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Trajectories of brain white matter development in young children with prenatal alcohol exposure

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Abstract

Prenatal alcohol exposure (PAE) is associated with alterations to brain white matter microstructure. Previous studies of PAE have demonstrated different findings in young children compared to older children and adolescents, suggesting altered developmental trajectories and highlighting the need for longitudinal research. 122 datasets in 54 children with PAE (27 males) and 196 datasets in 89 children without PAE (45 males) were included in this analysis. Children underwent diffusion tensor imaging between 2 and 8 years of age, returning approximately every 6 months. Mean fractional anisotropy (FA) and mean diffusivity (MD) were obtained for 10 major brain white matter tracts and examined for age-related changes using linear mixed effects models with age, sex, group (PAE vs. control) and an age-by-group interaction. Children with PAE had slower decreases of MD over time in the genu of the corpus callosum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus. No significant age-by-group interactions were noted for FA. These findings show slower white matter development in young children with PAE than in unexposed controls. This connects previous cross-sectional findings of lower MD in young children with PAE to findings of higher MD in older children and adolescents with PAE, and further helps to understand brain development in children with PAE. This deviation from typical development trajectories may reflect altered brain plasticity, which has implications for cognitive and behavioral learning in children with PAE.

KEYWORDS
brain, children, fetal alcohol spectrum disorder, neuroimaging, prenatal alcohol exposure, white matter

1 | INTRODUCTION

Prenatal alcohol exposure (PAE) can result in a spectrum of serious consequences for the developing fetus including brain alterations, growth deficiency, craniofacial abnormalities, and physical health challenges (Cook et al., 2016). Brain structure and function are particularly vulnerable to the teratogenic effects of alcohol, with disruptions to neural and glial mechanisms, like proliferation, migration, synaptogenesis, and myelination (Goodlett et al., 2005; Petrelli et al., 2018; Wilhelm & Guizzetti, 2016). Effects vary with dose, timing, and pattern of PAE, but these neurological changes can lead to lifelong cognitive, communication, motor, behavioral, and mental health challenges for individuals with PAE (Cook et al., 2016; Mattson et al., 2019). In some cases, those with PAE will eventually be

diagnosed with fetal alcohol spectrum disorder (FASD), a severe and pervasive manifestation of neurodevelopmental impairments stemming from PAE (Cook et al., 2016), which has an estimated prevalence of 2–5% in North America (Flannigan et al., 2018; May et al., 2018).

Neurological changes associated with PAE have been identified using magnetic resonance imaging (MRI), including widespread reductions in cortical and subcortical volume, cortical surface area, cortical gyrification (Archibald et al., 2001; Astley et al., 2009; Rajaprakash et al., 2014), and increases and/or decreases in cortical thickness (Robertson et al., 2016; Yang et al., 2012) compared to unexposed controls (Donald, Eastman, et al., 2015; Nguyen et al., 2017). Diffusion tensor imaging (DTI) is sensitive to brain myelination, axon diameter, and packing (Beaulieu, 2002). To date, DTI studies of PAE have been predominantly cross-sectional and show heterogenous brain differences from infancy to adulthood (~2 weeks—32 years) (Ghazi Sherbaf et al., 2018). Newborns with PAE show lower diffusivity in the superior longitudinal fasciculus (SLF) compared to unexposed newborns (Donald, Roos, et al., 2015) and alterations throughout the brain (Taylor et al., 2016). Similarly, young children (2–7 years) generally show higher fractional anisotropy (FA) and/or lower mean diffusivity (MD) in brain white matter compared to unexposed children (Kar et al., 2021; Roos et al., 2021). In contrast, a broad range of literature in school-aged children, adolescents, and adults (~5–32 years) has consistently reported the opposite—lower FA and/or higher MD compared to unexposed controls—across white matter (Fan et al., 2016; Lebel et al., 2008; Paolozza et al., 2017; Sowell et al., 2008; Wozniak et al., 2006; Wozniak et al., 2009) with only a few exceptions (Fryer et al., 2009; Lebel et al., 2008; Uban et al., 2017). To date, one study has examined white matter microstructure longitudinally, showing steeper decreases of MD in the SLF, the inferior longitudinal fasciculus (ILF), and the superior fronto-occipital fasciculus (SFOF) in 5–15-year olds with PAE compared to unexposed controls (Treit et al., 2013). Thus, white matter alterations are present at all ages and across regions of the brain, but their manifestations vary by age. Together, these results suggest that brain development occurs atypically in children with PAE, but longitudinal studies spanning early childhood are needed to understand trajectories and connect findings in younger and older children with PAE.

Here, we investigated the association between PAE and developmental trajectories of white matter microstructure between 2 and 8 years of age for the first time. Based on previous research in younger (Kar et al., 2021; Roos et al., 2021; Taylor et al., 2016) and older children (Treit et al., 2013), we hypothesized that young children with PAE would demonstrate slower increases in FA and slower decreases in MD compared to unexposed controls.

2 | METHODS AND MATERIALS

2.1 | Participants with PAE

Children between 2 and 7 years of age with PAE were recruited through caregiver support groups, early intervention services, and Alberta Children's Services in Alberta, Canada. Exclusion criteria were birth before 34 weeks' gestation, children for whom English was not a primary language, history of head trauma, a diagnosis of autism, Cerebral palsy, epilepsy or any other medical or genetic disorder associated with serious motor or cognitive disability, and contraindications to MRI (e.g., metal implants, dental braces). Children with attention deficit hyperactivity disorder (ADHD), learning disabilities, language delays, and/or mental health diagnoses were included, as these diagnoses are frequently comorbid with PAE. In total, 57 children with confirmed PAE were recruited; 1 child was excluded for an incidental finding on the MRI scan and 2 children did not feel comfortable receiving an MRI scan, leaving 54 children with PAE for analyses. At their first MRI scan, children with PAE were aged 2.49–6.97 years (5.21 ± 1.11 years; 27 males/27 females) and included one pair of twins, one pair of non-twin full-siblings, one set of three non-twin full-siblings, and four pairs of non-twin half-siblings. None of these participants were diagnosed with FASD or any alcohol-exposure related diagnosis (e.g., fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder) as most clinics in Alberta, Canada do not assess children for FASD until they are at least 7 years old (Cook et al., 2016; Flannigan et al., 2019; McLachlan et al., 2015). Children and caregivers were invited to return approximately every 6 months for a follow-up MRI scan over several years. In total, we collected 122 datasets (full age range is 2.48–8.07 years; mean age at scan is 5.66 ± 1.17 years) and average time between visits was 0.73 ± 0.28 years (0.35–1.64 years). The average time between the first and last scan was 1.21 ± 0.43 years (0.51–1.98 years). Data here include 13 children with only one scan time point, 20 children with two scans, 15 with three scans, and 6 with four scans (Figure 1).

Detailed information about each child's prenatal and/or postnatal adverse experiences were obtained using their child welfare file (containing information from birth families, social workers, police records, and medical files) and/or from a semi-structured interview with current caregivers, caseworkers, and/or birth families. A previously reported framework was used to comprehensively evaluate their prenatal and postnatal exposures (Lebel et al., 2019) and profiles are described in a previous study in this sample (Kar et al., 2021). All participants had confirmed PAE. 31% ($n = 17$) had confirmed PAE greater than or equal to the threshold indicated by the Canadian Diagnostic Guidelines for FASD (Cook et al., 2016): ≥7 drinks in one week and/or two or more binge episodes (≥4 drinks at one time) during pregnancy; 69% ($n = 37$) had confirmed PAE of an unspecified amount. 94% ($n = 51$) of participants with PAE also had prenatal exposure to other substances. 74% ($n = 40$) had adverse postnatal experiences such as neglect, physical/sexual/emotional abuse, witnessing violence and/or substance use, and/or multiple caregiver transitions. The remaining 26% ($n = 14$) of participants with PAE had no postnatal adverse exposures. No participants with PAE were residing with their biological parents; all were in adoptive, foster, or kinship care. The average age of stable placement, after which there were no more postnatal adverse experiences (as defined above), ranged from 0 to 4.08 years (0.92 ± 1.14 years). In demographic surveys completed at the child's

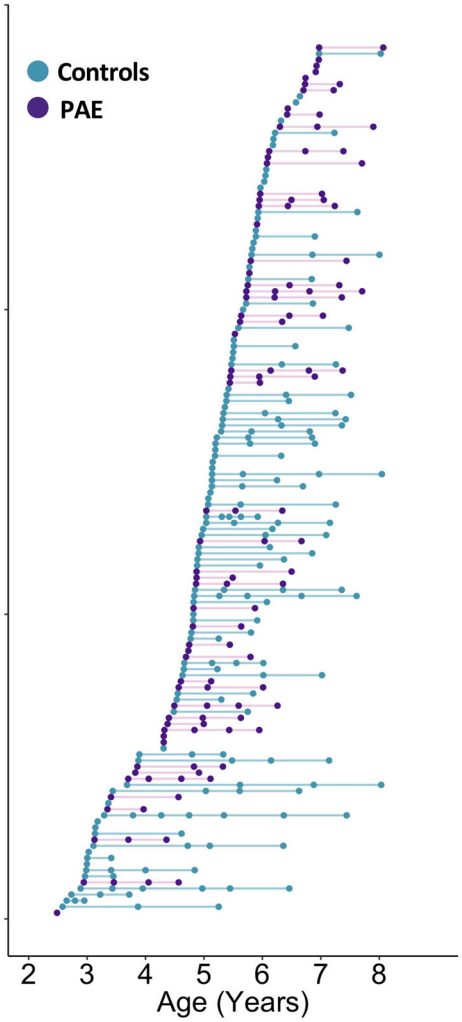

FIGURE 1 Age at MRI scans for participants (controls shown in blue, children with prenatal alcohol exposure (PAE) shown in purple). Each of the scans (196 control scans, 122 PAE scans) are represented by a circle while each of the participants (54 PAE, 89 controls) have a unique row with their scans connected by a line. There were no significant differences in average age or age at first scan between groups.

scan, current caregivers reported the child's ethnicity and household income. 53.7% of children were First Nations, 29.6% were White, 5.6% were multiracial (First Nations and White), and the remaining 11.1% were missing data. The median household income was 75,000–99,999 CAD (~59,700–79,600 USD).

2.2 | Control participants

Typically-developing participants were recruited from Calgary and surrounding areas as well as from the ongoing Alberta Pregnancy Outcomes and Nutrition (APrON) study (Kaplan et al., 2014). Inclusion criteria were born >36 weeks' gestation, spoke English as a primary language, had no contraindications to MRI scans as well as had no history of developmental disorders or brain trauma. A total of 89 typically-developing children were included as unexposed controls (Reynolds et al., 2019; Reynolds et al., 2020). For their first MRI scan, children were 2.58–6.96 years of age (4.90 ± 1.05 years; 43 males/46 females) and the sample included two pairs of non-twin full-siblings. Children and caregivers were invited to return approximately every 6 months for a follow-up scan for a total of 196 datasets (range of age at scan is 2.58–8.04 years; mean age at scan ± SD of 5.46 ± 1.24 years) and with average time between visits being 0.83 ± 0.41 years (0.11–2.71 years). The average time between the first and last scan was 1.63 ± 0.89 years (0.30–4.35 years). Data here include 27 children with only one scan time point, 27 children with two scans, 14 with three scans, 12 with four scans, 3 with five scans, 3 with six scans, and 1 with seven scans (Figure 1).

Control participants had confirmed absence of PAE and prenatal exposure to other substances based on prospective questionnaires and interviews completed with the mother during pregnancy as well as no reports of postnatal adversities (i.e., abuse, neglect). Control participants were still residing with their biological parent(s) at the time of their MRI scan. Caregivers completed demographic surveys at the child's scan where they reported their maternal and paternal ethnicity as well as household income. 74.2% of children were White, 13.5% were multiracial, 1.1% were Asian, and the remaining 11.2% were missing data. The median household income was 100,000–124,999 CAD (~79,600–99,600 USD).

Parent/guardian written informed consent and child verbal assent were obtained for each subject. The University of Calgary Conjoint Health Research Ethics Board (CHREB) approved this study (REB14-2266, REB13-020).

2.3 | Neuroimaging data acquisition

MRI scans were completed on a research-dedicated GE 3T MR750w system with a 32-channel head coil at the Alberta Children's Hospital. Families were given reading materials to prepare children at home and were offered one or more practice sessions in an MRI simulator (Thieba et al., 2018). To minimize head motion throughout the scan, foam padding was used, and children were able to watch a movie using headphones, a projector, and a screen. Whole-brain diffusion weighted images were acquired in 4:03 min using single shot spin echo echo-planar imaging sequence with: 1.6 × 1.6 × 2.2 mm resolution (resampled to 0.78 × 0.78 × 2.2 mm on scanner), TR = 6750 ms; TE = 79 ms, 30 gradient encoding directions at $b = 750$ s/mm^2, and 5 interleaved images without diffusion encoding at $b = 0$ s/mm^2.

2.4 | Neuroimaging data processing

Each DTI scan was visually inspected for quality, and volumes with artifacts or motion corruption were removed (Reynolds et al., 2019; Walton et al., 2018). Children with PAE had 18–30 diffusion weighted volumes (26 ± 4) and 3–5 non-diffusion weighted volumes (5 ± 1) remaining after removal of motion-corrupted volumes, while

unexposed controls had 18–30 diffusion weighted volumes (mean ± SD 28 ± 3) and 3–5 non-diffusion weighted volumes (5 ± 0) remaining. Using ExploreDTI (V4.8.6), data were preprocessed which involved corrections for signal drift, Gibbs ringing, subject motion, and eddy current distortions (Leemans et al., 2009). Afterwards, semi-automated deterministic streamline tractography was used to delineate 10 major white matter tracts: the corpus callosum (genu, body, splenium), and the fornix as well as the cingulum, pyramidal tract, uncinate fasciculus, SLF, ILF, and inferior fronto-occipital fasciculus (IFOF) (Lebel et al., 2008; Lebel, Gee, et al., 2012; Reynolds et al., 2019). Guides for region of interest semi-automated tractography can be found online at: https://doi.org/10.6084/m9.figshare.7603271 (Reynolds et al., 2020). The minimum FA threshold was set to 0.20 to initiate and continue tracking, and the angle threshold was set to 30° to minimize spurious fibers (Lebel et al., 2008; Reynolds et al., 2019). Each tract was manually quality checked and additional exclusion regions were drawn as required to remove spurious fibers. FA, MD, axial diffusivity (AD), and radial diffusivity (RD) values were calculated for every tract, separately for left and right hemisphere and subsequently averaged where relevant (i.e., all tracts except the corpus callosum and fornix). Diffusion measures were averaged between left and right hemisphere tracts as there is little evidence for asymmetry of FA and MD based on previous a previous study in this sample (Kar et al., 2021). As well, FA and MD were calculated across all streamlines in the whole brain to provide global white matter measures.

2.5 | Statistical analysis

Using SPSS (Version 25), two-tailed *t* tests were used to test group differences (i.e., unexposed controls vs. children with PAE) for child's age at first scan, average age at scan across all visits, number of diffusion-weighted volumes, time between each scan, and time between first and last scan; a chi-squared test was used to test group differences for sex and ethnicity, and a Kruskal–Wallis test was used to test group differences of income. Linear mixed models were completed using RStudio version 1.1.463 (RStudio Team, 2020) using the "lme4" (Bates et al., 2015) and "lmerTest" (Kuznetsova et al., 2017) packages. For the first analysis, linear mixed models were run to determine linear age-related changes in FA and MD for each tract and for global white matter. Developmental trajectories were compared between PAE and unexposed control groups. Linear ($y = \text{age} + \text{sex} + \text{group} + \text{age} \times \text{group} + [1|\text{Subject}]$) terms were modelled, with age, sex, and interactions modelled as fixed factors and subject modelled as a random factor. Restricted maximum likelihood (REML) was set to false. A significant age-by-group interaction indicates different linear trajectories between groups (PAE vs. control). If the interaction was not significant, it was removed, and the model was run without it. To further investigate tracts showing significant group differences in FA or MD, linear mixed models was used to determine linear age-related changes in AD and RD using the same model. False discovery rate (FDR) was used to correct for 22 multiple comparisons (2 tract parameters—FA, MD—for 10 individual tracts and the whole brain), with significance set at $q < 0.05$. MD, RD, AD values were scaled by 1000 to make them similar to other measures for analysis.

Three supplementary analyses were run. First, the number of remaining diffusion weighted volumes was added as a covariate to the linear mixed model analysis to account for motion in the scans ($y = \text{age} + \text{sex} + \text{group} + \text{age} \times \text{group} + \text{number of diffusion-weighted volumes} + [1|\text{Subject}]$). Second, age at stable placement was added as a covariate to the linear mixed model analysis to account for the duration of exposure to postnatal adversities ($y = \text{age} + \text{sex} + \text{group} + \text{age} \times \text{group} + \text{age at stable placement} + [1|\text{Subject}]$) (Andre et al., 2020). Lastly, income and ethnicity were added as covariates to the linear mixed model analysis to account for sociodemographic backgrounds of children ($y = \text{age} + \text{sex} + \text{group} + \text{age} \times \text{group} + \text{income} + \text{ethnicity} + [1|\text{Subject}]$).

2.6 | Consent

Parent/guardian written informed consent and child verbal assent were obtained for each subject.

3 | RESULTS

3.1 | Participant characteristics

There were no significant group differences for age at first scan, average age across all scans, sex, or non-diffusion weighted images remaining (Table 1). The PAE group had significantly less time between each scan ($p = .037$) and significantly less time between the first and last scan ($p = .002$) compared to the control group. Unexposed controls had significantly more diffusion-weighted volumes remaining ($p < .001$), significantly higher income ($p < .001$), and significantly different ethnicities ($p < .001$) compared to children with PAE.

3.2 | Fractional anisotropy

There were no significant group-by-age interactions for FA in the whole brain or any individual tracts. Main effects of group were noted for FA in the genu ($p = .003$, $q = 0.018$) and the body ($p = .025$, $q = 0.042$) of the corpus callosum, where children with PAE had higher FA compared to unexposed controls. There was also a main effect of group for FA in the fornix ($p = .018$, $q = 0.033$), such that children with PAE had lower FA compared to controls (Table 2).

3.3 | Mean diffusivity

The age-by-group interaction was significant for MD in the whole brain ($p = .012$, $q = 0.030$). Among individual tracts, the age-by-group

TABLE 1 Participant characteristics

	PAE	Control	
	(*n* = 54; 122 datasets)	(*n* = 89; 196 datasets)	*p*
Age at first scan (years)	5.21 ± 1.11 (2.48–6.97)	4.90 ± 1.05 (2.58–6.96)	.097
Age at all scans (years)	5.66 ± 1.17 (2.48–8.07)	5.46 ± 1.24 (2.58–8.04)	.147
Time between each scan (years)	0.73 ± 0.28 (0.35–1.64)	0.83 ± 0.41 (0.11–2.71)	.037*
Time between first and last scan (years)	1.21 ± 0.43 (0.51–1.98)	1.63 ± 0.89 (0.30–4.35)	.002*
Sex	27 males/27 females	43 males/46 females	.491
Income	75,000–99,999 CAD (∼59,700–79,600 USD)	100,000–124,999 CAD (∼79,600–99,600 USD)	<.001*
Ethnicity	29.6% White 53.7% First Nations 5.6% multiracial	74.2% White 1.1% Asian 13.5% multiracial	<.001*
Diffusion-weighted images	26 ± 4 (18–30)	28 ± 3 (18–30)	<.001*
Non-diffusion weighted images	5 ± 1 (3–5)	5 ± 0 (3–5)	.057

Note: Demographic data is provided for both groups. Significant differences ($p < .05$) are noted with *.

interactions for MD were significant in the genu of the corpus callosum ($p = .031$, $q = 0.049$), the inferior longitudinal fasciculus ($p = .006$, $q = 0.018$), the inferior fronto-occipital fasciculus ($p = 0.002$, $q = 0.012$), and the uncinate fasciculus ($p = .016$, $q = 0.032$). For all interaction effects, children with PAE showed slower decreases in MD compared to unexposed controls. There was also a significant main effect of group in the whole brain and all tracts with interactions effects, where children with PAE had lower MD compared to controls (Table 3, Figure 2).

3.4 | Axial and radial diffusivity

Significant age-by-group interactions were present for RD in the genu of the corpus callosum ($p = .003$; $q = 0.004$), the ILF ($p < .001$; $q < 0.001$), the IFOF ($p < .001$; $q < 0.001$), and the uncinate fasciculus ($p < .001$; $q < 0.001$). A main effect of group was present in all tracts with significant interactions. RD was lower and showed slower decreases across age in children with PAE compared to unexposed controls (Table S1). Significant age-by-group interactions were present for AD in the genu ($p = .020$; $q = 0.029$), the ILF ($p < .001$; $q < 0.001$), the IFOF ($p < 0.001$; $q < 0.001$), and the uncinate fasciculus ($p < .001$; $q < 0.001$). A main effect of group was present in all tracts with significant interactions. Similar to RD, the PAE group showed lower AD and slower decreases across age compared to unexposed controls (Table S2).

3.5 | Supplementary analyses

The main effect of group for FA in the body of the corpus callosum was no longer significant after controlling for age at stable placement or income and ethnicity of participants. The main effect of group for FA in the fornix was no longer significant after controlling for income and ethnicity of participants. All other group main effects and age-by-group interactions remained significant after accounting for the number of remaining diffusion-weighted volumes, age at stable placement, or income and ethnicity.

4 | DISCUSSION

Here we show altered development= trajectories of white matter microstructure in young children with PAE for the first time. Compared to unexposed controls, the PAE group showed slower white matter development in frontal and temporal tracts, demonstrating deviations from typical white matter development trajectories and suggesting reduced brain plasticity. This ties together previous work in young children and older children with PAE and has implications for cognitive and behavioral learning and outcomes in children with PAE.

Young children with PAE showed slower age-related decreases of MD in the genu of the corpus callosum, IFOF, ILF, and uncinate fasciculus compared to unexposed controls. Previous cross-sectional studies in infants, toddlers, and young children (2–7 years) with PAE have shown lower MD in white matter (Kar et al., 2021; Roos et al., 2021; Taylor et al., 2016) whereas studies in older children and adolescents (∼5–32 years) with PAE have shown higher MD (Fan et al., 2016; Ghazi Sherbaf et al., 2018; Lebel et al., 2008; Sowell et al., 2008; Wozniak et al., 2006). Our results connect these previous findings by describing altered development trajectories. Before ∼6–8 years of age, children with PAE show lower MD, but then the lines cross over and after ∼6–8 years of age, children with PAE have higher MD. Interestingly, children with autism also show altered development trajectories with lower MD initially, then higher MD later, though the shift occurs at an earlier age (Wolff et al., 2018). The only other longitudinal study of white matter microstructure in children

TABLE 2 Linear mixed model results for fractional anisotropy (FA)

Fractional anisotropy (FA)	PE (SE)	*t*	*p*
Whole brain			
Intercept	0.422 (0.002)	183.302	<.001
Age	0.006 (0)	16.538	<.001
Sex	−0.001 (0.002)	−0.631	.529
Group	0.003 (0.002)	1.862	.065
Genu of corpus callosum			
Intercept	0.449 (0.004)	103.917	<.001
Age	0.008 (0.001)	11.702	<.001
Sex	−0.009 (0.003)	−3.184	.002
Group	0.009 (0.003)	2.994	**.003***
Body of corpus callosum			
Intercept	0.458 (0.004)	99.198	<.001
Age	0.007 (0.001)	9.441	<.001
Sex	−0.001 (0.003)	−0.174	.862
Group	0.007 (0.003)	2.269	**.025***
Splenium of corpus callosum			
Intercept	0.512 (0.004)	135.930	<.001
Age	0.006 (0.001)	9.893	<.001
Sex	−0.003 (0.003)	−1.228	.221
Group	0.002 (0.003)	0.594	.553
Fornix			
Intercept	0.341 (0.005)	62.271	<.001
Age	0.007 (0.001)	7.657	<.001
Sex	−0.003 (0.003)	−1.040	.300
Group	−0.007 (0.003)	−2.392	**.018***
Cingulum			
Intercept	0.379 (0.005)	76.980	<.001
Age	0.008 (0.001)	9.796	<.001
Sex	−0.001 (0.003)	−0.415	.679
Group	0 (0.003)	−0.093	.926
SLF			
Intercept	0.393 (0.004)	98.182	<.001
Age	0.006 (0.001)	9.759	<.001
Sex	0.005 (0.003)	1.780	.077
Group	−0.003 (0.003)	−1.247	.214
ILF			
Intercept	0.38 (0.004)	86.013	<.001
Age	0.009 (0.001)	13.021	<.001
Sex	0.003 (0.003)	0.861	.390
Group	0 (0.003)	−0.021	.983
IFOF			
Intercept	0.393 (0.004)	103.351	<.001
Age	0.009 (0.001)	15.200	<.001
Sex	0.003 (0.003)	1.157	.249
Group	0.001 (0.003)	0.269	.788

TABLE 2 (Continued)

Fractional anisotropy (FA)	PE (SE)	*t*	*p*
Pyramidal			
Intercept	0.452 (0.003)	131.545	<.001
Age	0.007 (0.001)	11.949	<.001
Sex	−0.003 (0.002)	−1.192	.235
Group	0.004 (0.002)	1.650	.101
UF			
Intercept	0.349 (0.004)	90.857	<.001
Age	0.007 (0.001)	12.258	<.001
Sex	0.001 (0.003)	0.497	.620
Group	0.005 (0.003)	2.017	*.046*

Note: Results are shown for linear mixed models comparing age-related brain changes between children with PAE and unexposed controls. Significant differences in the group parameter that survived multiple comparison correction are marked in bold and with *. Nominally significant differences that did not survive multiple comparison correction are marked in *italics*. If interactions were not significant, they were removed from the model.

with PAE also showed altered development in frontal and temporal tracts, where 5- to 15-year olds with FASD showed steeper decreases for MD in the ILF, the SLF, and the SFOF (Treit et al., 2013). This shows that atypical trajectories persist throughout childhood and adolescence, though the nature of deviation from typical development appears to vary with the age of participants. Steeper decreases in late childhood/early adolescence may represent a "catch-up" period to compensate for slower development earlier on.

Slower white matter development may indicate altered brain plasticity in response to injury from PAE teratogenesis (Lebel, Mattson, et al., 2012) and possibly other prenatal and postnatal adverse exposures (Bick & Nelson, 2016; Callaghan & Tottenham, 2016; Gee & Casey, 2015). During early childhood, an interplay of genetics and environmental experiences drive white matter maturation including increases in myelination, synaptic proliferation and pruning, increases in axon diameter and packing, and decreases in water content (Chang et al., 2015; Dean et al., 2015; Deoni et al., 2012; Genc et al., 2017). These processes are reflected by increases in FA and decreases in MD with age across the brain (Hermoye et al., 2006; Krogsrud et al., 2016; Reynolds et al., 2019). In our study, these fundamental developmental patterns were preserved in young children with PAE but proceeded at slower rates. Dramatic changes to the brain are typically a hallmark of early childhood and complement ongoing cognitive and behavioral learning (Black et al., 2017; Brown & Jernigan, 2013). In line with our findings, previous work in older children with PAE has shown less change in gray matter volume over time (Lebel, Mattson, et al., 2012), suggesting that reduced plasticity may be apparent in both white and gray matter. Aligned with theories of developmental origins of health and disease or prenatal programming (Hartman & Belsky, 2018; Hellemans et al., 2010), teratogenic disruptions to foundational neural and glial mechanisms may reduce postnatal brain plasticity and moderate long-term developmental outcomes in children. Insufficient plasticity may lower the brain's potential to learn from environmental experiences in the same manner as controls contributing to inefficient brain networks, delayed specialization of brain tracts, and cognitive and behavioral impairments (Johnson et al., 2015; Tooley et al., 2021). Further research is needed to identify whether these changes are adaptive or compensatory as well as identifying optimal windows of brain plasticity well-suited for learning and interventions.

The frontal and temporal tracts with altered development patterns are implicated in cognitive and behavioral functions that are frequently impaired in young children with PAE. The IFOF and the ILF are involved in visual processing and language (Almairac et al., 2015), the uncinate fasciculus plays a role in cognition, social–emotional processing, and memory (Olson et al., 2015) and the corpus callosum is a midline tract that plays a role in interhemispheric integration and motor skills (Aboitiz & Montiel, 2003; Grohs et al., 2018). Correspondingly, PAE has been associated with impairments in expressive and receptive language (Hanlon-Dearman et al., 2020; McGee et al., 2009; O'Leary et al., 2009), internalizing and externalizing behaviors and symptoms (Easey et al., 2019; Khoury et al., 2018), as well as gross and fine motor challenges (Barr et al., 1990; Hanlon-Dearman et al., 2020; Kalberg et al., 2006) in early childhood. Some studies in older children with PAE have shown structure–function associations with white matter cross-sectionally (Ghazi Sherbaf et al., 2018) and longitudinally, where decreases in MD of the SLF were associated with better reading skills among children with FASD (Treit et al., 2013). The young children with PAE studied here may also have neurodevelopmental impairments corresponding to white matter differences but further analyses are needed to uncover the nature of any structure–function associations.

Trajectories of brain development are better predictors of cognitive and behavioral outcomes than brain structure at a single timepoint (Giedd & Rapoport, 2010). This highlights the importance of our longitudinal analysis and the need for future longitudinal studies around PAE. Specifically, trajectories that converge towards typicality predict better clinical outcomes in large, longitudinal samples of children diagnosed with autism (Andrews et al., 2021; Ecker et al., 2010; Tunç et al., 2019) and ADHD (Shaw et al., 2006). Further studies are needed to investigate whether atypical trajectories of white matter tracts, such as those seen here, coincide with the progression of neurodevelopmental challenges in young children with PAE (Hanlon-

TABLE 3 Linear mixed model results for mean diffusivity (MD)

Mean diffusivity (MD)	PE (SE)	*t*	*p*
Whole brain			
Intercept	0.954 (0.005)	201.169	<.001
Age	−0.013 (0.001)	−16.836	<.001
Sex	−0.007 (0.003)	−2.403	.018
Group	−0.025 (0.009)	−2.839	**.005***
Age-by-group	0.004 (0.001)	2.523	**.012***
Genu of corpus callosum			
Intercept	1.067 (0.011)	100.363	<.001
Age	−0.024 (0.002)	−12.908	<.001
Sex	0.012 (0.005)	2.464	.015
Group	−0.057 (0.019)	−2.938	**.004***
Age-by-group	0.007 (0.003)	2.164	**.031***
Body of corpus callosum			
Intercept	0.998 (0.009)	111.753	<.001
Age	−0.014 (0.001)	−9.92	<.001
Sex	−0.014 (0.005)	−2.537	.012
Group	−0.041 (0.017)	−2.467	**.014***
Age-by-group	0.006 (0.003)	1.99	*.048*
Splenium of corpus callosum			
Intercept	0.932 (0.008)	135.930	<.001
Age	−0.008 (0.001)	−6.077	<.001
Sex	−0.01 (0.005)	−2.177	.031
Group	0.007 (0.005)	1.508	.134
Fornix			
Intercept	1.521 (0.036)	42.729	<.001
Age	−0.017 (0.006)	−3.149	.002
Sex	−0.025 (0.025)	−1.040	.300
Group	−0.035 (0.025)	−1.381	.169
Cingulum			
Intercept	0.911 (0.006)	76.980	<.001
Age	−0.009 (0.001)	−9.185	<.001
Sex	−0.009 (0.004)	−2.282	.024
Group	−0.002 (0.004)	−0.404	.687
SLF			
Intercept	0.89 (0.005)	172.363	<.001
Age	−0.01 (0.001)	−12.469	<.001
Sex	−0.01 (0.003)	1.780	.004
Group	0.001 (0.004)	0.156	.876
ILF			
Intercept	0.984 (0.007)	136.564	<.001
Age	−0.018 (0.001)	−14.796	<.001
Sex	−0.016 (0.004)	−3.916	.390
Group	−0.036 (0.013)	−2.67	**.008***
Age-by-group	0.006 (0.002)	2.782	**.006***

TABLE 3 (Continued)

Mean diffusivity (MD)	PE (SE)	*t*	*p*
IFOF			
Intercept	0.986 (0.006)	157.022	<.001
Age	−0.017 (0.001)	15.200	<.001
Sex	−0.005 (0.004)	−1.458	.147
Group	−0.044 (0.012)	−3.777	**<.001***
Age-by-group	0.006 (0.002)	3.174	**.002***
Pyramidal			
Intercept	0.879 (0.004)	211.508	<.001
Age	−0.008 (0.001)	−12.72	<.001
Sex	−0.009 (0.003)	−3.177	.002
Group	−0.003 (0.003)	1.650	.347
UF			
Intercept	0.995 (0.007)	147.972	<.001
Age	−0.016 (0.001)	−14.287	<.001
Sex	0.004 (0.003)	1.247	.620
Group	−0.045 (0.012)	−3.639	**<.001***
Age-by-group	0.005 (0.002)	2.427	**.016***

Note: Results are shown for linear mixed models comparing age-related brain changes between children with PAE and unexposed controls. Significant differences in the group parameter or the age-group interaction that survived multiple comparison correction are marked in bold and with *. Nominally significant differences in the group or age–group interaction terms that did not survive multiple comparison correction are marked in *italics*. If interactions were not significant, they were removed from the model.

Abbreviations: PE, parameter estimate; SE, standard error; UF, uncinate fasciculus.

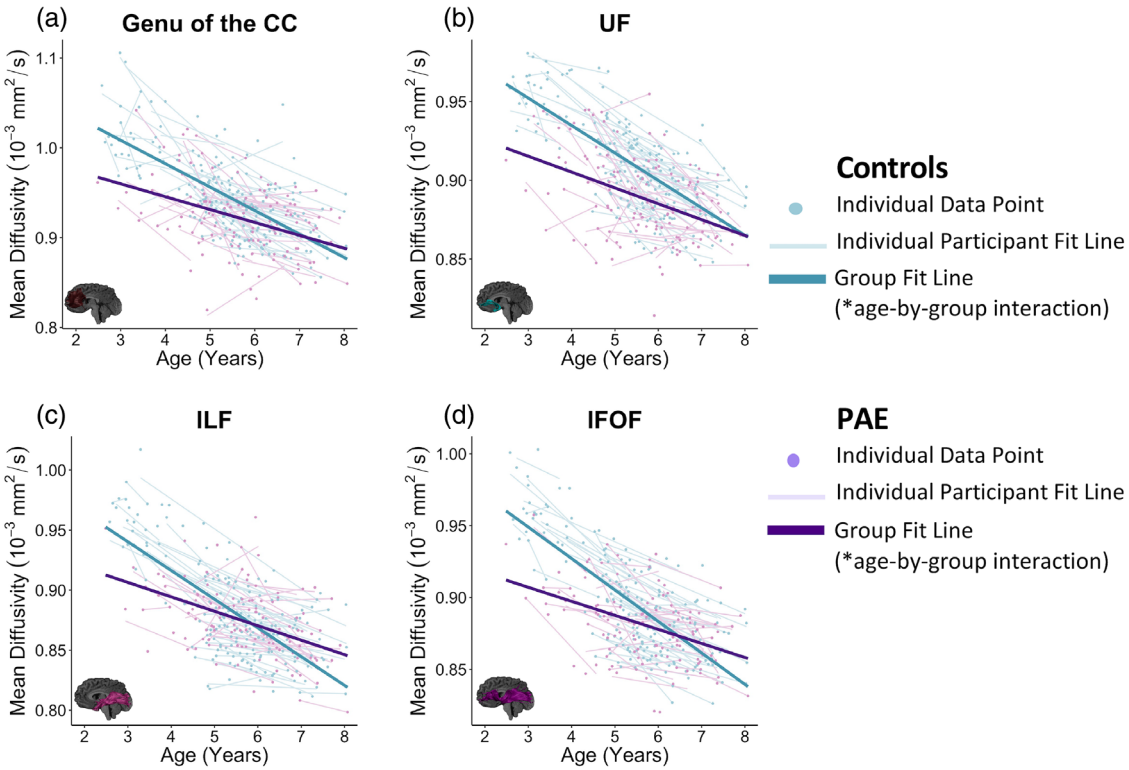

FIGURE 2 Mean diffusivity (MD) across ages in children with PAE compared to controls. Significant main effects of group and age-by-group interactions were present for the genu of the corpus callosum (a), the uncinate fasciculus (b), the inferior longitudinal fasciculus (c), and the inferior fronto-occipital fasciculus (d), where children with PAE had lower MD and slower decreases in MD with age compared to controls. CC, corpus callosum; UF, uncinate fasciculus; ILF, inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus

Dearman et al., 2020; Rockhold et al., 2020; Subramoney et al., 2018). For example, the onset of challenges may relate to the distinct trajectories of early maturing tracts (e.g., ILF, IFOF) compared to later maturing tracts (e.g., uncinate fasciculus) (Reynolds et al., 2019) . Additionally, exploring whether diverse white matter trajectories converge on a single, homogenous neurodevelopmental outcome (equifinality) or whether individual trajectories of white matter diverge into a variety of neurodevelopmental outcomes (multifinality) may offer further clinical insight into the mechanisms of impairments associated with PAE (Cicchetti & Rogosch, 1996). Aside from predicting the continuum of disability (Giedd & Rapoport, 2010), trajectories can also inform the development and evaluation of intervention strategies. Establishing baseline developmental trajectories in young children with PAE may be useful to create targeted interventions and monitor their therapeutic efficacy, as gradually "normalizing" trajectories of white matter volume have been associated with better neurodevelopmental outcomes in those with ADHD (Castellanos et al., 2002; Giedd & Rapoport, 2010).

This study has several limitations. First, brain alterations may vary with differences in the timing, pattern, and amount of PAE in tandem with other maternal and fetal variables such as genetics or exposure to other substances (Minnes et al., 2011; Paintner et al., 2012) along with postnatal adversities (Astley, 2010; Flannigan et al., 2021; Hemingway et al., 2020; Lebel et al., 2019). Future studies with larger samples of children with more follow-up timepoints may be better able to disentangle different patterns of prenatal and postnatal exposures. Second, children with PAE are often diagnosed with psychiatric co-morbidities and may be receiving medications, both of which can affect brain development in early childhood. Other potential confounding variables include differences in income and ethnicity, as well as the inclusion of siblings in the study. Future research with more demographically matched samples would be better able to control for possible confounders. We used a linear fit to examine trajectories given our relatively small sample and narrow age range; however, age-related changes during early childhood are non-linear (Reynolds et al., 2019). PAE was confirmed in all cases, but as is typical in human studies of PAE, precise information about dosage and timing is challenging to obtain retrospectively. Prospective studies may capture PAE in more detail and explore associations of white matter development with dose and timing of exposure.

5 | CONCLUSIONS

Here, in the first study to map trajectories of white matter development in 2–8-year-old children with PAE, we show slower white matter development in frontal and temporal tracts in young children with PAE relative to unexposed controls, connecting prior cross-sectional studies and suggesting altered brain plasticity. Insight into atypical trajectories has implications for predicting the onset and progression of cognitive and behavioral impairments during early childhood and may help optimize interventions to support young children with PAE.

AUTHOR CONTRIBUTIONS

Preeti Kar: conceptualization, methodology, formal analysis, investigation, writing the original draft and visualization, reviewing, and editing the draft. Jess E. Reynolds: formal analysis, investigation, reviewing and editing the draft. W. B. Gibbard: conceptualization, methodology, reviewing and editing the draft, funding acquisition. Carly McMorris: methodology, reviewing and editing the draft. Christina Tortorelli: methodology, reviewing and editing the draft. Catherine Lebel: conceptualization, methodology, writing the original draft, visualization, formal analysis, investigation, reviewing and editing the draft, project administration, funding acquisition, resources supervision for PK and JER.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT

Neuroimaging data for typically-developing controls is publicly available on the Open Science Framework: https://osf.io/axz5r/ (J. Reynolds et al., 2020). Neuroimaging data for children with prenatal alcohol exposure is available upon request from the corresponding author.

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SUPPORTING INFORMATION

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