**Longitudinal Structural and Diffusion Weighted Neuroimaging
of Young Children Born Preterm**

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Category of study. This is a cohort population study. Earlier publications drew participants from the same project (8-11), thus some of the procedural details are the same.

Consent statement. We obtained written, informed consent from the participants' parent/legal guardian, and verbal assent from participants who were at least seven years old.

Impact

- The present study examines young children born less than 33 weeks of gestation without severe neonatal complications longitudinally and with multimodal neuroimaging.
- Young children born preterm had lower volumes of several subcortical gray and white matter structures. Despite the differences in volume, white matter microstructure was not significantly different following preterm birth.
- From 5 to 7 years of age, we did not find any age by term interaction effects, suggesting that structural brain development in children born preterm and full-term follows a similar trajectory.

Abstract

Background:

Children born preterm are at risk for diffuse injury to subcortical gray and white matter. This study's objective was to examine structural brain development of young children born preterm.

Methods:

Participants were 47 children born preterm (less than 33 weeks gestational age) and 28 children born full-term. None of the children born preterm had significant brain injury. Children received structural and diffusion weighted MRI scans at 5, 6, and 7 years of age. The effect of preterm birth on volume of subcortical gray matter, and volume, fractional anisotropy (FA) and mean diffusivity (MD) of white matter tracts was examined via general linear models.

Results:

Volumes of thalamus, brain stem, cerebellar white matter, and several cerebral fiber tracts were smaller, and ventricles were larger in children born preterm compared to full-term controls. We found no significant effect of preterm birth on diffusivity measures. Despite developmental changes and growth, group differences were present and similarly strong at all three ages.

Conclusion:

Even in the absence of significant neonatal brain injury, preterm birth has a persistent impact on early brain development. The lack of a significant birth status by age interaction suggests a delayed developmental trajectory.

Introduction

About 10% of the population worldwide are born before 37 weeks of gestation, about 2% are born before 33 weeks of gestation (1). Early exposure to the extrauterine environment increases the risk for persistent changes in brain structure and function due to perinatal brain injury. Volpe described “encephalopathy of prematurity” as a complex pattern of injury associated with preterm birth (2). This includes diffuse white matter injury that particularly affects periventricular regions (periventricular leukomalacia; PVL) and neuronal/axonal disease. Encephalopathy of prematurity can be detected through structural and diffusion weighted magnetic resonance imaging. It is primarily associated with lower fractional anisotropy (FA) and higher mean diffusivity (MD) in white matter tracts, lower subcortical volumes, lower cortical surface area, and altered cortical thickness (2).

Improved outcomes following preterm birth are associated with medical advances such as the use of surfactant and antenatal steroids that lower incidence of cystic PVL (3,4). Nevertheless, even children born preterm without severe neonatal complications remain more likely to experience the long-term consequences of altered structural brain development. Early childhood is a time of rapid brain development; the brain continues growing, myelination and maturation of white matter tracts continues, the cortical surface area expands, and cortical thickness decreases (5). However, little is known about the impact of preterm birth on brain development in early childhood. We therefore conducted a longitudinal study of brain and cognitive development in children born preterm at 5, 6, and 7 years of age, when neuropsychological development is also rapid. In agreement with studies of older children and adolescents (6,7), we showed that children who were born preterm had lower performance in

executive functions, phonological processing, visual processing, motor functions and academic achievement than children born full-term (8–10).

At age 5, the children born preterm in our sample also showed regional differences cortical thickness, surface area, and sulcal depth (11). The cortex was significantly thinner in temporal and parietal regions, and significantly thicker in occipital and inferior frontal regions. In addition, children born preterm showed significantly reduced surface area in the fusiform gyrus, lower sulcal depth in the posterior parietal and inferior temporal regions, and greater sulcal depth in the middle temporal and medial parietal regions.

Subcortical structures are vulnerable to early extrauterine exposure. Several studies have reported reduced subcortical volumes, namely the amygdala, hippocampus, basal ganglia, and thalamus in children, adolescents, and young adults born preterm (12–18). The basal ganglia comprise several gray matter nuclei, including caudate nucleus, putamen, and pallidum. They receive, process and relay cortical information to the thalamus. Brain stem volumes have been shown to be smaller following preterm birth in children and adolescents (19,20). In addition, preterm birth has been associated with reductions in white matter volumes, particularly in the cerebellar white matter, and corpus callosum (19–21).

Diffusion weighted imaging (DTI) measures the diffusion of water molecules within neural compartments. This method is highly sensitive to changes in tissue microstructure associated with white matter development. Mean diffusivity (MD) declines with age during development while fractional anisotropy (FA) increases (22). Studies of preterm children, adolescents, and young adults have reported altered diffusion on later developing projections and associated pathways (23–26). Long association fibers, including the superior longitudinal fasciculus, inferior longitudinal fasciculus, cingulum, and uncinate fasciculus, are especially

affected. In addition, preterm birth affects the anterior thalamic radiations that connect the thalamus to the frontal cortex, the corticospinal tracts that connect the cerebral cortex to the spinal cord, and the corpus callosum that primarily connects the two hemispheres (27–29).

We used multimodal imaging to examine subcortical gray matter volume, white matter volume, and white matter integrity in our longitudinal group of children at 5, 6, and 7 years of age who were born less than 33 weeks of gestation without severe neurological abnormalities in the early 2010's. The aims of this study were to (a) examine the brain volume of subcortical gray matter structures and white matter fiber tracts and (b) to examine diffusivity measures of white matter tracts. Because we previously showed in this study cohort that children born preterm had lower performance in a number of neuropsychological tests and altered cortical morphometry, we expected to find widespread differences in brain structure. Specifically, we predicted that volumes would be smaller following preterm birth and that white matter integrity would be affected as demonstrated by lower FA and higher MD in key white matter tracts.

Method

Participants

Our sample consisted of 47 children born preterm (before 33 weeks of gestation) and 28 children born full-term (38–41 weeks of gestation) who had quality-controlled T1- and diffusion-weighted scans at three time points (age 5, 6, and 7). Table 1 summarizes the participant characteristics. Preterm participants had lower gestational age at birth and lower birth weight than their full-term peers. There were no significant group differences in age at scan, sex, maternal education, household income, race, and ethnicity.

Inclusion criteria for the study required all participants to be fluent in English, to have a Full Scale IQ > 75, and no MRI contraindications such as metallic implants or severe anxiety.

We recruited the preterm participants primarily through the UC San Diego High Risk Infant Follow-Up Clinic. Exclusion criteria were 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 neonatal complications, we excluded participants with significant brain injury such as intraventricular hemorrhage grade 3 or 4, cystic PVL, or moderate to severe ventricular dilation. Our preterm sample included four participants that were small for gestational age, five with bronchopulmonary dysplasia, and six that 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, including brain injury. The Institutional Review Board at UC San Diego approved this study. We obtained written, informed consent from the participants' parent/legal guardian, and verbal assent from participants who were at least seven years old.

Design and Procedure

Full-scale IQ

Full-scale IQ at age 5 was measured via the Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV). Data is missing from one full-term participant.

MRI Acquisition and Processing

MRI data were 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 Neurocognition and Genetics (PING) project was used in this study (30). The scanning sequence included a three-

plane localizer, a 3D T1-weighted inversion prepared RF-spoiled gradient echo scan using prospective motion correction (PROMO, 26) 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 (32,33), using the automated segmentation and labeling procedure for subcortical volumes, and automated, probabilistic, atlas-based analysis of white matter tracts (34). Two trained experts inspected the images and included only images with minimal to no movement or scanner artifacts, and no errors registration and segmentation in FreeSurfer. Quality of the images was assessed at all stages of processing. In this study we only included participants with complete, quality controlled T1- and diffusion-weighted MRI scans, leading to a final sample of 47 preterm and 28 full-term participants.

We analyzed the subcortical volumes of the following structures: amygdala, hippocampus, caudate nucleus, pallidum, putamen, thalamus, brain stem, cerebellar white matter (WM), intracranial volume (ICV), and the summated ventricles. In addition, we analyzed volumes, FA, and MD of the anterior thalamic radiation (ATR), cingulum (CGM), cortico-spinal tract (CST), corpus callosum (CC), inferior longitudinal fasciculus (ILF), temporal and posterior superior longitudinal fasciculus (tSLF, pSLF) and uncinate fasciculus (Unc).

Statistical Analyses

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

Brain measures were analyzed bilaterally, using the sum of both sides for volumes, and the average of both sides for DTI measures. We used general linear models to estimate effects of preterm birth on brain measures. The models included term status (preterm vs. full-term) as a between-subjects factor, and age (5, 6, or 7 years) as a within-subjects factor; sex was included as a covariate. Analyses of brain volumes also included the estimated total intracranial volume (ICV) as a covariate (32,35) to control for inter-individual variability in global brain size and for normalization of subcortical volumes of specific structures. We chose ICV as this measure as it has been used in similar studies and thus allows for direct comparison of findings (e.g. 17,31). We conducted post-hoc analyses of significant preterm birth brain effects. Brain variables with a moderate or strong effect of preterm birth were further analyzed cross-sectionally through univariate general linear models with term status as a fixed effect, covaried for sex, and volume variables additionally covaried for ICV.

We reported effect sizes using partial eta squared (η_p^2) for term status and covariates, and generalized eta square (η_G^2) for age (within-subject factor) (37,38). We interpreted effect sizes based on Cohen's thresholds for small, medium, and large effects for eta squared statistics of .01, .06, and .14 (39).

Results

Volumes of grey and white matter, and ventricles

Table 2 shows the effects of age, term status, and their interaction on gray matter volume, after correction for ICV and sex. Volumes of gray matter structures generally increased with age in both preterm and full-term group. Preterm birth had a significant, strong effect on thalamus and brain stem volume. The effect of birth status on tract volumes are presented in Table 3. A number of tracts showed significantly smaller volumes in children born preterm compared to full-term. We found a moderate to strong effect of birth status on volumes of cerebellar WM, CGM, CST and tSLF. In addition, the summated volume of all ventricles was significantly larger in children born preterm compared to full-term (Table 4). Term status did not have an effect on ICV itself.

All measures with the exception of ventricles showed a significant effect of age at scan (all $p \leq .007$). The effect of age is mainly weak or moderate. None of the measures showed an age by sex or age by ICV interaction effect (all $\eta_G^2 \leq .007$). Sex and ICV had significant moderate to strong effects on brain volumes.

We performed follow up analyses of the structures with a significant effect of term status cross-sectional for age 5, 6, and 7 (Figure 1). Figure 1 shows the size of the effect of term status on volumes of thalamus, brain stem, cerebellar WM, CGM, CST, tSLF, Unc, and the ventricles across preterm and full-term groups, adjusted for ICV and sex. As reflected by the lack of an age by term interaction effect, the differences between full-term and preterm group are fairly similar across the three ages for most structures. CGM shows an increase in the size of the effect of term status over time, while the effect of term status on thalamus, cerebellar WM, CST and Unc is largest at age 6.

Diffusivity measures of white matter fiber tracts

Means of FA and MD were generally similar for children in both groups. The effect of term status on FA and MD of white matter tracts is presented in Table 3. None of the white matter tracts showed a significant effect of preterm birth on these diffusivity measures. All measures showed a significant effect of age (all $p < .001$), with increasing age corresponding to increasing FA and decreasing MD. The strength of the age effect was small to medium. Sex did not have a significant effect on these diffusivity measures, with the exception of ILF ($p = .023$, $\eta_p^2 = .07$). Neither the age by sex nor the age by term effects were significant (all $p > .05$, $\eta_p^2 \leq .002$).

Full-scale IQ

Full-scale IQ at age 5 was measured via the Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV) and was significantly different between the full-term and preterm children with an average the scaled score of 108.4 and 102.4, respectively (Table 1, $F[1,73] = 4.568$, $p = .036$).

Discussion

This study investigated the impact of preterm birth on brain development in early childhood. We analyzed structural and diffusion weighted MR images to examine subcortical gray and white matter volumes, and FA and MD of white matter tracts. Volumes of the thalamus, brain stem, cerebellar white matter, cingulum, corticospinal tract, temporal superior longitudinal fasciculus, and uncinate fasciculus were smaller, while ventricles were larger following preterm birth. This is consistent across age 5 to 7, without an age by term interaction. We found no differences in FA or MD on the whole tract level in our sample. Preterm participants had

significantly lower IQ compared to full-term participants at age 5, although both groups scored in the average range.

Subcortical gray matter volumes

Consistent with previous literature, we found reduced subcortical gray matter structures. This means that even without significant neonatal complications, there are persistent effects of preterm birth on brain volumes. Our results compare to a study of 5–12-year-old children born preterm and tested at two time points about a year apart. They found effect sizes that are similar in strength despite having less strict selection criteria than ours (21). Moreover, they also report the lack of an age by term interaction effect and argue that it reflects similar but delayed developmental trajectories in children born full-term and preterm. This finding is consistent across other study populations of different age and geographical location (17,19). The consistently reduced subcortical gray matter volumes likely reflect early neuronal loss due to perinatal injury. With age, this neuronal loss cannot be made up and thus persists into childhood and adulthood. It is also possible that mechanisms that lead to preterm birth in the first place continue throughout postnatal development, such as intrauterine growth restriction. However, only four children of the preterm group were born small for gestational age.

Despite other studies having reported reduced volumes of hippocampus and amygdala in children born preterm compared to full-term, we did not find significant differences between the two groups. This may indicate increased protection of the limbic system to subtle perinatal injury. An argument for this is the early development of limbic white matter tracts (40). The more mature oligodendrocytes in limbic fibers at the time of birth may have a protective function for the limbic gray matter structures. In contrast, the thalamocortical connection develop predominantly in the third trimester, comprise a more immature population of oligodendrocytes

and are thus more vulnerable to perinatal brain injury, leading to reduced thalamic volume (27,40,41). Reduced thalamic volume at term-equivalent age in infants born preterm has been associated with lower cognitive and behavioral outcomes, including IQ, academic achievement, and motor function at seven years of age (42). In addition, we found reduced cerebellar and brain stem volume as has recently been reported at term equivalent age in infants born preterm (43). These structures are also included in Volpe's characterization of encephalopathy of prematurity (2,44). Our study indicates that these effects are still present today and persist into childhood.

Differences in white matter tract volumes, but not FA and MD

We found that the volume but not the diffusivity measures of several white matter tracts were altered in the children born preterm. Volume reflects the gross morphology of the white matter tract. In contrast, FA and MD are thought to reflect the microstructure of a given tissue. With development, FA increases with alignment of axons in white matter tracts and myelination. Conversely, MD decreases with increased myelination because the myelin sheet reduces the extracellular space and thus reduces diffusivity (45). Even though none of the structures that we examined reached formal significance as defined by $p < .05$, FA of CGM, and MD of CST and CC near this threshold, with effect sizes between .044 and .052. It is possible that a more segmented analysis of these tracts would reveal more considerable differences in specific parts of the tract.

Studies of preterm birth show some inconsistencies regarding DTI findings. Altered white matter microstructure as in PVL was once thought to be one of the main consequences of preterm birth (2,46). Consistently, a recent study of infants born preterm shows reduced FA and increased MD at term-equivalent age (47). Other studies found that these effects are less pronounced, i.e. only detectable in a small segment of the tract, or not present at all (48,49). For

example, a study of a Norwegian cohort of individuals born in the 2000's showed that white matter microstructure and connectivity were only marginally affected by preterm birth (19).

These discrepancies may be due to small sample sizes and variations in external factors that are likely to influence neurodevelopmental outcomes in addition to the impact of preterm birth. One of the main sources of variation between study samples are the prenatal and neonatal health care standards that differ by geographical area (50) and year of birth (51). In addition, our sample consists of children with average IQ and without severe neonatal complications. Feldman and colleagues have previously argued that FA and MD may not be sensitive enough to differentiate this kind of high-functioning sample of children born preterm from full-term controls (49).

It is unclear why we find a moderate to strong effect of preterm birth on white matter tract volume despite the lack of differences in DTI measures. However, volume and DTI measures reflect different tissue properties. A study of aging older adults only shows limited, moderate correlations between volume and FA (52). They argue that the correlation was mainly driven by radial diffusivity, hinting towards myelination being the common factor that explains this relationship. White matter tract volume has not been as widely studied in recent years. However, the present literature generally agrees with our findings. For example, adults born preterm show reduced volume of the cingulum, which is associated to impaired memory function (36). Furthermore, we can speculate that studies that showed reduced volume in corpus callosum in children and adolescents born preterm may also find reduced volumes of other white matter tracts if examined (19,21).

Ventricles and intracranial volume

The pronounced increase in the size of the ventricles is consistent with other studies (19), and given the lack of group differences in ICV, may explain the reduction in gray and white matter volumes. The early impact of preterm birth may have a persistent effect on subcortical volume but not white matter microstructure. Instead of a decreased whole brain volume (as approximated here by ICV), the ventricles are increased, the cellular tissue is decreased, and the ICV is about the same in both groups. This fits to our previous findings of considerable alterations in cortical thickness but not surface area at age 5 of this same cohort.

Strengths and limitations

Strengths of our study are the longitudinal, multi-model design with a full data set of children who had complete, quality controlled structural and diffusion weighted MR imaging at three time points. Furthermore, studies investigating the brain development in children born preterm starting at the young age of 5 years are rare and give a unique insight into developmental trajectories in early childhood.

Limitations are the fairly small data set of 47 children born preterm and 28 children born full-term. As such we may be overestimating the effect of preterm birth and/or not be able to detect other, more subtle effects. Big data sets promise to produce more reliable results. That being said, our results add to the growing body of literature examining brain and cognitive development following preterm birth in various populations around the globe.

Conclusion

Even in the absence of severe neonatal complications, preterm birth leads to persistent alterations in brain development. In our study group of children born between 24 and 32 weeks of gestation volumes of thalamus, brain stem, cerebellar white matter, cingulum, corticospinal

tract, uncinate fasciculus, and temporal superior longitudinal fasciculus were smaller, while ventricles were larger compared to full-term controls. The volume differences are persistent from 5 to 7 years of age and are likely to be associated with reduced cognitive functioning and academic achievement. This is particularly important as children start formal schooling in this age range, which opens opportunities for interventions in a school setting.

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Table 1*Participant characteristics.*

	Preterm <i>n</i> = 47	Full-term <i>n</i> = 28	Effect size	<i>p</i> value
GA at birth in weeks mean (SD, min-max)	29.7 (2.2, 24–32.9)	39.8 (0.7, 38–41)	$\eta^2=.883$	<.001
Birth weight in g mean (SD, min-max)	1307 (442, 625–2450)	3435 (543, 2353–4423)	$\eta^2=.824$	<.001
Age at imaging: mean (SD)				
Time 1 (Age 5)	5.3 (.4)	5.3 (.3)	$\eta^2=.001$	.809
Time 2 (Age 6)	6.4 (.4)	6.4 (.3)	$\eta^2=.002$	.733
Time 3 (Age 7)	7.4 (.4)	7.4 (.3)	$\eta^2<.001$	.923
Sex (female)	53%	46%	$V=.065$	.571
Maternal education absolute (relative frequency)				
1) high school degree	5 - 11%	3 - 11%	$\eta^2=.017$	.196
2) 1–3 year college	17 - 36%	6 - 21%		
3) college degree	16 - 34%	10 - 36%		
4) graduate degree	9 - 19%	9 - 32%		
Household income absolute (relative frequency)				
1) below \$50,000	8 - 17%	1 - 4%	$\eta^2=.013$	.341
2) \$50,000 – <\$100,000	12 - 26%	14 - 50%		
3) \$100,000 – <\$200,000	15 - 32%	12 - 43%		
4) \$200,000 and above	10 - 21%	0 - 0%		
Missing information	2 - 4%	1 - 4%		
Race absolute (relative frequency)				
African American	1 - 2%	0 - 0%	$V=.194$	.588
Asian	4 - 9%	4 - 14%		
Caucasian	35 - 74%	18 - 64%		
Mixed/other	6 - 13%	6 - 21%		
Missing information	1 - 2%	0 - 0%		
Ethnicity (Hispanic/Latinx)	19 - 40%	9 - 32%	$V=.083$	.473
Full-scale IQ (age 5) ^a	102.4 (13.0)	108.4 (8.9)	$\eta^2=.060$	.036

Note. Group comparisons were performed via ANOVA $F[1,74]$ for GA at birth, birth weight, and age at testing; via Mann-Whitney U test for maternal education, and household income; and via Chi-square test for sex, race, and ethnicity. GA: gestational age; g: grams, ^a data from one full-term participant is missing.

Table 2*Effect of term status, age, and age by term interaction on gray matter volumes*

Variable	Term		Age ^a		Age by term	
	η_p^2	<i>p</i>	η_G^2	<i>p</i>	η_G^2	<i>p</i>
Amygdala	.004	.62	.092	<.001	.006	.14
Hippocampus	.011	.37	.088	<.001	~.0	1.00
Caudate	.009	.41	.002	.003	~.0	.34
Putamen	.017	.27	.018	<.001	~.0	.48
Thalamus	.16	<.001	.072	<.001	.002	.18
Brain Stem	.14	.001	.13	<.001	~.0	.96

Note. $N = 75$. Statistics are from ANCOVAs of subcortical gray matter and white matter structures with term status (preterm vs. term) as a between-subjects effect, age (5, 6, and 7 years) as a within-subjects effect, and ICV and sex as a covariate. ^a Linear age effect, $df = 1$

Table 3*Effect of term status, age, and age by term interaction on white matter volumes*

Variable	Term		Age ^a		Age by term	
	η_p^2	<i>p</i>	η_G^2	<i>p</i>	η_G^2	<i>p</i>
Cerebellar WM	.16	<.001	.11	<.001	.001	.20
ATR	.032	.13	.119	<.001	~.0	.35
CGM	.16	<.001	.055	<.001	.001	.093
CST	.098	.007	.25	<.001	~.0	.70
CC	.047	.067	.079	<.001	~.0	.89
ILF	.042	.082	.086	<.001	.003	.060
tSLF	.070	.023	.053	<.001	~.0	.72
pSLF	.021	.23	.058	<.001	~.0	.97
Unc	.056	.043	.088	<.001	.003	.044

Note. $N = 75$. Statistics are from ANCOVAs of white matter structures with term status (preterm vs. term) as a between-subjects effect, age (5, 6, and 7 years) as a within-subjects effect, and ICV and sex as a covariate. WM: white matter, ATR: anterior thalamic radiation, CGM: Cingulum, CST: Cortico-spinal tract, CC: Corpus callosum, ILF: inferior longitudinal fasciculus, tSLF: temporal superior longitudinal fasciculus, pSLF: posterior longitudinal fasciculus, Unc: uncinate fasciculus.

^a Linear age effect, $df = 1$

Table 4*Effect of term status, age, and age by term interaction on ventricles and ICV*

Variable	Term		Age ^a		Age by term	
	η_p^2	<i>p</i>	η_G^2	<i>p</i>	η_G^2	<i>p</i>
Ventricles	.101	.006	~0	.16	~.0	.74
ICV	.004	.58	.028	<.001	~.0	.85

Note. $N = 75$. Statistics are from ANCOVAs of subcortical gray matter and white matter structures with term status (preterm vs. term) as a between-subjects effect, age (5, 6, and 7 years) as a within-subjects effect, and ICV and sex as a covariate. ICV: intracranial volume.

^a Linear age effect, $df = 1$

Table 5*Effect of term status, age, and age by term interaction on diffusivity measures of white matter tracts*

Variable	Term		Age ^a		Age by term	
	η_p^2	<i>p</i>	η_G^2	<i>p</i>	η_G^2	<i>p</i>
Fractional anisotropy						
ATR	.030	.14	.059	<.001	.011	.38
CGM	.048	.060	.010	<.001	.048	.061
CST	.009	.41	.10	<.001	.022	.21
CC	.004	.59	.017	<.001	.036	.10
ILF	.028	.15	.081	<.001	.059	.036
tSLF	.006	.52	.047	<.001	.029	.15
pSLF	.013	.34	.048	<.001	.023	.20
Unc	.034	.11	.055	<.001	.003	.67
Mean diffusivity						
ATR	.035	.11	.086	<.001	.016	.28
CGM	.002	.68	.096	<.001	.014	.31
CST	.052	.050	.053	<.001	~.0	.98
CC	.044	.072	.035	<.001	.013	.33
ILF	.003	.66	.052	<.001	~.0	.94
tSLF	.027	.16	.057	<.001	.001	.75
pSLF	.021	.22	.059	<.001	.003	.62
Unc	.011	.37	.093	<.001	.063	.031

Note. $N = 75$. Statistics are from ANCOVAs of fractional anisotropy and mean diffusivity measures of white matter tracts with term status (preterm vs. term) as a between-subjects effect, age (5, 6, and 7 years) as a within-subjects effect, and sex as a covariate. The quadratic age effect and interactions with age, which were generally small or near zero, are not shown; see text for details. ATR: anterior thalamic radiation, CGM: Cingulum, CST: Cortico-spinal tract, CC: Corpus callosum, ILF: inferior longitudinal fasciculus, tSLF: temporal superior longitudinal fasciculus, pSLF: posterior longitudinal fasciculus, Unc: uncinate fasciculus.

^a Linear age effect, $df = 1$

Figure 1

Volumes of gray and white matter, and ventricles at age 5, 6, and 7 with a significant effect of preterm birth, sorted by strength of effect. The solid line at .14 illustrates the threshold for a strong effect, the dashed line at .06 the threshold for a moderate effect, the dotted line at .01 the threshold for a weak effect.

ROI: region of interest, CGM: cingulum, CWM: cerebellar white matter, CST: corticospinal tract, Unc: uncinete fasciculus, tSLF: temporal superior longitudinal fasciculus.