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White Matter Tract Properties and Mathematics Skills: A Longitudinal Study of Children Born Preterm and Full-term

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Abstract

Children born preterm are at increased risk for white matter injury, impaired cognitive development and lower academic achievement. Here, we examined the association between fractional anisotropy and volume of select white matter tracts at age 5 with mathematics skills at age 7 in children born preterm (<33 weeks gestational age, n=52) without severe neurological complications and children born full-term (38-41 weeks gestational age, n=34). The preterm group had significantly lower mathematics scores and lower volume in several white matter tracts. Using multiple linear regression models, we examined white matter tracts that have previously been associated with mathematical cognition. We found a significant interaction with term status: fractional anisotropy of the corticospinal tract, and volume of corticospinal tract and parietal superior longitudinal fasciculus were significantly associated with mathematics skills in children born full-term, but not in children born preterm. These findings indicate white matter plasticity following preterm birth.

Keywords: preterm birth; mathematics; longitudinal; white matter; diffusion MRI

Introduction

Preterm birth affects about 10% of all live births and is one of the leading causes of infant morbidity (Blencowe et al., 2013). Children born preterm are at increased risk for white matter injury, which often presents as systemic and subtle alterations (Back, 2017). On structural and diffusion weighted MRI scans it is primarily associated with lower fractional anisotropy (FA), a measure of water diffusion directionality, lower subcortical volumes, lower cortical surface area and altered cortical thickness (Volpe, 2009).

In addition, preterm birth has been associated with impaired executive functions, reduced phonological processing skills, and lower academic achievement, particularly in mathematics (Akshoomoff et al., 2017; Johnson et al., 2011; Rose et al., 2011). These cognitive deficits are likely associated with differences in brain development. To date, the association between brain structure and mathematics skills has rarely been studied in preterm populations. Collins et al. (2019) found widespread bilateral associations between FA and mathematics skills in 13-year-old children born preterm.

In typically and atypically developing populations mathematics skills have been associated with a network of interconnected brain regions, including prefrontal, posterior parietal, and occipito-temporal areas (Peters & De Smedt, 2018). The respective white matter tracts involved in mathematical cognition are mainly long association fibers,

such as the inferior longitudinal fasciculus (ILF), temporal and parietal superior longitudinal fasciculus (tSLF, pSLF), and inferior frontal occipital fasciculus (IFO). Increased FA in these tracts has been associated with higher arithmetic scores (Matejko & Ansari, 2015). In addition, FA of the corticospinal tract (CST) has been associated with mathematics skills in children with fetal alcohol syndrome (Lebel et al., 2010) and in typically developing adults (Matejko et al., 2013). All of these white matter tracts also showed higher FA in a group of mathematically gifted children compared to age matched controls (Navas-Sánchez et al., 2014). In addition to FA, the association between white matter tract volume and cognitive skills is beginning to be examined. For example, Esteban-Cornejo et al. (2019) recently found an association between white matter volume and mathematics skills. While this research is still in its infancy, it could add valuable insight into the relationship between brain structure and function.

Early childhood is a time of rapid brain development; the brain continues growing, white matter tracts continue maturing, the cortical surface area expands, and cortical thickness decreases (Brown & Jernigan, 2012). Little is known about the impact of preterm birth on these processes in children between 5 and 7 years of age, when neuropsychological development is also rapid.

The Present Study

This study is part of a comprehensive longitudinal study of brain and cognitive development in children born preterm (Adrian et al., 2020; Hasler et al., 2020; Hasler & Akshoomoff, 2019; Sawyer et al., 2021). In this study we examined the effect of preterm birth on mathematics skills, and FA and volume of five white matter tracts (ILF, tSLF, pSLF, IFO, CST). Our aim was to examine the predictive value of these white matter tract characteristics at age 5 on mathematics skills at age 7 in children born preterm without severe neurological complications and full-term controls. We hypothesized to find an association between white matter properties of the selected tracts and mathematics skills in children born full-term. If the same association is present in children born preterm, it would indicate that similar brain structures are recruited when solving mathematics problems. If the pattern of association differs in children born preterm, it would suggest involvement of different networks of white matter tracts and thus adaptation of brain structure following preterm birth.

Method

This data is part of a larger longitudinal study examining cognitive and brain development in children born preterm.

Participants

Our sample consisted of 52 children born preterm (before 33 weeks of gestation) and 34 children born full-term (38-41 weeks of gestation). Our participants had quality-controlled T1- and diffusion weighted MRI scans at age 5, and completed the Test for Early Mathematics Ability – Third Edition (TEMA-3, Ginsburg & Baroody, 2003) at age 7. Table 1 summarizes the demographic characteristics of our participants. By definition, preterm participants had lower gestational age and birth weight than full-term participants. The groups did not differ in sex, maternal education, household income, race, ethnicity, age at MRI and age at mathematics testing.

All participants were required to be primarily English speaking, to have a Full-Scale IQ > 75, and no MRI contraindications such as metallic implants or severe anxiety. The preterm participants were primarily recruited through the UC San Diego High Risk Infant Follow Up Clinic. They were excluded if they had any severe congenital, physical or neurological disabilities, genetic/chromosomal abnormalities likely to affect development, or an acquired neurological injury unrelated to preterm birth. Because the objective of this study was to examine the impact of preterm birth on brain development in children without severe neurological complications, we excluded participants with significant brain injury such as intraventricular hemorrhage grade 3 or 4, cystic PVL, or moderate to severe ventricular dilation; three were small for gestational age, five had bronchopulmonary dysplasia and seven had intraventricular hemorrhage grade 1. None of the children had PVL. Full-term participants were excluded if they had a history of neurological, psychiatric or developmental disorders. This study was approved by the Institutional Review Board at UC San Diego. Written, informed consent was obtained from the participants legal guardians, and verbal assent was obtained from participants who were at least seven years old.

Mathematics Skills Testing

Mathematics skills were assessed with the TEMA-3. It comprises up to 72 items, which require different skill sets to complete, including verbal counting, numerical comparison, numeral literacy and calculation. Here we used the TEMA-3 standardized Math Ability Score (MAS) score as a measure of overall performance.

Full-Scale IQ Testing

Full-Scale IQ was assessed at age 5 with with the Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV, Wechsler, 2012). We used FSIQ primarily as a descriptor of our study sample, rather than a covariate in our analyses (Dennis et al., 2009).

Table 1: Participant characteristics

	Preterm (n = 52)	Full-term (n = 34)	<i>p</i> ($\eta_{(p)}^2$)
GA at birth (weeks):	29.7	39.8	<.001
Mean (min-max)	(24.0 - 32.9)	(38.0 - 41.0)	(.883)
Birth weight (g):	1324	3414	<.001
Mean (min-max)	(625 - 2450)	(2353 - 4423)	(.821)
Gender (female)	26 (50%)	16 (47%)	.828 (n/a)
Maternal education			.097 (n/a)
High school	6 (13%)	3 (14%)	
1-3 years college	19 (38%)	8 (23%)	
College graduate	18 (38%)	12 (32%)	
Graduate degree	9 (13%)	11 (32%)	
Household income			.32 (n/a)
< \$50k	8 (15%)	1 (3%)	
\$50k - \$99k	14 (27%)	17 (50%)	
\$100k - \$199k	18 (35%)	15 (44%)	
> \$200k	10 (19%)	0 (0%)	
Race			.21 (n/a)
Black	1 (2%)	0 (0%)	
Asian	4 (8%)	5 (15%)	
White	40 (77%)	20 (59%)	
Mixed	6 (12%)	9 (26%)	
Missing data	1 (2%)	0 (0%)	
Ethnicity			.56 (n/a)
Hispanic	20 (38%)	11 (32%)	
Non-Hispanic	32 (62%)	23 (68%)	
Age at MRI	5.3 (40.4)	5.4 (0.3)	.43 (.008)
Age at Math Testing	7.3 (0.4)	7.4 (0.3)	.67 (.002)
WPPSI-IV: FSIQ	102 (12)	109 (8.7)	.005 (.090)

GA: gestational ag; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, 4th edition; FSIQ: Full-Scale Intelligence Quotient

MRI Acquisition and Processing

MRI data was collected at the Center for Functional MRI and processed at the Center for Multimodal Imaging and Genetics at UC San Diego. The MRI scans were acquired on a 3.0 Tesla General Electric Discovery MR750 scanner with an 8-channel phased-array head coil. The imaging protocol and data processing pipeline of the Pediatric Imaging Neuro-cognition and Genetics (PING) project was used in this study (Jernigan et al., 2016). The scanning sequence included a three-plane localizer, a 3D T1-weighted inversion prepared RF-spoiled gradient echo scan using prospective motion correction (PROMO) for cortical and subcortical

segmentation, a 3D T2-weighted variable flip angle fast spin echo scan, also using PROMO, for detection and quantification of white matter lesions and segmentation of CSF, and a high angular resolution diffusion imaging (HARDI) scan with 30 diffusion directions and integrated B0 distortion correction (DISCO) for segmentation of white matter tracts and measurement of diffusion parameters.

Image analyses were performed in FreeSurfer version 5.3.0, using the automated segmentation and labeling procedure for subcortical volumes, and automated, probabilistic, atlas-based analysis of white matter tracts (Hagler et al., 2009). Images were inspected by two trained experts and only included if they had minimal to no movement or scanner artifacts, and no errors in terms of registration and segmentation in FreeSurfer.

We analyzed the bilateral volume and mean tract FA of five white matter tracts: ILF, tSLF, pSLF, IFO, and CST.

Statistical Analyses

Statistical analyses were performed in IBM SPSS Statistics for Macintosh, Version 26 and R Studio Version 1.3.959 with R Version 4.0.1. Demographic participant characteristics, IQ scores, and TEMA-3 scores were compared between groups using ANOVAs, Mann Whitney U, and chi-square tests as appropriate.

White matter tracts were analyzed bilaterally, using the sum of the hemispheres for volumes, and the average for diffusion tensor imaging (DTI) measures. We first compared these variables between preterm and full-term groups via ANOVAs for mean tract FA, and via ANCOVAs, covaried for intracranial volume (ICV), for tract volume. Covarying for ICV allows us to examine localized effects by normalizing white matter tract volumes. It also serves to control for inter-individual variability in global brain size.

To examine the predictive value of white matter tract volume and FA at age 5 on mathematics skills at age 7 we conducted a series of hierarchical regression models. The base model includes sex and group (preterm coded as 1, full-term coded as 0) to predict mathematics scores. We then included mean tract FA and tract volume, respectively, of select tracts as a main factor in the model. Next we included the interaction effect of group (term status) and FA and volume, respectively, to examine if group moderates the predictiveness of the white matter tract property on mathematics scores. Models of white matter tract volume additionally included ICV.

Effect sizes were analyzed for all statistical analyses. Cohen's thresholds for small, medium, and large effects for $\eta^2(p)$ statistics are .01, .06, and .14, and for accounted variance R^2 and ΔR^2 .01, .09, and .25, respectively (Cohen, 1988). Instead of correcting the significance level for multiple comparisons, we are focusing on the strength of the observed effects to evaluate whether they are significant.

Results

Group Comparison of Mathematics Skills

The preterm group had lower mean mathematics scores at age 7 compared to the full-term group (Table 2, Figure 1). Despite a 10-point difference (99 vs 109), children in the preterm group scored within the average range.

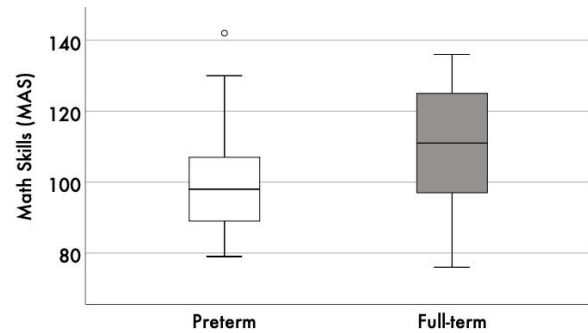


Figure 1: Math skills at 7 years of age, assessed via the standardized Math Ability Score (MAS) of the TEMA-3

Table 2: Mathematics skills, mean tract FA, and tract volumes in children born preterm and full-term.

	Preterm (n = 52) Mean (SE)	Full-term (n = 34) Mean (SE)	p ($\eta^2(p)^2$)
Mathematics Skills			
TEMA-3: MAS	99 (2.0)	109 (2.5)	.003 (.103)
Mean tract fractional anisotropy			
ILF	.418 (.003)	.411 (.003)	.09 (.035)
tSLF	.431 (.003)	.429 (.004)	.57 (.004)
pSLF	.409 (.003)	.405 (.004)	.44 (.007)
IFO	.422 (.003)	.427 (.004)	.31 (.013)
CST	.517 (.003)	.521 (.004)	.44 (.007)
Tract volume (in mm³, covaried for ICV)			
ILF	14902 (181)	15249 (224)	.23 (.017)
tSLF	10449 (146)	10951 (181)	.034 (.053)
pSLF	13232 (166)	13495 (205)	.32 (.012)
IFO	17228 (209)	18040 (258)	.017 (.067)
CST	10595 (80)	10878 (98)	.028 (.057)

TEMA-3: Test for Early Math Ability, 3rd edition; MAS:

Standardized Math Ability Score; ILF: inferior longitudinal fasciculus, tSLF/pSLF: temporal/parietal superior longitudinal fasciculus; IFO: inferior frontal occipital fasciculus; CST: cortical spinal tract; ICV: intracranial volume; SE: standard error.

Group Comparison of White Matter Tracts

At age 5, none of the examined white matter tracts had significant differences in FA between preterm and full-term groups (Table 2). IFO volume was significantly lower in the preterm group, with a moderate effect of term status. Volumes of tSLF and CST showed a weak effect of term status. ILF and pSLF did not show a significant effect of preterm birth.

Association Between White Matter Tracts at Age 5 and Mathematics Skills at Age 7

The results of multiple regression models predicting mathematics skills at age 7 by mean tract FA and volume of ILF, tSLF, pSLF, IFO, and CST at age 5 are presented in Table 3. The base model including sex and group (term status) explained 14.5% of the variance in mathematics skills with both of these factors as significant predictors. Models 1A–10A include the mean tract FA or volume of one of these white matter tracts as additional main effect. Models 1B–10B include the interaction of group with main tract FA or volume as an additional effect.

Among the models using mean tract FA as an additional predictor (1A–5B), only model 5B showed a significant increase of 12.0% in explained variance. This increase is mainly explained through the interaction effect between mean tract FA of CST and group. Figure 2A illustrates this interaction effect: mean tract FA of CST is moderately associated with mathematics skills in children born full-term ($R^2=22.3\%$), but not significantly associated in children born preterm ($R^2=0.6\%$).

Among the models using tract volume as an additional predictor (6A–10B), all models with a volume by group interaction effect explain significantly more variance than the models without the interaction effect (i.e., the B models fit better than the A models). However, only models 8B and 10B, including the interaction between group and volume of pSLF and CST, respectively, increased the explained variance significantly compared to the base model. Similar to model 5B, the interaction effect is characterized by a weak to moderate association of pSLF and CST volume, respectively, with mathematics skills in the full-term group, and a lack of such association in the preterm group (Figure 2B,C).

Discussion

The aim of our study was to examine the associations between white matter tract properties at age 5 and mathematics skills at age 7 in children born preterm and full-term. Our sample of children born preterm had significantly lower mathematics scores than children born full-term, although still in the average range. These average to high scores may be due to the recruitment of participants without significant neonatal complications, and our convenience sample with relatively high socioeconomic status.

Based on previous studies of white matter tracts associated with mathematical cognition, we focused on ILF, tSLF, pSLF, IFO and CST (Matejko & Ansari, 2015). There were

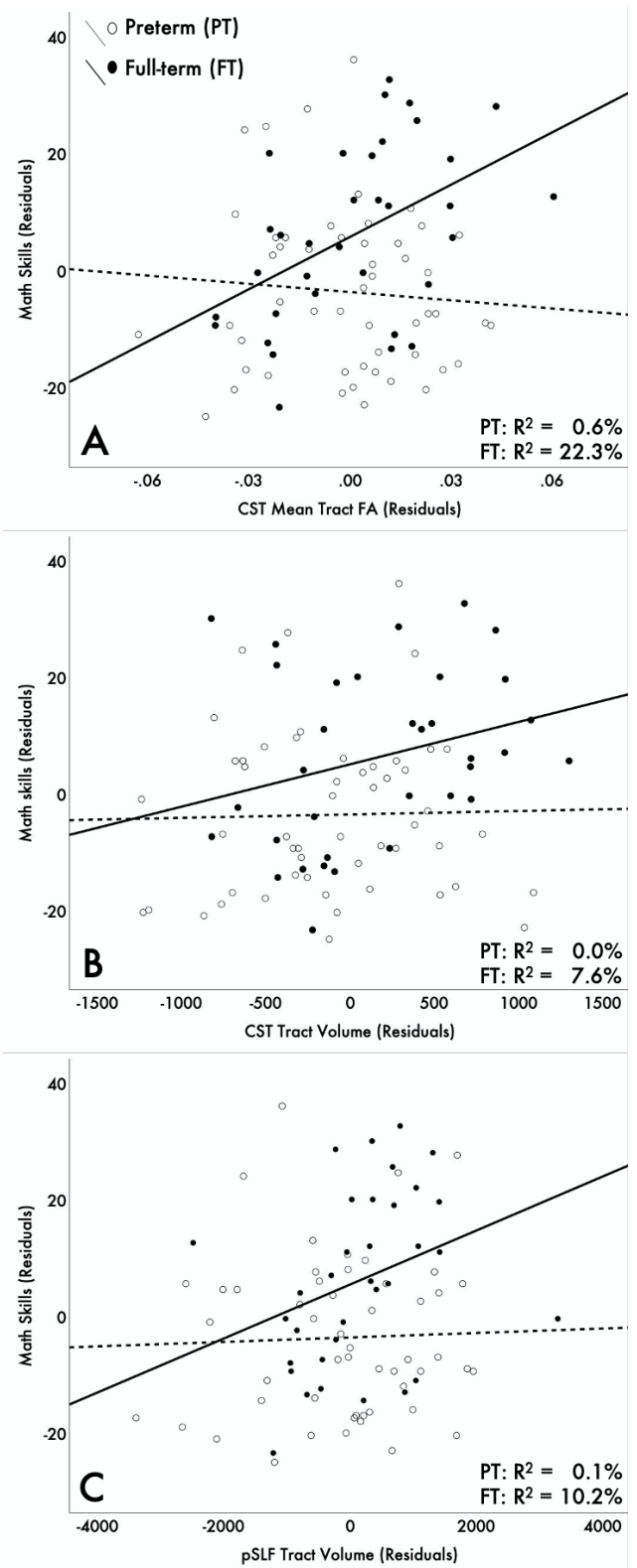


Figure 2: Regression residuals of (A) FA of CST, (B) volume of CST, and (C) volume of pSLF at age 5 and math skills at age 7 in children born preterm (PT) and full-term (FT) after controlling for sex, age at MRI scan (tracts only), and ICV (volume only). CST: corticospinal tract, pSLF: parietal superior longitudinal fasciculus.

Table 3: Prediction of math skills at age 7 by white matter tract properties at age 5

Models of White Matter Tract FA Predicting Math Scores											
	Base Model	Model 1A	Model 1B	Model 2A	Model 2B	Model 3A	Model 3B	Model 4A	Model 4B	Model 5A	Model 5B
Sex	-0.21^a	-0.21^a	-0.22^a	-0.22^a	-0.21^a	-0.24^a	-0.24^a	-0.21^a	-0.21^a	-0.20 ⁰	-0.17 ⁰
Group	-0.31^b	-0.32^b	3.98	-0.31^b	1.03	-0.30^b	1.12	-0.31^b	3.25	-0.31^b	6.90^c
ILF		0.04	0.33 ⁰								
ILF x Group			-4.37 ⁰								
tSLF				-0.12	-0.02						
tSLF x Group					-1.35						
pSLF						-0.16	-0.05				
pSLF x Group							-1.43				
IFO								0.05	0.29 ⁰		
IFO x Group									-3.55 ⁰		
CST										0.05	0.47^b
CST x Group											-7.20^a
ΔR^2 (%) [A-B]			1.0 ⁰		0.4		0.5		2.9 ⁰		11.8^c
ΔR^2 (%) Base		0.2	1.2	1.4	1.8	2.5	3.0	0.3	3.2	0.2	12.0^b
Total R ² (%)	14.5^b	14.7^b	17.7^b	15.9^b	16.3^b	17.0^b	17.5^b	14.8^b	17.7^b	14.7^b	26.5^c
Adj. R ² (%)	12.5^b	11.6^b	13.6^b	12.8^b	12.2^b	14.0^b	13.4^b	11.6^b	13.6^b	11.6^b	22.9^c

Models of White Matter Tract Volumes Predicting Math Scores											
	Base Model	Model 6A	Model 6B	Model 7A	Model 7B	Model 8A	Model 8B	Model 9A	Model 9B	Model 10A	Model 10B
Sex	-0.21^a	-0.19 ⁰	-0.20 ⁰	-0.18	-0.18	-0.18	-0.17	-0.19 ⁰	-0.20 ⁰	-0.17	-0.18
Group	-0.31^b	-0.31^b	1.47 ⁰	-0.30^b	1.35 ⁰	-0.30^b	1.56^a	-0.31^b	1.45 ⁰	-0.30^b	2.11^a
ICV		0.02	0.03	-0.04	-0.08	-0.13	-0.15	0.03	0.03	-0.17	-0.22
ILF		0.02	0.31								
ILF x Group			-1.80^a								
tSLF				0.12	0.45^a						
tSLF x Group					-1.64^a						
pSLF						0.22	0.58^b				
pSLF x Group							-1.87^a				
IFO								0.00	0.30		
IFO x Group									-1.74^a		
CST										0.25	0.68^a
CST x Group											-2.40^b
ΔR^2 (%) [A-B]			5.8^a		5.1^a		5.9^a		4.8^a		7.3^b
ΔR^2 (%) Base		0.1	4.9	0.7	4.8	2.2	8.1^a	0.1	4.9	1.2	8.5^a
Total R ² (%)	14.5^b	14.6^a	20.4^b	15.2^b	20.3^b	16.7^b	22.6^c	14.6^a	19.4^b	15.7^b	23.0^c
Adj. R ² (%)	12.5^b	10.4^a	15.4^b	11.0^b	15.4^b	12.6^b	17.8^c	10.4^a	14.3^b	11.6^b	18.2^c

Standardized beta coefficients. ⁰p<.1, ^ap<.05, ^bp<.01, ^cp<.001. Coefficients with p<.05 are bolded. ΔR^2 (%) Base: Increase in explained variance in reference to Base Model, ΔR^2 (%) [A-B]: Increase in explained variance of Model B compared to Model A. ILF: inferior longitudinal fasciculus, tSLF/pSLF: temporal/parietal superior longitudinal fasciculus; IFO: inferior frontal occipital fasciculus; CST: cortical spinal tract; ICV: intracranial volume

no group differences in FA across these white matter tracts while tSLF, IFO, and CST showed a weak to moderate effect of term status on volume. We found that mean tract FA of CST at age 5 was significantly associated with mathematics skills at age 7 in full-term but not preterm children. We similarly found this moderating effect of term status in the association between white matter tract volumes and math. Including a group by tract volume interaction effect explained significantly more variance than models that only included the main effects.

Contrary to our expectations we did not find an association between ILF, tSLF, and IFO in FA or volume in the full-term group. This may be due to the relatively young age of our participants in comparison to the majority of other studies of typically developing children. Another explanation may also be the type of task, which encompasses problems that require a variety of different mathematics skills. Disentangling specific subcategories of skills, such as numerical magnitude comparison and calculation, may give more sensitive measures and thus reveal associations between select white matter tracts and specific mathematics skills.

Nevertheless, the divergent pattern of association for CST and pSLF in children born full-term and preterm indicates that different networks of brain regions may be involved when solving mathematics problems in the two groups. Interestingly, our findings are consistent with a similar study examining associations between tract FA at age 6 and reading skills at age 8 in children born preterm and full-term (Bruckert et al., 2019). The authors found a moderating effect of term status on the association between tract FA of selected tracts and reading skills. They concluded that children born preterm may rely on alternate pathways to achieve reading at a similar level as children born full-term. The similarity of our and their findings may be due to the highly verbal nature of the TEMA-3. Verbal skills are necessary for the completion of many of the items, and some items specifically test for skills such as “verbal counting” (Ryoo et al., 2015). Overall, the lack of association for mathematics and reading skills in children born preterm may be indicative of white matter plasticity following preterm birth.

Alternatively, children born preterm may rely on similar pathways as children born full-term and the measures we used in our study were not sensitive enough to detect this association. FA and volume are structural measures, and it may be plausible that a functional analysis would uncover that the same network is being recruited for mathematics skills in both groups.

Limitations of our study include that our participants are a convenience sample, with a fairly high socioeconomic status, FSIQ in the average range, and a majority of Non-Hispanic White participants. Future studies should prioritize the recruitment of a more diverse sample that is more reflective of the preterm population at large.

Conclusion

Ours is the first study to examine the association between white matter tract FA and volume at age 5 and mathematics skills at age 7 in a preterm born population. Our findings give valuable insight into brain development following preterm birth and the relationship between brain structure and function. This knowledge may be important to inform interventions aimed at increasing academic achievement in children born preterm.

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