BRAIN STRUCTURAL MATURATION AND COGNITIVE ABILITIES IN EARLY LIFE

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ABSTRACT

Jessica Bullins Girault: Brain Structural Maturation and Cognitive Abilities in Early Life
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The first two years of life mark the most dynamic period of postnatal brain maturation, during which time cortical expansion and myelination reach peak developmental rates. Cortical morphology and white matter (WM) microstructure have been linked to cognition in older adults and children, yet we know remarkably little about how the brain matures to support emergent cognition. This is a critical gap in knowledge, as the first years of life mark a sensitive period in child development when atypical brain and behavioral phenotypes may become apparent. In this report, we examined cortical thickness (CT), surface area (SA), and WM fiber integrity in 450 typically-developing children at birth, age 1, and age 2 in association with assessments of motor, language, and general cognitive abilities at ages 1 and 2. Results revealed that generally thicker, larger cortices and more mature WM tract properties in early life related to better performance on cognitive tasks, suggesting that increased synaptogenesis, elaborations in dendritic arborization, and myelination may confer benefits for infant cognitive development. We found several expected brain-cognition relationships, with CT in regions associated with motor planning and execution and regions associated with language processing and production related to motor and language scores, respectively. Results between cognition and WM integrity were less specific, with tract properties across many fibers spanning the brain relating to cognition across domains. This finding, along with the fact that the majority of significant WM results were of a predictive nature, prompted further study into the organization of WM at birth and

future outcomes. Using a deep learning approach, we successfully predicted 2-year cognitive outcomes using WM connectivity patterns at birth. Taken together, these results suggest that cortical structure and the organization and microstructural integrity of WM pathways at birth serve as a foundation upon which subsequent fine-tuning of brain structure takes place to support emergent cognition in infancy and toddlerhood. These findings offer novel insight into how prenatal and postnatal brain structural maturation support infant and toddler cognitive abilities and fills important gaps in our current understanding of the neurobiology of emergent language, motor, and cognitive abilities in early life.

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PREFACE

Chapter 1 contains introductory and background information relevant to this dissertation. The chapter ends with an outline of the research aims presented in this report. The sections in this chapter on neurodevelopment, MRI, and brain development have been previously published (Bullins J, Jha SC, Knickmeyer RC, Gilmore JH. (2016). Brain Development During the Preschool Period. *The Handbook of Preschool Mental Health* (2nd Edition). Ed. Joan Luby. New York: The Guilford Press.)

Chapter 2 is a research chapter presenting findings from a study of the predictive ability of early cognitive scores for school-age intelligence. This chapter is a published manuscript (Girault, J. B., et al. (2018). The predictive value of developmental assessments at 1 and 2 for intelligence quotients at 6. Intelligence, 68, 58–65.)

Chapter 3 is a research chapter that addresses our first specific aim detailing the associations between cortical structure and cognition.

Chapter 4 is a research chapter addressing our second specific aim describing associations between white matter tract maturation and cognition in early life. This chapter is a manuscript currently under review at *Human Brain Mapping*.

Chapter 5 is a research chapter presenting findings from a study of the predictive ability of white matter connectivity at birth for future cognitive outcomes.

Chapter 6 contains a summary of findings, integration of results, outline of contributions to the field, developmental mechanisms, and potential future directions for research.
All references are presented at the end of this report.

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LIST OF ABBREVIATIONS

AD	Axial Diffusivity
ASD	Autism Spectrum Disorder
CT	Cortical Thickness
CSF	Cerebral Spinal Fluid
DTI	Diffusion Tensor Image
EL	Expressive Language
ELC	Early Learning Composite
FA	Fractional Anisotropy
FM	Fine Motor
fMRI	Functional Magnetic Resonance Imaging
GM	Gross Motor
ICV	Intracranial Volume
IQ	Intelligence Quotient
MRI	Magnetic Resonance Image
MSEL	Mullen Scales of Early Learning
RD	Radial Diffusivity
RL	Receptive Language
ROI	Region of Interest
SA	Surface Area
sMRI	Structural Magnetic Resonance Image
WM	White Matter
VR	Visual Reception

CHAPTER ONE: INTRODUCTION[1]

For more than a century, scientists have studied the neural underpinnings of behavior. In the past few decades, developmental neuroscientists have made remarkable advances in understanding the genetic and cellular mechanisms governing the formation of neural circuitry important for human cognition. We have been able to understand how neurons form, how their identities are decided, how they connect to form functional groups, and how these connections are modified by experience. In the course of these discoveries it has become clear that humans have a unique and prolonged period of neurodevelopment that is largely marked by fine-tuning of circuitry beginning postnatally and extending into early childhood when the foundations of motor, language, and executive functions are established.

In this introductory chapter I will discuss brain development that occurs postnatally and into the preschool period, with a special emphasis on the brain's most rapid period of dynamic growth in the first two years of life. The chapter will begin with an introduction to the mechanisms of brain development and the use of magnetic resonance imaging as a tool for studying the human brain. Following this introduction, I will provide a detailed picture of how the brain develops in early life. Afterwards we will explore the role of brain development in

[1] The sections in this chapter on prenatal and early postnatal brain development, imaging human brain development, and macrostructural human brain development and corresponding figures have been previously published (Bullins J, Jha SC, Knickmeyer RC, Gilmore JH. (2016). Brain Development During the Preschool Period. *The Handbook of Preschool Mental Health* (2nd Edition). Ed. Joan Luby. New York: The Guilford Press.). Text and figures have been reprinted with the permission of Guilford Press, with additional editing by the author.

cognitive development, and review evidence that the first two years of life mark a sensitive period in human brain development that may have important implications for subsequent cognitive and behavioral development. Finally, I will conclude by presenting the rationale and aims for this dissertation project.

PRENATAL AND EARLY POSTNATAL BRAIN DEVELOPMENT

Brain development is governed by both genetic mechanisms and environmental exposures. Timed, spatially defined gene expression determines how the brain wires itself by controlling the birth, differentiation, and migration of neurons and their synaptic connectivity. After their birth, neurons take on a distinct morphology, migrate to a specific location, and make connections with a target cell population. These processes take the brain, which begins with a smooth (lissencephalic) surface, and shape it into a convoluted structure wired together by axonal fiber bundles.

Neurogenesis and Migration

Brain development begins around the 2nd week of gestation with the formation of the neural tube, which divides into three sections that will give rise to the forebrain, midbrain, and hindbrain. A further division of the forebrain vesicle into the telencephalon and diencephalon occurs, from which the cerebral cortex and subcortical structures will arise, respectively (Stern, 2001; Stiles & Jernigan, 2010). Following these divisions are cascades of cellular events that signal the beginning of neurogenesis at the subventricular zone around week five. Neurons then differentiate and migrate to their designated position in the now-forming layers of the cortex (Stiles & Jernigan, 2010). This process takes place in an 'inside-out' manner, with the oldest

born neurons migrating to the outermost layer. Neuronal migration peaks between the 12th -20th weeks of gestation (de Graaf-Peters & Hadders-Algra, 2006).

Synaptogenesis and Pruning

Following migration, neurons extend axons and dendrites to form connections to their synaptic partners. Studies in primates have shown that synapses begin to form shortly after neurogenesis and are continually remodeled thereafter, with peak refinement taking place largely after week 20 and continuing into the perinatal period (Kostović, Judas, Rados, & Hrabac, 2002). Brain systems develop at temporally distinct rates with synaptogenesis reaching its most mature prenatal-state in somatosensory regions earlier than visual ones (Kostović & Rakic, 1990). Dendritic arborization and synaptogenesis accelerate in the third trimester and by gestational week 32, the cortex has adult-like laminar structure (P. Rakic, 1995). In week 34 synaptogenesis peaks, with 40,000 new synapses formed every second – a process that continues into postnatal life (P. Rakic, Bourgeois, & Goldman-Rakic, 1994). To balance with the over-production of synapses, pruning occurs via apoptosis to cull unnecessary or incorrect connections (S. Rakic & Zecevic, 2000). Studies in human cortex find rapid development of synapses, dendritic spines and dendritic tree complexity that peaks in the first few years of life (Huttenlocher & Dabholkar, 1997; Petanjek, Judas, Kostović, & Uylings, 2008; Petanjek et al., 2011).

Myelination

Once neurons are positioned in the cortex and have sent out their local connections via dendritic trees, they extend long-range axons that form fiber bundles connecting different cortical and subcortical regions. These axons will later be wrapped in a lipophilic substance called myelin to form the white matter of brain (Dubois, Dehaene-Lambertz, Kulikova, &

Poupon, 2014; Stiles, Brown, Haist, & Jernigan, 2015). Myelination is a crucial process for the enhancement of neural signaling, as myelin is an electrical insulator that allows for fast information transfer between neurons. Myelination begins during week 28 and follows an inside-out, back to front manner, such that subcortical regions myelinate first (Brody, Kinney, Kloman, & Gilles, 1987). At birth, relatively few axons are sheathed in myelin, and thus the majority of this process occurs in the first years of life. White matter maturation is largely concurrent with experience-dependent plasticity and learning (Dubois et al., 2014).

Brain Development during Early Life

In the early postnatal period glial proliferation, axonal formation, and dendritic arborization result in dramatic increases in brain volume and cortical surface area while synaptic pruning acts to regulate these processes (Gilmore et al., 2007; Knickmeyer et al., 2008; Lyall et al., 2015). Concurrently, but much more slowly, myelination results in an increase of white matter volume and a maturation of microstructural integrity along tracts (Geng et al., 2012; Knickmeyer et al., 2008). The development of gray and white matter via synaptogenesis, pruning, synaptic remodeling, and myelination are fundamental to establishing neural circuits. How these specific processes contribute to shaping brain development in the preschool period will be discussed following a critical introduction to magnetic resonance imaging and its uses for the *in-vivo* study of the human brain.

IMAGING HUMAN BRAIN DEVELOPMENT

Magnetic resonance imaging (MRI) has vastly increased our understanding of the living human brain through its applications for studying cortical and subcortical structures via structural

MRI (sMRI), white matter tractography via diffusion tensor MRI (DTI), and brain functional activation and connectivity via functional MRI (fMRI). MRI has become increasingly popular for studying trajectories of human brain development as it poses no medical threat and provides unparalleled access to the human brain *in-vivo*.

Principles of MRI

MRI is based on the principles of nuclear magnetic resonance (NMR), which relies on atomic nuclei having different physical properties that can be identified analytically. MRI capitalizes on this concept and uses different magnetic frequencies to disrupt nuclei, causing naturally spinning protons to align with the magnetic field. These protons can then be knocked out of alignment by a second, short magnetic pulse; the rate at which they realign to the magnetic field will differ based on the local environment of the proton – or in other words will differ based on the type of tissue in which the proton resides. MRI can distinguish between the brain's two main tissue types – gray matter and white matter (WM) – and cerebral spinal fluid (CSF). The intensity of gray matter, WM, and CSF will be largely dependent on the acquisition parameters of the MRI, and this principle can be helpful in assessing brain structure (see different examples of MRIs across early development in **Figure 1.1**).

Structural MRI

sMRI uses different image types (T1w, T2w; **Figure 1.1**) to delineate gray matter containing cell bodies, glia, and unmyelinated connections from WM containing myelinated (or pre-myelinated) axons (Prastawa, Gilmore, Lin, & Gerig, 2005; Zatorre, Fields, & Johansen-Berg, 2012). Differentiating these two tissue types can give us great insight into how the brain is

structured and is useful for analyzing the cortical surface, the WM skeleton, and subcortical nuclei. The longest-standing image analysis technique for sMRI is the generation of brain volumes, beginning with the calculation of CSF volumes in the late 1980s (Condon et al., 1986). This requires segmenting the brain into tissue types based on their intensity and calculating the amount of each tissue in the entire brain (global volumes), or in a specific region of interest (ROI) within the brain. These volumes reflect the number of 3D pixels (voxels) within the image that match the contrast intensity of each tissue type. Voxels are typically $1mm^3$ - $2mm^3$ and can contain anywhere from several thousand to tens of thousands of neurons (Lenroot & Giedd, 2006). It was found in a post-mortem study that there were ~7,000 neurons/$1mm^3$ in the amygdala and ~40,000 neurons/$1mm^3$ in the cortex of a 3-year-old human brain (Schumann & Nordahl, 2011). This highlights that human neuroimaging, while reflective of underlying neural mechanisms, has limited ability to reveal information at the microscopic level. In addition to volumetric analyses, the field has advanced to examining the cortical surface through 3D reconstructions. This can involve measuring cortical surface area, thickness, and gyrification (Lyall et al., 2015; Wang et al., 2014). sMRI can also be used to study the size and shape morphometry of subcortical nuclei and lateral ventricles (Styner, Gerig, Lieberman, Jones, & Weinberger, 2003).

Diffusion Tensor MRI

DTI is a powerful MRI technique for the visualization and characterization of WM in the brain. DTI capitalizes on the principles of diffusion and the fact that water diffuses differently in gray matter and CSF than in WM. In CSF and among cell bodies in gray matter, water is allowed to diffuse freely in an isotropic manner. However, axons coated in myelin restrict water to

diffuse along a principle direction, creating anisotropic diffusion. DTI can capture measures of both the degree and directionality of diffusion. The degree of diffusion (usually indexed by a measured called fractional anisotropy or FA) describes the microstructure of the WM bundles, for example higher values of FA reflect higher degrees of myelination (Feldman, Yeatman, Lee, Barde, & Gaman-Bean, 2010). Understanding the directionality of the water diffusion is critical for fiber tract reconstruction, which allows us to probe different anatomical and functional pathways in the brain. While powerful, DTI has limitations in its ability to resolve crossing fibers and thus track with the same anatomical precision as tracer studies in postmortem tissue (Qiu, Mori, & Miller, 2015). Interpretations of DTI results may also undermine the importance of water in other biological mechanisms like membrane and protein dynamics (Qiu et al., 2015; C. Thomas et al., 2014).

Functional MRI

fMRI is used to detect changes in the blood oxygen level-dependent (BOLD) signal generated by an increase in deoxygenated blood (which has a different magnetic signal that tissue or arterial blood following neural activation (Gore, 2003). fMRI can be combined with cognitive and behavioral assessments to measure how the brain performs tasks or responds to particular stimuli, typically referred to as task-based fMRI. The brain can also be studied at rest (resting-state fMRI) – meaning that no stimuli are used to evoke responses, but neuronal activity is still present and synchrony can be observed between connected brain regions (Biswal, Yetkin, Haughton, & Hyde, 1995). Coordinated activity reveals large-scale neural networks that can be extracted during resting-state or task-based fMRI and provide insight into how the brain functions (Bullmore & Sporns, 2009). fMRI has limitations, including a lag in temporal

resolution and the inability to distinguish between excitatory or inhibitory activation (Gore, 2003).

Imaging the Brain during Early Development

Neuroimaging studies of infants and young children have inherent challenges and limitations. Subject cooperation and movement in the scanner as well as the need to collect data while sleeping in very young children prove difficult in a practical sense. Image analysis during this period also has unique challenges including low contrast to noise ratio, contrast changes and intensity inhomogeneity due to myelination, small and variable size of anatomical shapes, and rapid changes in morphology over time (Prastawa et al., 2005). Despite these technical limitations, MRI has proved to be an invaluable tool for studying human brain development.

MACROSTRUCTURAL HUMAN BRAIN DEVELOPMENT

Brain maturation during the preschool period is marked by dynamic and expansive anatomical and functional growth. The brain experiences its most rapid period of growth in the first two years of life – doubling in size during the first year and reaching 80% of adult volume by the second year (Knickmeyer et al., 2008). The brain continues to grow and reshape itself at a slower rate from 2 to 6 years, when it has obtained 90% of its adult volume (Lenroot & Giedd, 2006). This growth is the result of many complex mechanisms that contribute to the development of the cortex, subcortical nuclei, and white matter pathways that lay the foundations that will be built upon and remodeled via mechanisms of plasticity and learning throughout the lifespan.

The Developing Cortex

The volume of the cortex nearly doubles in the first year of life, and the majority of this growth is driven by the expansion of gray matter which likely reflects underlying dendritic arborization, axonal elongation and remodeling, and glial proliferation (Gilmore et al., 2007; 2012; Knickmeyer et al., 2008). The second year of life shows more modest growth, with cortical gray matter volume increasing around 18% (**Figure 1.2**; (Gilmore et al., 2012)). The cortex also exhibits regionalized differences in volumetric growth rates, with primary motor and sensory cortices growing slower in the first year of life than association cortices, a pattern that continues into the second year (Gilmore et al., 2012). Studies of cortical thickness (CT) and surface area (SA) have shown that this volumetric increase in gray matter in the first few years of life is primarily driven by SA expansion, which doubles from birth to two years of age (Lyall et al., 2015).

At birth the primary sensory and motor cortices are the thinnest, while thicker regions include the association cortices related to higher-order functioning. These patterns are generally stable throughout the first two years, with thinner regions growing more slowly than thicker regions in the first year (average increase of 30%) and less overall growth taking place in the second year (5% increase) when the cortex has reached 97% of adult thickness values (**Figure 1.3**; (Li, Nie, Wang, Shi, Lyall, et al., 2014b; Lyall et al., 2015)). Studies of children age 5-11 showed thinning across large areas of the cortex and showed a low rate of thickening in Broca's and Wernicke's areas which are important for language development (Sowell et al., 2004). Recent studies of children (4 years and older) and adults show that CT decreases across the lifespan at steady rates (Amlien et al., 2016; Brown & Jernigan, 2012). This highlights that CT

develops fastest in the first years of life and that this period may uniquely exhibit rapid thickening.

SA expansion does not follow the same patterning as CT and also develops at different rates, in line with research showing that these two components of cortical structure are genetically distinct (Chen et al., 2013; Lyall et al., 2015; Panizzon et al., 2009). The expansion of the cortex is regionally heterogeneous, with growth rates from birth to two years ranging from 7-150% and the fastest growing regions being sensory-specific association cortices (**Figure 1.3**; (Lyall et al., 2015)). Rapid growth of visual, auditory, and sensorimotor cortices may be related to the expansion of topographic maps from sensory input and experience. SA exhibits its fastest period of growth in the first two years of life, and by age two has reached 69% of adult values (Lyall et al., 2015), and continues to slowly grow until peaking around age 12 and then declining thereafter (Amlien et al., 2016; Raznahan et al., 2011). This suggests that the first two postnatal years mark a critical period for the regulation of cortical and total brain size – an idea supported by studies of children with autism spectrum disorder who exhibit increased SA before age two (Hazlett et al., 2011).

To allow for the drastic increase in SA relative to the skull, cortical gyrification increases in early development as well. Major cortical folding of gyri and sulci are present at birth, and only tertiary folding structures undergo development after birth (Li et al., 2013). In the first year of life, cortical gyrification increases 16%, followed by 6% in the second year (**Figure 1.3**; (Li, Nie, Wang, Shi, Lyall, et al., 2014b)). Regionalized differences in cortical gyrification are observed, with association areas being the highest, meaning they have the most cortex exposed to the outer surface (Li, Nie, Wang, Shi, Lyall, et al., 2014b). The spatial location of sulci was found to be consistent across this developmental window, and also related to overall brain

volume, once again highlighting that cortical folding is an important mechanism for early brain growth (Meng, Li, Lin, Gilmore, & Shen, 2014).

Growth of Subcortical Nuclei

Subcortical maturation in the first years of life follows the same general growth pattern as the rest of the brain, with the largest increase in volume in the first year and a more modest level of growth thereafter (Gilmore et al., 2012; Raznahan et al., 2014; Utsunomiya, Takano, Okazaki, & Mitsudome, 1999). The majority of subcortical nuclei (amygdala, thalamus, caudate, putamen, pallidum) double in size in the first year, except for the hippocampus, which increases about 85% in volume (**Figure 1.2**; (Gilmore et al., 2012)). Findings from a sample of infants scanned from birth to 3 months of age recapitulate these findings, showing that the hippocampus grows most slowly (47% increase) when compared to other subcortical nuclei (52-66% increase) (D. Holland et al., 2014). Another study of children from 3 to 13 months found that the putamen grows faster than the rate of overall brain growth during this period (Choe et al., 2013). Later studies show that from age 5-25 there is a gradual increase in subcortical volumes, which peak in during puberty (earlier in females than males), up to a few years after the peak in cortical volumes (Raznahan et al., 2014). These data suggest that subcortical nuclei grow rapidly in the first years of life and are later modified as part of the developmental process during adolescence.

Cerebellar Growth

The cerebellum is the fastest brain structure in the first two years of life, growing 240% in volume from birth to 2 years of age (**Figure 1.2**; (Knickmeyer et al., 2008)). In the first 90 days alone the cerebellum doubles in size (D. Holland et al., 2014), and shows accelerated

growth beyond that of total brain growth from 3 to 13 months of age (Choe et al., 2013). Given the important role of the cerebellum in motor function, its dramatic growth may be required to facilitate rapid motor gains in early life.

White Matter Maturation

WM volume grows slightly over 10% in the first year of life and about 20% in the second (**Figure 1.2**; (Knickmeyer et al., 2008)), however, there is much maturational change that is not reflected by volume growth, but instead via changes in diffusion signal due to myelination and organization of axons. Postmortem studies have shown that myelination occurs rapidly from mid-gestation through the first two years of life and follows a strict topographical pattern, with myelination occurring in proximal before distal, sensory before motor, projection before association, and occipital before frontal fiber pathways (Brody et al., 1987).

Myelination increases the most in the first year of life, reflected by fiber tracts exhibiting a 9-44% increase in anisotropic diffusion (indexed by FA), most of which increase more than 25% (**Figure 1.4**; (Geng et al., 2012; Gilmore et al., 2007)). The second year shows a much lower increase in FA ranging from 5-9% (**Figure 1.4**; (Geng et al., 2012)). More direct assessment of myelin content *in-vivo* by studies of myelin water fraction (MWF) show that by 2.5 years myelin content in the brain has reached 80% of adult values (Deoni, Dean, O'Muircheartaigh, Dirks, & Jerskey, 2012). At birth, callosal tracts connecting the hemispheres are less myelinated, but have more organized axonal and fascicular structures than other tracts and also mature the fastest in the first two years. Projection tracts responsible for sensory and motor functions are the most myelinated and mature at birth, and mature at the slowest rate thereafter. Association tracts for higher-level integration (arcuate, uncinate, and inferior

longitudinal fasciculus) are consistently lower in maturational state than other tracts from birth to two years of age (Geng et al., 2012). These results are in line with the early maturation of sensory and motor skills and the later development of higher order processing (Qiu et al., 2015).

Functional Brain Development

The functional development of the human brain during the first two years of life is just as complex and dynamic as its structural development. Studies of resting-state functional connectivity networks in young children reveal that visual and sensorimotor networks are present at birth and mature rapidly in the first two years of life (Lin et al., 2008). In particular, it was shown that connectivity in sensorimotor cortices precedes that in the visual areas and that percent brain volume contributing to the signal increased with age (Lin et al., 2008). This work highlights both the temporal and spatial dynamics of functional brain development in early life, and is in line with the progression of synaptogenesis in the cortex (Kostović & Rakic, 1990).

In addition to changes in cortical activity, the topology or "structure" of brain networks also develops in early life. From birth to two years, changes in topology are shown by a shift from immature, short-range connections at birth to adult-like, long-range connections that are important for efficient information transfer between anatomically distant regions (Di Martino et al., 2014; Gao et al., 2011). This maturation is reflected by an increase in density of longer connections from 25% at birth to 46% in the first year and roughly the same in the second (**Figure 1.4**; (Gao et al., 2011)). Interestingly, there are different hubs (connection centers) in early life than in adulthood. While adults have hubs in higher-order processing regions such as the prefrontal and medial-parietal regions, neonates and infants show hubs in regions more associated with motor and visual skills (Gao et al., 2011). Studies in older children (7-9 years)

reveal that there are still stark contrasts between brain network architecture between children and adults, which is in agreement with the prolonged maturation of higher-order cognitive systems (Fair et al., 2008).

Studies of canonical brain networks in infants and young children reveal interesting patterns of development. The default mode network (DMN)– present during rest and representative of undirected mental states– is comprised of functional synchrony between the posterior cingulate cortex (PCC), medial prefrontal cortex, lateral temporal cortex and inferior parietal lobule and has been related to behavioral performance and emotional measures (Greicius, 2008). At birth the DMN is incomplete and primitive in nature, but then expands in both space and connectivity strength during the first year of life, and by age two it is largely similar to that observed in adults (Gao, Zhu, et al., 2009b). During this age range, we see that the PCC portion of the network is the strongest, and may be the main hub of the network from a developmental standpoint (Gao, Zhu, et al., 2009b).

Dorsal attention networks follow a similar pattern of development, expanding from an immature network at birth to a more adult-like network by two years of age (Gao et al., 2013). This improvement in overall network integration occurs most rapidly in the first year and coincides with the functional specialization of the default and dorsal attention networks. Specifically, in neonates the hub regions between the two networks are largely overlapped, but this spatial overlap is significantly reduced at one year and nearly vanishes by two years (Gao et al., 2013). This suggests that networks at birth interact and house similar functions but become progressively specialized to their specific roles through experience and learning.

BRAIN STRUCTURE, FUNCTION, AND EMERGING COGNITION

It is generally thought that the fundamental prerequisites for cognitive development are established *in-utero* and continue to develop across the first years of life, as sensory and motor systems develop first, followed by systems that support higher-order integration in adults. However, it remains largely unknown how the brain matures to support the emergence of complex cognition in infancy and toddlerhood. A plethora of developmental cognitive science research has revealed that the infant is surprisingly capable of many complex tasks such as recognizing their native language (Mehler et al., 1988), imitating facial gestures and movements (Meltzoff & Moore, 1977), and discriminating numerical information (Izard, Sann, Spelke, & Streri, 2009). Before the age of 2, infants develop social skills (Hamlin, Wynn, & Bloom, 2007), interpret the goals of an actor (Southgate, Johnson, & Csibra, 2008), represent hidden objects (Luo, Baillargeon, Brueckner, & Munakata, 2003), and begin to learn the syntax structure important for language comprehension and production (Marquis & Shi, 2012). However, it is still quite difficult to determine the age of emergence of such cognitive tasks and others in preverbal infants. Infants are limited in language and motor skills that prevent their response to specific cognitive tasks, therefore their lack of response could either indicate that the cognitive function being tested is not present, or the infant lacks the ability to respond in a way that we would canonically recognize in relation to that specific ability (Cusack, Ball, Smyser, & Dehaene-Lambertz, 2016).

Neuroscience offers a lens through which to view the emergence of cognition in infancy by allowing one to probe, non-invasively, neural responses to cognitive tasks without requiring a direct response from the infant (Cusack et al., 2016). By combining such tools with a developmental study design, researchers gain access to the neural architecture that supports, and

is adaptively refined by, human cognitive development. During the last decade, brain imaging of infants has shaken the dogma that frontal brain areas are too immature to be active in infants (Cusack et al., 2016). Functional connectivity research has shown that there is an active frontal component to resting state networks as early as the fetal period (Thomason et al., 2014) that continues to be active through infancy and into toddlerhood (Gao et al., 2011; 2013; 2015a; Gao, Alcauter, Smith, Gilmore, & Lin, 2015b; Gao et al., 2014; Gao, Zhu, et al., 2009b; Lin et al., 2008). Recent work has begun to probe these frontal networks to reveal that there is a specification to frontal activation based on different stimuli. For example, the presentation of sentences, and presumably verbal working memory, engages the inferior frontal gyrus (which houses Broca's area) in preverbal infants (Dehaene-Lambertz et al., 2006), whereas exposure to the native language, and thus speech perception, in infants recruits the dorsolateral prefrontal and inferior parietal cortices, which store phonological information in adults (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). Additionally, distinct responses have been shown to the mother's voice and an unknown female voice in the middle prefrontal and orbitofrontal areas (Dehaene-Lambertz et al., 2010). These findings challenge the classical view that higher-order regions are inconsequently active in young infants, but instead suggests that the frontal cortex is developing to support emerging cognition in infancy (Cusack et al., 2016).

Parallel studies of infant structural brain development also reveal that the brain is constructed *in-utero* to support cognition. The majority of research on infant brain structure and cognition comes from studies of prematurely born infants. This body of research highlights two main points: (1) premature children have less developed brains a birth and often show signs of cognitive delays in early life, and (2) early brain structure can be predictive of later cognitive outcomes (Peterson et al., 2000). More recent work in typically developing children supports the

predictive ability of early brain structure and maturational profiles for general cognitive ability (Deoni et al., 2014; O'Muircheartaigh et al., 2014). Interestingly, differences in the maturational profiles of WM in the first few years of life were seen between children who score above, at, and below average on the Mullen Scales of Early Learning (Deoni et al., 2014; O'Muircheartaigh et al., 2014). Another study showed WM tracts associated with working memory in adults were also related to working memory scores in 1 year olds, even after controlling for general developmental level (Short et al., 2013). Thalamo-cortical connectivity is also related to working memory at both 1 and 2 years of age, indicating an important role for sensory-integration networks in early cognition (Alcauter et al., 2014). It should be noted, however, that the relationships between brain and cognitive measures are typically moderate and may fluctuate with age (Walhovd et al., 2016), suggesting that additional variables which may influence brain and cognitive development, such as socioeconomic status (Noble et al., 2015), deserve further attention in studies of how the brain develops to support cognition.

Cognitive development, like brain development, is an ongoing process that begins at birth and continues across the lifespan. Cognitive development involves the reshaping and fine-tuning of cortical circuits as part of neuro-plastic responses to environmental input and experience. Neuroimaging work suggests that infant learning takes place within cognitive circuitry that is already wired similarly to that of the adult brain, and that the brain at birth provides a biological framework that favors learning (Cusack et al., 2016). Additional work is needed to understand how the brain matures during the dynamic period of early postnatal development to support emergent cognition in normative development. The primary research from this dissertation work presented in the following chapters seeks to address this gap in knowledge and will further delve into associations between brain structure and cognition in infancy and toddlerhood.

THE FIRST TWO YEARS OF LIFE: A SENSITIVE PERIOD IN BRAIN DEVELOPMENT

The first two years of life mark an exceptionally dynamic, rapid period of postnatal development during which the rate of brain structural maturation far surpasses that of other developmental stages. Cognitive neuroscientists and developmental psychologists alike view the first few years of life as a sensitive period of human development, during which time the effects of early life experiences are strong and exact potentially lasting consequences on child development. Such sensitive periods in development are of interest to researchers and clinicians because they represent times in development during which certain capacities are readily shaped by experience (Knudsen, 2004), and thus are both vulnerable to insult and amenable to intervention.

Work from the Bucharest Early Intervention Project has demonstrated that the effects of experience in early life shapes the structure of the brain and subsequent cognitive abilities. This study followed three groups of children in Bucharest, Romania: an institutionalized group who lived virtually their whole lives in an institutional setting, a foster care group which includes children who were institutionalized a birth and then placed in foster homes, and a never-institutionalized group of children living with their biological families in the Bucharest region (Tierney & Nelson, 2009). Results from this study revealed that children raised in institutional settings lack experiences that stimulate healthy growth and thus show patterns of physical and cognitive growth that are stunted and delayed. Brain activity patterns in these children are also significantly different when compared to children that have never been institutionalized (Marshall, Fox, Bucharest Early Intervention Project Core Group, 2004). Importantly, these studies revealed that children who were placed in foster care before the age of 2 showed patterns of brain activity (Marshall, Reeb, Fox, Nelson, & Zeanah, 2008), IQ performance (Nelson et al.,

2007), and language abilities (Windsor, Glaze, Koga, Bucharest Early Intervention Project Core Group, 2007) that were more similar to never-institutionalized children than do those children placed in foster care after turning 2 years old. This body of work suggests that early experience and the early life environment are critical for supporting normative, "healthy" brain and cognitive development.

Additional neuroimaging work suggests that not only does environmental deprivation shape the development of the brain, but that varying levels of access to recourses – as indicated by differences in socioeconomic status – are reflected in brain structural and functional developmental trajectories in the first years of life. A study of volumetric brain growth from birth to age 4 found that, from infancy, children of low-income families had lower volumes of gray matter in frontal and parietal cortices (Hanson et al., 2013). This study also found that overall trajectories of gray matter growth during infancy and childhood differed based on socioeconomic status, such that children from low-income families had slower trajectories of brain development. Interestingly, a graded effect was revealed, such that families from middle socioeconomic standing showed an intermediate trajectory between slow-growing gray matter volumes in low-income and faster developing gray matter volumes in high-income offspring (Hanson et al., 2013). A study of functional resting state networks across infancy and toddlerhood found modest associations between maternal education and household income (as proxy measures of socioeconomic status) at 6 months of age such that higher education and income levels associated with stronger functional brain connectivity in sensorimotor and default-mode networks (Gao et al., 2015a). Taken together, these results suggest that access to resources may play an important role in children's brain development. Such findings are supported by animal model research showing that enriched environments during pup rearing is associated with

changes in brain structure including increases in dendritic branching and length, the number of dendritic spines and the size of synapses on certain neurons, as well as improved learning and memory and anxiety reduction (Nithianantharajah & Hannan, 2006).

The promise for intervention during this sensitive period of brain development is becoming apparent. A randomized controlled trial of a developmental intervention, marked by sensory-motor stimulation, found that early intervention starting within 72 hours of preterm birth (gestational age between 28 and 33 weeks) and continuing until 2 weeks of age (corrected for prematurity), improved neurobehavioral functioning, increased coherence between frontal and occipital brain regions, and resulted in higher anisotropy levels (as a reflection of more mature fibers) in the left internal capsule (Als et al., 2004). This same trial found that the behavioral improvements were apparent at 9-month follow-up as well (Als et al., 2004), though other studies have suggested that brief early interventions may not have consequences beyond toddlerhood (Orton, Spittle, Doyle, Anderson, & Boyd, 2009). In order to aid in the improvement of outcomes for children at risk, it is imperative to establish a clear understanding of how the brain matures to support cognition, and use this information to build evidence-based interventions that consider the brain as a biological framework for cognitive development.

Additionally, it is becoming increasingly apparent that neurodevelopmental disorders, like autism spectrum disorder (ASD), have their origins in very early brain development. Research on children at risk for developing ASD has amounted much evidence in the last decade. Some of the most prominent findings include cerebral enlargement in early childhood (Hazlett et al., 2011; M. D. Shen et al., 2013) and atypical development of functional and structural connectivity (Wolff et al., 2012; 2017). Additional differences include cortical structure, corpus callosum morphology, and extra-axial cerebrospinal fluid volumes (Hazlett et al., 2011; M. D.

Shen et al., 2013; Wolff et al., 2015). These differences in early brain development occur between control groups, children at risk who do not develop ASD, and those who have risk and do develop ASD – providing insight into how risk can either convert to clinical diagnosis or subclinical symptomatology. Differences in these developmental trajectories can be observed as early as 6 months of age using both neuroimaging and cognitive assessments (Wolff et al., 2015), and recent work has found that using machine learning techniques brain images from 6 months of age can be used to predict ASD diagnoses at 24 months, a classification that is largely driven by cortical morphological features (Hazlett et al., 2017). This suggests that alterations in brain development precede cognitive deficits and call for a deeper, clearer understanding of how the brain matures to support complex cognition in early infancy so that interventions can be targeted to promote optimal brain development, and thus improved cognitive and behavioral outcomes.

Studies of infants of mothers with SCZ have also produced insights into the perinatal and early life abnormalities present in these high-risk offspring. Our group presented the first evidence that neonatal brain structure may be abnormal in males at risk for SCZ (Gilmore, Kang, et al., 2010a). This study found that male offspring of mothers with SCZ had larger than normal gray matter, CSF, and lateral ventricle volumes when compared to controls (Gilmore, Kang, et al., 2010a). Interestingly, at-risk female offspring did not differ from healthy subjects. High-risk male offspring also show a more disconnected phenotype, with altered gray matter and WM connectivity at birth (F. Shi et al., 2012). Cortical structure may also be altered in high-risk neonates (Li et al., 2016). Studies of childhood onset SCZ (defined as having a clinical diagnosis before age 13) show subjects with childhood onset SCZ have distinct neurodevelopmental trajectories marked by progressive loss of gray matter, delayed and disrupted WM maturation, and a progressive decline in cerebellar volume from around age 7 into the teenage years

(Rapoport & Gogtay, 2011). There is still a critical need to study how SCZ, and other neurodevelopmental disorders, unfold.

Developmental trajectory research holds the key to understanding when, where, and how alterations in brain maturation occur and contribute to changes in phenotypic outcomes. It is likely that the variety of existing neurodevelopmental disorders are produced by a vast array of deviations from normal trajectories of growth. While some disorders may reflect a delay or acceleration in neurodevelopmental processes, others may show a halting of the process altogether, or worse yet, a complete "derailment" from normality (Shaw, Gogtay, & Rapoport, 2010). Understanding how early, sensitive, periods of brain maturation contribute to typical cognitive abilities will provide invaluable insights into the neurobiological framework that supports adaptive cognitive development. Only when we have a clear picture of how normal variation in brain structure contributes to typical variation in cognitive abilities will we truly be able to identify atypical trajectories and mechanistically study the underlying pathophysiology.

RATIONALE AND DISSERTATION AIMS

Much work has been done to chart the developmental patterns of early postnatal brain maturation. It has been shown that the cortex grows rapidly during this time, with dramatic cortical surface area expansion and dynamic thickening and thinning of the cortex occurring in the first two years of life (Li, Lin, Gilmore, & Shen, 2015; Li, Nie, Wang, Shi, Lyall, et al., 2014b; Lyall et al., 2015). Concurrently, but on a more protracted timeline, white matter fibers become more mature and myelinated (Gao, Lin, et al., 2009a; Geng et al., 2012), with peak myelination rates occurring in the first year of life (Dubois et al., 2014). Both cortical structure (Burgaleta, Johnson, Waber, Colom, & Karama, 2014; Colom et al., 2013; Schnack et al., 2015;

Shaw et al., 2006) and white matter fiber maturation (Penke et al., 2010; Zatorre et al., 2012) have been linked to cognition in older children and adults, but little work has been done to study how these morphological features of the developing brain support emergent cognition in infancy and toddlerhood. Given that the first two years of life constitute a sensitive period of both brain and cognitive development (Tierney & Nelson, 2009), and that the emergence of cognitive deficits and atypical brain phenotypes associated with neurodevelopmental disorders, including autism spectrum disorder, during this developmental period (Hazlett et al., 2011; Wolff et al., 2015), it is of critical importance to establish a clear understanding of the neurobiological framework that supports adaptive cognition.

The work presented in this dissertation aimed to examine the relationships between human brain structural maturation and cognitive abilities in the first two years of life in a typically-developing sample of infants and toddlers. The ultimate goal of this work is to identify the neurobiological framework that supports early cognitive development. Insights from this work will aid in our understanding of what neurodevelopmental processes contribute to adaptive development, how brain-cognition relationships emerge and evolve across infancy and into toddlerhood, and how trajectories of structural brain maturation contribute to differences in cognitive abilities. These goals were achieved by pursuing the aims and supplementary studies outlined below:

Study 1 / Chapter 2: Understand the predictive value of early developmental assessments for later intelligence in our sample.

Much work has been done to understand the continuity and stability of intelligence across the lifespan, and it has been found that school-age intelligence quotients (IQs) are fairly stable predictors of adult ability (Bradway & Thompson, 1962; Deary, Pattie, & Starr, 2013; Deary,

Whiteman, Starr, Whalley, & Fox, 2004; McCall, 1977). However, studies in younger children and infants have been less conclusive – with correlations between infant and toddler scores of general ability explaining anywhere from <1% to 25% of the variance in cognitive scores at school age (Bayley, 1949; McCall, Hogarty, & Hurlburt, 1972). These early studies generally found that the later a test was given during infancy and toddlerhood, the more predictive it was of future school-age ability. Additionally, no study had reported the correlations between the Mullen Scales of Early Learning (Mullen, 1995) – the primary cognitive assessment used in the Early Brain Development Study at UNC and for this dissertation work – and later child IQs.

In this study, we assessed the predictive value of the Mullen Scales of Early Learning (MSEL) Early Learning Composite Score (ELC) at ages 1 and 2 for Stanford Binet abbreviated IQ scores (ABIQ) at age 6 in 512 child participants with at least one infant ELC score and a 6-year ABIQ score. We generated correlations between ELC and ABIQ scores that account for the family structure of our dataset (i.e. twin-pairs and siblings) and used a data-driven variable selection technique to identify which child and demographic factors contributed to the prediction of 6-year scores. As a sensitivity analysis, we also separated our sample based on gestational age a birth and birth complications to test for potential differences in predictive ability based on perinatal complications. We also split the sample into twin and single-born children to test for potential effects of gestational number on the predictive ability of cognition across early life. We hypothesized that scores at age 2 would be better predictors of ABIQ scores at age 6 and the MSEL ELC score would have similar predictive value to other developmental assessments.

Aim 1 / Chapter 3: Determine the relationships between cortical maturation and cognition in the first two years of life.

Mounting evidence indicates the neocortex as a morphological correlate of intelligence and cognitive ability in adolescents and adults. Cortical thickness (CT) and surface area (SA) have been independently (Burgaleta et al., 2014; Colom et al., 2013; Shaw et al., 2006) and recently, jointly (Schnack et al., 2015) linked to cognitive ability in older children and adults. A longitudinal study in children and adolescents showed that the rate of change in CT was more predictive of cognitive ability than any static measurement of thickness (Shaw et al., 2006), suggesting that the dynamic pattern of cortical development and maturation drive individual differences in cognitive ability. Despite the amount of research investigating the neural correlates of cognition in older children and adults, very little work has been done to determine the correlations between cognitive ability and cortical structure in early life when developmental trajectories of CT and SA are rapidly unfolding (Li et al., 2015; Lyall et al., 2015).

In this aim, we sought to determine the association between CT and SA following birth, at age 1, and at age 2 and cognitive measures of general ability, language, motor, and visual reception skills at ages 1 and 2 years in a sample of 487 healthy children. Using this unique longitudinal dataset, we tested cross-sectional relationships between CT and SA and cognition at ages 1 and 2, predictive relationships between CT and SA at birth and age 1 for future cognitive performance, and how changes in CT and SA across the first two years of life relate to cognitive performance at age 2. We hypothesized that CT and SA measures in the first two years of life would be related to present and future cognitive performance, that brain-cognition relationships would be similar to those found in adults, and that trajectories of cortical maturation will be important for cognition at age 2. This study is the first to investigate how CT and SA contribute to cognitive ability in the

early postnatal period in a normative sample and our results identify the first neuroanatomical correlates of cognition during this age range in a large cohort of healthy young children.

Aim 2 / Chapter 4: Identify relationships between WM tract development and cognitive abilities in the first two years of life.

The rapid development of postnatal white matter (WM) development has been well studied in-vivo using diffusion tensor imaging (DTI), a technique that probes the diffusivity of water molecules in the brain. In WM, diffusion anisotropy, commonly measured by fractional anisotropy (FA), is high, while isotropic diffusion, measured by axial and radial diffusivity (AD, RD), is low relative to gray matter and unmyelinated WM (Dubois et al., 2014). In the first two years of life, these metrics change rapidly as fibers are organized into bundles, premyelination is initiated, and myelination occurs; FA increases, while AD and RD decrease (Dubois et al., 2014; Geng et al., 2012). Post-mortem studies have shown that myelination in early life follows an inside-out, front-to-back progression in the brain (Brody et al., 1987), and neuroimaging studies of WM development report similar findings (Deoni et al., 2011; Gao, Lin, et al., 2009a; Geng et al., 2012). While it appears that the sequence of myelination mirrors that of cognitive development, given that myelination occurs in primary sensory tracts before motor tracts and in projection pathways before higher-order association pathways (Guillery, 2005), it remains largely unknown as to how WM matures to support cognition (Walhovd, Tamnes, & Fjell, 2014).

There is significant evidence to support a link between cognition and WM microstructure, as determined with diffusion weighted imaging in adults (Zatorre et al., 2012), including findings correlating the integrity of major WM fiber bundles with information processing speed in healthy older adults (Penke et al., 2010), language learning in young adults (Mamiya, Richards, Coe, Eichler, & Kuhl, 2016), and improvements in working memory through training (Takeuchi et al.,

2010). Recent studies have begun to elucidate the links between early WM development and cognition in healthy infants and toddlers (Deoni et al., 2014; S. J. Lee et al., 2017; O'Muircheartaigh et al., 2013; Short et al., 2013), but there is still a critical need to understand how tract-specific measures of WM contribute to early cognitive abilities.

The goal of this aim is to determine the relationship of tract-based measures of FA, AD, and RD derived from neonatal, 1-year, and 2-year DTIs to cognitive measures of general ability, language, motor, and visual reception skills at ages 1 and 2 years in a sample of 447 healthy children. We hypothesized that tract-based measures of WM integrity would be related to present (cross-sectional) and future (longitudinal) cognitive ability, with more mature properties (higher FA, lower AD and RD) relating to better cognitive performance. We also explored how trajectories of maturation across the first two years of life in these WM tracts predicted cognitive ability at age 2, which to our knowledge, has not been done on a tract-by-tract basis.

Study 3 / Chapter 5: Determine the predictive ability of infant white matter connectivity for subsequent cognitive ability at age 2.

In a complementary approach to that of Aim 2, we decided to probe the relationships between WM structural connectivity and cognition. This approach allows us to take a more circuit-level approach of investigating brain connectivity, rather than considering the maturation of tracts in terms of myelination. At birth, the human brain is a highly connected network of largely unmyelinated axons that will serve as the foundation upon which future fine-tuning of cortical circuitry takes place. By week 30 of gestation, major pathways underlying rich-club organization in the brain are established (Ball et al., 2014), and by birth white matter (WM) networks exhibit a small world architecture (Yap et al., 2011), suggesting that the foundational wiring of brain circuitry is established *in-utero* and is in place by the time of normal birth, a finding which has

been supported by tractography studies (Dubois et al., 2008; Huang et al., 2006). Recent studies have begun to reveal interesting links between individual differences in structural connectomic features in pediatric populations and future cognitive and behavioral performance (Ball et al., 2015; Kawahara et al., 2017; Wee et al., 2016).

In this study, we extend work from the burgeoning new field of developmental connectomics to study how WM connectomes at birth relate to individual differences in cognitive abilities at age 2, across a period of rapid, dynamic brain development (Geng et al., 2012; Gilmore et al., 2012; Knickmeyer et al., 2008; Lyall et al., 2015), in a heterogeneous sample of 115 infant participants followed longitudinally. The goals of this project were to (1) determine the predictive ability of WM connectomes at birth for subsequent cognition, and (2) identify features of the WM connectome at birth that are particularly important for determining individual differences in cognitive abilities in toddlerhood. In order to achieve these goals, we used a deep learning approach to classify infants based on their cognitive performance at age 2 using features from WM connectomes at birth. Specifically, we classified participants as scoring below average (BA), average (AV), or above average (AA) on the Mullen Early Learning Composite (ELC) at age 2 (Mullen, 1995), an assessment of general cognitive ability in infants and young children. To probe the generalizability of the results obtained from this approach, we trained and tested the model in a sample of full term (n = 78) infants and replicated our findings in a sample of preterm (n = 37) infants that were unknown to the classification model. Next, in order to directly predict the ELC score itself, and thus gain an understanding how precisely our method can predict future performance, we fed the strength of the classification accuracy for each infant into a regression prediction model. Finally, we employed a backtrack fingerprinting approach (Hazlett et al., 2017) to extract the features of the WM connectome at birth that were important for classifying

participants based on their cognitive performance at 2 years of age. We expected that WM connectivity at birth would be predictive of future cognitive ability at age 2.

The research presented in this dissertation is the first comprehensive study of brain structural maturation and cognitive abilities in healthy children. We report the first major findings linking brain structure in the first two years of life to present and future abilities, and are the first to predict cognitive outcomes at age 2 with high accuracy using white matter connectivity profiles at birth. Additionally, we report the first study of the predictive value of the Mullen Scales of Early Learning for subsequent cognition. These results fill a critical gap in the literature and provide important insight into brain-cognition relationships across a sensitive period of development. We additionally report the usefulness of structural neuroimaging measures as biomarkers of cognitive abilities during infancy and toddlerhood and discuss our results in the context of important environmental factors like socioeconomic status. Our findings provide foundational information about how the brain matures to support cognition that will be important for the field as we continue to try and understand how individual differences in brain development contribute to both adaptive and maladaptive cognitive and behavioral outcomes.

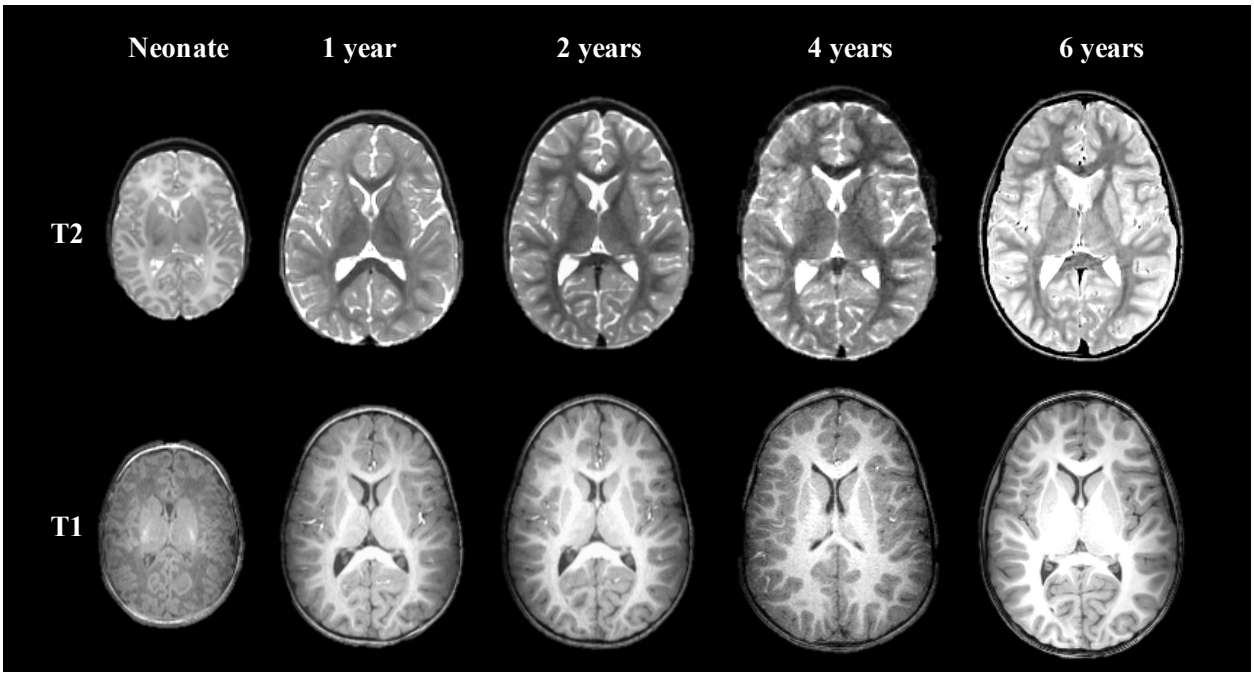


Figure 1.1. Structural MRIs of the brain from birth to 6 years.

T1-weighted (top) and T2-weighted (bottom) images are shown for a single subject taken shortly after birth through age 6 years.

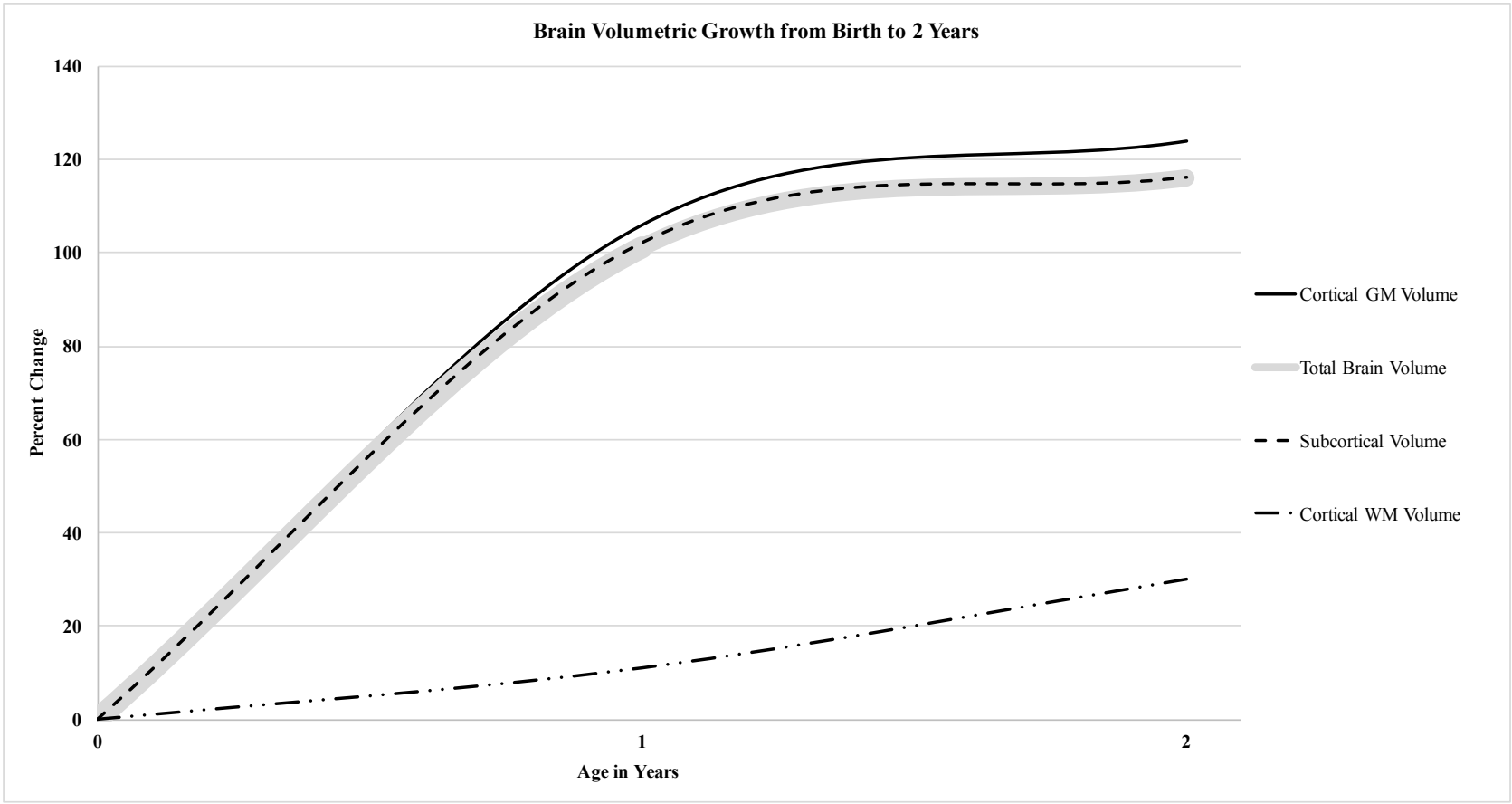


Figure 1.2. Brain volumetric growth from birth to two years.

Brain volumetric growth is shown for cortical gray matter (GM), total brain volume, subcortical volume, and cortical WM volume as a percent change relative to values at birth.

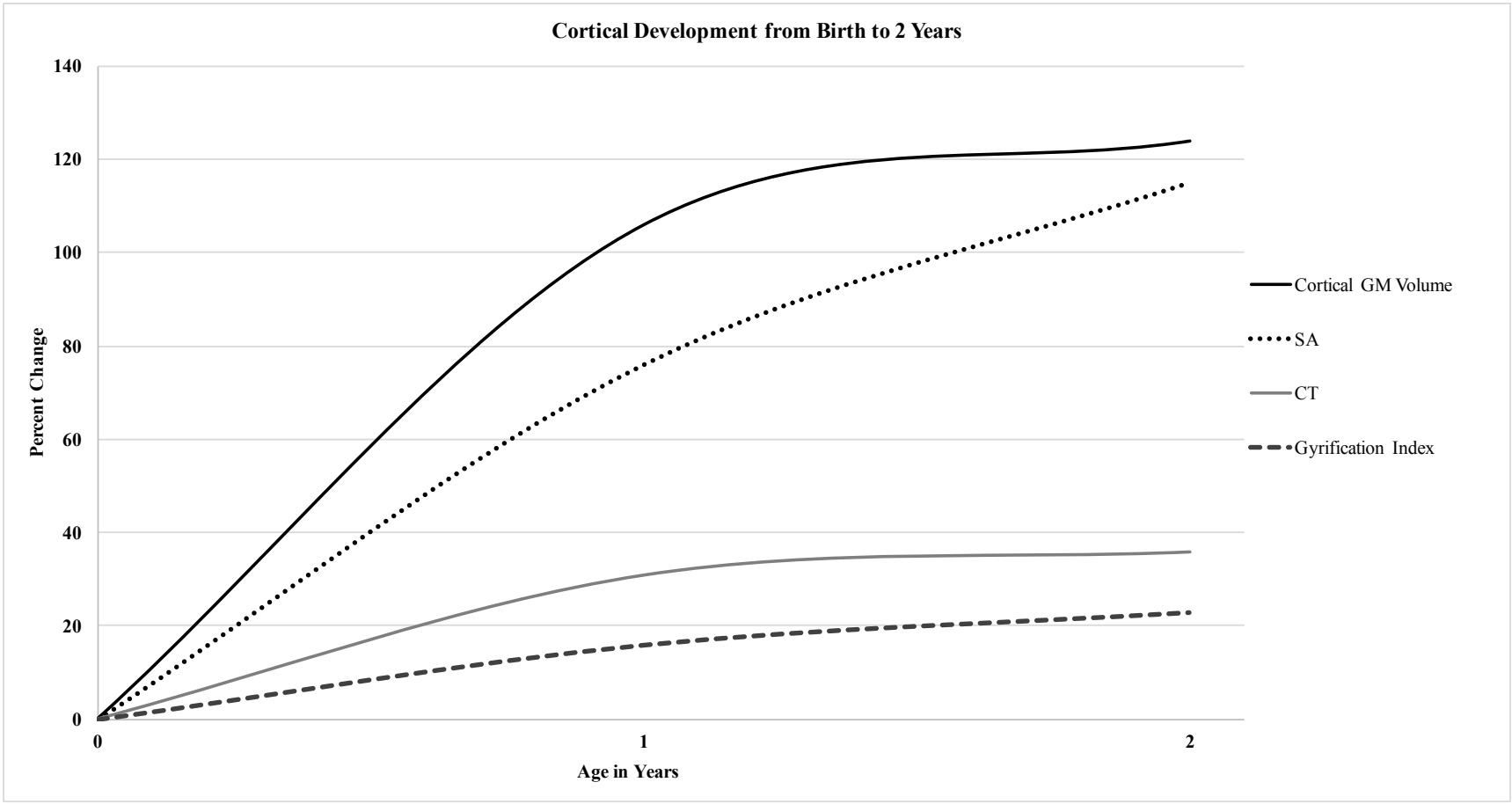


Figure 1.3. Cortical development from birth to 2 years.

Growth rates are shown for cortical gray matter (GM) volume, SA, CT, and gyrification index as a percent change relative to values at birth.

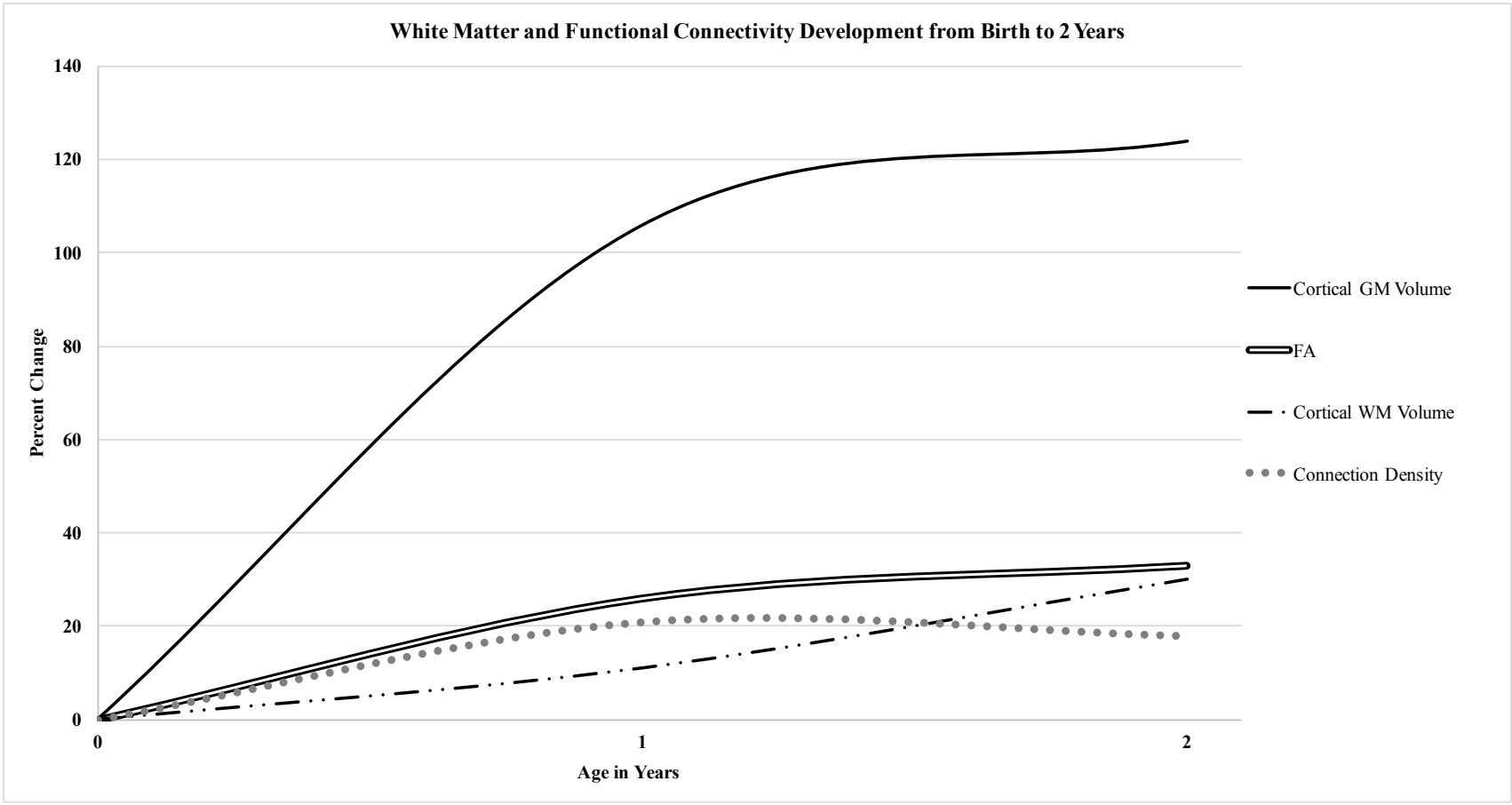


Figure 1.4. White matter and functional connectivity development from birth to 2 years.

Growth rates are shown for cortical gray matter (GM) volume, FA, cortical WM volume, and connection density as a percent change relative to values at birth.

CHAPTER TWO: THE PREDICTIVE VALUE OF DEVELOPMENTAL ASSESSMENTS AT AGE ONE AND TWO YEARS FOR INTELLIGENCE QUOTIENTS AT AGE SIX[2]

INTRODUCTION

Decades of research have revealed that intelligence is related to mental health, academic achievement, occupational status, life success, and longevity (Deary et al., 2013; Gottfredson, 1997; Keyes, Platt, Kaufman, & McLaughlin, 2016; Whalley & Deary, 2001). Twin and family studies find that the continuity of intelligence across the lifespan is driven largely by genetic factors, though environmental influences are notable during childhood (Bartels, Rietveld, Van Baal, & Boomsma, 2002; Bishop et al., 2003; Brant et al., 2013). Intelligence is also a marker of brain development and functioning, including trajectories of structural maturation across the lifespan (Schnack et al., 2015; Shaw et al., 2006) and patterns of functional brain activation (Gray, Chabris, & Braver, 2003) differing based on cognitive ability. Genome-wide association studies show that genes linked to brain development are markers of individual differences in cognitive ability (Davies et al., 2016), and that genetic correlations between intelligence in childhood and old age are high (Deary et al., 2013). This body of research highlights that intelligence is dynamically influenced by biological and environmental processes that contribute to unique developmental trajectories.

Much work has been done to understand the continuity and stability of intelligence across the lifespan, and it has been found that school-age intelligence quotients (IQs) are fairly stable

[2] This chapter has been previously published (Girault JB, et al. (2018). The Predictive Value of Developmental Assessments at 1 and 2 for Intelligence Quotients at 6. *Intelligence, 68*, 58–65).

predictors of adult ability (Bradway & Thompson, 1962; Deary et al., 2004; 2013; McCall, 1977). However, studies in younger children and infants have been less conclusive. In a sample of roughly fifty children, the Berkley Growth Study revealed that infant test scores (averaged between ages 10, 11, and 12 months) modestly correlated with school age scores (averaged between ages 5, 6, and 7 using different assessments; $r = 0.20$), while scores averaged between ages 18, 21, and 24 months correlated highly ($r = 0.50$) with school-age scores (Bayley, 1949). In a 1972 review (McCall et al.), data were combined from four studies (including the Berkley Growth Study) using different cognitive tests; the median correlation reported between 19-30 month test scores and 5-7 year scores ($r = 0.41$) was similar to those observed by Bayley and colleagues (1949), while the correlation between school-age scores and scores from 7-12 month-olds was notably smaller ($r = 0.06$). In general, it was found that the later a test is given during infancy and toddlerhood, the better its predictive ability for subsequent outcomes (McCall et al., 1972).

Recent studies of the predictive value of such assessments focus almost exclusively on at-risk populations such as premature and very-low-birth-weight cohorts (Bode, D'Eugenio, Mettelman, & Gross, 2014; Hack et al., 2005; Leversen et al., 2012; Potharst et al., 2012; Soysal et al., 2014). Results from these studies provide conflicting evidence about the predictability of early tests for subsequent performance, which may be due to the unique characteristics of these at-risk populations, where some children overcome early deficits while others remain on a delayed trajectory. For example, infant scores from very premature children (Bode et al., 2014), those with neurological impairments (Hack et al., 2005) or perinatal complications (Potharst et al., 2012) were more highly correlated with their subsequent school-age performance, whereas infant scores showed limited predictive value for premature children without major impairments (Leversen et al., 2012).

Other recently published work reporting correlations between infant and school-age cognitive scores include large-scale twin and family studies. In a sample of over 1,000 twins and biological and adopted siblings, Bishop and colleagues (2003) found that infant scores at ages 1 and 2 correlated with principle components derived from cognitive tests at age 7 ($r = 0.18$ and 0.37, respectively; related participants included in correlations). Another study of 14,000 twins in the UK found that parent reports of 2-year-olds' cognitive ability was correlated with phone-administered portions of cognitive tests at age 7 ($r = 0.23$) (Stumm, Gale, Batty, & Deary, 2009). It is important to note that determining the predictive ability of infant cognition for subsequent intelligence scores was not the primary purpose of either of those studies.

The generalizability of much of the previous work is limited by small sample sizes (Bayley, 1949; Fagan, Holland, & Wheeler, 2007; McCall, Eichorn, Hogarty, Uzgiris, & Schaefer, 1977), focus on special populations (Bode et al., 2014; Hack et al., 2005; Leversen et al., 2012; Potharst et al., 2012; Soysal et al., 2014), or lack of participant diversity (Bishop et al., 2003; Ronalds, De Stavola, & Leon, 2005). Results from twin-only studies, while large-scale, may also be difficult to generalize to other populations given that twins have lower IQs in childhood (Bishop et al., 2003; Ronalds et al., 2005), and potentially different cognitive developmental trajectories than single-born children. Therefore, it remains unknown how well the correlations between infant and school-age intelligence reported in the literature generalize across more diverse samples.

The goal of the present study is to investigate the predictive value of cognitive assessments at 1 and 2 years of age for subsequent IQ at age 6 in a relatively large, heterogeneous, longitudinal sample of single- and twin-born children. This study is novel in several respects. First, it is one of the largest studies of the predictive ability of infant cognitive scores for school-age intelligence to date, with 521 subjects in the sample. Second, results are derived from a sample that is generally

representative of the U.S. population (U S Census, 2016b), whereas many previous studies were conducted in predominantly Caucasian-only samples, or those with less than 10% of participants from other racial or ethnic groups. Finally, to our knowledge, this is the first study to test the predictive ability of the Early Learning Composite (ELC) from the Mullen Scales of Early Learning (MSEL; (Mullen, 1995) for school-age intelligence scores in a healthy sample, despite its use in several longitudinal studies of development in the context of brain-behavior relations and its widespread use in autism spectrum disorders research (Deoni et al., 2014; Gilmore et al., 2007; S. J. Lee et al., 2017; Wolff et al., 2012). We expected ELC scores to show similar correlations with school-age intelligence scores as those reported using other infant tests, with scores at age 2 being a stronger predictor of IQ at age 6 than measures at age 1. In order to test the robustness of our findings and compare our results with those previously published, we also ran sensitivity analyses subdividing the sample into subsets with and without birth complications (prematurity and/or perinatal complications), and split by gestation number into twins and singletons. We expected that our results would be similar between the full sample and the subset without birth complications, but hypothesized that the premature subset may show a different trend based on previously reported inconsistencies in the literature with this at-risk group. We also expected similar predictive patterns between early cognition and later IQ in twins and singletons given the similarity in effect sizes reported across samples in the literature. Finally, we explored the effects of demographic factors on infant and school-age cognitive scores, expecting that variables related to socioeconomic status (SES) and perinatal characteristics would be both predictive of and related to individual differences in ability.

MATERIALS AND METHODS

Participants

Participants were part of the UNC Early Brain Development Study of early childhood brain development in singletons and twins (Gilmore et al., 2007). Pregnant women were recruited during the second trimester of pregnancy at the Prenatal Diagnostic Clinics of the University of North Carolina Hospital and Duke University Medical Center by flyers and study staff. Mothers were excluded from the current study for pregnancy complications (major illness, using illegal drugs, or severe infection), or a diagnosis of a major psychiatric disorder. All offspring participants, born between 2003 and 2014, underwent cognitive testing at ages 1, 2, and 6 years. We retrospectively identified 521 children with at least cognitive test scores from at least two ages, no major medical issues, and no psychiatric diagnoses up to age 6. We chose to exclude subjects on the basis of maternal and child psychiatric diagnoses as we have a substantial enrichment of this population in our total subject pool due to recruiting mothers with psychiatric illness as part of other lines of research in the lab. Our sample is generally representative of the local area (U S Census, 2016a) and the U.S. population (U S Census, 2016b) in terms of race and ethnicity, though our sample over-represents African Americans in both regards (12.9% of local population, 13.3% of national population, 21.3% of our sample), and under-represents Asians (5.7% of national population, 1.5% of our sample) and American Indians (1.3% of national population, 0.4% of our sample), compared to current national statistics. Hispanics are underrepresented in these data (8.4% of national population, 4.8% of our sample) because some children could not undergo cognitive testing in English. **Table 2.1** outlines the demographic characteristics of the entire sample. Informed written consent and parental permission were obtained for all participants and all study protocols were approved by the Institutional Review Boards of UNC and Duke.

In sensitivity analyses testing the robustness of our results, we subdivided the sample into subsets with and without birth complications and split by gestation number into twins and singletons. Those with birth complications (n = 116, 22% of entire sample) included all subjects born at <32 weeks gestation and spending >24 hours in the neonatal intensive care unit (NICU). Twin versus singleton analyses were only conducted on subjects without birth complications (n = 405, 78% of entire sample) to avoid an over-representation of very premature subjects in the twin sample. We compared a sample of 175 twins to 230 singletons. For details on demographics for the subsets, see **Table S2.1** and **Table S2.2**.

Cognitive Assessments

Cognitive ability was assessed in the Infant and Child Assessment lab at the Frank Porter Graham Child Development Institute at UNC-Chapel Hill. Experienced testers were trained and supervised by a developmental psychologist with extensive assessment experience. At ages 1 and 2 years, we used the Mullen Scales of Early Learning (MSEL). At age 1, infants were assessed while being held in the lap of a parent, guardian, relative, or, rarely, study staff in the case of twins if only one parent or relative accompanied the family. At age 2, children were seated on their own during testing, with a parent, guardian, or relative present in the room. Performance on the four MSEL cognitive Scales (Visual Reception, Fine Motor, Expressive and Receptive Language) are conventionally combined into an Early Learning Composite (ELC) standard score (range: 49-155, M =100, SD =15). The ELC has high internal consistency (median = 0.91) and reliability (median = 0.84 for the cognitive scales during these testing ages), and principal factor loadings of the scales lend support for the construct validity of the ELC as a general measure of cognitive ability (Mullen, 1995).

The MSEL was used in this prospective study of brain development specifically because of its potential to capture uneven development in different cognitive abilities (Akshoomoff, 2006; De Giacomo & Fombonne, 1998; Filipek et al., 1999). Compared to the commonly used second edition of the Bayley Scales of Infant Development (Bayley II; (Bayley, 1993)), which was the version available at the start of this longitudinal study, the MSEL has the advantage of providing standardized T-scores that factor in age at testing for each of the scales, as well as age equivalent independent measures of gross and fine motor, visual reception, and expressive and receptive language scores. In contrast, the Bayley II generated a Mental Developmental Index (MDI) which assessed cognition through evaluating sensory perception, knowledge, memory, problem solving, and early language that could not be decomposed to probe specific cognitive versus language deficits (Lowe, Erickson, Schrader, & Duncan, 2012). Due to the fact that, as part of the larger study of brain development, we were collecting data on a heterogeneous population including infants born to mothers with diagnosed psychiatric illness, we wanted to ensure the ability to test specific deficits in distinct developmental domains (i.e. language vs. motor). Importantly, however, the ELC standard score derived from the fine motor, visual reception, expressive, and receptive language scales is highly correlated with the Bayley MDI ($r = 0.70$, $n = 103$ between 6 and 15 months of age), according to a study presented in the MSEL technical manual (Mullen, 1995).

Intelligence at age 6 was assessed in the same Infant and Child Assessment lab by experienced testers, supervised by the same developmental psychologist, using the 5th Edition of the Stanford-Binet Intelligence Scales (SB5; (Roid, 2003)). At age 6, children were typically tested alone while a parent was present directly outside the room on the other side of one-way glass, but parents were given the option to sit in the room as the SB5 was administered. The outcome used

in this analysis is the abbreviated IQ (ABIQ) measure (range: 50-150, M =100, SD =15) derived from scores on the verbal knowledge and non-verbal fluid reasoning tasks reflecting the child's lexical knowledge and ability to solve problems. These two tests serve as the "routing" tests, which are used to determine the entry level for subsequent tests of verbal and non-verbal abilities. The ABIQ has an internal consistency of 0.91 and a test-retest reliability of 0.84, and correlates highly with the full-scale IQ, which can only be derived from significantly longer testing sessions (Roid, 2003).

A total of 509 1-year ELC scores (ELC1), 499 2-year ELC scores (ELC2), and 275 6-year ABIQ scores (ABIQ6) were used in this study. All included participants had at least two test scores, 487 had both ELC scores, 263 had ELC1 and ABIQ6, 253 had ELC2 and ABIQ6, and 241 had all three cognitive assessment scores. Our participants, on average, performed slightly better on the MSEL and SB5 than the normalization samples (**Table 2.1**).

Statistical Analysis

The relation between ELC scores and ABIQ6 was estimated using Generalized Estimating Equations (GEE) treating each family (twins and siblings) as a cluster, accounting for possible correlations in observational data from twins and siblings. GEE estimates allow for consistent estimates of the relationship between ELC and ABIQ6 even if there is correlation within families (twins and siblings). Unlike other methods that can account for such correlation, like mixed effects models, GEE estimates are consistent even if the underlying correlation structure between families is unknown or misspecified. Using methods similar to Yan and Fine (2004) which allow for modelling the effects of covariates on the correlation parameters, we were able to estimate correlations between infant cognitive scores for the same participant over time and for scores

between twins and siblings. These analyses permitted covariates in the model for predicting ABIQ6 scores, with the best fitting model selected using quasi-Akaike's Information Criterion (QIC) (Pan, 2004). Potential variables included sex, gestation number (twin or singleton), gestational age at birth (days), maternal and paternal education (years), chronological age at the time of the assessment administration (days), and the number of months since start of assessment collection in the study (to account for possible drift in cognitive testing administration due to changes in personnel over the 10-year study period), as well as the interaction between all the variables and cognitive scores. Initially models were run including only ELC scores as explanatory variables. QIC was used to determine whether the model with only ELC1, only ELC2, or both was best. Next, in addition to the ELC scores, covariates mentioned above were added to the model. The final model selected through QIC to predict ABIQ6 included ELC2, sex, age at SB5 testing, paternal education, gestation number, and months since start of SB testing. Additionally, models were run using the same approach to estimate the relation between ELC1 and ELC2 scores and demographic variables. We also used the GEE model to calculate correlations between ELC1, ELC2, and ABIQ6 scores so that we can estimate the variance in later ABIQ explained by early cognitive performance, allowing for comparison to previously published works.

Some of our infants were lost to follow up or were not old enough to have taken the SB5 at the time of data analysis. Of those old enough to have taken the SB5 at age 6, 32% of subjects did not take the test. We investigated the missingness using a binomial GEE in which the outcome variable was a binary indicator variable for whether or not the child had an ABIQ6 score. Potential explanatory variables were ELC1, ELC2, calendar year and month for taking the ELC1 test, maternal and paternal education, gestation number and gestational age at birth. An independent working correlation matrix was used with each family treated as a cluster. The final model was

chosen using QIC and is reported in **Table 2.2**. We found that increased paternal education resulted in reduced likelihood of follow-up 6-year SB5 assessments, possibly related to changing paternal employment locations (and thus a family relocation) in the 4 to 5 years following the earlier assessments. Given the recruitment area and proximity to the University, it is possible that fathers may have completed graduate degrees, internships, or residencies at the University and relocated afterwards. The data showed trending significance for taking the MSEL at age 1 later in the study increasing the odds of a follow up, while conversely suggesting that higher ELC1 scores resulted in a decreased likelihood of 6-year follow-up. Since participants were not lost to follow up at random, a linear mixed model was employed as a sensitivity check because they are valid under a weaker missing at random assumption and provide a check the GEE findings. Results were highly similar between the two models and only the GEE is reported here (see **Table S2.3**) for linear mixed model results).

RESULTS

Prediction of 6-year ABIQ

Models using only ELC scores as predictors of ABIQ6 scores revealed that a one-point increase in ELC1 and ELC2 predicts an increase in ABIQ6 of 0.16 points (SE = 0.06, p = 0.01), and 0.41 points (SE = 0.06, p = <0.001), respectively (**Table 2.3**). Uncorrected scatterplots of these data can be seen in **Figure 2.1(B-C)**. When both ELC scores were in the model together, ELC1 was not predictive of ABIQ6, while a one-unit increase in ELC2 increased the expected ABIQ6 by 0.40 points (SE = 0.06, p = <0.001). This demonstrates that after controlling for ELC2, the additional knowledge of ELC1 does not significantly contribute to the prediction of ABIQ6. Correlations calculated between ELC1, ELC2 and ABIQ6 based on the GEE model reveal that

ELC1 scores account for 2.8% of the variance in ABIQ6 (r = 0.169, SE = 0.066), while ELC2 scores account for 21.3% of the variance in ABIQ6 (r = 0.461, SE = 0.061). It should be noted that the GEE *estimates* are model coefficients and should be interpreted such that unit-wise increases in each predictor variable result in a unit-wise change in the response variable, while GEE *correlations* are measures of the strength of a linear association between predictor and response variables that can be interpreted similarly to Pearson's correlations. The similarity in magnitude between the GEE estimates and correlations is coincidental, as they compare different associations between scores.

Results from the full model (**Table 2.4**) estimated a one-point increase in ELC2 predicted an increase in ABIQ6 of 0.28 (SE = 0.06, p = <0.001), when holding all other covariates constant. A one-day increase in age at 6-year testing led to an increase in expected ABIQ6 of 0.04 points (SE = 0.02, p = <0.001). Date of the 6-year assessment was not significantly related to ABIQ6 (SE = 0.04, p = 0.06). Every additional year of paternal education accounted for an increase of 1.18 points in offspring ABIQ6 (SE = 0.25, p = <0.001). In a separate model, we replaced paternal with maternal education, and results were highly similar (**Table S2.4**) This was expected given the strong correlations between maternal and paternal education (r =0.67), and their correlations with household income (r = 0.49 and r = 0.42, respectively) in our sample. There was a trend for males to score 2.77 points lower than females at age 6, though it did not reach statistical significance (SE = 0.02, p = 0.08). The strongest predictor of ABIQ6 was gestation number; when controlling for all other covariates, twins scored 6.11 points lower than singletons (SE = 1.61, p = <0.001). Gestational age at birth was not selected in the model.

In a set of sensitivity analyses, we tested the robustness of the predictive value of ELC scores for ABIQ6. We found that results from the full sample were in line with those found in a

subset of participants without birth complications (n = 405; ≥32 weeks gestation, ≤ 24 hours in the neonatal intensive care unit (NICU)), though they did not replicate in a subset of children born very prematurely or with birth complications (n = 116; <32 weeks gestation, >24hrs in NICU). When comparing the predictive ability of infant cognitive scores for ABIQ6 between twins (n = 157) and singletons (n = 230), we found that predictions were stronger among twins, particularly from age 1 to age 6. See **Table 2.5** for a summary of results across samples.

Infant Cognitive Scores

We estimated correlations between ELC1 and ELC2 scores to be 0.30 (SE = 0.05, p = <0.001) and found that correlations between scores of twins (r = 0.70, SE = 0.06, p = <0.001) and siblings (r = 0.41, SE = 0.22, p = 0.06) taken at the same age were higher than those for the same child over time (results verified with Pearson correlations; **Table 2.6**). Scatterplots showing unadjusted associations between ELC1 and ELC2 are shown in **Figure 2.1(A)**. The model investigating the relation between infant scores and other demographic variables (**Table 2.7**) revealed that at age 1, twins did not score significantly lower than singletons (p = 0.39), but by age 2, twins scored 11.47 points lower than single-born children, when all other variables in the model are held constant (se = 2.46, p = 1.60E04). Every additional year of paternal education predicted an increase of 1.61 points in ELC2 (se = 0.25, p = 1.20E-04), but a decrease of 0.53 points in ELC1 (se=0.19, p=7.01E-03). Holding all other variables constant, each additional day of age led to a decrease in expected ELC1 of 0.16 points (se=0.5, p=1.02E-03), and a 0.14-point increase in ELC2 (se= 0.06, p=0.02). Finally, each additional month after the start of data collection led to an expected increase in ELC1 scores of 0.15 points (se=0.02, p= 6.50E-12), but did not significantly impact ELC2 scores (p=0.12), holding all other variables constant.

DISCUSSION

In the present study, we show that scores on cognitive assessments at age 2 are significant predictors of intelligence scores at age 6 in a large, heterogeneous sample. As expected, scores at age 1 were far less predictive. These associations are of similar magnitude to those published in the literature on typically developing samples and twins using other infant developmental assessments (Bayley, 1949; Bishop et al., 2003; McCall, 1977), where correlations between scores taken around age 2 and age 6 ranged from 0.37 to 0.50 compared to our finding of a correlation of 0.46. This suggests that the MSEL has similar predictive power to other infant tests. Importantly, we also show that the relation between infant and school-age ability vary based on individual difference factors including prematurity, birth complications resulting in extended NICU stay, and gestation number. Together, these results extend our understanding of the predictive value of infant cognitive tests for later intelligence by informing us of the extent to which such predictions have the ability to generalize to more diverse populations.

The low predictive ability of cognitive tests at age 1, which accounted for less than 3% of the variance in 6-year cognitive performance, may be related to the large dependence of many tests, including the MSEL, on language comprehension, which is limited at this age, and items that involve maternal report. Mothers differ: some are able to readily provide a list of words their children know and understand, while others are less prepared to present such a list, but may provide additional information over the course of the assessment. Infants and toddlers also differ dramatically in their comfort with the testing environment. Some infants are comfortable from beginning of the testing session, in a new place, with new people, to use the words that they know, or to respond by copying what the tester had demonstrated, while others take significantly more time to acclimate to the testing environment.

In addition, the absence of strong prediction may also be related to the generally inevitable lack of methodological continuity in the testing of various constructs across early childhood, given the dramatic changes in skill levels in multiple domains between infants and 5- to 7-year-old children, and the differences in the test items given at these very different ages. As skills and test items become more similar, one would expect increasing concordance; this is certainly a developmental issue, as the repertoire that is available to the infant changes dramatically over this overall time frame. This may be partly reflected in our finding that correlations between infant scores from family members taken at the same age are stronger than the correlations between scores for the same child at ages 1 and 2.

Finally, some developmentalists, such as Piaget, would argue that a discontinuous shift in cognitive processing occurs between the first and second year of life such that younger infants are limited to more sensorimotor based forms of cognition that later shift to representational thinking by age 2 which is more consistent with cognition in adults (Müller, Carpendale, & Smith, 2011). This could account for the lack of correlation seen between the scores at ages 1 and 6, though more recent work would suggest that cognitive development is more continuous than previously thought, such that even very young infants possess at least a very rudimentary conceptual system (Mandler, 2007; Moore & Meltzoff, 2004). Elements of such a rudimentary conceptual system may be demonstrated in clever research designs, but may not be present in many of the items in traditional assessments.

It is important to highlight that even though scores at age 2 are better predictors than those obtained at age 1, every ELC2 point only accounted for a predicted increase of 0.41 points in ABIQ6 scores, accounting for roughly 21% of the variance in 6-year scores, leaving a large portion of variability unexplained. This is in line with previous research concluding that early cognitive

scores should not be used alone to identify infants at-risk for future poor performance (Colombo, 1993). Also of note, we observed an increase in cognitive scores from the beginning of the study to the end of assessment collection for ELC1, but not ELC2 or ABIQ6. This may be related to changes in personnel, an increase in their experience and training, or changes in the larger community environment or subject population over time. Because we noticed this trend, we controlled for months since the start of data collection, which is approximately a decade long; however, this might be considered as a limitation of our study.

In our sample, we observed that twins score more than 6 points lower on the ABIQ6 than singletons. These findings are consistent with previous reports (Ronalds et al., 2005), but often go undiscussed in heritability studies of cognition (Bishop et al., 2003; Stumm & Plomin, 2015). Importantly, we found that the predictive ability of scores at ages 1 and 2 for subsequent school-age IQ were notably higher for twins compared to singletons, with the ELC1 being nearly three times as predictive in twins. This may be due to differences in demographic characteristics between families of twins and singletons in our sample, however Ronalds and colleagues (2005) found that twins have lower IQ scores at ages 7 and 9 than singleton children in the same family. The lower intelligence scores of twins may reflect reduced fetal growth and shorter gestation, though we excluded participants that were born very prematurely and spent more than a day in the NICU in our sensitivity analyses. Additionally, none of our models selected gestational age at birth as a significant factor predicting infant or school-age cognitive scores. However, it is important to note that MSEL scores were adjusted for gestational age at birth, and thus hinder our ability to understand the impact of gestational age on scores at ages 1 and 2. The notable increase in predictive ability of infant scores for 6-year IQ scores in twins remains puzzling, but could

potentially be related to twin-twin interactions or twin-specific parenting styles (Rutter & Redshaw, 1991) that could shape the child's learning environment across development.

Another important factor contributing to cognitive scores was parental education, which may be a proxy of SES effects, as paternal and maternal education in this sample are highly correlated with each other and with household income. SES has been found to be significantly associated with the development of intelligence in a large twin study, with those from low SES families scoring approximately 6 points lower on IQ tests at age 2 than those from high SES backgrounds – an effect that nearly tripled by age 16 (Stumm & Plomin, 2015). The effects of parental education were smaller in our sample, with every additional year of either maternal or paternal education contributing to an increase of roughly 1 point in children's 6-year scores.

Our sample contained a subset of participants born prematurely or with birth complications resulting in a stay in the NICU. When we included this at-risk group in our main analysis, it did not change the findings. However, when analyzed alone, we observed particularly low, non-significant correlations between infant cognitive scores and school-age IQ. This sample only included participants without any major medical issues or psychiatric disorders up to age 6, and thus we may have analyzed a potentially "resilient" group. These findings echo those showing that premature children without neurological abnormalities have the lowest predictions from infancy to later outcomes (Hack et al., 2005), presumably because there is more variability in outcomes. Alternatively, the predictive value of infant tests in at-risk groups may be inherently lower because other factors, such as access to resources and postnatal care, are more important or deterministic than early test scores in predicting later outcomes.

Our study revealed important information about the predictive ability of infant cognitive scores for school-age IQ; namely that by age 2, infant cognitive ability is a fairly strong predictor

of outcomes 4 years later, across a period marked by tremendous cognitive gains (Kagan, Herschkowitz, & Herschkowitz, 2005). These results would suggest that the foundations of later intelligence are largely in place by age 2, which is in line with work illustrating the heightened plasticity of the first two postnatal years for both cognitive and brain development (Gilmore et al., 2012; Lyall et al., 2015; Nelson et al., 2007). Importantly, this work is also in agreement with the large body of research highlighting the long-lasting impact of early life experience on subsequent development (Lupien, McEwen, Gunnar, & Heim, 2009; Sonuga-Barke et al., 2017). Taken together, these results emphasize that this period of early childhood, particularly before age 2, is one that deserves additional study from developmental science and intervention-based perspectives. Interestingly, individual difference factors relating to cognition in this study, namely paternal education, have also been linked to infant brain structure (Knickmeyer et al., 2016), highlighting the need for future studies of the potential mechanisms by which brain-cognition relations emerge across ontogeny and may be influenced by sociodemographic factors. Finally, studies that focus on identifying measures of cognitive continuity across early development will be key to understanding how infant abilities may form the basis of later intelligence.

Table 2.1: Sample Characteristics

	Mean (Std Dev)/Percent
Sex (% Male)	50.10
Gestation (% Twins)	52.4
Gestational Age at Birth (Days)	260.58 (20.47)
Duration in NICU* (Days)	4.48 (12.86)
Days Since Birth ELC1	393.36 (26.86)
Days Since Birth ELC2	759.48 (30.25)
Days Since Birth ABIQ6	2230.84 (62.72)
ELC1	114.34 (13.45)
ELC2	108.16 (15.33)
ABIQ6	104.03 (14.14)
Maternal Education (Years)	15.90 (3.07)
Paternal Education (Years)	15.42 (3.29)
Total Household Income ($)	79,053.56 (57,440.40)
Maternal Ethnicity (%)	
White/Black/Asian/Indian	76.8 / 21.3 / 1.5 / 0.4
Hispanic	4.8
Paternal Ethnicity (%)	
White/Black/Asian/Indian/Unknown	70.4 / 24.2 / 3.3 / 0.6 / 1.5
Hispanic	5.4

**NICU = Neonatal Intensive Care Unit*

Table 2.2: Model of Missing Data

Parameter	Estimate	Standard Error	P-Value
Intercept	4.24	1.37	2.00E-03
ELC1	-0.02	0.01	0.08
Paternal Education in Years	-0.13	0.04	1.70E-03
Months Since Start of 1yr MSEL Testing	0.01	0.01	0.06
Scale	1.01	0.09	

n=361, 264 clusters

Table 2.3: ELC Scores as Predictors of ABIQ6

	ELC1			ELC2			Both		
	Estimate	Standard Error	P-Value	Estimate	Standard Error	P-Value	Estimate	Standard Error	P-Value
ELC1	0.16	0.06	0.0125				0.03	0.06	0.58
ELC2				0.41	0.06	3.00E-12	0.40	0.06	1.70E-10
QIC	1249			1199			1201		

Table 2.4: Full GEE Model Predicting ABIQ6

	Parameter	Estimate	Standard Error	P-Value
Mean	Intercept	107.28	1.59	< 2E-16
	ELC2 (centered)	0.28	0.06	1.50E-06
	Sex (Male)	-2.77	1.59	0.08
	Age in Days (centered)	0.04	0.02	7.64E-03
	Paternal Education in Years (centered)	1.18	0.25	2.30E-06
	Gest Number (Twin)	-6.11	1.61	1.50E-04
	Months Since Start of SB5 Testing	0.07	0.04	0.06
Scale	Intercept	119	13.1	

n=235, 174 clusters. *Note*: males and twins are base variables for binary sex and gestation number covariates.

Table 2.5: The Predictive Value of ELC Scores for ABIQ6 Across Samples

		ELC1			ELC2		
Sample	*N*	*Estimate*	*SE*	*P-Value*	*Estimate*	*SE*	*P-Value*
Full Sample	521	**0.16**	**0.06**	**0.012**	**0.41**	**0.06**	**3.00E-12**
≥32wks, ≤24hr NICU	405	**0.17**	**0.08**	**0.030**	**0.43**	**0.06**	**6.10E-15**
<32wks, >24hr NICU	116	0.11	0.11	0.309	0.26	0.18	0.150
Twins	175	**0.31**	**0.11**	**0.006**	**0.45**	**0.90**	**<0.001**
Singletons	230	0.12	0.09	0.210	**0.39**	**0.07**	**9.00E-08**

Note: Results compiled from GEE models using only ELC1 or ELC2 as predictors. Bolded and highlighted results are significant.

Table 2.6: Within Subject and Within-Family Correlations of ELC Scores

	GEE Correlations			Pearson Correlations	
	r	Standard Error	P-value	*r*	P-value
Same Child Over Time	0.30	0.05	1.97E-09	0.30	1.00E-11
Twins Same Age	0.70	0.06	< 2.2E-16	0.78	< 2.2E-16
Siblings Same Age	0.41	0.22	0.06	0.45	1.51E-04

Table 2.7: Full GEE Model Predicting ELC Scores

Parameter	Estimate	Standard Error	P-Value
Intercept	200.56	27.25	1.80E-13
Year 2	-71.97	35.60	0.04
Sex (Male)	-2.21	1.18	0.06
Gest Number (Twin)	-1.79	2.09	0.39
Gestational Age at Birth	-0.08	0.05	0.09
Paternal Education in Years	-0.53	0.19	7.01E-03
Age in Days	-0.16	0.05	1.02E-03
Months Since Start of 1yr MSEL Testing	0.15	0.02	6.50E-12
Year 2*Gest Number (Twin)	-9.26	2.46	1.60E-04
Year 2*Paternal Education in Years	1.61	0.25	1.20E-10
Year 2*Age in Days	0.14	0.06	0.02
Year 2*Months Since Start of 2yr MSEL Testing	-0.05	0.03	0.12

Note: Because the reference group for year (i.e. year 1 or year 2) is year 1, the coefficients for effects of year 2 are calculated by adding the coefficients for the single term (i.e. Gestation Number (Twin)) plus the coefficient for the interaction term (i.e. Year 2 * Gest Number (Twin)).

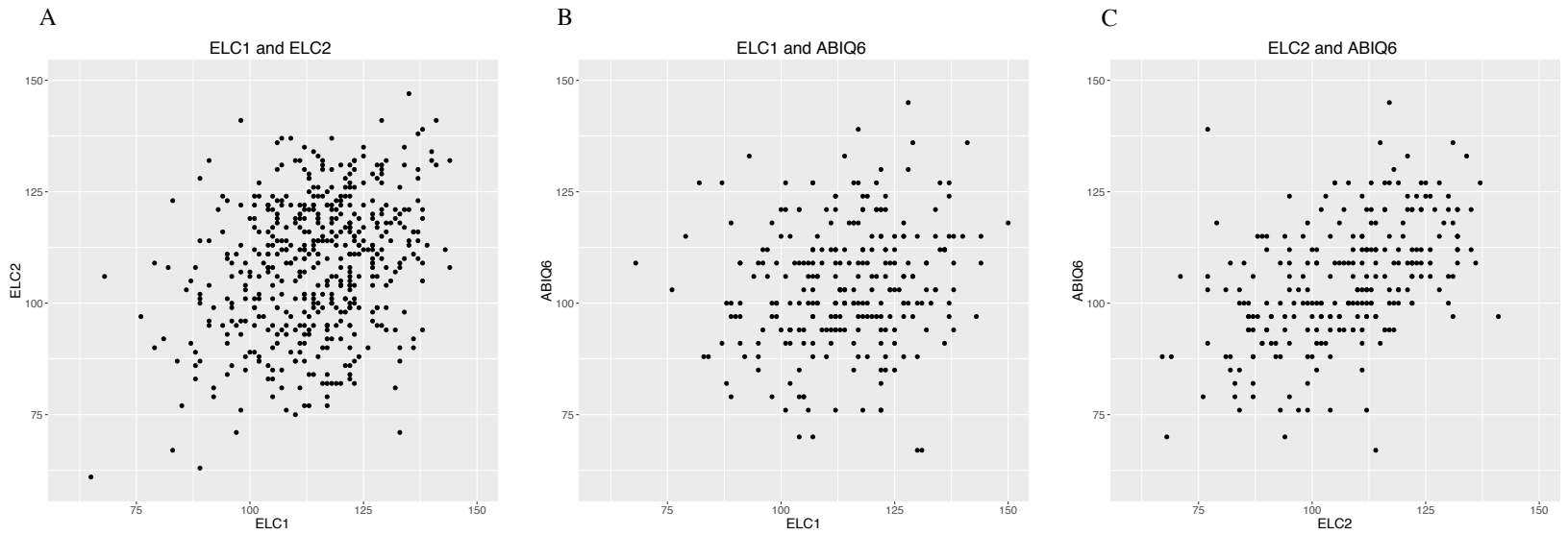


Figure 2.1. Relationships between ELC1, ELC2, and ABIQ6.

Raw plots of the relationships between ELC1 and ELC2 (A), ELC1 and ABIQ6 (B), and ELC2 and ABIQ6 (C).

Table S2.1 Demographics of Children with and without Birth Complications

	≥32wks gestation, ≤24hrs NICU	<32wks gestation, >24hrs NICU
	Mean (Std Dev)/Percent	Mean (Std Dev)/Percent
Sex (% Male)	52.84	40.52
Gestation (% Twins)	43.21	84.48
Gestational Age at Birth (Days)	268.36 (12.67)	233.42 (19.33)
Duration in NICU (Days)	0.04 (0.21)	19.95 (20.90)
Days Since Birth ELC1	386.74 (23.35)	417.27 (25.12)
Days Since Birth ELC2	751.62 (25.34)	787.59 (29.74)
Days Since Birth ABIQ6	2223.30 (65.66)	2253.03 (46.88)
ELC1	114.61 (13.61)	113.40 (12.86)
ELC2	109.30 (15.18)	104.18 (15.28)
ABIQ6	105.18 (13.97)	100.64 (14.17)
Maternal Education (Years)	16.19 (3.03)	14.91 (2.98)
Paternal Education (Years)	15.72 (3.36)	14.38 (2.81)
Total Household Income ($)	81574.19 (58371.10)	70,607.23 (53,588.50)
Maternal Race / Ethnicity (%)		
White/Black/Asian/Indian	78.77/19.01/1.98/0.25	69.83/29.31/0.00/0.86
Hispanic	4.69	5.17
Paternal Race / Ethnicity (%)		
White/Black/Asian/Indian/Unknown	71.85/21.98/3.95/0.25/1.98	65.52/31.90/0.86/1.72/0.00
Hispanic	5.19	6.03

Table S2.2 Demographics of Twin and Singleton Comparison Samples

	Twins	Singletons
	Mean (Std Dev)/Percent	Mean (Std Dev)/Percent
Sex (% Male)	60.57	46.96
Gestational Age at Birth (Days)	257.99 (7.79)	276.25 (9.61)
Duration in NICU (Days)	0.07 (0.26)	0.02 (0.15)
Days Since Birth ELC1	399.19 (23.37)	377.31 (18.43)
Days Since Birth ELC2	765.31 (23.47)	741.50 (21.68)
Days Since Birth ABIQ6	2227.04 (55.33)	2220.22 (73.18)
ELC1	113.11 (13.73)	115.74 (13.44)
ELC2	103.59 (14.13)	113.53 (14.55)
ABIQ6	100.42 (13.62)	109.13 (13.05)
Maternal Education (Years)	15.83 (3.15)	16.46 (2.92)
Paternal Education (Years)	15.30 (3.20)	16.04 (3.45)
Total Household Income ($)	83825.02 (68305.99)	79807.19 (49288.12)
Maternal Race / Ethnicity (%)		
White/Black/Asian/Indian	73.71/24.00/1.71/0.57	82.61/15.22/2.17/0.00
Hispanic	5.14	4.35
Paternal Race / Ethnicity (%)		
White/Black/Asian/Indian/Unknown	62.86/29.14/5.71/0.00/2.29	78.70/16.52/2.61/0.43/1.74
Hispanic	5.14	5.22

Table S2.3 Linear Mixed Effects Model Predicting ABIQ6 – Full Sample

	Parameter	Estimate	Standard Error	P-Value
Fixed Effects	Intercept	107.62	1.62	< 2E-16
	ELC2 (centered)	0.28	0.05	1.24E-07
	Sex (Male)	-2.94	1.53	0.05
	Age in Days (centered)	0.04	0.02	0.02
	Paternal Education in Years (centered)	1.17	0.24	7.64E-07
	Gest Number (Twin)	-6.02	1.74	5.43E-04
	Months Since Start of SB5 Testing	0.06	0.04	0.08
Random Effects	Twins (SD)	5.55		
	Residual (SD)	9.37		

n=235, 181 clusters

Table S2.4 Full GEE Model Predicting ABIQ6 – Maternal Education

	Parameter	Estimate	Standard Error	P-Value
Mean	Intercept	106.66	1.63	< 2E-16
	ELC2 (centered)	0.30	0.06	1.40E-06
	Sex (Male)	-1.95	1.62	0.23
	Age in Days (centered)	0.04	0.02	1.34E-02
	Maternal Education in Years (centered)	0.94	0.26	3.00E-04
	Gest Number (Twin)	-6.01	1.67	3.30E-04
	Months Since Start of SB5 Testing	0.08	0.04	0.05
Scale	Intercept	125	13.7	

n=235, 174 clusters

CHAPTER THREE: CORTICAL STRUCTURE AND COGNITION IN INFANTS AND TODDLERS

INTRODUCTION

Mounting evidence indicates the neocortex as a morphological correlate of intelligence and cognitive ability in adolescents and adults. Regional and hemispheric cortical gray matter volumes have been positively correlated with cognitive ability from late childhood into adulthood (Narr et al., 2007; Posthuma et al., 2003). More recent studies have begun to break down cortical volume into its two main constituents: cortical thickness (CT) and surface area (SA). These more specific measures of cortical morphology have also been independently (Burgaleta et al., 2014; Colom et al., 2013; Posthuma et al., 2002; Shaw et al., 2006) and recently, jointly (Schnack et al., 2015) linked to cognitive ability. A longitudinal study in children and adolescents showed that the rate of change in CT was more predictive of cognitive ability than any static measurement of thickness (Shaw et al., 2006), suggesting that the dynamic pattern of cortical development and maturation drive individual differences in cognitive ability. Despite the amount of research investigating the neural correlates of cognition in older children and adults, very little work has been done to determine the correlations between cognitive ability and cortical structure in early life when developmental trajectories of CT and SA are rapidly unfolding (Li et al., 2015; Lyall et al., 2015).

The first two years of postnatal brain development are marked by robust growth and dynamic cortical maturation. Cortical gray matter doubles in volume during the first year of life, and by age 2 the brain has reached 80% of its adult volume (Gilmore et al., 2012; Knickmeyer et al., 2008). The rapid growth of the cortex during infancy is driven primarily by the expansion of

SA, which increases at more than three times the rate of CT (Lyall et al., 2015). Interestingly, CT reaches 97% of its adult value by age 2 and shows similar heterogeneous cortical patterns to those seen in adults (Lyall et al., 2015), indicating that CT, while slower growing than SA, is largely determined during this critical period of brain development. The differential developmental patterns of CT and SA are no surprise, as these two cortical components are controlled by genetically distinct mechanisms (Chen et al., 2013; 2012; 2011; Panizzon et al., 2009), and differentially influenced by prenatal and perinatal child-level and environmental factors (Jha et al., 2018). While neonatal SA is primarily influenced by sex, birth weight, and gestational age at birth, neonatal CT is impacted by environmental variables including parental education level and maternal ethnicity, as well as postnatal age at the time of scan (Jha et al., 2018). These studies further highlight the need to decompose volumetric studies of the cortex into CT and SA, which are distinctly influenced by genetic and environmental factors that may in turn shape cognition.

During the early postnatal period, rapid gray matter growth coincides with the acquisition and refinement of sensorimotor, visual, and language skills that allow for information processing and the development of cognition (Kagan et al., 2005). Studies in older children and adults reveal that increased CT in a distributed network of cortical regions associated with intellectual performance including the dorsal lateral prefrontal cortex, anterior cingulate gyrus, inferior parietal cortex, and regions in the temporal cortex (Burgaleta et al., 2014; Goh et al., 2011; Karama et al., 2009; 2011; Narr et al., 2007; Shaw et al., 2006; Sowell et al., 2004). While less is known about the relationship with SA and cognition, recent studies have shown positive correlations between regional SA and cognitive ability in areas spanning the frontal and prefrontal cortices in young adults (Colom et al., 2013), frontal, lateral temporal and inferior parietal cortices in older adults (Vuoksimaa et al., 2015), and total SA across the lifespan (Schnack et al., 2015). However, little

work has been done to confirm that these same relationships between cortical structure and cognition exist in early life.

It is important to elucidate the postnatal neuroanatomical correlates of cognitive functioning so that patterns of typical development can be identified early in life. Understanding normal brain-behavior relationships may be the key to identifying aberrant developmental patterns in children at risk for diseases associated with alterations in cognitive functioning and cortical structure such as schizophrenia (Cannon et al., 2015; Nenadic, Yotter, Sauer, & Gaser, 2014; Rimol et al., 2012), autism (Hazlett et al., 2011; 2017), and attention deficit hyperactivity disorder (Shaw et al., 2012). A recent study demonstrating that infant cortical structure at six months of age was highly predictive of later ASD diagnosis (Hazlett et al., 2017), emphasizes the urgency of studying and understanding how cortical morphology relates to cognition during the early postnatal period.

In the present study, we sought to determine the association between CT and SA following birth, at age 1, and at age 2 and cognitive measures of general ability, language, motor, and visual reception skills at ages 1 and 2 years in a sample of 487 healthy children. Using this unique longitudinal dataset, we tested cross-sectional relationships between CT and SA and cognition at ages 1 and 2, predictive relationships between CT and SA at birth and age 1 for future cognitive performance, and how changes in CT and SA across the first two years of life relate to cognitive performance at age 2. This information will offer insights into how cortical morphology relates to cognition in early life and will aid in our understanding of how useful CT and SA are as biomarkers of ability during infancy and toddlerhood. We hypothesized that CT and SA measures in the first two years of life would be related to present and future cognitive performance, that brain-cognition relationships would be similar to those found in adults, and that trajectories of cortical maturation

will be important for cognition at age 2. Our study is the first to investigate how CT and SA contribute to cognitive ability in the early postnatal period in a normative sample and our results identify the first neuroanatomical correlates of cognition during this age range in a large cohort of healthy young children.

MATERIALS AND METHODS

Participants

Participants were part of the UNC Early Brain Development Study, an ongoing study of human brain development in singletons and twins (Gilmore et al., 2007). Pregnant women were recruited from outpatient obstetrics and gynecology clinics at the University of North Carolina Hospitals and Duke University Medical Center. Mothers were excluded from the study for major illness or use of illegal drugs during pregnancy. All offspring underwent magnetic resonance imaging shortly after birth, and at ages 1 and 2 years. Cognitive assessments were also collected at 1- and 2-year visits. We retrospectively identified 487 subjects with at least one structural magnetic resonance image (sMRI) that produced usable CT and SA data and at least one cognitive assessment who met the following inclusion criteria: no diagnosis of major psychiatric disorder in the mother, born at ≥ 32 weeks gestation (moderately premature to full term), spent ≤ 24 hours in the neonatal intensive care unit following birth, had no major abnormalities noted on any MRI, and had no major medical issues or illnesses reported up to age 2. **Table 3.1** outlines the demographic characteristics of the sample. Informed written consent and parental permission was obtained from at least one parent of all child participants and all study protocols were approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

Image Acquisition

All sMRIs used in this study were acquired between 2004 and 2014 using either a Siemens Allegra head-only 3T scanner (neonates: N = 355 (85%), 1-year-olds: N = 230 (85 %), 2-year-olds: N = 151 (77%)) or a Siemens TIM Trio 3T scanner (neonates: N = 63 (15%), 1-year-olds: N = 40 (15 %), 2-year-olds: N = 45 (23%)), which replaced the Allegra in 2011 (Siemens Medical System, Inc., Erlangen, Germany). Infants were scanned during unsedated, natural sleep after being fitted with earplugs and secured using a vacuum-fixed immobilization device.

Proton density and T2 weighted structural images for neonates were acquired on the Allegra using a turbo-spin echo sequence (TSE, TR = 6200ms, TE1 = 20ms, TE2 = 119ms, flip angle = 150°, spatial resolution = 1.25mm x 1.25mm x 1.95mm, N = 166) or a "fast" turbo-spin echo sequence using a decreased TR, a smaller image matrix, and fewer slices (TSE, TR range = 5270ms-5690ms, TE1 range = 20ms-21ms, TE2 range = 119ms-124ms, flip angle = 150°, spatial resolution = 1.25mm x 1.25mm x 1.95mm, N = 189). For the Trio, participants were initially scanned using a TSE protocol (TR=6200ms, TE1=17, TE2=116ms, flip angle=150°, spatial resolution= 1.25mm x 1.25mm x 1.95 mm, N = 4) while the rest were scanned using a 3DT2 SPACE protocol (TR=3200ms, TE=406, flip angle=120°, spatial resolution= 1mm x 1mm x 1mm, N=58).

T1-weighted images for 1- and 2-year-olds were acquired on the Allegra using a 3D magnetization prepared rapid gradient echo sequence (MP-RAGE TR = 1880-1900ms, TE = 4.38ms, flip angle = 7°, spatial resolution = 1mm x 1mm x 1mm, N = 381). T1 images on the Trio were collected using a lower echo time (MP-RAGE TR = 1860-1900ms, TE = 3.74ms, flip angle = 7°, spatial resolution = 1mm x 1mm x 1mm, N = 95).

All T1 and T2 weighted MRIs used in this study were visually inspected by two expert raters. Raters scored images based on motion artifacts on a scale from 1 to 4, with 1 being the highest quality images with no visible artifacts to slight artifacts in a few slices and 4 being the lowest quality images with moderate to heavy artifacts in a few to many slices. Each rater underwent an inter- and intra-reliability test and each image was scored by two raters. Raters score were averaged, unless they differed by two or more points, in which case raters met to discuss the image and generate a consensus score. Raters also determine the usability of the image, where images of the poorest quality (category 4) were excluded if the artifacts spanned more than a few slices.

Image Analysis

CT and SA measures were derived using a pipeline previously described by Li et al. (2016) and Jha et al. (2018). All MR images were preprocessed for tissue segmentation using a standard infant-specific pipeline (Li et al., 2013) that includes automated skull-stripping and manual editing of non-brain tissue, removal of the cerebellum and brain stem, corrections for intensity inhomogeneity, and rigid alignment of T1- and T2-weighted images into an average atlas space (F. Shi et al., 2011). Gray matter, white matter (WM), and cerebrospinal fluid (CSF) were segmented by applying a standalone infant-specific patch driven coupled level sets method (Wang et al., 2014). Non-cortical regions were masked and tissues were divided into the left and right hemisphere. A deformable surface method (Li, Nie, Wang, Shi, Gilmore, et al., 2014a; Li et al., 2012) was applied to the tissue segmentations in order to reconstruct the inner, middle, and outer cortical surfaces. This method involved a topological correction of WM volume to ensure spherical topology, a tessellation of the corrected WM to generate a triangular mesh, and the deformation of

the inner mesh towards the reconstruction of each cortical surface while preserving the initial topology. All surfaces for the left and right hemisphere were visually examined for accurate mapping.

The inner surface was defined as the boundary between gray matter and WM, and the outer surface as the boundary between the gray matter and CSF. A third surface, the middle cortical surface, was defined as the layer lying in the geometric center of the inner and outer surfaces of the cortex. CT was computed for each vertex as the average value of the minimum distance from the inner to the outer and outer to the inner surfaces. SA was computed based on the central cortical surface. The cortical surface was parcellated into 78 cortical regions of interest (ROI) based on an infant-specific parcellation atlas (Gilmore et al., 2012; Tzourio-Mazoyer et al., 2002), as shown in Jha et al. (2018). The average CT and total SA for each ROI were calculated as a mean of the values at each vertex within the region.

Cognitive Assessments

Cognitive ability was assessed at ages 1 and 2 using the Mullen Scales of Early Learning (MSEL). Child measures of gross motor (GM), fine motor (FM), visual reception (VR), expressive and receptive language (EL, RL) were collected by experienced testers. Performance on the latter four MSEL cognitive scales were analyzed as raw scores, and their age-standardized t-scores were combined into an Early Learning Composite (ELC) standardized score (range: 49-155, mean =100, sd =15). The ELC has high internal consistency (median = 0.91) and reliability (median = 0.84 for the cognitive scales during these testing ages), and principal factor loadings of the scales lend support for the construct validity of the ELC as a general measure of cognitive ability (Mullen, 1995), much like an intelligence quotient. The primary measure of interest for this study was the

ELC, though we also investigated MSEL raw scale scores (not normalized for age) for each of the four cognitive domains. We specifically chose to study raw scores because we are interested in understanding how a child's actual performance relates to brain development, instead of attempting to interpret the relationships between brain development and a child's degree of difference from a normative sample, a rationale which has been previously described (Naigles et al., 2017). A subset of the MSEL assessments (4% and 6% of MSEL tests at ages 1 and 2, respectively) were conducted in Spanish to match the native language of the child. Descriptive statistics of the MSEL scores can be seen in **Table 3.2**.

Statistical Analysis

We tested our primary hypothesis that CT and SA in early life is related to cognitive ability by calculating raw, unadjusted Pearson's correlations between global, overall average CT, total SA, and regional CT and SA and each MSEL score over time. All possible cross-sectional and predictive relationships were assessed: (1) CT and SA at birth correlating with MSEL scores at ages 1 and 2, (2) CT and SA at age 1 correlating with MSEL scores at age 1 and 2, and (3) CT and SA at age 2 correlating with MSEL scores at age 2.

We then investigated the usefulness of CT and SA as a biomarker of cognitive ability in very young children by modelling the effects of CT and SA on MSEL scores while controlling for other factors that are known to relate to the MSEL scores: gestational age at birth, age at testing, sex, and maternal education level. We additionally included a nuisance variable, MSEL test date ($DATE_{MSEL}$), controlling for the number of months since study inception to account for any sample drift or variation in cognitive testing administration due to personnel turnover during the ten-year

data collection period. These factors were previously identified in overlapping samples (**Chapter 2 / Chapter 4**, manuscripts under review).

We additionally probed relationships between child and demographic factors and global and regional CT and SA. We found that total and regional SA at birth are correlated with gestational age at birth, as has been previously reported by our group (Jha et al., 2018), such that longer gestation is associated with larger total and regional SA (**Figure 3.1D)**. These effects are largely not present at ages 1 and 2 (**Figure 3.1E-F**). We also replicated findings from Jha et al. (2018) showing that higher levels of maternal education are associated with thinner cortices in offspring at birth (**Figure 3.2A**), and that infants who were born prematurely had thicker cortices following preterm birth (**Figure 3.1A)**. We also found that total SA at birth, age 1, and age 2 were positively correlated with maternal education level (**Figure 3.2D-F**), and regional associations between maternal education and SA emerge at age 1 and persist to age 2 (**Figure 3.2E-F**). Finally, we found that relationships between CT and gestational age at birth change over time such that later born infants have thicker cortices at age 1 and 2 while preterm infants have thinner cortices (**Figure 3.1B-C**).

To account for such relationships in the data, all adjusted correlations included gestational age, age at MSEL testing, sex, maternal education, and gestation number, along with nuisance variables controlling for MRI scanner (Allegra or Trio) and MSEL test date. These adjusted models were constructed in a similar manner to the raw Pearson's correlations, such that both cross-sectional and predictive relationships were assessed.

Finally, as an exploratory analysis, we employed a longitudinal modeling technique to test whether trajectories of CT and SA development across the first two years of life are related to cognitive development. Specifically, we tested if CT and SA at birth (as a reflection of prenatal

brain development; CT_0, SA_0), the change in these properties in the first year of postnatal life ($dCT_{1,0}$, $SA_{1,0}$; calculated as a simple subtraction of the parameter at the earlier age from that of the later age), or the change in CT and SA in the second year of life ($dCT_{2,1}$, $dSA_{2,1}$) related to MSEL 2-year scores, our latest testing point. To do this, we used linear mixed effects models predicting 2-year scores including all three time points (i.e. CT_0, $dCT_{1,0}$, and $dCT_{2,1}$) simultaneously while controlling for gestational age (GA), maternal education (MEDUY), age at MSEL testing (Age_{MSEL}), sex and nuisance variables related MRI scanner (Scanner) and MSEL test date ($DATE_{MSEL}$). Only subjects with complete longitudinal data– scans at birth, age 1, and age 2 and cognitive data at age 2 – were included in these analyses, and one twin from each pair was treated as a repeated measure. The statistical model for CT predicting ELC at age 2 (ELC_2) is shown below:

$$ELC_2 = \beta_0 + \beta_{FA_0} CT_0 + \beta_{dCT_{1,0}} dCT_{1,0} + \beta_{dCT_{2,1}} dCT_{2,1} + \beta_{GA} GA +$$
$$\beta_{Age_{MSEL}} Age_{MSEL} + \beta_{sex} sex + \beta_{MEDUY} MEDUY + \beta_{Scanner_0} Scanner_0 +$$
$$\beta_{Scanner_1} Scanner_1 + \beta_{Scanner_2} Scanner_2 + \beta_{DATE_{MSEL}} DATE_{MSEL} + \varepsilon$$

where ELC_2 is the dependent variable and CT_0, $dCT_{1,0}$, $dCT_{2,1}$, GA, Age_{MSEL}, sex, $MEDUY$, $Scanner_0$, $Scanner_1$, $Scanner_2$, and $DATE_{MSEL}$ are the independent variables, and ε is the random error. The model for SA predicting any MSEL 2-year score were constructed in the same manner.

Sample sizes for all analyses are reported in **Table 3.3**. All results from CT and SA analyses are corrected for multiple comparisons using False Discovery Rate (Benjamini & Hochberg, 1995), such that each model predicting MSEL scores using regional cortical measurements is corrected for the number of ROIs analyzed. Sensitivity analyses were also performed where we additionally corrected for cubic root of ICV (for regional CT results), and total SA (for regional

SA results), and motion score. All statistical analyses were performed using SAS statistical software, version 9.4.

RESULTS

Average CT

Results from unadjusted correlation analyses revealed no significant correlations between average CT at birth or age 1 and ELC scores at age 1, however average CT at age 1 was positively correlated with ELC scores at age 2 ($r = 0.14$, $p < 0.05$; **Figure 3.3D**). Average CT at birth and age 1 were positively correlated with GM scores at age 1 ($r = 0.11$, $p < 0.05$ and $r = 0.14$, $p < 0.05$, respectively; **Figure 3.3A**, **Figure 3.3B**). Average CT at age 1 was positively correlated with concurrent FM, EL, and RL scores at age 1 ($r = 0.19$, $p < 0.01$, $r = 0.15$, $p < 0.05$, and $r = 0.13$, $p < 0.05$, respectively; **Figure 3.3B**). Average CT at ages 1 and 2 were positively correlated with RL scores at age 2 ($r = 0.19$, $p < 0.01$ and $r = 0.17$, $p < 0.05$; **Figure 3.3D-E**), and average CT at age 2 was positively correlated with EL scores at age 2 ($r = 0.16$, $p < 0.05$; **Figure 3.3D**).

After controlling for covariates (gestational age at birth, gestation number, sex maternal education level, scanner, and MSEL test date), average CT at age 1 remained significantly positively correlated with GM at age 1, and GM at age 1 ($r = 0.13$, $p < 0.05$) is still significantly correlated with future average CT at age 2 ($r = 0.21$, $p < 0.01$). Average CT at birth is no longer significantly correlated with GM scores at age 1, and average CT at age 1 is no longer significantly correlated with FM, EL, or RL at age 1. Average CT at ages 1 and 2 remain significantly positively correlated with RL scores at age 2 ($r = 0.19$, $p < 0.01$ and $r = 0.17$, $p < 0.05$), and average CT at age 2 remains significantly correlated with EL at age 2 ($r = 0.16$, $p < 0.05$).

Regional CT

Results from unadjusted correlation analyses revealed no significant correlations between regional CT at birth or age 1 and ELC scores at age 1. CT at age 1 in the left precentral gyri, bilateral regions in the frontal and prefrontal cortices, regions overlapping with Broca's area in the right hemisphere, bilateral anterior cingulate, bilateral middle temporal gyri, and regions in the bilateral parietal cortices were positively correlated with ELC scores at age 2, while CT in the bilateral lingual gyri were negatively associated with ELC scores at this age (**Figure 3.4**). CT at age 2 in the right insula was positively correlated with ELC scores at age 2 (**Figure 3.5**).

CT at age 1 was correlated with concurrent motor scores. CT at age 1 in the left frontal middle, occipital superior, and left postcentral gyri, the left paracentral lobule, and the bilateral superior parietal cortices was positively correlated with GM scores at age 1 (**Figure 3.4**), while CT in the left olfactory cortex was negatively correlated with GM at the same age. CT at age 1 in the left primary motor cortex, bilateral regions in the frontal, prefrontal, and parietal cortices, bilateral anterior cingulate, right superior and middle temporal cortices, right olfactory cortex, and right middle cingulate were positively correlated with FM scores at age 1(**Figure 3.4**). Additionally, CT at age 1 in the right frontal interior triangularis, which overlaps with Broca's area, was positively correlated with concurrent RL scores at age 1 (**Figure 3.4**). There were no significant correlations between CT at birth, age 1, or age 2 and 1-year VR or EL scores.

CT at age 1 was correlated with language scores at age 2. CT at age 1 in the bilateral primary motor cortex, bilateral regions in the frontal cortex, bilateral middle temporal gyri, and bilateral anterior cingulate was positively correlated with EL scores at age 2 (**Figure 3.4**). CT at age 1 in bilateral regions in frontal and parietal cortices, including regions covering Wernicke's and Geschwind's areas, the bilateral middle temporal gyrus, regions overlapping with Broca's area

in the right hemisphere, the bilateral anterior cingulate, and right middle cingulate were positively correlated with RL scores at age 2 (**Figure 3.4**). CT at age 2 in the left primary motor, right frontal inferior operculum overlapping with Broca's area, and right frontal middle orbital cortex were positively related to concurrent EL scores at age 2; CT at this age in the right insula was positively correlated with RL scores at age 2 (**Figure 3.5**). CT in the right insula at age 2 was also positively correlated with VR scores at the same age. CT in the left lingual gyrus at age 2 was negatively correlated with 2-year FM scores (**Figure 3.5**).

After controlling for covariates, all associations between GM and FM at age 1 and CT at age 1 are no longer present, except the relationship between the superior parietal cortex and 1-year GM scores. Average CT at age 1 is still significantly correlated with GM scores at age 1 ($r = 0.13$, $p < 0.05$) and GM scores at age 1 remain significantly correlated with future average CT at age 2 ($r = 0.21$, $p < 0.01$). However, average CT at birth is no longer significantly correlated with GM scores at age 1, and average CT at age 1 is no longer related to concurrent FM, EL, or EL scores. As for associations with cognitive scores at age 2 after covariate correction, many of the associations between CT at age 1 and EL scores at age 2 remain (**Figure 3.5**), and the associations between CT in the right insula and the ELC, VR, and RL scores also remain significant (**Figure 3.5**). Average CT at age 1 remains significantly correlated with RL scores at age 2 ($r = 0.18$, $p <0.05$), and average CT at age 2 is still associated with EL and RL scores at the same age ($r = 0.18$, $p < 0.05$ and $r = 0.19$, $p < 0.05$, respectively).

Total SA

Results from unadjusted correlation analyses revealed no significant correlations between total SA at birth or age 1 and ELC scores at age 1, however total SA at birth was positively

correlated with ELC scores at age 2 ($r = 0.17$, $p < 0.01$; **Figure 3.3C**). There were no significant correlations between total SA at birth or age 1 and 1-year MSEL scale scores. Total SA at birth was positively correlated with FM, EL, and RL scores at age 2 ($r = 0.17$, $p < 0.01$, $r = 0.11$, $p < 0.05$, and $r = 0.16$, $p < 0.01$, respectively; **Figure 3.3C**), and total SA at age 2 was positively correlated with VR scores at age 2 ($r = 0.17$, $p < 0.05$; **Figure 3.3E**).

After controlling for covariates there are no longer any significant correlations between total SA at birth and ELC, FM, EL, or RL scores at age 2, or total SA at age 2 and concurrent VR scores.

Regional SA

There were no significant unadjusted correlations between regional SA and ELC scores at age 1. SA at birth in the left precentral gyrus, bilateral postcentral gyri, bilateral regions in the frontal and parietal cortices, right insula, bilateral middle cingulate, right posterior cingulate, left lingual, bilateral occipital medial, bilateral fusiform, bilateral precuneus, and bilateral middle and inferior temporal gyri are positively correlated with the ELC at age 2 (**Figure 3.6**). There were no significant correlations between SA at ages 1 or 2 and 2-year ELC scores.

There were sparse results between regional SA and cognition at age 1. SA at birth in the right heschl's gyrus is positively correlated with GM scores at age 1 ($r = 0.17$, $p < 0.05$; not visible in **Figure 3.6**). There are no significant relationships between regional SA at any age and FM, EL, RL, or VR scores at age 1.

Regional SA at birth in the left precentral, bilateral postcentral gyri, bilateral regions in the frontal, parietal, temporal, and occipital cortices, the bilateral insula, bilateral anterior and middle cingulate cortices, right posterior cingulate, right parahippocampal, left lingual, bilateral fusiform,

and bilateral precuneus were positively correlated with FM scores at age 2 (**Figure 3.6**). SA at birth in the bilateral frontal middle orbital, left middle cingulate, bilateral fusiform, and bilateral middle temporal gyri were positively related to RL scores at age 2 (**Figure 3.6**).

Sparse results were also noted between regional SA at ages 1 or 2 and 2-year cognitive scores. SA at age 2 in the right middle temporal gyrus was positively correlated with VR scores at the same age ($r = 0.26$, $p < 0.01$). There were no significant correlations between regional SA at any age and GM or EL scores at age 2.

After controlling for covariates, there are no significant correlations between regional SA at birth and cognition at ages 1 or 2. Significant correlations emerge between SA at age 1 in the right precentral gyrus and FM scores at age 2 ($r = 0.24$, $p <0.05$). Correlations also emerge between SA at age 1 in the left frontal middle orbital gyrus and at age 2 in the right middle temporal gyrus and VR scores at age 2 ($r = 0.24$, $p < 0.05$ and $r = 0.29$, $p < 0.01$, respectively). All other correlations between SA at ages 1 or 2 and cognitive scores are no longer significant.

Longitudinal Analyses

Longitudinal analyses revealed no significant relationships between the developmental change in CT or SA during the first or second year of life and cognitive scores at age 2 when adjusting for other covariates in the model.

Sensitivity Analyses

Controlling for ICV (cubic ICV for CT or total SA for regional SA results) or motion score in addition to other covariates did not substantially change the majority of results. Controlling for motion score did rescue significant results between CT at age 1 and future RL scores at age 2 in

regions overlapping with Broca's, Wernicke's and Geschwind's areas and regions in the temporal lobe that were no longer significant after adjusting for covariates (**Figure 3.7**). Results between average CT and cognition were largely the same, though a significant correlation emerged after controlling for motion between CT at birth and RL scores at age 2 ($r = 0.18$, $p < 0.05$). Additionally, controlling for motion recovered significant correlations between total SA at birth and FM scores at age 2 ($r = 0.11$, $p < 0.05$) and total SA at age 2 and VR scores at the same age ($r = 0.15$, $p < 0.05$), which were significant in raw Pearson's correlation analyses and not significant after adjusting for basic covariates.

DISCUSSION

In the present study, we report the first associations between global and regional CT and SA and cognitive abilities in infants and toddlers. We found that that generally thicker, larger cortices in early life related to better performance on cognitive tasks testing motor, language, and visual reception abilities, suggesting that increased synaptogenesis, elaborations in dendritic arborization, or delayed myelination may confer benefits for infant cognitive development. We found several expected brain-cognition relationships, with regions associated with motor planning and execution correlating with FM and GM scores and regions associated with language processing and production relating to EL and RL scores. We generally found more significant relationships between CT and cognition than SA and cognition in infancy and toddlerhood; though regional SA at birth was widely associated with 2-year ELC and FM scores. Analyses controlling for variables related to children's cognitive scores, including maternal education level, sex, gestational age, and gestation number, reveal that correlations are greatly weakened and largely no longer significant after adding these variables in to the model. This suggests that while there are relationships between CT, SA, and cognition during this developmental period, their effect

sizes are small and other readily-available child-level and environmental variables may be better suited as predictors of future outcome than MRI-derived measures of cortical structure. However, some correlations did survive adjustment for covariates, which highlighted the relationship between CT in the right insula at age 2 and concurrent VR, EL, RL, and ELC scores. Other relationships that survived adjustment include expected brain-cognition relationships between 2-year CT in regions overlapping Broca's area and the superior temporal gyrus and EL scores at age 2, and SA in the right precentral gyrus at age 1 correlating with future FM performance at age 2. Finally, our longitudinal models revealed that there were no significant associations between developmental changes in CT and SA in the first or second year of life, suggesting that associations between the rates of cortical thinning and cognition often reported in studies of older children and adults (Schnack et al., 2015; Shaw et al., 2006) may emerge later in development.

In general, we found that thicker, larger cortices related to better cognitive performance across domains in many regions that canonically support motor, language, and general cognition. ELC scores at age 2, a measure overall cognitive ability, were predicted by regionally larger SA in areas spanning the bilateral frontal, temporal, parietal, and medial cortices at birth. CT at age 1 was correlated with future ELC scores at age 2 in a set of bilateral regions constrained to the fronto-parietal network and anterior cingulate implicated in cognitive control and attentional processes (Cai et al., 2016), and the middle temporal and lingual gyri which are responsible for processing sensory information (Jung & Haier, 2007). Interestingly, these regions map extremely well to those implicated in the parieto-frontal integration theory of intelligence based on a review of human neuroimaging studies (Jung & Haier, 2007), suggesting that the structural development of this cognitive network is set in place during early infancy. Finally, we also found that CT in the right insula at age 2 was correlated with concurrent cognitive ability, which is interesting given the

insula's role in integrating information across distinct cognitive and emotional networks (Chang, Yarkoni, Khaw, & Sanfey, 2013). Our findings that cortical structure at birth and age 1 predict future cognition at age 2, and that cognition at age 2 is related to current cortical structure suggest that cognitive abilities are, at least in part, determined by preceding prenatal and postnatal brain development and related to present cortical structure in regions important for general cognition and network integration. We found no associations between early cortical structure and general cognitive ability at age 1, which may be due to the transient nature of cognitive scores at this age which have little bearing on later performance (**Chapter 1**, manuscript under review).

Many expected structure-function relationships were found between infant cortical structure and early cognitive abilities. CT in several regions involved in sensory motor processing at age 1 were related to concurrent GM ability. These regions include the left postcentral gyrus housing the homunculus, bilateral superior parietal cortex involved in motor planning and visuo-motor integration (Desmurget et al., 1999), left paracentral lobule related to motor and sensory processing (Rizzolatti & Luppino, 2001), left frontal middle gyrus which is thought to relay goal-directed motor behavior (Corbetta & Shulman, 2002), as well as the left occipital superior cortex involved in spatial visual processing (Haxby et al., 1991). Overall, this suggests that GM scores at age 1 are linked to the structure of primary motor and association cortices responsible for movement and movement planning. This further suggests that cortical structures by the end of the first year of life, at least in primary sensory and sensory association areas, are developed to perform domain-specific functions as seen in older children and adults. Such a hypothesis is in line with cortical maturational trajectories during this developmental period, such that sensory and motor regions of the cortex mature at a faster rate than higher-order association areas (Lyall et al., 2015).

Thicker cortices at age 1 also related to concurrent FM scores in several regions involved in motor behaviors including the left precentral, left frontal superior and bilateral frontal middle cortices which relay goal-directed attentional and motor behaviors (Corbetta & Shulman, 2002), the bilateral anterior cingulate, right middle cingulate, left postcentral, and the bilateral superior and inferior parietal cortices involved in motor planning (Rizzolatti & Luppino, 2001). Regions involved in language processing were also found to be related to FM scores at age 1, including regions housing Broca's, Wernicke's and Geschwind's areas, and the right superior and middle temporal cortices. The interdependencies of the MSEL tasks may drive such results, as language comprehension is important for completing FM tasks on the MSEL, for example the child needs to follow directions related to stacking blocks, turning pages in a book, and inserting pennies into a slot. Additionally, larger SA in regions spanning the cortex at birth were related to higher FM scores at age 2, suggesting an association between prenatal brain growth and subsequent motor development through infancy.

Language scores at age 1 were generally not related to cortical structure across infancy, though receptive language in 1-year-olds was found to positively correlate with CT in a region which comprises part of Broca's area. Many correlations of a predictive nature, however, were present between CT at age 1 and future language scores at age 2. CT in regions in the frontal, parietal, occipital, temporal, and midline association cortices related to higher order processing, motor, visual and language processing at age 1 predicted EL and RL scores. Finally, thicker right insular cortices at age 2 was significantly associated with higher receptive language scores at the same age, while thicker cortex in regions overlapping Broca's area were related to expressive language. Additionally, SA in a small set of regions at birth – the bilateral frontal middle orbital, middle temporal, and fusiform gyri, as well as the left middle cingulate – were predictive of future

receptive language outcomes at age 2. Results appeared to be less domain specific with language scores, such that language regions (Broca's, Geschwind's, middle temporal gyri), sensory-motor regions (occipital cortices, primary motor cortex), and regions responsible for higher-order cognition (cingulate, prefrontal cortex) were found to associate with language scores at age 2. This could be due to the non-specific nature of the language assessments, which often rely on other related cognitive constructs like auditory memory and auditory-visual integration (Mullen, 1995), or could possibly reflect a large-scale cortical network that is involved in early language learning that later becomes fine-tuned to adult-like regions through interactive specialization (M. H. Johnson, 2000; 2011), as has been previously suggested (Redcay, Haist, & Courchesne, 2008; Swanson et al., 2015).

Thicker cortices have been consistently linked to better cognitive performance in older children and adults (Burgaleta et al., 2014; Choi et al., 2008; Colom et al., 2013; Goh et al., 2011; Karama et al., 2011; Luders, Narr, Thompson, & Toga, 2009; Narr et al., 2007; Schnack et al., 2015; Shaw et al., 2006; Sowell et al., 2004), and we have now extended these results to demonstrate early postnatal origins of such relationships starting around age 1. Fewer studies have focused on relationships between SA and cognition, but those that have demonstrate that larger SA is related to higher general intelligence (Colom et al., 2013; Fjell et al., 2015; Vuoksimaa et al., 2015; Yang et al., 2013). Our work showing that SA at birth is related to future cognition is consistent with these findings and suggests that prenatal mechanisms driving SA expansion *in-utero* may be particularly important for emerging cognition. The fact that generally thicker, larger cortices correlated with better performance suggests that increased synaptogenesis, elaborations in dendritic arborization, or delayed myelination, and thus prolonged plasticity, confer benefits for cognitive development. Some of our regional CT results were of the opposite direction, with

thinner cortices predicting better cognitive scores. These findings may suggest that some brain regions have a differential association between CT and cognition, which has been shown previously (Goh et al., 2011; Shaw et al., 2006). Finally, global analyses revealed that greater total SA and average CT were related to better cognitive outcomes across infancy, suggesting that mechanisms driving CT and SA development across the brain may be important for cognitive development in the first two years of life.

The majority of significant results from these analyses were between CT, as opposed to SA, and cognition. CT and SA have been shown to be genetically distinct in studies of twins (Chen et al., 2013; Panizzon et al., 2009). In support of this idea, studies have shown that polymorphisms in microcephaly genes affect regional SA in humans (Rimol et al., 2010), while rodent studies have found that manipulation of transcription factors Ngn1/2 and Tlx during development results in changes to CT, but not SA (Pontious, Kowalczyk, Englund, & Hevner, 2007). The radial unit hypothesis suggests that SA is determined by the number of cortical minicolumns, which is dependent upon the rate of cell proliferation and programmed cell death within symmetrically-dividing radial glial cells of the ventricular zone (P. Rakic, 2009). CT, however, is thought to be determined by changes in proliferation kinetics of asymmetrically-diving neural progenitor cells as well as changes in the size or number of neurons or glia and their processes (P. Rakic, 1995; 2009). Bennet and colleagues (2011) estimated that the volume of gray matter in the adult human cortex is composed mainly of dendrites (30% of cortical volume) and axons (29%), suggesting that the positive associations between CT and cognition are likely due to greater amounts of axonal processes and thus increased cortico-cortical connectivity (Lyall et al., 2015). The recently proposed supragranular layer hypothesis (Nowakowski, Pollen, Sandoval-Espinosa, & Kriegstein, 2016) posits that around mid-neurogenesis, radial glial scaffolds become discontinuous, during

which time self-renewing divisions of outer radial glial cells increase the SA of the supragranular layers, while neurogenic divisions of these glial cells increase the thickness of these layers. This highlights a particularly interesting evolutionary mechanism for the expansion of the suprgranular layers which are thought to give rise to many primate-specific cognitive abilities (Nowakowski et al., 2016), and further suggests that neurodevelopment beginning in the second trimester of pregnancy may be particularly important for establishing the foundations of cortico-cortical connections important for cognition.

It has been shown that CT and SA follow different developmental trajectories across early infancy (Lyall et al., 2015) and adulthood (Schnack et al., 2015), further supporting the conceptualization of CT and SA as relatively independent processes which may have differential associations to cognition. A recent study found that neonatal CT and SA are impacted by different sets of environmental factors, with SA more strongly influenced by sex and obstetric history and CT more strongly influenced by socioeconomic and ethnic disparities (Jha et al., 2018). This study also found that during the neonatal period, heterogeneous growth patterns were observed in regional CT, while heterogeneity in regional SA growth was nominal (Jha et al., 2018). In light of our own results, this suggests that perhaps CT, shaped more by environmental experiences, is dynamically changing in early life to support experience-dependent learning and cognitive development in infancy and toddlerhood, whereas SA at birth, shaped largely by genetic and prenatal factors, may set the stage for future cortical expansion and have a more global brain-wide association with cognition thereafter.

In light of the environmental influences exacted on both brain and cognitive development, it is no surprise that the majority of our results are no longer significant after adding these variables to the model. Regional CT and SA, on average, accounted for between about 3-5% of the variance

in cognitive scores when no other variables were included in the model, highlighting that while there are correlations between cortical structure and cognition during these ages, they are modest at best. These correlations are of a similar magnitude to those previously reported (Schnack et al., 2015; Shaw et al., 2006) suggesting that the strength of the associations between cortical structure and cognition are similar across development. In comparison, maternal education and gestational age at birth account for roughly 14% and 12%, respectively, of the variance in children's 2-year cognitive scores, dwarfing the effects of cortical structure on cognition. We also found influences of maternal education and gestational age at birth on cortical structure, with maternal education accounting for less than 2% of the variation in CT and SA at birth, 8% of the variation in SA at age 1, and less than 4% of the variation in SA at age 2. Gestational age at birth only influenced neonatal cortical structure, accounting for roughly 4% of the variance in CT and 11% of the variance in SA. This suggests that maternal education and gestational age at birth exact influences on both brain and cognitive development and deserve further systematic study to understand the mechanisms by which these influences occur. Additionally, we found that controlling for motion in addition to other covariates rescued some correlations between CT and cognition, particularly with language scores, suggesting that motion may contribute added noise to the imaging data that should be considered.

Interestingly, however, some results do survive correction for covariates, which suggests these regions may play a potentially important role in contributing to individual differences in cognitive development in infancy and toddlerhood and are perhaps informative neuroimaging biomarkers. The relationship between CT in the right insula at age 2 and concurrent VR, EL, RL, and ELC scores highlights a potentially interesting role for the insular cortex in general cognitive functioning. Mounting evidence from functional MRI studies suggest that the insula is

instrumental in integrating disparate functional systems involved in processing affect, sensorimotor information, and general cognition and is well suited to provide an interface between feelings, cognition, and action (Chang et al., 2013). Our findings suggest that by age 2, the insula may be structurally developing to support such a role in cognitive processing. Other recent work suggests that the development of the insula may warrant further study, as the insula is a high-expanding cortical region during childhood and adolescence (Fjell et al., 2015), and disruptions in its regulation of central executive and default mode networks has been implicated in pathogenic states including schizophrenia (Namkung, Kim, & Sawa, 2017). Additional relationships that survived adjustment include expected brain-cognition relationships between 2-year CT in regions overlapping Broca's area and the superior temporal gyrus and EL scores at age 2, and SA in the right precentral gyrus at age 1 correlating with future FM performance at age 2. These findings indicate that by age 1, the primary motor cortex is structurally developed to support future motor function and that by age 2 cortical areas responsible for speech production and language processing are organized to provide a foundation for burgeoning language abilities in toddlerhood.

From a developmental perspective, we identified both a predictive and cross-sectional nature between cortical structure and cognition in early life. We found that SA at birth and CT at ages 1 and 2 were important for future cognitive performance at 2 years of age. This indicates that SA at birth holds important information for future cognitive development, but may not be directly linked to cognition at ages 1 and 2. This may be due to smaller sample sizes at these ages which limit our ability to detect significant effects, or perhaps other cortical properties, like CT, are more important for determine cognition at later ages. We did, however, find that total SA at age 2 was related to concurrent visual reception scores, suggesting the association with SA at later ages is detectable, even if weak, at the global level. Relationships between CT and cognition emerge at

age 1 and persist through age 2 in this sample, studies in older children and adults would suggest this association likely continues throughout the lifespan (Schnack et al., 2015; Shaw et al., 2006). Finally, the majority of our results were of a predictive nature, which indicates that the development of cortical structures prior to cognitive assessments may be more important for determining cognition than structure at the time of assessment.

To our surprise, we found no associations between developmental changes in CT and SA across the first two years of life with cognitive abilities at age 2. This may be a limitation of smaller sample sizes with full longitudinal data, or a relatively low number of sampling points for the imaging data (birth, age 1, and age 2). Alternatively, it could suggest that the associations between the rates of cortical maturation and cognition often reported in studies of older children and adults (Schnack et al., 2015; Shaw et al., 2006) may emerge later in development, especially given that these studies associated cortical thinning with cognition, while in early brain development, most of the cortex is still thickening across the first two years of life (Lyall et al., 2015). This also highlights that developmentally distinct mechanisms contribute to cognition across the lifespan. In infancy, thickening of the cortex, through increased cortico-cortical connections via synaptogenesis and dendritic arborization, confers cognitive benefits. In later childhood and into adolescence however, cortical thinning that occurs (Raznahan et al., 2011; Walhovd et al., 2016; Wierenga, Langen, Oranje, & Durston, 2014) via apoptotic mechanisms contributing to synaptic pruning and circuit refinement, reflects greater cognitive abilities (Schnack et al., 2015; Shaw et al., 2006). Finally, in adulthood, work suggests that thicker cortices, likely a reflection of slowed apoptotic mechanisms and conservation of neurons and their connections, confer benefits during aging (Schnack et al., 2015). This body of work highlights the

importance of taking a developmental perspective in studying brain-cognition relationships which adaptively fluctuate across ontogeny.

Strengths of this study include the use of a large, normative sample including longitudinal neuroimaging and laboratory-based cognitive assessments and the implementation of cutting-edge pediatric image analysis methods. Limitations reflect the inherent difficulties of studying infants and toddlers, including shifts in image contrast that can affect cortical surfaces measures (Walhovd, Fjell, Giedd, Dale, & Brown, 2017), and issues with testing young children including temperament and language abilities. Additionally, we did find that controlling for motion impacted some findings, suggesting that consideration of motion should be handled in a systematic way when performing such analyses. Despite these limitations, our study substantially contributes to the field by offering insights into how cortical structure across infancy and toddlerhood is related to emerging cognition.

This study is the first to investigate the relationships between CT, SA, and emerging cognitive abilities in a large, normative sample. We report novel findings that larger surface area at birth and thicker cortices at ages 1 and 2 confer a cognitive advantage in infancy and toddlerhood. We find many expected brain-cognition relationships, suggesting that cortical areas supporting language, motor, and general cognitive abilities are structurally developed to support adult-like functions as early as 1 year of age. We also found that CT may be a particularly important morphological indicator of ability, which is influenced by environmental variables that shape both brain and cognition. Taken together, this work highlights the importance of prenatal and early postnatal cortical development for cognition in infants and toddlers.

Table 3.1 Participant Demographics

Child Characteristics	**N, Mean (SD, Percent)**
Gestational Age at Birth (Days)	266.89 (12.31)
Birth Weight (grams)	3011.0 (572.76)
Stay in NICU	21 (4.31%)
Age at Neo MRI (days)	25.73 (11.12)
Age at 1yr MRI (days)	391.60 (22.02)
Age at 2yr MRI (days)	755.63 (26.10)
Age at 1yr Mullen (days)	388.10 (22.91)
Age at 2yr Mullen (days)	752.77 (26.99)
Male	259 (53.18%)
Female	228 (46.82%)
Single Gestation	237 (48.67%)
Twin Gestation	250 (51.33%)
Zygosity	
Dizygotic Twins	144 (58.54%)
Monozygotic Twins	88 (35.77%)
Opposite Sex Twins	14 (5.69%)
Parental Characteristics *	
Maternal Age (years)	30.25 (5.39)
Paternal Age (years)	32.38 (6.16)
Mother Education (years)	15.63 (3.29)
Father Education (years)	15.21 (3.67)
Total Household Income ($)	$74,538 ($54,526)
Maternal / Paternal Race	
White	375 (77.00%) / 349 (71.66%)
American Indian or Alaskan Native	2 (0.41%) / 1 (0.21%)
African American	97 (19.92%) / 109 (22.38%)
Asian	13 (2.67%) / 20 (4.11%)
Not Reported	0 (0%) / 8 (1.64%)
Maternal / Paternal Ethnicity	
Hispanic	51 (10.47%) / 57 (11.70%)
Non-Hispanic	436 (89.53%) / 425 (87.27%)
Not Reported	0 (0%) / 5 (1.03%)

**reported at the time of the child's birth*

Table 3.2. Descriptive Statistics of Mullen Scores

	YEAR 1 (N = 469)	**YEAR 2 (N = 375)**
	Mean(SD)	*Mean(SD)*
ELC	115.95 (13.26)	107.60 (15.17)
GM-rs	18.05 (2.88)	27.30 (1.85)
FM-rs	17.42 (1.72)	25.62 (2.09)
VR-rs	17.9 (2.18)	27.13 (3.45)
EL-rs	14.15 (1.96)	23.99 (3.65)
RL-rs	14.18 (2.05)	26.0 (3.18)

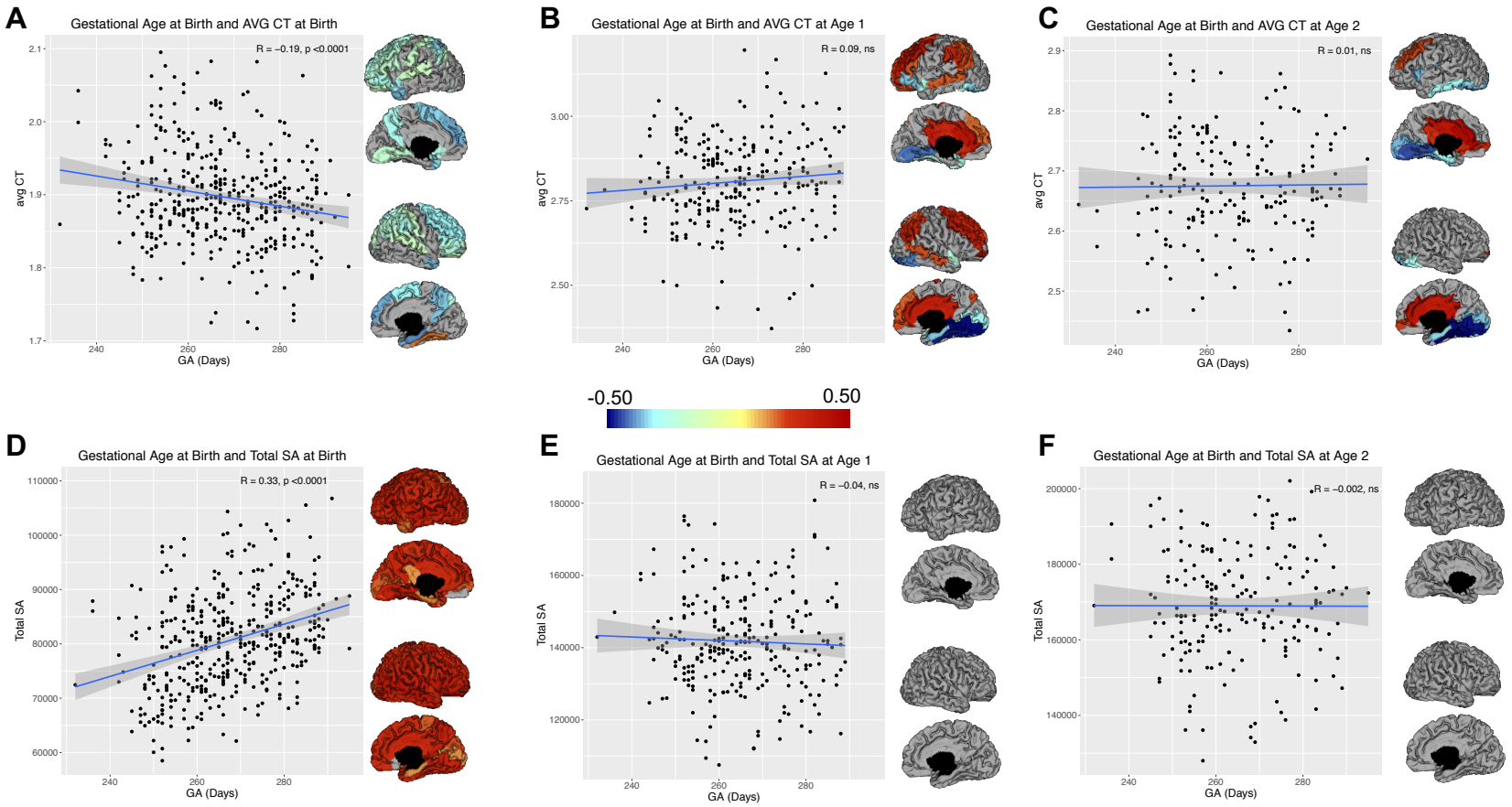


Figure 3.1 Gestational age and CT and SA across infancy and toddlerhood.

Gestational age at birth associations are shown for both regional and average CT at birth, age 1, and age 1 (A-C) and total and regional SA (D-F).

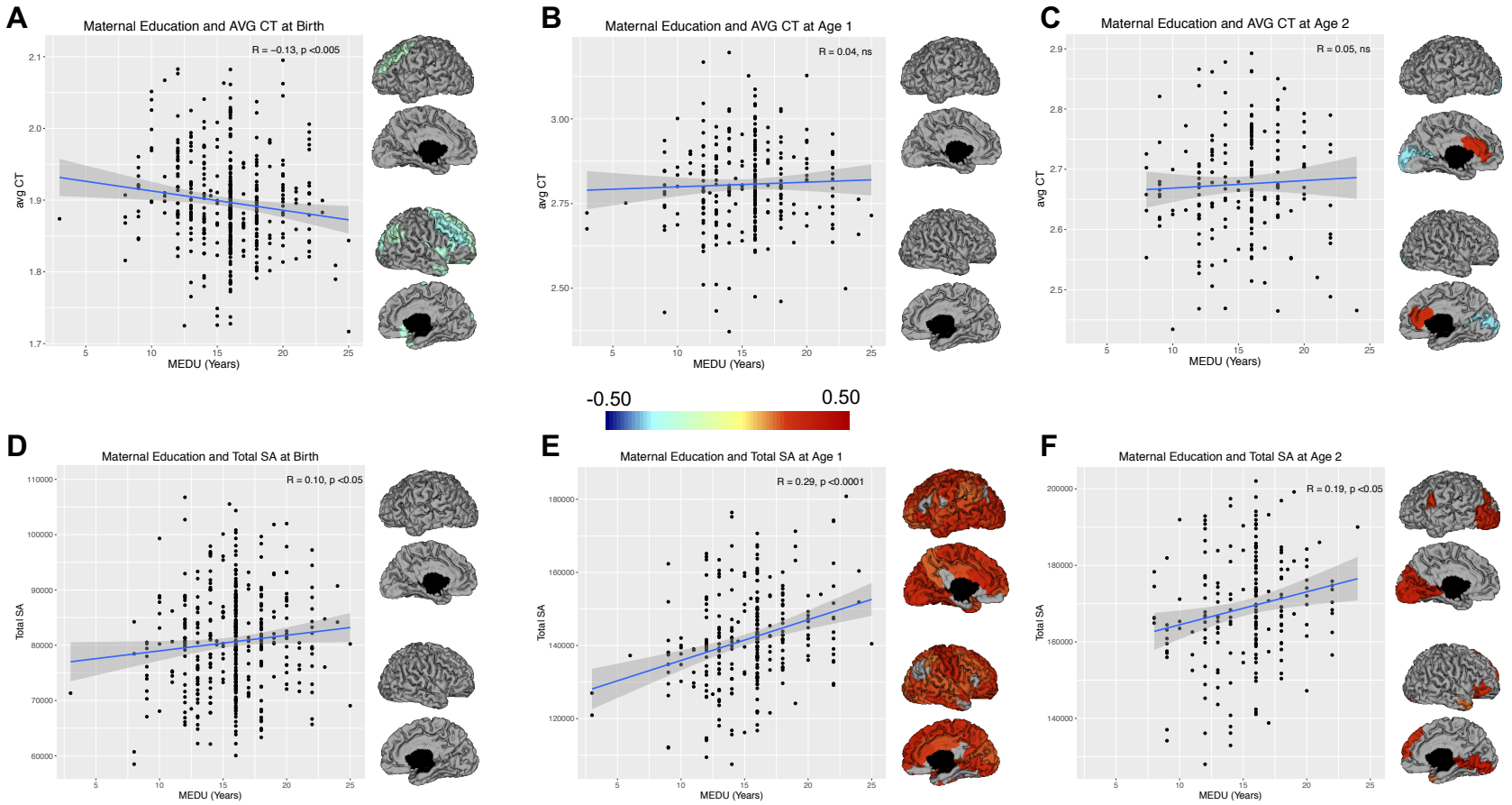


Figure 3.2. Maternal Education and CT and SA across infancy and toddlerhood.

Maternal education associations are shown for both regional and average CT at birth, age 1, and age 1 (A-C) and total and regional SA (D-F).

Table 3.3. Sample Sizes Across Experiments

	N (% of entire sample)
Neonatal CT/SA - 1yr MSEL	**402** (82.55%)
Neonatal CT/SA - 2yr MSEL	**319** (65.50%)
1yr CT/SA - 1yr MSEL	**269** (55.24%)
1yr CT/SA - 2yr MSEL	**206** (42.30%)
2yr CT/SA - 2yr MSEL	**183** (37.58%)
Longitudinal Model	**81** (16.63%)

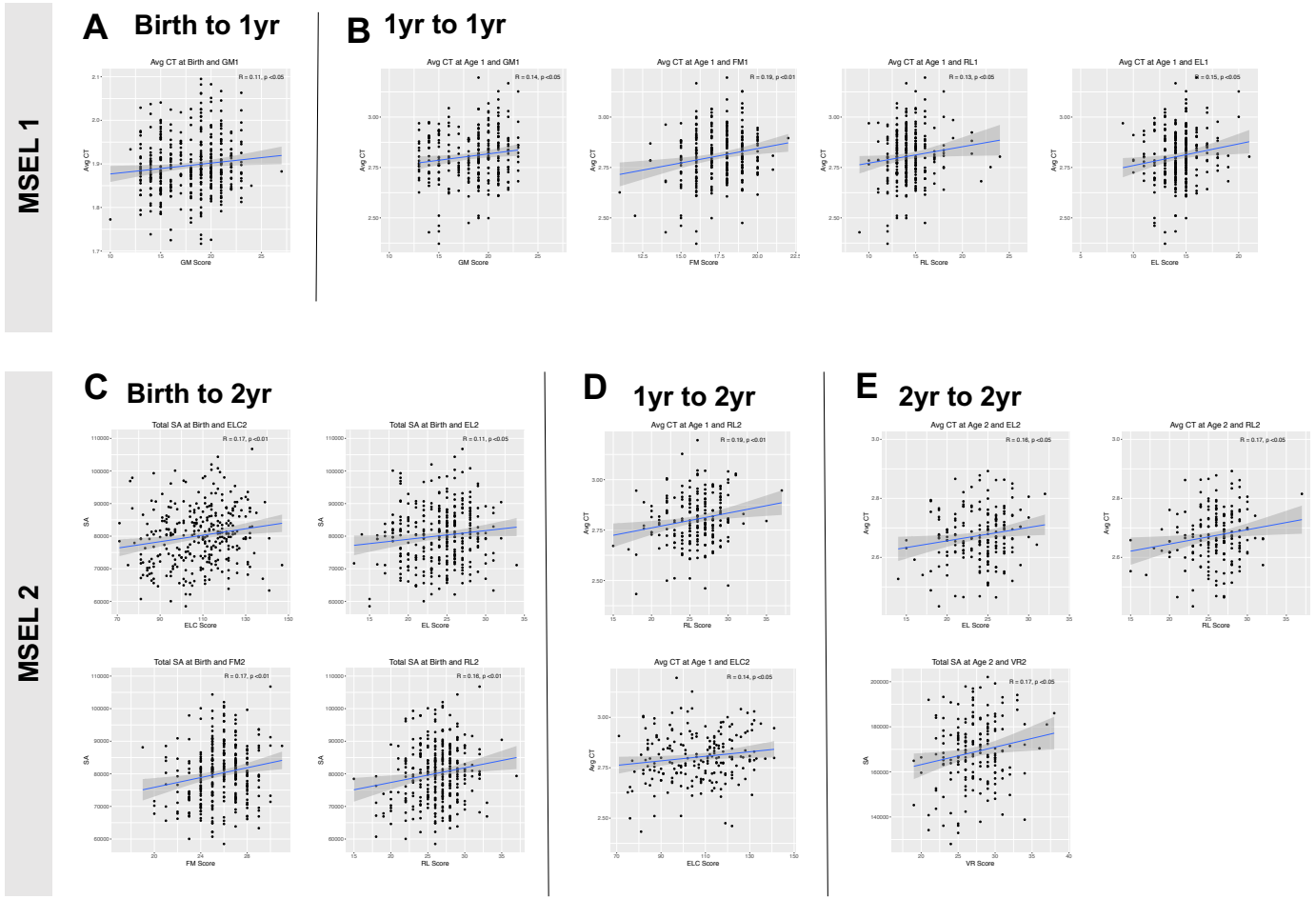


Figure 3.3. Significant correlations between average CT and total SA and MSEL scores.

Significant correlations are shown between MSEL scores at age 1 and CT and SA at birth (A) and age 1 (B), and MSEL scores at age 2 and CT and SA at birth (C), age 1 (D), and age 2 (E).

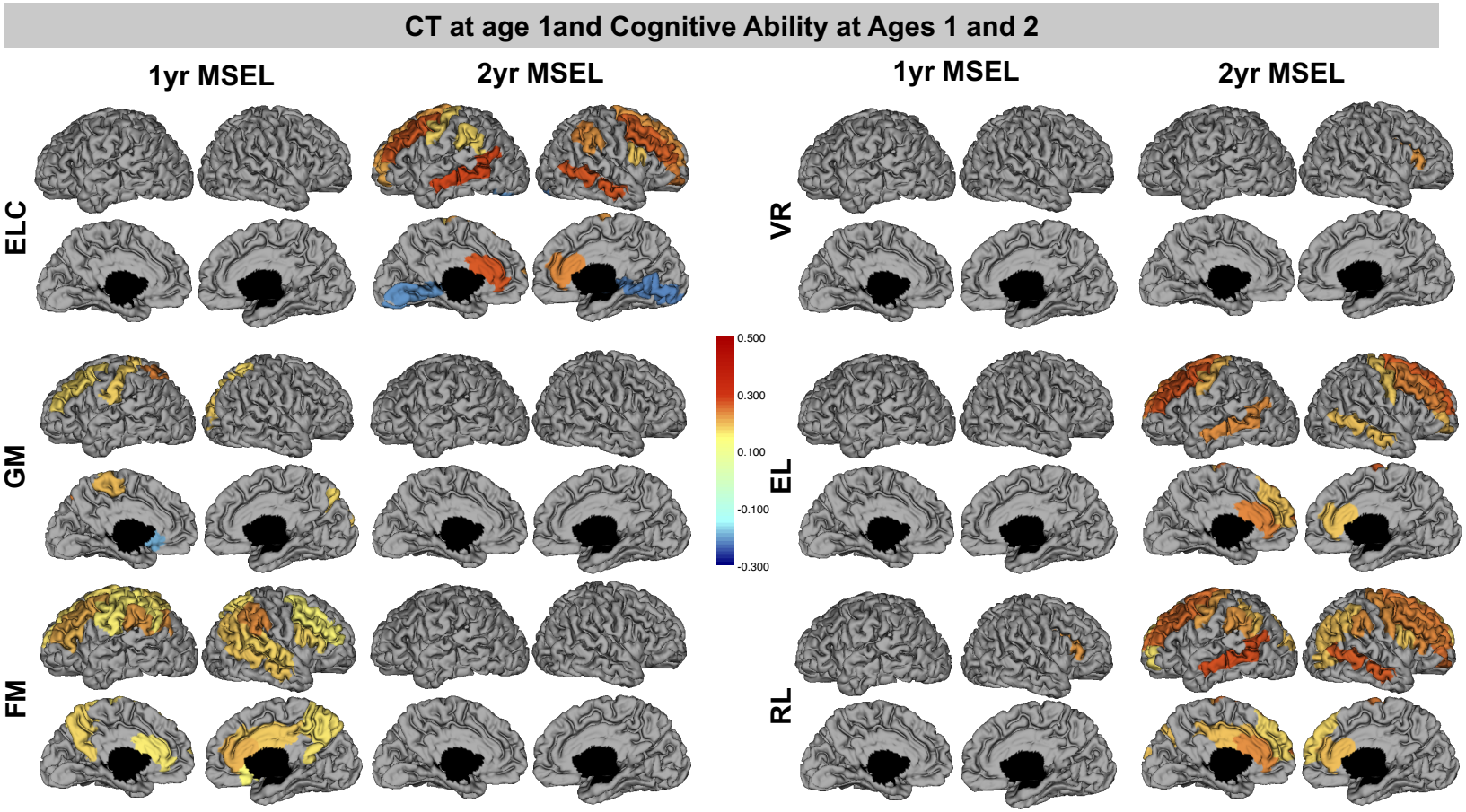


Figure 3.4. Significant raw, unadjusted correlations between CT at age 1 and cognitive abilities at ages 1 and 2.

Significant raw correlations are shown between regional CT at age 1 and ELC, GM, FM, VR, EL, and RL scores at ages 1 and 2. Significant associations are colored by the strength of correlation, with positive associations show in yellow-to-red colors and negative associations shown in blue. All results are FDR corrected for multiple comparisons and significant at the level of $p < 0.05$.

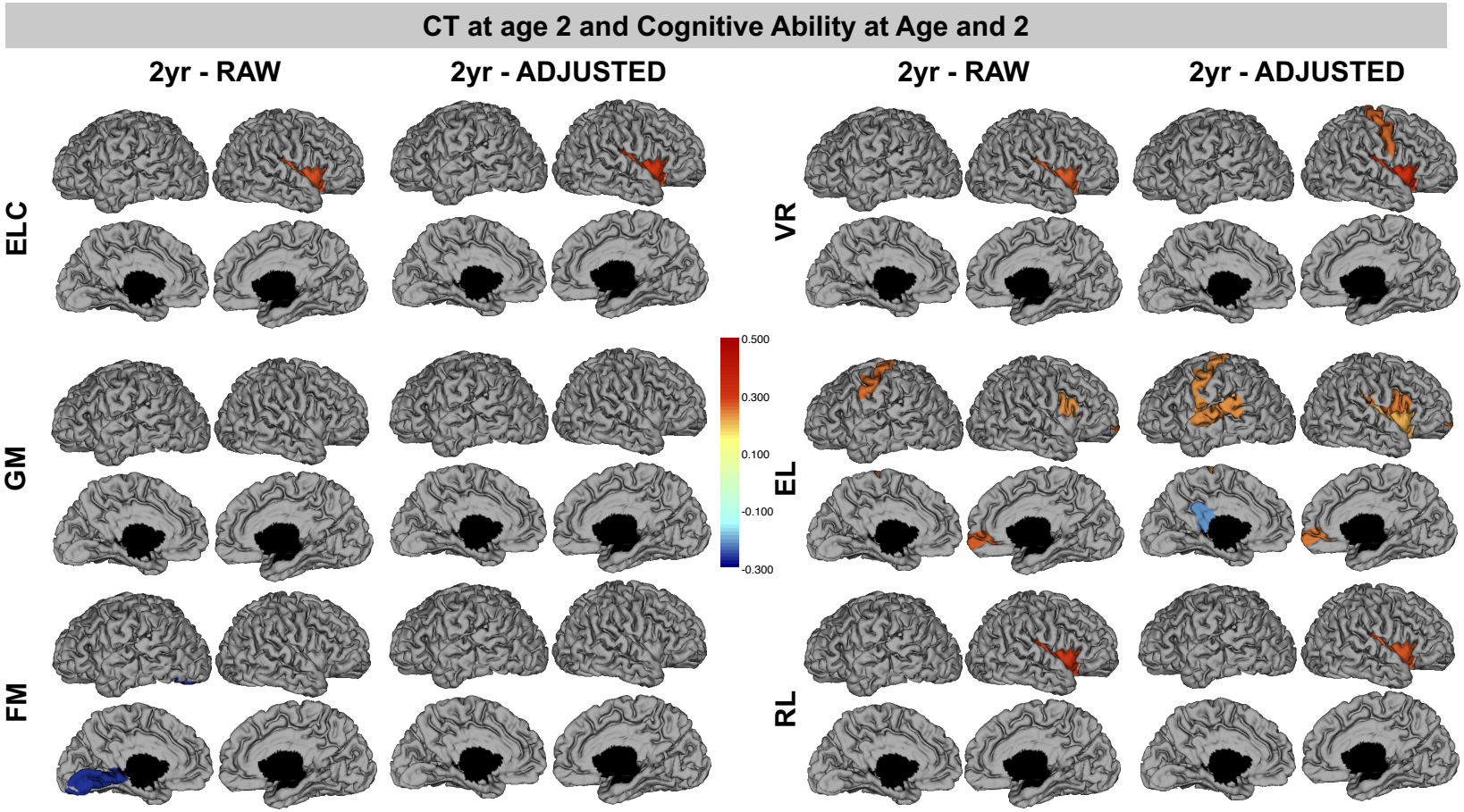


Figure 3.5. Significant raw and adjusted correlations between CT at age 2 and cognitive abilities at age 2.

Significant correlations are shown between regional CT at age 2 and ELC, GM, FM, VR, EL, and RL scores at age 2 for both raw correlations and those adjusted for covariates. Significant associations are colored by the strength of correlation, with positive associations show in yellow-to-red colors and negative associations shown in blue. All results are FDR corrected for multiple comparisons and significant at the level of $p < 0.05$.

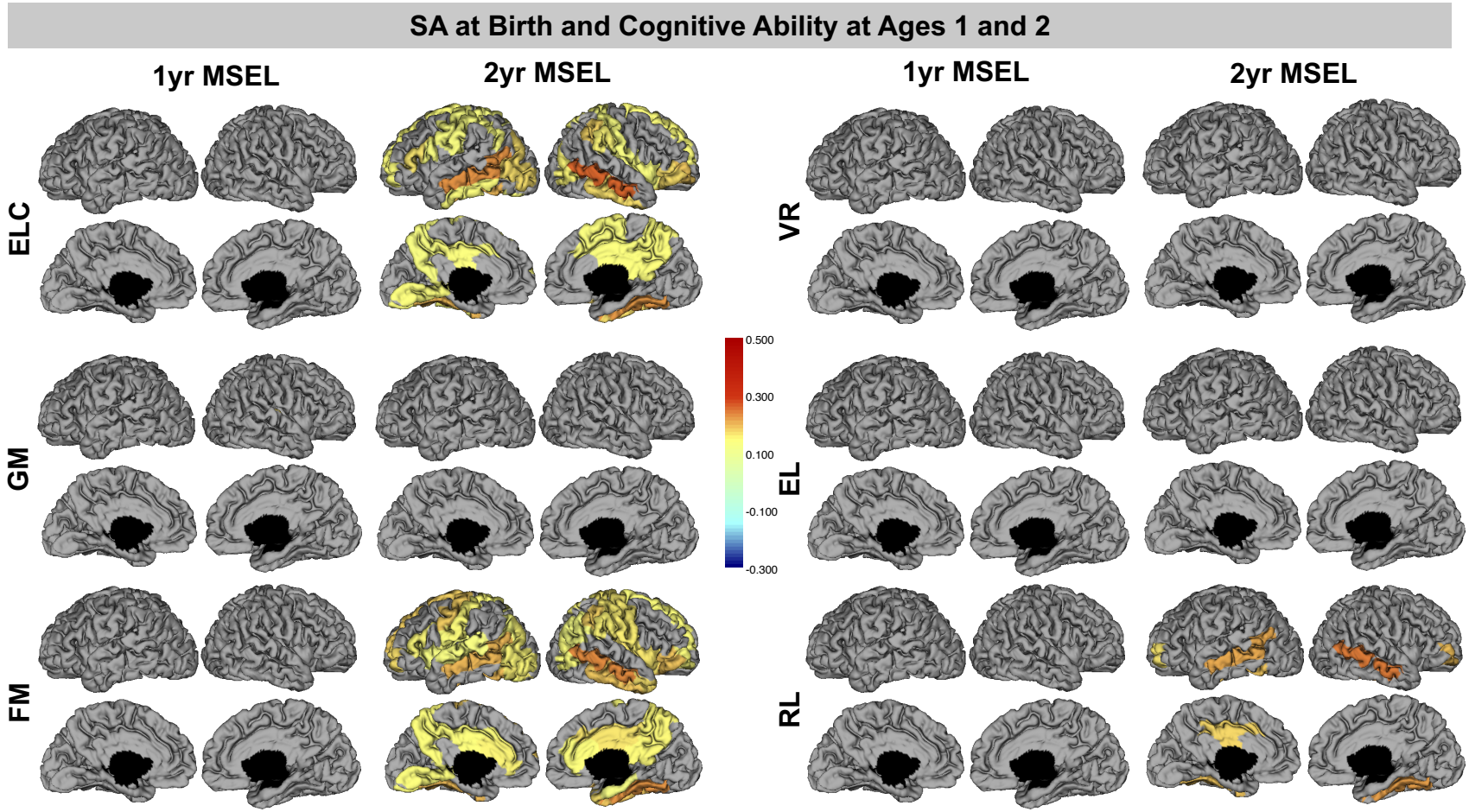


Figure 3.6. Significant raw, unadjusted correlations between regional SA at birth and cognition at ages 1 and 2.

Significant raw correlations are shown between regional SA at birth and ELC, GM, FM, VR, EL, and RL scores at ages 1 and 2. Significant associations are colored by the strength of correlation, with positive associations show in yellow-to-red colors and negative associations shown in blue. All results are FDR corrected for multiple comparisons and significant at the level of $p < 0.05$.

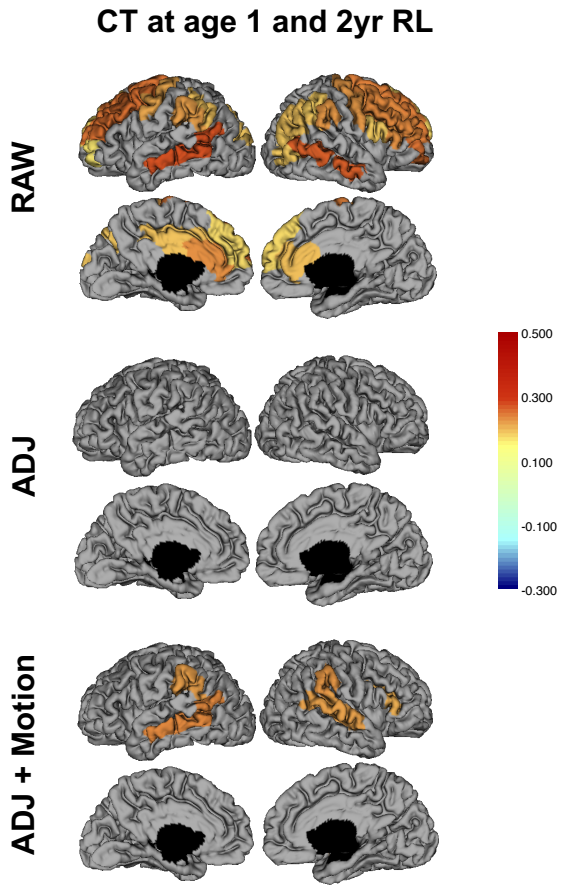


Figure 3.7 Effects of correcting for motion.

Raw, unadjusted correlations between CT at age 1 and RL scores at age 2 (top), are shown in comparison with null results when adjusting for covariates (middle), and rescued regional results when additionally controlling for main covariates and motion (bottom). Significant associations are colored by the strength of correlation, with positive associations show in yellow-to-red colors and negative associations shown in blue. All results are FDR corrected for multiple comparisons and significant at the level of $p < 0.05$

CHAPTER FOUR: WHITE MATTER MICROSTRUCTURAL DEVELOPMENT AND COGNITIVE ABILITY IN THE FIRST TWO YEARS OF LIFE[3]

INTRODUCTION

The first two years of life mark an accelerated, dynamic period of postnatal brain development in the human lifespan. During this time, the brain more than doubles in size (Knickmeyer et al., 2008), the cortex expands rapidly (Li, Nie, Wang, Shi, Lyall, et al., 2014b; Lyall et al., 2015), and the rate of brain white matter (WM) myelination peaks (Dubois et al., 2014). The rapid development of postnatal WM development has been well studied *in-vivo* using diffusion tensor imaging (DTI), a technique that probes the diffusivity of water molecules in the brain. In WM, diffusion anisotropy, commonly measured by fractional anisotropy (FA), is high, while isotropic diffusion, measured by axial and radial diffusivity (AD, RD), is low relative to gray matter and unmyelinated WM (Dubois et al., 2014). In the first two years of life these metrics change rapidly as fibers are organized into bundles, premyelination is initiated, and myelination occurs; FA increases, while AD and RD decrease (Dubois et al., 2014; Geng et al., 2012). Post-mortem studies have shown that myelination in early life follows an inside-out, front-to-back progression in the brain (Brody et al., 1987), and neuroimaging studies of WM development report similar findings (Deoni et al., 2011; 2012; Gao, Lin, et al., 2009a; Geng et al., 2012). During this same period, the cognitive capacities of infants advance from that of basic functions to complex

[3] This chapter is currently under review at *Human Brain Mapping* (Girault JB, et al. (*Under Review*). White Matter Microstructural Development and Cognitive Ability in the First Two Years of Life.).

tasks including the refinement of fine and gross motor skills, processing of visual cues, and the comprehension and production of language. While it appears that the sequence of myelination mirrors that of cognitive development, given that myelination occurs in primary sensory tracts before motor tracts and in projection pathways before higher-order association pathways (Guillery, 2005), it remains largely unknown as to how WM matures to support cognition (Walhovd et al., 2014).

It is hypothesized that one potential mechanism by which the brain mediates cognition is through optimized, rapid information transfer between connected cortical and subcortical regions via myelinated axons (Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006; Nagy, Westerberg, & Klingberg, 2004). Axons wrapped in myelin sheaths conduct action potentials and neuronal signals at much faster rates due to the insulative properties of myelin (Dubois et al., 2014). Additionally, it has been shown that myelination can occur in an activity-dependent manner, such that oligodendrocytes appear to selectively myelinate axons which receive more input from neurons (Fields, 2015; Wake et al., 2015), thus myelination likely plays a crucial role in shaping structural connectivity, communication between brain regions, and ultimately learning and cognition. Given that the sequential development of myelination in the brain mirrors cognitive development, myelination may be a prerequisite for the development of specific cognitive domains in early life. Additionally, neural activity that occurs during learning may accelerate myelination and increase WM integrity, a process that could be particularly prominent during early life when learning occurs rapidly.

There is significant evidence to support a link between cognition and WM microstructure, as determined with diffusion weighted imaging in adults (Zatorre et al., 2012), including findings correlating the integrity of major WM fiber bundles with information processing speed in healthy

older adults (Penke et al., 2010), language learning in young adults (Mamiya et al., 2016), and improvements in working memory through training (Takeuchi et al., 2010). However, there have been few studies of how these WM-cognition relationships emerge across ontogeny, particularly during the early postnatal period of rapid WM maturation development (Gao, Lin, et al., 2009a; Geng et al., 2012; Knickmeyer et al., 2008; Mukherjee et al., 2002) when individual differences in neurodevelopment may have lasting consequences on cognitive ability.

Recent studies have begun to elucidate the links between early WM development and cognition in healthy infants and toddlers. WM integrity of fiber tracts supporting working memory in adults were related to visuospatial working memory performance in 1-year-olds (Short et al., 2013), suggesting that tract-specific functionality may arise very early in life. Studies of myelin water fraction (MWF), a more direct assessment of myelin content in the brain, found that trajectories of MWF across the first five years of life were related to cognitive ability (Deoni et al., 2014), and that growth trajectories of individual WM regions were related to language and general cognitive abilities in young children (O'Muircheartaigh et al., 2013). Finally, Lee and colleagues (2017) found that common factors of DTI parameters from twelve major fiber bundles linked to cognition in adults were related to and predictive of cognitive performance across the first two years of life. Taken together, these studies suggest that both global and local WM development may be reflective of cognitive development across the early childhood.

The goal of this study is to determine the relationship of tract-based measures of FA, AD, and RD derived from neonatal, 1-year, and 2-year DTIs to cognitive measures of general ability, language, motor, and visual reception skills at ages 1 and 2 years in a sample of 447 healthy children, extending our previous study of DTI common factors (S. J. Lee et al., 2017). This information will help to better understand how these measures of WM microstructure perform as

biomarkers of present and future cognitive ability, especially when taking into account other, readily-available child and demographic variables. We hypothesized that tract-based measures of WM integrity would be related to present (cross-sectional) and future (longitudinal) cognitive ability, with more mature properties (higher FA, lower AD and RD) relating to better cognitive performance. We also explored how trajectories of maturation across the first two years of life in these WM tracts predicted cognitive ability at age 2, which to our knowledge, has not been done on a tract-by-tract basis.

MATERIALS AND METHODS

Participants

Participants were part of an ongoing study of human brain development in singletons and twins (Gilmore et al., 2007; S. J. Lee et al., 2017). Pregnant women were recruited from outpatient obstetrics and gynecology clinics at the University of North Carolina Hospitals and Duke University Medical Center. Mothers were excluded from the study for major illness or use of illegal drugs during pregnancy. All offspring underwent magnetic resonance imaging shortly after birth, and at ages 1 and 2 years. Cognitive assessments were also collected at 1- and 2-year visits. We retrospectively identified 447 subjects with at least one diffusion weighted image (DWI) that produced usable quantitative tractography data *and* at least one cognitive assessment who met the following inclusion criteria: no diagnosis of major psychiatric disorder in the mother, born at ≥ 32 weeks gestation (moderately premature to full term), spent ≤ 24 hours in the neonatal intensive care unit following birth, had no major abnormalities noted on any MRI, and had no major medical issues or illnesses reported up to age 2. **Table 4.1** outlines the demographic characteristics of the sample. Informed written consent and parental permission was obtained from at least one parent

of all child participants and all study protocols were approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

Image Acquisition

DWI data were acquired using a single-shot echo-planar imaging spin-echo sequence at 3T on either a Siemens Allegra head-only scanner or a Siemens Tim Trio (Siemens Medical System, Inc., Erlangen, Germany), which replaced the Allegra in 2011. For earlier collected Allegra DWI data, a 6-direction protocol was used with the following parameters: Repetition Time (TR)/ Echo Time (TE) = 5,200/73 ms, slice thickness = 2 mm, and in-plane resolution = 2 x 2 mm^2, with a total of 45 slices in 6 unique directions using *b* value of 1,000 s/mm^2 and 1 baseline image (*b* value = 0) per sequence. This sequence was repeated five times (generating a total of 35 DWIs) to improve signal-to-noise. For the remaining Allegra DWI data, 42 directions of diffusion sensitization were acquired with a *b* value of 1,000 s/mm^2 in addition to seven baseline (*b* value = 0) images (generating a total of 49 DWIs). The parameters for the 42-direction data were as follows: TR/TR/Flip angle = 7,680/82/90°, slice thickness = 2mm, and in-plane resolution = 2 x 2 mm^2, with a total of 60 to 72 slices. The rest of the study subjects scanned on the Tim Trio followed the same sequencing parameters as the 42-direction Allegra protocol detailed above. For information on the number of scans collected with each scanner and protocol, see **Table 4.2**.

Diffusion Tensor Imaging Analysis

A study-specific, automated quality control (QC) protocol was applied to all raw DWI data using DTIPrep (http://www.nitrc.org/projects/dtiprep) which detected slice-wise and gradient-wise intensity and motion artifacts and corrected for motion and eddy current effects (Oguz et al.,

2014). Diffusion images with large motion artifacts and missing or corrupted gradients were excluded from further processing. Skull and non-brain tissue were removed using Brain Extraction Tool (S. M. Smith, 2002), and tensors were estimated using a weighted least-squares algorithm (Goodlett, Fletcher, Gilmore, & Gerig, 2009). The neonatal and pediatric (1- and 2-yr) DTI atlases (https://www.nitrc.org/projects/uncebds_neodti) were created using the UNC-UTAH NAMIC DTI framework (www.nitrc.org/projects/dtiatlasbuilder) outlined by Verde and colleagues (2014). A total of 45 homologous tracts were defined in both atlases using streamline tractography in 3D Slicer (http://www.slicer.org). For basic descriptions of the subset of 29 tracts used in our analyses, see **Figure 4.1**; for details on tractography, see the appendix from Lee et al. (2015). Pair-wise registration was performed to map individual subject DTIs into atlas space. Resulting deformation fields were used to map atlas fibers into individual subject space, where profiles of from FA, AD, and RD were extracted at evenly spaced points (arc lengths) along each fiber tract (DTI-Reg, DTIAtlasFiberAnalyzer; http://www.slicer.org). Each tract from each subject underwent QC prior to statistical analysis using FADTTSter (http://www.nitrc.org/projects/fadttster); subjects were excluded on a tract-by-tract basis if their correlations with the population average FA profile was <0.70. Some tracts were less reliably reproduced in individuals and had higher failure rates than others. Average FA, AD, and RD values were computed for each tract. Additionally, terminal arc lengths from some tracts were not included in tract-average calculations due to high noise.

Cognitive Assessments

Cognitive ability was assessed at ages 1 and 2 using the Mullen Scales of Early Learning (MSEL). Child measures of gross motor (GM), fine motor (FM), visual reception (VR), expressive and receptive language (EL, RL) were collected by experienced testers. Performance on the latter

four MSEL cognitive scales were analyzed as raw scores, and their age-standardized t-scores were combined into an Early Learning Composite (ELC) standardized score (range: 49-155, mean =100, sd =15). The ELC has high internal consistency (median = 0.91) and reliability (median = 0.84 for the cognitive scales during these testing ages), and principal factor loadings of the scales lend support for the construct validity of the ELC as a general measure of cognitive ability (Mullen, 1995), much like an intelligence quotient. The primary measure of interest for this study was the ELC, though we also investigated MSEL raw scale scores (not normalized for age range) for each of the four cognitive domains. We specifically chose to study raw scores because we are interested in understanding how a child's *actual* performance relates to brain development, instead of attempting to interpret the relationships between brain development and a child's degree of difference from a normative sample, a rationale which has been previously described (Naigles et al., 2017). A subset of the MSEL assessments (5% and 7% of MSEL tests at ages 1 and 2, respectively) were conducted in Spanish to match the native language of the child. Descriptive statistics of ELC scores can be seen in **Table 4.1**, statistics for all other cognitive raw scale scores at ages 1 and 2 and correlations between cognitive scores across time can be seen in **Table S4.1** and **Table S4.2**.

Statistical Analysis

We tested our primary hypothesis that early brain WM microstructure is related to cognitive ability by calculating raw, unadjusted Pearson's correlations between tract-average FA, AD, and RD and each MSEL score over time. All possible cross-sectional and predictive relationships were assessed: (1) WM at birth correlating with MSEL scores at ages 1 and 2, (2)

WM at age 1 correlating with MSEL scores at age 1 and 2, and (3) WM at age 2 correlating with MSEL scores at age 2 (See **Figure 4.2** for schematic).

We then investigated the usefulness of WM microstructure as a biomarker of cognitive ability in very young children by modelling the effects of WM microstructure on MSEL scores while controlling for other factors that are known to relate to the MSEL scores: gestational age at birth, age at testing, sex, and maternal education level. We additionally included a nuisance variable, MSEL test date ($DATE_{MSEL}$), controlling for the number of months since study inception to account for any sample drift or variation in cognitive testing administration due to personnel turnover during the ten-year data collection period. These factors were previously identified in an overlapping sample by Girault et. al. (**Chapter 1**, manuscript under review), and were further confirmed in the current dataset using mixed effects models. Mixed model results relating child and demographic factors to MSEL scores are summarized in **Table S4.3** and are discussed below.

Factors influencing 1-year MSEL scores were chronological age at testing, MSEL test date, gestational age at birth, and sex. All of these variables had very small impacts on changes in MSEL scores at age 1; with a one-unit increase in age at MSEL, MSEL test date, and gestational age accounting for less than a tenth of a point of change in MSEL scores. Sex differences were more pronounced, with males scoring more than two points lower than females on the ELC at age 1.

MSEL scores at age 2 were most consistently related to maternal education, with every additional year of education conferring nearly a two-point increase in ELC scores. Some scales significantly varied based on age at testing, though the effect sizes were quite small. Gestational age at birth was positively related to fine motor and expressive language scores at age 2, where ten additional days in the womb relating to a 0.5-point increase in fine motor and a 0.8-point increase in expressive language scores. Sex effects were more pronounced, with males scoring

approximately one point lower on fine motor and visual reception, and nearly five points lower on the ELC at age 2. Gestation number significantly impacted 2-year ELC and receptive language scores, with twins scoring 5.6 points and 1.24 points lower than singletons, respectively.

We additionally probed relationships between child and demographic factors and DTI parameters by tract. We found that FA, AD, and RD at birth are strongly correlated with gestational age at birth, as has been previously reported (Dubois et al., 2014; Geng et al., 2012; Partridge et al., 2004) such that greater time in the womb reflects greater maturation (higher FA, lower AD and RD; **Table S4.4**). These effects are largely not present at ages 1 and 2. This may be due to the significantly lower inter-subject variability in DTI metrics at ages 1 and 2 when compared to birth (**Table S4.5**). Given the strong relationship between gestational age and gestation number ($r = -0.71$, $p < 0.0001$), we also split the sample into twins and singletons and found that the correlations between gestational age and DTI parameters followed the same pattern for AD and RD, although FA at birth was correlated only with gestational age in singletons; twins exhibited weaker correlations between FA and gestational age such that they did not reach statistical significance. Sex differences were observed in a few tracts at birth and at age 1; females exhibited lower AD in the bilateral ILF and higher FA in the bilateral UNC at birth and lower AD in the bilateral ILF and splenium at age 1. Maternal education was not found to correlate with AD or RD at any age, but was correlated with FA at age 1 in three tracts: the bilateral CF-M (*left*: $r = 0.18$, $p = 0.033$; *right*: $r = 0.20$, $p = 0.020$) and the right CT-Par ($r = 0.20$, $p = 0.020$).

To account for such relationships in the data, all adjusted correlations and mixed models included gestational age, age at MSEL testing, sex, maternal education, and gestation number, along with nuisance variables controlling for DTI protocol information (A6, A42, T42) and MSEL test date. These adjusted models were constructed in a similar manner to the raw Pearson's

correlations, such that both cross-sectional and predictive relationships were assessed (**Figure 4.2**). Models included partial Pearson's correlations – for ease of comparing effect sizes to unadjusted correlations – and mixed-effects models, which allow us to account for the relatedness of twins in our sample by treating one twin from each pair as a repeated measure with compound symmetric covariance structure.

Due to the strong correlations of FA, AD, and RD at birth along all tracts with gestational age, and the modest association between gestational age and MSEL scores at age 2, an analysis was also performed to test the hypothesis that white matter at birth mediates the impact of gestational age at birth on cognition at age 2. The mediation analysis involved four steps: (1) show that gestational age at birth and ELC scores at age 2 are correlated, (2) show that gestational age at birth is correlated with the mediator, FA, AD, and RD at birth, treating the mediator as a response variable, (3) show that FA, AD, and RD at birth affect ELC scores at age 2 while controlling for gestational age, and (4) use a Sobel test to evaluate the significance of the mediation. All steps were tested using linear regression models, with FA, AD, and RD for each tract tested separately.

Finally, as an exploratory analysis, we employed a longitudinal modeling technique to test whether trajectories of brain development across the first two years of life are related to cognitive development. Specifically, we tested if brain WM at birth (as a reflection of prenatal brain development; FA_0, AD_0, RD_0), the change in WM properties in the first year of postnatal life ($dFA_{1,0}$, $dAD_{1,0}$, $dRD_{1,0}$; calculated as a simple subtraction of the parameter at the earlier age from that of the later age), or the change in WM properties in the second year of life ($dFA_{2,1}$, $dAD_{2,1}$, $dRD_{2,1}$) related to MSEL 2-year scores, our latest testing point. To do this, we used linear mixed effects models predicting 2-year scores including all three WM measures (i.e. FA_0, $dFA_{1,0}$, and $dFA_{2,1}$) simultaneously while controlling for gestational age (GA), maternal education (MEDUY),

age at MSEL testing (Age_{MSEL}), sex and nuisance variables related to DTI protocol at each age (ScanDir) and MSEL test date ($DATE_{MSEL}$). Only subjects with complete longitudinal data– scans at birth, age 1, and age 2 and cognitive data at age 2 – were included in these analyses, and one twin from each pair was treated as a repeated measure. The statistical model for FA predicting ELC at age 2 (ELC_2) is shown below:

$$ELC_2 = \beta_0 + \beta_{FA_0} FA_0 + \beta_{dFA_{1,0}} dFA_{1,0} + \beta_{dFA_{2,1}} dFA_{2,1} + \beta_{GA} GA +$$
$$\beta_{Age_{MSEL}} Age_{MSEL} + \beta_{sex} sex + \beta_{MEDUY} MEDUY + \beta_{Scanner_0} ScanDir_0 +$$
$$\beta_{Scanner_1} ScanDir_1 + \beta_{Scanner_2} ScanDir_2 + \beta_{DATE_{MSEL}} DATE_{MSEL} + \varepsilon$$

where ELC_2 is the dependent variable and FA_0, $dFA_{1,0}$, $dFA_{2,1}$, GA, Age_{MSEL}, sex, $MEDUY$, $ScanDir_0$, $ScanDir_1$, $ScanDir_2$, and $DATE_{MSEL}$ are the independent variables, and ε is the random error. The models for AD and RD predicting any MSEL 2-year score were constructed in the same manner.

Sample sizes for all analyses are reported in **Table S4.6**. All results from DTI analyses are corrected for multiple comparisons using False Discovery Rate (Benjamini & Hochberg, 1995), such that each model predicting MSEL scores using tract data is corrected for the number of tracts analyzed per DTI parameter (FA, AD, RD). For the unadjusted Pearson's correlations between DTI parameters and MSEL scores which did not include gestation number as a covariate, we also split the sample into twins and singletons to test for the potential group differences in brain-cognition associations. All statistical analyses were performed using SAS statistical software, version 9.4.

RESULTS

The Predictive Value of WM for Present and Future Cognition

Unadjusted Pearson's correlations were computed between tract-average FA, AD, and RD at birth, and ELC scores at ages 1 and 2 (**Table 4.3, Table 4.4**). There were no significant correlations of FA, AD, or RD for any tract at birth with ELC scores at age 1 (**Table 4.3**). In contrast, there were widespread significant correlations across multiple tracts between, FA, AD, and RD, and FA at birth and ELC score at 2 years (**Table 4.4**). Correlations with AD and RD were negative, such that lower, or more mature values were associated with higher scores, while higher (more mature) FA values at birth were associated with higher scores at age 2. DTI parameters at age 1 were not significantly associated with ELC scores at the same age (**Table 4.5**), and only a single negative association of FA in the right CGC tract at age 1 and 2-year ELC scores was found (**Table S4.7**). There were also very few significant cross-sectional associations of tract-based DTI parameters with ELC scores, only 2 at age 1 (FA in the left CT-M and splenium) and none at age 2 (**Table S4.8**).

Examination of relationships between the five MSEL scales (fine and gross motor, expressive and receptive language, visual reception) and tract-based DTI parameters revealed interesting associations. There were widespread significant associations of FA, AD, and RD across most tracts at birth and fine motor scores at age 1 (**Table 4.3**). In addition, there were several significant associations between AD and RD at birth and expressive and receptive language at age 1, especially in cortico-thalamic, arcuate, and association tracts, including the IFOF, ILF, SLF, and CGC. There were widespread associations of FA and RD at birth with gross motor and receptive language at age 2 and widespread associations of AD and RD at birth with fine motor and expressive language at age 2 (**Table 4.4**). FA in several association tracts at birth were correlated with visual reception at age 2. There were no significant associations between year 1

DTI parameters and year 2 MSEL scales except for FA in the left CGC and receptive language and FA in the right ARC-TP and fine motor scores.

There were widespread cross-sectional associations of FA and RD with gross and fine motor scores at age 1; AD was less frequently associated with motor scores. AD, and especially RD, was associated with expressive language at age 1 (**Table 4.5**). There were no cross-sectional associations at age 2.

Sensitivity analyses splitting the sample into twins and singletons revealed similar results (data not shown). Most correlations were of a similar magnitude and direction, although they did not always reach statistical significance, likely due to a reduction in sample sizes.

DTI Measures of WM as Biomarkers of Cognitive Ability

A very different pattern of associations emerged after adjusting correlations for covariates, including gestational age, gestation number, age at assessment, sex, MSEL test date, maternal education, and DTI protocol. A summary of the number of statistically significant results across analyses and by parameter (FA, AD, RD) can be seen in **Figure 4.3**.

As with the unadjusted results, there were no significant correlations between DTI parameters in any tract at birth and ELC scores at age 1; there were fewer significant associations with fine motor and receptive language scale scores. (**Table 4.6**). In contrast to the widespread significant unadjusted associations between DTI parameters at birth and MSEL scores at age 2, there were none for adjusted correlations (**Table S4.9**). There were no significant associations for DTI parameters at age 1 and any MSEL score at age 2 (**Table S4.10**).

There were fairly widespread cross-sectional associations at age 1 for and FA and RD and ELC scores, in contrast to no significant associations for unadjusted correlations (**Table 4.7**).

However, there were fewer significant correlations with fine and gross motor scores, and no correlations with expressive language compared to unadjusted results. At age 2, adjusted and unadjusted results were very similar; there were no significant associations, except AD in left ARC-FP and right ILF with receptive language (**Table S4.11**).

Linear mixed models treating each twin from a twin-pair as repeated measures were conducted to account for the relatedness of twins. The results from these analyses are highly similar to those from partial correlations, though fewer FA results are found to be significant, possibly due to the reduction in the number unique subjects, and the ELC at age 2 was found to be positively related to AD in the left SLF.

Mediation Analysis

Analyses testing for the mediating effect of WM at birth on the association between gestational age and ELC scores at age 2 returned no significant results for any tract, and thus including FA, AD, or RD at birth had no impact on the association between gestational age and 2yr ELC scores. Mediation analyses were conducted on the entire sample, a subset of subjects excluding one twin from each pair, and the singletons only – results (not shown) were highly similar between models.

Longitudinal Changes in WM and 2-year Cognitive Scores

Mixed effects models testing for the relationships between WM properties at birth (FA_0, AD_0, RD_0), the change in WM properties from birth to age 1 ($dFA_{1,0}$, $dAD_{1,0}$, $dRD_{1,0}$) and the change from age 1 to age 2 ($dFA_{2,1}$, $dAD_{2,1}$, $dRD_{2,1}$), while controlling for covariates, revealed a few significant results (**Table 4.8**). Higher ELC scores were predicted by a slower decrease in AD from 1 to 2 years in the right SLF. Higher receptive language scores at age 2 were predicted by

slower decreases in RD from 1 to 2 years in several tracts including the bilateral ARC-FT, right CF-M, right ARC-TP, right CT-PM, the left CT-M, left CGC, left IFOF, left ILF, and left SLF. Higher receptive language scores were also predicted by a faster decrease from 1 to 2 years in RD in the left CT-PFC, and less increase in FA in the left CT-Par. Higher gross motor scores were predicted by a slower increase in FA from birth to 1 year in the left UNC, while higher visual reception was predicted by higher FA at birth in the left CT-PM.

DISCUSSION

In the present study, we found widespread unadjusted correlations between tract-average measures of FA, AD, and RD at birth and cognitive outcomes at ages 1 and 2, suggesting that white matter microstructure at birth is modestly predictive of cognitive function at age 2 years. We also found that WM microstructure at age 1, especially RD, was related to concurrent cognition, suggesting that RD may be a particularly important factor reflecting individual differences in WM development at this age. Analyses controlling for variables related to children's cognitive scores and WM integrity, such as maternal education, sex, and gestational number, reveal that FA, AD and RD at birth may not be useful biomarkers of infant ability, as correlations weakened and became nonsignificant as other covariates with stronger associations to cognition were introduced in the model. However, some correlations between FA and AD at birth and fine motor and receptive language scores at age 1, as well as correlations between FA, AD, and RD at age 1 and concurrent ELC and gross and fine motor scores remained significant. Finally, our exploratory analysis investigating the relationship between developmental trajectories of tract-based WM from birth to age 2 and cognition at age 2 revealed that generally slower rates of change in RD in the second year of life, possibly reflecting more protracted myelination, related to better

receptive language scores across a few projection and many association fibers, some of which are known support language development in children and adults. Taken together, our findings suggest that early postnatal WM integrity is important for infant cognition, though its role in cognitive development should be considered alongside other important child and demographic factors, such as sex, gestational age and gestation number, and maternal education level.

White Matter at Birth and Future Cognition

The majority of the significant correlations were found between WM measures at birth and subsequent cognition, and the remaining findings were largely between WM at age 1 and concurrent cognition. This suggests that WM microstructure at birth carries particularly important information for future cognitive development, even up to two years post-birth. The brain undergoes substantial development in utero, with processes of neurogenesis and neural migration dominating during the majority of the second trimester, followed by synapse formation and refinement occurring during the late second into the third trimester. Around week 28 of gestation, oligodendrocytes begin to myelinate long-range axons, though relatively few axons are fully myelinated at birth (Stiles, Reilly, Levine, Trauner, & Nass, 2012). At birth, major fiber bundles are present, organized, and "adult-like" in their structure, enough so to be reliably reproduced in our study and others (Dubois et al., 2008; Dubois, Hertz-Pannier, Dehaene-Lambertz, Cointepas, & Le Bihan, 2006; Hermoye et al., 2006) using neuroanatomically-driven fiber tractography techniques. Brain connectivity studies using probabilistic tractography have also shown that hubs of major WM networks found in adults are in place by 30 weeks gestation (Ball et al., 2014). Taken together, the findings suggest that prenatal brain development sets the stage for foundational WM microstructure and subsequent infant cognitive abilities.

The lack of significant brain-cognition relationships between WM at ages 1 and 2 and general cognition at age 2 is puzzling given that cognitive ability at age 2 is a more stable predictor of school-age intelligence (**Chapter 1**, manuscript under review). The lack of such findings could be attributed to reduced power to detect effects from smaller sample sizes. Alternatively, given that the standard deviation in FA, AD, and RD among individuals is significantly lower at ages 1 and 2 than at birth, is possible that individual differences between WM integrity at these ages lack the ability, on their own, to predict variance in cognitive scores at age 2. Finally, it is also possible that WM integrity at ages 1 and 2 represent transient individual differences without long-term consequences.

RD: A Marker of Overall White Matter Integrity During Brain Development

Of all uncorrected correlations, RD accounted for the largest proportion of the significant findings, while AD and FA accounted for equal portions of the remaining findings. As expected, the direction of findings suggest that better cognitive scores are associated with greater levels of maturation in fiber bundles (lower RD and AD, higher FA). Interpreting the biological mechanisms underlying changes in diffusion parameters is not trivial, especially in the context of early development when many processes may simultaneously contribute to the diffusion signal. In humans, RD and FA change most rapidly across the first years of life, with AD showing lower rates of maturation (Geng et al., 2012). Additionally, tracts do not appear to maintain the same rank-order (i.e. lowest RD tracts at birth are not the lowest RD tracts at age 2), suggesting that rates of RD development could be important individual difference factors (Geng et al., 2012). Finally, Dubois and colleagues (Dubois et al., 2014) posit that, while FA and AD are good markers of fiber organization and are sensitive to characterizing fiber compactness and structure, the

interpretation of their changes across early development may be difficult to discern given that they may increase or decrease in response to various developmental events including premyelination (FA increases, AD increases), myelination (FA increases, AD could decrease or remain the same), and the myelination of crossing fibers (FA decreases as the secondary bundle myelinates, AD decreases). On the other hand, RD consistently decreases across the different stages of WM development, making it a relatively strong marker of overall maturation, particularly during infancy (Dubois et al., 2014). Our findings echo this, with RD being the most consistent predictor of cognition in infants. However, we found no relationships between RD and cognition at age 2, suggesting that there may be a ceiling effect in the developmental trajectory of RD, making it difficult to relate to variation in cognitive scores at this age.

Interestingly, previous work had identified that common factors of AD at birth, age 1, and age 2 were related to ELC scores at ages 1 and 2 whereas common factors of FA and RD at only age 1 were related to ELC scores (S. J. Lee et al., 2017). The apparent differences in findings are likely best explained by the inherent differences in the study design and methodology. The previous study investigated correlations between data-derived common factors of DTI parameters with the goal of studying groups of developmentally-related tracts and their associations with child ability, whereas in this study we directly performed tract-wise correlations to achieve a better understanding of the neurobiology of early cognition by probing specific brain-cognition relationships. Additionally, Lee and colleagues (2017) performed their factor analysis using twelve major fiber bundles implicated in cognition in older adults (Penke et al., 2010), whereas in the present study we included seventeen more tracts which included motor, sensorimotor, and higher-order association fibers like the SLF, IFOF, and additional segments of the arcuate. However, importantly, these studies do have commonalities among their major findings, which are discussed

further below, and include the age-specific nature of brain-cognitions relationships, very similar effect sizes, and the potentially important role for protracted WM development in supporting cognition.

White Matter Spanning the Brain is Associated with Cognition Across Domains

Generally, we found widespread relationships between WM tracts and cognitive scores, suggesting that global brain WM integrity is related to cognition at early ages, as opposed to tract-specific findings. This is particularly true for WM at birth and its relationships to cognition in infancy; fine motor, expressive language, and receptive language scores are all correlated with similar tracts, which include arcuate language tracts, sensory relay projection tracts, and higher-order association tracts. The same is true for the correlations between all motor and language scores at age 1 and concurrent WM integrity. Such widespread associations are not surprising as microstructure is highly correlated across tracts at birth (S. J. Lee et al., 2017). At age 1, however, visual reception scores appear to have more functionally-specific correlations with tracts shown to be related to visual processing in adults and children. For example, the bilateral ILF, the right SLF, and the splenium were found to relate to visual reception at age 2, and it is known that the SLF and ILF play important roles in the processing of visual information (Shinoura et al., 2009; Thiebaut de Schotten et al., 2011) and the splenium may also support visual perception through interhemispheric transfer of visual information (C. G. Gross, Bender, & Mishkin, 1977) as well as visual orienting (Elison, Wolff, et al., 2013b).

The widespread associations found between WM integrity and infant cognition may also be the result of imprecise measurement of specific cognitive tasks in infancy due to the difficulty of testing infants and tapping individual cognitive constructs which often depend on language

skills for instruction and response. Infant cognitive tasks also rely heavily on a child's fine motor skills, and thus the observed correlations between infant cognition across domains and sensorimotor projections tracts from the brainstem and thalamus to the cortex are likely true associations, given the types of cognitive tasks administered. Additionally, widespread correlations may be reflective of the highly plastic nature of the infant brain, in which tracts have yet to develop their functionally specific role in cognition. Alternatively, the high correlations of WM properties between tracts (S. J. Lee et al., 2017) and coordinated development among tracts at these ages may make it difficult to discern which tracts are specifically contributing to domain-specific cognition. A previous study from our group also found global associations between a common factor of WM development and general infant cognition (S. J. Lee et al., 2017), while another earlier study showed tract-specific correlations with working memory scores (Short et al., 2013), suggesting that tapping specific cognitive domains using different task-based assessments may be necessary to identify functionally specific results.

WM Integrity as a Biomarker of Cognition

To determine how informative WM microstructure is as a biomarker of infant cognition, we tested for the effects of WM on MSEL scores while controlling for other variables correlated with infant cognition in our sample. In doing so, we found that many of the brain-cognition relationships observed with unadjusted Pearson's correlations were no longer significant and substantially reduced in effect size. There were no longer any significant correlations between WM at birth and 2-year MSEL scores. Many fewer correlations were found between WM at birth and fine motor and receptive language scores at age 1, and they were not with RD, but with FA and AD.

Interestingly, correlations between ELC scores and WM at age 1 emerged after controlling for covariates, mostly with RD, and spread across nearly all WM tracts tested. Similar patterns of findings remained between WM at age 1 and concurrent gross and fine motor scores; no correlations remained with receptive or expressive language or visual reception scores after controlling for covariates. Brain-cognition correlations were detected between AD at age 2 and receptive language scores at age 2 in the left ARC-TP and SLF, two tracts which run parallel to each other and have been implicated in language. However, the direction of effect is opposite of what we would expect; that is, higher AD being correlated with better scores. This opposite relationship with AD has been observed before between AD at ages 1 and 2 and cognition at age 2 (S. J. Lee et al., 2017), and may suggest that children with more protracted AD development in language tracts perform better on these assessments. Taken together, we can see that while WM at birth no longer remains a good predictor of later outcomes, concurrent brain-cognition relationships at age 1 either emerge or remain largely similar, and several functionally specific relationships emerge at age 2 between tract WM and receptive language scores, suggesting that the usefulness of WM as a biomarker varies over time. The age-specific nature of the relationships between WM and cognition in the first two years of life were also noted in a previous study (S. J. Lee et al., 2017). This varying nature in brain-cognition relationships across development may be due to the differences in the reliability of infant cognitive scores across ages, potential differences in the impact of covariates on cognition over time, or simply limitations of our neuroimaging measures to capture subtle, but likely important, dynamic brain-cognition relationships in a single snapshot.

The effect sizes noted in our study are relatively weak, with the absolute value of adjusted correlations between WM tract properties and infant and toddler cognitive scores ranging from

0.13 to 0.25. These effect sizes are nearly identical to those from a previous publication using a factor analysis approach (S. J. Lee et al., 2017), and very similar to those reported in older adults between general factors explaining WM and processing speed (Penke et al., 2010). Effect sizes reported in studies linking WM to working memory in 1-year-olds (Short et al., 2013) and adults (Takahashi et al., 2010) show slightly higher correlations ranging from roughly 0.3 to 0.5. Taken together, these findings suggest that WM microstructure has very modest associations with general ability and slightly higher associations with specific domains such as working memory, but interestingly, these associations appear to be relatively stable across development.

Longitudinal Trajectories of WM Development and Cognition

As an exploratory analysis, we employed a longitudinal model to test whether trajectories of brain development across the first two years of life are related to cognitive scores at age 2. We found that generally slower decreases in RD from age 1 to 2, and to a lesser extent AD, predicted better cognitive scores, namely receptive language scores. Between ages 1 and 2, slower rates of change in AD in the right SLF predicted higher ELC scores at age 2, while slower rates of change in RD in a few projection tracts, the bilateral ARC-FT, and the left lateralized CGC, IFOF, ILF, and SLF predicted higher receptive language scores. These relationships suggest that a prolonged period of WM development and plasticity may be beneficial in creating WM pathways that better support subsequent cognitive development, and in this case particularly language development, in young children. However, faster decreases in RD from ages 1 to 2 in the left CT-PFC did predict higher receptive language scores at age 2, suggesting the effects may be tract-specific. This highlights the dynamic nature of early WM development and its relationship to cognition.

Of note, the receptive language scale is the only inter-sensory scale on the MSEL, meaning

that both auditory and visual information are presented during the course of testing. Infants and toddlers are tested on their ability to understand verbal instructions, auditory-spatial, and auditory-quantitative concepts, such as relative position, size, and length comparisons. For this reason, it is promising that we were able to identify that developmental rates of change in RD in tracts that are known to relate to language (ARC-FT, SLF), as well as tracts which are part of the visual information processing stream (IFOF, ILF), were related to receptive language scores at age 2. Some studies have also shown that the IFOF and ILF play a role in language, though their exact functions remain unclear (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Moritz-Gasser, Herbet, & Duffau, 2013). The CGC was also implicated in receptive language ability; the CGC is primarily thought to play a role in higher-order cognitive control in adults (Metzler-Baddeley et al., 2012; Takahashi et al., 2010) and it may serve a similar role in infants and toddlers. Additionally, we found that protracted development of both AD and RD in the SLF related to higher ELC and receptive language scores at age 2, respectively. The SLF has been implicated in a variety of cognitive functions including working memory (Short et al., 2013; Vestergaard et al., 2011) and language (Alexander, Naeser, & Palumbo, 1987; Kreisler et al., 2000). Protracted development of the SLF has been previously reported from birth to age 5 (Zhang et al., 2007), suggesting that prolonged maturation and possibly prolonged plasticity in this fiber tract may be particularly important for children's cognitive development. A study of myelin content in the brain during early life found that children with more protracted global myelin developmental trajectories performed better on cognitive assessments (Deoni et al., 2014), suggesting that the effect may also be global.

The Contribution of Demographic Factors to WM Microstructure and Cognition

Demographic factors contributed to both brain WM properties and cognitive scores across infancy. WM microstructural properties at birth were strongly correlated with gestational age, such that greater time in the womb reflected greater maturation (higher FA, lower AD and RD) as has been previously reported in several studies (Dubois et al., 2014; Geng et al., 2012; Partridge et al., 2004). Effects of gestational age on DTI measures were not observed at later ages, though research in the field suggests differences in WM properties between preterm and full-term infants may persist into childhood (Constable et al., 2008; Yung et al., 2007). We found that the relationships between gestational age and AD and RD were observed in both twins and singletons, though FA was not related to gestational age in twins. A previous study from our group found that there were no differences in the relationship between FA and gestational age between twins and singletons when modelling developmental trajectories of FA in regions-of-interest from major WM fibers using Gompertz functions (Sadeghi, Gilmore, & Gerig, 2016), suggesting that the lack of correlation between FA and gestational age in twins seen here could be related to the tract-based method or linear modeling approach and deserves further study. We observed sex differences in a few tracts at birth and age 1, with females exhibiting more mature tract properties in the bilateral ILF at birth and age 1, the bilateral UNC at birth, and the splenium of the corpus callosum at age 1, suggesting that females in our sample exhibit greater maturation in areas connecting the temporal poles to the frontal and occipital cortices. We suggest caution in the interpretation of these results as the goal of this study was not to investigate sex differences in brain development, but to consider them in the context of contributing to differences in brain-cognition relationships. Maternal education was not found to correlate with AD or RD in any tract, at any age, and only correlated with FA in 3 of 29 tracts at age 1, specifically corticofugal tracts connecting to the motor

cortex and the right corticothalamic projection to the parietal cortex.

Cognitive scores also varied as a function of certain demographic factors. MSEL scores between ages 1 and 2 were moderately correlated ($0.24 \leq r \leq 0.34$) and influenced by both unique and overlapping sets of demographic and child factors. MSEL scores at age 1 were influenced, though only mildly, by age-related variables including chronological age at testing, MSEL test date, and gestational age at birth, whereas gestational age at birth is only related to fine motor and expressive language scores at age 2. Maternal education was only related to MSEL scores at age 2, with each additional year of maternal education accounting for a nearly two-point increase in ELC scores in offspring; the difference between a mother having a high-school education and a college degree conferred roughly a 7-point (nearly half a standard deviation) advantage to their offspring. This effect could be due to shared genetics between mother and child (Deary et al., 2013), greater socioeconomic advantages (Stumm & Plomin, 2015), potential differences in parenting based on education level (Carr & Pike, 2012), or likely some combination of all three. Our finding that only MSEL scores at age 2, and not age 1, are related to maternal education level is likely due to the increased sophistication of the assessment demands in the 2-year measurements, which then also have a higher correlation with later childhood intelligence, whereas measures at age 1 are less reliably related to a child's later performance (**Chapter 1**, manuscript under review).

Scores at both ages were impacted by sex, with females scoring roughly 2.5 points higher on the ELC at age 1 and nearly 5 points higher on the ELC at age 2 than males. Early differences in cognition between the sexes have been reported, although these differences appear to attenuate with age (Stumm & Plomin, 2015). The factor with the largest impact on ELC scores was gestation number; by age 2, twins scored 5.6 points lower on the age-standardized ELC than did singletons. Differences in cognitive scores between twins and singletons have been previously reported in this

sample and others, with a roughly 6-point difference in IQ being noted across the lifespan (Bishop et al., 2003; Ronalds et al., 2005; Stumm & Plomin, 2015).

Taken together, we can see that there are both shared and unique demographic factors that contribute to WM microstructure and cognitive scores across the first two years of life. Namely, gestational age at birth seems to have an important contribution to WM integrity at birth, but relatively little contribution to later WM. Gestational age at birth has a direct effect on ELC scores at age 2 which are not mediated by WM at birth, however when gestational age at birth is included alongside other variables including maternal education and gestational number, its effect on cognition at age 2 is minimal. Alternatively, maternal education significantly impacts offspring MSEL scores at age 2, but has little to no bearing on earlier MSEL scores or WM development. Sex and gestation number, on the other hand, contribute, at least to some extent, to both brain and cognitive development across infancy and into toddlerhood.

Limitations

Results should be considered in the context of several limitations. Interpreting measures of WM microstructure derived from DTI is not trivial. While we have some knowledge as to how FA, AD and RD develop over time, and how they may relate to primary developmental processes such as fiber organization, premyelination, and myelination, we cannot be certain that other confounding factors such as crossing fibers and partial volume effects are not influencing the diffusion of water molecules in the brain (Dubois et al., 2014; Vos, Jones, Viergever, & Leemans, 2011). The quantitative tractography method utilized in this study was well suited to discern specific brain-cognition associations, however the majority of our results did not show tract-specific functionality, nor very many parameter-specific trends, and therefore it may be more

fruitful to characterize WM development in early life using connectomics approaches which may be better descriptors of global WM structure and do not necessitate interpreting diffusion metrics. The generalizability of our study may also be impacted by the relatively large sample of twin-born subjects in our dataset. However, despite observed cognitive differences between twins and singletons, we suspect that patterns of brain-cognition relationships are similar across groups, given that there were not major differences in WM development between twins and singletons. Finally, there are inherent limitations with studying infants and toddlers with regards to both imaging techniques and cognitive assessments. Motion in the scanner is always a concern, but to mitigate these effects we performed rigorous automated and manual quality control on both the scans and individual tracts from each subject and excluded subjects with data that were not of usable quality. Cognitive assessments are often difficult to collect in young children due to limited language and variable temperament, however our data were collected by experienced testers and independently reviewed to ensure that scores reflect child ability.

Conclusion

Our study has shown that there are widespread correlations between tract-average measures of FA, AD, and RD at birth and cognitive outcomes at ages 1 and 2. We also found that WM microstructure at age 1 was related to concurrent cognition. We demonstrated that RD may be a particularly important marker of individual differences in WM development, and that protracted development of RD, possibly reflecting prolonged plasticity, in many tracts between the ages of 1 and 2 is correlated with better receptive language and general cognitive performance. We also found that cognition at age 2 was poorly predicted by WM properties across infancy when other child and demographic factors were included in the model. Namely, maternal education and

gestational number were most highly correlated with 2-year cognitive scores. Taken together, our findings suggest that early postnatal WM integrity is important for infant cognition, though its usefulness in predicting cognitive outcomes is limited when considered alongside other important child and demographic factors. Future research is needed to better understand how global WM organization relates to cognitive development in early life. Longitudinal studies of complex network organization using non-linear multivariate approaches may be more fruitful.

Table 4.1 Participant Demographics

Child Characteristics	**N, Mean (SD, Percent)**
Gestational Age at Birth (days)	266.68 (12.44)
Birth Weight (grams)	2984.3 (581.20)
Stay in NICU	19 (4.25%)
Age at Neo MRI (days)	27.25 (15.08)
Age at 1yr MRI (days)	90.65 (24.90)
Age at 2yr MRI (days)	756.48 (31.30)
Age at 1yr Mullen (days)	388.60 (23.43)
Age at 2yr Mullen (days)	752.99 (26.58)
1yr ELC	116.37 (12.88)
2yr ELC	107.75 (15.51)
Male / Female	240 (53.69%)
Female	207 (46.31%)
Single Gestation	211 (47.20%)
Twin Gestation	236 (52.80%)
Zygosity	
Dizygotic Twins	137 (58.80%)
Monozygotic Twins	85 (36.48%)
Opposite Sex Twins	11 (4.72%)
Parental Characteristics *	
Maternal Age (years)	30.23 (5.47)
Paternal Age (years)	32.11 (5.96)
Mother Education (years)	15.61 (3.37)
Father Education (years)	15.19 (3.68)
Total Household Income ($)	$74,128 ($55,575)
Maternal / Paternal Race	
White	339 (75.84%) / 319 (72.50%)
American Indian or Alaskan Native	2 (0.45%) / 0 (0%)
African American	95 (21.25%) / 103 (23.41%)
Asian	11 (2.46%) / 18 (4.09%)
Maternal / Paternal Ethnicity	
Hispanic	50 (11.19%) / 58 (13.12%)
Non-Hispanic	397 (88.81%) / 384 (86.88%)

**reported at the time of the child's birth*

Table 4.2. Diffusion Tensor Imaging Acquisition Protocols
Scan frequencies are listed by year and scanner and direction protocol. Percentages for each scanner and direction combination are listed by year and for all scans.

Scanner & Direction	*Neonate*	*Year 1*	*Year 2*	*Total Scans*
Allegra, 6 Direction (A6)	183 (55.12%)	87 (34.12%)	61 (33.70%)	331 (43.1%)
Allegra, 42 Direction (A42)	100 (30.12%)	119 (46.67%)	78 (43.09%)	297 (38.67%)
Trio, 42 Direction (T42)	49 (14.76%)	49 (19.22%)	42 (23.30%)	140 (18.23%)

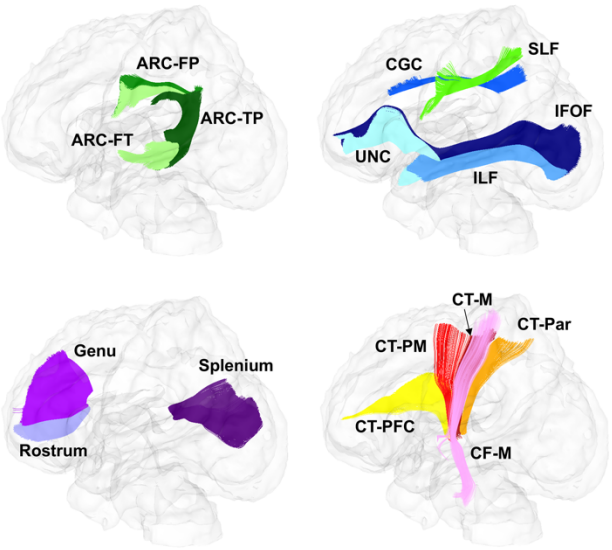


Figure 4.1. Neonatal and Pediatric White Matter Tracts.
Tracts analyzed in the study are displayed. Abbreviations for tracts are as follows: Arcuate fronto-parietal (ARC-FP), fronto-temporal (ARCT-FT), and temporo-parietal (ARC-TP) segments, cingulum (CGC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), uncinate (UNC), genu, rostrum, splenium, corticofugal motor tracts (CF-M; pink, partially transparent to show parallel CT-M), and the corticothalamic prefrontal (CT-PFC), premotor (CT-PM), motor (CT-M; dark maroon indicated with a black arrow), and parietal (CT-Par) tracts. To denote left or right, "(L)" or "(R)" are added to tract abbreviations in tables. Tracts on display are from the neonatal atlas; 1 and 2-year tracts are structurally similar, but were constructed in pediatric atlas space as described in the methods.

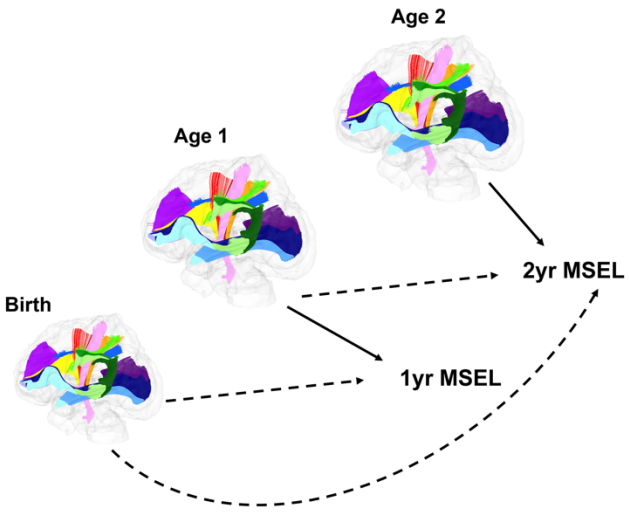


Figure 4.2. Study Schematic.

We tested for possible predictive (dashed lines) and cross-sectional (solid lines) brain-cognition relationships in our dataset. Arrows between each imaging and MSEL collection time-point indicates a tested relationship.

Table 4.3. Unadjusted Pearson's Correlations between DTI Parameters at Birth and Cognitive Scores at age 1.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	ELC - 1yr			GM - 1yr			FM - 1yr			EL - 1yr			RL - 1yr			VR - 1yr		
Tract	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**
ARC-FP (L)	*0.00*	*-0.02*	*0.06*	*-0.13*	*-0.12*	*0.06*	**-0.14**	**-0.19**	**0.23**	*-0.07*	*-0.09*	*0.10*	*-0.07*	*-0.09*	*0.13*	*-0.04*	*-0.08*	*0.13*
ARC-FP (R)	*-0.06*	*-0.09*	*0.12*	*-0.04*	*-0.03*	*0.02*	*-0.10*	**-0.14**	**0.17**	*-0.07*	*-0.07*	*0.05*	**-0.14**	**-0.16**	*0.16*	*-0.11*	*-0.13*	*0.15*
ARC-FT (L)	*-0.06*	*-0.05*	*0.05*	*-0.08*	*-0.06*	*0.01*	**-0.14**	**-0.20**	**0.23**	*-0.08*	*-0.08*	*0.05*	*-0.11*	*-0.11*	*0.11*	*-0.09*	*-0.10*	*0.10*
ARC-FT (R)	*-0.05*	*-0.09*	*0.11*	*-0.10*	*-0.08*	*0.04*	**-0.18**	**-0.21**	**0.22**	*-0.10*	*-0.12*	*0.11*	**-0.15**	**-0.15**	*0.12*	*-0.09*	*-0.10*	*0.11*
ARC-TP (L)	*-0.06*	*-0.08*	*0.11*	*-0.05*	*-0.07*	*0.14*	*-0.08*	*-0.12*	**0.19**	*-0.08*	*-0.11*	*0.08*	*-0.08*	*-0.09*	*0.08*	*-0.12*	*-0.13*	*0.11*
ARC-TP (R)	*-0.06*	*-0.07*	*0.08*	*-0.08*	*-0.10*	*0.09*	**-0.17**	**-0.20**	**0.21**	*-0.13*	*-0.13*	*0.10*	**-0.15**	**-0.14**	*0.09*	*-0.09*	*-0.09*	*0.08*
CF-M (L)	*-0.11*	*-0.12*	*0.07*	*-0.13*	**-0.16**	*0.13*	**-0.25**	**-0.25**	**0.15**	*-0.12*	**-0.17**	*0.15*	**-0.14**	**-0.17**	*0.13*	*-0.10*	*-0.10*	*0.07*
CF-M (R)	*-0.14*	*-0.14*	*0.08*	*-0.10*	*-0.15*	*0.12*	**-0.24**	**-0.27**	**0.20**	**-0.17**	**-0.18**	*0.13*	**-0.18**	**-0.17**	*0.10*	*-0.08*	*-0.12*	*0.10*
CGC (L)	*-0.15*	*-0.08*	*-0.07*	*-0.14*	*-0.13*	*0.01*	**-0.19**	**-0.23**	**0.12**	**-0.15**	*-0.12*	*-0.01*	**-0.17**	**-0.14**	*0.00*	*-0.06*	*-0.06*	*0.03*
CGC (R)	*-0.08*	*-0.07*	*0.00*	*-0.08*	*-0.12*	*0.10*	**-0.12**	**-0.21**	**0.18**	*-0.10*	*-0.13*	*0.08*	*-0.13*	**-0.14**	*0.04*	*-0.03*	*-0.04*	*0.03*
CT-M (L)	*-0.12*	*-0.11*	*0.06*	*-0.14*	*-0.14*	*0.09*	**-0.27**	**-0.26**	**0.18**	*-0.13*	*-0.17*	*0.15*	**-0.17**	**-0.15**	*0.08*	*-0.13*	*-0.11*	*0.06*
CT-M (R)	*-0.12*	*-0.11*	*0.05*	*-0.13*	*-0.14*	*0.09*	**-0.28**	**-0.26**	**0.17**	**-0.16**	**-0.16**	*0.09*	**-0.17**	**-0.16**	*0.08*	*-0.10*	*-0.11*	*0.09*
CT-Par (L)	*-0.11*	*-0.11*	*0.08*	*-0.15*	**-0.16**	*0.10*	**-0.24**	**-0.25**	**0.20**	*-0.12*	**-0.16**	*0.15*	**-0.17**	**-0.16**	*0.11*	*-0.09*	*-0.09*	*0.06*
CT-Par (R)	*-0.13*	*-0.12*	*0.08*	*-0.13*	**-0.16**	*0.14*	**-0.24**	**-0.25**	**0.20**	**-0.16**	**-0.18**	*0.13*	**-0.16**	**-0.17**	*0.13*	*-0.08*	*-0.10*	*0.08*
CT-PFC (L)	*-0.07*	*-0.06*	*0.06*	*-0.13*	*-0.10*	*0.04*	**-0.18**	**-0.20**	**0.21**	*-0.10*	*-0.10*	*0.10*	*-0.11*	*-0.10*	*0.10*	*-0.08*	*-0.09*	*0.09*
CT-PFC (R)	*-0.06*	*-0.05*	*0.03*	*-0.13*	*-0.10*	*0.01*	**-0.17**	**-0.19**	**0.19**	*-0.10*	*-0.09*	*0.05*	*-0.09*	*-0.08*	*0.08*	*-0.05*	*-0.07*	*0.08*
CT-PM (L)	*-0.09*	*-0.09*	*0.07*	*-0.12*	*-0.10*	*0.05*	**-0.23**	**-0.24**	**0.19**	**-0.15**	**-0.15**	*0.12*	**-0.14**	**-0.14**	*0.10*	*-0.10*	*-0.11*	*0.07*
CT-PM (R)	*-0.09*	*-0.09*	*0.06*	*-0.12*	*-0.11*	*0.04*	**-0.23**	**-0.25**	**0.19**	**-0.15**	*-0.13*	*0.08*	**-0.16**	**-0.15**	*0.08*	*-0.09*	*-0.12*	*0.10*
IFOF (L)	*-0.05*	*-0.07*	*0.06*	*-0.14*	*-0.10*	*0.01*	**-0.15**	**-0.21**	**0.21**	*-0.12*	*-0.12*	*0.06*	*-0.10*	*-0.10*	*0.07*	*-0.02*	*-0.07*	*0.11*
IFOF (R)	*-0.06*	*-0.08*	*0.06*	*-0.15*	*-0.12*	*0.04*	**-0.16**	**-0.21**	**0.22**	*-0.12*	*-0.12*	*0.07*	**-0.13**	*-0.12*	*0.08*	*-0.05*	*-0.08*	*0.10*
ILF (L)	*-0.07*	*-0.08*	*0.04*	*-0.09*	*-0.08*	*0.03*	**-0.13**	**-0.21**	**0.21**	*-0.11*	*-0.11*	*0.04*	*-0.11*	*-0.10*	*0.05*	*-0.04*	*-0.08*	*0.09*
ILF (R)	*-0.09*	*-0.09*	*0.06*	*-0.16*	*-0.12*	*0.02*	**-0.18**	**-0.25**	**0.22**	*-0.12*	*-0.12*	*0.06*	**-0.16**	**-0.13**	*0.05*	*-0.10*	*-0.09*	*0.05*
SLF (L)	*-0.06*	*-0.05*	*0.00*	*-0.11*	*-0.10*	*0.05*	**-0.19**	**-0.21**	**0.17**	*-0.04*	*-0.07*	*0.09*	*-0.09*	*-0.10*	*0.08*	*-0.09*	*-0.09*	*0.06*
SLF (R)	*-0.10*	*-0.13*	*0.13*	*-0.05*	*-0.04*	*0.02*	**-0.17**	**-0.19**	**0.15**	*-0.07*	*-0.10*	*0.09*	**-0.15**	**-0.18**	*0.14*	*-0.12*	*-0.14*	*0.14*
UNC (L)	*-0.08*	*-0.09*	*0.10*	*-0.09*	*-0.07*	*0.01*	**-0.16**	**-0.20**	**0.22**	*-0.10*	*-0.10*	*0.08*	*-0.10*	*-0.10*	*0.09*	*-0.05*	*-0.08*	*0.10*
UNC (R)	*-0.08*	*-0.08*	*0.07*	*-0.12*	*-0.10*	*0.04*	**-0.18**	**-0.21**	**0.20**	*-0.10*	*-0.10*	*0.07*	*-0.11*	*-0.10*	*0.07*	*-0.06*	*-0.08*	*0.08*
CC-Genu	*-0.05*	*-0.08*	*0.09*	*-0.12*	*-0.10*	*0.07*	**-0.18**	**-0.23**	**0.24**	*-0.09*	*-0.11*	*0.10*	*-0.08*	*-0.10*	*0.11*	*-0.06*	*-0.08*	*0.10*
CC-Rostrum	*-0.05*	*-0.08*	*0.09*	*-0.10*	*-0.11*	*0.07*	**-0.17**	**-0.22**	**0.20**	*-0.08*	*-0.09*	*0.08*	*-0.07*	*-0.09*	*0.08*	*-0.06*	*-0.09*	*0.09*
CC-Splenium	*-0.08*	*-0.09*	*0.06*	*-0.10*	*-0.12*	*0.07*	**-0.13**	**-0.25**	**0.25**	*-0.12*	**-0.18**	*0.14*	*-0.09*	*-0.11*	*0.07*	*-0.05*	*-0.07*	*0.09*

Table 4.4. Unadjusted Pearson's Correlations between DTI Parameters at Birth and Cognitive Scores at age 2.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	ELC - 2yr			GM - 2yr			FM - 2yr			EL - 2yr			RL - 2yr			VR - 2yr		
Tract	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**
ARC-FP (L)	**-0.21**	**-0.22**	**0.19**	*-0.14*	**-0.15**	**0.14**	**-0.17**	**-0.16**	*0.12*	**-0.16**	**-0.16**	*0.14*	*-0.14*	**-0.17**	**0.18**	*-0.17*	*-0.18*	*0.14*
ARC-FP (R)	**-0.19**	**-0.18**	*0.13*	*-0.08*	*-0.10*	*0.10*	*-0.09*	*-0.09*	*0.08*	**-0.19**	**-0.17**	*0.11*	*-0.12*	**-0.15**	*0.12*	*-0.13*	*-0.13*	*0.10*
ARC-FT (L)	**-0.23**	**-0.19**	*0.07*	*-0.08*	*-0.11*	*0.13*	**-0.19**	**-0.16**	*0.07*	**-0.20**	**-0.15**	*0.03*	*-0.17*	**-0.16**	*0.08*	*-0.13*	*-0.12*	*0.06*
ARC-FT (R)	**-0.22**	**-0.20**	**0.14**	*-0.13*	*-0.11*	*0.09*	**-0.16**	**-0.15**	*0.09*	**-0.16**	**-0.15**	*0.11*	*-0.17*	**-0.17**	**0.14**	*-0.15*	*-0.14*	*0.11*
ARC-TP (L)	*-0.12*	*-0.13*	*0.09*	*-0.12*	*-0.14*	*0.07*	*-0.07*	*-0.09*	*0.07*	*-0.11*	*-0.12*	*0.07*	*-0.10*	*-0.11*	*0.04*	*-0.01*	*-0.03*	*0.06*
ARC-TP (R)	**-0.21**	**-0.22**	**0.18**	*-0.08*	*-0.09*	**0.14**	**-0.15**	**-0.17**	*0.13*	**-0.18**	**-0.17**	*0.13*	*-0.16*	**-0.17**	**0.17**	*-0.16*	*-0.15*	*0.14*
CF-M (L)	**-0.15**	**-0.17**	0.11	*-0.06*	**-0.14**	**0.16**	**-0.16**	**-0.15**	*0.07*	*-0.11*	**-0.14**	*0.11*	*-0.06*	**-0.14**	**0.15**	*-0.07*	*-0.11*	*0.09*
CF-M (R)	**-0.13**	**-0.20**	**0.17**	*-0.06*	**-0.14**	**0.16**	**-0.15**	**-0.18**	*0.12*	*-0.12*	**-0.16**	*0.13*	*-0.04*	**-0.16**	**0.20**	*-0.07*	*-0.13*	*0.13*
CGC (L)	**-0.16**	**-0.16**	*0.03*	*-0.11*	**-0.14**	*0.09*	**-0.15**	**-0.17**	*0.05*	**-0.17**	**-0.15**	*-0.01*	*-0.09*	*-0.11*	*0.05*	*-0.06*	*-0.09*	*0.06*
CGC (R)	**-0.20**	**-0.14**	*-0.06*	*-0.10*	*-0.13*	*0.07*	**-0.20**	**-0.16**	*-0.05*	**-0.16**	*-0.12*	*-0.04*	*-0.11*	*-0.09*	*0.00*	*-0.15*	*-0.11*	*-0.02*
CT-M (L)	**-0.21**	**-0.19**	*0.11*	*-0.10*	**-0.15**	**0.15**	**-0.20**	**-0.17**	*0.08*	**-0.18**	**-0.16**	*0.11*	*-0.13*	**-0.15**	**0.14**	*-0.12*	*-0.13*	*0.09*
CT-M (R)	**-0.16**	**-0.21**	**0.19**	*-0.07*	**-0.15**	**0.20**	**-0.17**	**-0.19**	*0.14*	**-0.13**	**-0.16**	*0.13*	*-0.08*	**-0.15**	**0.18**	*-0.08*	*-0.14*	**0.16**
CT-Par (L)	**-0.17**	**-0.18**	**0.13**	*-0.10*	**-0.15**	**0.15**	**-0.16**	**-0.17**	*0.11*	**-0.16**	**-0.15**	*0.11*	*-0.09*	**-0.14**	**0.15**	*-0.08*	*-0.13*	*0.13*
CT-Par (R)	**-0.17**	**-0.20**	**0.16**	*-0.11*	**-0.17**	**0.18**	**-0.15**	**-0.19**	*0.15*	**-0.15**	**-0.16**	*0.10*	*-0.08*	**-0.15**	**0.17**	*-0.09*	*-0.15*	*0.14*
CT-PFC (L)	**-0.16**	**-0.15**	*0.11*	*-0.13*	*-0.13*	*0.12*	**-0.17**	**-0.18**	*0.13*	**-0.13**	*-0.12*	*0.09*	*-0.12*	*-0.12*	*0.11*	*-0.10*	*-0.09*	*0.07*
CT-PFC (R)	**-0.15**	**-0.17**	**0.16**	*-0.09*	*-0.13*	**0.16**	**-0.19**	**-0.20**	**0.16**	*-0.12*	**-0.13**	*0.12*	*-0.10*	**-0.13**	**0.16**	*-0.08*	*-0.10*	*0.11*
CT-PM (L)	**-0.20**	**-0.21**	**0.13**	*-0.11*	*-0.12*	*0.11*	**-0.19**	**-0.17**	*0.09*	**-0.19**	**-0.18**	*0.11*	*-0.12*	**-0.16**	**0.16**	*-0.12*	*-0.14*	*0.12*
CT-PM (R)	**-0.16**	**-0.20**	**0.17**	*-0.08*	**-0.14**	**0.17**	**-0.19**	**-0.19**	*0.12*	**-0.16**	**-0.17**	*0.12*	*-0.06*	**-0.15**	**0.20**	*-0.06*	*-0.13*	**0.15**
IFOF (L)	*-0.12*	**-0.19**	**0.21**	*-0.12*	**-0.14**	**0.15**	**-0.16**	**-0.20**	**0.18**	*-0.11*	**-0.15**	*0.14*	*-0.07*	**-0.15**	**0.19**	*-0.06*	*-0.12*	**0.17**
IFOF (R)	**-0.16**	**-0.19**	**0.19**	*-0.13*	**-0.14**	**0.15**	**-0.17**	**-0.21**	**0.19**	**-0.15**	**-0.16**	*0.13*	*-0.10*	**-0.16**	**0.19**	*-0.08*	*-0.12*	**0.15**
ILF (L)	**-0.13**	**-0.20**	**0.20**	*-0.09*	*-0.13*	*0.13*	*-0.12*	**-0.18**	**0.17**	**-0.13**	**-0.15**	*0.12*	*-0.08*	**-0.17**	**0.21**	*-0.07*	*-0.14*	**0.17**
ILF (R)	**-0.21**	**-0.25**	**0.19**	*-0.14*	**-0.14**	*0.10*	**-0.15**	**-0.21**	**0.19**	**-0.19**	**-0.20**	*0.12*	*-0.15*	**-0.22**	**0.19**	*-0.13*	*-0.18*	**0.17**
SLF (L)	**-0.19**	**-0.17**	*0.08*	*-0.08*	**-0.14**	**0.17**	**-0.15**	**-0.14**	*0.07*	**-0.19**	**-0.16**	*0.07*	*-0.12*	**-0.13**	*0.10*	*-0.10*	*-0.10*	*0.05*
SLF (R)	**-0.19**	**-0.21**	**0.15**	*-0.11*	**-0.16**	**0.17**	**-0.18**	**-0.19**	*0.15*	**-0.18**	**-0.20**	*0.14*	*-0.15*	**-0.15**	*0.10*	*-0.11*	*-0.13*	*0.11*
UNC (L)	**-0.19**	**-0.22**	**0.22**	*-0.12*	**-0.14**	**0.16**	**-0.21**	**-0.22**	**0.19**	**-0.15**	**-0.16**	*0.15*	*-0.13*	**-0.17**	**0.19**	*-0.10*	*-0.15*	**0.17**
UNC (R)	**-0.22**	**-0.23**	**0.19**	*-0.13*	**-0.14**	**0.15**	**-0.22**	**-0.23**	**0.18**	**-0.19**	**-0.18**	*0.13*	*-0.14*	**-0.17**	**0.17**	*-0.11*	*-0.14*	**0.16**
CC-Genu	**-0.19**	**-0.19**	**0.14**	*-0.10*	*-0.12*	*0.12*	**-0.21**	**-0.21**	**0.16**	**-0.13**	**-0.13**	*0.10*	*-0.13*	**-0.14**	*0.12*	*-0.11*	*-0.11*	*0.08*
CC-Rostrum	**-0.20**	**-0.17**	*0.09*	*-0.09*	**-0.14**	**0.15**	**-0.20**	**-0.20**	*0.13*	**-0.14**	*-0.12*	*0.07*	*-0.14*	*-0.12*	*0.08*	*-0.12*	*-0.09*	*0.04*
CC-Splenium	*-0.09*	**-0.21**	**0.22**	*-0.11*	*-0.12*	*0.11*	*-0.10*	**-0.17**	**0.15**	*-0.08*	**-0.22**	**0.23**	*-0.04*	**-0.17**	**0.23**	*-0.06*	*-0.13*	**0.16**

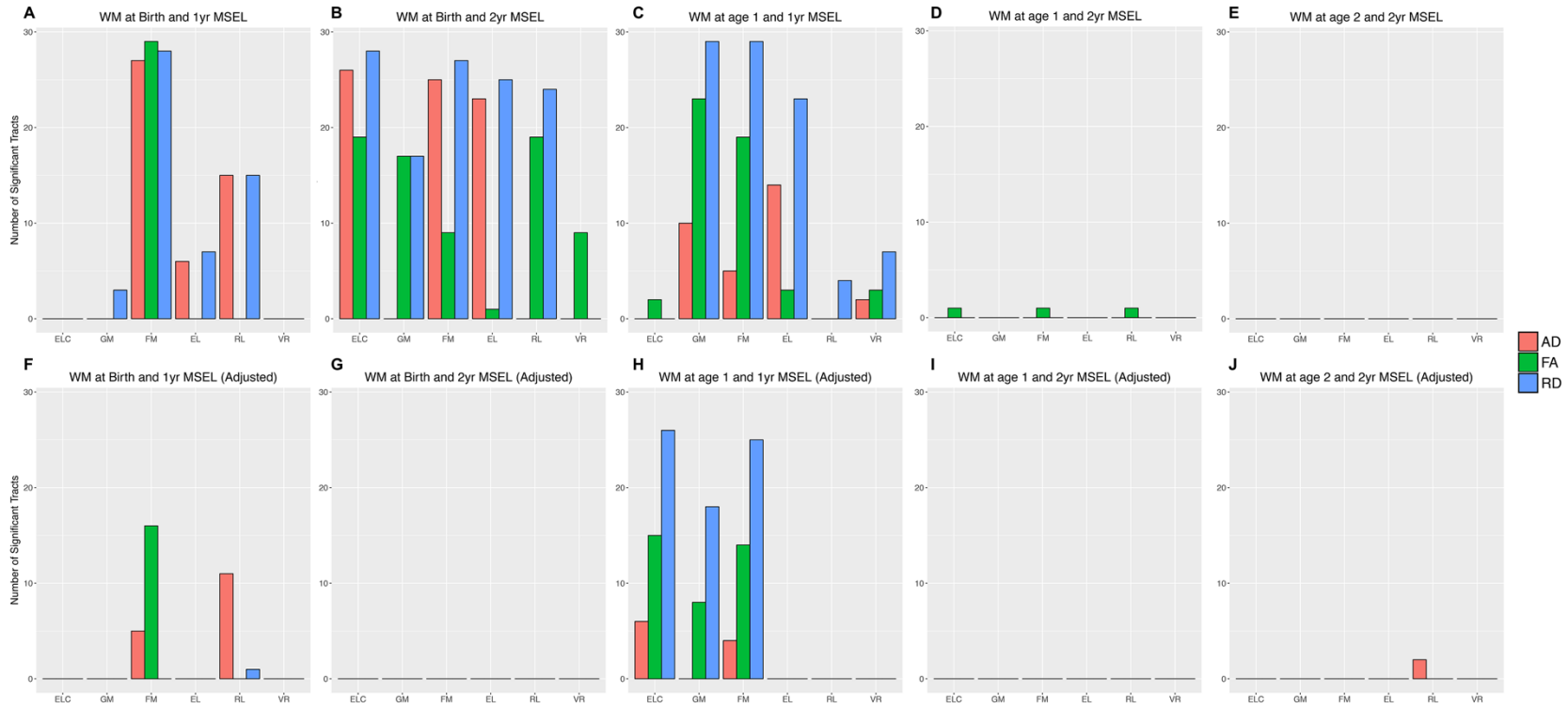


Figure 4.3. Summary of tract-based correlations with early cognitive abilities.

Summary files display the number of tracts with significant correlations to MSEL scores (ELC = Early Learning Composite, GM = Gross Motor, FM = Fine Motor, EL = Expressive Language, RL = Receptive Language, VR = Visual Reception) for each predictive and cross-sectional relationship for raw (A-E) and adjusted (F-J) analyses.

Table 4.5. Unadjusted Pearson's Correlations between DTI Parameters at age 1 and Cognitive Scores at age 1.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	ELC - 1yr			GM - 1yr			FM - 1yr			EL - 1yr			RL - 1yr			VR - 1yr		
Tract	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**
ARC-FP (L)	*-0.01*	*-0.07*	*0.04*	*-0.04*	**-0.19**	**0.18**	*-0.02*	**-0.18**	**0.19**	*-0.04*	**-0.18**	*0.15*	*0.04*	*-0.12*	*0.13*	*0.00*	*-0.15*	*0.16*
ARC-FP (R)	*-0.04*	*-0.11*	*0.05*	*-0.06*	**-0.17**	**0.16**	*-0.10*	**-0.20**	*0.13*	*-0.05*	**-0.17**	*0.14*	*-0.11*	*-0.11*	*0.01*	*-0.12*	**-0.16**	*0.05*
ARC-FT (L)	*-0.17*	*-0.09*	*0.00*	*-0.12*	**-0.19**	**0.14**	*-0.09*	**-0.17**	*0.13*	**-0.18**	**-0.17**	*0.06*	*-0.09*	*-0.07*	*0.03*	*-0.15*	*-0.11*	*0.06*
ARC-FT (R)	*-0.09*	*-0.11*	*0.07*	*-0.10*	**-0.17**	**0.19**	*-0.14*	**-0.22**	**0.19**	**-0.17**	**-0.19**	*0.13*	*-0.12*	*-0.13*	*0.10*	*-0.15*	**-0.22**	*0.17*
ARC-TP (L)	*-0.05*	*-0.13*	*0.13*	*-0.06*	**-0.20**	**0.22**	*-0.06*	**-0.22**	**0.22**	*-0.13*	**-0.24**	**0.18**	*0.01*	*-0.12*	*0.16*	*-0.09*	**-0.21**	**0.19**
ARC-TP (R)	*0.02*	*-0.09*	*0.11*	*0.01*	**-0.15**	**0.22**	*-0.04*	**-0.19**	**0.22**	*-0.12*	**-0.18**	*0.11*	*-0.05*	*-0.11*	*0.10*	*-0.06*	**-0.18**	*0.17*
CF-M (L)	*-0.07*	*-0.18*	*0.16*	*-0.13*	**-0.23**	**0.18**	*-0.15*	**-0.22**	**0.15**	**-0.19**	**-0.21**	*0.13*	*-0.04*	**-0.18**	*0.16*	*-0.03*	*-0.13*	*0.13*
CF-M (R)	*-0.07*	*-0.10*	*0.08*	**-0.16**	**-0.23**	**0.18**	*-0.14*	**-0.20**	**0.15**	**-0.14**	**-0.17**	*0.12*	*-0.08*	*-0.15*	*0.12*	*-0.07*	*-0.05*	*0.03*
CGC (L)	*-0.08*	*-0.06*	*-0.02*	*-0.05*	**-0.21**	**0.16**	*-0.08*	**-0.15**	*0.09*	*-0.11*	**-0.13**	*0.03*	*-0.06*	*-0.07*	*-0.01*	*-0.07*	*-0.09*	*0.02*
CGC (R)	*-0.07*	*-0.09*	*0.03*	*-0.08*	**-0.21**	*0.12*	*-0.05*	**-0.16**	*0.10*	*-0.11*	**-0.17**	*0.06*	*-0.04*	*-0.09*	*0.04*	*-0.10*	*-0.12*	*0.02*
CT-M (L)	*-0.01*	*-0.16*	**0.19**	**-0.22**	**-0.26**	**0.16**	*-0.14*	**-0.19**	*0.12*	**-0.17**	**-0.19**	*0.11*	*-0.07*	**-0.19**	*0.16*	*-0.01*	*-0.14*	*0.16*
CT-M (R)	*-0.13*	*-0.10*	*0.02*	**-0.24**	**-0.25**	**0.15**	**-0.17**	**-0.14**	*0.04*	**-0.18**	-0.10	*0.02*	*-0.17*	*-0.13*	*0.00*	*-0.10*	*-0.04*	*-0.03*
CT-Par (L)	*-0.09*	*-0.15*	*0.13*	**-0.22**	**-0.25**	**0.16**	*-0.11*	**-0.22**	**0.22**	**-0.21**	**-0.27**	*0.15*	*-0.14*	**-0.17**	*0.11*	*-0.07*	*-0.11*	*0.12*
CT-Par (R)	*-0.09*	*-0.08*	*0.03*	**-0.19**	**-0.17**	*0.11*	**-0.23**	**-0.22**	*0.10*	**-0.18**	**-0.19**	*0.10*	*-0.14*	*-0.13*	*0.07*	*-0.11*	*-0.06*	*0.00*
CT-PFC (L)	*-0.08*	*-0.03*	*-0.05*	**-0.17**	**-0.21**	**0.16**	-0.18	**-0.20**	*0.12*	*-0.10*	*-0.08*	*0.03*	*-0.02*	*-0.01*	*-0.02*	*-0.09*	*-0.04*	*-0.04*
CT-PFC (R)	*-0.11*	*-0.11*	*0.01*	**-0.21**	**-0.22**	*0.10*	*-0.15*	**-0.25**	**0.19**	**-0.18**	**-0.17**	*0.04*	*-0.04*	*-0.09*	*0.07*	*-0.08*	*-0.11*	*0.06*
CT-PM (L)	*0.01*	*-0.13*	*0.17*	*-0.14*	**-0.20**	**0.16**	*-0.07*	**-0.19**	**0.19**	*-0.11*	**-0.14**	*0.11*	*-0.04*	*-0.12*	*0.12*	*-0.01*	*-0.09*	*0.11*
CT-PM (R)	*-0.09*	*-0.10*	*0.04*	**-0.25**	**-0.24**	*0.12*	**-0.17**	**-0.18**	*0.08*	**-0.17**	*-0.12*	*0.04*	*-0.15*	*-0.10*	*0.00*	*-0.10*	*-0.05*	*-0.02*
IFOF (L)	*-0.06*	*-0.11*	*0.06*	*-0.10*	**-0.23**	**0.18**	*-0.01*	**-0.22**	**0.24**	*-0.05*	**-0.16**	*0.13*	*-0.06*	*-0.11*	*0.07*	*-0.04*	*-0.14*	*0.10*
IFOF (R)	*-0.12*	*-0.10*	*0.05*	*-0.04*	**-0.26**	**0.26**	*-0.02*	**-0.25**	**0.27**	*-0.08*	**-0.20**	*0.17*	*-0.07*	*-0.12*	*0.10*	*-0.04*	*-0.15*	*0.12*
ILF (L)	*-0.07*	*-0.14*	*0.10*	**-0.16**	**-0.26**	**0.21**	*-0.04*	**-0.24**	**0.27**	*-0.09*	**-0.18**	*0.15*	*-0.07*	*-0.15*	*0.14*	*-0.02*	**-0.18**	**0.20**
ILF (R)	*-0.08*	*-0.13*	*0.11*	*-0.12*	**-0.24**	**0.23**	*-0.06*	**-0.26**	**0.29**	*-0.11*	**-0.25**	**0.24**	*-0.08*	*-0.16*	*0.13*	*0.01*	**-0.17**	**0.20**
SLF (L)	*-0.11*	*-0.08*	*0.00*	*-0.10*	**-0.17**	**0.14**	*-0.13*	**-0.21**	**0.17**	*-0.13*	**-0.17**	*0.09*	*-0.11*	*-0.12*	*0.05*	*-0.12*	*-0.14*	0.09
SLF (R)	*-0.19*	*-0.09*	*-0.03*	*-0.13*	**-0.13**	*0.07*	**-0.19**	**-0.19**	*0.08*	**-0.16**	**-0.13**	*0.04*	*-0.14*	*-0.07*	*-0.02*	**-0.19**	*-0.11*	*0.00*
UNC (L)	*-0.04*	*-0.03*	*0.01*	*-0.03*	**-0.16**	**0.15**	*-0.03*	**-0.14**	**0.15**	*-0.05*	*-0.08*	*0.06*	*-0.02*	*-0.02*	*0.01*	*-0.04*	*-0.03*	*0.00*
UNC (R)	*-0.02*	*-0.06*	*0.04*	*0.04*	**-0.19**	**0.21**	*0.00*	**-0.20**	**0.21**	*-0.03*	*-0.10*	*0.08*	*0.07*	*-0.07*	*0.12*	*-0.05*	*-0.08*	*0.04*
CC-Genu	*-0.03*	*-0.03*	*0.03*	**-0.27**	**-0.23**	*0.12*	*-0.11*	**-0.24**	**0.24**	**-0.18**	**-0.17**	*0.13*	*-0.15*	*-0.12*	*0.07*	*-0.11*	*-0.06*	*0.01*
CC-Rostrum	*-0.07*	*-0.02*	*-0.02*	*-0.17*	**-0.23**	**0.17**	**-0.20**	**-0.25**	**0.19**	**-0.16**	*-0.12*	*0.04*	*-0.09*	*-0.06*	*0.03*	**-0.19**	*-0.11*	*0.02*
CC-Splenium	*-0.10*	*-0.19*	**0.19**	*-0.10*	**-0.23**	**0.24**	*-0.06*	**-0.23**	**0.30**	**-0.17**	**-0.24**	**0.21**	*-0.16*	**-0.19**	*0.17*	*-0.14*	**-0.18**	*0.15*

Table 4.6. Adjusted Pearson's Correlations between DTI Parameters at Birth and Cognitive Scores at age 1.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	ELC - 1yr			GM - 1yr			FM - 1yr			EL - 1yr			RL - 1yr			VR - 1yr		
Tract	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**
ARC-FP (L)	*-0.03*	*-0.07*	*0.13*	*-0.13*	*-0.12*	*0.06*	*-0.02*	*-0.06*	**0.14**	*-0.02*	*-0.06*	*0.10*	*-0.06*	*-0.08*	*0.12*	*-0.02*	*-0.02*	*0.06*
ARC-FP (R)	*-0.06*	*-0.10*	*0.14*	*-0.05*	*-0.04*	*0.03*	*-0.03*	*-0.06*	*0.10*	*-0.04*	*-0.05*	*0.04*	*-0.14*	*-0.15*	*0.14*	*-0.11*	*-0.12*	*0.12*
ARC-FT (L)	*-0.04*	*-0.08*	*0.13*	*-0.07*	*-0.06*	*0.01*	*-0.03*	*-0.09*	**0.15**	*-0.01*	*-0.05*	*0.08*	*-0.08*	*-0.09*	*0.11*	*-0.04*	*-0.04*	*0.03*
ARC-FT (R)	*-0.07*	*-0.10*	*0.12*	*-0.09*	*-0.07*	*0.02*	*-0.07*	*-0.09*	*0.11*	*-0.06*	*-0.07*	*0.07*	**-0.14**	*-0.13*	*0.08*	*-0.05*	*-0.05*	*0.05*
ARC-TP (L)	*-0.01*	*-0.04*	*0.11*	*-0.05*	*-0.08*	*0.15*	*0.04*	*0.02*	*0.09*	*0.02*	*-0.02*	*0.04*	*-0.07*	*-0.09*	*0.09*	*-0.08*	*-0.08*	*0.04*
ARC-TP (R)	*-0.07*	*-0.07*	*0.09*	*-0.07*	*-0.08*	*0.08*	*-0.05*	*-0.08*	*0.11*	*-0.07*	*-0.07*	*0.07*	**-0.14**	*-0.11*	*0.05*	*-0.05*	*-0.03*	*0.00*
CF-M (L)	*-0.14*	*-0.13*	*0.07*	*-0.08*	*-0.13*	*0.11*	**-0.17**	*-0.14*	*0.05*	*-0.07*	*-0.12*	*0.12*	**-0.14**	*-0.14*	*0.08*	*-0.08*	*-0.02*	*-0.04*
CF-M (R)	*-0.15*	*-0.15*	*0.09*	*-0.06*	*-0.10*	*0.09*	**-0.17**	*-0.16*	*0.10*	*-0.12*	*-0.12*	*0.09*	**-0.20**	*-0.14*	*0.05*	*-0.05*	*-0.04*	*0.01*
CGC (L)	*-0.09*	*-0.11*	*0.06*	*-0.10*	*-0.10*	*0.03*	*-0.08*	*-0.13*	**0.14**	*-0.05*	*-0.09*	*0.09*	**-0.14**	*-0.15*	*0.06*	*-0.03*	*-0.01*	*-0.02*
CGC (R)	*-0.01*	*-0.07*	*0.10*	*-0.03*	*-0.08*	*0.11*	*-0.02*	*-0.09*	**0.14**	*0.00*	*-0.07*	*0.13*	*-0.10*	*-0.13*	*0.05*	*0.01*	*0.04*	*-0.05*
CT-M (L)	*-0.16*	*-0.15*	*0.10*	*-0.08*	*-0.12*	*0.10*	**-0.17**	*-0.16*	*0.10*	*-0.07*	*-0.13*	*0.16*	**-0.18**	*-0.14*	*0.07*	*-0.10*	*-0.03*	*-0.03*
CT-M (R)	*-0.14*	*-0.13*	*0.09*	*-0.08*	*-0.11*	*0.09*	**-0.19**	*-0.14*	*0.08*	*-0.09*	*-0.11*	*0.09*	**-0.17**	*-0.14*	*0.06*	*-0.04*	*-0.02*	*-0.01*
CT-Par (L)	*-0.11*	*-0.13*	*0.11*	*-0.09*	*-0.13*	*0.10*	*-0.13*	*-0.14*	**0.13**	*-0.04*	*-0.11*	*0.15*	**-0.15**	*-0.14*	*0.09*	*-0.06*	*-0.02*	*-0.03*
CT-Par (R)	*-0.13*	*-0.14*	*0.13*	*-0.08*	*-0.15*	*0.14*	**-0.15**	*-0.14*	*0.11*	*-0.10*	*-0.13*	*0.13*	**-0.17**	*-0.15*	*0.11*	*-0.04*	*-0.03*	*0.00*
CT-PFC (L)	*-0.08*	*-0.10*	*0.13*	*-0.13*	*-0.11*	*0.05*	*-0.06*	*-0.09*	**0.14**	*-0.05*	*-0.08*	*0.13*	*-0.11*	*-0.11*	*0.12*	*-0.05*	*-0.04*	*0.02*
CT-PFC (R)	*-0.06*	*-0.08*	*0.11*	*-0.13*	*-0.10*	*0.03*	*-0.06*	*-0.09*	*0.12*	*-0.05*	*-0.06*	*0.09*	*-0.08*	*-0.09*	*0.11*	*0.00*	*-0.02*	*0.02*
CT-PM (L)	*-0.10*	*-0.11*	*0.10*	*-0.06*	*-0.07*	*0.05*	*-0.11*	*-0.13*	**0.13**	*-0.08*	*-0.11*	*0.13*	*-0.13*	*-0.13*	*0.10*	*-0.03*	*-0.02*	*0.00*
CT-PM (R)	*-0.11*	*-0.11*	*0.09*	*-0.09*	*-0.09*	*0.05*	*-0.11*	*-0.12*	*0.11*	*-0.09*	*-0.09*	*0.08*	**-0.16**	*-0.13*	*0.07*	*-0.04*	*-0.04*	*0.01*
IFOF (L)	*-0.02*	*-0.09*	*0.14*	*-0.12*	*-0.11*	*0.04*	*-0.03*	*-0.10*	**0.15**	*-0.05*	*-0.08*	*0.09*	*-0.07*	*-0.09*	*0.09*	*0.03*	*-0.02*	*0.05*
IFOF (R)	*-0.03*	*-0.10*	*0.15*	*-0.14*	*-0.12*	*0.06*	*-0.04*	*-0.11*	**0.16**	*-0.05*	*-0.08*	*0.10*	*-0.09*	*-0.11*	*0.11*	*0.01*	*-0.03*	*0.06*
ILF (L)	*-0.03*	*-0.09*	*0.11*	*-0.08*	*-0.09*	*0.05*	*-0.04*	*-0.12*	**0.15**	*-0.04*	*-0.08*	*0.07*	*-0.08*	*-0.09*	*0.06*	*0.00*	*-0.02*	*0.03*
ILF (R)	*-0.07*	*-0.11*	*0.11*	*-0.17*	*-0.11*	*0.00*	*-0.08*	*-0.16*	**0.16**	*-0.06*	*-0.08*	*0.06*	*-0.12*	*-0.12*	*0.07*	*-0.02*	*-0.03*	*0.03*
SLF (L)	*-0.06*	*-0.08*	*0.08*	*-0.11*	*-0.10*	*0.03*	*-0.10*	*-0.11*	*0.09*	*0.01*	*-0.05*	*0.11*	*-0.08*	*-0.10*	*0.09*	*-0.07*	*-0.04*	*-0.02*
SLF (R)	*-0.14*	*-0.17*	*0.16*	*-0.08*	*-0.06*	*0.03*	*-0.10*	*-0.11*	*0.10*	*-0.07*	*-0.10*	*0.09*	**-0.18**	**-0.20**	*0.13*	*-0.12*	*-0.13*	*0.10*
UNC (L)	*-0.07*	*-0.11*	*0.16*	*-0.12*	*-0.09*	*0.04*	*-0.05*	*-0.11*	**0.17**	*-0.05*	*-0.08*	*0.11*	*-0.11*	*-0.12*	*0.12*	*-0.04*	*-0.05*	*0.05*
UNC (R)	*-0.07*	*-0.11*	*0.14*	*-0.13*	*-0.14*	*0.09*	*-0.07*	*-0.11*	**0.15**	*-0.05*	*-0.08*	*0.11*	*-0.12*	*-0.13*	*0.11*	*-0.06*	*-0.05*	*0.04*
CC-Genu	*-0.04*	*-0.10*	*0.14*	*-0.12*	*-0.12*	*0.09*	*-0.05*	*-0.12*	**0.17**	*-0.02*	*-0.08*	*0.12*	*-0.05*	*-0.09*	*0.12*	*-0.02*	*-0.03*	*0.05*
CC-Rostrum	*-0.02*	*-0.08*	*0.12*	*-0.10*	*-0.13*	*0.10*	*-0.04*	*-0.11*	**0.14**	*0.00*	*-0.05*	*0.09*	*-0.05*	*-0.08*	*0.09*	*-0.02*	*-0.03*	*0.04*
CC-Splenium	*-0.04*	*-0.10*	*0.11*	*-0.10*	*-0.09*	*0.03*	*-0.04*	*-0.15*	**0.18**	*-0.07*	*-0.13*	*0.13*	*-0.06*	*-0.05*	*0.02*	*0.02*	*0.01*	*0.01*

Table 4.7. Adjusted Pearson's Correlations between DTI Parameters at age 1 and Cognitive Scores at age 1.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	ELC - 1yr			GM - 1yr			FM - 1yr			EL - 1yr			RL - 1yr			VR - 1yr		
Tract	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**
ARC-FP (L)	*-0.04*	**-0.13**	*0.13*	*0.01*	*-0.08*	*0.09*	*-0.04*	*-0.10*	*0.10*	*0.01*	*-0.06*	*0.08*	*0.04*	*-0.03*	*0.05*	*-0.05*	*-0.08*	*0.07*
ARC-FP (R)	*0.00*	**-0.16**	**0.15**	*0.05*	*-0.07*	*0.13*	*-0.01*	**-0.14**	**0.15**	*0.10*	*-0.06*	*0.14*	*-0.01*	*-0.03*	*0.01*	*-0.06*	*-0.09*	*0.04*
ARC-FT (L)	*-0.10*	*-0.11*	*0.12*	*-0.03*	*-0.10*	*0.12*	*-0.06*	*-0.11*	*0.11*	*-0.06*	*-0.07*	*0.05*	*0.00*	*0.01*	*0.02*	*-0.12*	*-0.04*	*0.04*
ARC-FT (R)	*-0.04*	**-0.14**	**0.17**	*0.03*	*-0.06*	*0.13*	*-0.07*	*-0.13*	*0.13*	*-0.04*	*-0.07*	*0.07*	*0.00*	*-0.01*	*0.04*	*-0.09*	*-0.12*	*0.10*
ARC-TP (L)	*-0.06*	**-0.17**	**0.17**	*0.04*	*-0.07*	*0.13*	*-0.03*	**-0.14**	*0.14*	*-0.04*	*-0.12*	*0.11*	*0.06*	*-0.02*	*0.07*	*-0.11*	*-0.14*	*0.09*
ARC-TP (R)	*0.02*	**-0.15**	**0.17**	*0.14*	*-0.01*	*0.15*	*0.02*	*-0.12*	**0.16**	*-0.02*	*-0.06*	*0.05*	*0.01*	*-0.02*	*0.03*	*-0.03*	*-0.13*	*0.11*
CF-M (L)	**-0.18**	**-0.22**	**0.14**	*-0.05*	**-0.15**	*0.13*	**-0.20**	**-0.18**	*0.08*	*-0.14*	*-0.11*	*0.05*	*-0.07*	*-0.13*	*0.09*	*-0.09*	*-0.08*	*0.04*
CF-M (R)	*-0.12*	**-0.14**	*0.10*	*-0.08*	**-0.17**	*0.15*	*-0.15*	**-0.16**	*0.09*	*-0.06*	*-0.09*	*0.08*	*-0.05*	*-0.11*	*0.08*	*-0.08*	*0.01*	*-0.04*
CGC (L)	*-0.11*	**-0.19**	*0.11*	*0.03*	**-0.15**	**0.17**	*-0.09*	**-0.14**	*0.08*	*-0.04*	*-0.08*	*0.06*	*-0.04*	*-0.08*	*0.04*	*-0.08*	*-0.13*	*0.06*
CGC (R)	*-0.06*	**-0.17**	*0.11*	*0.01*	**-0.15**	*0.14*	*-0.02*	**-0.13**	*0.11*	*-0.01*	*-0.10*	*0.08*	*0.02*	*-0.07*	*0.08*	*-0.09*	*-0.12*	*0.04*
CT-M (L)	*-0.12*	**-0.21**	**0.19**	*-0.14*	**-0.19**	*0.13*	**-0.17**	**-0.16**	*0.07*	*-0.11*	*-0.11*	*0.06*	*-0.10*	*-0.16*	*0.11*	*-0.04*	*-0.11*	*0.10*
CT-M (R)	**-0.18**	**-0.15**	0.08	*-0.16*	**-0.24**	**0.19**	*-0.16*	**-0.13**	*0.05*	*-0.10*	*-0.07*	*0.04*	*-0.15*	*-0.12*	*0.03*	*-0.10*	*-0.01*	*-0.03*
CT-Par (L)	*-0.11*	**-0.22**	**0.19**	*-0.15*	**-0.15**	*0.10*	*-0.09*	**-0.19**	**0.19**	*-0.12*	*-0.18*	*0.11*	*-0.12*	*-0.14*	*0.07*	*-0.07*	*-0.09*	*0.08*
CT-Par (R)	*-0.13*	**-0.14**	*0.10*	*-0.10*	*-0.10*	*0.08*	**-0.19**	**-0.19**	*0.11*	*-0.08*	*-0.12*	*0.08*	*-0.07*	*-0.09*	*0.08*	*-0.05*	*-0.01*	*-0.02*
CT-PFC (L)	**-0.18**	**-0.20**	**0.15**	*-0.12*	**-0.21**	**0.24**	**-0.19**	**-0.25**	**0.19**	*-0.05*	*-0.11*	*0.14*	*-0.04*	*-0.07*	*0.09*	*-0.14*	*-0.11*	*0.03*
CT-PFC (R)	**-0.18**	**-0.21**	*0.13*	*-0.16*	**-0.16**	*0.09*	*-0.16*	**-0.22**	**0.16**	*-0.14*	*-0.12*	*0.05*	*-0.04*	*-0.06*	*0.06*	*-0.10*	*-0.08*	*0.02*
CT-PM (L)	*-0.15*	**-0.22**	**0.16**	*-0.06*	**-0.14**	*0.14*	*-0.11*	**-0.19**	**0.15**	*-0.09*	*-0.09*	*0.06*	*-0.11*	*-0.11*	*0.07*	*-0.08*	*-0.09*	*0.04*
CT-PM (R)	**-0.17**	**-0.17**	*0.09*	*-0.17*	**-0.22**	**0.16**	*-0.15*	**-0.17**	*0.11*	*-0.08*	*-0.09*	*0.07*	*-0.13*	*-0.10*	*0.01*	*-0.10*	*-0.03*	*-0.02*
IFOF (L)	*-0.04*	**-0.17**	**0.15**	*-0.05*	**-0.15**	*0.13*	*-0.03*	**-0.19**	**0.18**	*0.01*	*-0.08*	*0.09*	*-0.06*	*-0.04*	*0.01*	*-0.05*	*-0.09*	*0.04*
IFOF (R)	*-0.06*	**-0.14**	*0.12*	*-0.01*	**-0.16**	**0.18**	*-0.02*	**-0.19**	**0.20**	*-0.01*	*-0.08*	*0.09*	*-0.04*	*-0.01*	*0.01*	*-0.04*	*-0.07*	*0.03*
ILF (L)	*-0.03*	**-0.16**	**0.17**	*-0.10*	**-0.16**	*0.14*	*-0.04*	**-0.19**	**0.20**	*-0.01*	*-0.06*	*0.07*	*-0.03*	*-0.06*	*0.05*	*-0.02*	*-0.12*	*0.11*
ILF (R)	*-0.01*	**-0.14**	**0.18**	*-0.07*	*-0.10*	*0.11*	*-0.04*	**-0.17**	**0.20**	*-0.03*	*-0.10*	*0.12*	*-0.02*	*-0.02*	*0.02*	*0.05*	*-0.06*	*0.10*
SLF (L)	*-0.14*	**-0.13**	*0.09*	*0.00*	*-0.06*	*0.08*	*-0.10*	**-0.13**	*0.12*	*-0.04*	*-0.05*	*0.05*	*-0.08*	*-0.04*	*0.00*	*-0.13*	*-0.07*	*0.02*
SLF (R)	**-0.16**	**-0.16**	*0.10*	*-0.01*	*-0.06*	*0.08*	*-0.14*	**-0.17**	*0.12*	*-0.03*	*-0.07*	*0.09*	*-0.05*	*-0.04*	*0.04*	*-0.16*	*-0.10*	*0.02*
UNC (L)	*-0.10*	**-0.20**	**0.15**	*0.00*	**-0.17**	**0.19**	*-0.05*	**-0.14**	*0.14*	*-0.01*	*-0.09*	*0.09*	*-0.05*	*-0.06*	*0.03*	*-0.10*	*-0.08*	*-0.02*
UNC (R)	*-0.03*	**-0.16**	**0.15**	*0.08*	**-0.15**	**0.22**	*-0.03*	**-0.17**	**0.17**	*0.02*	*-0.06*	*0.09*	*0.06*	*-0.05*	*0.10*	*-0.10*	*-0.05*	*-0.03*
CC-Genu	*-0.09*	**-0.14**	*0.15*	*-0.14*	**-0.17**	*0.13*	*-0.04*	**-0.19**	**0.21**	*-0.07*	*-0.14*	*0.16*	*-0.08*	*-0.09*	*0.07*	*-0.06*	*0.01*	*-0.04*
CC-Rostrum	*-0.08*	*-0.12*	*0.12*	*-0.05*	**-0.19**	**0.21**	*-0.13*	**-0.22**	**0.20**	*-0.03*	*-0.08*	*0.09*	*0.03*	*0.00*	*0.04*	*-0.11*	*-0.05*	*-0.02*
CC-Splenium	*0.03*	*-0.12*	**0.17**	*0.05*	*-0.09*	*0.15*	*0.05*	**-0.14**	**0.23**	*0.00*	*-0.06*	*0.08*	*0.01*	*-0.02*	*0.05*	*0.00*	*-0.04*	*0.04*

Table 4.8. Developmental Changes in DTI Parameters Relate to Cognitive Scores at age 2.
Results from mixed effects models predicting MSEL scores at age 2 from DTI parameters at birth (FA0, AD0, RD0) and changes in DTI parameters in the first ($dFA_{1,0}$, $dAD_{1,0}$, $dRD_{1,0}$) and second ($dFA_{2,1}$, $dAD_{2,1}$, $dRD_{2,1}$) year of life. Models are adjusted for sex, gestation number, gestational age, maternal education, age at MSEL testing, MSEL test date, and DTI protocol.

Tract	MSEL Score	Effect	Estimate[a]	Interpretation[b]	Std. Error[c]	DF[d]	FDR Pval[f]	N Subs[g]	N Obs[h]
SLF (R)	ELC 2	$dAD_{2,1}$	2.29×10^5	*Slower Decrease, Higher Score*	6.20×10^4	37.29	0.020	52	57
ARC-FT (L)	RL2	$dRD_{2,1}$	4.32×10^4	*Slower Decrease, Higher Score*	1.49×10^4	16.38	0.028	58	66
ARC-FT (R)	RL2	$dRD_{2,1}$	6.07×10^4	*Slower Decrease, Higher Score*	2.19×10^4	25.60	0.028	59	65
ARC-TP (R)	RL2	$dRD_{2,1}$	5.29×10^4	*Slower Decrease, Higher Score*	1.78×10^4	32.99	0.020	59	67
CF-M (R)	RL2	$dRD_{2,1}$	4.50×10^4	*Slower Decrease, Higher Score*	1.04×10^4	6.94	0.017	58	66
CGC (L)	RL2	$dRD_{2,1}$	4.25×10^4	*Slower Decrease, Higher Score*	1.12×10^4	12.32	0.017	56	64
CT-M (L)	RL2	$dRD_{2,1}$	4.14×10^4	*Slower Decrease, Higher Score*	9.42×10^3	7.07	0.017	59	67
CT-PM (R)	RL2	$dRD_{2,1}$	5.02×10^4	*Slower Decrease, Higher Score*	1.08×10^4	9.41	0.017	59	57
IFOF (L)	RL2	$dRD_{2,1}$	3.72×10^4	*Slower Decrease, Higher Score*	9.6×10^3	9.86	0.017	59	67
ILF (L)	RL2	$dRD_{2,1}$	2.73×10^4	*Slower Decrease, Higher Score*	1.26×10^4	23.32	0.017	55	61
SLF (L)	RL2	$dRD_{2,1}$	3.42×10^4	*Slower Decrease, Higher Score*	9.28×10^3	9.19	0.020	56	63
CT-Par (L)	RL2	$dFA_{2,1}$	-62.22	*Slower Increase, Higher Score*	10.77	5.41	0.049	59	67
UNC (L)	GM2	$dFA_{1,0}$	-68.30	*Slower Increase, Higher Score*	5.20	4.69	0.002	58	66
CT-PFC (L)	RL2	$dRD_{2,1}$	-2.19×10^4	*Faster Decrease, Higher Score*	6.29×10^3	6.78	0.028	59	66
CT-PM (L)	VR2	FA_0	100.51	*Greater at birth, Higher Score*	29.88	47.25	0.044	59	67

[a]Model estimate
[b]Interpretation: higher MSEL scores at age 2 are predicted by slower decreases over time in AD or RD (positive estimates), slower increases in FA (negative estimates), faster decreases in AD or RD, or greater FA at birth (positive estimate).
[c]Standard error
[d]Degrees of freedom
[f]FDR-corrected p-value
[g]Number of unique subjects in the analysis
[h]Number of total subjects in the analysis, treating one twin from each pair as repeated measures

Table S4.1. Descriptive Statistics of Mullen Scales of Early Learning Scores

Descriptive statistics (Mean(SD)) are shown for all cognitive scores at ages 1 and 2 for the full sample, and the sample split by sex and gestation number. For the full sample the range of scores [Min, Max] are shown. Sample sizes for each group are also reported, with Wilcoxon p-values testing for group differences reported for sex and gestation. Stars denote significance level (* ≤ 0.05, ** ≤ 0.001, *** < 0.0001).

	Full Sample	**Sex**			**Gestation Number**		
YEAR 1	**N = 432**	**Female (N=200)**	**Male (N=232)**	*P-value*	**Singletons (N=205)**	**Twins (N=227)**	*P-value*
ELC	116.37(12.88) [78, 150]	117.52(13.13)	115.38(12.60)	0.0463*	116.68(13.15)	116.09(12.64)	0.7329
GM	18.13(2.90) [10, 27]	18.40(2.94)	17.90(2.85)	0.0651	17.83(2.97)	18.39(2.82)	0.0513
FM	17.46(1.70) [11 22]	17.49(1.58)	17.44(1.79)	0.9131	17.68(1.56)	17.26(1.79)	0.0232*
VR	17.95(2.17) [9, 26]	18.26(2.19)	17.68(2.12)	0.0073**	17.84(2.30)	18.05(2.04)	0.2907
EL	14.25(1.84) [8, 21]	14.43(1.92)	14.09(1.76)	0.096	14.26(1.93)	14.23(1.76)	0.8029
RL	14.21(1.96) [8, 24]	14.53(2.12)	13.93(1.76)	0.0013**	14.15(1.71)	14.26(2.16)	0.8628
YEAR 2	**N = 350**	**Female (N=153)**	**Male (N=197)**	*P-value*	**Singletons (N=170)**	**Twins (N=181)**	*P-value*
ELC	107.75(15.51) [67, 147]	110.65(15.44)	105.49(15.22)	0.0019**	113.34(14.57)	102.46(14.52)	<.0001***
GM	27.40(1.82) [21, 33]	27.38(1.76)	27.42(1.86)	0.9788	27.45(1.90)	27.35(1.74)	0.8084
FM	25.64(2.13) [17, 31]	25.93(2.16)	25.41(2.09)	0.0276*	26.19(1.76)	25.12(2.32)	<.0001***
VR	27.07(3.49) [17, 38]	27.61(3.52)	26.65(3.42)	0.0027**	27.77(3.52)	26.41(3.34)	<.0001***
EL	24.11(3.59) [14, 34]	24.67(3.69)	23.68(3.46)	0.0062**	25.17(3.36)	23.12(3.53)	<.0001***
RL	25.97(3.19) [15, 37]	26.24(2.97)	25.77(3.35)	0.3141	26.95(3.25)	25.06(2.86)	<.0001***

Table S4.2. Pearson's Correlations between MSEL Scores at Ages 1 and 2

Within-subject Pearson's correlations (*r)* were computed for all cognitive scores at ages 1 and 2. All scores are significantly correlated between years, though correlations are of only modest strength.

	r	**p-value**	**N**
MCOMP	0.27	5.64E-07	335
GM	0.30	1.98E-08	335
FM	0.34	8.64E-11	336
VR	0.25	4.86E-06	335
EL	0.25	3.24E-06	336
RL	0.24	9.58E-06	336

Table S4.3. Mixed Model Summary Results Relating Covariates to MSEL Scores.
Mixed models were run testing for relationships between MSEL scores and all child and demographic factors of interest – chronological age at MSEL testing (days), MSEL test date (months since start of data collection), maternal education (years), gestational age at birth (days), gestation number (singleton vs. twin), and sex (male vs. female). Gestation number and Sex were represented as categorical variables and results are presented here showing singletons (S) relative to twins and males (M) relative to females. Cells highlighted in gray represent significant results.

		Age at Testing		**Test Date**		**Maternal Education**		**Gestational Age at Birth**		**Gestation Number**		**Sex**	
		Estimate	*P-val*	*Estimate*	*P-val*	*Estimate*	*P-val*	*Estimate*	*P-val*	*Estimate*	*P-val*	*Estimate*	*P-val*
YEAR 1 MSEL	**ELC**	**-0.12**	**0.0004**	**4.7E-03**	**<0.0001**	-0.26	0.2247	-0.09	0.2416	1.21	0.5208	**-2.48**	**0.05**
	GM	**0.04**	**<0.0001**	**7.3E-04**	**<0.0001**	-0.07	0.1343	**0.05**	**0.0050**	-0.32	0.442	-0.47	0.0993
	FM	**0.03**	**<0.0001**	**2.4E-04**	**0.0123**	-0.02	0.5324	**0.04**	**0.0002**	0.37	0.1191	0.10	0.5304
	EL	**0.02**	**<0.0001**	**7.4E-04**	**<0.0001**	**-0.08**	**0.0078**	**0.03**	**0.0195**	0.12	0.65	**-0.38**	**0.0325**
	RL	**0.03**	**<0.0001**	**5.2E-04**	**<0.0001**	-0.03	0.3675	**0.03**	**0.0109**	-0.03	0.9114	**-0.48**	**0.0098**
	VR	**0.04**	**<0.0001**	**3.5E-04**	**0.0044**	0.04	0.1997	**0.03**	**0.0119**	-0.04	0.9041	**-0.51**	**0.0158**
YEAR 2 MSEL	**ELC**	-0.02	0.6338	8.5E-04	0.3389	**1.77**	**<0.0001**	0.16	0.0879	**5.60**	**0.0138**	**-4.71**	**0.0032**
	GM	0.01	0.0707	-2.2E-04	0.0802	0.04	0.2582	0.01	0.4874	0.06	0.8539	0.04	0.846
	FM	**0.02**	**0.0015**	1.0E-04	0.4308	**0.11**	**0.0022**	**0.05**	**0.0005**	0.40	0.2109	**-0.59**	**0.01**
	EL	**0.02**	**0.0034**	3.5E-04	0.1025	**0.30**	**<0.0001**	**0.08**	**0.0003**	0.76	0.1645	**-1.15**	**0.0025**
	RL	0.01	0.1182	1.3E-04	0.5157	**0.35**	**<0.0001**	0.03	0.1566	**1.24**	**0.0116**	-0.58	0.093
	VR	0.01	0.0757	2.5E-06	0.9909	**0.36**	**<0.0001**	0.02	0.4223	0.86	0.111	**-1.07**	**0.0057**

Table S4.4 Correlations Between Gestational Age and DTI Parameters at Birth
Pearson's correlations between Gestational Age at Birth and AD, RD, and FA at birth are shown by tract with FDR-corrected p-values.

		AD		RD		FA	
Tract	***N***	***Pearson's r***	***fdr p-val***	***Pearson's r***	***fdr p-val***	***Pearson's r***	***fdr p-val***
ARC-FP (L)	311	-0.36	<.0001	-0.39	<.0001	0.36	<.0001
ARC-FP (R)	274	-0.29	<.0001	-0.31	<.0001	0.25	<.0001
ARC-FT (L)	328	-0.34	<.0001	-0.37	<.0001	0.29	<.0001
ARC-FT (R)	326	-0.34	<.0001	-0.37	<.0001	0.31	<.0001
ARC-TP (L)	218	-0.38	<.0001	-0.42	<.0001	0.33	<.0001
ARC-TP (R)	331	-0.37	<.0001	-0.39	<.0001	0.30	<.0001
CF-M (L)	332	-0.30	<.0001	-0.36	<.0001	0.25	<.0001
CF-M (R)	332	-0.30	<.0001	-0.37	<.0001	0.27	<.0001
CGC (L)	323	-0.36	<.0001	-0.34	<.0001	0.07	0.1931
CGC (R)	304	-0.32	<.0001	-0.36	<.0001	0.12	0.0386
CT-M (L)	332	-0.35	<.0001	-0.38	<.0001	0.28	<.0001
CT-M (R)	332	-0.35	<.0001	-0.40	<.0001	0.32	<.0001
CT-Par (L)	332	-0.30	<.0001	-0.34	<.0001	0.26	<.0001
CT-Par (R)	332	-0.33	<.0001	-0.38	<.0001	0.29	<.0001
CT-PFC (L)	332	-0.39	<.0001	-0.41	<.0001	0.33	<.0001
CT-PFC (R)	332	-0.39	<.0001	-0.41	<.0001	0.35	<.0001
CT-PM (L)	332	-0.38	<.0001	-0.39	<.0001	0.25	<.0001
CT-PM (R)	332	-0.39	<.0001	-0.42	<.0001	0.30	<.0001
IFOF (L)	332	-0.35	<.0001	-0.43	<.0001	0.37	<.0001
IFOF (R)	331	-0.37	<.0001	-0.43	<.0001	0.38	<.0001
ILF (L)	330	-0.29	<.0001	-0.39	<.0001	0.31	<.0001
ILF (R)	332	-0.32	<.0001	-0.41	<.0001	0.32	<.0001
SLF (L)	318	-0.32	<.0001	-0.36	<.0001	0.25	<.0001
SLF (R)	290	-0.36	<.0001	-0.35	<.0001	0.18	0.0024
UNC (L)	330	-0.48	<.0001	-0.49	<.0001	0.40	<.0001
UNC (R)	328	-0.48	<.0001	-0.51	<.0001	0.42	<.0001
Genu	332	-0.42	<.0001	-0.43	<.0001	0.35	<.0001
Rostrum	332	-0.46	<.0001	-0.46	<.0001	0.34	<.0001
Splenium	332	-0.29	<.0001	-0.31	<.0001	0.17	0.0018

Table S4.5 Intersubject Variability in DTI Metrics Between Ages
Average standard deviations (SD) across tracts at birth, age 1, and age 2 were calculated. Two-tailed t-tests were used to test for significant differences in SD in AD, RD, and FA between age groups. (A) displays the average SD for each metric and age. (B) displays results of significance testing. At birth, the SD were significantly larger than those at ages 1 or 2. Only SD in RD was significantly different between ages 1 and 2, with higher SD at age 1.

(A)	Birth	Age 1	Age 2
AD	7.00E-05	4.09E-05	4.04E-05
RD	7.74E-05	3.42E-05	3.00E-05
FA	2.10E-02	1.85E-02	1.89E-02

(B)	Birth vs. 1yr		Birth vs. 2yr		1yr vs. 2yr	
	t-value	*p-value*	*t-value*	*p-value*	*t-value*	*p-value*
AD	**11.35063**	**< .00001**	**11.77944**	**< .00001**	0.24671	0.806033
RD	**15.64213**	**< .00001**	**17.40542**	**< .00001**	**2.94221**	**0.004733**
FA	**2.76695**	**0.007653**	**2.0861**	**0.041567**	-0.46684	0.642429

Table S4.6 Sample Sizes Across Analyses
Average sample sizes across all 29 tracts, the percent of the total subject sample (N = 447), and the range of sample sizes across tracts are reported for each primary analysis. For mixed effects models, sample size characteristics are reported for unique subjects, along with the sample size and range of the repeated measures sample (one twin per twin-pair).

	Pearson's Correlations	**Mixed Effects Models**	
		Unique Subs	**Rep. Meas.**
	N (% of entire sample); [Min, Max]	*N (% of entire sample); [Min, Max]*	*N [Min, Max]*
Neo DTI - 1yr MSEL	**307** (69%); [207, 317]	**253** (57%); [181, 259]	**56** [28, 60]
Neo DTI - 2yr MSEL	**251** (56%); [168, 260]	**212** (47%); [151, 217]	**43** [20, 46]
1yr DTI - 1yr MSEL	**251** (56%); [232, 254]	**204** (46%); [190, 206]	**48** [43, 49]
1yr DTI - 2yr MSEL	**193** (43%); [176, 195]	**161** (36%); [150, 163]	**33** [27, 33]
2yr DTI - 2yr MSEL	**169** (38%); [160, 171]	**137** (31%); [130, 138]	**33** [29,33]
Longitudinal		**57** (13%); [39, 59]	**7** [4, 8]

Table S4.7. Unadjusted Pearson's Correlations Between DTI Parameters at age 1 and 2yr MSEL Scores.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	White Matter at age 1 and 2yr MSEL Scores																	
	ELC - 2yr			GM - 2yr			FM - 2yr			EL - 2yr			RL - 2yr			VR - 2yr		
Tract	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**
ARC-FP (L)	*0.03*	*-0.05*	*0.05*	*0.04*	*0.09*	*-0.06*	*-0.02*	*-0.11*	*0.12*	*0.05*	*-0.03*	*0.05*	*0.21*	*0.01*	*-0.03*	*0.02*	*-0.04*	*0.05*
ARC-FP (R)	*-0.05*	*0.03*	*-0.08*	*-0.05*	*0.08*	*-0.11*	*-0.09*	*-0.05*	*-0.01*	*-0.03*	*0.03*	*-0.07*	*0.04*	*0.07*	*-0.13*	*-0.06*	*0.01*	*-0.06*
ARC-FT (L)	*-0.06*	*0.01*	*-0.02*	*0.05*	*0.10*	*-0.06*	*-0.14*	*-0.08*	*0.05*	*-0.04*	*0.03*	*-0.06*	*0.02*	*0.07*	*-0.10*	*-0.07*	*0.00*	*-0.01*
ARC-FT (R)	*-0.01*	*-0.03*	*0.02*	*0.01*	*0.04*	*-0.03*	*-0.05*	*-0.09*	*0.10*	*0.01*	*0.03*	*-0.04*	*0.07*	*0.02*	*-0.03*	*-0.04*	*-0.07*	*0.05*
ARC-TP (L)	*-0.09*	*-0.03*	*-0.03*	*0.06*	*0.05*	*-0.02*	*-0.11*	*-0.10*	*0.05*	*-0.04*	*-0.02*	*-0.04*	*0.05*	*-0.02*	*-0.10*	*-0.10*	*-0.03*	*-0.03*
ARC-TP (R)	*0.01*	*-0.07*	*0.12*	*0.12*	*-0.01*	*0.13*	*0.06*	*-0.13*	**0.23**	*-0.01*	*-0.06*	*0.07*	*0.11*	*-0.03*	*0.06*	*-0.06*	*-0.06*	*0.05*
CF-M (L)	*-0.10*	*-0.12*	*0.07*	*0.13*	*0.07*	*-0.01*	*-0.04*	*-0.12*	*0.09*	*-0.12*	*-0.09*	*0.02*	*0.15*	*-0.06*	*0.06*	*-0.07*	*-0.08*	*0.05*
CF-M (R)	*-0.02*	*-0.15*	*0.18*	*0.11*	*0.05*	*0.00*	*0.01*	*-0.14*	*0.19*	*-0.04*	*-0.10*	*0.10*	*0.12*	*-0.07*	*0.12*	*-0.02*	*-0.11*	*0.14*
CGC (L)	*-0.15*	*0.02*	*-0.12*	*0.05*	*0.04*	*0.00*	*-0.15*	*-0.05*	*-0.04*	*-0.12*	*0.02*	*-0.12*	*0.05*	*0.07*	*-0.14*	*-0.07*	*0.04*	*-0.09*
CGC (R)	*-0.21*	*0.12*	**-0.24**	*0.03*	*0.10*	*-0.07*	*-0.20*	*0.02*	*-0.16*	*-0.15*	*0.14*	*-0.22*	*-0.09*	*0.16*	**-0.25**	*-0.17*	*0.10*	*-0.21*
CT-M (L)	*-0.09*	*-0.11*	*0.03*	*0.07*	*0.03*	*-0.04*	*-0.07*	*-0.13*	*0.06*	*-0.10*	*-0.06*	*-0.02*	*0.05*	*-0.04*	*0.02*	*-0.04*	*-0.07*	*0.03*
CT-M (R)	*0.04*	*-0.09*	*0.11*	*0.08*	*0.01*	*0.01*	*0.02*	*-0.08*	*0.11*	*0.02*	*-0.05*	*0.06*	*0.10*	*0.00*	*0.05*	*0.07*	*-0.01*	*0.06*
CT-Par (L)	*-0.08*	*-0.06*	*0.03*	*0.04*	*0.05*	*-0.02*	*-0.13*	*-0.10*	*0.05*	*-0.08*	*-0.03*	*-0.07*	*-0.01*	*-0.02*	*0.01*	*-0.07*	*-0.07*	*0.05*
CT-Par (R)	*0.02*	*-0.01*	*0.05*	*0.01*	*0.06*	*-0.09*	*-0.06*	*-0.09*	*0.09*	*0.05*	*0.01*	*0.02*	*0.08*	*0.05*	*0.00*	*0.04*	*0.00*	*0.05*
CT-PFC (L)	*-0.04*	*-0.03*	*-0.01*	*0.03*	*0.00*	*0.04*	*-0.07*	*-0.07*	*0.04*	*0.03*	*0.02*	*-0.03*	*0.08*	*-0.02*	*-0.05*	*-0.04*	*-0.01*	*-0.04*
CT-PFC (R)	*-0.03*	*-0.06*	*0.01*	*0.05*	*0.03*	*0.01*	*-0.05*	*-0.13*	*0.10*	*0.01*	*0.00*	*-0.01*	*0.09*	*0.00*	*-0.05*	*-0.04*	*-0.06*	*0.01*
CT-PM (L)	*-0.04*	*-0.06*	*0.05*	*0.14*	*0.16*	*-0.10*	*-0.07*	*-0.10*	*0.06*	*-0.05*	*0.00*	*-0.03*	*0.14*	*0.03*	*0.03*	*-0.05*	*-0.06*	*0.04*
CT-PM (R)	*0.00*	*-0.06*	*0.05*	*0.04*	*0.03*	*-0.03*	*-0.02*	*-0.09*	*0.09*	*0.00*	*-0.03*	*0.01*	*0.09*	*0.03*	*0.01*	*0.04*	*-0.01*	*0.03*
IFOF (L)	*-0.01*	*0.00*	*0.00*	*0.09*	*0.03*	*0.03*	*-0.12*	*-0.13*	*0.06*	*0.03*	*0.04*	*-0.02*	*0.08*	*0.07*	*-0.07*	*-0.02*	*0.01*	*-0.01*
IFOF (R)	*-0.11*	*-0.05*	*-0.02*	*0.08*	*0.03*	*0.03*	*-0.16*	*-0.16*	*0.08*	*-0.05*	*0.00*	*-0.03*	*0.08*	*0.06*	*-0.09*	*-0.10*	*-0.05*	*-0.01*
ILF (L)	*0.01*	*0.01*	*0.00*	*0.11*	*0.02*	*0.06*	*-0.10*	*-0.11*	*0.06*	*0.01*	*0.08*	*-0.08*	*0.14*	*0.03*	*-0.04*	*0.03*	*0.02*	*0.00*
ILF (R)	*-0.07*	*-0.07*	*0.06*	*0.09*	*0.03*	*-0.01*	*-0.12*	*-0.15*	*0.12*	*-0.06*	*-0.02*	*0.01*	*0.07*	*0.00*	*0.01*	*-0.06*	*-0.09*	*0.08*
SLF (L)	*-0.07*	*-0.06*	*0.00*	*0.02*	*0.08*	*-0.05*	*-0.10*	*-0.09*	*0.05*	*-0.03*	*-0.05*	*0.00*	*0.20*	*-0.04*	*-0.06*	*-0.07*	*-0.07*	*0.00*
SLF (R)	*0.02*	*-0.03*	*0.04*	*0.00*	*0.10*	*-0.12*	*-0.05*	*-0.08*	*0.05*	*0.02*	*0.01*	*-0.02*	*0.15*	*0.01*	*0.00*	*0.01*	*-0.03*	*0.04*
UNC (L)	*-0.02*	*-0.09*	*0.08*	*0.14*	*0.08*	*0.04*	*-0.07*	*-0.17*	*0.14*	*0.01*	*-0.02*	*0.02*	*0.15*	*0.02*	*0.00*	*-0.03*	*-0.08*	*0.06*
UNC (R)	*-0.03*	*-0.04*	*0.02*	*0.14*	*0.03*	*0.08*	*-0.10*	*-0.15*	*0.09*	*0.05*	*-0.01*	*0.02*	*0.10*	*0.04*	*-0.04*	*-0.03*	*-0.03*	*0.00*
CC-Genu	*0.02*	*0.07*	*-0.11*	*0.06*	*-0.02*	*0.08*	*-0.03*	*-0.03*	*0.01*	*0.04*	*0.07*	*-0.09*	*0.09*	*0.09*	*-0.12*	*0.03*	*0.12*	*-0.16*
CC-Rostrum	*-0.10*	*0.04*	*-0.14*	*-0.05*	*-0.13*	*0.15*	*-0.12*	*-0.07*	*0.01*	*-0.07*	*0.04*	*-0.12*	*-0.10*	*0.07*	*-0.16*	*-0.10*	*0.05*	*-0.15*
CC-Splenium	*0.04*	*0.02*	*0.01*	*0.02*	*0.10*	*-0.09*	*-0.01*	*-0.07*	*0.11*	*0.01*	*0.00*	*0.01*	*0.01*	*0.03*	*-0.02*	*0.02*	*0.02*	*0.00*

Table S4.8. Unadjusted Pearson's Correlations Between DTI Parameters at age 2 and 2yr MSEL Scores.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	White Matter at age 2 and 2yr MSEL Scores																	
	ELC - 2yr			GM - 2yr			FM - 2yr			EL - 2yr			RL - 2yr			VR - 2yr		
Tract	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**
ARC-FP (L)	*0.17*	*0.03*	*0.06*	*-0.05*	*-0.07*	*0.02*	*-0.06*	*-0.09*	*0.05*	*0.19*	*-0.01*	*0.11*	*0.21*	*0.09*	*0.01*	*0.12*	*0.04*	*0.02*
ARC-FP (R)	*-0.02*	*0.12*	*-0.15*	*-0.03*	*-0.02*	*-0.01*	*-0.08*	*-0.04*	*-0.02*	*0.03*	*0.08*	*-0.09*	*0.04*	*0.13*	*-0.14*	*-0.04*	*0.09*	*-0.13*
ARC-FT (L)	*0.00*	*0.03*	*-0.04*	*-0.08*	*-0.06*	*0.00*	*-0.13*	*-0.09*	*0.02*	*0.04*	*0.00*	*0.00*	*0.02*	*0.12*	*-0.12*	*-0.02*	*0.06*	*-0.09*
ARC-FT (R)	*0.03*	*0.03*	*-0.03*	*-0.01*	*-0.05*	*0.04*	*-0.05*	*-0.09*	*0.08*	*0.05*	*-0.01*	*0.01*	*0.07*	*0.07*	*-0.06*	*-0.03*	*0.04*	*-0.08*
ARC-TP (L)	*0.04*	*0.00*	*0.04*	*-0.10*	*-0.10*	*0.02*	*-0.05*	*-0.10*	*0.09*	*0.05*	*0.00*	*0.02*	*0.05*	*0.05*	*-0.01*	*0.02*	*0.03*	*0.02*
ARC-TP (R)	*0.04*	*0.03*	*0.02*	*0.02*	*-0.09*	*0.08*	*-0.06*	*-0.10*	*0.09*	*0.05*	*0.01*	*0.03*	*0.11*	*0.05*	*0.03*	*-0.01*	*0.07*	*-0.07*
CF-M (L)	*0.07*	*0.09*	*-0.06*	*0.13*	*0.09*	*-0.03*	*0.02*	*0.06*	*-0.06*	*0.09*	*0.05*	*0.01*	*0.15*	*0.12*	*-0.04*	*0.03*	*0.02*	*-0.02*
CF-M (R)	*0.10*	*-0.06*	*0.15*	*-0.03*	*-0.15*	*0.13*	*-0.05*	*-0.11*	*0.09*	*0.04*	*-0.03*	*0.07*	*0.12*	*0.01*	*0.10*	*0.09*	*-0.07*	*0.14*
CGC (L)	*0.00*	*-0.01*	*0.03*	*-0.11*	*-0.07*	*0.02*	*-0.09*	*-0.13*	*0.09*	*0.02*	*0.02*	*0.01*	*0.05*	*0.06*	*0.00*	*0.05*	*0.00*	*0.03*
CGC (R)	*-0.13*	*0.15*	*-0.20*	*0.09*	*0.05*	*0.01*	*-0.06*	*0.17*	*-0.16*	*-0.13*	*0.05*	*-0.13*	*-0.09*	*0.17*	*-0.20*	*-0.16*	*0.11*	*-0.18*
CT-M (L)	*0.00*	*-0.01*	*0.03*	*-0.11*	*-0.07*	*0.02*	*-0.09*	*-0.13*	*0.09*	*0.02*	*0.02*	*0.01*	*0.05*	*0.06*	*0.00*	*0.05*	*0.00*	*0.03*
CT-M (R)	*0.05*	*0.04*	*0.00*	*-0.05*	*-0.03*	*-0.01*	*-0.15*	*-0.05*	*-0.03*	*0.06*	*0.05*	*0.00*	*0.10*	*0.08*	*-0.01*	*0.06*	*0.07*	*-0.02*
CT-Par (L)	*0.02*	*0.03*	*0.04*	*-0.13*	*-0.11*	*0.03*	*-0.10*	*-0.11*	*0.09*	*-0.02*	*0.10*	*-0.11*	*-0.01*	*0.01*	*0.02*	*0.08*	*0.05*	*0.09*
CT-Par (R)	*0.08*	*0.03*	*0.04*	*-0.13*	*-0.05*	*-0.05*	*-0.10*	*-0.10*	*0.07*	*0.07*	*0.05*	*-0.01*	*0.08*	*0.01*	*0.02*	*0.12*	*0.04*	*0.06*
CT-PFC (L)	*0.11*	*0.15*	*-0.13*	*-0.05*	*-0.11*	*0.11*	*-0.05*	*-0.02*	*-0.05*	*0.13*	*0.12*	*-0.04*	*0.08*	*0.08*	*-0.07*	*0.12*	*0.19*	*-0.18*
CT-PFC (R)	*0.06*	*0.05*	*-0.06*	*-0.02*	*-0.11*	*0.08*	*-0.07*	*-0.06*	*-0.04*	*0.13*	*0.10*	*-0.03*	*0.09*	*0.05*	*-0.04*	*0.00*	*0.02*	*-0.07*
CT-PM (L)	*0.11*	*0.01*	*0.09*	*-0.10*	*-0.03*	*-0.02*	*-0.10*	*-0.08*	*0.03*	*0.09*	*0.05*	*0.03*	*0.14*	*0.03*	*0.07*	*0.14*	*0.01*	*0.12*
CT-PM (R)	*0.04*	*0.04*	*0.00*	*-0.10*	*-0.07*	*-0.01*	*-0.16*	*-0.05*	*-0.05*	*0.07*	*0.03*	*0.03*	*0.09*	*0.08*	*-0.02*	*0.06*	*0.07*	*-0.01*
IFOF (L)	*0.10*	*0.02*	*0.06*	*0.03*	*-0.06*	*0.07*	*-0.01*	*-0.07*	*0.06*	*0.14*	*0.00*	*0.11*	*0.08*	*0.06*	*0.00*	*0.10*	*0.04*	*0.04*
IFOF (R)	*0.01*	*-0.01*	*0.00*	*0.01*	*-0.04*	*0.05*	*-0.11*	*-0.13*	*0.06*	*0.07*	*0.00*	*0.04*	*0.08*	*0.04*	*-0.03*	*-0.01*	*0.01*	*-0.04*
ILF (L)	*0.13*	*0.05*	*0.07*	*0.01*	*-0.08*	*0.06*	*0.01*	*-0.04*	*0.06*	*0.16*	*0.05*	*0.09*	*0.14*	*0.07*	*0.05*	*0.12*	*0.07*	*0.03*
ILF (R)	*0.03*	*-0.02*	*0.06*	*0.00*	*-0.08*	*0.06*	*-0.07*	*-0.13*	*0.14*	*0.05*	*0.01*	*0.03*	*0.07*	*0.01*	*0.03*	*0.02*	*-0.03*	*0.05*
SLF (L)	*0.14*	*0.02*	*0.06*	*-0.07*	*-0.06*	*0.02*	*-0.03*	*-0.05*	*0.02*	*0.18*	*0.03*	*0.09*	*0.20*	*0.07*	*0.04*	*0.08*	*0.03*	*0.01*
SLF (R)	*0.14*	*0.01*	*0.09*	*-0.03*	*-0.02*	*-0.03*	*-0.04*	*-0.12*	*0.10*	*0.13*	*0.01*	*0.07*	*0.15*	*0.02*	*0.09*	*0.06*	*0.03*	*0.01*
UNC (L)	*0.11*	*0.12*	*-0.02*	*0.00*	*-0.02*	*0.04*	*-0.04*	*-0.04*	*0.02*	*0.15*	*0.07*	*0.07*	*0.15*	*0.17*	*-0.05*	*0.12*	*0.17*	*-0.08*
UNC (R)	*0.03*	*0.08*	*-0.03*	*0.06*	*-0.04*	*0.08*	*-0.06*	*-0.05*	*0.00*	*0.04*	*0.03*	*0.03*	*0.10*	*0.14*	*-0.04*	*0.00*	*0.08*	*-0.07*
CC-Genu	*0.03*	*0.13*	*-0.13*	*-0.09*	*-0.16*	*0.11*	*-0.10*	*0.02*	*-0.06*	*0.07*	*0.06*	*0.00*	*0.09*	*0.15*	*-0.13*	*-0.01*	*0.13*	*-0.17*
CC-Rostrum	*-0.12*	*0.10*	*-0.17*	*-0.10*	*-0.15*	*0.11*	*-0.11*	*0.05*	*-0.11*	*-0.01*	*0.05*	*-0.03*	*-0.10*	*0.06*	*-0.12*	*-0.15*	*0.09*	*-0.19*
CC-Splenium	*0.00*	*-0.09*	*0.17*	*-0.03*	*-0.11*	*0.10*	*-0.01*	*-0.14*	*0.19*	*0.00*	*-0.11*	*0.19*	*0.01*	*-0.05*	*0.10*	*-0.03*	*-0.09*	*0.15*

Table S4.9. Adjusted Pearson's Correlations Between DTI Parameters at Birth and 2yr MSEL Scores.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	White Matter at Birth and 2yr MSEL Scores - Adjusted																	
	ELC - 2yr			GM - 2yr			FM - 2yr			EL - 2yr			RL - 2yr			VR - 2yr		
Tract	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**	**AD0**	**RD0**	**FA0**
ARC-FP (L)	*-0.07*	*-0.08*	*0.08*	*-0.15*	*-0.14*	*0.10*	*-0.05*	*-0.04*	*0.02*	*-0.02*	*-0.03*	*0.05*	*-0.02*	*-0.04*	*0.07*	*-0.09*	*-0.09*	*0.06*
ARC-FP (R)	*-0.06*	*-0.05*	*0.05*	*-0.09*	*-0.09*	*0.07*	*0.00*	*0.00*	*0.02*	*-0.09*	*-0.07*	*0.05*	*-0.02*	*-0.03*	*0.04*	*-0.06*	*-0.05*	*0.05*
ARC-FT (L)	*-0.08*	*-0.05*	*-0.01*	*-0.09*	*-0.10*	*0.08*	*-0.07*	*-0.04*	*0.00*	*-0.07*	*-0.02*	*-0.04*	*-0.04*	*-0.03*	*0.00*	*-0.04*	*-0.03*	*0.01*
ARC-FT (R)	*-0.07*	*-0.05*	*0.05*	*-0.15*	*-0.12*	*0.07*	*-0.03*	*-0.02*	*0.00*	*-0.03*	*-0.01*	*0.02*	*-0.05*	*-0.04*	*0.05*	*-0.07*	*-0.06*	*0.06*
ARC-TP (L)	*0.03*	*0.03*	*-0.01*	*-0.12*	*-0.12*	*0.03*	*0.05*	*0.05*	*-0.03*	*0.02*	*0.03*	*-0.03*	*0.00*	*0.01*	*-0.05*	*0.06*	*0.05*	*0.03*
ARC-TP (R)	*-0.04*	*-0.05*	*0.09*	*-0.08*	*-0.09*	*0.12*	*-0.01*	*-0.03*	*0.03*	*-0.03*	*-0.02*	*0.04*	*-0.02*	*-0.03*	*0.09*	*-0.06*	*-0.05*	*0.08*
CF-M (L)	*-0.04*	*-0.05*	*0.03*	*-0.10*	*-0.15*	*0.13*	*-0.08*	*-0.03*	*-0.04*	*-0.01*	*-0.02*	*0.03*	*0.02*	*-0.04*	*0.07*	*-0.01*	*-0.03*	*0.03*
CF-M (R)	*-0.02*	*-0.07*	*0.08*	*-0.09*	*-0.15*	*0.14*	*-0.07*	*-0.05*	*0.01*	*-0.02*	*-0.02*	*0.02*	*0.06*	*-0.05*	*0.11*	*-0.01*	*-0.05*	*0.06*
CGC (L)	*0.00*	*-0.04*	*0.05*	*-0.15*	*-0.15*	*0.03*	*-0.02*	*-0.06*	*0.07*	*-0.03*	*-0.03*	*0.00*	*0.04*	*0.00*	*0.04*	*0.04*	*-0.02*	*0.07*
CGC (R)	*-0.06*	*-0.02*	*-0.07*	*-0.15*	*-0.13*	*0.00*	*-0.09*	*-0.05*	*-0.08*	*0.00*	*0.02*	*-0.04*	*0.03*	*0.02*	*-0.01*	*-0.07*	*-0.05*	*-0.03*
CT-M (L)	*-0.08*	*-0.07*	*0.03*	*-0.15*	*-0.15*	*0.11*	*-0.09*	*-0.05*	*-0.02*	*-0.05*	*-0.04*	*0.03*	*-0.02*	*-0.04*	*0.05*	*-0.04*	*-0.05*	*0.04*
CT-M (R)	*-0.01*	*-0.06*	*0.08*	*-0.09*	*-0.15*	*0.17*	*-0.06*	*-0.07*	*0.03*	*0.01*	*-0.02*	*0.03*	*0.05*	*-0.03*	*0.08*	*0.02*	*-0.05*	*0.09*
CT-Par (L)	*-0.05*	*-0.07*	*0.05*	*-0.15*	*-0.15*	*0.11*	*-0.06*	*-0.06*	*0.01*	*-0.05*	*-0.03*	*0.01*	*-0.01*	*-0.04*	*0.06*	*-0.03*	*-0.07*	*0.08*
CT-Par (R)	*-0.03*	*-0.08*	*0.08*	*-0.15*	*-0.18*	*0.15*	*-0.05*	*-0.07*	*0.05*	*-0.04*	*-0.03*	*0.00*	*0.03*	*-0.05*	*0.08*	*-0.02*	*-0.08*	*0.09*
CT-PFC (L)	*-0.01*	*0.00*	*-0.02*	*-0.13*	*-0.11*	*0.07*	*-0.04*	*-0.04*	*0.00*	*0.01*	*0.04*	*-0.04*	*0.01*	*0.02*	*-0.02*	*-0.01*	*0.01*	*-0.04*
CT-PFC (R)	*0.00*	*-0.01*	*0.02*	*-0.10*	*-0.11*	*0.11*	*-0.06*	*-0.06*	*0.04*	*0.02*	*0.03*	*-0.02*	*0.02*	*0.01*	*0.03*	*0.01*	*0.00*	*0.01*
CT-PM (L)	*-0.06*	*-0.08*	*0.06*	*-0.14*	*-0.11*	*0.07*	*-0.08*	*-0.04*	*-0.01*	*-0.06*	*-0.05*	*0.03*	*0.01*	*-0.04*	*0.08*	*-0.03*	*-0.06*	*0.06*
CT-PM (R)	*0.00*	*-0.05*	*0.07*	*-0.11*	*-0.14*	*0.12*	*-0.08*	*-0.05*	*0.00*	*-0.03*	*-0.02*	*0.01*	*0.08*	*-0.01*	*0.10*	*0.04*	*-0.02*	*0.07*
IFOF (L)	*0.01*	*-0.02*	*0.06*	*-0.14*	*-0.13*	*0.09*	*-0.04*	*-0.06*	*0.05*	*0.01*	*0.01*	*-0.01*	*0.03*	*0.01*	*0.04*	*0.01*	*-0.02*	*0.06*
IFOF (R)	*-0.01*	*-0.03*	*0.04*	*-0.15*	*-0.13*	*0.10*	*-0.03*	*-0.06*	*0.05*	*-0.02*	*0.01*	*-0.03*	*0.01*	*-0.01*	*0.04*	*0.00*	*-0.02*	*0.05*
ILF (L)	*-0.02*	*-0.04*	*0.06*	*-0.10*	*-0.12*	*0.08*	*-0.01*	*-0.04*	*0.07*	*-0.03*	*0.00*	*-0.01*	*0.00*	*-0.03*	*0.08*	*-0.01*	*-0.03*	*0.07*
ILF (R)	*-0.05*	*-0.08*	*0.08*	*-0.13*	*-0.14*	*0.09*	*-0.02*	*-0.06*	*0.08*	*-0.07*	*-0.04*	*-0.02*	*-0.02*	*-0.06*	*0.09*	*-0.03*	*-0.07*	*0.10*
SLF (L)	*-0.07*	*-0.07*	*0.04*	*-0.10*	*-0.14*	*0.14*	*-0.05*	*-0.04*	*0.03*	*-0.08*	*-0.06*	*0.02*	*-0.02*	*-0.04*	*0.05*	*-0.05*	*-0.04*	*0.02*
SLF (R)	*-0.06*	*-0.12*	*0.16*	*-0.11*	*-0.15*	*0.14*	*-0.07*	*-0.11*	*0.13*	*-0.05*	*-0.11*	*0.16*	*-0.03*	*-0.05*	*0.07*	*-0.03*	*-0.08*	*0.12*
UNC (L)	*-0.01*	*-0.04*	*0.07*	*-0.13*	*-0.13*	*0.11*	*-0.06*	*-0.07*	*0.05*	*0.01*	*0.01*	*0.00*	*0.03*	*0.00*	*0.04*	*0.01*	*-0.03*	*0.07*
UNC (R)	*-0.05*	*-0.05*	*0.06*	*-0.15*	*-0.13*	*0.09*	*-0.08*	*-0.08*	*0.05*	*-0.03*	*-0.01*	*-0.01*	*0.01*	*0.00*	*0.03*	*-0.01*	*-0.04*	*0.07*
CC-Genu	*-0.04*	*-0.04*	*0.03*	*-0.11*	*-0.11*	*0.08*	*-0.08*	*-0.09*	*0.06*	*0.02*	*0.01*	*0.00*	*0.00*	*0.00*	*0.01*	*-0.02*	*-0.03*	*0.01*
CC-Rostrum	*0.02*	*0.00*	*0.01*	*-0.10*	*-0.12*	*0.11*	*-0.05*	*-0.06*	*0.04*	*0.06*	*0.04*	*-0.01*	*0.05*	*0.03*	*0.00*	*0.02*	*0.01*	*-0.01*
CC-Splenium	*0.03*	*-0.11*	*0.19*	*-0.10*	*-0.12*	*0.08*	*-0.01*	*-0.06*	*0.08*	*0.01*	*-0.12*	*0.18*	*0.06*	*-0.08*	*0.18*	*0.01*	*-0.06*	*0.12*

Table S4.10. Adjusted Pearson's Correlations Between DTI Parameters at age 1 and 2yr MSEL Scores.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	White Matter at age 1 and 2yr MSEL Scores - Adjusted																	
	ELC - 2yr			GM - 2yr			FM - 2yr			EL - 2yr			RL - 2yr			VR - 2yr		
Tract	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**	**AD1**	**RD1**	**FA1**
ARC-FP (L)	*0.02*	*-0.02*	*0.01*	*-0.07*	*0.01*	*-0.05*	*-0.08*	*-0.13*	*0.10*	*0.05*	*0.01*	*0.00*	*0.01*	*0.03*	*-0.07*	*0.00*	*-0.04*	*0.03*
ARC-FP (R)	*-0.09*	*0.03*	*-0.12*	*-0.13*	*0.03*	*-0.10*	*-0.11*	*-0.07*	*-0.01*	*-0.01*	*0.05*	*-0.10*	*-0.07*	*0.06*	*-0.17*	*-0.09*	*-0.01*	*-0.08*
ARC-FT (L)	*-0.07*	*0.05*	*-0.06*	*-0.06*	*0.05*	*-0.06*	*-0.17*	*-0.09*	*0.07*	*-0.02*	*0.08*	*-0.09*	*-0.04*	*0.10*	*-0.13*	*-0.08*	*0.01*	*-0.02*
ARC-FT (R)	*-0.07*	*-0.02*	*-0.01*	*-0.08*	*-0.01*	*-0.02*	*-0.10*	*-0.11*	*0.12*	*-0.03*	*0.05*	*-0.09*	*-0.01*	*0.05*	*-0.09*	*-0.10*	*-0.07*	*0.03*
ARC-TP (L)	*-0.08*	*0.02*	*-0.08*	*-0.05*	*-0.02*	*-0.03*	*-0.14*	*-0.09*	*0.02*	*0.01*	*0.06*	*-0.08*	*-0.13*	*0.03*	*-0.14*	*-0.09*	*0.01*	*-0.06*
ARC-TP (R)	*-0.01*	*-0.04*	*0.07*	*0.02*	*-0.11*	*0.15*	*0.02*	*-0.13*	*0.20*	*0.01*	*0.01*	*0.00*	*0.03*	*0.01*	*0.03*	*-0.08*	*-0.02*	*0.00*
CF-M (L)	*-0.13*	*-0.07*	*0.01*	*-0.05*	*-0.04*	*0.01*	*-0.12*	*-0.13*	*0.08*	*-0.14*	*-0.04*	*-0.03*	*-0.07*	*-0.03*	*-0.01*	*-0.12*	*-0.05*	*0.00*
CF-M (R)	*-0.01*	*-0.10*	*0.13*	*-0.01*	*-0.04*	*0.03*	*-0.01*	*-0.14*	*0.20*	*-0.02*	*-0.07*	*0.08*	*0.03*	*-0.04*	*0.06*	*-0.04*	*-0.08*	*0.10*
CGC (L)	*-0.09*	*-0.01*	*-0.04*	*-0.05*	*-0.06*	*0.01*	*-0.13*	*-0.12*	*0.05*	*-0.04*	*0.02*	*-0.04*	*-0.07*	*0.04*	*-0.09*	*0.00*	*0.01*	*-0.01*
CGC (R)	*-0.20*	*0.08*	*-0.21*	*-0.07*	*0.03*	*-0.08*	*-0.21*	*-0.06*	*-0.09*	*-0.08*	*0.11*	*-0.15*	*-0.16*	*0.12*	*-0.22*	*-0.16*	*0.04*	*-0.16*
CT-M (L)	*-0.13*	*-0.08*	*0.00*	*-0.10*	*-0.04*	*-0.04*	*-0.17*	*-0.14*	*0.04*	*-0.14*	*-0.03*	*-0.05*	*-0.07*	*-0.02*	*0.00*	*-0.07*	*-0.05*	*0.02*
CT-M (R)	*0.02*	*-0.03*	*0.05*	*-0.03*	*-0.05*	*0.02*	*-0.04*	*-0.09*	*0.11*	*-0.02*	*-0.04*	*0.03*	*0.07*	*0.03*	*0.00*	*0.03*	*0.00*	*0.03*
CT-Par (L)	*-0.12*	*-0.07*	*0.02*	*-0.10*	*-0.09*	*0.02*	*-0.20*	*-0.15*	*0.08*	*-0.05*	*0.02*	*-0.07*	*-0.07*	*-0.03*	*0.00*	*-0.10*	*-0.08*	*0.05*
CT-Par (R)	*-0.01*	*0.06*	*-0.06*	*-0.07*	*-0.01*	*-0.05*	*-0.10*	*-0.08*	*0.05*	*0.05*	*0.10*	*-0.09*	*0.02*	*0.09*	*-0.11*	*-0.01*	*0.03*	*-0.02*
CT-PFC (L)	*-0.10*	*-0.06*	*-0.01*	*-0.05*	*-0.05*	*0.04*	*-0.13*	*-0.12*	*0.08*	*0.02*	*0.04*	*-0.04*	*-0.13*	*-0.08*	*-0.04*	*-0.08*	*-0.03*	*-0.02*
CT-PFC (R)	*-0.12*	*-0.08*	*0.00*	*-0.02*	*0.01*	*-0.03*	*-0.13*	*-0.15*	*0.09*	*-0.05*	*0.00*	*-0.05*	*-0.08*	*-0.02*	*-0.08*	*-0.12*	*-0.09*	*0.02*
CT-PM (L)	*-0.09*	*-0.08*	*0.03*	*0.00*	*0.09*	*-0.10*	*-0.16*	*-0.14*	*0.05*	*-0.09*	*0.00*	*-0.05*	*0.01*	*-0.01*	*0.00*	*-0.10*	*-0.09*	*0.04*
CT-PM (R)	*-0.04*	*-0.03*	*0.01*	*-0.08*	*-0.02*	*-0.04*	*-0.10*	*-0.11*	*0.09*	*-0.07*	*-0.02*	*-0.02*	*0.04*	*0.04*	*-0.04*	*-0.02*	*-0.01*	*0.01*
IFOF (L)	*-0.07*	*0.03*	*-0.09*	*0.02*	*-0.01*	*0.02*	*-0.18*	*-0.12*	*0.01*	*0.03*	*0.09*	*-0.08*	*-0.07*	*0.07*	*-0.13*	*-0.06*	*0.02*	*-0.05*
IFOF (R)	*-0.14*	*0.01*	*-0.09*	*0.00*	*-0.04*	*0.05*	*-0.20*	*-0.15*	*0.05*	*-0.05*	*0.05*	*-0.09*	*-0.07*	*0.08*	*-0.14*	*-0.13*	*-0.02*	*-0.05*
ILF (L)	*-0.02*	*0.05*	*-0.08*	*0.03*	*-0.04*	*0.06*	*-0.14*	*-0.11*	*0.03*	*0.02*	*0.15*	*-0.14*	*-0.04*	*0.03*	*-0.09*	*0.02*	*0.04*	*-0.04*
ILF (R)	*-0.11*	*-0.04*	*-0.01*	*0.00*	*-0.05*	*0.04*	*-0.16*	*-0.15*	*0.08*	*-0.09*	*0.03*	*-0.07*	*-0.05*	*0.01*	*-0.05*	*-0.11*	*-0.07*	*0.03*
SLF (L)	*-0.05*	*0.00*	*-0.03*	*-0.10*	*0.01*	*-0.06*	*-0.13*	*-0.08*	*0.05*	*0.02*	*0.02*	*-0.02*	*-0.05*	*0.01*	*-0.09*	*-0.06*	*-0.03*	*-0.01*
SLF (R)	*-0.05*	*-0.02*	*-0.03*	*-0.10*	*0.04*	*-0.13*	*-0.11*	*-0.12*	*0.05*	*0.00*	*0.04*	*-0.06*	*-0.01*	*0.03*	*-0.07*	*-0.05*	*-0.03*	*0.01*
UNC (L)	*-0.10*	*-0.04*	*-0.03*	*0.04*	*0.06*	*-0.01*	*-0.14*	*-0.15*	*0.09*	*0.00*	*0.06*	*-0.08*	*-0.07*	*0.04*	*-0.09*	*-0.09*	*-0.07*	*0.00*
UNC (R)	*-0.06*	*-0.01*	*-0.04*	*0.03*	*0.01*	*0.01*	*-0.19*	*-0.15*	*0.03*	*0.05*	*0.03*	*-0.03*	*-0.01*	*0.05*	*-0.07*	*-0.07*	*-0.02*	*-0.03*
CC-Genu	*-0.09*	*0.07*	*-0.14*	*-0.05*	*-0.04*	*0.04*	*-0.14*	*-0.08*	*0.03*	*-0.05*	*0.05*	*-0.10*	*-0.06*	*0.07*	*-0.14*	*-0.05*	*0.10*	*-0.16*
CC-Rostrum	*-0.23*	*-0.02*	*-0.14*	*-0.09*	*-0.11*	*0.09*	*-0.20*	*-0.11*	*0.01*	*-0.14*	*0.00*	*-0.12*	*-0.18*	*0.01*	*-0.16*	*-0.19*	*0.00*	*-0.15*
CC-Splenium	*0.07*	*0.03*	*0.00*	*-0.02*	*0.03*	*-0.06*	*0.04*	*-0.08*	*0.13*	*0.06*	*0.03*	*0.01*	*0.02*	*0.04*	*-0.04*	*0.06*	*0.04*	*-0.01*

Table S4.11. Adjusted Pearson's Correlations Between DTI Parameters at age 2 and 2yr MSEL Scores.
Shaded cells are statistically significant, with negative correlations shown in red and positive correlations shown in green. Significant cells are shaded from lightest to darkest based on significance level: ≤ 0.05, ≤ 0.01, ≤ 0.001.

	White Matter at age 2 and 2yr MSEL Scores - Adjusted																	
	ELC - 2yr			GM - 2yr			FM - 2yr			EL - 2yr			RL - 2yr			VR - 2yr		
Tract	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**	**AD2**	**RD2**	**FA2**
ARC-FP (L)	*0.19*	*0.03*	*0.08*	*-0.09*	*-0.09*	*0.04*	*-0.04*	*-0.07*	*0.05*	*0.20*	*-0.01*	*0.11*	**0.23**	*0.08*	*0.02*	*0.14*	*0.05*	*0.05*
ARC-FP (R)	*0.03*	*0.09*	*-0.07*	*-0.06*	*-0.03*	*0.00*	*0.00*	*-0.03*	*0.04*	*0.08*	*0.08*	*-0.05*	*0.09*	*0.10*	*-0.06*	*-0.02*	*0.07*	*-0.06*
ARC-FT (L)	*0.09*	*0.04*	*0.02*	*-0.04*	*-0.08*	*0.04*	*-0.06*	*-0.07*	*0.08*	*0.09*	*0.01*	*0.04*	*0.11*	*0.13*	*-0.06*	*0.09*	*0.08*	*-0.02*
ARC-FT (R)	*0.05*	*0.07*	*-0.03*	*0.00*	*-0.05*	*0.06*	*0.01*	*-0.04*	*0.07*	*0.05*	*0.03*	*-0.01*	*0.11*	*0.11*	*-0.06*	*0.01*	*0.07*	*-0.06*
ARC-TP (L)	*0.13*	*0.03*	*0.05*	*-0.12*	*-0.12*	*0.02*	*0.03*	*-0.05*	*0.08*	*0.12*	*0.04*	*0.01*	*0.13*	*0.08*	*0.00*	*0.10*	*0.05*	*0.03*
ARC-TP (R)	*0.15*	*0.07*	*0.05*	*0.02*	*-0.10*	*0.10*	*0.04*	*-0.04*	*0.10*	*0.14*	*0.05*	*0.06*	*0.22*	*0.08*	*0.08*	*0.07*	*0.11*	*-0.03*
CF-M (L)	*0.06*	*0.03*	*0.00*	*0.10*	*0.06*	*-0.02*	*0.01*	*0.05*	*-0.06*	*0.06*	*0.00*	*0.05*	*0.14*	*0.07*	*0.01*	*-0.03*	*-0.06*	*0.03*
CF-M (R)	*0.03*	*-0.06*	*0.09*	*-0.05*	*-0.16*	*0.12*	*-0.05*	*-0.09*	*0.07*	*-0.01*	*-0.01*	*0.01*	*0.06*	*0.01*	*0.03*	*0.03*	*-0.07*	*0.09*
CGC (L)	*-0.08*	*-0.04*	*0.01*	*-0.17*	*-0.07*	*0.00*	*-0.12*	*-0.12*	*0.05*	*-0.07*	*0.01*	*-0.03*	*-0.04*	*0.04*	*-0.03*	*-0.04*	*-0.02*	*0.00*
CGC (R)	*-0.05*	*0.12*	*-0.13*	*0.12*	*0.05*	*0.03*	*0.02*	*0.15*	*-0.11*	*-0.06*	*0.04*	*-0.08*	*-0.02*	*0.16*	*-0.14*	*-0.10*	*0.08*	*-0.12*
CT-M (L)	*-0.08*	*-0.04*	*0.01*	*-0.17*	*-0.07*	*0.00*	*-0.12*	*-0.12*	*0.05*	*-0.07*	*0.01*	*-0.03*	*-0.04*	*0.04*	*-0.03*	*-0.04*	*-0.02*	*0.00*
CT-M (R)	*-0.03*	*0.00*	*-0.01*	*-0.07*	*-0.05*	*0.00*	*-0.18*	*-0.08*	*-0.02*	*0.01*	*0.03*	*-0.02*	*0.03*	*0.03*	*-0.01*	*0.00*	*0.04*	*-0.03*
CT-Par (L)	*0.01*	*0.00*	*0.08*	*-0.17*	*-0.18*	*0.06*	*-0.05*	*-0.07*	*0.09*	*-0.04*	*0.10*	*-0.10*	*-0.03*	*-0.03*	*0.04*	*0.11*	*0.02*	*0.14*
CT-Par (R)	*0.07*	*0.05*	*0.02*	*-0.17*	*-0.07*	*-0.04*	*-0.08*	*-0.05*	*0.03*	*0.04*	*0.09*	*-0.07*	*0.06*	*0.01*	*0.00*	*0.10*	*0.04*	*0.06*
CT-PFC (L)	*0.05*	*0.07*	*-0.06*	*-0.09*	*-0.18*	*0.17*	*-0.05*	*-0.05*	*0.01*	*0.10*	*0.09*	*-0.02*	*0.00*	*-0.01*	*0.00*	*0.05*	*0.10*	*-0.11*
CT-PFC (R)	*-0.04*	*-0.01*	*-0.04*	*-0.02*	*-0.11*	*0.09*	*-0.09*	*-0.07*	*0.00*	*0.08*	*0.09*	*-0.05*	*0.01*	*0.01*	*-0.03*	*-0.07*	*-0.01*	*-0.07*
CT-PM (L)	*0.03*	*-0.06*	*0.10*	*-0.15*	*-0.04*	*-0.05*	*-0.11*	*-0.08*	*0.03*	*0.04*	*0.03*	*0.01*	*0.07*	*-0.02*	*0.08*	*0.06*	*-0.05*	*0.11*
CT-PM (R)	*-0.06*	*-0.02*	*-0.01*	*-0.14*	*-0.07*	*-0.03*	*-0.21*	*-0.07*	*-0.05*	*-0.01*	*-0.01*	*0.01*	*0.00*	*0.03*	*-0.03*	*-0.03*	*0.03*	*-0.03*
IFOF (L)	*0.08*	*-0.03*	*0.10*	*0.02*	*-0.10*	*0.10*	*0.01*	*-0.05*	*0.06*	*0.11*	*-0.04*	*0.13*	*0.05*	*0.01*	*0.03*	*0.09*	*-0.01*	*0.09*
IFOF (R)	*0.06*	*-0.02*	*0.04*	*0.03*	*-0.06*	*0.08*	*-0.06*	*-0.08*	*0.05*	*0.10*	*-0.01*	*0.07*	*0.13*	*0.04*	*0.01*	*0.05*	*-0.01*	*0.02*
ILF (L)	*0.12*	*0.02*	*0.09*	*-0.02*	*-0.13*	*0.07*	*0.01*	*-0.01*	*0.04*	*0.11*	*0.03*	*0.08*	*0.11*	*0.03*	*0.07*	*0.10*	*0.02*	*0.05*
ILF (R)	*0.01*	*-0.04*	*0.07*	*-0.01*	*-0.11*	*0.08*	*-0.05*	*-0.08*	*0.10*	*0.01*	*0.02*	*0.01*	*0.05*	*-0.01*	*0.04*	*0.01*	*-0.05*	*0.08*
SLF (L)	*0.19*	*0.04*	*0.10*	*-0.09*	*-0.08*	*0.04*	*0.01*	*-0.02*	*0.04*	*0.21*	*0.05*	*0.10*	**0.25**	*0.07*	*0.09*	*0.13*	*0.04*	*0.05*
SLF (R)	*0.17*	*0.00*	*0.13*	*-0.02*	*-0.03*	*0.00*	*0.04*	*-0.10*	*0.13*	*0.16*	*0.02*	*0.08*	*0.19*	*0.01*	*0.13*	*0.09*	*0.03*	*0.05*
UNC (L)	*0.10*	*0.05*	*0.05*	*-0.04*	*-0.08*	*0.07*	*-0.02*	*-0.06*	*0.07*	*0.16*	*0.04*	*0.11*	*0.13*	*0.11*	*0.01*	*0.08*	*0.07*	*0.00*
UNC (R)	*0.08*	*0.02*	*0.05*	*0.08*	*-0.07*	*0.12*	*-0.02*	*-0.06*	*0.04*	*0.08*	*0.00*	*0.08*	*0.15*	*0.11*	*0.03*	*0.02*	*0.02*	*0.01*
CC-Genu	*-0.03*	*0.05*	*-0.05*	*-0.07*	*-0.16*	*0.12*	*-0.10*	*-0.03*	*0.02*	*0.02*	*0.00*	*0.05*	*0.05*	*0.09*	*-0.08*	*-0.04*	*0.10*	*-0.13*
CC-Rostrum	*-0.14*	*0.02*	*-0.09*	*-0.08*	*-0.16*	*0.12*	*-0.09*	*0.02*	*-0.06*	*-0.03*	*0.00*	*0.02*	*-0.12*	*-0.01*	*-0.06*	*-0.14*	*0.04*	*-0.14*
CC-Splenium	*0.07*	*-0.07*	*0.18*	*0.01*	*-0.10*	*0.09*	*0.08*	*-0.07*	*0.17*	*0.04*	*-0.12*	*0.19*	*0.07*	*-0.01*	*0.08*	*0.05*	*-0.04*	*0.13*

CHAPTER FIVE: WHITE MATTER CONNECTOMES AT BIRTH ACCURATELY PREDICT COGNITIVE ABILITIES AT AGE TWO

INTRODUCTION

At birth, the human brain is a highly connected network of largely unmyelinated axons that will serve as the foundation upon which future fine-tuning of cortical circuitry takes place via processes including synaptogenesis, dendritic arborization, and myelination (Dubois et al., 2014). By week 30 of gestation, major pathways underlying rich-club organization in the brain are established (Ball et al., 2014), and by birth white matter (WM) networks exhibit a small world architecture (Yap et al., 2011), suggesting that the foundational wiring of brain circuitry is established *in-utero* and is in place by the time of normal birth, a finding which has been supported by tractography studies (Dubois et al., 2008; Huang et al., 2006). The structural connectome, as a physical network, has important implications for both cortical structural development (Essen, 1997) and functional brain connectivity (Hagmann et al., 2010; Park & Friston, 2013; Sporns, 2013).

The structural connectome is more adult-like at birth than the functional connectome, with structural hubs including regions in the medial frontal, parietal, and hippocampal areas (Huang et al., 2015; van den Heuvel et al., 2015) along with regions in the posterior cingulate and insula (Ball et al., 2014), whereas functional networks at birth have hubs in primary sensory, auditory, and sensorimotor areas (Cao, He, Dai, Liao, et al., 2017a; Fransson, Åden, Blennow, & Lagercrantz, 2010). Interestingly, cross-sectional developmental studies have shown that coupling between structural and functional networks increases from 30 weeks gestation into adulthood

(Hagmann et al., 2010; van den Heuvel et al., 2015). This body of work highlights the possibility that early-maturing structural connectomes serve as the initial foundation upon which diverse functional networks are built (Cao, Huang, & He, 2017b).

Importantly, the structural connectome must provide enough flexibility to support dynamic large-scale functional reorganization that has been shown to occur during cognitive tasks (J. R. Cohen & D'Esposito, 2016). Recent studies have begun to reveal interesting links between individual differences in structural connectomic features in pediatric populations and future cognitive and behavioral performance. White matter connections between the thalamus and cortex have been related to cognitive abilities at age 2 in preterm infants (Ball et al., 2015), and structural connectomes at birth have been used to derive unique subject communities that were related to maternal reports of child behaviors at ages 2 and 4 in full-term infants (Wee et al., 2016). A recently developed methodological approach for using deep convolutional neural networks outlined the utility of this method in predicting cognitive and motor scores at age 2 from structural connectomes at birth in very preterm infants (Kawahara et al., 2017). Additionally, WM tractography in infants revealed that the microstructural integrity of fiber pathways spanning the brain at birth was important for 2-year cognition across domains (**Chapter 3**, manuscript under review). This recent work suggests that WM connectivity at birth, and the microstructural integrity of these connections, are important for future cognitive and behavioral outcomes in toddlerhood.

In the present study, we extend work from the burgeoning new field of developmental connectomics to study how WM connectomes at birth relate to individual differences in cognitive abilities at age 2, across a period of rapid, dynamic brain development (Geng et al., 2012; Gilmore et al., 2012; Knickmeyer et al., 2008; Lyall et al., 2015), in a heterogeneous sample of infant participants followed longitudinally. The goals of this project were to (1) determine the predictive

ability of WM connectomes at birth for subsequent cognition, and (2) identify features of the WM connectome at birth that are particularly important for determining individual differences in cognitive abilities in toddlerhood. In order to achieve these goals, we used a deep learning approach to classify infants based on their cognitive performance at age 2 using features from WM connectomes at birth. Specifically, we classified participants as scoring below average (BA), average (AV), or above average (AA) on the Mullen Early Learning Composite (ELC) at age 2 (Mullen, 1995), an assessment of general cognitive ability in infants and young children. To probe the generalizability of the results obtained from this approach, we trained and tested the model in a sample of full term infants and replicated our findings in a sample of preterm infants that were unknown to the classification model. Next, in order to directly predict the ELC score itself, and thus gain an understanding how precisely our method can predict future performance, we fed the strength of the classification accuracy for each infant into a regression prediction model. Finally, we employed a backtrack fingerprinting approach (Hazlett et al., 2017) to extract the features of the WM connectome at birth that were important for classifying participants based on their cognitive performance at 2 years of age.

MATERIALS AND METHODS

Participants

Participants were part of the ongoing Early Brain Development Study at UNC Chapel Hill (Gilmore et al., 2007; S. J. Lee et al., 2017). Pregnant women were recruited from outpatient obstetrics and gynecology clinics at the University of North Carolina Hospitals and Duke University Medical Center. All offspring underwent magnetic resonance imaging shortly after birth and were followed through early childhood, receiving cognitive assessments at age 2. We

retrospectively identified 115 infants with 42-direction diffusion weighted images (DWI), T1- and T2-weighted MRIs, and reconstructed white matter (WM) surfaces who passed our quality control (see section below on Network Generation) *and* successfully completed cognitive assessments at age 2. We did not exclude participants for perinatal complications, medical illness, or potential developmental delay based on cognitive assessments; our goal was to use the most heterogeneous dataset available to us for the prediction analysis. Additionally, 14% (n = 16) of infants in our sample were born to mothers with a diagnosed psychiatric illness. To test for the robustness of the classification, we built our classification model using data from full term (FT) infants (≥ 37 weeks gestation; n = 78) and applied it to preterm (PT) infants (< 37 weeks; n= 37). Informed written consent and parental permission was obtained from at least one parent of all child participants and all study protocols were approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

Cognitive Assessment

Cognitive ability was assessed at age 2 using the Mullen Scales of Early Learning (MSEL) (Mullen, 1995). Child measures of fine motor, visual reception, expressive and receptive language were collected by experienced testers. Age-standardized t-scores from these four scales were combined into an Early Learning Composite (ELC) standardized score (range: 49-155, mean =100, sd =15). The ELC has high internal consistency (median = 0.91) and reliability (median = 0.84 for the cognitive scales during these testing ages), and principal factor loadings of the scales lend support for the construct validity of the ELC as a general measure of cognitive ability (Mullen, 1995), much like an intelligence quotient.

Image Acquisition

All MRI and DWI images used in this study were acquired between 2009 and 2012 using either a Siemens Allegra head-only 3T scanner (N=85) or a Siemens TIM Trio 3T scanner (N=30), which replaced the Allegra in 2011 (Siemens Medical System, Inc., Erlangen, Germany). Infants were scanned during unsedated, natural sleep after being fitted with earplugs and secured using a vacuum-fixed immobilization device.

Proton density and T2 weighted structural images were acquired on the Allegra using a turbo-spin echo sequence (TSE, TR = 6200ms, TE1 = 20ms, TE2 = 119ms, flip angle = 150°, spatial resolution = 1.25mm x 1.25mm x 1.95mm, N = 6) or a "fast" turbo-spin echo sequence was collected on the Allegra using a decreased TR, a smaller image matrix, and fewer slices (TSE, TR range = 5270ms-5690ms, TE1 range = 20ms-21ms, TE2 range = 119ms-124ms, flip angle = 150°, spatial resolution = 1.25mm x 1.25mm x 1.95mm, N=79). For the Trio, participants were initially scanned using a TSE protocol (TR=6200ms, TE1=17, TE2=116ms, flip angle=150°, spatial resolution= 1.25mm x 1.25mm x 1.95 mm, N = 4) while the rest were scanned using a 3DT2 SPACE protocol (TR=3200ms, TE=406, flip angle=120°, spatial resolution= 1mm x 1mm x 1mm, N=26).

T1-weighted images were acquired on the Allegra using a 3D magnetization prepared rapid gradient echo sequence (MP-RAGE TR = 1820ms, TE = 4.38ms, flip angle = 7°, spatial resolution = 1mm x 1mm x 1mm, with matrix dimensions of 256 x 192, N = 5 or 256 x 144, N = 80). T1 images on the Trio were collected using a lower echo time (MP-RAGE TR = 1820ms, TE = 3.75ms, flip angle = 7°, spatial resolution = 1mm x 1mm x 1mm, N = 30).

DWI data were acquired using a single-shot echo-planar imaging spin-echo sequence. For all DWI data, 42 directions of diffusion sensitization were acquired with a *b* value of 1,000 s/mm^2

in addition to seven baseline (*b* value = 0) images (generating a total of 49 DWIs). The parameters for the 42-direction data were as follows: TR/TR/Flip angle = 7,680/82/90°, slice thickness = 2mm, and in-plane resolution = 2 x 2 mm^2, with a total of 60 to 72 slices.

WM Surface Generation

Cortical surfaces for each infant were generated using a pipeline previously described (Jha et al., 2018; Li et al., 2016). All MR images were preprocessed for tissue segmentation using a standard infant-specific pipeline (Li et al., 2013). Specific steps included skull stripping and manual editing of non-brain tissue, removal of the cerebellum and brain stem, corrections for intensity inhomogeneity, and rigid alignment of T2-weighted images into an average atlas space (F. Shi et al., 2011). Gray matter, white matter (WM), and cerebrospinal fluid (CSF) were segmented by applying a standalone infant-specific patch driven coupled level sets method (Wang et al., 2014). Non-cortical regions were masked and tissues were divided into the left and right hemisphere. A deformable surface method (Li et al., 2012; Li, Nie, Wang, Shi, Gilmore, et al., 2014a) was applied to the tissue segmentations in order to reconstruct the WM and gray matter surfaces. This method involved a topological correction of WM volume to ensure spherical topology, a tessellation of the corrected WM to generate a triangular mesh, and the deformation of the WM mesh towards the reconstruction of each cortical surface while preserving the initial topology. All surfaces for the left and right hemisphere were visually examined for accurate mapping. The cortical surface, and corresponding WM surface, was parcellated into 78 regions of interest based on an infant-specific parcellation atlas (Gilmore et al., 2012; Tzourio-Mazoyer et al., 2002), see Jha et al. (Jha et al., 2018) for visualizations. For probabilistic tractography, only the WM surfaces were used.

Structural Network Generation

A study-specific, automated quality control (QC) protocol was applied to all raw DWI data using DTIPrep (www.nitrc.org/projects/dtiprep) which detected slice-wise and gradient-wise intensity and motion artifacts and corrected for motion and eddy current effects (Oguz et al., 2014). Diffusion images with large motion artifacts and missing or corrupted gradients were excluded from further processing. Skull and non-brain tissue were removed using Brain Extraction Tool (S. M. Smith, 2002), and tensors were estimated using a weighted least-squares algorithm (Goodlett et al., 2009). All infants with cortical surfaces, T1 images, and DWIs that passed QC (N = 246) were collected. T1 images were registered into DWI space using a rigid registration in ANTS. A deformation field was computed from the T1 images to the DWIs using ANTS. The deformation field was applied to the cortical surfaces. The registration of all the WM surfaces to the DWIs were visually inspected in 3D Slicer to ensure accuracy in alignment; 219 cases (89%) passed registration QC. Our dataset was derived from the 219 who passed QC and who were followed up and have cognitive testing data at age 2, this resulted in a dataset of 115 infants.

Probabilistic tractography was performed using CIVILITY (Puechmaille, Styner, & Prieto, 2017), a cloud-based interactive tool for the processing and visualization of white matter connectome data. CIVILITY utilizes FSL tools bedpostx, probtrackx2 (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). Prior to tractography, Bayesian estimation of diffusion parameters was computed to allow for data-driven selection of the number of supported fiber orientations at each voxel (bedpostx), accounting for multiple orientations and crossing fibers (Behrens et al., 2007). For our analyses, we used two tensors for voxel fitting. ExtractSurfaceLabels (https://github.com/NIRALUser/ExtractLabelSurfaces) was then used to extract each region from the WM surface and update a seed list for tractography. Probabilistic tractography was then

performed using probtrackx2 (Behrens et al., 2007), with the number of samples (streamlines per voxel) set to 3000, a step-length of 0.75mm, and seed sphere sampling size of 0.5mm.

Resulting matrices (78 x 78) containing the number of streamlines connecting each region of interest (ROI) were then normalized such that the degree of region-to-region connections were scaled from 0 to 1. The normalized matrices were used in the deep learning approach described below.

ELC 2-year Score Prediction Pipeline

As illustrated in **Figure 5.1**, the proposed two-step pipeline approach (i.e. the output of one model becomes the input to a second model) includes the construction of two models: *classification* followed by *prediction*. Since infant WM connectivity is used to predict a precise ELC score at age 2, it may be unrealistic to construct one model, i.e. single neural network, that has a reasonable amount of accuracy without dramatically overfitting it. To mitigate overfitting, the proposed design splits one difficult machine learning problem into two easier ones. More specifically, we start with an easier classification problem (ELC group classification) that is then followed by a more difficult prediction problem (ELC 2-year score prediction). This design choice is very reasonable and practical: Essentially, the ELC classification model directs an infant WM connectome to one of three fine-tuned ELC 2-year score prediction models based on an above average (AA), average (AV), or below average (BA) ELC group classification. In general, our pipeline is applied as follows: First an infant WM connectome is reshaped into a connectivity feature vector, which is then input to the ELC classification model. Next, the ELC group classification result is directed to the matching 2-year ELC prediction model (AA, AV, or BA).

Finally, the ELC group classification value, or confidence value, is input into the ELC group prediction model and a 2-year ELC score is found.

ELC 2-year Score Prediction Pipeline Training

Both models (classification and prediction) in our pipeline are trained and tested using a 10-fold cross-validation strategy, furthermore our cross-validation approach only uses FT infant WM connectomes. In general, the cross-validation strategy first evenly divides (as best as possible) infants into ten different folds, where no twin pair is in the same fold, then infants are randomly assigned to each fold, and the ratio of BA, AV, and AA infants are maintained in each fold. At each iteration, one-fold (i.e. the left-out fold) is used to test the model, and the remaining nine folds are used to train the model. The iterative strategy terminates when each fold becomes the test fold. At completion, ten different trained pipelines (classification model and prediction model) are created.

For the ELC group score classification model, the optimal momentum (p_m) and learning rate (p_{lr}) neural network model parameters were found by incorporating a grid search procedure in our cross-validation strategy. Specifically, an independent two-dimension grid-search procedure was performed for each left-out-fold, where the values stored at grid coordinate (p_m, p_{lr}) were the mean and standard deviation classification values. In particular, p_m was adjusted in increments of 0.05 starting at 0.001 and ending at 1.0, while p_{lr} was adjusted in increments of 0.0001 starting at 0.0005 and ending at 0.01. When the grid-search completes, the parameter values that achieved the highest classification accuracy are selected. It should be noted that when the decay value was set to a particularly small value ($\sim 10^{-6}$), it had little to no effect on the classification accuracy, so this model parameter was not included in our grid-search procedure.

ELC 2-year Group Score Classification Model

The upper triangular portion of the 78 x 78 FT infant WM connectivity matrices were reshaped into one dimensional connectivity feature vectors where each connectivity feature vector has 3,003 WM connections. The connectivity feature vectors, along with their associated group ELC classification labels, were then used to train a dense neural network that defines one input layer, five hidden layers, and one output layer. In particular, the input layer has 3003 neural network nodes, one for each WM connection in the connectivity feature vector, and the output layer has 3 neural network nodes, one for each ELC group score. One additional supervised learning layer was added when the model is trained that also has 3 neural network nodes. Once the supervised training step completes the supervised training layer was removed, and the number of neural network nodes in the output layer were used for ELC group score classification. For example, given a connectivity feature vector if the output of the neural network is AA=0.2, AV=0.65 and BV=0.4, then the infant is classified as average (AV) with confidence equal to 0.65. More specifically, classification confidence is a real number in [0 1], where a value of one implies the neural network is 100% confident the infant was assigned to the correct ELC group.

ELC 2-year Score Prediction Models

The ELC group confidence values generated of the ELC 2-year group score model were then used to train three different linear regression models (one for each ELC group) that were used to predict the actual ELC score at age 2. For each prediction model, one predictor variable (ELC group confidence) and one response variable (2-year ELC score) were used to train the linear regression model, e.g. only AA neural network ELC group confidence values and their corresponding 2-year ELC scores were used to train the AA 2-year ELC score prediction model.

In general, the linear regression model exploits a very intuitive relationship, for example, AA ELC group confidence values should be correlated with AA 2-year ELC scores. Furthermore, if the linear regression model has a high correlation coefficient, then this suggests the ELC group predication model can accurately find a precise 2-year ELC score, that is a 2-year ELC score prediction model is fine-tuned to the associated ELC group.

Extraction of the Connectivity Fingerprint

To identify the WM connectivity features driving classification accuracy, and thus important for predicting future cognitive performance, a backtrack approach similar to that described by Hazlett et al. (2017) was employed to identify a systematic WM connectivity pattern, or *connectivity fingerprint* for short. In general, our approach works its way backward through the layers of the trained neural network (using FT infants only) to the input layer, and follows the nodes that have the largest contribution to the layer directly above. When the backtrack approach completes each WM connection, in the connectivity feature vector, is assigned a normalized weight that indicates its contribution to classification accuracy, i.e. higher weight confers greater contribution. Next, using the assigned weight values the connectivity fingerprint is formed by including only those WM connections that account for top 20% of the total weight.

Application of the ELC 2-year Prediction Pipeline

Even though the 10-fold cross-validation strategy provides a standard approach to objectivity measure ELC classification and prediction accuracy of FT infants, the concern then becomes: (1) Can we achieve similar prediction accuracy of the approach when applied to infant WM connectome data that are not full term, and (2) using the ten different prediction pipelines,

created by the 10-fold cross-validation strategy, how should the ELC 2-year score be reported? To address these two concerns the ELC prediction pipeline was used to predict the 2-year ELC score of a second WM connectome dataset that only included PT infants. Since the prediction pipelines are trained using FT infants, this would closely simulate a real setting where the term of the pregnancy may be more variable (i.e. does not go full term). Furthermore, many model-based approaches may typically predict a single ELC 2-year score, which may not be statistically meaningful. Instead, given a WM connectome, our approach will generate ten 2-year ELC scores (one for each prediction pipeline), then the prediction results can be used to estimate a mean 2-year ELC score with standard deviation.

RESULTS

Participants

Parental and child demographic information for 78 full term (born at ≥ 37 weeks gestation; FT) and 37 preterm (< 37 weeks; PT) infant participants are presented in **Table 5.1**. PT infants were born earlier (t = 13.17, df = 51, $p < 0.0001$) weighed less at birth (t = 9.39, df = 70, p < 0.0001), and had longer stays in the neonatal intensive care unit (NICU; t = -5.35, df = 36, $p <$ 0.0001) following birth. In an effort to achieve term-age equivalent data, PT infants were scanned later after birth (t = -8.39, df = 52, p < 0.0001) and brought back later for their 2-year cognitive assessments (t = -6.57, df = 71, $p < 0.0001$). Twins were over-represented in the PT compared to FT group (χ^2 = 1.09, df = 1, $p < 0.0001$). There were no demographic differences between PT and FT groups based on maternal or paternal age, education level, or income, nor were there any differences in mean 2-year ELC scores or male to female ratios. The range of gestational age at birth and ELC scores for FT and PT infants is shown in **Figure 5.2**.

Classification of ELC Score Group

Classification labels were generated by grouping infants into three categories based on their performance on the 2-year ELC relative to others in our sample: above average (AA; N_{FT} = 18, N_{PT} = 9) average (AV; N_{FT} = 41, N_{PT} = 19), and below average (BA; N_{FT} = 19, N_{PT} = 9). The ELC score group (BA, AV, BA) classification model was trained on the 78 FT infants using a 10-fold cross-validation approach and achieved 79% (*SD* = 2.68%) accuracy. We additionally tested our approach on the 37 PT infants using each trained model generated by our 10-fold approach, where classification accuracy was determined as the mean accuracy across all 10 ELC score group models. The PT classification accuracy was 74% (*SD* = 2.68%).

Prediction of ELC Scores

Results comparing the predicted ELC score to actual scores can be seen in **Figure 5.3A** for FT infants and **Figure 5.3B** for PT infants. Correlations between predicted and actual scores were high for both FT (r = 0.947, df = 76, $p < 0.0001$) and PT infants (r = 0.967, df = 35, $p < 0.0001$; for mean predicted score across 10 folds). The mean absolute error across individuals for the prediction was 4.3 points for FT and 3.14 points for PT infants.

Connectivity Fingerprint

The connectivity fingerprint shown in **Figure 5.4** defines 20 brain regions, and 30 WM connections that are important for accurate classification based on ELC score group (BA, AV, AA). Highest degree brain regions important for classification (**Figure 5.4B**) include the left frontal inferior triangularis (comprising part of Broca's area), right insula, and right supplemental motor area, right rectus gyrus, and left anterior cingulate. Additional brain regions of lower degree

that contribute to classification include the bilateral precentral (primary motor cortex) and frontal superior medial gyri, the right frontal inferior orbital gyrus, left insula, right middle cingulate, right parahippocampus, right angular gyrus, and left calcarine, fusiform and parietal superior gyri.

WM connections with the highest contribution to classification (**Figure 5.4A**) include connections between the pre- and post-central gyri in the left hemisphere, and long-range connections between the primary visual cortex and frontal inferior triangularis in the left hemisphere, the occipital inferior cortex and precentral gyrus in the right hemisphere, and the primary visual cortex and precentral gyrus in the left hemisphere. Cross-hemispheric connections of high weight (weight > 7) included connections between the parts of the right supplemental motor area (rolandic operculum) and frontal inferior triangularis in the left hemisphere, and a connection between the left superior parietal cortex and frontal inferior triangularis in the right hemisphere.

DISCUSSION

Using a developmental connectomics framework coupled with a deep learning approach, we have demonstrated the ability to accurately predict an infant's cognitive performance at age 2 using WM connectivity matrices generated from scans at birth. Specifically, we demonstrated that taking a two-step approach by first classifying infants based on their cognitive performance group – below average, average, and above average – and then using results from this group classification to directly predict ELC scores, allowed us to achieve estimates of children's cognitive scores two years later that are highly correlated with their actual scores. Importantly, we found that our prediction model, which was trained using WM data from term-born infants, was applicable to preterm infants, despite known associations between prematurity and altered WM development (Elitt & Rosenberg, 2014). Finally, to our knowledge, we report the first results identifying regions in the neonatal WM connectome that are important for supporting emergent cognitive abilities at

age 2 in both full-term and preterm infants. This study demonstrates the importance of fetal brain development for subsequent cognition and suggests that the WM connectome may be an important biomarker of cognitive abilities during early postnatal development that deserves further study.

A distributed WM network consisting of nodes spanning the cortex at birth – with the highest degree nodes confined to the frontal lobe, namely an area comprising part of Broca's area in the left hemisphere, and right insula – contributed to classification accuracy based on cognitive scores two years post-birth. These findings are consistent with previous reports that rich club regions in the infant WM connectome include regions in the medial frontal cortex and insula (Ball et al., 2014). Interestingly, studies linking infant WM connectomes to parental reports of children's behavior at age 4 also found connectivity to the right insula to be an important predictor of future externalizing behavior (Wee et al., 2016), and Kawahara and colleagues found a WM hub in the middle frontal gyrus in preterm infants to be related to cognitive abilities at age 2 (Kawahara et al., 2017). These findings, along with the results from our study, suggest that frontal lobe WM connections and connections to the insula play an important role in early learning and cognition. This is no surprise, as the frontal lobe plays a critical role in executive function and general intelligence (J. Duncan et al., 2000), and the insula has been shown to integrate information across brain networks responsible for cognition and emotion (Chang et al., 2013). Additionally, functional connectivity in the left pre- language area (which will later become Broca's area) in the fetal brain was predictive of gestational age at birth, with later-born infants showing higher connectivity to left language regions *in-utero* than those who would go on to be born preterm (Thomason et al., 2017). This research, along with our finding that structural connectivity at birth to Broca's area is related to future cognition, suggests that the development of language circuitry that occurs *in-utero* is important for postnatal cognitive development.

Cortico-cortical connections that were most important to classifying infants based on their cognitive scores two years later include connections between sensory, motor, and language regions. Our finding that short range connections between the primary motor and somatosensory cortices are predictive of future cognition is particularly interesting given the importance of motor development to cognitive development in infancy, which allows for infant exploration, perceptual learning, and social interaction (Campos et al., 2000; Gibson & Pick, 2000).A recent study found that at age 1, several brain functional networks, including motor networks spanning the pre- and post-central gyri, were important for present and future gross motor performance (Marrus et al., 2018). This suggests a potential role for the *in-utero* development of somato-motor structural connectivity that may lay the foundation for the emergence of functional connections that support motor and cognitive development in infancy. Additionally, we found that long-range connections between regions in the occipital cortex and primary motor cortex were also important for prediction, suggesting that visuo-motor integration, a known component of motor development in children (Kulp, 1999) that is disrupted in children with autism spectrum disorders (Nebel et al., 2016), may be subserved by WM connections established during fetal brain development. Finally, long-rage cortico-cortical connections between a region housing Broca's area in the left hemisphere and the left primary visual cortex, right rolandic operculum, and left superior parietal cortex were also important for predicting future cognition, suggesting that connectivity to the left inferior frontal language areas may play an important role in infant cognition.

Results from this study suggest that WM connectomes at birth, as a reflection of fetal brain development, have important implications for future cognitive developmental capacities in children. Structural connections in the developing brain are built through genetically regulated cascades of cellular events that govern neurogenesis and migration and promote an exuberance of

connections via processes of axon guidance, synaptogenesis and dendritic arborization (Stiles & Jernigan, 2010). In the final trimester, the infant structural connectome undergoes substantial refinement through apoptotic mechanisms that promote pruning of neuronal processes, a process which continues through early postnatal life (Innocenti & Price, 2005). Despite the substantial amount of axonal pruning during the end of gestation and during the first two postnatal months, we are still able to use WM connectivity features at birth, from a group of full-term and preterm infants, to predict future outcomes. This suggests that the foundational wiring of the brain important for future cognition is set in place *in-utero*, and may have lasting impacts on child development.

Neuroimaging research has greatly improved our understanding of human brain function and development; however, it has largely fallen short of informing clinical or educational practice that improves people's lives (Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015). Thus, as the field advances, there is a critical need to identify neuroimaging biomarkers that can aid in improving diagnostic criteria and identifying people at risk for poor mental health and cognitive outcomes so that adequate interventions can be designed and implemented. Our study using non-invasive neuroimaging biomarkers, in this case WM connectomes, to predict infants' future cognitive performance is an important step in this direction. Machine learning, and particularly deep learning, have been instrumental in neuroimaging research by allowing abstract and complex patterns between brain structural and functional features and cognitive and clinical phenotypes to be revealed (D. Shen, Wu, & Suk, 2017; Vieira, Pinaya, & Mechelli, 2017). In this study, we trained a deep learning classification model to use infant WM connectomes at birth to predict future cognitive outcomes 2 years post-birth. The classification accuracies were relatively high; we achieved 79% in full-term and 73% in preterm infants. These results are quite remarkable

considering the substantial amount of refinement that the WM network, and underlying fiber tracts, will undergo in the first two postnatal years (Dubois et al., 2014; Gao, Lin, et al., 2009a; Geng et al., 2012), coupled with the fact that we performed a multi-class classification based on normal variation in general cognitive abilities, as opposed to a binary outcome based on clinical diagnosis.

Given the potential clinical relevance of predicting cognitive scores directly, we used classification strengths from the ELC group classification model as inputs in a regression prediction model to estimate each infant's future cognitive score at age 2. This two-step process achieved very high correlations between predicted and actual scores, within just a few points of the actual score in many cases. The mean absolute error between predicted and actual scores are, on average, comparable to the standard errors of measurement for the ELC, which range between about 3 and 4 score points for 2-year-olds, and reflect a band of error around the mean, or "true", score that would be obtained if an individual could be tested repeatedly without influences of practice or other factors (Mullen, 1995). This level of accuracy is imperative if you wish to use neuroimaging markers, or 'neuromarkers', to guide cognitive and behavioral interventions in young children. Another recent study proposed a deep learning approach for directly predicting cognitive scores at age 2 from WM networks of preterm infants; however, the correlations between the predicted and ground-truth scores were much weaker, with correlations of only 0.19 for general cognitive scores and 0.31 for motor scores (Kawahara et al., 2017). This suggests that taking the difficult problem of direct score prediction from neuroimaging data, and breaking it down into two tractable problems – a group-level classification followed by regression prediction model – may be a better suited approach. This idea is further supported by findings in adults, where Finn and colleagues (Finn et al., 2015) used functional connectivity fingerprints to predict individual differences in fluid intelligence and found correlations of 0.50 between actual and predicted scores.

Results of that magnitude, while important findings, do not provide high enough correlations for use in an applied setting. While our method is far from ready for clinical application, it shows promise for the ability to directly predict scores with good accuracy, which may be particularly important for identifying infants at birth who are at risk for going on to score in clinically significant ranges of developmental delay.

Importantly, our models, which are trained using data from full-term infants, robustly predicted future cognitive scores with similar accuracy using WM connectomes from preterm infants. Preterm birth is associated with alterations in WM microstructural development (Partridge et al., 2005) and cortical development (Rathbone et al., 2011). Preterm infants are at risk for poor cognitive outcomes (Bode et al., 2014) and neurodevelopmental disorders including attention deficit hyperactivity disorder and autism, which have been linked to disruptions in brain connectivity (Liston, Cohen, Teslovich, Levenson, & Casey, 2011; Uddin, Supekar, & Menon, 2013). Additionally, recent investigations of functional connectivity in human fetuses *in-utero* found that those that went on to be born prematurely showed altered connectivity patterns that occurred in a graded manner, such that the most premature infants showed the most altered connectivity patterns *in-utero* (Thomason et al., 2017). This work suggests that negative outcomes associated with prematurity may have origins in pre-existing intrauterine neurological conditions, as opposed to extrauterine factors occurring after preterm birth. Despite the inherent differences between brain development in full-term and preterm infants, our ability to accurately predict cognitive scores in both groups suggests there exists an underlying set of organizational principles that govern structural network topology and have important implications for cognitive development. This highlights the potential usefulness of WM connectomes as neuromarkers of cognition across heterogeneous infant populations.

This study has many strengths. Our sample included both full-term and preterm infants with high resolution diffusion magnetic resonance imaging data followed longitudinally for cognitive assessment. The methods employed in this study are cutting edge and allow for a data-driven approach to identifying regions in the WM connectome related to future cognitive abilities. Additionally, we replicated our findings in a preterm sample that is clinically distinct and was unknown to the model which was trained on the full-term sample. Finally, to our knowledge, we conducted the first study to assess the predictive ability of WM connectomes at birth for future cognitive outcomes in full-term and preterm subjects. Despite these strengths, our study has limitations including the use of a cortical-only atlas for probabilistic tractography, which does not consider cortico-subcortical connections which may be important for emerging cognition (Ball et al., 2015). Also, while our sample size is comparable to other studies of this nature, it will be important to replicate these findings in other longitudinal datasets, for example, using data from the publicly available Baby Connectome Project.

In conclusion, findings from this study revealed that the infant WM connectome is predictive of cognitive performance at age 2, which highlights the importance of WM development *in-utero* for subsequent cognition. We also report the first evidence of WM structural hubs and connections that have implications for cognitive abilities in toddlerhood in a healthy sample. Our work has implications for screening and intervention, and suggests that future work should focus on identifying the ways in which prenatal mechanisms of WM development are influenced by genetic factors as well as the intra- and extrauterine environment to shape individual differences in structural connectomes that serve as a biological foundation for learning.

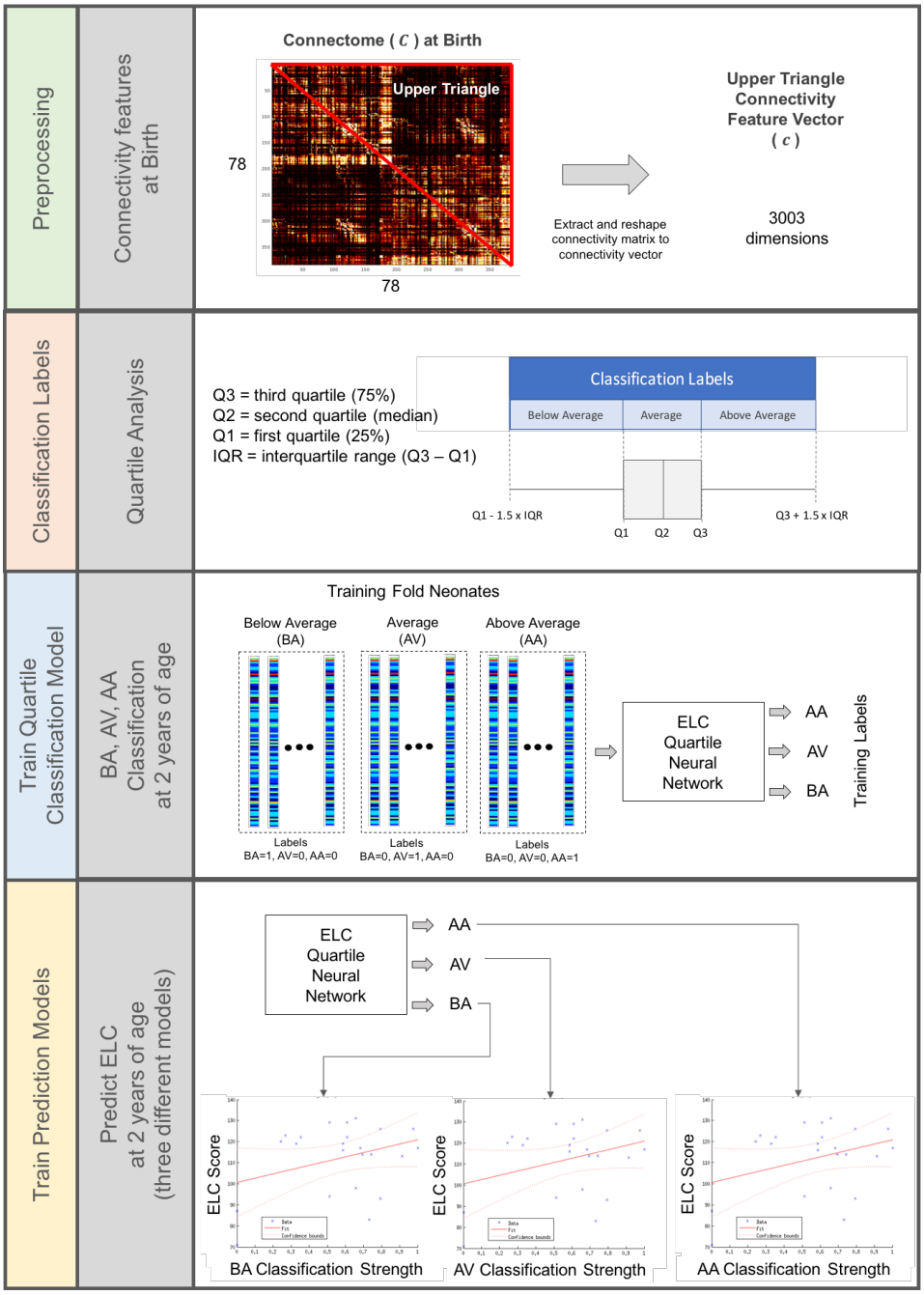


Figure 5.1. Approach for predicting ELC scores at age 2 from WM connectomes at birth.

Data were preprocessed to reshape WM connectivity matrices (78 x 78 cortical regions) at birth into connectivity feature vectors by computing the reciprocal of the coefficient of variation (i.e. the ratio of the mean to standard deviation) of the fiber count for each pairs of regions (78 x 77/2 = 3003 region pairs). Classification labels were generated by grouping subjects into three categories based on their performance on the 2-year ELC relative to others in our sample: above average (AA) average (AV), and below average (BA). A classification model predicting ELC group (BA, AV, AA) was then trained and tested on the 78 FT subjects using a leave-one-out cross-validation approach. Finally, classification strengths (average accuracy across testing folds for each subject) were then fed into a regression prediction model to directly estimate the ELC score at age 2 for each ELC group.

Table 5.1. Participant Demographic Information

	Full Term (N = 78)	**Preterm (N = 37)**			
	Mean (SD)	*Mean (SD)*	*T-test**	*df*	*P-value*
Gestational Age Birth (days)	272.40 (9.28)	238.68 (14.21)	13.17	51	<0.0001
Birth Weight (grams)	3095.10 (480.52)	2188.22 (485.13)	9.39	70	<0.0001
Stay in NICU (days)	0.01 (0.11)	10.89 (12.37)	-5.35	36	<0.0001
Age at MRI (days)	23.14 (9.86)	45.19 (14.47)	-8.39	52	<0.0001
Age at 2yr MSEL (days)	747.36 (22.0)	779.08 (25.14)	-6.57	63	<0.0001
2yr ELC	106.4 (15.93)	105.19 (15.85)	0.40	71	0.6922
Maternal Age (years)	29.97 (5.76)	29.95 (6.14)	0.02	67	0.9812
Paternal Age (years)	32.42 (5.98)	32.0 (8.40)	0.28	54	0.7843
Maternal Education (years)	14.96 (3.30)	15.89 (3.23)	-1.44	72	0.1533
Paternal Education (years)	15.01 (3.73)	15.36 (2.98)	-0.52	85	0.601
Household Income ($)	$72,260 (62,909)	$88,537 (64,870)	-1.23	65	0.2213
	N	*N*	*Chi Sq.*		*P-value*
Male / Female	41 / 37	24 / 13	1.09		0.2975
Singleton / Twin	49 / 29	4 / 33	25.27		<0.0001

** calculated using Welch's two-sample, two-tailed t-test assuming unequal variance*

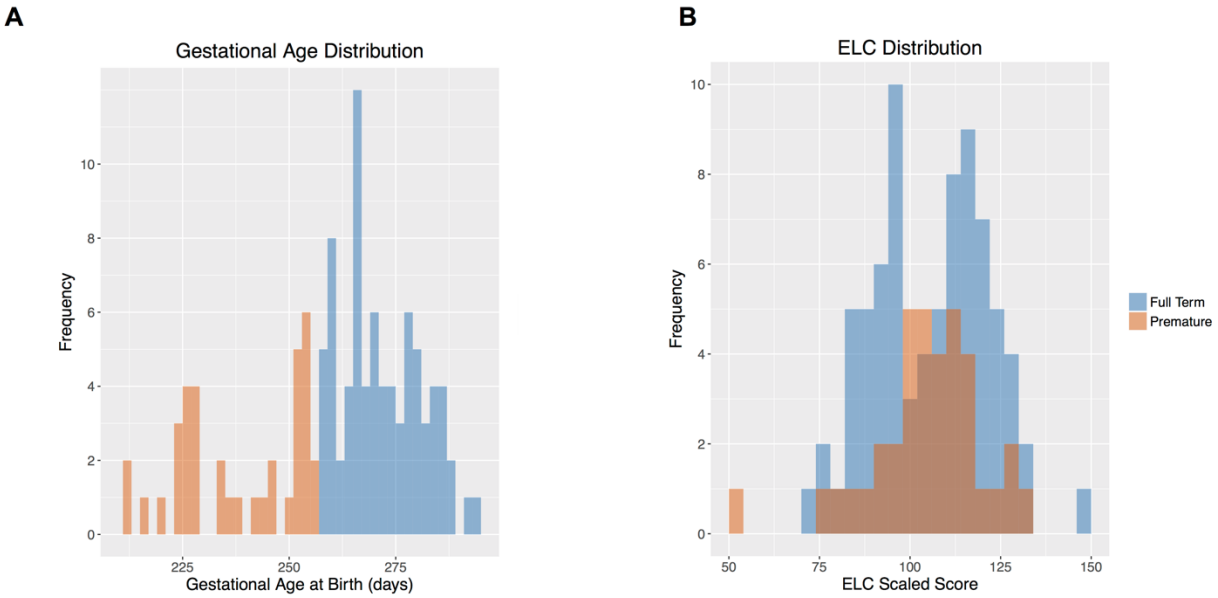


Figure 5.2. Participant Gestational Age at Birth and ELC Distributions.

Participant distributions for gestational age at birth (A) and ELC scores at age 2 (B) are presented. Data from FT subjects are shown in blue and PT subjects are shown in orange.

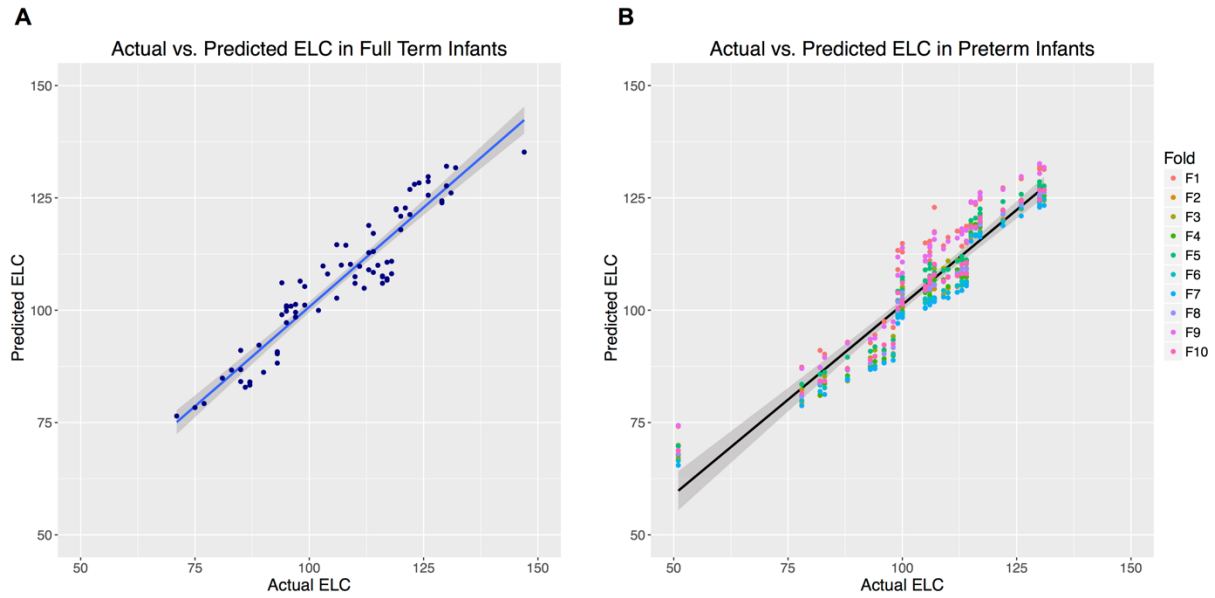
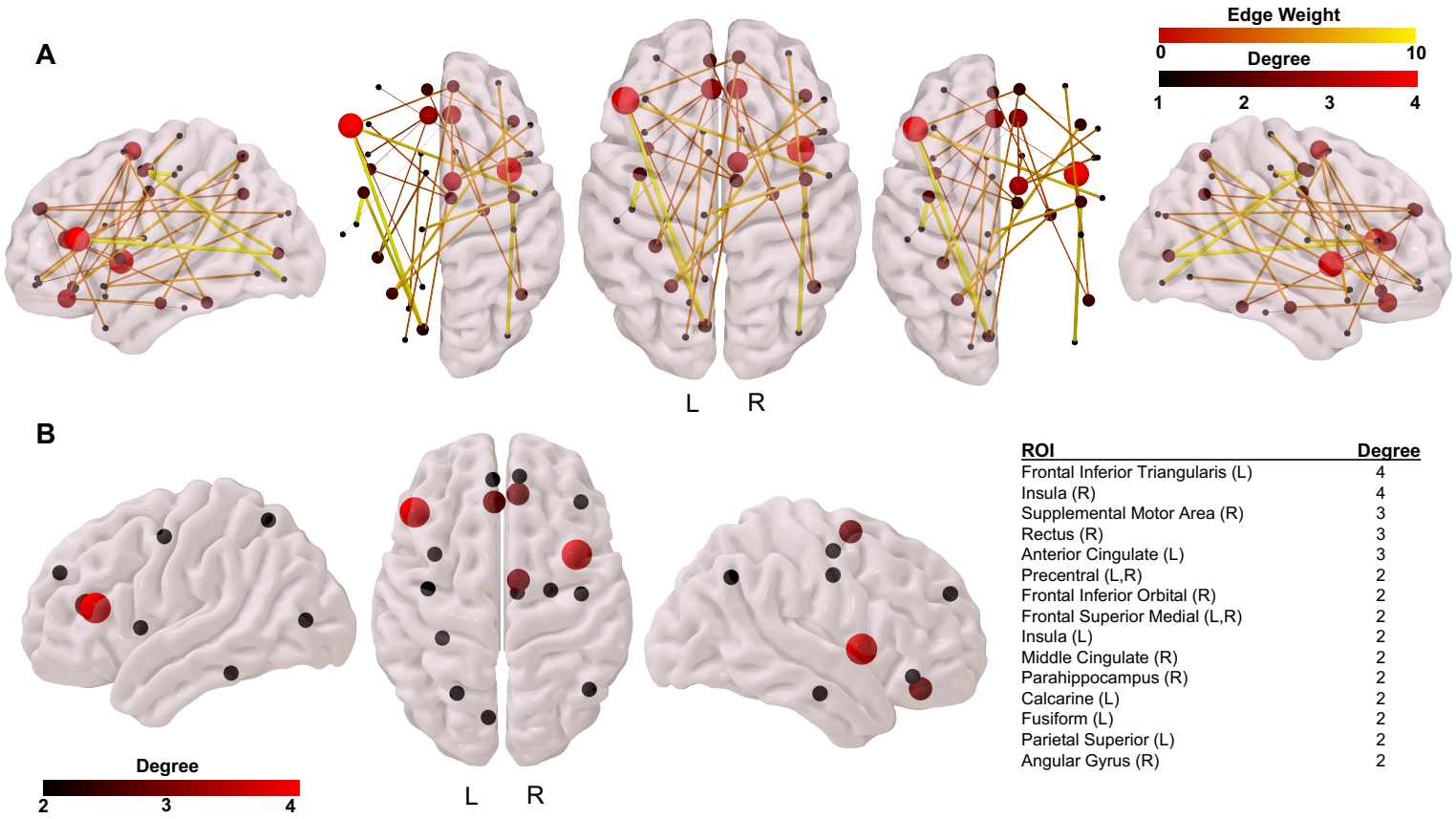


Figure 5.3 Correlations between actual and predicted 2-year cognitive scores.

Estimated ELC scores generated through regression prediction models are plotted against each FT infant's actual ELC score, along with linear regression lines (blue line) and shaded 95% confidence intervals (A). Regression prediction models were run for each classification fold for PT infants, and estimated ELC scores for each fold are shown in (B), along with the linear regression line (black line) for the mean predicted score across folds and a 95% confidence interval for the regression fit.



ROI	Degree
Frontal Inferior Triangularis (L)	4
Insula (R)	4
Supplemental Motor Area (R)	3
Rectus (R)	3
Anterior Cingulate (L)	3
Precentral (L,R)	2
Frontal Inferior Orbital (R)	2
Frontal Superior Medial (L,R)	2
Insula (L)	2
Middle Cingulate (R)	2
Parahippocampus (R)	2
Calcarine (L)	2
Fusiform (L)	2
Parietal Superior (L)	2
Angular Gyrus (R)	2

Figure 5.4: Connectivity fingerprint of WM connections driving ELC group classification accuracy.

Results from the backtrack approach identifying features of the input WM connectomes that are most responsible for ELC group classification accuracy are shown in (A), where nodes (brain regions) in this fingerprint subnetwork are colored by degree (number of connections to the node) and edges are colored by their weight (0,10). Highest degree nodes (degree > 2) in the subnetwork are visualized in (B) along with a listing of these anatomical regions from the parcellation atlas.

CHAPTER SIX: INTEGRATION, CONCLUSIONS, AND FUTURE DIRECTIONS

SUMMARY OF FINDINGS

The work presented in the dissertation comprises the first comprehensive study of how cortical structure and white matter organization and integrity in the first two years of life relate to individual differences in language, motor, and cognitive abilities in infancy and toddlerhood.

In **Study 1/Chapter 1** we established that the Mullen Scales of Early Learning composite score (ELC) at age 2 is predictive (at a similar level to other developmental assessments) of school-age intelligence, while scores at age 1 are far less predictive. We also reported that twins score significantly lower than singletons by age 6, and that infants born very prematurely or with birth complications had variable IQ outcomes at age 6 that were not predicted by infant scores.

In **Aim 1/Chapter 2** we examined the relationships between CT and SA and cognitive performance across infancy and toddlerhood in a large, normative sample. Our findings – the first report of the associations between global and regional CT and SA and cognitive abilities in this age range – suggested that generally thicker, larger cortices in early life confer cognitive benefits in infancy and toddlerhood. The majority of our findings were with CT. We found several expected brain-cognition relationships, with CT in regions associated with motor planning and execution and regions associated with language processing and production related to motor and language scores, respectively. Results were weakened when other demographic variables, including gestational age and maternal education level, were included in the model. Finally, our longitudinal models revealed no significant associations between developmental

changes in CT and SA in the first or second year of life. Taken together, our findings suggest that: (1) cognitive abilities in early life are, at least in part, determined by preceding prenatal and postnatal brain development and related to present cortical structure in regions important for cognition, (2) CT in this age range appears to be a stronger morphological indicator of cognition, (3) processes that drive SA expansion prenatally and CT expansion in infancy – namely synaptogenesis, dendritic arborization, and the elaboration of other cellular processes and connections – may be important for building circuitry that supports emergent cognition, and (4) cortical measures are modest biomarkers, at best, accounting for a relatively small percentage of the variance in cognitive scores compared to other demographic factors like maternal education.

In **Aim 2/Chapter 3** we examined the associations between WM tract integrity and cognitive abilities in the first two years of life in a typically-developing sample. Results from this study revealed widespread associations between FA, AD, and RD at birth and cognitive abilities at ages 1 and 2, and widespread associations between RD at age 1 and concurrent cognition. Controlling for demographic variables greatly weakened brain-cognition results. Longitudinal analyses revealed that generally slower rates of change in RD in the second year of life were related to better language performance in tracts known to support higher-order cognition. These findings suggest that: (1) WM microstructure at birth plays a role in supporting cognitive abilities across infancy, (2) RD may be a particularly important biomarker of overall WM development, (3) myelination, fiber organization, and axon diameter may be important for supporting cognitive development in early life, and (4) protracted myelination, and thus increased plasticity, in the second year of life may be important for language learning.

In **Study 3/Chapter 4** we extended our findings from Aim 2 to determine the predictive value of WM connectivity at birth for general cognitive ability at age 2. In this study, we used a

deep learning approach to classify infants based on their cognitive scores at age 2 using WM connectomes at birth. We were able to classify both full-term and preterm infants as scoring below average, average, or above average on cognitive assessments at age 2 with very good accuracy. We were also able to use results from these models to directly predict each infant's 2-year ELC score. Predicted scores were highly correlated with actual scores. These results highlight: (1) the importance of *in-utero* WM network development for building the structural foundation that supports cognitive development in toddlerhood, (2) that WM networks can serve as a strong biomarker of future cognition when the analytic approach involves the WM network and can account for complex relationships between brain and cognitive data, and (3) that mechanisms controlling circuit formation, including neurogenesis and axon guidance, may be particularly important for wiring the brain to support cognition.

These findings offer novel insight into how prenatal and postnatal brain structural maturation support infant and toddler cognitive abilities and fill important gaps in our current understanding of the neurobiology of emergent language, motor, and cognitive abilities in early life.

CONTRIBUTIONS TO THE FIELD

Developmental Assessments: A Modern Take on Prediction

In **Study 1/Chapter 1** we reported, for the first time, the predictive ability of the Mullen Scales of Early Learning ELC score for school-age IQ. The MSEL is used in ongoing studies of brain development in both normative populations (Deoni et al., 2014; O'Muircheartaigh et al., 2013) and in samples with children at risk for neurodevelopmental disorders including ASD (Marrus et al., 2018; Swanson et al., 2015). We have now provided evidence that ELC scores from the MSEL at age 2 can be considered predictive of school-age IQ in a similar manner to

other commonly used developmental assessments like the Bayley (Bayley, 1993). While our findings were in line with much other work in the field showing the predictive value of infant tests for later outcomes, we added important insight into how these predictions hold across twins and singletons, between children with and without birth complications, and in a more racially and ethnically diverse sample than had been used in past literature. Our study also includes the most recently born sample of children to date, which may be important given the reported increases in IQ over generations (Blair, Gamson, Thorne, & Baker, 2005; Flynn & Weiss, 2007), and the potential impacts of technology on child development that may not have been captured in older-born samples (Radesky & Christakis, 2016). Finally, our results also suggest that averaging Mullen scores between age 1 and age 2, as has been done in some prior work under the rationale of using a more "stable" measurement, may not be appropriate as the 1-year scores are significantly less predictive than the 2-year scores of later childhood performance.

Insights into Brain-Cognition Relationships in an Unprecedented Sample

The studies presented in this dissertation provide the first account of brain-cognition relationships in a large, normative sample of infants and toddlers. The few studies that have reported relationships between WM integrity and cognitive ability in the first years of life used less than half the number of participants we have in our sample (Deoni et al., 2014; O'Muircheartaigh et al., 2013), report findings in smaller samples split between controls and at-risk children (Swanson et al., 2015; Wolff et al., 2012), or focus exclusively on premature infants (Cui et al., 2017; Keunen et al., 2017; Ullman et al., 2015; Woodward, Clark, Bora, & Inder, 2012). There have been no prior studies of CT and SA development during early infancy and its associations to cognition. Therefore, results from this study provide the first comprehensive

evidence of structural brain-cognition relationships in early infancy. The generalizability of our work goes far beyond what is currently available in the literature, and allows for hypothesis generation that is needed to push the field forward as we attempt to uncover how the brain matures to support cognitive development in early life.

Additionally, we studied multiple cognitive domains including gross motor, fine motor, visual reception, expressive language and receptive language, as well as general cognition. This depth of work has not been reported in healthy children of this age range, to our knowledge, in the field of developmental cognitive neuroscience. We provide key insights into which brain regions and white matter fibers are related to each cognitive domain, allowing for a clear picture to emerge concerning structure-function relationships and the contribution of brain structures to multiple cognitive domains. While one might expect to find adult-like structure-function relationships, our findings suggest that this is not always the case, and provides researchers with insight into the unique neurobiology that supports emergent language, motor, and general cognitive skills in the first years of life.

The Neurobiology and Neuroimaging Biomarkers of Early Cognitive Development

In **Aim 1/Chapter 2**, we found many important relationships between cortical structure and cognition. However, regional CT and SA, on average, accounted for only between 3-5% of the variance in cognitive scores when no other variables were included in the model. This highlights that while there are correlations between cortical structure and cognition during these ages, they are modest at best. Results that survived correction for covariates suggested that CT in the right insula may be a particularly useful biomarker of cognition in this age range, and that the cellular organization of the insular cortex by age 2 may be important for concurrent cognitive

abilities. This is particularly interesting given that the insula is thought to play an important role in integrating disparate functional brain systems (Chang et al., 2013), is a high-expanding cortical region with potential evolutionary significance (Fjell et al., 2015), and has been implicated in pathogenic states including schizophrenia (Namkung et al., 2017). These corrected analyses also revealed findings indicating that by age 1, the primary motor cortex is structurally developed to support future motor function and that by age 2 cortical areas responsible for speech production and language processing are organized to provide a foundation for burgeoning language abilities in toddlerhood.

Results from **Aim 2/Chapter 3** revealed that WM microstructural relationships with cognition were generally less specific, and indicated that brain-wide WM integrity at ages 1 and 2 was important for supporting cognition across domains. The effect sizes of the correlations found were of a similar magnitude to those between CT, SA, and cognition – explaining between 2-8% of the variation in cognitive scores – once again suggesting modest brain-cognition associations. Longitudinal analyses revealed that protracted development in RD in many higher-order tracts including the bilateral SLF, bilateral fronto-temporal segment of the arcuate, the right temporo-parietal arcuate, left cingulum bundle, bilateral cortico-thalamic projections, and left IFOF, ILF, and uncinate were related to higher language and general cognitive scores. This work suggests that initially global WM integrity at birth and age 1 followed by specific protracted development in higher-order tracts in the second year of life lay the foundations for cognitive abilities in infancy and toddlerhood.

Using a machine learning approach, we were able to dramatically improve the usefulness of brain measures as biomarkers of future cognitive scores. The direct correlations between brain measures – CT, SA, and regional WM integrity – explained less than 8% of the variance in

cognitive scores, which are in line with effect sizes seen in adolescent and adult samples (Colom et al., 2013; S. J. Lee et al., 2017; Penke et al., 2010; Shaw et al., 2006). Results from **Study 2/Chapter 4** revealed correlations between actual and predicted cognitive scores of 0.95. This is substantially better than correlations between actual and predicted scores in other published findings of 0.19 - 0.31 in young children (Kawahara et al., 2017) and 0.50 in adults using functional data (Finn et al., 2015). These findings highlight that while the direct correlations between WM microstructure in any one brain region and cognition are low, the complex, multi-feature combination of brain phenotypes can be very useful in predicting future outcomes. Perhaps this is due the inherent differences between measuring WM microstructure, which evolves across the lifespan as the result of local neurodevelopmental processes, namely myelination, whereas WM networks arise as the result of global brain developmental mechanisms that occur *in utero* and are refined afterwards, but are largely stable at the time of birth. Finally, we also found that the approach used to perform classification and prediction are very important to the prediction accuracy. There is still much work needed to determine the potential clinical application of such an approach, but studies in ASD infants using cortical morphological features at 6 months to predict ASD diagnosis at 24 months (Hazlett et al., 2017) show promise for such techniques moving forward.

Overall, the findings from this work comprise the first comprehensive study of the neurobiology underlying early cognition and highlight the usefulness of WM connectome features at birth for predicting 2-year outcomes with high accuracy. These findings contribute to the field by offering researchers with hypothesis-generating ideas for future mechanistic study into early cognitive development. Specifically, these findings suggest future work should probe the structure and connectivity of the insula, WM integrity in higher-order tracts like the SLF,

UNC, IFOF, and ILF, and cortical structure and connectivity of frontal, parietal, and temporal cortices in relation to emergent cognition in infancy and toddlerhood.

BRAIN DEVELOPMENTAL MECHANISMS: CONTRIBUTIONS TO COGNITION

One very clear finding emerged from this dissertation work: brain structure at birth is predictive of future cognitive outcomes. This focuses our attention to the importance of *in-utero* brain development for building the biological framework that supports cognitive development, and gives rise to a key question: *what environmental and genetic factors shape prenatal brain development to generate subtle variations in brain structure that subserve future individual differences in cognitive functioning?*

Shaping Prenatal Brain Development: The Role of the Environment and Epigenetics

As discussed in the introductory chapter, prenatal brain development is a highly regulated process governed by genetic mechanisms and environmental exposures. The timing and regionalization of gene expression control the birth, differentiation, and migration of neurons and their synaptic connectivity, ultimately shaping how the brain is wired. Brain development begins with neurulation shortly after conception, then neurogenesis and gliogenesis take place between weeks 4 and 12, followed by processes of neural migration which continues through the end of gestation, as well as synaptogenesis and apoptosis, and later myelination, that continue after birth (Stiles & Jernigan, 2010). Disruptions in any of these processes may have lasting consequences, as has been suggested by findings that maternal immune activation (Knuesel et al., 2014), maternal stress (Bale, 2015), and maternal drug use (B. L. Thompson, Levitt, & Stanwood, 2009)

during pregnancy cause alterations in brain development that increase risk for poor cognitive, behavioral, neurological and mental health outcomes in offspring.

The exact mechanisms by which *in-utero* insults from stress, viral infection, or drug exposure alter brain development remain elusive. However, we do know that epigenetic reprogramming of brain development can occur through physiological signals from the maternal milieu (cytokines, lipids, stress hormones, glucose, insulin, etc.) that transmit information from the *in-utero* environment to the developing fetus and that physiological disturbances caused by maternal stress, infection, and nutrition share some common developmental endpoints including increased risk for ASD, schizophrenia, and poor cognitive outcomes (Bale, 2015). The common outcomes across insults, coupled with the fact that there are a limited number of biochemical inputs that a given cell can respond to, it is likely that different insults act on the same signaling cascades and downstream effectors to promote epigenetic changes in DNA methylation (Bale, 2015). However, many questions remain regarding how these epigenetic processes are promoted, and specifically what level of stressor is warranted to activate epigenetic machinery and exact change in the developing fetus. Additionally, it will be important to understand whether "normative" exposures to stress and inflammation during pregnancy may effect epigenetic change, and whether these could contribute to subtle differences in brain development that give rise to typical variation in cognitive abilities. Results from our studies demonstrate that maternal education (and by proxy socioeconomic status) influences both cortical development at birth and subsequent cortical and cognitive development in healthy children, which may suggest that stressors associated with lower socioeconomic status epigenetically regulate fetal brain development and, subsequently, later brain and cognitive development, though additional work is needed to test such a hypothesis. Alternatively, one might expect that inherited genetic material

may be more influential on brain development than epigenetic regulation given conditions of a relatively homeostatic prenatal maternal environment are met, and that differences in brain development associated with socioeconomic status are in fact inherited traits.

Potential Genetic Contributions to Brain Development and General Cognitive Ability

Twin studies from the Early Brain Development Study at UNC have revealed that total intracranial volume, gray matter and white matter volumes, and tract-based measures of WM integrity (FA, AD, RD) are highly heritable in early life (Gilmore, Schmitt, et al., 2010b; S. J. Lee et al., 2015). These findings are in line with those from studies of adults and aging adults and suggest that the heritability of white matter volumes are fairly constant across the lifespan while heritability of gray matter volumes may increase from infancy into childhood and adulthood (Gilmore, Schmitt, et al., 2010b). General cognitive ability and intelligence are also highly heritable, with shared genetic factors accounting for between 50 – 80% of the variation in intelligence (Posthuma, de Geus, & Boomsma, 2001). Heritability of intelligence has also been shown to increase from infancy (20%) to childhood (40%) to adulthood (60%), possibly through gene by environment interactions in which children select, modify, and create environments correlated with their genetic propensities (Plomin & Stumm, 2018).

While both brain structure and intelligence are known to be heritable, the genetic basis of neurobiological differences that contribute to normative variations in cognition across the population remains unknown. Recent genome wide association studies (GWAS) have begun to identify a host of genes important for cognition that are linked to neurodevelopment. One recent study found that 187 independent loci from 538 genes were related to educational attainment, which is highly correlated with intelligence, in a sample of nearly 250,000 adults (Hill et al.,

2018). Gene set analyses in this study, which identify groups of genes and their joint effects, revealed that genes related to neurogenesis, regulation of nervous system development, regulation of cell development, neuronal differentiation, oligodendrocyte differentiation, and maintenance of synapses were enriched in their cognitive GWAS results. This implicates a variety of neurodevelopmental mechanisms, many of which are processes that occur at high rates during fetal development (neurogenesis, neuronal differentiation) and the early postnatal period (oligodendrocyte differentiation as a precursor to myelination).

Another recent study by Davies and colleagues (2016) replicated findings that cognition is associated with *CADM2* (Ibrahim-Verbaas et al., 2016), a gene on chromosome 3 which encodes a synaptic cell adhesion molecule and is important in maintaining synaptic circuitry in the central nervous system (L. A. Thomas, Akins, & Biederer, 2008). *CADM2* is part of the immunoglobulin superfamily and is likely involved in long-term signal depression and potentiation (Ibrahim-Verbaas et al., 2016), and has been shown to be widely expressed in the developing (postnatal) and adult brain in mice (L. A. Thomas et al., 2008). Long term depression and potentiation (LTD, LTP) have long been recognized as the functional expression of neural plasticity that is responsible for storing information in the form of memories and promoting learning via changes in synaptic strength between neuronal connections (Sweatt, 2016). Therefore, the finding that a gene encoding a synaptic cell adhesion molecule involved in maintaining synapses and possibly promoting LTP and LTD, is associated with cognition points to synaptic plasticity as a possible key player in determining intelligence in humans. Synaptic plasticity is thought to play a crucial role in the maturation of brain circuits as it allows for experience-dependent strengthening, and thus preservation, of certain synapses against programmed synaptic pruning (Forsyth & Lewis, 2017). Mounting evidence also suggests that

disruptions in synaptic plasticity across development may contribute to cognitive deficits and psychosis observed in patients with schizophrenia (Forsyth & Lewis, 2017). Results from our studies also implicate synaptic plasticity in cognitive development as relative cortical thickness across infancy (as a reflection of the number of neurons/synapses/dendrites/ and thus level of synaptic pruning) and delayed myelination in the second year of life (and thus prolonged synaptic plasticity) were correlated with cognitive outcomes in toddlerhood. However, it is important to note that the GWAS studies mentioned above were conducted in middle-aged to older adult populations and it is possible that they capture the protective effects of *CADM2* and cell adhesion molecules on maintaining information processing speed and cognition through aging as opposed potential ontogenetic benefits of *CADM2* for intelligence.

Taken together, these results highlight the importance of genes which regulate neurodevelopmental processes for adult cognition. Building a clearer understanding of the genetic variants that influence brain development and cognition will provide insight into the normal variation in these processes which determine many life outcomes including mental health, academic achievement, and life success (Deary, Penke, & Johnson, 2010) and may ultimately increase our understanding of neurodevelopmental disorders that disrupt brain development and cognition.

IMPLICATIONS FOR INTERVENTION-BASED RESEARCH

The work presented in this dissertation sheds light on key areas for future intervention research. Firstly, we demonstrate that neuroimaging biomarkers at birth can be very accurate predictors of infants' later cognitive performance. These findings open the door to the possibility of applying such a method to a large, heterogeneous sample of infants to predict domain-specific

cognitive deficits. This could have great clinical utility given the heterogeneous nature of neurodevelopmental disorders in terms of both cognitive deficits and brain phenotypes. It would be very interesting to combine data from several of the ongoing studies of early brain and cognitive development in typically developing (Deoni et al., 2014; D. Holland et al., 2014; Soh et al., 2014; Spann, Bansal, Rosen, & Peterson, 2014) and at-risk children (Grewen et al., 2014; Hazlett et al., 2017), as well as data that will soon be available through the Baby Connectome Project, to build a predictive model of child cognitive abilities. If predictions from such a heterogeneous dataset were accurate, this could be a very useful tool for identifying children at risk for poor future outcomes and assigning follow-up or intervention targeted to specific cognitive and behavioral domains.

Our findings also highlighted the importance of the prenatal period and suggest that environmental factors like maternal education exact influences on both brain and cognitive development. This calls for future research to focus on identifying prenatal characteristics important for predicting brain structure at birth and dissecting the causal mechanistic pathway(s) between environmental stressors (like low socioeconomic status), brain development, and cognition. Such studies would benefit from collecting data from obstetric records on maternal and fetal health, utilizing questionnaires to determine levels of maternal psychosocial stress and access to quality health care during pregnancy, and collecting biological data, like salivary cortisol, to quantitatively capture maternal stress. While there is evidence of associations between maternal stress, indexed by maternal cortisol levels, during pregnancy and child behavior (Bergman, Sarkar, Glover, & O'Connor, 2010; Davis & Sandman, 2010), there have been no studies assessing the effects of maternal stress during pregnancy on human fetal brain development. A recent study has demonstrated that infants born to mothers who experienced

childhood maltreatment had significantly lower gray matter volumes than control infants (Moog et al., 2018), suggesting that the effects of stress can be inter-generational, and deserve future study in the context of brain and behavioral development. Identifying which prenatal factors put infants at risk for poor cognitive outcomes and understanding the mechanism by which these factors alter brain development will be key to implementing effective interventions for at-risk children.

FUTURE DIRECTIONS

Future directions for the field have been defined above and include (1) investigating the epigenetic and genetic contributions brain structure and cognition in infancy, (2) seeking to expand the use of neuroimaging biomarkers to predict a wide range of cognitive deficits, and (3) systematically studying the effects of maternal health and the prenatal environment on fetal brain development. Future directions for this body of work, placed in the larger context of the next steps for the field, include (1) using data from other large-scale neuroimaging studies to replicate the findings presented in this report, (2) integrating and extending the work from this thesis to consider the contributions of gray matter, white matter, and functional connectivity development, simultaneously, to infant cognitive development and (3) lengthening the developmental window of study to include school-age time-points to gain a clearer picture of how the brain matures across early childhood to support complex cognition in young children.

Replicating Findings in other Developmental Samples

Replicating the findings from our studies are essential to providing a clear picture of the neurobiology of early cognitive development. We would hope to see the brain-cognition relationships – namely that thicker, larger cortices and more mature WM properties confer better

cognitive outcomes – and developmental patterns – brain structure at birth and slower maturation of WM in the second year of life predicting later outcomes – observed in our study replicate in other samples. It will also be important to extend the findings of our study to include children who are not "typically developing" as defined in our study, including children born very preterm or spending more than a day in the neonatal intensive care unit, children born to mothers with a psychiatric illness, or children who themselves have been diagnosed with a developmental disorder. Comparing findings from our relatively healthy sample to those from studies of at-risk children will aid in our understanding of how the brain matures to support infant cognition. For example, work in children with ASD have shown that the splenium plays an important role in language (Swanson et al., 2015) and visual orienting (Elison, Paterson, et al., 2013a) in early life. Our results support these observations, as the splenium was found to be related to visual reception, but also extend the findings to suggest the splenium also plays a role in motor and general cognition in infancy and toddlerhood. Most studies to date have taken a hypothesis-directed approach to selecting regions or tracts of interest in an *a-priori* manner based on their role in adult cognition (Elison, Paterson, et al., 2013a; Short et al., 2013; Swanson et al., 2015), but in doing so may miss important emergent relationships that are demonstrated in our study. Future hypothesis-generating work should be done to test the robustness of the findings from our study, and better define brain cognition relationships in early life.

Gray Matter, White Matter, and Functional Connectivity: A Multi-Modal Approach

Structural brain maturation has important implications for functional brain development. At birth, the human brain is a highly connected network of largely unmyelinated axons that will serve as the foundation upon which future fine-tuning of cortical circuitry takes place via processes

including synaptogenesis, dendritic arborization, and myelination (Dubois et al., 2014). The WM connectome, as a physical network of axonal connections, is thought to play an important role in both the developmental of cortical folding (Essen, 1997) and functional brain connectivity (Hagmann et al., 2010; Park & Friston, 2013; Sporns, 2013). Developmental research suggests that the WM connectome is more adult-like at birth than the functional connectome (Cao, He, Dai, Liao, et al., 2017a; Fransson et al., 2010; Huang et al., 2015; van den Heuvel et al., 2015), and that coupling between WM networks and functional networks increases from 30 weeks gestation into adulthood (Hagmann et al., 2010; van den Heuvel et al., 2015). This body of work highlights the possibility that early-maturing WM connectomes shape cortical development and serve as the initial foundation upon which diverse functional networks are built (Cao, Huang, & He, 2017b). Yet, very little work has been done to chart the coordinated development of WM connectivity, CT across the cortex, and functional connectivity in early postnatal development, and no studies have linked multi-modal brain development in infancy and toddlerhood to future cognition.

While addressing such a research question is quite complex, one potential approach would be to generate connectivity matrices of white matter (WM connectivity networks; WCNs) and functional connections (functional connectivity networks; FCNs) and compare them with cortical structural covariance networks (matrix of correlations between CT in each pair of brain regions; CCNs) using the same brain parcellation atlas (**Figure 6.1A**). It will also be important to see how these networks develop across infancy, which would require generating maturational WCNs, CCNs, and FCNs that represented the change in connectivity or correlation between brain regions from birth to age 1 and from age 1 to age 2 (**Figure 6.1B**). Finally, the coordination between CT covariance, white matter connectivity, and functional connectivity will need to be considered by calculating region-to-region correlations between WNCs, FCNs, and CCNs (**Figure 6.1C**).

Based on findings in the literature, I hypothesize that coupling of WCNs and FCNs are strongest (**Figure 6.2A**) and increase across development as functional network topology becomes more mature and reflective of the underlying WM architecture (van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009), with greater strength of connections between brain regions appearing in WCNs before FCNs. I would also expect that WCNs are correlated with CCNs and that this coupling would be most apparent at the end of the first year of life when peak myelination rates would produce changes in the gray matter-white matter boundary which inherently influences CT measurements (Sowell et al., 2004) and DTI tractography algorithms through changes in the level of anisotropic diffusion in the brain (Dubois et al., 2014). Finally, previous work from our group has shown that CCNs are somewhat correlated with FCNs, but interestingly, that FCNs are in place before CCNs (Geng et al., 2017), which suggests that perhaps region-specific co-activation of functional networks may guide the maturation and refinement of CCNs across development. Therefore, I would expect that WCNs are in place first, building the foundation for CCNs, and that over time WCNs and FCNs both influence the development of CCNs (**Figure 6.2B**).

In terms of links with cognitive development, it will be important to determine (1) if brain connectivity features (i.e. region to region connections, or connections to hub regions) important for predicting cognition are similar across WCNs, FCNs, and CCNs, (2) at which age or during what developmental window these networks are most predictive of future cognition, (3) what the relative contributions are of each network to predicting cognitive abilities, and (4) how coordinated development of WCNs, FCNs, and CCNs relate to cognitive development. I would expect that similar connectivity features for WCNs and FCNs would relate to cognitive performance given their hypothesized close coupling, and some overlap in the findings with CCNs (**Figure 6.2C**)

In terms of the developmental timeline, I would expect WCNs and FCNs at birth, CCNs at age 1 and 2, and maturational changes in WCNs and FCNs in the second year of life to be associated with cognitive outcomes at age 2 (**Figure 6.2D**). This is based on results from our studies which found that WM microstructure and WCNs at birth were predictive of later outcomes, WM microstructural changes in the second year of life were related to 2-year scores, and that CT at ages 1 and 2 were related to present and future cognition, coupled with the working hypothesis that WM network topology at birth drives functional connectivity development. In terms of the relative contributions of each network to cognition, I would hypothesize that WCNs and FCNs have the highest predictive value (**Figure 6.2E**) given that they are most developed during this age range, and that WCNs may have the most predictive power given that FC networks in early life are still relatively immature (Gao, Lin, Grewen, & Gilmore, 2016). Finally, I expect that given the known associations between WCNs and FCNs (Park & Friston, 2013), that the coordinated development of these two network types will have the largest impact on infant and toddler cognition (**Figure 6.2F**).

Results from such a study would be essential in detailing the sequence of structural and functional network developing in early life and identifying how coordinated developmental change between these networks give rise to emergent cognition in infancy.

Extending the Developmental Window: Can we predict school-age abilities?

Determining if the long-term predictive ability of infant brain structure is another major next step for this body of work. I propose that we extend the developmental window to test for associations between brain structure at birth and cognition at age 6. There is evidence that cognition and intelligence become more stable and predictive of adult ability around age 6

(Bradway & Thompson, 1962; Deary et al., 2004; 2013; McCall, 1977), and thus if we were able to use infant brain structures to predict cognition at this age it would suggest very strong prenatal origins of lifetime intelligence. Some existing work suggests that brain volumes (Keunen et al., 2016) and WM microstructure (Keunen et al., 2017) at birth are predictive of school-age cognitive abilities in children born very preterm. I would hypothesize that such predictions would likely extend to children born at later gestational ages, and that WM connectivity values may serve as the best predictors of later outcomes. By age 6 we also have the opportunity to tap in to a variety of cognitive and behavioral domains that are inaccessible in the infant – including theory of mind, executive function, and anxiety and depression-like behaviors – which could also shed light on the neurobiology supporting the emergence of complex cognitive abilities and behavioral traits.

OVERALL CONCLUSIONS

In summary, our results reveal that brain structure at birth and across infancy and toddlerhood is related to emergent cognitive abilities. We reported that generally thicker, larger cortices and more mature WM tract properties in early life related to better performance on cognitive tasks, suggesting that increased synaptogenesis, elaborations in dendritic arborization, and myelination may confer benefits for infant cognitive development. We found several expected brain-cognition relationships with regional CT, while results between cognition and WM integrity were less specific. The predictive value of CT or SA in any one brain region or WM integrity of any one tract paled in comparison to the predictive ability of cortico-cortical WM connectivity for cognitive outcomes at age 2, suggesting that the field should consider complex, brain-wide architecture when investigating cognition, at least in this age range. Taken together, these results highlight that cortical structure and the organization and microstructural

integrity of WM pathways at birth serve as a foundation upon which subsequent fine-tuning of brain structure takes place to support emergent cognition in infancy and toddlerhood. These findings offer novel insight into how prenatal and postnatal brain structural maturation support infant and toddler cognitive abilities and fill important gaps in our current understanding of the neurobiology of emergent language, motor, and cognitive abilities in early life.

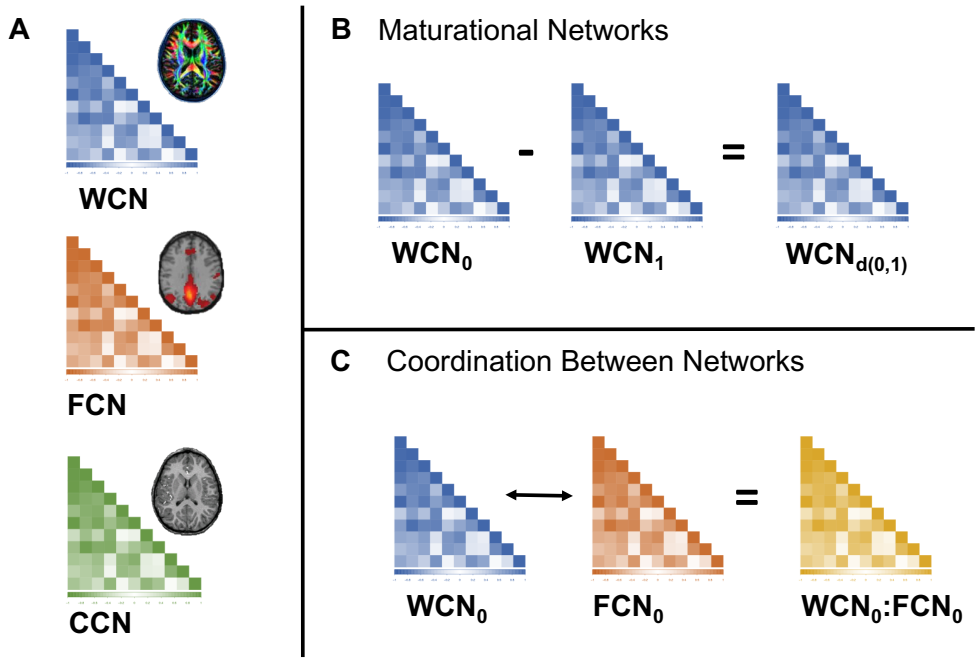


Figure 6.1 Construction of Brain Structural and Functional Networks.

White matter connectivity networks (WCNs) and functional connectivity networks (FCNs) are constructed from region-based connectivity values (relative proportion of tractography streamlines or strength of coordinated functional signal, respectively) and cortical covariance networks (CCNs) contain the correlations between CT values between each brain region (**A**). Maturational networks are constructed by calculating the developmental change between networks constructed at different ages (**B**). Coordination between networks can conceptualized as the correlation between the connectivity values for each network by ROI pair at each age or between maturational networks (**C**).

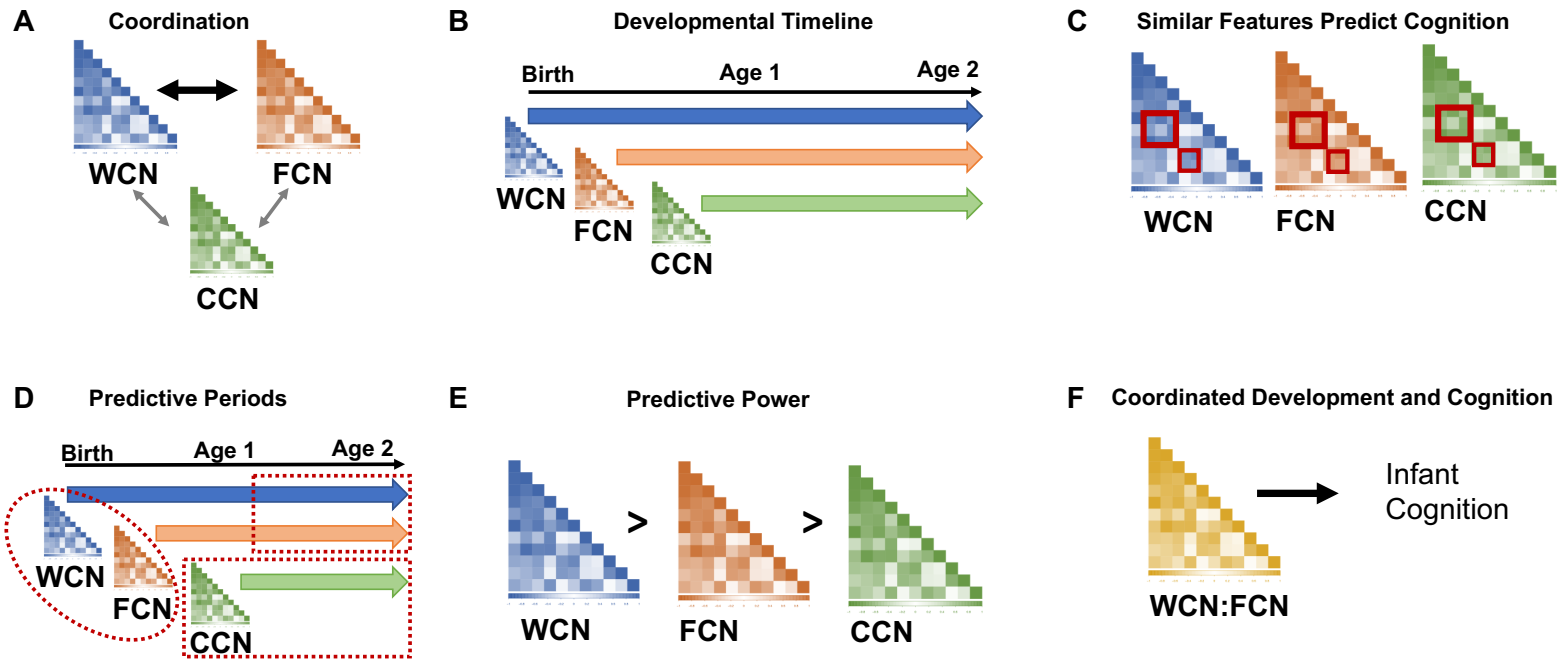


Figure 6.2. Expected Results Concerning Network Coordination, Developmental Timeline, and Predictive Cognitive Ability.

Expected results include: (**A**) higher correlations between WCNs and FCNs than with either and CCNs, (**B**) WCNs develop first, followed by FCNs and CCNs, (**C**) similar regional connectivity and covariance structures across WCNs, FCNs, and CCNs predict cognition, (**D**) WCNs and FCNs at birth, CCNs at ages 1 and 2, and WCNs and FCNs in the second year of life will be the most predictive developmental periods for cognition at age 2, (**E**) WCNs will have the greatest predictive power for cognition in early development, followed by FCNs and CCNs, and (**F**) coordinated development between WCN:FCN across the first two years will be correlated with cognition at age 2.

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