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Brain Development and Mathematics Skills Following Preterm Birth: A Longitudinal Study of 5- to 7-Year-Old Children

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Brain Development and Mathematics Skills Following Preterm Birth: A Longitudinal Study of 5- to 7-Year-Old Children

A dissertation submitted in partial satisfaction of the requirements
for the degree

Doctor of Philosophy

in

Cognitive Science with Specialization in Anthropogeny

by

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2022

The Dissertation of Julia Anna Adrian is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

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DEDICATION

I dedicate this dissertation to individuals who were born preterm around the world, particularly the children who participated in this research.

And to my son Philipp, who at the time of this writing is just a few weeks away of being born.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SUPPLEMENTARY TABLES

LIST OF ABBREVIATIONS

AD	Axial diffusivity
ATR	Anterior thalamic radiation
ANOVA	Analysis of variance
ANCOVA	Analysis of co-variance
CC	Corpus callosum
CGM	Cingulum
CSF	Cerebrospinal fluid
CST	Corticospinal tract
CTOPP-2	Comprehensive Test of Phonological Processing, 2nd edition
CWM	Cerebral white matter
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FSIQ	Full scale intelligence quotient
GA	Gestational age
ICV	Intracranial volume
IFOF	Inferior frontal occipital fasciculus
ILF	Inferior longitudinal fasciculus
MD	Mean diffusivity
MRI	Magnetic resonance imaging
pSLF	Parietal superior longitudinal fasciculus
PVL	Periventricular leukomalacia
RD	Radial diffusivity
SD	Standard deviation

SLF	Superior longitudinal fasciculus
SST	Stop signal task
SWM	Spatial working memory
TEMA-3	Test for Early Mathematics Ability, 3rd edition
tSLF	Temporal superior longitudinal fasciculus
UF	Uncinate fasciculus
VMI	Visual motor integration
WM	White matter
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence, 4th edition

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ABSTRACT OF THE DISSERTATION

Brain Development and Mathematics Skills Following Preterm Birth:
A Longitudinal Study of 5- to 7-Year-Old Children

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Children born before 33 weeks of gestation have an increased risk for early brain injury, as well as cognitive, behavioral, and academic deficits. The aim of this dissertation was to contribute to a more comprehensive understanding of brain and cognitive development following preterm birth. All three studies used data from a cohort of children recruited before starting kindergarten (5 years of age) who were followed up after one and two years. At each timepoint, children completed structural and diffusion weighted MRI, as well as a battery of cognitive and behavioral tests. Forty-seven to 51 children born preterm (24–32 weeks gestational age), and 27 to 28 children born full-term were included in each study.

The first study examined the effect of preterm birth on number and arithmetic skills, and how it is mediated by related cognitive functions. Number and arithmetic skills were lower in children born preterm. The performance gap in number skills decreased over time,

while the performance gap in arithmetic skills increased. The effect of preterm birth on number and arithmetic skills was mediated by phonological processing, visual-motor integration, and inhibitory control, but not spatial working memory. Phonological processing showed the strongest mediating effect.

The second study examined the effect of preterm birth on development of subcortical gray matter and white matter volumes, and diffusivity measures of white matter tracts. Children born preterm had smaller volumes of thalamus, brain stem, cerebellar white matter, cingulum, corticospinal tract, inferior frontal occipital fasciculus, uncinate fasciculus, and temporal superior longitudinal fasciculus, while their ventricles were larger 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 5, 6, and 7 years.

The third study examined the association between white matter tract diffusivity measures and mathematics skills at 5 and 7 years of age. Fractional anisotropy of the right and left corticospinal tract, left inferior longitudinal fasciculus, and left inferior frontal occipital fasciculus showed a significant interaction effect with term status. This moderating effect of preterm birth may be indicative of reorganization and plasticity of functional networks following early injury due to prematurity.

These findings help to delineate the developmental trajectory of brain and cognitive development during early childhood following preterm birth. This knowledge may provide guidance for opportunities for support of children born preterm and their families, such as targeted evaluation and use of interventions.

CHAPTER 1: GENERAL INTRODUCTION

Preterm birth is defined as live birth before 37 completed weeks of gestation. Worldwide, about 15 million children are born preterm every year, with rates of preterm birth ranging between 5 and 18% (Blencowe et al., 2013). In the USA in 2020, 10.1% of all infants were born before 37 weeks of gestation, and 2.7% before 34 weeks of gestation (Martin et al., 2021). Morbidity generally increases with lower gestational age at birth and lower birth weight, and decreases with higher quality medical care (Allen et al., 2011). With advances in medical interventions, particularly surfactants and ventilators, and antenatal steroids given to the mother, incidences of respiratory distress syndrome are considerably reduced (Grytten et al., 2017), and the likelihood of survival is very high (Helenius et al., 2017).

There is a wide variability of outcomes following preterm birth. As preterm birth affects all organ systems, it is associated with increased risk of a variety of impairments, including deficits in cognitive, behavioral, and motor development (Crump, 2020; Synnes & Hicks, 2018). Furthermore, it is associated with lower academic achievement, with prominent deficits in mathematics (Akshoomoff et al., 2017; Taylor et al., 2009). These deficits are present not only in children with serious neonatal complications but have also been observed in children with a relatively benign health history and are persistent after adjusting for IQ (Aylward, 2014; Johnson, 2007; Pritchard et al., 2009).

Preterm birth further impacts typical brain development, likely through both an initial injury due to early exposure to the extrauterine environment, as well as dysmaturational events that affect subsequent development (Volpe, 2019). Structural and diffusion-weighted magnetic resonance imaging studies show lower subcortical gray and white matter volumes, as well as alterations in white matter microstructure and cortical morphology (Ball et al., 2012; Sripada et al., 2018). Neuropathology following preterm birth has been linked to impaired cognitive functioning in children and adolescents (Nagy et al., 2004; Skranes et al., 2007; Taylor et al., 2011). Studies focusing on the association between white matter structure and mathematics skills in children following preterm birth are limited, even though preterm birth has consistently been linked to both lower mathematics achievement and white matter injury.

This dissertation consists of analyses of a longitudinal data set of MRI, DTI, and neuropsychological data of children born preterm (less than 33 weeks of gestation) and children born full-term at 5, 6, and 7 years of age. The aim was to contribute to our understanding of the neuropsychological and neuroanatomical developmental trajectories following preterm birth, with a focus on mathematics skills and white matter microstructure. The following chapters deal with cognitive functions associated with mathematics skills (study 1), volumes and DTI measures of white matter tracts and volumes of gray matter (study 2), and the association between DTI measures of white matter tracts and mathematics skills (study 3) following preterm birth. These studies contribute to the current body of literature in three important ways. First, since this was a longitudinal study from age 5 to 7, it allowed us to investigate brain and cognitive development during a critical time in which the children received their first formal classroom instruction. Second, this sample of children born preterm did not have severe brain injury and did not have evidence of disability. This contrasts with most current studies that often focus on more severe cases. However, with the improvements in medical care, it is likely that severe morbidities decrease, and the impact of preterm birth becomes more subtle. Third, the assessment of neuropsychological outcomes with structural and diffusion weighted MRI in the same participants enabled the examination of connections between brain structure and function, with implications for neuroplasticity and alternative brain organization.

Typical Brain Development

Brain development is a protracted process, starting in the third week post conception and continuing well into adulthood.

Intrauterine brain development

During the embryonic period, undifferentiated cells undergo blastulation and gastrulation, which gives rise to the three germ cell lines: endoderm, mesoderm, and ectoderm. Ectodermal cells will differentiation into neural progenitor cells and eventually neurons, oligodendrocytes, and astrocytes. Neurogenesis starts in the embryonic period and is largely completed by mid-gestation. Neurons proliferate at the ventricular and subventricular zones in the center of the brain, first by symmetrical and later asymmetrical cell division. From there they migrate radially outwards to form subcortical grey matter and the neocortex. Migration of neurons into the six-layered neocortex structure follows an inside-out pattern: the deeper layers of the cortex are built by earlier migrating neurons while the more superficial layers are built by later migrating neurons. Migratory processes are highly organized and ordered in time and space. Neural migration peaks between 3 and 5 months of gestation, at which point the cerebral cortex contains its full set of neurons. Gyrification starts early and continues postnatally. The longitudinal fissure, dividing the two hemispheres, starts to form at 8 weeks of gestation, while most other primary sulci form between week 14 and 26. Secondary and tertiary sulci and gyri form after migration is completed. The number of gyri increases fastest between 26 and 28 weeks. Organization of brain cells occurs from 5 months of gestation until years after birth. It includes the establishment and differentiation of subplate neurons, orientation and layering of cortical neurons, dendritic and axonal arborization, gliogenesis and synaptogenesis, apoptosis and synaptic pruning (Semple et al., 2013; Stiles & Jernigan, 2010; Volpe, 2008).

Myelination begins in the second trimester and continues into adulthood. In the central nervous system, myelination generally follows the pattern of proximal before distal pathways, sensory before motor pathways, projection before association fibers, central cerebral before central poles, and occipital poles before fronto-temporal poles (Volpe, 2008). Among the earliest white matter structures to form are the thalamocortical and corticothalamic pathways, transferring sensorimotor information to the cortex and back (Stiles & Jernigan, 2010).
The peak myelination period is during the first two years after birth when mature, myelin-producing oligodendrocytes become abundant. Oligodendrocytes develop actively during weeks 24 to 40 of gestation: from oligodendroglial progenitors to pre-oligodendrocytes, to immature oligodendrocytes into mature myelin-producing oligodendrocyte. At 28 weeks, pre-oligodendrocytes make up 90% of the total oligodendrocyte population. Between weeks 28 to 40, they develop into immature oligodendrocytes, which account for 50% of the population at term (Back et al., 2001). Preterm birth happens amid this rapid development. Because of their immature status, pre-oligodendrocytes and immature oligodendrocytes are especially vulnerable to ischemia and inflammation, and such an insult may lead to a pattern of brain injury called encephalopathy of prematurity (Volpe, 2009).

Postnatal brain development

Brain development continues postnatally, with much of our knowledge stemming from MRI studies. Although global trends in structural brain development can be observed, there is considerable variation from structure to structure and individual to individual (Jernigan et al., 2011). Volume of the cranial vault increases during the first decade of life and remains stable afterwards. Subcortical grey matter volumes increase over the first years postnatally but declines during adolescence and adulthood (Gilmore et al., 2012; Gogtay & Thompson, 2010). Cortical surface area expands until, about 10 years of age and decreases thereafter (Brown et al., 2012). Development of cortical thickness shows a pattern of widespread, regionally specific, cortical thinning, as well as areas of cortical thickening during childhood and adolescence. Myelination plays a crucial role in the interpretation of the developmental pattern of gray matter morphology. In addition to regressive events such as synaptic pruning, apparent reductions in grey matter volume such as cortical thinning could be reflective of increase in myelination (and thus volume) of the underlying white matter (Brown & Jernigan, 2012).

A common way to examine white matter tract development is through diffusion weighted imaging. Diffusion weighted imaging can be analyzed by fitting a diffusion tensor to each voxel that estimates the movement of protons (mainly within water molecules) along each of the principal axes (Diffusion Tensor Imaging, DTI). DTI yields measures of diffusivity: *fractional anisotropy* (FA) is a measure of relative directionality of diffusion. Mean diffusivity (MD) is a measure of mean water movement along all axes, axial diffusivity (AD) and radial diffusivity (RD) are measures of water movement parallel and perpendicular, respectively, to the principal direction of diffusion (Johansen-Berg & Behrens, 2013). Anatomically, these are associated with the content of hydrogen nuclei in tissue, packing of parallel axons, axonal diameter, and myelination (Counsell et al., 2014; Dubois et al., 2014; Jeurissen et al., 2013). At birth, FA of cerebral white matter is low (Hermoye et al., 2006). With development, FA of white matter tracts generally increases, while MD decreases (Figure 1.1). This likely reflects the decline of unrestricted water diffusion in extracellular spaces due to denser packing of axons, because of continuing myelination and increase in axonal diameter (Suzuki et al., 2003). Long projection fibers reach adult levels of FA earliest, followed by commissural fibers and association fibers (Lebel & Beaulieu, 2011).

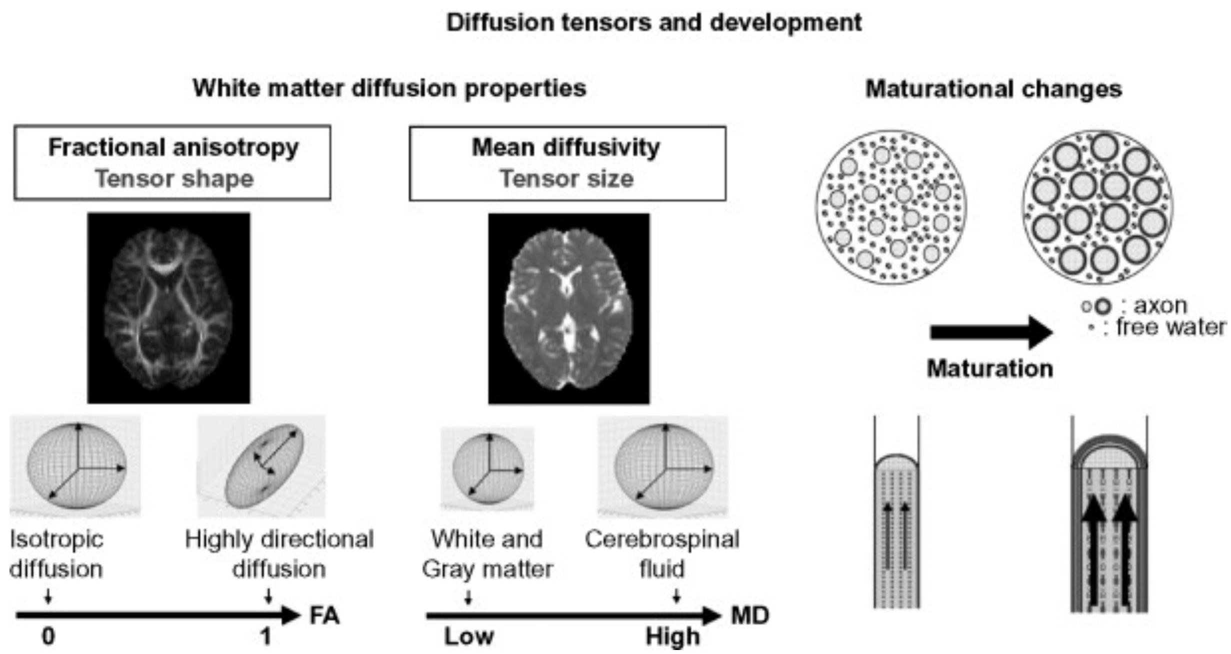

Figure 1.1: Diffusion tensors and development

(a) Tensor size reflects magnitude of diffusion. Tensors for voxels in CSF spaces are large and spherical (or isotropic): all 3 eigenvalues the same and all high. Tensors in gray matter are smaller (less free water) but also isotropic: all 3 eigenvalues the same and all low.
(b) Tensor shape reflects directionality of diffusion. Tensors for voxels in fiber tracts are elongated (or anisotropic) presumably because diffusion of water molecules is higher within axons and along the axonal and myelin surfaces than perpendicular to the fiber tracts: principal eigenvalue (parallel diffusivity) higher than others (perpendicular diffusivity)—high "fractional anisotropy."
(c) As fiber tracts mature, axons and their myelin sheaths become larger and the water in extra-axonal space decreases. Less free water reduces all 3 eigenvalues (as in (a)) But because diffusion along fiber membranes is preserved or increased, principal eigenvalue (parallel diffusivity) is decreased less than other eigenvalues (perpendicular diffusivity). Therefore, perpendicular diffusivity and fractional anisotropy are most affected by fiber tract development. Alterations of fiber organization (coherence, tortuosity) may also contribute to anisotropy.

Figure and caption reproduced with permission from Jernigan et al. (2011)

Preterm Birth and Brain Development

During the preterm period (~24-37 weeks of gestation), intrauterine brain development includes multiple complex and dynamic processes (Figure 1.2). This leaves the brain particularly vulnerable to exogenous and endogenous insults, such as hypoxia-ischemia, inflammation, excitotoxicity, and free-radical attack. Injury acquired during this vulnerable time can worsen by disturbing future development (Volpe, 2009).

Encephalopathy of prematurity

Encephalopathy of prematurity describes a type of brain injury common in preterm children. It has two distinct components: a primary disruption of white matter development by injury of developing oligodendrocytes and a secondary disruption of neuronal-axonal maturation (Volpe, 2009).

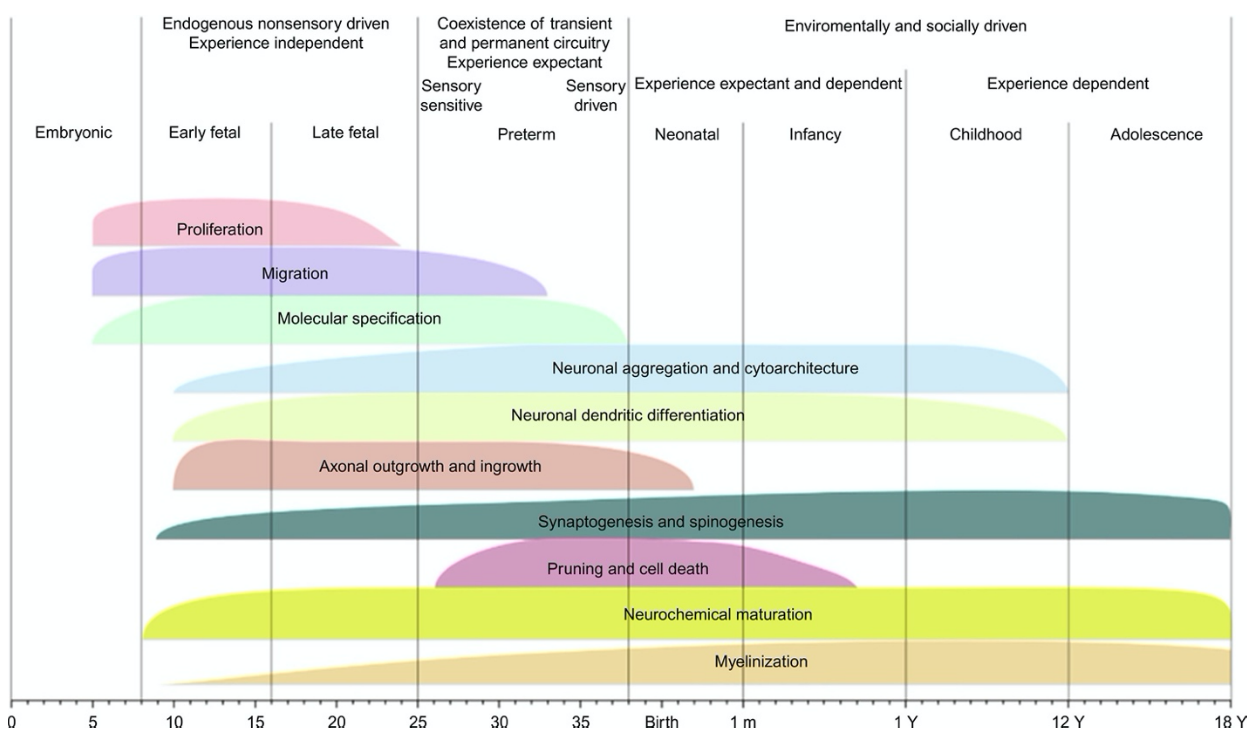

Figure 1.2: Key neurodevelopmental processes prenatally and postnatally
Reproduced with permission from Wallois et al. (2020)

White matter injury (periventricular leukomalacia, PVL) is often adjacent to the lateral ventricles and can be focal–with localized, macroscopic necroses–or diffuse. Typically, white matter injury is diffuse and necroses are only microscopic in size. This type of white matter injury is called ‘non-cystic’ PVL. Non-cystic PVL is characterized by an initial decrease in pre-myelinating oligodendrocytes (pre-oligodendrocytes and immature oligodendrocytes), followed by astrogliosis, microgliosis, and an increase of oligodendrocyte progenitors (Billiards et al., 2008; Haynes et al., 2003; Volpe, 2009; Volpe, Kinney, Jensen, & Rosenberg, 2011). The regenerating oligodendrocyte progenitors fail to mature properly, potentially because they are vulnerable to subsequent hypoxic-ischemic insults (Segovia et al., 2008). The vulnerable period for pre-oligodendrocytes is around 24-32 weeks of gestation, the same time that periventricular white matter injury occurs (Volpe et al., 2011).

Neuronal-axonal disease is thought to be a secondary disturbance, though the sequence of events remains unclear. It affects the cerebral white matter (axons and subplate neurons), thalamus, basal ganglia, cerebral cortex, brainstem, and cerebellum (Volpe, 2009). Cerebral white matter axons (projection, commissural, and association fibers) are particularly vulnerable in the preterm period, as they undergo rapid development (Volpe, 2009). Axonal injury leads to axonal degradation, which is present in diffuse white matter injury, and can be detected via DTI as altered FA (Dodson et al., 2017; Vangberg et al., 2006). Neuronal loss and gliosis are observed in the thalamus and basal ganglia. These structures show reduced volumes in MRI following preterm birth at term-equivalent age and later (Ball et al., 2012; Sripada et al., 2018). A consequence of thalamic injury may be axonal degradation, which in turn could affect myelination and cortical development (Volpe, 2009).

With advances in neonatal care, particularly reduction of respiratory distress syndrome, incidences of cystic PVL have declined dramatically (Gano et al., 2015). However, diffuse white matter injury is still common following preterm birth, particularly in the presence of hypoxia-ischemia and inflammation (Huang et al., 2017). Cell proliferation, maturation, and organization may be altered even in the absence of observable insults, and the long-term impact is influenced by external factors of the postnatal environment (Aylward, 2014).

Neuroimaging studies of the preterm brain

Neuroimaging studies are a useful tool to study the association between brain structure and cognitive function. Some of the manifestation of encephalopathy of prematurity which can be seen on MRI scans are summarized in Figure 1.3.

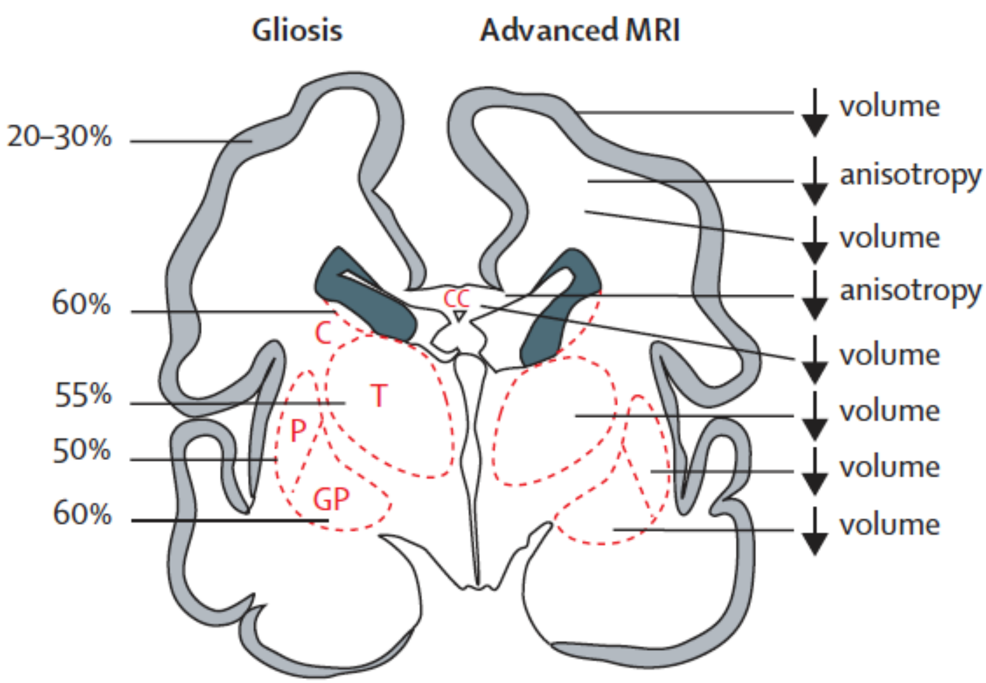

Figure 1.3: Observation of diffuse white matter injury
by frequency of gliosis (left) and abnormalities detected by volumetric and diffusion tensor MRI. Coronal sections of cerebrum. C=caudate, CC=corpus callosum, GP=globus pallidus, P=putamen, T=thalamus
Reproduced with permission from Volpe (2009)

Several studies have reported altered measures of diffusivity following preterm birth, though the direction of alteration differs between tracts (e.g., Anjari et al., 2007; Eikenes, Løhaugen, Brubakk, Skranes, & Håberg, 2011; Skranes et al., 2007; Young et al., 2017). For example, children born <31 weeks of gestation had decreased FA in uncinate fasciculi and forceps major, and increased FA in right anterior thalamic radiation, inferior fronto-occipital fasciculi, and inferior longitudinal fasciculi (Dodson et al., 2017). Similar differences were found in adolescents born preterm (Travis et al., 2015). The degree of white matter alterations are related to the degree of prematurity (gestational age at birth and birth weight), and complications in the neonatal period (Ball et al., 2012, 2013; Malavolti et al., 2017; Pavaine et al., 2016).

White matter integrity and cerebral white matter volumes have been linked to cognitive functioning in children and adolescents born preterm (Nagy et al., 2004; Skranes et al., 2007; Taylor et al., 2011). FA of corpus callosum, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, uncinate fasciculi, and anterior thalamic radiations was associated with visual-motor integration in young adults born preterm (Sripada et al., 2015). Longitudinal studies of the association between structure and function are often designed with a DTI scan at an earlier age and cognitive/academic assessment at a later age. For example, thalamocortical connectivity at term-equivalent age has been shown to predict cognitive functioning at 2 years of age (Ball et al., 2015). FA at term-equivalent age has also been linked to working memory and early mathematics at age 5 in children born <30 weeks' gestational age (Ullman et al., 2015). One study of 7-year old children born very preterm examining the link between corpus callosum development and academic achievement found lower FA compared to full-term controls, and a positive association between FA and performance on a standardized test for mathematics (Thompson et al., 2015).

Another study investigated white and grey matter volumes of 6- to 7-year old children born very preterm and their mathematics skills. They found correlation of brain volumes with a number comparison task, but not with a standardized math task which comprises a variety of skills (Starke et al., 2013). There are several methodological weaknesses with the study, including the absence of a full-term control group. However, the study also hints towards the necessity of investigating specific cognitive/mathematics skills for association with brain measures. The reason that no correlation of the general mathematics test performance and brain structure could be found, may be that it was hidden by using a general score representing proficiency in several specific skills.

Preterm birth has been associated with volume reductions in subcortical grey matter structures, particularly the thalamus, amygdala, caudate nucleus, basal ganglia and hippocampus (Ball et al., 2012; Nosarti et al., 2014; Sølsnes et al., 2016; Sripada et al., 2018). These volume reductions have been liked to adverse neurodevelopmental outcomes, including poorer attention and IQ (Bjuland et al., 2014; Lean et al., 2017).

Preterm Birth and Cognitive Development

Children born very preterm (<33 weeks of gestation) have an increased risk of developing impairments across many cognitive domains, which can start early and persist into adulthood (Aarnoudse-Moens et al., 2009; Anderson, 2014; Nosarti et al., 2010). Reported rates of adverse outcomes following preterm birth vary, presumably due to differences in study cohort and outcome measures. One meta-analysis of population studies estimates that in high-income countries 29% of children born between 28 and 31 weeks of gestation, and 58% of children born before 28 weeks exhibit mild to severe neurodevelopmental impairment at 2 – 5 years of age. These rates are higher for those born in low-income countries (Blencowe et al., 2013).

The wide range of impairments following preterm birth includes neurosensory impairments, including deficits in vision and hearing, lower executive function skills, as well as motor impairments (Blencowe et al., 2013). Instead of severe disabilities such as major motor deficits, the most common neurodevelopmental sequelae are impairments that are low in severity but high in prevalence (Volpe, 2009). Children born before 33 weeks of gestation generally have IQ scores in the normal range, with an average decrease of 1.5 – 2.5 points for each week they were born earlier (Johnson, 2007). In some individuals born preterm mild to moderate impairment might only be identified later in life, when cognitive demands are high (Aylward, 2014). These more subtle consequences of preterm birth include learning problems and lower academic achievement (Aylward, 2014). Differences in visual and perceptual skills, executive functions, and cognitive functioning have been reported in children born preterm, and are important for educational outcomes (Anderson, 2014).

This dissertation comprises three studies focused on mathematics skills and structural brain development in young children born preterm. Chapter 2 examines the relationship between cognitive functions and mathematics skills in children born preterm and full-term. Chapter 3 compares volumes of subcortical gray matter structures and white matter tracts, and diffusivity measures of white matter tracts between preterm and full-term groups. Chapter 4 utilizes our findings from the previous two studies to examine the association between mathematics skills and diffusivity measures of white matter tracts following preterm birth. Chapter 5 connects the main findings of the three studies to other research on the same study cohort. It further discusses considerations for the interpretation of our results and avenues for future research.

CHAPTER 2:
COGNITIVE FUNCTIONS MEDIATE THE EFFECT OF PRETERM BIRTH ON MATHEMATICS SKILLS IN YOUNG CHILDREN

The content within this section, titled “Chapter 2: Cognitive functions mediate the effect of preterm birth on mathematics skills in young children” reflects material from a paper that has been published in the journal Child Neuropsychology. The full citation is as follows:

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Abstract

Children born preterm are at risk for cognitive deficits and lower academic achievement. Notably, mathematics achievement is generally most affected. Here, we investigated the cognitive functions mediating early mathematics skills and how these are impacted by preterm birth. Healthy children born preterm (gestational age at birth < 33 weeks; $n = 51$) and children born full term ($n = 27$) were tested at ages 5, 6, and 7 years with a comprehensive battery of tests. We categorized items of the TEMA-3: Test for Early Mathematics Abilities Third Edition into number skills and arithmetic skills. Using multiple mediation models, we assessed how the effect of preterm birth on mathematics skills is mediated by spatial working memory, inhibitory control, visual-motor integration, and phonological processing. Both number and arithmetic skills showed group differences, but with different developmental trajectories. The initial poorer performance observed in the preterm children decreased over time for number skills but increased for arithmetic skills. Phonological processing, visual-motor integration, and inhibitory control were poorer in children born preterm. These cognitive functions, particularly phonological processing, had a mediating effect on both types of mathematics skills. These findings help define and chart the trajectory of the specific cognitive skills directly influencing math deficit phenotypes in children born very preterm. This knowledge provides guidance for targeted evaluation and treatment implementation.

Introduction

Preterm birth (before 37 weeks of gestation) occurs in about 10% of all live births (Chawanpaiboon et al., 2019) and can be associated with brain injury and other health issues (Ramachandrappa & Jain, 2009; Volpe, 2009). Advances in neonatal medical care have improved survival rates and severity of health outcomes (Grytten et al., 2017). Nevertheless, even in the absence of severe disabilities, children born preterm often suffer from developmental, cognitive, and behavioral problems (Anderson, 2014).

Children born preterm before 33 weeks of gestation are especially at increased risk for deficits in cognitive functions and academic achievement (Johnson et al., 2011), specifically in mathematics (Aarnoudse-Moens, Oosterlaan, Duivenvoorden, van Goudoever, & Weisglas-Kuperus, 2011; Akshoomoff et al., 2017; Taylor, Espy, & Anderson, 2009). Lower educational outcomes following this level of preterm birth have been reported in early school age (Pritchard et al., 2009; Taylor et al., 2018), adolescence (Litt et al., 2012; Rose et al., 2011), and adulthood (Løhaugen et al., 2010). Little is known about the developmental trajectory of emerging mathematics skills in preterm children.

In the general population, school-entry mathematics skills are a strong predictor of later academic achievement (Duncan et al., 2007). Middle-school mathematics skills have been shown to mediate the relationship between preterm birth and adult wealth (Basten et al., 2015). Here we focus on the development of mathematics skills in the critical early school-age period.

Mathematics comprises multiple skills

One major issue regarding the study of children's early mathematics development is that it is often seen as one skill, rather than the variety of different skills that constitute mathematics ability. Standardized achievement tests used with children and adults are typically designed to span a wide age range, sample a broad array of academic skills based on age expectations, and provide one overall score (e.g. Woodcock, McGrew, & Mather, 2007). In younger children, the Test for Early Mathematics Ability, Third Edition (TEMA-3, Ginsburg & Baroody, 2003) has been used in studies of typically and atypically developing children (Fuhs & McNeil, 2013; Hasler & Akshoomoff, 2019; Kull & Coley, 2015; Mazzocco, Feigenson, & Halberda, 2011; Schneider et al., 2017). While most studies used the overall scaled *Mathematics Ability Score* to assess children's performance, the TEMA-3 also provides raw scores of "informal" and "formal" mathematics abilities. Informal mathematics abilities include numbering, counting, magnitude comparisons, and using fingers or other markers to solve simple arithmetic problems. In comparison, formal math skills are abilities learned in school including the understanding and use of numerals, exact magnitude specification, and memorized facts for addition, subtraction, and multiplication. Libertus et al. (2013) found that young children's numerical approximation abilities predicted their informal but not formal mathematics abilities. While the TEMA-3 informal and formal distinction is useful, it is based on descriptive face-valid qualities. In this study, we followed the guidance from Ryoo et al. (2015) to create categories of specifically defined math skills. Two types of mathematics skills were defined (see Table 2.1): (a) *number skills*, including items that are related to the ordering based on numerical magnitudes such as counting and number comparison skills (28 items), and (b) *arithmetic skills*, including items that are related to manipulation of numbers such as calculation skills with problems that are presented in story form or via equations (36 items). While test items in these categories require distinct sets of skills, number and arithmetic skills do not develop independent from each other. During early school age, arithmetic skills have been shown to be predicted by (particularly symbolic) number skills (Lyons et al., 2014).

Distinct cognitive functions contribute to mathematics skills

Mathematics performance requires the integration of a complex set of skills. Previous work has identified working memory and inhibitory control, visual-motor integration, and phonological processing as critical components contributing to mathematics abilities (De Smedt et al., 2010; Geary & Moore, 2016; Kulp, 1999). A specific cognitive function might be more important for one type of mathematics skill than for another one. For example, Lan, Legare, Ponitz, Li, & Morrison (2011) found that working memory uniquely predicted calculation skills in preschoolers, while counting skills were predicted both by working memory and inhibition. Dividing mathematics skills into number and arithmetic skills thus provides the opportunity to study the influence of cognitive functions on specific mathematics skills, particularly those functions that are impacted by preterm birth.

Executive functions are a robust predictor of mathematics skills in full-term and preterm children. In a longitudinal study of over 1200 typically developing children, Ribner, Willoughby, & Blair (2017) found that executive function skills at age 5 strongly predicted mathematics achievement in 5th grade. Working memory might underpin mathematics skills when it is necessary to mentally retain and retrieve relevant information. Inhibitory control may contribute more to the suppression of inappropriate but mentally prevalent answers or strategies (Bull & Lee, 2014). Rose et al. (2011) suggested a *cascade of effects* from prematurity to slower processing speed, to poorer executive functions (working memory), and finally lower academic achievement, after examining 11-year-old preterm children with a birth weight of< 1750g. Executive function deficits were also reported in 3–5 year old preterm children and found to meditate the effect of gestational age on behavioral problems (Loe et al., 2014).

Visual-motor integration has not been studied extensively but is a potential mediator between preterm birth and low mathematics performance because preterm children have an increased risk of visual-motor integration deficits (Geldof et al., 2012). Deficits in visual-motor integration have been shown to be associated with lower mathematics performance in typically developing children (Sortor & Kulp, 2003). A recent study of children born extremely preterm (before 28 weeks gestation) showed involvement of visual-motor integration in mathematics performance (Taylor et al., 2018).

In addition, verbal skills contribute to mathematics performance. Language functions are involved when solving mathematics problems, for example through representation and manipulation of magnitudes in form of number words. Specifically, the extant literature shows that phonological processing makes a specific contribution to mathematics abilities. Phonological processing includes the ability to perceive, produce, discriminate, and manipulate specific sounds of a language. In a typically developing cohort, phonological difficulty at age 5 was associated with deficits in formal mathematics components at age 7 (Jordan et al., 2010). Phonological awareness is a specific part of phonological processing that describes the ability to concatenate and remove phonological segments to form words. De Smedt, Taylor, Archibald, & Ansari (2010) reported a specific and unique association between phonological awareness and single-digit arithmetic skills in typically developing children at age 10. Deficits in phonological awareness, phonological processing, and other language outcomes have been reported in preterm children (Vohr, 2014), though fewer studies have investigated the link between phonology and mathematics in preterm children.

Most studies investigating mathematics performance in full-term and preterm children examine overall performance on standardized mathematics tests, which include a variety of different skills. It is thus difficult to understand which specific mathematics skills are affected at different ages. It remains an open question whether number and arithmetic skills are differentially affected by preterm birth and if other cognitive functions, such as working memory, inhibitory control, visual-motor integration, and phonological processing are related to these mathematics skills. We chose to examine these particular cognitive functions based on recent research linking them to mathematics skills in children who were born preterm (Hasler & Akshoomoff, 2019; Tatsuoka et al., 2016; Taylor et al., 2018; van Veen et al., 2019). Furthermore, studies that investigate the effect of cognitive functions on mathematics skills often only study one of those functions (e.g., working memory) at a time. This does not allow us to understand how large the effects of these cognitive functions are in comparison to one another.

Our study first compared the status of number skills and arithmetic skills in children born preterm and full-term. Next, using mediation analysis, we determined which cognitive functions mediated the relationship between preterm birth and mathematics skills. Our study addresses limitations in prior research by including multiple cognitive functions in the same model, namely working memory, inhibitory control, visual-motor integration, and phonological processing.

Method

Participants

We recruited 51 children born preterm (24–32 weeks gestational age) and 27 children born full-term (38–41 weeks gestational age). Participant characteristics are summarized in Table 2.2. By definition, the preterm group had a significantly lower gestational age at birth and birth weight. There were no significant group differences in terms of sex, age at testing, household income, and race. Maternal education was lower in children born preterm compared to full-term.

The preterm participants were recruited primarily from the UC San Diego High-Risk Infant Follow Up Clinic. Inclusion criteria for the preterm sample were gestational age at birth of < 33 weeks and absence of severe congenital, physical, or neurological disabilities. Children were excluded if they had a history of severe brain injury (intraventricular hemorrhage of grade 3-4, cystic periventricular leukomalacia, moderate-severe ventricular dilation), genetic/chromosomal abnormalities affecting development, severe disability (e.g. bilateral blindness, cerebral palsy), or acquired neurological disorders unrelated to preterm birth. Of the 51 children born preterm, 10 were born extremely preterm (< 28 weeks of gestation); additionally, 16 children were born with very low birth weight (1000g–1500g) and 17 with extremely low birth weight (< 1000g). Six preterm participants had intraventricular hemorrhage of grade 1-2 (later resolved), none had periventricular leukomalacia, five had bronchopulmonary dysplasia, and five were small for gestational age.

The full-term participants were recruited through the Center for Human Development at UC San Diego. Inclusion criteria for the full-term sample were gestational age at birth of > 37 weeks and no history of neurological, psychiatric, or developmental disorders. Additionally, all participants were required to be native English speakers. As the data of this study is part of a larger project that includes MRI imaging, participants were excluded if they had a history of anxiety and/or metal implants that would interfere with scanning. The Institutional Review Board at UC San Diego approved the study. Legal guardians gave written informed consent, and children of age 7 years and older gave assent.

Design and procedure

We used a longitudinal design with each child receiving a comprehensive battery of cognitive and academic tests, health and demographic questionnaires and MRI imaging at three time points at approximate ages of 5, 6, and 7 years. Baseline testing was performed within six months of starting kindergarten, age at testing across the three assessments is described in Table 2.2. Partial behavioral and MRI results are described elsewhere (Hasler et al., 2020; Hasler & Akshoomoff, 2019).

Assessment of mathematics skills

We assessed mathematics skills using the Test for Early Mathematics Ability, 3rd Edition (TEMA-3; Ginsburg & Baroody, 2003). The TEMA-3 is designed for children between 3 and 8 years old and includes72 items that a subset may be given based on age and performance. Overall performance is expressed in sum raw score of correct items and the standardized Mathematics Ability Score (mean=100, SD=15). These measures are commonly used to characterize 'mathematics ability' in children. Ryoo et al. (2015) grouped the 72 test items from the TEMA-3 into seven categories: Verbal Counting, Counting Objects, Numerical Comparison, Set Construction, Calculation, Number Facts, Numeral Literacy that were validated by confirmatory factor analysis from their sample of 389 children. Their factor structure fit the longitudinal data better than the "formal" and "informal" TEMA-3 mathematics dichotomy. While the Ryoo et al. (2015) categorization scheme may be more theoretically useful, each of the seven categories contained only a small number of items and may be vulnerable to statistical instability. Furthermore, some of the items in different categories require the same type of skill. For example, items from the categories Set Construction, Calculation, and Number Facts all require the manipulation of numbers (arithmetic). Similarly, items in the Verbal Counting, Counting Objects, and Numerical Comparison clusters require ordering numbers based on the magnitudes they represent.

Based on the types of skills required to solve the problems, we clustered the TEMA-3 items by combining categories from Ryoo et al. (2015) into *number skills* and *arithmetic skills* (see Table 2.1). The category number skills comprises 28 items from the subcategories Verbal Counting, Counting Objects, and Numerical Comparison as defined by Ryoo et al. (2015). These items require the participant to order quantities by magnitude. The arithmetic skills category includes the 36 items from the subcategories Set Construction, Calculation, and Number Facts. These items require the participant to manipulate numbers to solve abstract and concrete (story-form) problems. One subcategory, Numeral Literacy, required participants to read and write numbers, a skill different from the other subcategories. These items were excluded from the present analyses.

Assessment of cognitive functions

Spatial working memory

We assessed spatial working memory via the Cambridge Neuropsychological Testing Automated Battery (*CANTAB® Cognitive Assessment Software*, 2017) Spatial Working Memory Task (SWM). This task is designed for participants from 4 to 99 years of age. It is a nonverbal, computerized task presented on a touch screen. The screen shows colored squares, the participant has to find a token that is hidden behind one of them. Once the token is found it is hidden again behind one of the squares under which it was not previously hidden. The participant has to use spatial working memory to successfully and efficiently find the hidden token and not search under the same square twice. Task difficulty increased by increasing the number of squares. Task performance is measured inversely through the number of errors made (number of squares that are searched multiple times, “between errors”). To simplify interpretation of the results, the inverse of this error measure is used for analysis, such that a more positive measure of SWM corresponds to better spatial working memory.

Inhibitory control

We assessed inhibitory control via the CANTAB Stop Signal Reaction Task (SST), designed for ages 4 to 99 years. It is a ‘go/no-go’ style nonverbal, computerized task presented on a touch screen. The participants see a circle in the center of the screen and one rectangle on either side of it. When an arrow appears on the screen, the participant’s task is to touch the rectangle to which the arrow points as fast as possible. If they hear the auditory stop signal the participant has to inhibit their response and not touch the screen. Task performance is measured through the stop signal reaction time (SSRT). To simplify interpretation of the results and normalize the distribution, the inverse logarithm of this reaction time measure is used for analysis such that a more positive measure of the SST corresponds to higher inhibitory control.

Visual-motor integration

We assessed visual-motor integration using the Beery VMI 6th Edition (VMI; Beery, 2004), designed for ages 2 to 100 years. The participant’s task is to copy geometric figures. There are specific scoring instructions for each item, resulting in 0 or 1. The test is completed if three consecutive items were failed to be copied correctly. VMI raw scores were used in the analyses as the performance scores for the other cognitive and academic tasks were not adjusted for age.

Phonological processing

We assessed phonological processing via the Comprehensive Test of Phonological Processing Second Edition (CTOPP-2; Wagner, Torgesen, Rashotte, & Pearson, 2013). The CTOPP-2 is designed for ages 4:0 through 24:11 and contains a variety of subtests assessing phonological awareness, phonological memory, rapid symbolic naming, and rapid non-symbolic naming. Here we used the Elision subtest, which has been widely used in clinical and typical populations to measure phonological awareness. The participant's task is to omit a phonological segment (syllable/phoneme) of a word that they previously heard and say the word out loud. The result is another existing word, eg., "say 'always' without 'all'" [ways] or "say 'silk' without /l/" [sick]. Phonological awareness is measured as the sum of all correctly answered items out of a maximum of 34.

Statistical analysis

Statistical Analyses were performed with IBM SPSS Statistics (v. 26). Effect sizes were assessed for group comparisons: (partial) η^2 for non-parametric tests, ANOVAs and ANCOVAs, and Cramer's V for χ^2 tests. Because mothers of preterm children reported less education on average then mothers of full-term children, we used maternal education as a covariate in our analyses.

We assessed the mediating effect of cognitive functions on mathematics skills with multiple mediation analyses. A multiple mediation model analyzes if and to what extent the effect of preterm birth on mathematics skills can be accounted for by the effect of preterm birth on cognitive functions, which in turn influence mathematics skills. Direct and mediated effects were evaluated based on their effect size.

The multiple mediation analyses assessed:

(1) the total effect model, which considers the total effect of preterm birth on the outcome variable. This does not include the mediators.

(2) the direct (unmediated) effect of preterm birth on the outcome variable, when mediators are included.

(3) the indirect (mediating) effects of preterm birth on the outcome variable through the mediators.

We used separate multiple mediation models for the three testing times (age 5, 6, and 7 years) and both mathematics skills outcome variables (number and arithmetic skills), resulting in a total of six mediation models. Given the constraints of our relatively small sample, this cross-sectional approach allowed us to remain descriptively close to our data while highlighting differences across the three ages in identical samples.

Due to the intercorrelations of group, maternal education, and cognitive functions, the effect of group can switch from being negative (lower performance in the preterm group) to positive (higher group average in the preterm group, when controlling for other variables in the model). This is because the other variables assume some of the variance that group accounted for when alone in the model.

Results

Age and group differences in mathematics skills and cognitive function

Of primary interest are number and arithmetic skills—our outcome variables. The other two mathematics skill variables—TEMA-3 overall, scaled and percentage—are included for comparison. In addition, the cognitive function variables were analyzed subsequently as potential mediating variables. Group means at the three ages, adjusted for maternal education, are shown for mathematics skills variables in Figure 2.1 and for cognitive function variables in Figure 2.2. Table 2.3 provides statistics for repeated measures, trend analyses of covariance with age as the repeated measure, term status (preterm vs. full-term) as the between-groups factor, and maternal education as the covariate.

Age and group interacted for the number and arithmetic skills: mean differences between preterm and full-term groups decreased with age for number skills but increased with age for arithmetic skills. A repeated measures ANCOVA with type of mathematics skill as additional within-subject-variable found a strong and statistically significant interaction between time, group, and type of skill ($F[2,150] = 18.10$, $p < .001$, partial $\eta^2 = .194$) —indicating that the difference between the patterns for number and arithmetic skills—decreasing pre-term–full-term differences for number skills but increasing differences for arithmetic skills—was consequential. (The threshold for what we term small or weak, medium or moderate, and large or strong η^2 is .01, .06, and .14; Cohen, 1988.).

The number skills, arithmetic skills, and TEMA-3 overall raw score increased notably with age with linear trend effect sizes ranging from .19 to .43, *p*s < .001. As expected of a scaled score, the TEMA-3 overall scaled score did not show a linear trend. The mean scores of the preterm children were lower than the means from full-term children for all mathematics skills variables with effect sizes (η^2) ranging from .076 to .145 (see Figure 2.1 and, for effect sizes, Table 2.3).

Scores for cognitive functions increased with age with linear trend effect sizes ranging from .54 to .82, *p*s < .001. The mean scores for preterm children were lower than scores for the full-term children; in particular, the largest effects were observed for VMI, less so for Elision, and SST, and least (and not significantly) for SWM (see Table 2.3 for effect sizes). Age and group did not interact.

Non-parametric analyses of number and arithmetic skills

Adjusting for maternal education, number skill scores were negatively skewed for the full-term group at age 6 and arithmetic skill scores were positively skewed for the preterm group at all ages (standardized skews > 2.58 absolute). To check whether, apart from extreme scores, number and arithmetic skill scores were reasonably distributed, we examined box-and-whisker plots (see Figure 2.3). Such plots show distributions graphically, including extreme scores (defined as scores 1.5 times the interquartile range greater than the 75th or less than the 25th percentile; Tukey, 1977). The box-and-whisker plots confirm the pattern shown in Figure 2.1 that the difference between preterm and full-term medians, which are not influenced by extreme scores, decreased with age for the number skills scores (from 16.7, to 13.4, to 3.6) but increased with age for the arithmetic skills scores (from 0.7, to 6.9, to 19.4) for ages 5, 6, and 7, respectivley. We confirmed these impressions via non-parametric Mann-Whitney U tests showing that p values increased from .008, to .014, to .047 for numeric skills but decreased from .052, to < .001, to < .001 for arithmetic skills.

Simple and mediation models predicting number and arithmetic skills

Models predicting number skills for ages 5, 6, and 7 are shown in Figure 2.4; similar models predicting arithmetic skills are shown in Figure 2.5. Displayed first are two single-predictor models, one with term status as the predictor and the other with maternal education as the predictor, thus their path coefficients are simple Pearson correlations coefficients (rs). Full-term status was coded 0 and preterm status 1, thus negative coefficients for group signal lower average outcome means for the preterm than the full-term group. The figures also show the percentage of variance not accounted for by each model (i.e., the error variance).

Two-predictor, unmediated models—group and maternal education are the predictors—are displayed next; their path coefficients are the partial standardized coefficients of multiple regression (βs). All two predictor models showed redundancy, that is the βs are somewhat smaller than the corresponding rs due to the shared and overlapping influence of the two predictors that correlated $r = .22$, $p = .058$, acting in concert. Reflecting the interaction between group, age, and type of mathematics skill noted earlier, group was a stronger predictor of number skills at earlier ages but of arithmetic skills at later ages: the path coefficients decreased with age in magnitude from –.31 to –.26 to –.17 for number skills but increased from –.16 to –.28 to –.41 for arithmetic skills.

Figures 2.4 and 2.5 display the mediation models using cognitive functions as the mediators with maternal education as a covariate for number skills and arithmetic skills, respectively. Once mediators were added to the model, the path coefficients for term status declined, becoming inconsequential (< .10 absolute) for number skills and inconsequential, barely small, or small for arithmetic skills at ages 5, 6, and 7, respectively (defining small as .1 to .3 absolute; Cohen, 1988). With age, number skills models accounted for less variance, decreasing from 55% to 44% to 39%, whereas arithmetic skills models accounted for more, from 33% to 32% to 47%, for ages 5, 6, and 7, respectively. In sum, the addition of cognitive functions variables to the models rendered the influence of term status inconsequential, indicating that these cognitive functions variables together mediated most of the influence of term status on number and arithmetic skills.

Table 2.4 provides the statistics for the mediation models. The table shows how the total effect of term status (i.e., its simple correlation with outcome) can be decomposed into the direct effect of term status (i.e., its β with cognitive function scores and maternal education in the model); the direct, mediated effects of the cognitive functions (i.e., the product of their correlation [r] with term status and their partial standardized regression coefficient [β] when term status, other cognitive function scores, and maternal education are included the model); and the direct effect of maternal education (i.e., the product of its r with term status and its β when term status and cognitive function scores are included in the model). These direct effects sum to the simple correlation between term status and outcome.

We are now able to ask which particular mediators are noteworthy. One criterion is that both their constituent r and β coefficients need to be statistically significant (Baron & Kenny, 1986). Ten of the 24 mediating effects of the cognitive functions shown Table 2.4 meet the $p <$ .05 for both r and β criterion. However, this criterion, like statistical significance, depends on sample size. A criterion based on absolute effect size might be a better choice (Wilkinson, 1999). We suggest viewing mediating effects of .04 or larger as worthy of further consideration. Three additional mediating effects have an effect size larger than .04: One mediating effect with $p < .10$ for the r, and < .05 for the β, and two mediating effects with $p < .01$ for the r but was .132, and .155 for the β. These 13 mediating effects of cognitive functions are bolded in Table 2.4.

The mediator with the largest and most consistent direct effects was Elision; its direct effects averaged .117, were larger for number skills, and decreased with age. For number skills, the absolute effect coefficients accounted for 39%, 48%, and 39% of the total effect at ages 5, 6, and 7, respectively. VMI accounted for 24% of the total effect at age 5, and 37% at age 7, while the mediating effect was marginal at age 6. The mediating effects of SWM and SST on number skills were small at all time points, though at age 6 SWM had a significant mediating effect of –.051 (16%). The effect of maternal education on number skills increased over time both in absolute and relative size. Maternal education contributed 12%, 20%, and 29% of the total effect, respectively for ages 5, 6, and 7.

In contrast to number skills, the total and direct effect of group on arithmetic skills increased over time. Strikingly, the direct effect of group on arithmetic skills at age 7 accounted for 47% of the total effect. Like number skills, phonological processing is the strongest mediator among the cognitive functions included in the model. The mediating effect of phonological processing is largest in absolute and relative size at age 5 and decreases over time (their absolute effect coefficients account for 55%, 31%, and 17% of the total effect at ages 5, 6, and 7, respectively). Following the same pattern as for number skills, VMI and SST showed mediating effects at age 5 and 7, and SWM at age 6. The effect of maternal education on arithmetic skills accounted for 10–18% of the total effect of preterm birth.

Sex effects

Sex was not included as a variable in the mediation model as the number of boys and girls did not significantly differ between the groups. Nonetheless, to explore sex effects, we reanalyzed the previous trend analyses of number and arithmetic skills including sex as a between-subjects variable. The pattern of male–female differences differed by birth status; group by sex interaction $F(1,74) = 4.72$ and 4.24, $\eta_p^2 = .060$ and $.054$, $p = .022$ and $.043$, for number and arithmetic skills, respectively. Averaging across the three ages, preterm boys scored lower than girls on number skills (63% vs. 67%) and about the same on arithmetic skills (27% vs. 28%). In contrast, full-term boys scored higher than girls on both number (76% vs. 69%) and arithmetic skills (46% vs. 42%).

We considered whether the group by age interaction described earlier might have been moderated by sex. For number skills the answer is no. The strength of the age by group interaction was moderate and statistically significant, the same as for the numeric skills analysis shown in Table 2.3; $\eta_p^2 = .068$ and $.070$, $p = .023$ and $.020$, respectively. But both the age by sex and the age by group by sex interactions were small or less in magnitude and not statistically significant; $\eta_p^2 = .016$ and ~0, $p = .27$ and $.96$, respectively.

The answer is more complex for arithmetic skills. The age by group interaction was statistically significant, the same as for the arithmetic skills analysis shown in Table 2.3—η_p^2 = .20 and .18, p = < .001 for both, respectively. For arithmetic skills, however, both the age by sex and the age by group by sex interactions were moderate and statistically significant—η_p^2 = .072 and .11, p = .019 and .004, respectively. Follow-up analyses for each sex separately showed that the group by age interaction was statistically significant for boys but not statistically significant in girls—η_p^2 = .45 and .015, p = < .001 and = .46, respectively. The mean for boys in arithmetic skills showed divergence, increasing from 16% to 27% to 39% for preterm participants and from 18% to 36% to 65% for full-term participants. Means for girls did not diverge, increasing from 17% to 25% to 40% for preterm and from 18% to 29% to 45% for full-term children.

Discussion

Preterm birth can have a significant and negative impact on mathematics achievement. Our first aim was to shed light on the impact of preterm birth on two distinct kinds of mathematics skills: number and arithmetic skills. Analyses according to this division showed that there were considerable differences in the developmental trajectories both in the development of these skills *per se*, and in the development of these skills in preterm and full-term children. Only number and arithmetic skills showed a significant interaction effect of term status and time; this was neither reflected in overall mathematics ability nor in any of the assessed cognitive functions.

The poorer performance of preterm children compared with full-term children in number skills was largest at age 5 and decreased over time. Following preterm birth, children need longer to reach the same level of proficiency in number skills compared to children who were born full-term. That is, the deficit in counting and comparing magnitudes of numbers is not persistent.

Instead preterm children are delayed in their development of such skills but eventually “catch up.” A qualitatively similar developmental trajectory with a “catch-up” in performance across time has been reported for executive functions and receptive vocabulary in children born preterm (Luu et al., 2009; Ritter et al., 2013). To our knowledge, this is the first study of preterm children showing a “catch-up” in number skills performance. Some studies suggest that number skills continue to develop into adolescence (Lyons et al., 2014). Note that the dependent variable in those studies were reaction times rather than accuracy, and the TEMA-3 does not measure reaction times. Thus, our findings for a maturing of accuracy measures at age 7 does not contradict potential continued refinement of number skills measured in reaction time. Together, these studies hint towards a maturational delay in various skills following preterm birth. The underlying reason may be maturational delay of brain structures, specifically white matter tracts vulnerable to damage in very preterm birth (Volpe, 2009). In support, MRI studies of preterm children and full-term controls found that brain development in both groups follows a similar trajectory that is delayed for children who were born preterm (Sripada et al., 2018).

In contrast, there was an increase in the performance gap in arithmetic skills with age. Lower arithmetic skills may arise from lower number skills if number skills act as a scaffold to promote learning of arithmetic skills. Perhaps children born very preterm that show a delay in the typical acquisition of number may eventually “catch up” in their arithmetic skills. This seems unlikely. Others have found poorer than expected mathematics achievement among older children and adolescents who were born preterm (Akshoomoff et al., 2017; Litt et al., 2012; Taylor et al., 2009). Similar to our findings, a meta-analysis of 17 studies found that arithmetic performance of preterm children and adolescents (6–18 years of age) was 0.71 SD below full-term controls (Twilhaar et al., 2018). This hints towards persistent lower performance in complex mathematics skills following preterm birth. A persistent effect of preterm birth on arithmetic skills may be explained by persistent deficits in cognitive functions that contribute to these skills.

Our second aim sought to identify the specific cognitive functions that mediate number and arithmetic skills as children move from preschool through first grade. We used a mediation model, testing for the potentially mediating effect of spatial working memory, inhibitory control, visual-motor integration, and phonological processing. The assessment of the variety of skills, and analysis via multiple mediation models has several advantages: indirect effects of variables can be compared in the context of others, the direct effect of group can be determined, and the parameter estimation is more accurate. Importantly, theoretical causality drives mediation models, but does not provide proof of causality. The direction of influence here was determined by using non-academic cognitive functions (spatial working memory, inhibitory control, phonological processing, visual-motor integration) as mediators of the mathematics skills. The structure of our mediation models are in line with our previous study of 5-year old children born preterm (Hasler & Akshoomoff, 2019) and studies of children with spina bifida (Barnes et al., 2014); Raghubar et al., 2015).

Phonological processing was the strongest mediator for both number skills and arithmetic skills. This is consistent with previous studies showing the effect of early phonological skills on mathematics performance. Phonological awareness in preschool and kindergarten has been reported to be predictive of several distinct mathematics skills, including numeration and calculation (LeFevre et al., 2010). Phonological awareness has also been associated with arithmetic skills in older children (De Smedt et al., 2010), and shown to mediate the relationship between other developmental disorders (spina bifida) and calculation skills (Barnes et al., 2014).

This strong association may be explained by a shared network of brain regions associated with both phonological processing and mathematics skills. The temporo-parietal cortex, specifically the arcuate fasciculus are candidate regions. For example, Van Beek, Ghesquière, Lagae, & De Smedt (2014) found a correlation between the arcuate fasciculus microstructure and children's addition/multiplication skills. These effects disappear when covarying for phonological processing, pointing towards an involvement of phonological processing when solving mathematics problems.

In line with previous research, we found that visual-motor integration measured by the Beery VMI, was a strong mediator for both types of mathematics skills at age 5 and age 7. Performance on the VMI has been associated with mathematics skills in children at age 4 (Verdine et al., 2014), and 5-18 years (Carlson et al., 2013). This link has rarely been investigated in children born preterm. Perez-Roche et al. (2016) found an effect of visual abilities on school performance in small for gestational age children (though school performance was assessed with a parent questionnaire). Others have found a link between low motor and visuospatial function and low academic achievement in extremely preterm children (Marlow et al., 2007).

Inhibitory control had a mediating effect on arithmetic skills at age 7. In line with these findings, inhibitory control has been reported to be associated with procedural arithmetic skills in children and conceptual knowledge in adults (Gilmore et al., 2015). Inhibitory control has also been shown to be predictive of early mathematics skills in 3-5 year old children (Blair & Razza, 2007) and of arithmetic skills in fourth graders (Passolunghi & Siegel, 2001). However, these studies investigated the role of inhibition on mathematics in the absence of other cognitive functions, which is likely to account for different results.

The participants in the full-term group had higher maternal education than the preterm group. This may be due to them being a convenience sample. However, this might also be a closer representation of the true distribution of maternal education in the preterm and full-term population (Behrman & Butler, 2007; Thompson et al., 2006). Higher maternal education has been linked to better mathematics and reading performance, fewer behavioral problems, and less grade repetition (Carneiro et al., 2013; ElHassan et al., 2018). We included maternal education in the mediation model and, as expected, higher maternal education showed a significant positive effect on both number and arithmetic skills.

One might expect that the influence of social variables, such as maternal education, on mathematics would increase over time, and conversely that the influence of biological variables associated with prematurity would decrease. However, in a study of extremely preterm children 8 and 18 years of age, Doyle et al. (2015) found that the adverse effect of preterm birth persists over time. In line with their results, we found that the effect of group on arithmetic skills increased over time. Interestingly, not only the total effect of preterm birth, but also the direct effect increases from age 5 years to 7 years. In fact, at age 7 years only about half of the total effect of preterm birth on arithmetic skills was mediated by other cognitive functions. In contrast, the direct effect of preterm birth on number skills was statistically non-significant at all three time points, meaning the total effect of preterm birth was fully mediated by cognitive functions (mainly phonological processing and visual-motor integration).

In addition, at age 7, we found an interaction effect of sex and group, with males having significantly higher arithmetic skills scores than females in the full-term group only. There is a vast body of literature on gender differences and learning and education. Studies have shown that teachers' implicit gender bias affects achievement in children, and that children themselves develop gender stereotypes of males being "smarter" and "better in math" already in elementary school (Bian et al., 2017; Cvencek et al., 2011; Lavy & Sand, 2015). One possible explanation as to why we did not observe this effect in the preterm group might be that the differences in cognitive processing related to preterm birth do not effectively influence preterm males; that is, societal and cultural influences do not impact preterm children in the same way as full-term children. On the other hand, it might be that these influences are delayed in preterm children and may become evident later in their educational development.

A significant takeaway message from this study is that our healthy preterm children showed reliable adverse effects of preterm birth. Although severity of neonatal brain pathology is linked to cognitive outcomes in preterm children (Murray et al., 2014), preterm children on the healthy end of the continuum still show significant cognitive disparities that negatively impact their academic performance. The lack of severe disabilities is not an indication of typical developmental outcomes and any child born preterm requires assessment before formal education begins, with continued monitoring.

Conclusion

Inclusion of a broad variety of cognitive functions distinguishes this study and provides an important contribution to the literature. Previous work on the effect of cognitive functions on mathematics skills have primarily focused on functions within a single cognitive domain. Cognitive functions and academic skills in children develop dynamically between ages 5 and 7 and change in complexity. Our study gives valuable insight into how these skills are impacted by preterm birth and the contribution of cognitive functions on mathematics skills in both full-term and preterm birth children. Neuropsychological assessment of preterm children at 5 years of age has been shown to be predictive of cognitive functions and need for educational support at age

11 (Lind et al., 2019). Hence, the cognitive functions investigated here, particularly phonological processing, can be neuropsychological markers for early evaluation of children with increased risk for difficulties in mathematics.

Acknowledgments

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Chapter 2, in full, is a reprint of the material as it appears in *Child Neuropsychology*, 2020, Adrian, Julia Anna; Bakeman, Roger; Akshoomoff, Natacha; Haist, Frank, Routledge Taylor & Francis Group. The dissertation author was the primary investigator and author of this paper.

Table 2.1: Definition of number and arithmetic skills

	Category†	# items	Type of task
Number Skills	Verbal Counting	14	Counting until a certain number; tell the successor number
	Counting Objects	7	Counting objects
	Numerical Comparison	7	Which number is more; which number is closer to a third number
Arithmetic Skills	Set Construction	9	Division problems presented in story/money form
	Calculation	18	Calculation problems presented in story form or abstract
	Number Facts	9	Single digits addition (verbal, no story form, with time limit)
Not included	Numeral Literacy	8	Reading & writing numerals

Note. Number skills are measured by TEMA-3 test items that require ordering of numbers by magnitude. Arithmetic skills are measured through TEMA-3 test items that require manipulation of numbers.

†Category as defined by Ryoo et al. (2015)

Table 2.2: Participant characteristics

	Preterm n = 51	Full-term n = 27	Effect size (Test statistic, p-value)
GA at birth in weeks mean (SD, min-max)	29.4 (2.00, 25-32)	39.7 (0.77, 38-41)	η^2=.894 (F=643, *p*<.001)
Birth weight in g mean (SD, min-max)	1327 (439, 680-2410)	3410 (561, 2353-4422)	η^2=.806 (F=316, *p*<.001)
Sex (female)	47%	48%	V=.010 (χ^2=.008, *p*=.927)
Age at testing: mean (SD)			
Time 1 (Age 5)	5.3 (0.3)	5.4 (0.3)	η^2=.018 (F=1.37, *p*=.245)
Time 2 (Age 6)	6.4 (0.4)	6.4 (0.3)	η^2=.006 (F=.421, *p*=.518)
Time 3 (Age 7)	7.3 (0.4)	7.4 (0.3)	η^2=.005 (F=.420, *p*=.519)
Maternal education absolute (relative frequency)			
1) high school degree	7 - 14%	3 - 11%	η^2=.048
2) 1–3 year college	18 - 35%	5 - 19%	(U=514, *p*=.055)
3) college degree	21 - 41%	10 - 37%	
4) graduate degree	5 - 10%	9 - 33%	
Household income: absolute (relative frequency)			
1) below $50,000	8 - 16%	1 - 3%	η^2=.002
2) $50,000 – <$100,000	16 - 31%	13 - 45%	(U=621, *p*=.736)
3) $100,000 – <$200,000	18 - 35%	13 - 45%	
4) $200,000 and above	8 - 16%	1 - 3%	
Missing information	1 - 2%	1 - 3%	
Race absolute (relative frequency)			
African American	1 - 2%	0 - 0%	V=.281
Asian	2 - 4%	4 - 15%	(χ^2=6.15, *p*=.188)
Caucasian	40 - 78%	16 - 59%	
Mixed/other	7 - 14%	7 - 26%	
Missing information	1 - 2%	0 - 0%	
Ethnicity (Hispanic/Latinx)	19 - 37%	8 - 30%	V=.28 (χ^2=.454, *p*=.501)

Note. Group comparisons were performed via ANOVA F[1,77], effect size: partial η2 for GA at birth, birth weight, and age at testing; via Mann-Whitney U test, effect size: η2 for maternal education, and household income; and via Chi-square test, effect size: Cramer's V for sex, race, and ethnicity. GA: gestational age; g: grams.

Table 2.3: Analysis of covariance results for mathematics and cognitive function scores

Variable	Group (PT/FT)		Age		Age × Group	
	η^2	*p*	η^2	*p*	η^2	*p*
Mathematics scores						
TEMA-3 overall (scaled)	.076	.015	.031	.39	.042	.074
TEMA-3 overall (%)	.113	.003	.429	<.001	.005	.543
Number skills (%)	.104	.004	.425	<.001	.070	.020
Arithmetic skills (%)	.145	.001	.194	<.001	.180	<.001
Cognitive function scores						
SWM (inverse)	.030	.135	.172	<.001	.004	.609
SST (inverse log)	.096	.006	.126	.002	<.001	.940
VMI	.229	<.001	.214	<.001	.001	.821
Elision	.139	.001	.378	<.001	.001	.886

Note. Group, $n = 78$ (51 preterm, 27 full-term). Results are for repeated measures ANCOVA with age (5, 6, and 7 years) as the repeated measure, group as the between-groups factor (PT vs. FT), and maternal education as the covariate. PT: preterm, FT: full-term, TEMA-3: Test for Early Mathematics Ability, 3rd edition, SWM: Spatial Working Memory; SST: Stop Signal Task; VMI: Visual-motor Integration.

Table 2.4: Mediation analysis results for cognitive function scores

	Age 5			Age 6			Age 7		
	r with PT/FT	std. β for skill	effect coefficient	r with PT/FT	std. β for skill	effect coefficient	r with PT/FT	std. β for skill	effect coefficient
Num									
Group			-.061 (16%)			-.048 (15%)			.032 (-13%)
SWM	-.08	.03	-.002 (.5%)	**-.23***	**.22***	**-.051 (16%)**	-.09	.21*	-.019 (7.5%)
SST	-.22†	.14	-.031 (8.2%)	-.26*	.07	-.018 (5.5%)	-.22†	.02	-.004 (1.6%)
VMI	**-.43****	**.21***	**-.090 (24%)**	-.29*	-.02	.006 (-1.8%)	**-.40****	**.23***	**-.092 (37%)**
Elision	**-.37****	**.40****	**.148 (39%)**	**-.34****	**.46****	**-.156 (48%)**	**-.35****	**.28***	**-.098 (39%)**
M.Ed.	**-.22†**	**.21***	**.046 (12%)**	**-.22†**	**.29****	**-.064 (20%)**	**-.22†**	**.33****	**-.073 (29%)**
Total			-.378			.327			.252
Ari									
Group			.050 (-24%)			-.119 (35%)			-.219 (47%)
SWM	-.08	.10	-.008 (3.8%)	**-.23***	**.24***	**-.055 (16%)**	-.09	.16	-.014 (3.0%)
SST	-.22†	.11	-.024 (11%)	-.26*	.05	-.013 (3.8%)	**-.22†**	**.22***	**-.048 (10%)**
VMI	**-.43****	**.18**	**-.077 (36%)**	-.29*	-.04	.012 (-3.6%)	**-.40****	**.14**	**-.056 (12%)**
Elision	**-.37****	**.31***	**-.115 (55%)**	**-.34****	**.31****	**-.105 (31%)**	**-.35****	**.23***	**-.081 (17%)**
M.Ed.	-.22†	.16	-.035 (17%)	**-.22†**	**.27***	**-.059 (18%)**	**-.22†**	**.21***	**-.046 (10%)**
Total			-.211			-.337			-.466

Note. Group, n = 78 (51 preterm, 27 full-term). Mediating effects of .04 or greater are bolded. M.Ed: maternal education

† p < .10, * p <.05, ** p < .01

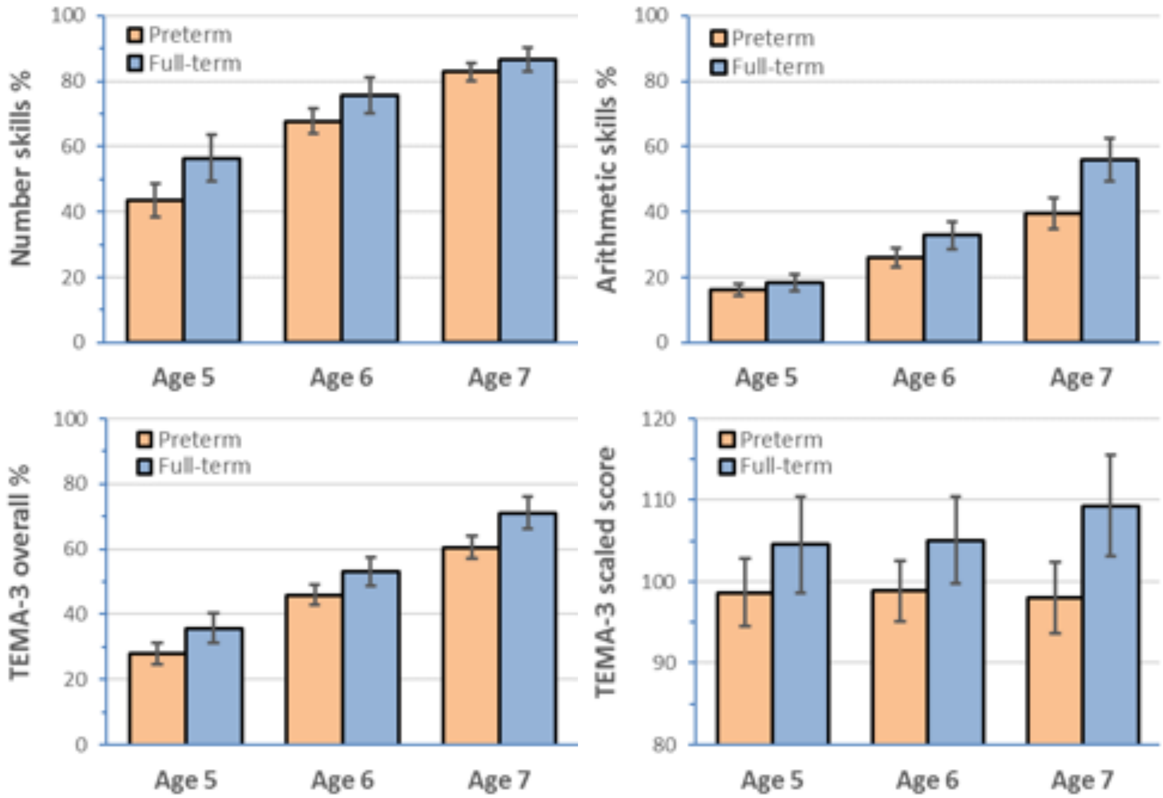

Figure 2.1: Development of mathematics skills from age 5 to age 7 for preterm and full-term groups

TEMA-3: Test for Early Mathematics Ability, 3rd edition. Error bars are 95% confidence intervals.

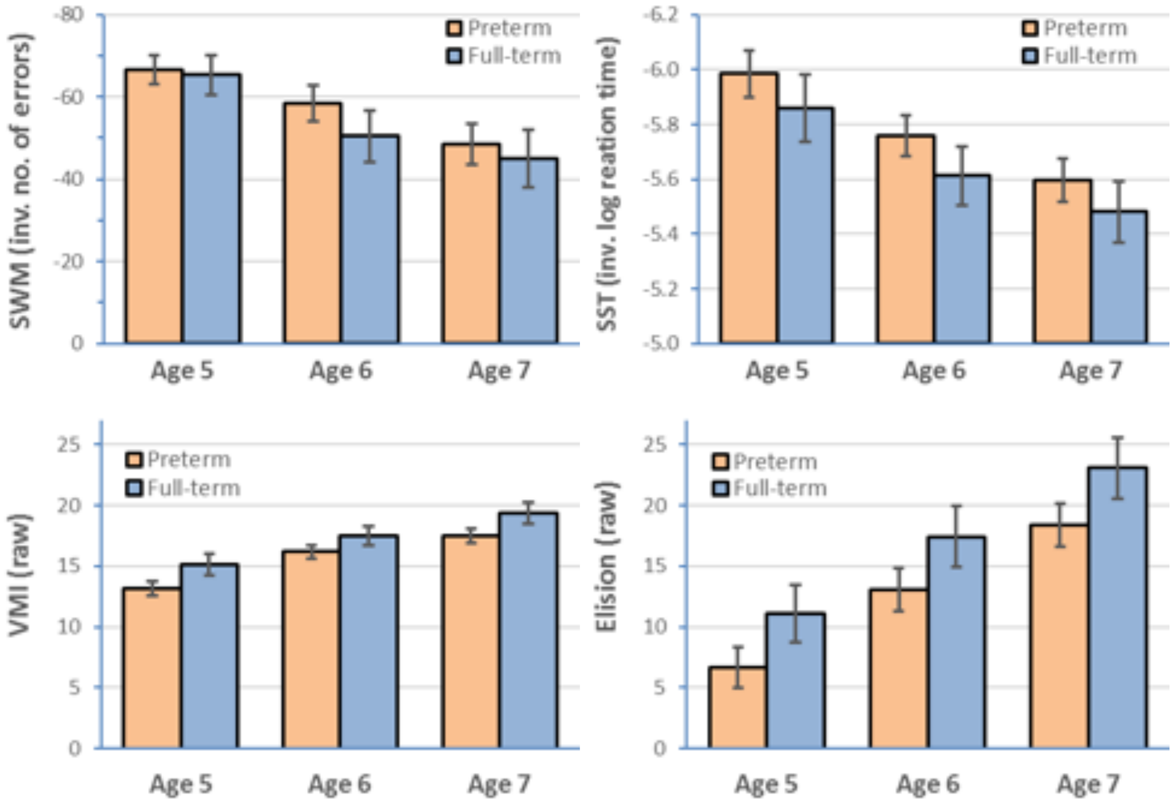

Figure 2.2: Development of cognitive functions from age 5 to 7 for preterm and full-term groups

SWM: spatial working memory, SST: stop signal task/test of inhibitory control, VMI: visual-motor integration, Elision: test of phonological processing. Error bars are 95% confidence intervals.

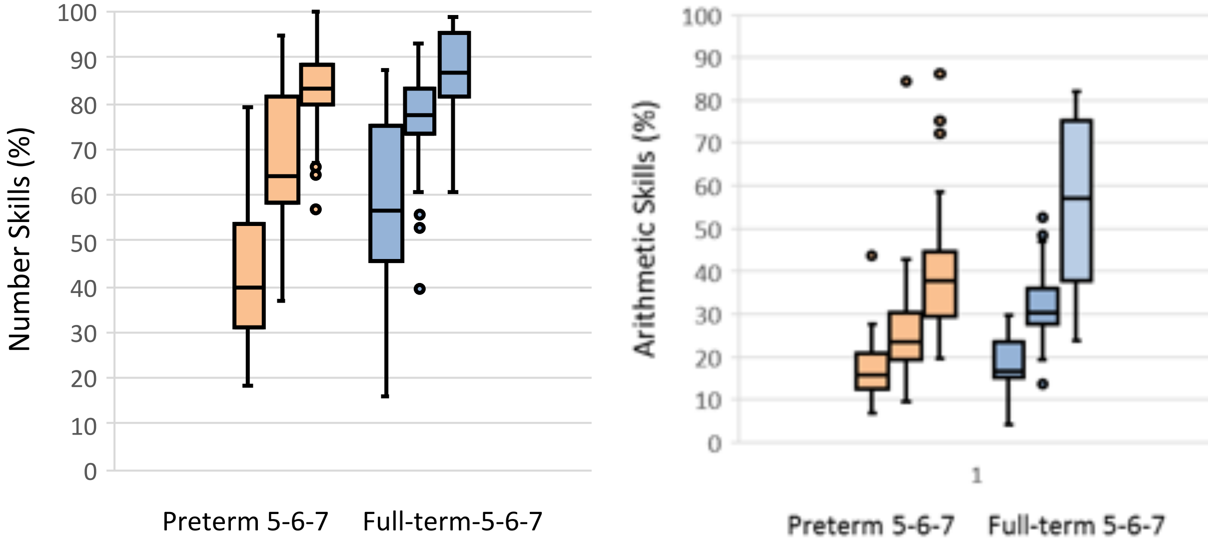

Figure 2.3: Box-and-whisker plots for preterm and full-term groups from age 5 to 7

The box includes scores from the 25th to the 75th percentile. The whiskers indicate the lowest and highest scores that are not extreme. Extreme scores, defined as any 1.5 times the interquartile range below the 25th or above the 75th percentile, are indicated with circles.

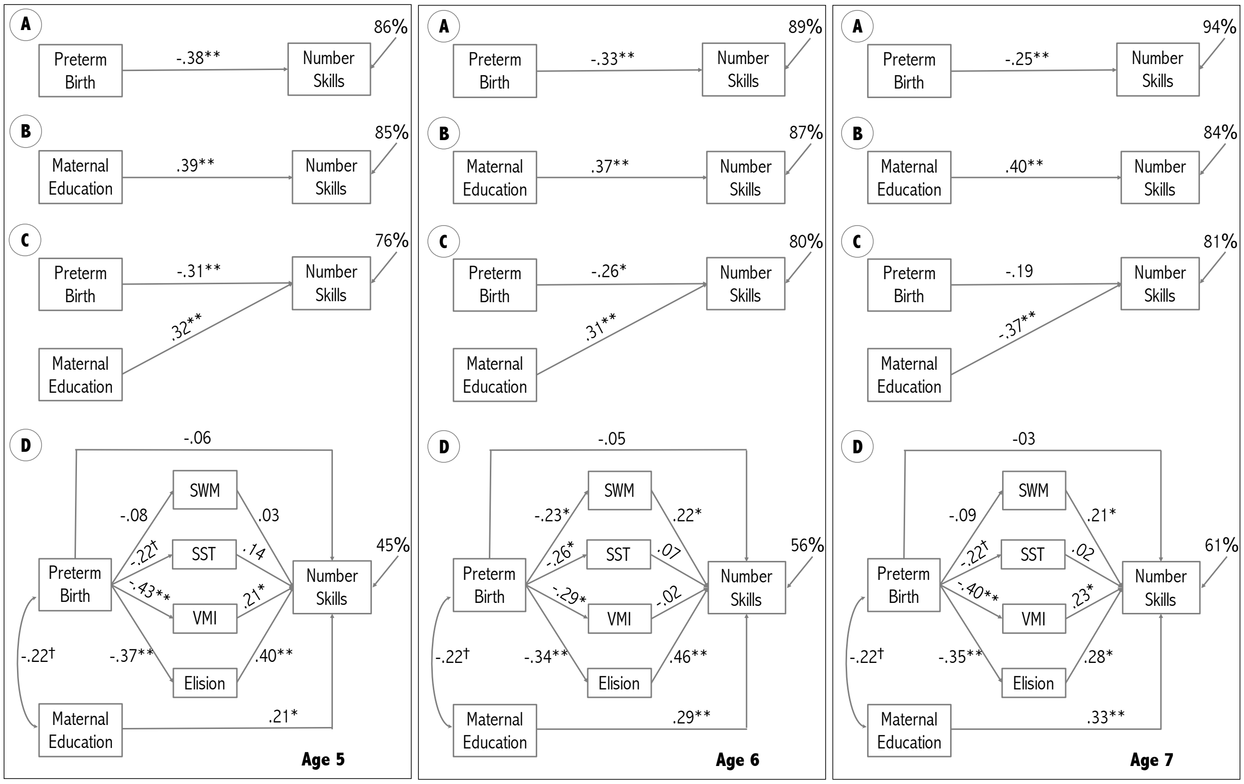

Figure 2.4: Path diagrams showing the link between group and maternal education, and their effect on number skills over time

A: Effect of preterm birth, B: Effect of maternal education, C: Joint effect of preterm birth and maternal education, D: Mediation models showing the mediating effect of SWM (spatial working memory), SST (stop signal task/inhibitory control), and VMI (visual-motor integration), and Elision (phonological processing) between group and mathematics skills. Coefficients on lines with a one directional arrow represent standardized betas, coefficients on lines with bi-directional arrows are the simple correlation coefficients (*r*). †† $p < .10$, * $p < .05$, ** $p < .01$

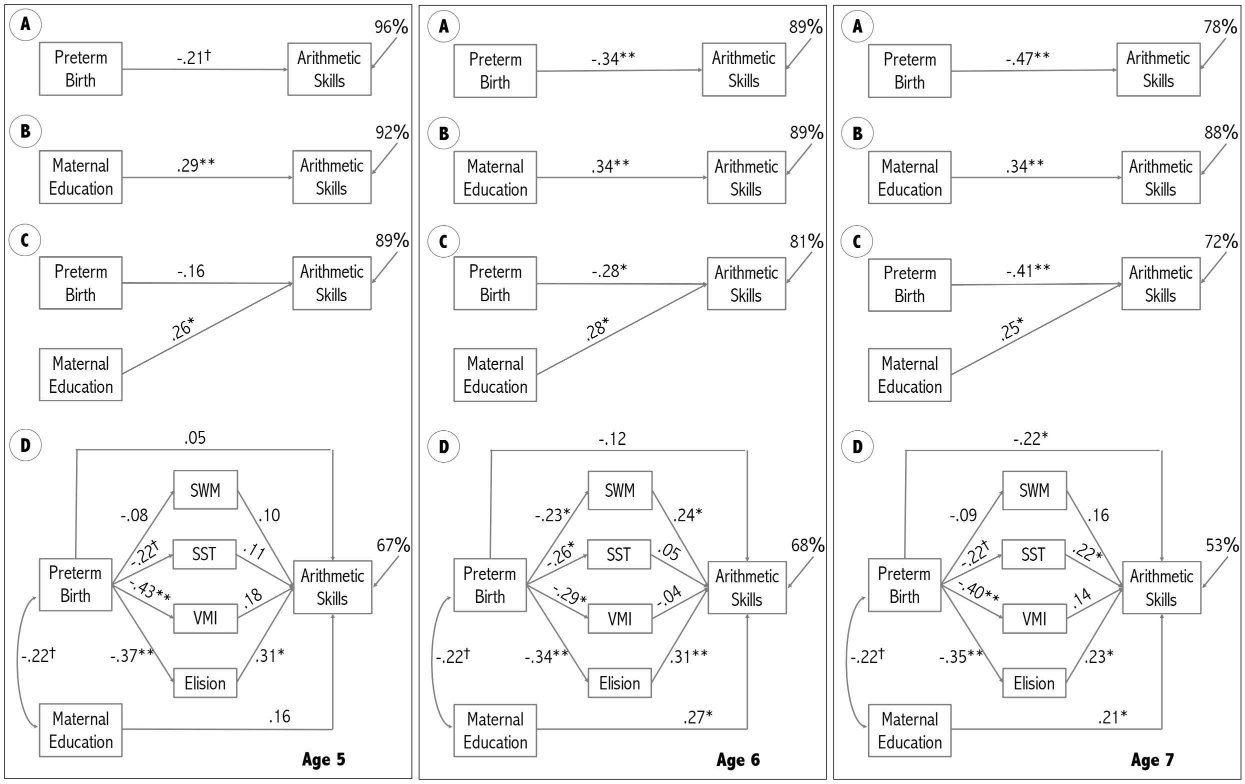

Figure 2.5: Path diagrams showing the link between group and maternal education, and their effect on arithmetic skills over time

A: Effect of preterm birth, B: Effect of maternal education, C: Joint effect of preterm birth and maternal education, D: Mediation models showing the mediating effect of SWM (spatial working memory), SST (stop signal task/inhibitory control), and VMI (visual-motor integration), and Elision (phonological processing) between group and mathematics skills. Coefficients on lines with a one directional arrow represent standardized betas, coefficients on lines with bi-directional arrows are the simple correlation coefficients (*r*). † $p < .10$, * $p < .05$, ** $p < .01$

CHAPTER 3:
LONGITUDINAL STRUCTURAL AND DIFFUSION WEIGHTED NEUROIMAGING OF YOUNG CHILDREN BORN PRETERM

The content within this section, titled "Chapter 3: Longitudinal structural and diffusion weighted neuroimaging of young children born preterm" reflects material from a paper that has been submitted and is under review for publication in the journal *Pediatric Neurology*. The full citation is as follows:

Adrian, J. A., Sawyer, C., Bakeman, R., Haist, F., & Akshoomoff, N. (2022). Longitudinal structural and diffusion weighted neuroimaging of young children born preterm. Under review at *Pediatric Neurology*.

Abstract

Background: Children born preterm are at risk for diffuse injury to subcortical gray and white matter.

Aim: To examine the development of subcortical gray matter and white matter volumes, and diffusivity measures of white matter tracts following preterm birth.

Study Design: Longitudinal cohort study.

Subjects: Forty-seven children born preterm (24–32 weeks gestational age) and 28 children born full-term. None of the children born preterm had significant neonatal brain injury. Children received structural and diffusion weighted MRI scans at 5, 6, and 7 years of age.

Outcome Measures: Volumes of amygdala, hippocampus, caudate nucleus, putamen, thalamus, brain stem, cerebellar white matter, intracranial space, and ventricles, and volumes, FA, and MD of anterior thalamic radiation, cingulum, cortico-spinal tract, corpus callosum, inferior frontal occipital fasciculus, inferior longitudinal fasciculus, temporal and parietal superior longitudinal fasciculus, and uncinate fasciculus.

Results: Children born preterm had smaller volumes of thalamus, brain stem, cerebellar white matter, cingulum, corticospinal tract, inferior frontal occipital fasciculus, uncinate fasciculus, and temporal superior longitudinal fasciculus, while their ventricles were larger 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 term status by age interaction suggests a delayed developmental trajectory.

Introduction

Preterm birth continues to be a prevalent health issue. About 10% of the population worldwide are born before 37 weeks of gestation with about 2% born before 33 weeks of gestation (Chawanpaiboon et al., 2019). 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 (Volpe, 2009). 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 (Volpe, 2009).

Early childhood is a time of rapid brain development. The white matter tracts are maturing and myelinating, the cortical surface area expands, and cortical thickness decreases (Brown & Jernigan, 2012). Little is known about the impact of preterm birth on brain development in early childhood when neuropsychological development is also rapid. Studies show that children who were born preterm have more difficulties with executive functioning, phonological processing, visual processing, motor functions, and academic achievement than children born full-term (Adrian et al., 2020; Akshoomoff et al., 2017; Hasler & Akshoomoff, 2019; Johnson et al., 2011; Sawyer et al., 2021).

Subcortical structures are vulnerable to early extrauterine exposure. Several studies have reported reduced subcortical volumes, including the amygdala, hippocampus, basal ganglia, and thalamus in children, adolescents, and young adults born preterm (Bjuland et al., 2014; Chau et al., 2019; Lax et al., 2013; Loh et al., 2020; Martinussen et al., 2009; Meng et al., 2016; Peterson, 2000). Brain stem volumes have been shown to be smaller following preterm birth in children and adolescents (Sølsnes et al., 2016; Taylor et al., 2011). In addition, preterm birth has been associated with reductions in white matter volumes, particularly in the cerebellar white matter, and corpus callosum (Sølsnes et al., 2016; Sripada et al., 2018; Taylor et al., 2011).

Diffusion tensor 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. MD declines with age during development while FA increases (Jernigan et al., 2011). Studies of preterm children, adolescents, and young adults have reported altered diffusion on later developing projections and associated pathways (de Kieviet et al., 2012; Ment et al., 2009; Pannek et al., 2014; Travis et al., 2015). Long association fibers, including the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior frontal occipital 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 (Ball et al., 2013; Thompson et al., 2011; Young et al., 2019).

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 neonatal complications in the early 2010's. The aims of this study were (a) to examine the brain volume of subcortical gray matter structures and white matter fiber tracts and (b) to examine diffusivity measures of white matter tracts. The children born preterm had lower performance in several neuropsychological tests and altered cortical morphometry (Adrian et al., 2020; Hasler et al., 2020; Hasler & Akshoomoff, 2019; Sawyer et al., 2021). We therefore predicted that volumes of subcortical gray matter and white matter tracts would be smaller following preterm birth and white matter integrity would be affected as demonstrated by lower FA and higher MD.

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 3.1 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, 25) 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 3.1, $F[1,73] = 4.568$, $p = .036$). Data is missing from one full-term participant.

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 3T GE Discovery MR750 scanner (GE Healthcare) with an eight-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 (Jernigan et al., 2016). The scanning protocol included a three-plane localizer, a 3D T1-weighted inversion recovery spoiled gradient echo using prospective motion correction (PROMO, (White et al., 2010)) (echo time = 3.5 ms, repetition time = 8.1 ms, inversion time = 640 ms, flip angle = 8°, receiver bandwidth = ±31.25 kHz, FOV = 24 cm, frequency = 256, phase = 192, slice thickness = 1.2 mm), 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 diffusion tensor imaging scan (30-

directions b-value = 1,000, TE = 83 ms, TR = 13,600 ms, frequency = 96, phase = 96, slice thickness = 2.5 mm).

Image analyses were performed in FreeSurfer version 5.3.0 (Fischl et al., 2002, 2004), using the automated segmentation and labeling procedure for subcortical volumes, and automated, probabilistic, atlas-based analysis of white matter tracts (Hagler et al., 2009). 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, 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 frontal occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), temporal and parietal superior longitudinal fasciculus (tSLF, pSLF) and uncinate fasciculus (UF). Figure 3.1 visualizes these white matter tracts.

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, 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 (Buckner et al., 2004; Fischl et al., 2002) 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) (Bakeman, 2005; Olejnik & Algina, 2003). We interpreted effect sizes based on Cohen's thresholds for small, medium, and large effects for eta squared statistics of .01, .06, and .14 (Cohen, 1988).

Results

Volumes of grey and white matter, and ventricles

Figure 3.2 visualizes the unadjusted volumes of subcortical grey matter and ventricles of the preterm and full-term groups. Table 3.2 shows the effects of age, term status, and their interaction on these volumes 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 summated volume of all ventricles was significantly larger in children born preterm compared to full-term. Term status did not have an effect on ICV itself. Several tracts were significantly smaller in children born preterm. We found a moderate to strong effect of term status on volumes of cerebellar WM, CGM, CST, IFOF and tSLF.

All measures apart from the 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 subcortical 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 3.3 shows the size of the effect of term status on volumes of thalamus, brain stem, cerebellar WM, CGM, CST, IFOF, tSLF, UF, 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 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, IFOF, and UF is largest at age 6.

Diffusivity measures of white matter fiber tracts

Figure 3.4 shows the unadjusted volumes of FA and MD in the preterm and full-term groups. Means of FA and MD were generally similar for children in both groups. Table 3.3 shows the effect of term status, age, and their interaction on whole tract FA and MD. 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, except for MD of ILF ($p = .023$, $\eta_p^2 = .07$). None of the tracts showed an age by sex effect on FA or MD (all $p > .05$, $\eta_p^2 \leq .002$).

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, inferior frontal occipital fasciculus, temporal superior longitudinal fasciculus, and uncinate fasciculus were smaller, while ventricles were larger following preterm birth. This was 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.

Volumes of grey and white matter, and ventricles

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 (Sripada et al., 2018). Moreover, they also reported the lack of an age by term interaction effect and argued that it reflects similar but delayed developmental trajectories in children born preterm and full-term. This finding is consistent across other study populations of different age and geographical location (Bjuland et al., 2014; Sølsnes et al., 2016). 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.

Unlike other studies, we did not find reduced volumes of hippocampus and amygdala in children born preterm compared to full-term. These discrepant results may reflect differences in patient population demographics, severity of prenatal or perinatal brain injury, clinical status, and MRI post-processing methods. The limbic system may be less affected by subtle perinatal injury as a result of the early development of limbic white matter tracts (Huang et al., 2006). 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 connections 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 (Ball et al., 2013; Huang et al., 2006; Volpe et al., 2011). 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 (Loh et al., 2017). We found reduced cerebellar and brain stem volume, as reported in infants born preterm (Wu et al., 2020). These structures are also included in Volpe's characterization of encephalopathy of prematurity (Volpe, 2009).

We previously showed that at age 5, the children born preterm in our sample had regional differences in cortical thickness, surface area, and sulcal depth (Hasler et al., 2020). 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. Together our studies indicate that these effects of preterm birth persist into childhood and continue to be present in children that were born in the early 2010's.

We found that the volume of several white matter tracts were altered in the children born preterm. Volume reflects the gross morphology of the white matter tract and has not been 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 (Caldinelli et al., 2017). 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 (Sølsnes et al., 2016; Sripada et al., 2018).

The pronounced increase in the size of the ventricles is consistent with other studies (Meng et al., 2016). Instead of a decreased whole brain volume (as approximated here by ICV), the cellular tissue is decreased, the ventricles are increased, and the ICV is about the same in both groups.

Diffusivity measures of white matter fiber tracts

We did not find a significant effect of preterm birth on FA and MD of key white matter tracts. 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 sheath reduces the extracellular space and thus reduces diffusivity (Dubois et al., 2014). 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.

There are some inconsistencies in DTI results across studies. Altered white matter microstructure, as in PVL, was once thought to be one of the main consequences of preterm birth (Volpe, 2009). Studies examining a Norwegian cohort of individuals born preterm between 1986-88 showed widespread alterations in white matter microstructure at in adolescence and young adulthood (Eikenes et al., 2011; Skranes et al., 2007). In contrast, a study of a more recent Norwegian cohort of individuals born in the 2000's showed that white matter microstructure and connectivity were only marginally affected by preterm birth (Sølsnes et al., 2016). Studies of American cohorts of children and adolescents born preterm during the 1990's to 2001 also found that the effects on white matter microstructure are less pronounced, i.e. only detectable in a small segment of the tract, or not present at all (Feldman et al., 2012; Travis et al., 2015).

The discrepancies in these findings may also 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 and year of birth (Grytten et al., 2017; Torchin et al., 2020). For example, the risk for moderate/severe non-cystic white matter injury has been shown to decrease in a study including children born between 1998 and 2011 who were evaluated at term-equivalent age (Gano et al., 2015). In addition, our sample did not include children with severe neurodevelopmental impairment or severe neonatal complications. Feldman and colleagues 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 (Feldman et al., 2012).

Strengths and limitations

Strengths of our study are the longitudinal, multi-modal design with a full data set of children who had 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.

This study was designed to specifically examine children born preterm without significant neonatal complications. This was assessed via a routine neonatal cranial ultrasound. However, a neonatal MRI would have been more conclusive and would have allowed us to more directly relate our current finding from childhood to the status of the brain at term-equivalent age. In addition, maternal education and household income was relatively high in our convenience sample. Our sample was somewhat biased towards children who could lie still in an MRI at five years of age. Therefore, with our fairly small data set of 47 children born preterm and 28 children born full-term we may not be able to detect other, more subtle effects. Big data sets promise to produce more reliable results. Nevertheless, our findings 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, inferior frontal occipital fasciculus, 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.

Acknowledgement

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Chapter 3, in full, is a reprint of the material as it has been submitted and is under review for publication in *Pediatric Neurology*, 2022, Adrian, Julia Anna; Sawyer, Carolyn; Bakeman, Roger; Haist, Frank; Akshoomoff, Natacha, Elsevier. The dissertation author was the primary researcher and author of this paper.

Table 3.1: Participant characteristics

	Preterm n = 47	Full-term n = 28	Effect size	p value
GA at birth in weeks mean (SD, min-max)	29.7 (2.2, 24–32.9)	39.8 (0.7, 38–41)	η^2=.883	<.001
Birth weight in g mean (SD, min-max)	1307 (442, 625–2450)	3435 (543, 2353–4423)	η^2=.824	<.001
Age at imaging: mean (SD)				
Time 1 (Age 5)	5.3 (.4)	5.3 (.3)	η^2=.001	.809
Time 2 (Age 6)	6.4 (.4)	6.4 (.3)	η^2=.002	.733
Time 3 (Age 7)	7.4 (.4)	7.4 (.3)	η^2<.001	.923
Sex (female)	53%	46%	V=.065	.571
Maternal education absolute (relative frequency)				
1) high school degree	5 - 11%	3 - 11%	η^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%	η^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)	η^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 3.2: Effect of term status, age, and age by term interaction on gray matter volumes

	Term		Age[a]		Age by term	
Variable	η_p^2	*p*	η_G^2	*p*	η_G^2	*p*
Gray matter volumes						
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
White matter volumes						
Cerebellar WM	.16	<.001	.11	<.001	.001	.20
ATR	.032	.13	.119	<.001	~.0	.35
CC	.047	.067	.079	<.001	~.0	.89
CGM	.16	<.001	.055	<.001	.001	.093
CST	.098	.007	.25	<.001	~.0	.70
IFOF	.091	.010	.092	<.001	~.0	.18
ILF	.042	.082	.086	<.001	.003	.060
tSLF	.070	.023	.053	<.001	~.0	.72
pSLF	.021	.23	.058	<.001	~.0	.97
UF	.056	.043	.088	<.001	.003	.044
Volumes of ventricles and ICV						
Ventricles	.101	.006	~.0	.16	~.0	.74
ICV	.004	.58	.028	<.001	~.0	.85

Note. N = 75. Statistics are from ANCOVAs with term status (preterm vs. term) as a between-subjects effect, age (5, 6, and 7 years) as a within-subjects effect, and intracranial volume (ICV) and sex as a covariate (ICV only covaried for sex). WM: white matter, ATR: anterior thalamic radiation, CGM: Cingulum, CST: Cortico-spinal tract, CC: Corpus callosum, IFOF: inferior frontal occipital fasciculus, ILF: inferior longitudinal fasciculus, tSLF: temporal superior longitudinal fasciculus, pSLF: posterior longitudinal fasciculus, UF: uncinate fasciculus. [a] Linear age effect, *df* = 1

Table 3.3: Effect of term status, age, and age by term interaction on diffusivity measures of white matter tracts

	Term		Age[a]		Age by term	
Variable	η_p^2	*p*	η_G^2	*p*	η_G^2	*p*
Fractional anisotropy						
ATR	.030	.14	.059	<.001	~.0	.71
CC	.004	.59	.017	<.001	~.0	.79
CGM	.048	.060	.010	<.001	~.0	.58
CST	.009	.41	.10	<.001	~.0	.73
IFOF	.011	.37	.058	<.001	~.0	.94
ILF	.028	.15	.081	<.001	~.0	.55
tSLF	.006	.52	.047	<.001	~.0	.24
pSLF	.013	.34	.048	<.001	~.0	.36
UF	.034	.11	.055	<.001	.001	.23
Mean diffusivity						
ATR	.035	.11	.086	<.001	~.0	.49
CC	.044	.072	.035	<.001	~.0	.83
CGM	.002	.68	.096	<.001	~.0	.95
CST	.052	.050	.053	<.001	.001	.14
IFOF	.052	.052	.036	<.001	~.0	.67
ILF	.003	.66	.052	<.001	~.0	.59
tSLF	.027	.16	.057	<.001	.002	.055
pSLF	.021	.22	.059	<.001	~.0	.27
UF	.011	.37	.093	<.001	~.0	.36

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, IFOF: inferior frontal occipital fasciculus, ILF: inferior longitudinal fasciculus, tSLF: temporal superior longitudinal fasciculus, pSLF: posterior longitudinal fasciculus, UF: uncinate fasciculus. [a] Linear age effect, $df = 1$

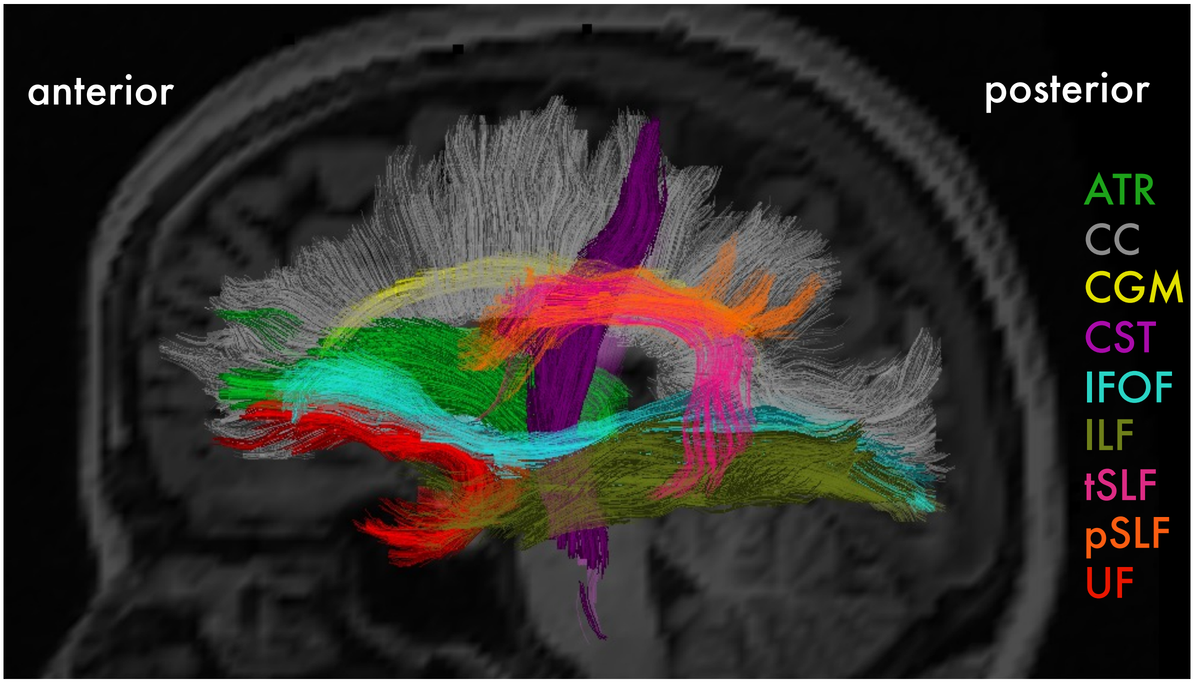

Figure 3.1: Visualization of the examined white matter tracts

Anterior thalamic radiation (ATR) in green, cingulum (CGM) in yellow, cortico-spinal tract (CST) in purple, corpus callosum (CC) in gray, inferior frontal occipital fasciculus (IFOF) in turquois, inferior longitudinal fasciculus (ILF) in olive, temporal superior longitudinal fasciculus (tSLF) in fuchsia, posterior longitudinal fasciculus (pSLF) in orange, uncinate fasciculus (UF) in red.

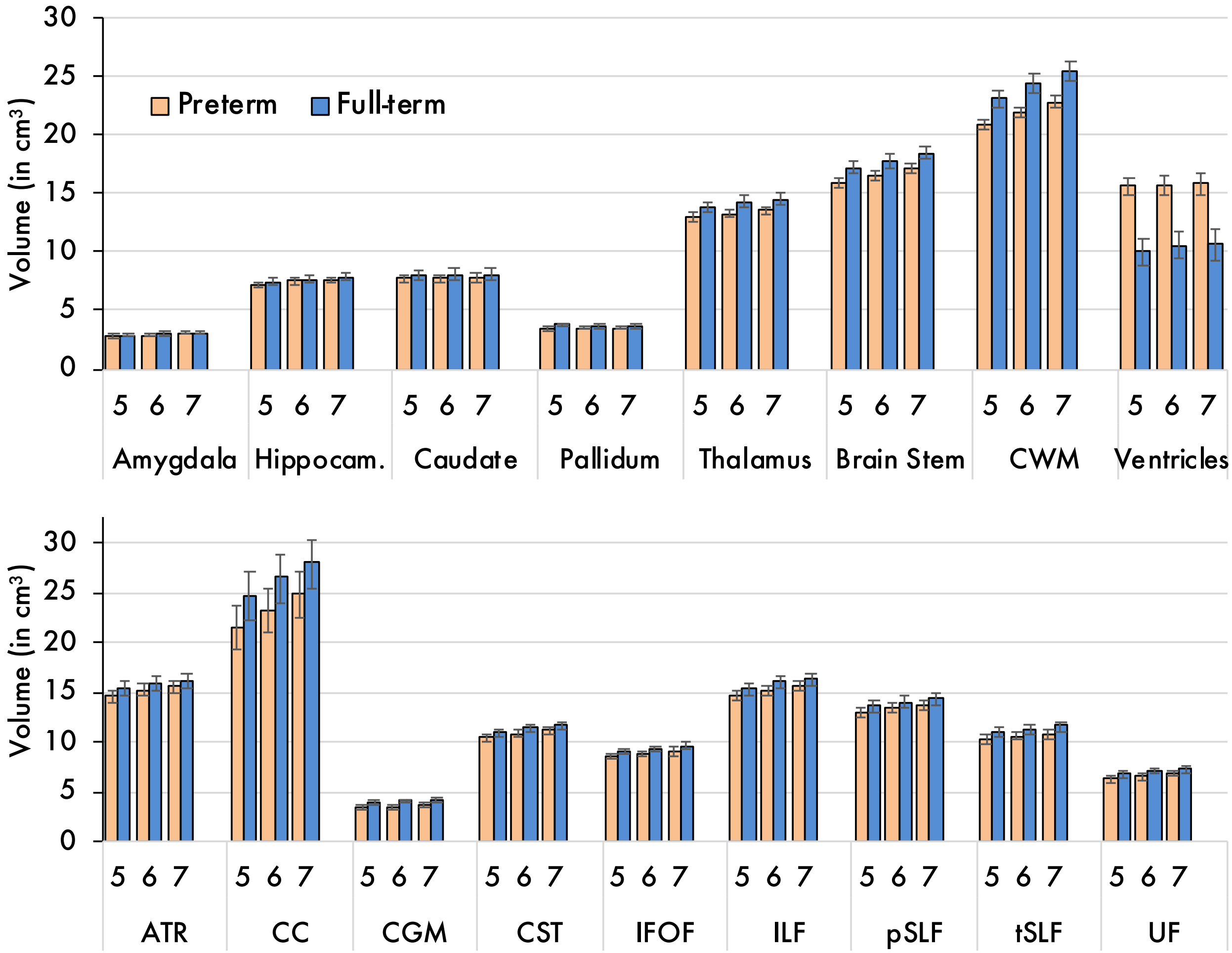

Figure 3.2: Volumes of subcortical structures by preterm and full-term group

Mean (95% CI) of volumes of subcortical gray matter structures, cerebellar white matter and ventricles (upper panel) and white matter tracts (lower panel) by preterm and full-term group. CWM: cerebellar white matter, ATR: anterior thalamic radiation, CGM: Cingulum, CST: Cortico-spinal tract, CC: Corpus callosum, IFOF: inferior frontal occipital fasciculus, ILF: inferior longitudinal fasciculus, tSLF: temporal superior longitudinal fasciculus, pSLF: posterior longitudinal fasciculus, UF: uncinate fasciculus.

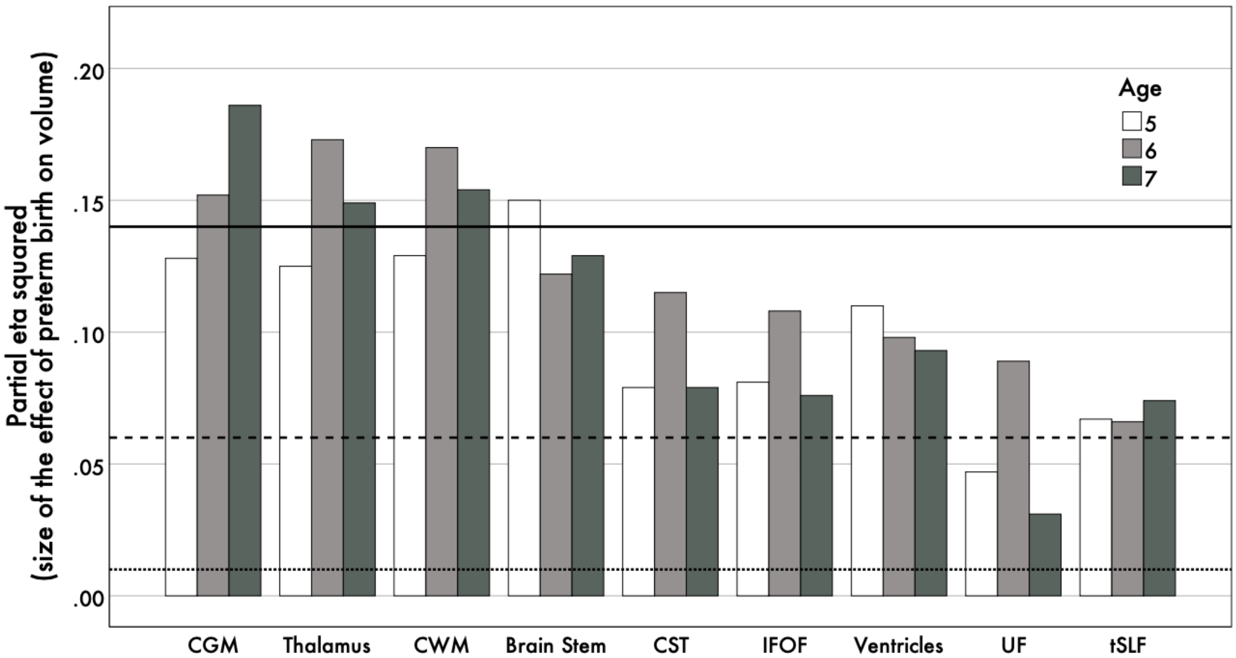

Figure 3.3: Volumes of gray and white matter, and ventricles at age 5, 6, and 7 with a significant effect of preterm birth

Structures 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. CGM: cingulum, CWM: cerebellar white matter, CST: corticospinal tract, IFOF: inferior frontal occipital fasciculus, UF: uncinate fasciculus, tSLF: temporal superior longitudinal fasciculus.

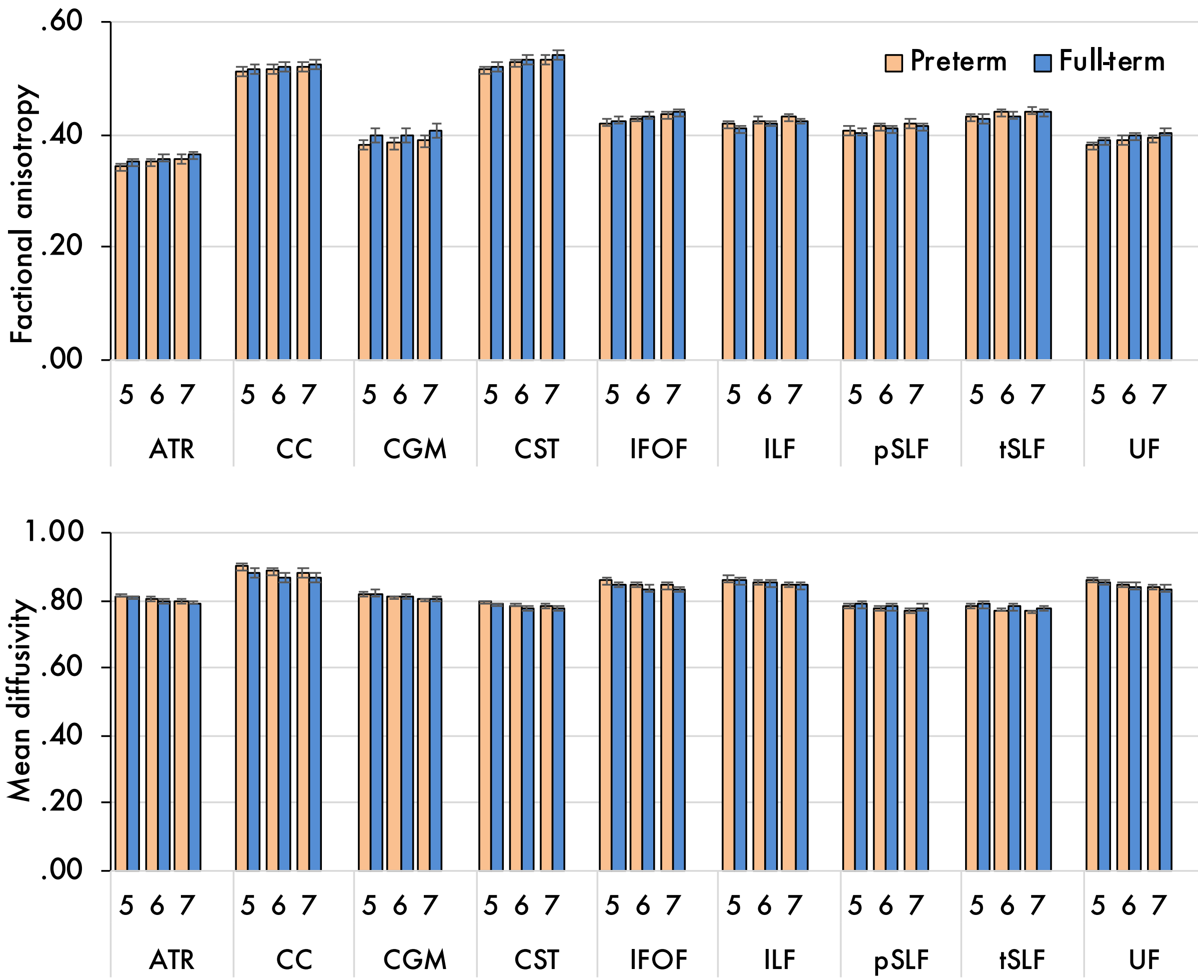

Figure 3.4: Fractional anisotropy, and mean diffusivity of white matter tracts by preterm and full-term group

Mean (95%CI). ATR: anterior thalamic radiation, CGM: Cingulum, CST: Cortico-spinal tract, CC: Corpus callosum, IFOF: inferior frontal occipital fasciculus, ILF: inferior longitudinal fasciculus, tSLF: temporal superior longitudinal fasciculus, pSLF: posterior longitudinal fasciculus, Unc: uncinate fasciculus.

CHAPTER 4:
ASSOCIATIONS BETWEEN MATHEMATICS SKILLS AND WHITE MATTER MICROSTRUCTURE IN CHILDREN BORN PRETERM

The content within this section, titled "Chapter 4: Associations between mathematics skills and white matter microstructure in children born preterm" reflects material from a paper that has been submitted and is under review for publication in the journal *Brain and Cognition*. The full citation is as follows:

Adrian, J. A., Pecheva, D., Sawyer, C., & Akshoomoff, N. (2022). Associations between mathematics skills and white matter microstructure in 5- to 7-year-old children born preterm. Under review at *Brain and Cognition*.

Abstract

Preterm birth has been shown to affect both white matter microstructure and mathematics skills however, little is known about the association between these two outcomes. In this study, we investigated the associations between diffusion tensor imaging measures of white matter microstructure and mathematics skills in 48 children born preterm and 27 children born full-term at 5 and 7 years of age. Using a hypothesis-driven ROI approach we studied white matter tracts previously associated with mathematical cognition and found differences in the associations between white matter microstructure and mathematics skills between children born preterm and full-term. Term status significantly moderated the effect of fractional anisotropy (FA) of several white matter tracts when predicting mathematics skills at 5 and 7 years of age. Post-hoc analyses of these effects revealed a positive association of FA in these tracts with mathematics skills in the full-term group, while this association was missing or negative in the preterm group. These differences may reflect adaptive processes following preterm birth and the recruitment of alternative pathways when solving mathematics, indicative of reorganization and plasticity of functional networks following early injury due to prematurity.

Introduction

Birth before 33 weeks of gestation is associated with long-term alterations in brain and cognitive development. In addition to other neurodevelopmental impairments, lower academic achievement in mathematics has been reported across several cohorts of children born preterm (Aarnoudse-Moens et al., 2011; Adrian et al., 2020; Akshoomoff et al., 2017; Taylor et al., 2009). Preterm birth puts individuals at risk of developing encephalopathy of prematurity, a distinct form of brain injury that includes cerebral white matter injury and neuronal-axonal dysmaturation (Volpe, 2019). In vivo diffusion tensor imaging (DTI) has been particularly useful in probing white matter microstructure alterations following preterm birth, as indexed by fractional anisotropy (FA), a measure of the directionality of water diffusion within tissues, and mean diffusivity (MD), a measure of the overall magnitude of diffusion (Feldman et al., 2010, 2012).

DTI measures of distinct white matter tracts have been associated with cognitive performance such as executive functions, reading, and overall IQ in children, adolescents, and young adults born preterm and full-term (Bruckert et al., 2019; Eikenes et al., 2011; Loe et al., 2019). Few studies have examined the associations between mathematics performance and brain microstructure, and even fewer have focused on developing populations. In typically developing populations mathematics skills have been associated with a network of interconnected brain regions, including prefrontal, posterior parietal, occipito-temporal, and hippocampal areas (Peters & De Smedt, 2018). Despite variation in methodologies, there is converging evidence for the involvement of the corpus callosum (CC), inferior longitudinal fasciculus (ILF), inferior frontal occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), and corticospinal tract (CST) in mathematical cognition (Matejko & Ansari, 2015). For example, arithmetic skills have been positively associated with FA in left ILF in typically developing children 8 years of age (van Eimeren et al., 2008), and with FA in the left ILF, bilateral IFOF and left SLF in children 10 years of age (Li et al., 2013). FA in left parietal areas including the left SLF and left CST has been associated with mathematics scores in typically developing young adults (Matejko et al., 2013). Bilateral CST, ILF, IFOF, SLF, and parts of the CC also showed higher FA in a group of mathematically gifted adolescents compared to age matched controls (Navas-Sánchez et al., 2014), and lower FA in right IFOF, right ILF, right CST, and bilateral SLF in a group of children with dyscalculia (Rykhlevskaia et al., 2009).

Only few studies have examined the association between mathematics skills and DTI measures of white matter in children born preterm. Kelly et al. (2016) and Collins et al. (2019) examined the association between mathematics skills and white matter FA in children born preterm and at term, at 7 and 13 years of age, respectively. Both studies found widespread bilateral associations between higher FA and lower MD with mathematics skills including in the IFOF, ILF, SLF, CC, and CST (Collins et al., 2019; Kelly et al., 2016).

Although lower performance on mathematics tests, as well as alterations in brain structure following preterm birth has been widely studied, the literature on the brain structure-function relationship is sparse, particularly with respect to mathematics. To date, the association between mathematics skills and white matter has not been examined in children born preterm as young as 5 years of age. Examining this relationship before the onset of formal schooling, and again two years later will contribute to our understanding of the impact of preterm birth on white matter microstructure and how it relates to academic achievement.

We sought to, first, investigate the relationship between mathematics skills and white matter DTI measures in children born preterm and full-term cross-sectionally at 5 and 7 years of age. We expected measures of FA in white matter to be positively associated with performance on math tests. Second, we aimed to investigate whether the longitudinal development of white matter microstructure is associated with an increase in mathematical skills between 5 and 7 years of age in the complete cohort, and if preterm birth affects this relationship. We hypothesized that greater increase in FA and decrease in MD of certain white matter tracts in this two-year span would be positively associated with an increase in mathematical test scores. In these analyses we focused on FA and MD of CC, CST, ILF, IFOF, and SLF, as these have previously been associated with mathematics skills in typically and atypically developing populations. For each of these two aims, we examined overall mathematics performance and more specifically number and arithmetic skills to investigate whether these associations are driven by specific mathematics skills.

Method

Participants

Our participants were 48 children born preterm before 33 weeks of gestation and 27 children born full-term. All participants had quality-controlled diffusion-weighted scans and completed a standardized mathematics test at two time points (ages 5 and 7 years). Table 4.1 summarizes the participant characteristics. There were no significant group differences in age at testing, 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. The objective of this study was to examine the impact of preterm birth on brain development in children without severe neonatal complications, therefore we excluded participants with intraventricular hemorrhage grade 3 or 4, cystic periventricular leukomalacia (PVL), or moderate to severe ventricular dilation. Our preterm sample included four participants that were small for gestational age, five with bronchopulmonary dysplasia, two with necrotizing enterocolitis, and seven that had intraventricular hemorrhage grade 1 or 2.

Full-term participants were recruited via the Center for Human Development at UC San Diego, through a data base of families who had previously consented to be contacted about studies. They 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

We measured full scale IQ at age 5 with the Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV, Wechsler, 2012). IQ data is missing from one full-term participant.

Mathematics skills

We measured mathematics skills at 5 years and 7 years of age with the Test for Early Mathematics Ability, 3rd Edition (TEMA-3). It is appropriate for children between 3 and 8 years of age and consists of up to 72 test items that require different skills to be solved. In addition to assessing overall mathematics skills (sum raw score of correct items), it is possible to cluster the items of the TEMA-3 into two categories, number skills and arithmetic skills (Adrian et al., 2020). Items in the number skills category (28 items) require ordering of quantities by magnitude such as counting objects or comparing numbers by magnitude. Arithmetic skills items (36 items) require manipulation of numbers, such as to solve abstract or concrete (story form) calculation problems. In this study we focused first on the predictiveness of white matter microstructure on overall mathematics skills and followed up with analyses on number skills and arithmetic skills more specifically.

MRI acquisition

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 3T GE Discovery MR750 scanner (GE Healthcare) with an eight-channel phased-array head coil. Imaging data were acquired and processed according to the protocols of the Pediatric Imaging Neurocognition and Genetics (PING) project, described in detail by (Jernigan et al., 2016). The scanning protocol included structural and diffusion MRI acquisitions. A 3D T1-weighted image was acquired with inversion recovery spoiled gradient echo using prospective motion correction (PROMO, White et al., 2010) with acquisition parameters: echo time (TE) = 3.5 ms, repetition time (TR) = 8.1 ms, inversion time (TI) = 640 ms, flip angle = 8°, receiver bandwidth = ±31.25 kHz, field of view (FOV) = 24 cm, frequency = 256, phase = 192, slice thickness = 1.2 mm. A 3D T2-weighted image was acquired with variable flip angle fast spin-echo scan, also using PROMO, for detection and quantification of white matter lesions and segmentation of CSF. Two axial 2D DTI pepolar scans were acquired in 30 noncolinear directions with b-value = 1,000, TE = 83 ms, TR = 13,600 ms, frequency = 96, phase = 96, slice thickness = 2.5 mm, and a single b=0 volume.

MRI data processing

Cortical and subcortical gray matter structures were segmented from structural MRI using FreeSurfer version 5.3.0 (Fischl et al., 2002, 2004). White matter tracts were segmented from diffusion MRI data using the automated segmentation and labeling procedure for probabilistic, atlas-based analysis (Hagler et al., 2009).

Quality of the images was assessed manually by two trained experts blinded to group membership at all stages of processing. Raw T1- and diffusion-weighted images were examined for motion artifacts, excessive distortion, operator error, scanner malfunction, as well as other artifacts and poor image quality. Only images with minimal to no movement or scanner artifacts, and no errors in registration and segmentation in FreeSurfer. AtlasTrack white matter tract segmentations were inspected for contiguity and overall quality. In this study we only included participants with complete, quality controlled T1- and diffusion-weighted MRI scans, leading to a final sample of 48 preterm and 27 full-term participants.

Conventional methods were used to calculate DTI measures (Basser et al., 1994; Pierpaoli et al., 1996). FA and MD for each tract were calculated by averaging across all voxels within the tract. We analyzed FA and MD of CC, and bilateral CST, IFOF, ILF, and SLF.

Statistical analyses

Statistical analyses were performed using R Studio version 1.3.959 with R version 4.0.1 (RStudio Team, 2020). Demographic participant characteristics, IQ scores, mathematics scores, and tract FA and MD were compared between groups using ANOVAs, Mann Whitney U, and chi-square tests as appropriate.

To examine the predictive value of mean tract FA and MD on mathematics skills we conducted a series of regression models. First, we examined if there was a significant main effect of FA or MD on mathematics skills, covaried for age at scan, sex, maternal education, and term status (preterm/full-term). Next, we included the interaction between term status and FA or MD, respectively, to examine if preterm birth moderates the predictiveness of the tract property on mathematics skills.

To further examine any significant interaction effects, we analyzed the association between residualized mathematics skills and residualized tract FA or MD across preterm and full-term participants, covaried for age, sex, and maternal education.

Furthermore, we performed linear regression models predicting mathematics skills based on mean tract FA or MD, covaried for age, sex, and maternal education separately for preterm and full-term groups.

Results

Group comparison of mathematics skills

Preterm participants had lower overall mathematics skills at age 5 ($\eta^2 = 0.100$, $p = .006$) and age 7 ($\eta^2 = 0.208$, $p = <.001$) compared to full-term participants (Figure 4.1). The increase in overall mathematics skills from 5 to 7 years was not significantly different between term-born and preterm children ($\eta^2 = 0.032$, $p = .122$). Number skills were lower in children born preterm compared to children born full-term at age 5 ($\eta^2 = 0.108$, $p = .004$), and age 7 ($\eta^2 = 0.096$, $p = .007$). There was a significantly higher increase in the absolute number skills score from 5 to 7 years in the preterm group ($\eta^2 = 0.060$, $p = .034$) compared to the full-term group, which decreased the achievement gap at age 7. Arithmetic skills at age 5 ($\eta^2 = 0.052$, $p = .050$), and age 7 ($\eta^2 = 0.262$, $p = <.001$) and the increase in arithmetic skills over this age range ($\eta^2 = 0.258$, $p = <.001$) were lower in children born preterm than children born full-term.

IQ at age 5 was significantly lower in children born preterm than full-term with mean standard scores of 102.2 and 109.1, respectively (Table 4.1).

Group comparison of white matter tracts

White matter tracts were generally similar in FA and MD across preterm and full-term groups (Figure 4.2). Several structures showed group differences that were nominally significant at the uncorrected $p < 0.05$ level. FA in the right ILF at age 5 ($\eta^2 = 0.055$, $p = .043$) was lower in the preterm group, while MD of the right IFOF at age 5 ($\eta^2 = 0.059$, $p = .035$) and the CC at age 5 ($\eta^2 = 0.058$, $p = .037$) was higher in children born preterm.

White matter microstructure and mathematics skills at age 5 and age 7

We performed a series of linear regression models predicting overall mathematics skills by mean tract FA or MD with and without a term status by tract interaction, covaried for age, sex, and maternal education. The results of these analyses are shown in Figure 4.3. The base model included age, sex, maternal education, and term status as predictors and explained 26.6% and 25.5% of the variance in overall mathematics skills at age 5 and 7, respectively. None of the models with a main effect of tract FA were significantly better at predicting math scores than the base model. Four models were better at predicting math scores when including a term status by tract FA interaction term. Right and left CST, left IFL, and left IFOF showed significant term status by tract FA interaction effects at age 5 and age 7 compared to the model with a main effect of tract FA only. At age 5, the increase in adjusted R^2 for the interaction effect of term status with right CST, left CST, left ILF, and left IFOF was 13.2%, 6.7%, 9.2%, and 6.0%, respectively, and at age 7 the increase in adjust R^2 was 15.9%, 8.6%, 3.6%, and 7.2%, respectively (Supplementary Table 4.1). The significant term status by tract FA interaction effects are shown as partial correlation plots between residualized mathematics score and residualized mean tract FA in Figure 4.4.

We also performed these analyses with mean tract MD instead of FA. Neither the main effect of mean tract MD nor the term status by tract MD interaction effect were significantly predictive of mathematics skills at either age for all tracts.

We analyzed the predictiveness of mean tract FA, covaried for age, sex, and maternal education, on mathematics skills separately for the preterm and full-term groups. In general, mean tract FA of right and left CST, left ILF, and left IFOF were positively associated with mathematics skills in children born full-term. Left IFOF showed the strongest association with mathematics skills, leading to an increase in adjusted R^2 compared to the base model of 11.3% and 25.9% at age 5 and 7, respectively. Right and left CST and left ILF showed weak to moderate positive associations, with increases in adjusted R^2 of 13.6%, 4.8%, and 6.6% at age 5, and 11.4%, 3.5%, and 10.4% at age 7, respectively. In contrast, FA of these tracts was not or only weakly associated with mathematics skills in the preterm group. Left ILF at age 5 explained 6.3% of additional variance, and right CST at age 7 explained 7.9% additional variance, with a negative association between FA and mathematics scores in children born preterm.

These patterns of associations are illustrated in Figure 4.5, which shows the standardized beta regression coefficients and p-values < .05 for analyses including only preterm or only full-term participants.

Association of white matter microstructure with number and arithmetic skills

We performed the same analyses to predict number skills and arithmetic skills instead of overall mathematics skills. The term status by tract FA of the right and left CST, left ILF, and left IFOF is significantly predictive of number skills at age 5 and arithmetic skills at age 7 (Supplementary Tables 4.2 and 4.3), and of overall mathematics skills at both time points. For number skills at age 7, the right and left CST also show the same interaction effect with term status. For arithmetic skills at age 5, only the right CST shows a significant interaction with term status.

Changes in white matter microstructure and development of mathematics skills from 5 to 7 years of age

Between 5 and 7 years of age FA of all tracts increased, while MD decreased in both the preterm and term-born groups. There were no significant group differences in change of FA or MD for any of the tracts.

Change in FA and MD of the left CST showed a significant weak effect on development of overall mathematics skills between 5 and 7 years of age across both groups (FA: $\Delta R^2 = 4.9\%$, $\beta = -0.235$, $p = .015$, MD: $\Delta R^2 = 5.4\%$, $\beta = 0.248$, $p = .011$). None of the tracts showed a significant interaction with term status.

Change in MD of right and left SLF showed a weak effect on change of number skills (right: $\Delta R^2 = 0.7\%$, $\beta = -0.101$, $p = .038$, left: $\Delta R^2 = 1.0\%$, $\beta = -0.113$, $p = .021$), while a change in MD of left CST showed a weak effect on change of arithmetic skills from 5 to 7 years of age ($\Delta R^2 = 1.5\%$, $\beta = 0.236$, $p = .012$). As with increase in overall mathematics skills, none of the tracts showed a significant interaction with term status.

Mathematics skills at age 5 was a significant predictor of change in mathematics skills from 5 to 7 (β between -0.419 and -0.474, all $p < .001$, Supplementary Table 4.4).

Discussion

In this study we found differences in the association of white matter microstructure as measured by DTI and mathematics skills in a cohort of young school-aged children born preterm and full-term. Based on previous studies of white matter tracts associated with mathematical cognition, we focused our analyses on five tracts: CC, CST, ILF, IFOF, and SLF (Matejko & Ansari, 2015). FA of the right and left CST, left ILF, and left IFOF showed a significant interaction effect of term status on mathematics skills. Higher FA in these tracts was associated with greater mathematics skills in children born full-term but not preterm. This pattern was seen at both 5 and 7 years of age, two time points which reflect the time before starting kindergarten and after two years of formal schooling. These differences may reflect adaptive processes following preterm birth and the recruitment of alternative pathways when solving mathematics problems.

Associations found in children born full-term

The CST which connects cortical regions with the brain stem has been associated with mathematical processing across several studies, despite being generally thought of as a motor pathway. We also found bilateral association with mathematics skills in children born full-term that persisted even when examining number skills or arithmetic skills separately. Involvement of the CST in mathematical cognition has been hypothesized to be related to using finger counting strategies (Matejko & Ansari, 2015). However, positive associations between FA of the CST has also been shown for more complex mathematics tests such as the math subtest of the PSAT in young adults (Matejko et al., 2013). Consistently, we found associations of the CST with both number and arithmetic skills.

The ILF, IFOF, and SLF are part of a distributed network of interconnected brain regions involved in mathematical cognition, including the prefrontal, posterior parietal, and occipito-temporal areas (Arsalidou & Taylor, 2011; Peters & De Smedt, 2018). The left lateralized association of FA of the ILF and IFOF with mathematics skills in children born full-term in our study is consistent with other studies of typically developing children (Li et al., 2013; van

Eimeren et al., 2008). In typically developing children, the association between FA of the SLF and addition and multiplication has previously been hypothesized to reflect the involvement of phonological processing skills during arithmetic operations (Van Beek et al., 2014). Contrary to our hypothesis, we did not find significant associations between FA or MD of the SLF and mathematics skills in either group. Interhemispheric connections, particularly inter-parietal connections, have been hypothesized to be important for numerical representations and processing. The isthmus of the CC, responsible for inter-parietal connections including connections between the bilateral IPS has been shown to be associated with numerical processing in children (Cantlon et al., 2011). Our lack of associations in FA of CC with mathematics skills may be explained by the fact that we examined the whole CC rather than specific subregions.

Our findings of the association of bilateral CST, left ILF, and left IFOF with general mathematics scores were similar at 5 and 7 years of age. When distinguishing between number and arithmetic skills, it becomes apparent that the associations found for overall mathematics skills were driven by number skills at age 5 and by arithmetic skills at age 7. One possible explanation for this is greater variation in number skills compared to arithmetic skills at age 5, while the opposite is true at age 7. Number skills such as verbal counting and comparison of quantities are basic skills for children by the end of first grade. On the other hand, arithmetic skills are learned through formal instruction in school and thus generally limited before starting kindergarten.

Lack of associations in children born preterm

The divergent pattern of association between full-term and preterm group may indicate the involvement of different networks of brain regions when solving mathematics. The analyses and findings reported in our study are similar to Bruckert et al. (2019), who examined the association between mean tract FA at age 6 and reading skills at age 8 in children born preterm and full-term. They too found significant term status by tract interaction, with significant positive associations between FA and reading in children born full-term but not in children born preterm. They concluded that children born preterm may rely on alternate pathways to achieve reading at a similar level as children born full-term. We propose the same may be true of mathematics skills. Furthermore, variables other than DTI measures of white matter tracts, that are not accounted for in our models, may have a greater impact on academic achievement in children born preterm. However, these have not been well characterized due to the heterogeneity of the preterm population.

Being born prematurely is often associated with exposure to hypoxia, ischemia, and inflammation which may lead to white matter injury (Back, 2017; Volpe, 2019). Even children who were born with more severe injury may perform well on cognitive and behavioral tasks. Yeatman & Feldman (2013) describe the case study of a 12-year-old child born preterm. Despite being diagnosed with PVL, severe damage to the white matter surrounding the ventricles, and lacking the arcuate fasciculi and the SLF bilaterally, this child had average scores on tests of expressive language, sentence repetition and reading. These intact functions with severe early white matter injury point towards the extensive potential for plasticity during neurodevelopment following preterm birth.

Other studies examining the association between white matter microstructure and mathematics skills have not found the term interaction effects we found here. At 13 years of age, both children born preterm and full-term showed associations between better mathematics performance and increased FA in widespread, bilateral white matter regions including ILF, IFOF, and SLF. Mathematics performance was also positively associated with neurite density, and negatively associated with MD across both groups (Collins et al., 2019). Higher fiber density, fiber-bundle cross-section, and combined fiber density and cross-section in visual, sensorimotor, and cortico-thalamic/thalamic-cortical tracts were positively associated with mathematics skills of children born preterm and full-term at 7 and 13 years of age (Collins et al., 2021).

These contrasting findings may be due to the smaller sample size of our study as well as differences in methodologies. Our study focused on younger children and consequently other types of mathematics skills. Furthermore, preterm participants in our study had less severe injury compared to participants in other studies, did not show significant differences regarding mean tract FA or MD compared to full-term controls, and scored in the average range for mathematics, although significantly worse than our full-term controls (Adrian et al., 2020, 2021; Hasler & Akshoomoff, 2019). DTI measures such as FA and MD are a good first reference point of underlying white matter microstructure but do not allow specification of cellular processes. It is therefore possible that fiber tract composition differed between the two groups despite similar outcomes in DTI measures. Differences in analyses of the diffusion weighted images, particularly ROI-based compared to whole brain-analysis, Neurite Orientation Dispersion and Density Imaging (NODDI), or Fixel-Based Analysis (FBA) may further explain our contrasting findings. In addition, we cannot exclude an effect of differences in the type of mathematics assessments used or study cohort composition.

It is always difficult to decide whether a lack of significant findings should be interpreted as “evidence of absence or absence of evidence”. One limitation of our study is the relatively small sample size which would prohibit the detection of smaller effects. Children born preterm may rely on similar pathways as children born full-term and thus the measures we used in our study may not have been sensitive enough to demonstrate this. FA and MD are structural measures, and it is plausible that a functional analysis would uncover that the same network is being recruited for mathematics skills in both groups. Considering other studies showing this moderating effect of preterm birth, we cannot exclude that the lack of association for mathematics and reading skills in children born preterm is indicative of white matter plasticity following preterm birth.

Negative associations in children born preterm

We did not predict the negative association between FA in left ILF at age 5 and right CST at age 7 with mathematics skills in the preterm group. Cases in which higher FA was associated with lower performance scores have previously been reported for visuospatial abilities in children born preterm (Tokariev et al., 2019) and other atypically developing populations. Higher FA in the CST has been associated with poorer motor skills in young adults born preterm (Hollund et al., 2018). The authors argued that instead of improved white matter integrity, higher FA is reflective of axon loss, poorer branching and demyelination in regions of crossing fibers. Higher FA of white matter tracts has not only been reported following preterm birth but also in other cohorts of atypically developing populations, such as individuals with Williams syndrome (Hoeft et al., 2007) and ADHD (Davenport et al., 2010).

Strengths and limitations

A strength of our study is the longitudinal design, allowing us to examine the brain structure-function relationship concurrently at age 5 and 7, as well as associations of the differences in performance with differences in white matter during this age range. Dividing up the TEMA-3, an established mathematics test for young children, into number and arithmetic skills further allowed us to examine whether any of the found associations were task-specific or more generally related to mathematical problem solving.

Here we chose a hypothesis-driven ROI approach to examine specific white matter tracts that have previously been associated with mathematical cognition. DTI measures such as FA and MD are commonly used to examine and report the composition of white matter tracts. As DTI measures such as FA and MD cannot specify the underlying cellular mechanisms but may be a first reference point for tract microstructure. Other approaches can parse apart effects that affect FA of a tract, such as axonal diameter, density, orientation, and crossing fibers. Using more advanced diffusion modeling approaches such as Neurite Orientation Dispersion and Density Imaging (NODDI) or fixel-based analyses (FBA) in addition to traditional DTI would give more insight into this microstructural composition of white matter tracts.

We acknowledge that our participants are a convenience sample with a high socioeconomic status, IQ in the average range, and a majority of non-Hispanic white participants. Recruitment of a larger and more diverse sample should be prioritized so future research is more reflective of the preterm population at large.

Conclusion

Despite similar white matter microstructure, children born preterm and full-term show differences in the association between tract FA and mathematics skills. Ours is one of only a few recent studies to examine this relationship and the first study to do so in children 5 years of age, before the onset of formal schooling. 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 improvement of academic achievement in children born preterm.

Acknowledgement

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Chapter 4, in full, is a reprint of the material as it has been submitted for publication in *Brain and Cognition*, 2022, Adrian, Julia Anna; Pecheva, Diliana; Sawyer, Carolyn; Akshoomoff, Natacha, Elsevier. The dissertation author was the primary researcher and author of this paper.

Table 4.1: Participant characteristics

	Preterm n = 48	Full-term n = 27	Effect size/ Test statistic	p value
GA at birth in weeks mean (SD, min-max)	29.8 (2.2, 24.0–32.9)	39.8 (0.7, 38.0–41.0)	η^2=.877	<.001
Birth weight in g mean (SD, min-max)	1319 (445, 625–2450)	3423 (548, 2353–4423)	η^2=.821	<.001
Age at imaging: mean (SD)				
Time 1 (Age 5)	5.3 (0.4)	5.3 (0.3)	η^2=.001	.769
Time 2 (Age 7)	7.3 (0.4)	7.3 (0.3)	η^2<.001	.964
Δ Age 5 to 7	2.0 (0.2)	2.0 (0.2)	η^2=.012	.352
Sex (female)	25 - 52%	11 - 41%	X^2=0.891	.345
Maternal education			U=556	.193
1) 10–11 years high school	1 - 2%	0 - 0%		
2) high school degree	5 - 10%	3 - 11%		
3) 1–3 year college	17 - 35%	5 - 19%		
4) college degree	16 - 33%	10 - 37%		
5) graduate degree	9 - 19%	9 - 33%		
Household income			U=693	.384
1) below $50,000	8 - 17%	1 - 4%		
2) $50,000 – <$100,000	13 - 27%	13 - 48%		
3) $100,000 – <$200,000	15 - 31%	12 - 44%		
4) $200,000 and above	10 - 21%	0 - 0%		
Missing information	2 - 4%	1 - 4%		
Race			X^2=3.38	.641
African American/Black	1 - 2%	0 - 0%		
Asian	4 - 8%	4 - 15%		
Caucasian/White	36 - 75%	18 - 67%		
Mixed	5 - 10%	5 - 19%		
Other	1 - 2%	0 - 0%		
Missing information	1 - 2%	0 - 0%		
Ethnicity (Hispanic/Latinx)	19 - 40%	9 - 33%	X^2=0.289	.591
FSIQ at age 5[a] mean (SD)	102.2 (13.0)	109.1 (8.9)	η^2=.069	.022

Note. Group comparisons were performed via ANOVA for GA at birth, birth weight, age at testing, and full scale IQ (FSIQ); 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.

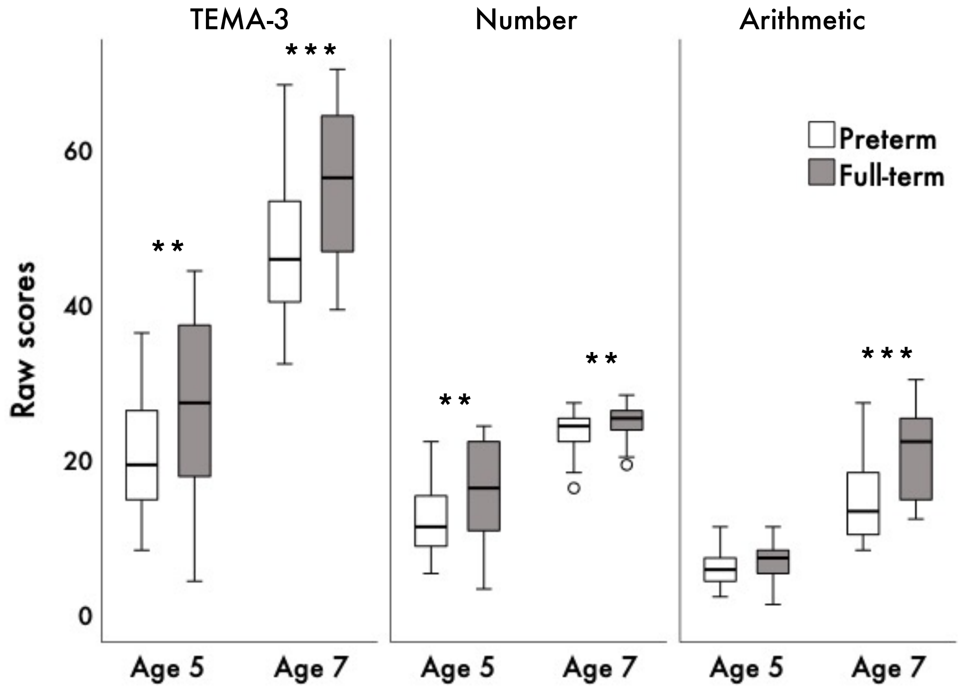


Figure 4.1: Box plots of overall mathematics skills as measured with the Test for Early Mathematics Ability, 3rd edition (TEMA-3), number skills and arithmetic skills at age 5 and age 7 by preterm and full-term group.

*** p < .001, ** p < .01, * p < .05.

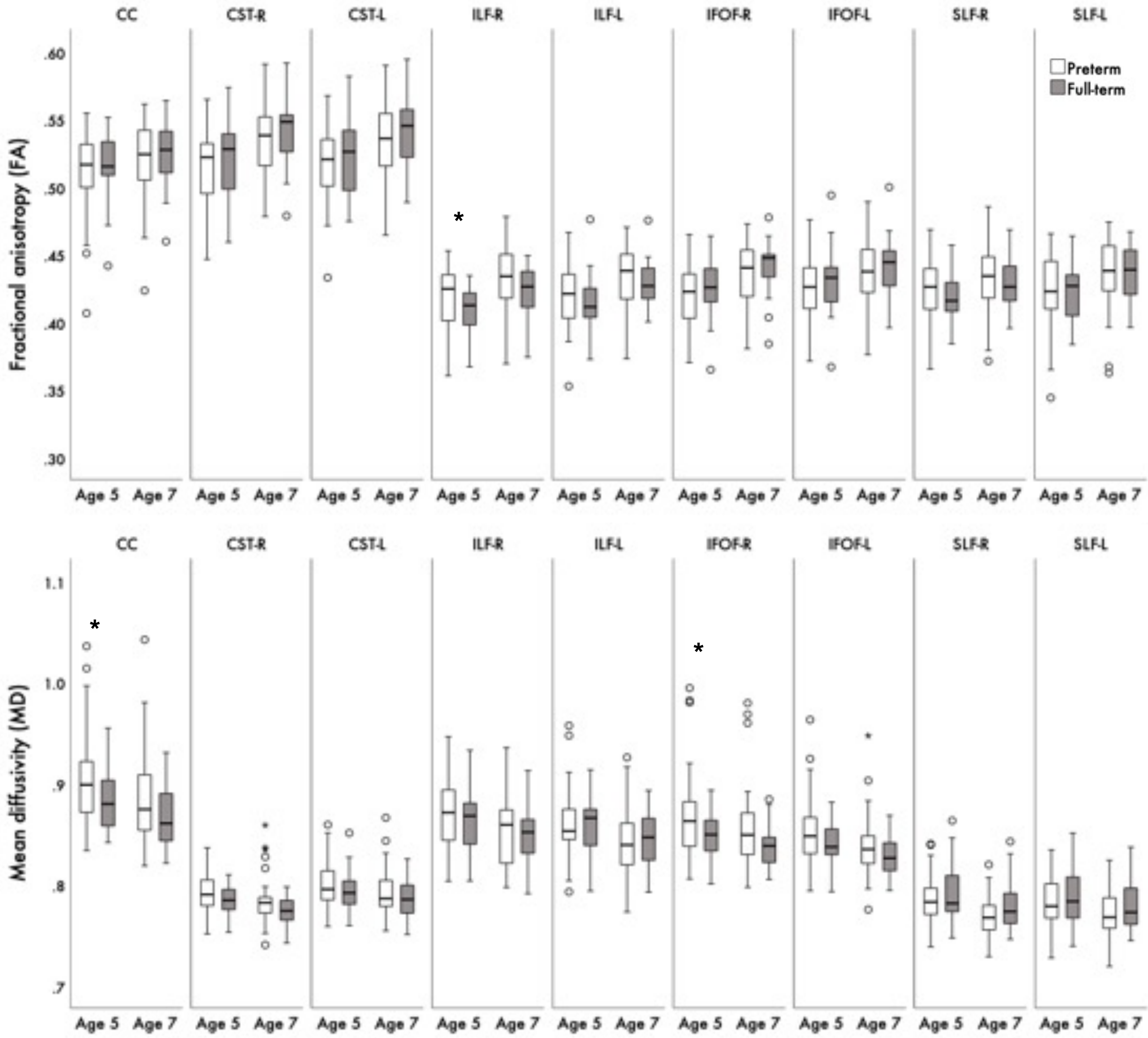
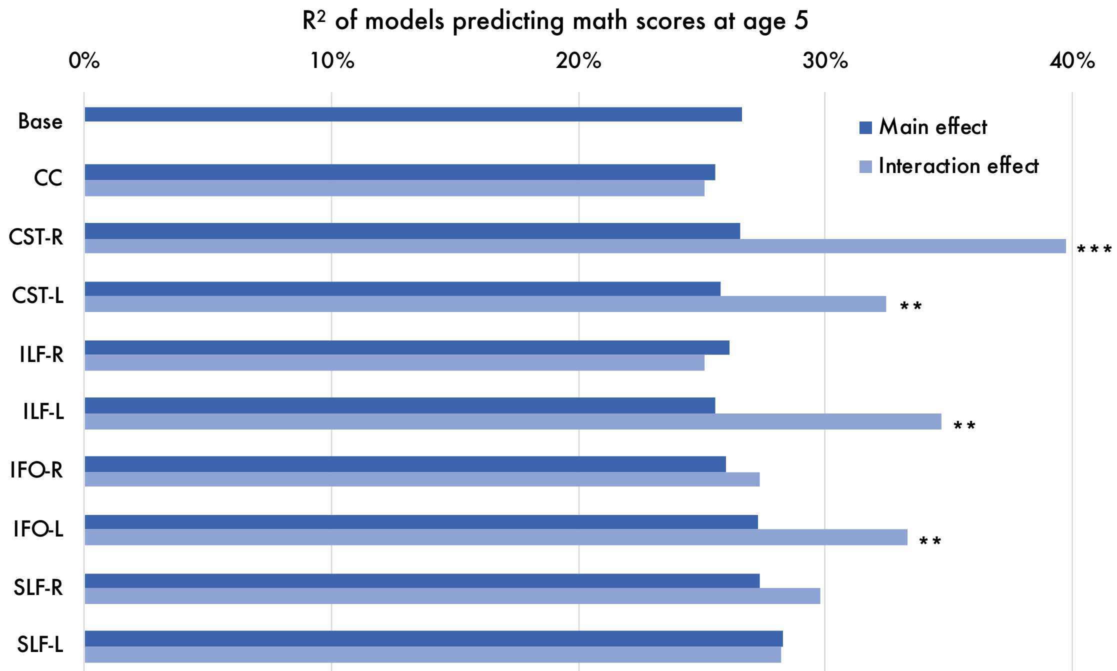


Figure 4.2: Box plots of FA and MD of white matter tracts at age 5 and age 7 by preterm and full-term group.

CC: corpus callosum, CST: corticospinal tract, ILF: inferior longitudinal fasciculus, IFOF: inferior frontal occipital fasciculus, SLF: superior longitudinal fasciculus, R: right, L: left, *** p < .001, ** p < .01, * p < .05.



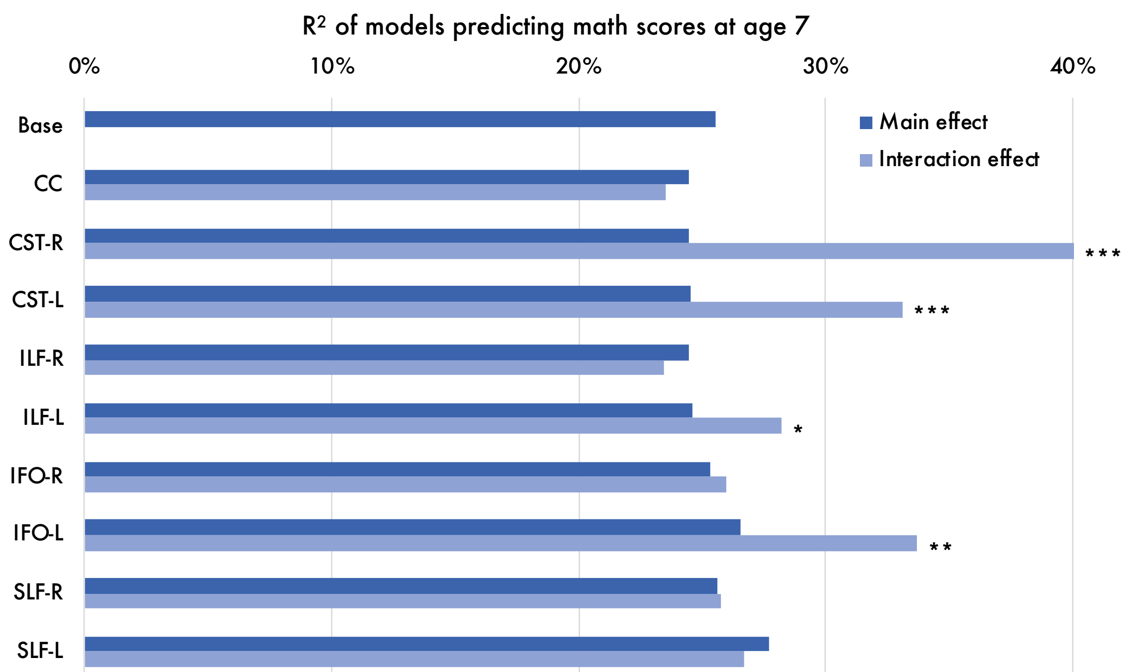
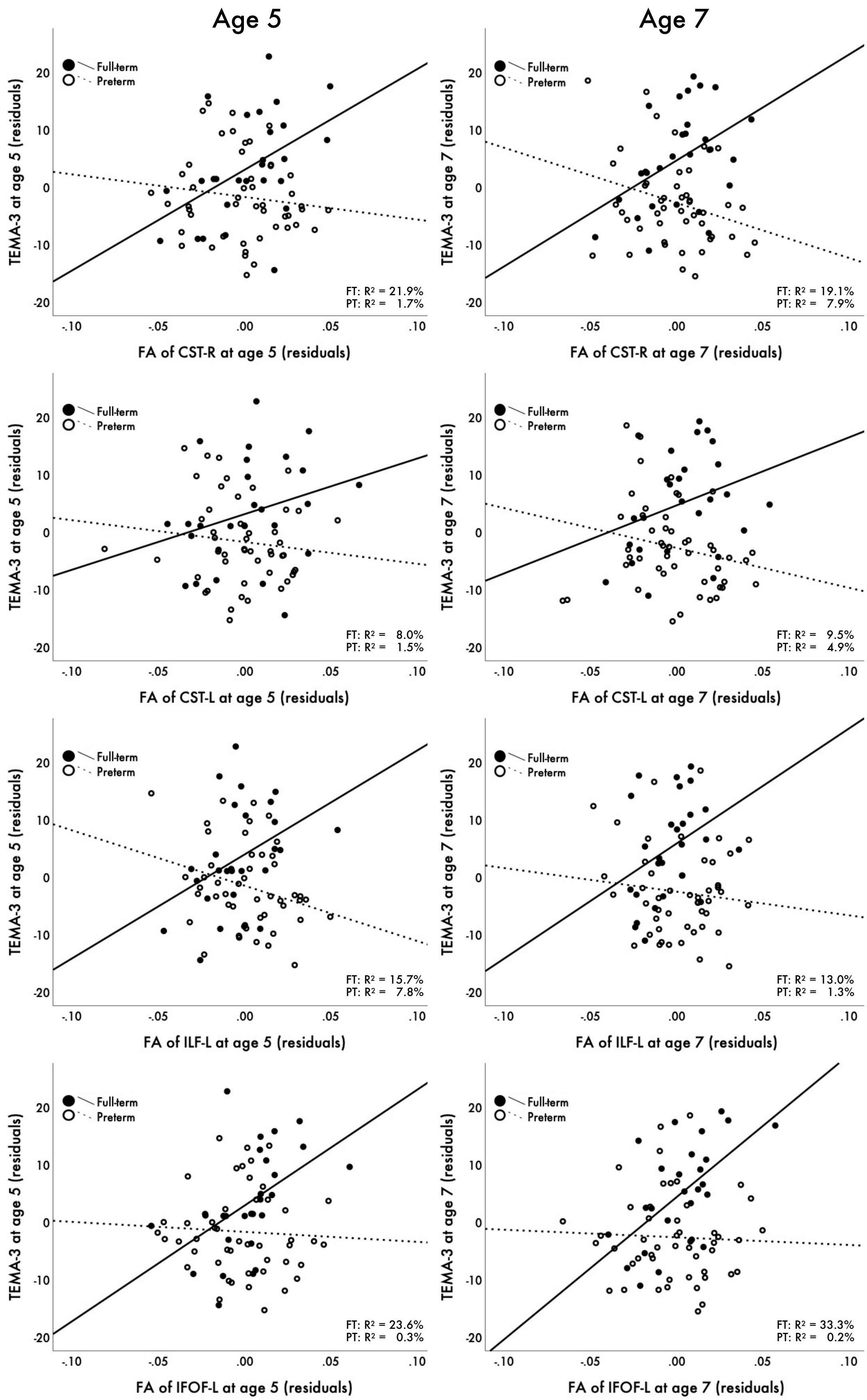


Figure 4.3: Bar graphs of R^2 of linear regressions predicting math scores

Age 5 (top) and age 7 (bottom). Base model includes age, sex, maternal education, and term status (preterm/full-term) as predictors. Main effect models (dark blue) additionally include mean tract FA as predictor, interaction effect models (light blue) additionally include the interaction between term-status and mean tract FA as predictor. Asterisks indicate that the interaction model is significantly better than the main effect model of the same tract. *** $p < .001$, ** $p < .01$, * $p < .05$. None of the models with a main effect of tract FA were significantly better than the base model.

Figure 4.4: Scatterplots of regression residuals of mean tract FA and mathematics skills

Residuals of mean tract FA of right and left CST (corticospinal tract), left ILF (inferior longitudinal fasciculus), and left IFOF (inferior frontal occipital fasciculus) and mathematics skills at age 5 (left column) and age 7 (right column) in children born full-term (FT, full circles, solid line) and preterm (PT, empty circles, dotted line) after controlling for age, sex, and maternal education.


Age 5
Age 7
Full-term
Preterm
TEMA-3 at age 5 (residuals)
TEMA-3 at age 7 (residuals)
FT: R² = 21.9%
PT: R² = 1.7%
FA of CST-R at age 5 (residuals)
FT: R² = 19.1%
PT: R² = 7.9%
FA of CST-R at age 7 (residuals)
FT: R² = 8.0%
PT: R² = 1.5%
FA of CST-L at age 5 (residuals)
FT: R² = 9.5%
PT: R² = 4.9%
FA of CST-L at age 7 (residuals)
FT: R² = 15.7%
PT: R² = 7.8%
FA of ILF-L at age 5 (residuals)
FT: R² = 13.0%
PT: R² = 1.3%
FA of ILF-L at age 7 (residuals)
FT: R² = 23.6%
PT: R² = 0.3%
FA of IFOF-L at age 5 (residuals)
FT: R² = 33.3%
PT: R² = 0.2%
FA of IFOF-L at age 7 (residuals)

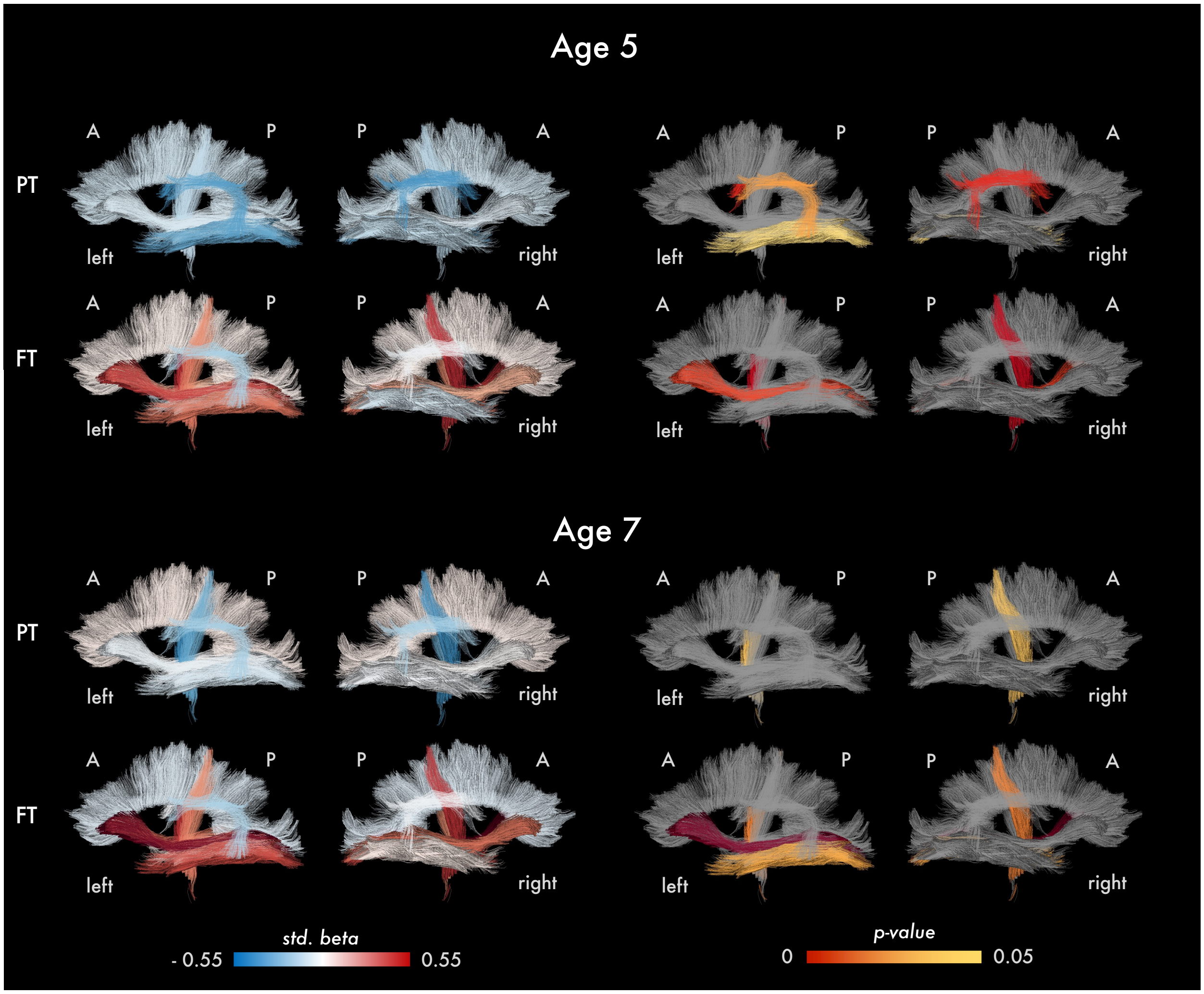


Figure 4.5: Associations of mean tract FA and mathematics skills at 5 and 7 years separately for preterm (PT) and full-term (FT) participants

Images on the left visualize standardized beta coefficients across the examined tracts (red indicates a positive association, blue a negative association between FA and mathematics skills); images on the right visualize the tracts with $p < 0.05$ for the associations (red to yellow indicate lower to higher p-values, grey indicates tracts with $p \geq 0.05$). A: anterior, P: posterior

Supplementary Table 4.1: Predictiveness of mean tract FA and MD, as main effect and in interaction with term status, on TEMA-3 at 5 and 7 years of age

	Main effect of tract			Interaction effect of tract by term status		
Age 5	std. β	*p*-value	Δ adj. R^2	std. β	*p*-value	Δ adj. R^2
FA CC	-0.019	0.853	-1.0%	-1.621	0.445	-0.4%
FA CST-R	0.107	0.328	0.0%	**-7.159**	**0.000**	**13.2%**
FA CST-L	0.048	0.653	-0.8%	**-5.310**	**0.007**	**6.7%**
FA ILF-R	-0.077	0.466	-0.5%	-0.724	0.753	-1.0%
FA ILF-L	-0.008	0.938	-1.1%	**-6.150**	**0.002**	**9.2%**
FA IFOF-R	0.065	0.530	-0.6%	-3.151	0.133	1.4%
FA IFOF-L	0.130	0.202	0.7%	**-4.731**	**0.009**	**6.0%**
FA SLF-R	-0.132	0.196	0.7%	-4.152	0.068	2.5%
FA SLF-L	-0.163	0.110	1.7%	-2.004	0.331	0.0%
MD CC	0.085	0.415	-0.3%	-0.582	0.836	-1.0%
MD CST-R	-0.018	0.866	-1.0%	10.868	0.051	3.1%
MD CST-L	0.052	0.612	-0.8%	5.341	0.206	0.7%
MD ILF-R	-0.001	0.995	-1.1%	-1.432	0.611	-0.8%
MD ILF-L	-0.063	0.544	-0.7%	-1.233	0.702	-0.9%
MD IFO-R	-0.024	0.823	-1.0%	-2.205	0.542	-0.7%
MD IFO-L	-0.122	0.242	0.4%	-1.409	0.716	-0.9%
MD SLF-R	0.189	0.067	2.5%	0.159	0.959	-1.0%
MD SLF-L	0.181	0.071	2.4%	1.773	0.574	-0.7%
Age 7	std. β	*p*-value	Δ adj. R^2	std. β	*p*-value	Δ adj. R^2
FA CC	-0.010	0.921	-1.1%	0.804	0.715	-1.0%
FA CST-R	-0.015	0.893	-1.1%	**-9.186**	**0.000**	**15.9%**
FA CST-L	-0.024	0.824	-1.0%	**-6.737**	**0.002**	**8.6%**
FA ILF-R	-0.004	0.968	-1.1%	-0.788	0.727	-1.0%
FA ILF-L	0.037	0.728	-0.9%	**-5.133**	**0.039**	**3.6%**
FA IFOF-R	0.091	0.378	-0.2%	-2.808	0.208	0.7%
FA IFOF-L	0.141	0.165	1.0%	**-5.569**	**0.005**	**7.2%**
FA SLF-R	-0.108	0.298	0.1%	-2.353	0.294	0.1%
FA SLF-L	-0.179	0.081	2.2%	0.116	0.955	-1.1%
MD CC	0.007	0.946	-1.1%	-2.982	0.254	0.4%
MD CST-R	-0.038	0.719	-0.9%	7.022	0.190	0.8%
MD CST-L	0.185	0.070	2.5%	2.342	0.586	-0.7%
MD ILF-R	-0.004	0.969	-1.1%	-2.437	0.408	-0.3%
MD ILF-L	-0.047	0.655	-0.9%	-0.053	0.987	-1.1%
MD IFO-R	-0.005	0.966	-1.1%	-4.831	0.189	0.8%
MD IFO-L	-0.062	0.562	-0.7%	-1.575	0.686	-0.9%
MD SLF-R	0.163	0.126	1.5%	-1.657	0.649	-0.8%
MD SLF-L	0.173	0.093	2.0%	-0.386	0.912	-1.1%

Note. Adjusted ΔR^2 of the main effect models is in reference to the base model including age, sex, and maternal education, adjusted ΔR^2 of the interaction effect models is in reference to the main effect model.

Supplementary Table 4.2: Predictiveness of mean tract FA and MD, as main effect, and in interaction with term status, on number skills at 5 and 7 years of age

	Main effect of tract			Interaction effect of tract by term status		
Age 5	std. β	p-value	Δ adj. R^2	std. β	p-value	Δ adj. R^2
FA CC	0.007	0.944	-1.0%	-1.208	0.562	-0.7%
FA CST-R	0.128	0.231	0.5%	**-6.683**	**0.000**	**11.4%**
FA CST-L	0.063	0.545	-0.6%	**-4.647**	**0.016**	**4.9%**
FA ILF-R	-0.088	0.397	-0.3%	-0.088	0.969	-1.0%
FA ILF-L	-0.016	0.874	-1.0%	**-5.733**	**0.003**	**7.9%**
FA IFOF-R	0.074	0.463	-0.5%	-2.791	0.175	0.9%
FA IFOF-L	0.129	0.198	0.7%	**-4.482**	**0.012**	**5.4%**
FA SLF-R	-0.129	0.195	0.7%	-3.186	0.154	1.1%
FA SLF-L	-0.139	0.164	1.0%	-1.413	0.487	-0.5%
MD CC	0.052	0.612	-0.8%	-1.021	0.712	-0.9%
MD CST-R	-0.047	0.651	-0.8%	9.130	0.094	1.9%
MD CST-L	-0.005	0.964	-1.0%	4.931	0.235	0.4%
MD ILF-R	-0.040	0.701	-0.9%	-1.719	0.532	-0.6%
MD ILF-L	-0.099	0.332	0.0%	-1.491	0.635	-0.8%
MD IFO-R	-0.065	0.538	-0.6%	-2.924	0.407	-0.3%
MD IFO-L	-0.158	0.120	1.5%	-2.410	0.522	-0.6%
MD SLF-R	0.170	0.093	1.9%	-0.609	0.843	-1.0%
MD SLF-L	0.162	0.099	1.8%	0.802	0.796	-0.9%
Age 7	std. β	p-value	Δ adj. R^2	std. β	p-value	Δ adj. R^2
FA CC	-0.050	0.644	-0.9%	1.376	0.549	-0.8%
FA CST-R	-0.009	0.937	-1.2%	**-8.078**	**0.001**	**11.9%**
FA CST-L	0.026	0.821	-1.1%	**-5.968**	**0.011**	**6.4%**
FA ILF-R	-0.080	0.466	-0.5%	-1.141	0.628	-0.9%
FA ILF-L	-0.001	0.992	-1.2%	-4.001	0.127	1.6%
FA IFOF-R	-0.031	0.773	-1.1%	0.103	0.965	-1.2%
FA IFOF-L	0.016	0.883	-1.2%	-2.274	0.292	0.2%
FA SLF-R	-0.192	0.075	2.6%	-0.208	0.929	-1.2%
FA SLF-L	-0.238	0.026	4.6%	1.233	0.566	-0.8%
MD CC	0.043	0.693	-1.0%	-4.038	0.139	1.5%
MD CST-R	0.026	0.817	-1.1%	1.931	0.733	-1.1%
MD CST-L	0.194	0.070	2.7%	5.797	0.196	0.8%
MD ILF-R	0.082	0.462	-0.5%	-5.039	0.098	2.1%
MD ILF-L	0.093	0.393	-0.3%	-3.584	0.281	0.2%
MD IFO-R	0.032	0.775	-1.1%	-7.964	0.037	4.0%
MD IFO-L	0.021	0.849	-1.1%	-5.004	0.219	0.6%
MD SLF-R	0.216	0.053	3.2%	-5.168	0.169	1.0%
MD SLF-L	0.219	0.041	3.7%	-3.947	0.273	0.2%

Note. Adjusted ΔR^2 of the main effect models is in reference to the base model including age, sex, and maternal education, adjusted ΔR^2 of the interaction effect models is in reference to the main effect model.

Supplementary Table 4.3: Predictiveness of mean tract FA and MD, as main effect, and in interaction with term status, on arithmetic skills at 5 and 7 years of age

	Main effect of tract			Interaction effect of tract by term status		
Age 5	std. β	*p*-value	Δ adj. R^2	std. β	*p*-value	Δ adj. R^2
FA CC	0.027	0.806	-1.1%	0.236	0.917	-1.2%
FA CST-R	0.099	0.400	-0.3%	**-4.908**	**0.019**	**5.5%**
FA CST-L	0.054	0.635	-0.9%	-4.134	0.051	3.5%
FA ILF-R	0.016	0.887	-1.2%	0.320	0.897	-1.2%
FA ILF-L	0.024	0.830	-1.2%	-3.626	0.092	2.3%
FA IFOF-R	0.120	0.275	0.3%	-1.687	0.453	-0.5%
FA IFOF-L	0.164	0.132	1.6%	-2.839	0.147	1.3%
FA SLF-R	-0.113	0.301	0.1%	-1.502	0.543	-0.8%
FA SLF-L	-0.112	0.308	0.1%	0.047	0.983	-1.2%
MD CC	-0.012	0.915	-1.2%	-1.171	0.698	-1.1%
MD CST-R	-0.093	0.411	-0.4%	6.631	0.267	0.3%
MD CST-L	0.035	0.751	-1.1%	2.457	0.589	-0.9%
MD ILF-R	-0.050	0.662	-1.0%	-2.633	0.380	-0.3%
MD ILF-L	-0.111	0.317	0.0%	-2.256	0.511	-0.7%
MD IFO-R	-0.083	0.468	-0.6%	-1.865	0.629	-0.9%
MD IFO-L	-0.182	0.101	2.1%	-1.692	0.680	-1.0%
MD SLF-R	0.069	0.538	-0.7%	-1.204	0.724	-1.1%
MD SLF-L	0.117	0.281	0.2%	0.130	0.970	-1.2%
Age 7	std. β	*p*-value	Δ adj. R^2	std. β	*p*-value	Δ adj. R^2
FA CC	0.016	0.874	-1.0%	0.836	0.691	-0.9%
FA CST-R	0.005	0.965	-1.0%	**-8.430**	**0.000**	**13.3%**
FA CST-L	-0.006	0.953	-1.0%	**-6.210**	**0.004**	**7.3%**
FA ILF-R	-0.003	0.979	-1.0%	-0.390	0.857	-1.0%
FA ILF-L	0.012	0.905	-1.0%	**-5.358**	**0.024**	**4.1%**
FA IFOF-R	0.087	0.378	-0.2%	-2.948	0.168	0.9%
FA IFOF-L	0.101	0.302	0.1%	**-5.091**	**0.008**	**5.9%**
FA SLF-R	-0.117	0.238	0.4%	-0.861	0.689	-0.8%
FA SLF-L	-0.190	0.053	2.7%	1.180	0.552	-0.6%
MD CC	-0.026	0.792	-0.9%	-2.670	0.287	0.2%
MD CST-R	-0.062	0.545	-0.6%	5.673	0.269	0.2%
MD CST-L	0.129	0.190	0.7%	2.453	0.556	-0.6%
MD ILF-R	-0.007	0.949	-1.0%	-2.714	0.335	-0.1%
MD ILF-L	-0.051	0.613	-0.7%	-0.321	0.917	-1.0%
MD IFO-R	-0.023	0.823	-0.9%	-3.189	0.367	-0.2%
MD IFO-L	-0.080	0.432	-0.4%	-0.354	0.924	-1.0%
MD SLF-R	0.166	0.104	1.6%	-1.636	0.639	-0.8%
MD SLF-L	0.179	0.069	2.3%	-0.289	0.931	-1.0%

Note. Adjusted ΔR^2 of the main effect models is in reference to the base model including age, sex, and maternal education, adjusted ΔR^2 of the interaction effect models is in reference to the main effect model.

Supplementary Table 4.4: Predictiveness of change in mean tract FA and MD, as main effect, and in interaction with term status, on change in math skills from 5 to 7 years

	Effect of math score age 5		Main effect of tract		
Main effect	std. β	p-value	std. β	p-value	Δ adj. R^2
FA CC	-0.448	< .001	-0.047	0.642	-0.8%
FA CST-R	-0.459	< .001	-0.134	0.179	0.8%
FA CST-L	-0.438	< .001	**-0.235**	**0.015**	**4.9%**
FA ILF-R	-0.445	< .001	-0.001	0.994	-1.0%
FA ILF-L	-0.454	< .001	-0.103	0.304	0.1%
FA IFOF-R	-0.445	< .001	-0.016	0.881	-1.0%
FA IFOF-L	-0.448	< .001	-0.064	0.538	-0.6%
FA SLF-R	-0.445	< .001	0.095	0.341	-0.1%
FA SLF-L	-0.462	< .001	-0.052	0.609	-0.8%
MD CC	-0.446	< .001	0.036	0.724	-0.9%
MD CST-R	-0.446	< .001	0.015	0.885	-1.0%
MD CST-L	-0.474	< .001	**0.248**	**0.011**	**5.4%**
MD ILF-R	-0.432	< .001	0.110	0.285	0.2%
MD ILF-L	-0.451	< .001	0.113	0.254	0.3%
MD IFO-R	-0.447	< .001	0.060	0.557	-0.7%
MD IFO-L	-0.450	< .001	0.028	0.784	-0.9%
MD SLF-R	-0.453	< .001	-0.115	0.258	0.3%
MD SLF-L	-0.419	< .001	-0.122	0.231	0.5%
	Effect of math score age 5		Interaction effect of tract by term status		
Interaction effect	std. β	p-value	std. β	p-value	Δ adj. R^2
FA CC	-0.446	< .001	0.236	0.917	-1.2%
FA CST-R	-0.460	< .001	**-4.908**	**0.019**	**5.5%**
FA CST-L	-0.438	< .001	-4.134	0.051	3.5%
FA ILF-R	-0.450	< .001	0.320	0.897	-1.2%
FA ILF-L	-0.463	< .001	-3.626	0.092	2.3%
FA IFOF-R	-0.439	< .001	-1.687	0.453	-0.5%
FA IFOF-L	-0.442	< .001	-2.839	0.147	1.3%
FA SLF-R	-0.440	< .001	-1.502	0.543	-0.8%
FA SLF-L	-0.445	< .001	0.047	0.983	-1.2%
MD CC	-0.475	< .001	-1.171	0.698	-1.1%
MD CST-R	-0.437	< .001	6.631	0.267	0.3%
MD CST-L	-0.472	< .001	2.457	0.589	-0.9%
MD ILF-R	-0.432	< .001	-2.633	0.380	-0.3%
MD ILF-L	-0.482	< .001	-2.256	0.511	-0.7%
MD IFO-R	-0.457	< .001	-1.865	0.629	-0.9%
MD IFO-L	-0.451	< .001	-1.692	0.680	-1.0%
MD SLF-R	-0.456	< .001	-1.204	0.724	-1.1%
MD SLF-L	-0.425	< .001	0.130	0.970	-1.2%

Note. Adjusted ΔR^2 of the main effect models is in reference to the base model including age, sex, and maternal education, adjusted ΔR^2 of the interaction effect models is in reference to the main effect model.

CHAPTER 5: GENERAL DISCUSSION

The three studies included in this dissertation demonstrated alterations in cognitive and brain development in children 5 to 7 years of age who were born before 33 weeks of gestation. Lower mathematics skills in the preterm group were mediated by related cognitive functions, particularly phonological processing. Volumes of thalamus, brain stem, cerebellar white matter, cingulum, corticospinal tract, inferior frontal occipital fasciculus, uncinate fasciculus, and temporal superior longitudinal fasciculus were smaller, while the ventricles were larger following preterm birth. Mean tract FA and MD of major white matter fibers were not significantly different in preterm and full-term groups. Nevertheless, associations between mean tract FA of bilateral corticospinal tracts, left inferior longitudinal and left inferior fronto-occipital fasciculus and mathematics skills showed a significant interaction effect with term group.

Connection to Previous and Concurrent Research of the Same Study Cohort

The data used in this dissertation was part of a larger data set acquired with the objective to examine neuropsychological and neuroanatomical impairments of children born before 33 weeks of gestation during early childhood. Study 1 (Chapter 2) specifically builds upon a previous study by Hasler & Akshoomoff (2019). They found that 5-year-old children born preterm scored lower on the TEMA-3, as well as tests of IQ, verbal comprehension, visual-motor integration, movement abilities, phonological processing, and parent-rated executive functions. Verbal comprehension, visual-motor integration, and phonological processing significantly mediated the group differences in mathematics skills (Hasler & Akshoomoff, 2019). Informed by these results, we expanded these analyses to include all three testing points (age 5, 6, and 7) and to examine the potential mediating effect of these cognitive functions on number and arithmetic skills. Additionally, Sawyer et al. (2021) found that children born preterm had lower scores on performance-based and parent-reported tests of executive functions, and tests of self-regulation, motor ability, and academic performance at 5, 6, and 7 years of age.

In addition to differences in cognitive and behavioral measures, our sample of children born preterm showed alterations in cortical morphometry compared to full-term controls (Hasler et al., 2020). The cortex in temporal and parietal regions was significantly thinner, while the cortex of occipital and inferior frontal regions was significantly thicker following preterm birth. Surface area of the fusiform gyrus was smaller in children born preterm but did not differ significantly in other cortical regions. Sulcal depth was shallower in posterior parietal and inferior temporal regions, and deeper in middle temporal and medial parietal regions. Since the development of cortical thickness, surface area, and sulcal depth is not fully understood in typically developing populations, it is unclear whether these differences between preterm and full-term participants reflect a delay or disruption of cortical morphology. The findings of Hasler et al. (2020) and Study 2 (Chapter 3) are consistent with findings in a cohort of children born preterm with very low birth weight in Norway in the 2000's. They, too, found increased cortical thickness in frontal and occipital regions, lower subcortical gray matter volumes, and a lack of differences in white matter microstructure as indexed with DTI parameters (Sølsnes et al., 2015, 2016). Together, this might indicate that medical advances led to more protection of white matter microstructure from the adverse effects of early extrauterine exposure.

Hasler et al. (2019) showed that at age 5, half the children of our preterm sample had a motor impairment ($\leq 15^{th}$ percentile), two thirds of which were boys. Both children born preterm with and without motor impairment had lower volumes of brain stem and cerebellar white matter, while the ventricles were larger compared to children born full-term. Volume and FA of forceps major were lower and MD higher in children born preterm with motor impairment, compared to children born preterm without motor impairments and children born full-term. In addition, FA of ATR, CC, and CGM were lower and MD of CC and IFOF were higher in children born preterm with motor impairment compared to children born full-term.

We have not specifically examined differences in brain structure of children born preterm with motor impairment at age 6 and 7. However, Sawyer et al. (2021) found that children born preterm showed lower motor ability across all three testing times. In Study 2 (Chapter 3) of this dissertation, we found that group differences in gray and white matter volume between children born preterm and children born full-term are similar in strength across the three testing times. Therefore, we can hypothesize that we would find similar differences as Hasler et al. (2019) in children born preterm with motor impairment at age 6 and 7.

Furthermore, alterations in the brain structure-function relationship following preterm birth might be more subtle than differences among groups with and without specific impairments. In Study 3 (Chapter 4) of this dissertation, we demonstrated that despite a lack of group differences in mean tract FA, the associations between mean tract FA and mathematics skills differed between children born preterm and full-term. This moderating effect has been shown across other cohorts of individuals born preterm (Bruckert et al., 2019) and it is possible that similar term group by tract interaction effects are present in the association of brain structure with other cognitive and behavioral variables, such as executive functions.

Taken together, our studies of this data set of children born preterm show that being born before 33 weeks of gestation can lead to a subtle and complex pattern of deficits in cognition and brain structure, as well as brain structure-function relationships even in the absence of severe neurological impairments. Many aspects of this rich data set have yet to be analyzed and enable further characterization of the neuroanatomical and neuropsychological profile of this cohort.

Considerations for the Interpretation of Our Findings

Longitudinal study design

One of the strengths of our study is the longitudinal design with three testing times over two years starting at 5 years of age. Longitudinal studies are time intensive and require a great deal of organization and relationship building with the participants to ensure high retention rates. Including an MRI is rare for longitudinal studies as it is expensive and effortful to perform. Our study therefore sets itself apart from others by providing an opportunity to connect behavioral phenotypes to structural brain differences. Few MRI studies are performed on children as young as five years of age as it requires participants to limit their head movement, which many five-year-old children are not able to do.

The period of time between 5 to 7 years of age is critical in child 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. In the USA, it is the start of schooling where children learn subjects, such as mathematics, through more formal instruction. However, these two years are only a small window into childhood development and continuous follow-up of our participants would provide a more comprehensive picture of the long-term impact of being born preterm.

Neuroimaging

We used diffusion weighted and T_1 weighted MRI in our studies. The concurrent acquisition and analyses of these different types of neuroimaging enables us to examine alterations in brain structure following preterm birth more comprehensively. In this study we were able to use the well-established imaging protocol and data protocol of the PING study (Jernigan et al., 2016). When examining brain volumes, we chose to correct for ICV. This allowed us to examine whether the volume of a certain structure, such as the thalamus, was proportionately different between preterm and full-term groups. We analyzed the diffusion weighted imaging with the diffusion tensor model, focusing on FA and MD as variables of interest. They are used as abstract measures of brain microstructure, as they index the degree and direction of water diffusion within a voxel or larger unit of volume. In study 2 and 3 we examined FA and MD of whole tracts. Thereby the diffusion tensor is averaged across all voxels within the tract. This type of analyses has been widely used and allowed valuable insight into typical and atypical development of brain structure (Feldman et al., 2010). However, some studies found that only parts of the white matter tracts show differences in FA following preterm birth (Dodson et al., 2017; Travis et al., 2015). With our ROI-based analyses we were not able to examine more subtle group differences. The ROI based approach was appropriate in our case since we aimed to examine tracts based on specific hypotheses and since it requires a smaller number of statistical comparisons and therefore increases the statistical power of our analyses.

A drawback of DTI is that within each voxel only one fiber orientation can be represented. This is especially problematic in regions of crossing fibers, where DTI measures cannot accurately reflect tissue microstructure. In contrast, more advanced diffusion models, such as neurite orientation dispersion and density imaging (NODDI; Zhang et al., 2012) and fixel-based analysis (FBA; Raffelt et al., 2017) allow for better characterization of complex fiber configurations by parsing apart the effects of different compartments on diffusion properties within each voxel. In a study with sufficient statistical power, whole brain analyses of these types of compartment models would be able to provide more detailed information on the impact of preterm birth on structural brain development.

Neuropsychological assessment

The cognitive, behavioral, and motor tests used in our study are standardized tests that are commonly used in developmental psychology and/or clinical settings. Many of the tests were designed for children within the age range of our study and thus could be used at all three time points. This enabled direct comparison of performance across the testing times. On the other hand, practice effects cannot be excluded and may account for some of the variance in performance. It is also possible that practice effects may differ between preterm and full-term groups. For mathematics skills specifically, we had the advantage of using two different tasks to assess performance: the Test for Early Mathematics Ability, 3^{rd} Edition and the Applied Problems subtest of the Woodcock-Johnson Test of Achievement, 3^{rd} Edition. Despite methodological differences, both tests showed lower performance in children born preterm at all time points (Adrian et al., 2020; Sawyer et al., 2021).

Representativeness and generalizability

Several factors need to be considered when comparing the results from our study to other studies and caution should be used before generalizing from our findings to the preterm population at large. One of these factors is the inclusion criteria for preterm and control participants. Our study specifically recruited children who were born before 33 weeks of gestation and who did not exhibit any severe neurological disability, such as cystic PVL, IVH grade 3 or 4, cerebral palsy, blindness, or deafness. These criteria were applied to specifically examine a subpopulation of children who were born preterm but are generally considered healthy. Other studies might have broader (anyone born before 37 weeks of gestation) or narrower (only children born extremely preterm, before 28 weeks of gestation) definitions of prematurity, use birth weight as their inclusion criteria for preterm birth, or include children with more complex neonatal courses. Our specific inclusion criteria allowed us to gain unique insight into the long-term impact of preterm birth with a relatively benign medical history. This might be particularly relevant as improvements in medical care over time will likely reduce the overall severity of outcomes linked to prematurity.

These inclusion criteria, however, pose challenges when trying to compare our findings with other studies. One could imagine that there is a causal relationship between the factors associated with preterm birth (infection, stress, environmental) and the severity of the health outcomes. With the data available to us in this study, it is not possible to determine which pre- and perinatal factors might be associated with being born preterm in our cohort. Further differences in methodology, such as neuroimaging methods or neuropsychological assessment, as well as range of ages examined need to be considered as well. Additionally, medical care standards for infants born preterm differ from country to country, birth year to birth year, and even hospital to hospital. It is therefore difficult to draw conclusions from our cohort of children with a high SES and living in a location with access to high care standards to individuals who were born preterm under other care conditions.

Our participants consist of a convenience sample of children in the San Diego area. For each testing time, the participants completed an MRI and underwent neuropsychological assessment on three additional sessions within the span of a few weeks. This requires a significant amount of effort and motivation from the participants and their families. Families of children born preterm, especially those with expectations of impairment, may be more likely to have an intrinsic interest in follow up examination of their children's brain structure and cognitive function (Castro et al., 2004). Families of healthy controls might have had different motivations for the participation in our study, leading to a possible selection bias. Additional selection biases may come from the requirement to avoid movement during the MRI, which might exclude children who lack this ability. Overall, our sample has a higher median household income compared to San Diego County. Ethnicity of our sample is similar to the population of San Diego County, however, non-Hispanic white participants are overrepresented, while Black participants are underrepresented (U.S. Census Bureau, 2019).

Future Directions

Many more interesting questions can be examined with our rich data set of 5- to 7-year-old children born preterm and full-term controls. An obvious next step would be to investigate the relationship between mathematics skills and other measures of brain structure, such as cortical morphology and subcortical volumes. Preliminary analyses show that lower thalamic volume is associated with worse performance in tests of mathematics, reading, and executive functions. Furthermore, it would be interesting to see if we find a similar pattern of association between white matter tracts and reading as we see with mathematics skills.

With the number of preterm and full-term participants in our study cohort we are able to discuss group level differences. However, we lack the power to examine individual differences. A larger data set would allow us to consider an individual's specific influences on potential causes of prematurity, pre- and perinatal interventions, as well as factors that influence their brain, cognitive, and behavioral development. These factors could be of genetic, epigenetic, or environmental nature.

An ideal way to study risk factors related to preterm birth and factors associated with the severity of the outcome following preterm birth would be through a large-scale, consortium-based study led by a team of interdisciplinary researchers. In addition to pediatricians and clinical psychologists, it would be valuable to include cell biologists into the design and execution of the study, to investigate the effect of placental factors, as well as educators to design and test targeted interventions. Even though lower academic achievement following preterm birth has been shown across several cohorts of children born preterm around the world, teachers have little knowledge of the long-lasting effects, particularly on mathematics skills (Johnson et al., 2015). Together, a team of interdisciplinary researchers would have the opportunity to comprehensively study preterm birth and be able to map out which factors are associated with which outcomes.

Current research on the long-term consequences of preterm birth is often deficit-based, with the goal to examine impairments. The general research bias to not publish “null-results” further contributes to the potential bias of over-emphasizing differences between children born preterm and full-term. Furthermore, studies often focus on cognitive functioning and academic achievement, outcome measures that are highly valued in our society. However, these measures are not necessarily the ones that parents are most concerned about and do not represent whether someone lives a meaningful life (Luu & Pearce, 2021). Individuals born extremely preterm (< 28 weeks’ gestation) or with extremely low birth weight (< 1000g) reported similar levels of quality of live and self-esteem as children born with normal birth weight (Roberts et al., 2013). In addition, parental quality of life 27 years after birth was not predicted by whether their children were born very preterm or with very low birth weight or by their children’s academic achievement (Wolke et al., 2017).

Preterm birth will continue to be a global health issue. Future research has a lot of potential to reduce the number of infants being born preterm, informing the quality of pre- and perinatal care, and improving the impact of interventions and follow-up services.

CONCLUSION

This dissertation sought to contribute to our understanding of potential consequences of preterm birth on brain and cognitive development. Children 5 to 7 years of age who were born before 33 weeks of gestation had IQ scores, mathematics skills, and other cognitive skills in the average range, although lower than our full-term participants. We found term group by age interactions in mathematics skills, with preterm participants showing a catch-up in number skills, and an increasing deficit in arithmetic skills. Phonological processing, inhibitory control, and visual-motor integration showed a mediating effect of preterm birth on mathematics skills. Subcortical gray and white matter volumes were lower following preterm birth. White matter tract microstructure as indexed by fractional anisotropy and mean diffusivity was not significantly different between groups, which may be reflective of improvements in medical care. Despite these similarities in diffusivity measures, associations of distinct white matter tracts with mathematics skills differed between children born preterm and full-term. This may be indicative of more subtle and complex neuroplastic processes following preterm birth that could affect the brain structure-function relationship.

The longitudinal design of this study starting at age 5, assessment of a broad variety of cognitive functions, and association with neuroimaging parameters, allowed us to examine developmental trajectories and structure-function relationships during a critical period of early development. It is my hope that these findings can promote opportunities for support of individuals born preterm and their families by informing research and development of targeted early evaluations and interventions.

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