. 4. A: The correlation between OC exposure and white matter volume, revealing statistically significant associations in regions including the right external capsule, posterior thalamic radiation, splenium, genu, and cingulum. B: Areas of gray matter with an association between GM volume and organophosphate exposure. This includes part of the left putamen and the insula. C: The association between OC exposure and fractional anisotropy of the main fiber tracts, with statistically significant associations observed in regions such as the external capsule, genu, posterior thalamic radiation, anterior limb of the internal capsule, forceps minor and major, and anterior corona radiata. All the observed correlations were positive.

using this data set [48], it is plausible to consider OC as a potential contributing factor to the observed differences in white matter structure between NFW and FW children.

4.2. NFW and FW children brain differences in frontal lobe

Several studies have previously linked pesticide exposure with the frontal lobe of the brain [31,64–66]. In the first functional neuroimaging study of prenatal OP exposure, Sagiv et al. [64] used functional near-infrared spectroscopy (fNIRS) coupled with tasks for working memory, cognitive flexibility, and language comprehension. Their results indicated that prenatal OP exposure alters brain activation during cognitive tasks, which included decreased brain activation in the bilateral prefrontal cortex during flexibility and N-back working memory tasks. Further investigation into the effects of OP on the brain's function demonstrated a decline in brain activity in the frontal lobe related to increased prenatal metabolites during a motor inhibition task [65]. Furthermore, changes in the size of the surface of the regions within the frontal lobe, including multiple regions within the MFC, have also been associated with OP exposure in children [31]. In the only neuroimaging study on OC, increases in the left frontal lobe activity during language comprehension, Sternberg working memory, and visuospatial tasks associated with childhood OC exposure were reported [66]. Our findings investigating neuroanatomical differences between FW and NFW children groups revealed an overlap of VBM and DTI analysis findings in the left medial frontal cortex (MFC). MFC has been associated with important cognitive functions such as decision-making, attention, and error processing [67–69]. Difficulties with attention, particularly attention deficit hyperactivity disorder (ADHD), has been linked to OC exposure [70–73]. Therefore, the observed structural difference in the MFC between NFW and FW children suggests a potential association with OC exposure.

4.3. Organochlorine and organophosphate pesticide associations with brain structure

We investigated the association between brain structure and pesticide exposures (OC and OP) to get further insight into the observed difference between the two groups. OP and OC pesticides originate from distinct chemical sources. OPs are synthesized from the esterification of phosphoric acid, while OCs are derived from chlorinated hydrocarbons [74]. Both types of pesticides are highly toxic, but they differ in their half-lives. OPs have short half-lives, which lead to their fast metabolization and, consequently, their elimination from the body, primarily through urine, within 24–48 h [75]. In contrast, OCs are recognized for their long half-lives (up to 10–15 years for some specific types) and their ability to accumulate in living organisms [74]. This characteristic makes OC highly hazardous. Our previous study of this data set revealed that while FW children had higher exposure to OP, NFW children had higher exposure to OC [49]. Furthermore, NFW children scored lower on cognitive assessments as compared to FW children, a difference found to be associated with increased OC exposure in NFW children [48]. As mentioned previously, OC pesticide exposure has been associated with neurological impairment, including ADHD [70–73] and autism [76] in children and increased risk of dementia and Alzheimer's disease [77], and Parkinson's disease in adults [78]. Based on these findings, we hypothesized that OC might contribute to the observed structural differences between the FW and NFW groups. Our results from investigating the relationship between white matter structure and OC exposure (number of types of OC exposure) support this hypothesis. TBSS analysis revealed a positive association between the FA of several regions of white matter tracts and OC exposure. The associated areas had a substantial overlap with our observed differences between NFW and FW, specifically in the internal and external capsule and genu. Additionally, OC exposure had an association with variations in white matter volume, including parts of the genu and splenium, which were previously observed in the comparison of NFW and FW. Finally, a single region in the gray matter also exhibited a relationship with OC exposure; however, it did not have any overlap with observed gray matter group differences observed in the frontal lobe. Our results indicate that OC exposure may impact white matter structure at a faster rate than gray matter. Our analyses yield no association between OP exposure and structural brain change.

4.4. White matter differences

Comprising half of the brain, white matter tracts make necessary connections for information flow within the neural network [81]. FA, as a measure of white matter integrity, has been linked to myelination and axonal packing [79]. While higher FA is typically believed to reflect greater fiber tract integrity, high FA has been associated with childhood trauma [80], attention-deficit/hyperactivity disorder (ADHD) [81,82], and Williams Syndrome in children [83]. These findings indicate that higher FA is not always associated with better fiber tracts, and the interpretation of FA may vary depending on the studied groups. Our observations suggest a potential link between exposure to OC and FA, which may contribute to adverse effects on the integrity of white matter in children. White matter enlargement can also be associated with brain abnormalities. An increase in white matter volume has been associated with motor impairment in autistic children [84] as well as multiple sclerosis [85] in adults. We found a positive correlation between white matter volume and OC in several regions, emphasizing the impact OC may have on brain development.

4.5. Association of findings with structural neuroimaging literature

To our knowledge, this is the first structural neuroimaging study that examines the association between brain structure and both OP and OC exposures in humans. Previous reports in the literature linking brain structure with pesticide exposure have focused exclusively on OPs. The reported findings on the association between OP and the brain have been varied. Rauh et al. were among the first to examine the relationship between morphological changes within the brain and OP [31]. They found that high prenatal exposure

coincided with enlargement of the temporal lobe as well as postcentral gyri, superior frontal gyrus, gyrus rectus, cuneus, and precuneus. Their additional analysis on the surface of the white matter demonstrated white matter enlargement as the driving factor of the observed cerebral enlargement. In a recent study with a large sample size, van den Dries et al. reported no association between OP exposure and cortical surface size of thickness [32]. Our study aligns with their findings, as we found no association between OP exposure and GM or WM volume. Van den Dries et al. also reported a negative association between FA and OP exposure. We did not observe this association in our study. However, we observed positive associations between WM measures (FA and volume) and OC, which was not investigated before.

The interpretation of our results in light of previous studies should be approached with caution due to several technical differences in our approach. These differences could potentially explain the lack of observed associations between OP exposure and brain structure. First, both previous studies have investigated prenatal exposure, while we investigated postnatal exposure. Second, we used an exposure measure from a single time point that may not represent the child's typical exposure. The measure was, however, made in close temporal proximity to the MRI scan. Third, although chemical concentrations detected in wristbands have been associated with the corresponding biological concentrations in urine and serum [54–56], it does not directly detect chemicals absorbed in the body. Previous studies utilized direct measures, such as quantifying OP concentrations in umbilical cord blood [31] and maternal urine [32]. In addition, we might miss the FA associations with OP exposure due to our relatively small sample size of 71 participants, while Van den Dries's study had 518 participants. Furthermore, the age range of the study groups varies: Ruah's study ($n = 40$) included children aged 5.9–11.2 years old, van den Dries' study included children aged 9–12 years old, and our study had children aged 8–9 years old. Therefore, children in our dataset may exhibit structural differences related to OP exposure in the next few years of their lives. It is also worth considering that our sample comprised both urban non-farmworker and rural farmworker families, while the other studies only focused on urban children. The socioeconomic status of these children could potentially influence their exposure to various types of pesticides. Lastly, our previous study showed lower IQ scores of NFW children compared to FW, with OC exposure explaining a significant portion of the differences between the two groups [48]. Therefore, while we do not disregard the effect of OP on brain structure, OC exposure may exhibit a different mechanism of action toward structural brain changes. Our findings suggest that OC exposure may exert a more pronounced impact on brain structure in this particular population that could be detectable even in smaller sample sizes.

5. Limitations

The research undertaken was not without limitations, as is often the case in scientific inquiry. First, although we were able to correlate OC exposure with brain anatomy, regression analysis was not possible with the OP wristband as the data was binary (exposed, not exposed). Further research should examine the association between continuous variables associated with OP exposure, such as metabolites or cholinesterase activity levels. Moreover, it is crucial to acknowledge that for OC exposure, we opted to utilize the number of exposures to different OC types rather than exposure levels. This decision was made due to variations in the scaling of different OC types, which necessitated a different approach for capturing the cumulative OC exposure. Second, we were not able to perform analyses comparable to prior studies as we did not have blood or urine assessments of pesticide exposure during the gestational period. The third limitation was the sample size of NFW children, which was smaller than FW children, reducing the study's statistical power. In addition, there were also two limitations with diffusion MRI data analysis. First, the DTI data lacked complementary data for correcting the field map distortion. Second, we used DTI instead of the advanced diffusion MRI analysis techniques, which account for more than one direction of fibers in each voxel. We opted for a simple imaging sequence that was short in duration as it can be challenging for children to remain still throughout the duration of long scans. Given the data that we collected, the DTI analysis technique was the preferred method.

6. Conclusion

Our results showed that NFW children have a higher gray and white matter volume, as well as higher FA of the white matter, compared to FW children in the medial frontal lobe. Furthermore, we found a significant positive association between OC and white matter structure (FA and volume), which also had a good overlap with the observed difference between NFW-FW groups. Given the higher OC exposure levels in NFW children observed in our previous study, these findings suggest that OC pesticide exposure might have a great impact on children's brain development. In addition, these findings suggest that OC pesticide exposure may exert a more substantial effect on white matter than gray matter during childhood. It is possible that alterations in white matter structural connectivity negatively impact the flow of information between brain regions, which could be associated with deficits in cognitive function. To the best of our knowledge, this study is the first study investigating the association between brain structure and OC exposure. Future work will further examine the cognitive and behavioral implications of the observed white and gray matter differences by utilizing longitudinal assessments of brain structure, cognitive function, and pesticide exposure.

Author contribution statement

Mohammadreza Khodaei, Kim A. Anderson, Richard P. Scott, Sean L. Simpson: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Dorothy L. Dobbins: Analyzed and interpreted the data; Wrote the paper. Paul J. Laurienti: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Thomas A. Arcury: Conceived and designed the experiments; Performed the experiments; Wrote the paper. Sara A. Quandt:

Conceived and designed the experiments; Wrote the paper. Jonathan H. Burdette: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kim Anderson, an author of this research, discloses a financial interest in MyExposure, which is marketing products related research reported in this paper. The terms of this arrangement have been reviewed and approved by Oregon State University in accordance with its policy on research conflicts of interest. DLD is currently a medical writer with MedThink SciCom but did not participate in this capacity for the preparation of this manuscript; was employed at Wake Forest Baptist Health at the time of this study; does not support the panethnic use of Latinx. There was no other report from the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21929.

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