ENVIRONMENTAL AND GENETIC INFLUENCES ON INFANT CORTICAL THICKNESS AND SURFACE AREA

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ABSTRACT

Shaili C Jha: Environmental and Genetic Influences on Infant Cortical Thickness and Surface Area
(Under the direction of Rebecca Knickmeyer)

Genetic and environmental influences on cortical thickness (CT) and surface area (SA) are thought to vary in a complex and dynamic way across the lifespan. It is established that CT and SA are genetically distinct in older children, adolescents, and adults and that heritability estimates vary across cortical regions. At these ages, various environmental factors have also been shown to have unique influences on cortical structure. Very little is known about how genetic and environmental factors determine infant CT and SA. This represents a critical knowledge gap, especially given compelling evidence that neuropsychiatric disorders have their ultimate origin in prenatal and early postnatal development. In this report, we examine the impacts of 17 major demographic and obstetric history variables on inter-individual variation in CT and SA in a unique sample of 805 neonates who received MRI scans of the brain around 2 weeks of age. Additionally, we examine genetic influences on CT and SA variation using a classical twin model in a subset of 376 twin neonates. Our results reveal that birth weight, postnatal age at MRI, gestational age at birth, and sex are significant predictors of SA and postnatal age at MRI, paternal education, and maternal ethnicity are significant predictors of CT. Additionally, we find that total SA is highly heritable and the relationship between total SA and average CT is under significant genetic control during infancy. Together, these results suggest that genetic, obstetric, demographic, and socioeconomic factors are important determinants of cortical development during infancy. Both genetic and environmental influences drive individual

differences in neonatal SA while variation in neonatal CT is largely explained by environmental factors such as paternal education and maternal ethnicity. These findings offer novel insight into how genetic and environmental influences shape infant cortical structure during a delicate and highly malleable period of neurodevelopment and fill important gaps in the current understanding of CT and SA.

To my ba and moti foi, the strongest, most resilient women I know. Your love and courage is the reason I am here today. To my uncles, aunts, and parents, who left everything they knew in order to provide a better future for their children. You all are my inspiration and strength. To my ninjhas. Thank you for believing in me, making me smile, and keeping me laughing through stressful times. And to Amit. Without your support and encouragement, this journey would not be possible.

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PREFACE

Chapter 1 provides a review of the basic processes of prenatal and early postnatal brain development. It also contains an introduction to pediatric MRI and cortical thickness and surface area development. This chapter ends with an outline of the research aims and hypotheses presented in this report.

Chapter 2 is a research chapter that addresses our first specific aim. It details the environmental influences on neonatal cortical thickness and surface area. This chapter is a manuscript currently under review at *Cerebral Cortex.*

Chapter 3 is a research chapter that addresses our second specific aim. It details the genetic influences on neonatal cortical thickness and surface area. This chapter is a manuscript in preparation.

Chapter 4 contains a summary of the key findings, an outline of the major contributions to the field, and potential future directions for follow-up research.

All references are presented at the end of the dissertation

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LIST OF ABBREVIATIONS

ASD	Autism Spectrum Disorders
CSF	Cerebrospinal Fluid
CT	Cortical Thickness
DZ	Dizygotic
GM	Gray Matter
GW	Gestational Week
GWAS	Genome Wide Association Study
ICV	Intracranial Volume
MRI	Magnetic Resonance Imaging
MZ	Monozygotic
SA	Surface Area
SES	Socioeconomic Status
SVZ	Subventricular Zone
VZ	Ventricular Zone
WM	White Matter

CHAPTER 1: INTRODUCTION

PRENATAL AND EARLY POSTNATAL BRAIN DEVELOPMENT

Embryonic development

The formation of the nervous system begins early in development, approximately 2 to 3 weeks post-conception, and continues well into adolescence. During the first gestational month, complex cascades of molecular signaling and gene-gene interactions initiate the processes of gastrulation and neurulation. During gastrulation, undifferentiated embryonic tissue become specialized into different stem cell lines, including neuroepithelial cells which serve as the precursors for all future neurons and glia. Through the process of neurulation, the first discernable structure of the nervous system, the neural tube, is formed (Stiles 2008). By the end of these fundamental developmental processes, the neural tube elaborates into the prosencephalon, mesencephalon, and rhombencephalon which eventually form the forebrain, midbrain, and hindbrain (Dudok et al. 2017) and the primary spatial organization of the brain and spinal cord is established. In the remaining embryonic period and continuing into the fetal period, there are increases in the size and complexity of the brain driven by cellular processes controlling the proliferation of neuronal progenitor cells, and the production, migration, and differentiation of neurons (Stiles and Jernigan 2010).

Neurogenesis, migration, and differentiation

Between embryonic days 25 to 42, neuroepithelial cells lining the central cavity of the neural tube begin to divide symmetrically, producing two identical neuroepithelial daughter

cells. Proliferation of neuroepithelial cells occurs within the ventricular zone (VZ) and is mediated by genes regulating cell cycle progression. Those controlling gap junctions, cell cycle length, cell cycle exit, and pro- and anti-apoptotic mechanisms that contribute to overall cortical size are particularly important (Sun and Hevner 2014). This period of self-renewing divisions exponentially expands the pool of precursor cells, generating a large population of founder cells. Disruptions in neuroepithelial expansion have effects on both lateral and radial expansion of the cortex and can impact overall cortical size. Examples of aberrant development include microcephaly, which results in a reduction in brain size and macrocephaly which is characterized by an increase in brain size (Homem et al. 2015).

After the period of symmetrical division is complete, neuroepithelial progenitors transition into radial glial cells, which maintain the properties of stem cells, and begin the production of cortical neurons. During this time, an additional proliferative zone, the subventricular zone (SVZ), emerges above the VZ and expands rapidly during fetal development. Neurogenesis in these proliferative regions is primarily driven by asymmetric cell divisions of radial glial cells. These divisions produce a radial glial progenitor cell which reenters the mitotic cell cycle and a daughter cell that is an intermediate progenitor, transient amplifying progenitor, subapical progenitor, or a basal radial glial cell (Jiang and Nardelli 2016). These populations of cells represent a diverse number of progenitor cell types capable of producing neurons and are characterized by the location where they undergo mitosis, the extent of cell polarity, and proliferative capacity (Taverna et al. 2014). Neurogenesis is controlled by a variety of extracellular signals from the CSF including insulin and fibroblast growth factors, Shh, and Wnts that stimulate and regulate the proliferation of progenitor cells and by neighboring

progenitor cells that provide intrinsic signaling through proteins like Notch and Numb to influence neuron fate (Taverna et al. 2014).

During prenatal corticogenesis, there are approximately 3.89 million neurons generated per hour. Rapid rates of neurogenesis are balanced by events of programmed cell death which begin as early as gestational week (GW) 7 (Stiles et al. 2015). The final pool of neurons at the end of neurogenesis is determined by the original pool of neuroepithelial cells, the switch from symmetrical to asymmetrical cell division, the duration of neurogenesis, and the balancing rates of cell death (Jiang and Nardelli 2016). Processes of symmetrical and asymmetrical cell division and resulting pools of progenitor cells and neurons play a crucial role in the ultimate tangential and radial organization of the cortex. These events are likely important determinants of the cortical structure and will be discussed in more detail in the chapters that follow.

After birth, neurons in the proliferative areas migrate toward the outer pial surface via varying mechanisms, dependent both on the timing and location of neurogenesis. Early in development, neurons migrate through means of somal translocation (Ortinau and Neil 2015) whereas later in development, neurons migrate radially along scaffolds provided by radial glial cells or tangentially via guidance cues (Nadarajah and Parnavelas 2002). Specifically, excitatory glutamatergic projection neurons generated in the VZ and the SVZ migrate radially whereas GABAergic interneurons, generated within the ganglionic eminence, migrate tangentially into the cortical plate (Silbereis et al. 2016). Neuronal migration is regulated by Cajal-Retzius cells which produce Reelin signaling to ensure neurons reach their proper location within the cortex and stop migrating (Stiles and Jernigan 2010). Genes involved in cytoskeletal regulation including the function and regulation of microtubules (such as *LIS1, TUBA1A, TUBB3, and DCX*) and actin (*FilaminA*) are also essential for proper neuronal migration (Liu 2011).

Overall, rates of migration peak between GW 13 and 21 (de Graaf-Peters and Hadders-Algra 2006) and result in the formation of a six-layer structure organized in an "inside-out" pattern. Specifically, early migrating neurons are located in deeper cortical layers and are predominantly neurons that project to subcortical areas such as the thalamus, brain stem, and spinal cord. Late-migrating neurons are positioned in subsequent outer cortical layers. These more superficial layers are composed of intracortical neurons that largely project locally within the cortex(Thomson and Lamy 2007; Cooper 2008). After corticogenesis and migration, graded signaling of transcriptional factors helps determine the proper radial and tangential position of neurons within the cortex (Sansom and Livesey 2009). Intrinsic and extrinsic cellular cues guide the differentiation of neurons resulting in subtypes that have unique cellular, chemical, morphological, and anatomical properties (Stiles 2008).

Synaptogenesis

After migration and differentiation are complete, neurons begin to integrate into the cortex as functional units capable of sending and receiving inputs. This process involves the development of axons and dendrites, the construction of pre- and postsynaptic machinery, and the formation of functional synapses. Attractive and repulsive chemical cues guide the development and fasciculation of axons. These include classical morphogens like Shh and Wnt, cell-adhesion molecules, and extracellular matrix molecules that together, provide both short and long-range cues that help axons reach their appropriate targets (Jiang and Nardelli 2016). Through the specialization of presynaptic axon terminals and postsynaptic membranes, functional synapses capable of transmitting electrical and chemical signals are formed.

All of these mechanisms begin prenatally but show accelerated development after birth and into the early postnatal period (Markant and Thomas 2013). Specifically, there is accelerated

dendrite growth during the 3rd trimester with high rates continuing into the 1st year of life. Within the first 6 months, there is tremendous elaboration of dendritic branches and increases in axonal length (Nimchinsky et al. 2002; de Graaf-Peters and Hadders-Algra 2006). In parallel, beginning at GW 23 (Markant and Thomas 2013) there is rapid generation of synapses that peaks within the first years of life, continuing well into postnatal development (Huttenlocher and Dabholkar 1997). Synaptogenesis is also a regionally heterogeneous process, with rapid increases in synaptic density observed first in the primary visual and auditory systems and much later in association areas like the frontal cortex. After peak rates of synaptogenesis, there is an overproduction of synapses during early postnatal life that is offset by mechanisms of synaptic elimination (Stiles 2008). By adolescence, nearly 50% of the synapses formed during infancy are pruned. These regressive processes ensure correct, efficient and refined connections within the cortex and are heavily influenced by environmental cues (Jiang and Nardelli 2016).

Gyrification

The rapid growth and elaboration of the cortex described in the previous sections is coupled with large-scale transformations in cortical morphology that begin around GW 23 (Budday et al. 2015) and result in the formation of a convoluted brain. Cortical folding enables the mammalian brain to expand and grow despite the constraints of the skull. The development of cortical convolutions begins with the emergence of the longitudinal fissure, which separates the left and right hemispheres. After that, primary sulci are formed between GW 14 to 26, secondary sulci are formed 30 to 35 weeks and tertiary sulci arise at 36 weeks and continue into postnatal development (Stiles and Jernigan 2010).

Many theories have been proposed to explain the emergence of cortical folding. For example, it is posited that external constraints imposed by the internal surface of the skull cause

the cortex to fold (Striedter et al. 2015). Other theories suggest that differential rates of intermediate and basal radial progenitor proliferation in the SVZ and rapid tangential expansion of the outer layers of cortex contribute to the development of gyri (Sun and Hevner 2014). The most popular theory of gyrification suggests that axonal tension between cortical areas generates a tangential force that causes the cortical sheet to fold (Van Essen 1997). Because there is no concrete model of cortical folding that is agreed upon (Striedter et al. 2015), the many genes involved are still under investigation. With that said, genes and molecular pathways essential in proliferation, migration and axonal growth are likely important. Moreover, genetic defects in *LIS1* and *DCX* genes are known to affect gyral development, resulting in lissencephaly, a cortical malformation and neurodevelopmental disorder characterized by a smooth, disorganized, and thickened cortex (Lian 2006).

Glial Development

While this chapter is largely focused on the overall development of cortical neurons, glial development is essential to proper neuronal function. After neurogenesis is complete, pro-neuronal factors are downregulated, and pro-glial transcription factors initiate the generation of glia from radial glial progenitors(Jiang and Nardelli 2016). Gliogenesis begins around mid-gestation, extends into postnatal life, and results in the formation of a diverse population of micro and macroglia including astrocytes and oligodendrocytes (Budday et al. 2015). Astrocytes serve a key role in the formation and maintenance of synapses. Oligodendrocytes play a pivotal role in neuronal signaling by myelinating axonal fibers and ensuring efficient transmission of electrical signals (Stiles et al. 2015). The myelination of fiber bundles begins in the third trimester, roughly around 32 weeks and continues in a regionally specific manner during the first

postnatal years (Qiu, Mori, et al. 2015). The process of myelination gives rise to the white matter of the brain observed in neuroimaging studies.

USING MRI TO STUDY BRAIN DEVELOPMENT

The use of in vivo brain imaging, specifically MRI, has led to a tremendous increase in our understanding of brain development at both structural and functional levels. MRI provides a safe, noninvasive, and standardized approach to measuring brain changes across the lifespan. During infancy, collecting neuroimaging data poses fundamental limitations related to the newborn's ability to remain asleep and still in a novel and noisy scanning environment (Luby 2017). Analyzing neuroimaging data during this period also presents unique challenges which include low contrast to noise ratio, intensity inhomogeneity across tissue types, smaller anatomical structures, and rapidly changing tissue contrasts (Gilmore et al. 2004; Prastawa et al. 2005). Despite these limitations, collaborative efforts between neuroscientists, radiologists, and computer scientists in the last two decades have led to the formation and refinement of infant-specific scanning protocols and image analysis tools that have provided researchers with an unprecedented window into the developing brain.

Using structural MRI, Knickmeyer et al. (2008) found that the total volume of the infant brain increases an astonishing 101% in the first year and an additional 15% in the second year of life. This unprecedented assessment of brain volumes revealed that the majority of postnatal growth is explained by gray matter (GM), which increases 149% in the first year alone. During this time, substantial regional differences in cortical gray matter are also present. Specifically, primary motor and sensory regions grow at slower rates compared to associations regions involved in higher-order cognitive functions (Gilmore 2012). Cortical gray matter volumes within the cortex can be further delineated into two additional components: cortical thickness

and surface area. These morphometric features are the focus of this report and will be discussed in more detail below.

CORTICAL THICKNESS AND SURFACE AREA

Cortical thickness and surface area are thought to be independent dimensions of cortical volume, driven by distinct genetic and evolutionary factors (Raznahan et al. 2011). Between rodents and primates there is a 2-fold increase in CT and an incredible 1,000-fold increase in SA (Rakic 2009). According to the radial unit hypothesis, this enormous enlargement of the cortical surface occurs early in the embryonic period and is driven by an increase in proliferative capacity of neural precursor cells within the cortex (Mitchell and Silver 2017). Specifically, extended periods of symmetrical division produce a larger pool of precursor cells and an increased number of cortical columns, leading to the laminar expansion of the cortex. On the other hand, an increase in CT is attributed to the number of neurons within each cortical column and the enlargement of neuronal processes, glial processes, and synapses (Rakic 1995). These processes are largely fetal and early postnatal. More recent studies suggest that the radial glial scaffold transforms into a discontinuous structure during mid-neurogenesis. This work has led to the "supragranular hypothesis" which posits that during the discontinuous phase, outer radial glial (oRG) cells go through self-renewing divisions, increasing the SA of supragranular layers, and neurogenic divisions, increasing the thickness of these layers (Nowakowski et al. 2016). These findings explain the disproportionate tangential expansion of the upper cortical layers in the developing brain. SA and CT development are also related to cortical folding and gyrification and are impacted by rates of programmed cell death occurring in both symmetrically dividing precursor cells and in neurons throughout development (Rakic 1995; Stiles 2008).

With the use of pediatric MR imaging, both CT and SA measures can be separately examined postnatally to better understand their developmental origins and growth patterns. A recent longitudinal study of healthy twins and singletons examined both global and regional trajectories of CT and SA in the first two years of life and found distinct patterns of development for each measure. Specifically, CT increased 36% and total SA increased an extraordinary 114% on average (Lyall et al. 2015), indicating that SA expansion is the primary driver of volumetric increases in GM. Interestingly, by age 2, CT measures reached 97% of adult values while SA measures reach about 69%. In the same subset of infants, cortical folding patterns were found to be conserved from birth to age 2, revealing major sulci and gyri are well developed and present by term birth (Hill et al. 2010; Li et al. 2013). After birth, increased gyrification of the cortex is largely driven by changes in association regions with increases of 16.1% in the first year and 6,6% in the second year of life (Li, Wang, et al. 2014). Studies of CT and SA (Li, Lin, et al. 2015; Lyall et al. 2015) during early brain development also show heterogeneous patterns of growth across the cortex. Specifically, sensory and motor regions are shown to mature earlier during development compared to regions involved with higher-order integrative functions. Overall, results from these studies capture extremely rapid expansion and growth of the cortex during early postnatal development, likely driven by dendritic development, synaptogenesis, and, gliogenesis, as well as complex patterns of cortical connectivity and cortical folding (Stiles 2008). By comparison, annual growth rates during middle and late childhood reach maximum values of only 0.005% and 0.015% for CT and SA respectively (Raznahan et al. 2011).

Overall, early postnatal development represents a window into the effects of prenatal brain development and is a critical stage for charting developmental trajectories. Rapid rates of CT and SA growth during infancy could result in heightened vulnerability to genetic and

environmental disruptions and are linked to risk for psychopathology. Specifically, preliminary studies of CT and SA in infants at high risk for schizophrenia suggest that CT development is altered in female neonates (Li et al. 2016). Abnormalities in SA are also observed in individuals at risk for autism spectrum disorders (ASD) in the first year of life (Hazlett et al. 2017). These studies demonstrate that the foundation of many psychiatric conditions is rooted in disturbances of early typical brain development and can be observed at structural levels through cortical phenotypes like CT and SA.

RATIONALE & SPECIFIC AIMS

As we review in this chapter, the prenatal and early postnatal periods represent a foundational phase of human brain development. During early life, tightly regulated patterns of gene expression and pre- and postnatal environmental influences shape the structure and function of the nervous system (Kandel 2013). The fetal period is characterized by strong temporal gradients of protein-coding genes that weaken during infancy, childhood, and adolescence (Kang et al. 2011) and by robust regional differences in gene expression that are replaced by global similarities in expression during infancy and early childhood (Pletikos et al. 2014; Silbereis et al. 2016). At the structural level, the prenatal and early postnatal period is characterized by rapid micro and macrostructural growth that result in large volumetric and morphometric changes (Knickmeyer et al. 2008; Stiles and Jernigan 2010; Gilmore et al. 2012; Lyall et al. 2015).

Imaging studies in our Early Brain Development Studies (EBDS) cohort demonstrate that genetic and environmental factors play an important role in explaining individual variation in brain structure during this early period. Classical twin studies reveal high heritability of regional gray and white matter volumes at 2 weeks of age (Gilmore et al. 2010) and a genome-wide association study (GWAS) has identified a significant genetic variant associated with neonatal

gray matter volumes (Xia et al. 2017). Recently, a population neuroscience study from our group revealed gestational age at MRI, gestational age at birth, sex, and birth weight as significant obstetric predictors of global and regional gray matter volumes (Knickmeyer et al. 2016).

The important next step is to establish which morphometric feature of gray matter volume (cortical thickness (CT) or surface area (SA)) reflect these environmental and genetic relationships. Previous studies have shown CT and SA to be genetically, evolutionarily, and phenotypically distinct. CT is thought to be driven by the number of neurons arranged in vertical proliferative columns while SA is determined by the number of columns present in the developing cortex (Rakic 1995; 2009). While our understanding of CT and SA development is expanding, very little is known about the underlying genetic and environmental influences during the early postnatal period. Given that the foundation of many psychiatric conditions is rooted in disturbances of early brain development (Wolff and Piven 2014; Birnbaum et al. 2015), it is vital to address the genetic and environmental factors that control variation in phenotypes such as cortical thickness and surface area during these largely understudied time points.

The objective of this research was to investigate the environmental and genetic determinants of neonatal cortical thickness and surface area. This objective was achieved by pursuing the aims highlighted below. Overall, by examining how genetic and environmental influences contribute to individual differences in CT and SA during a time point of rapid cortical growth and heightened developmental vulnerability, we will better understand how genes and prenatal factors influence brain structure and ultimately contribute to pathological abnormalities.

Aim 1/Chapter 2: Investigate the influence of major demographic and obstetric history variables on cortical thickness and surface area development during infancy

Twin studies demonstrate that environmental factors account for a substantial portion of inter-individual variance in brain structure during infancy (Gilmore et al. 2010). The so-called

'envirome' encompasses an almost infinite variety of exposures and experiences (Anthony 2001). Within this vast search space, prenatal and early postnatal environmental influences are likely to be particularly important. For example, subtle variations in birth weight exert robust influences on IQ and surface area well into adolescence (Raznahan et al. 2012). Similarly, effects of preterm birth show long-lasting influences on cortical thickness (Lax et al. 2013) and surface area (Zhang et al. 2015) during childhood. While these studies provide crucial insights into the persistent effects of prenatal influences on childhood and adolescent brain outcomes, they cannot address age-specific effects at birth. With comprehensive medical histories and well-established pediatric imaging protocols, we can assess the neurodevelopmental consequences of normative differences in birth weight, gestational age at birth and many other prenatal and postnatal environmental outcomes within the early postnatal period.

In a previous study of demographic, obstetric, and socioeconomic variables, we found that gestational age at MRI, gestational age at birth, sex, and birthweight were the most significant predictors of infant brain volumes, explaining 31% to 59% of the overall variance (Knickmeyer et al. 2016). How these factors influence cortical structure measures like CT and SA has not yet been studied. Thus, we examined the impact of 17 major demographic and obstetric history variables on inter-individual variation in CT and SA in a unique sample of 805 neonates who received MRI scans of the brain around 2 weeks of age. Given the unique developmental origins for CT and SA posited by the radial unit hypothesis, we theorized that different environmental factors would predict CT and SA development. Additionally, based on previous findings in later childhood and adulthood (Raznahan et al. 2011; Walhovd et al. 2012; Wierenga et al. 2014; Noble et al. 2015; Walhovd, Krogsrud, et al. 2016), we hypothesized that birth weight, sex, and socioeconomic status would determine individual variation in SA to a

greater extent than CT. The relationships we reveal may help explain individual variation in cognitive ability and risk for psychiatric and neurological disorders, all of which show associations with CT and SA.

Aim 2/Chapter 3: Determine genetic contributions to cortical thickness and surface area in infancy using a classical twin model and identify regions with shared genetic architecture

Genetic contributions to typical and atypical brain development have been studied through candidate gene approaches, genome-wide association studies (GWAS) and classical twin and family designs. The classical twin design compares the similarity of monozygotic (MZ) and dizygotic (DZ) twins to estimate the proportion of phenotypic variance attributable to genetics versus shared and unique environments. Thus far, these approaches have been applied primarily in school age children, adolescents and adults. During this age range, observed genetic effects may be confounded or obscured by years of gene-environment interactions, medication use, or other factors associated with disease risk such as alcoholism, drug abuse, and social stress. It is, therefore, necessary to perform imaging genetic studies at earlier time points in order to better assess genetic effects.

Research carried out by the Early Brain Development Study group at UNC has made significant strides toward uncovering genetic influences on brain volumes and white matter microstructure in infancy through twin studies (Gilmore, Schmitt, et al. 2010; Geng et al. 2012; Lee et al. 2015), a candidate gene study (Knickmeyer, Wang, Zhu, Geng, Woolson, Hamer, Konneker, Lin, et al. 2014) and a recent GWAS (Xia et al. 2017). Results from these studies clearly demonstrated that genetic factors play a key role in shaping neonatal brain structure. What remains unknown is whether these relationships are driven by genetic effects on cortical thickness and/or surface area. To address this critical gap, we assessed heritability estimates for global and regional CT and SA in 376 subjects 2 weeks after birth using a classical twin study.

Cross-ROI genetic correlations were also calculated in order to determine which cortical regions are genetically similar. Based on previous studies, we hypothesized that higher heritability estimates would be observed for SA compared to CT and for global CT and SA compared to regional CT and SA. Results from this analysis will reveal how genetically similar or unique cortical measures are during a time of heightened and dynamic CT and SA growth.

The research presented in this report is the first twin study of CT and SA during infancy. Our study is also the first to investigate a wide range of important environmental contributions to CT and SA. Our results will fill a critical gap in the understanding of normal brain development and the environmental and genetic influences on CT and SA. Specifically, we will be able to address how genes influence both CT and SA measures, how these changes regionally, and how they are correlated. Additionally, our work will provide much needed insight into how infant CT and SA differences may be driven by environmental, genetic and developmental factors. Promising findings from our work will enable us to prioritize cortical regions for future studies. By studying infants, we can assess pre- and perinatal variables of interest with a high degree of accuracy and ultimately provide data for a largely understudied period in development.

CHAPTER 2: ENVIRONMENTAL INFLUENCES ON INFANT CORTICAL THICKNESS AND SURFACE AREA

INTRODUCTION

Cortical thickness (CT) and surface area (SA) are two independent components of cortical volume most commonly studied using structural MRI. Although both measures change dynamically across the lifespan (Storsve et al. 2014; Lyall et al. 2015; Remer, Croteau-Chonka, Dean, D'Arpino, Dirks, Whiley, and Deoni 2017; Tamnes et al. 2017) recent research suggests that early-life events, especially those occurring in the pre- or perinatal period, have pervasive and long-lasting effects (Raznahan et al. 2012; Walhovd et al. 2012; Walhovd, Krogsrud, et al. 2016). Pre- and perinatal events may be especially important for atypical development as small differences early in life can have cascading effects on later outcomes (Karmiloff-Smith 1998; Masten and Cicchetti 2010). Notably, many neuropsychiatric disorders are characterized by altered global and/or regional CT and SA including schizophrenia and bipolar disorder (Rimol et al. 2012), autism (Ohta et al. 2016; Yang et al. 2016), and attention deficit hyperactivity disorder (Silk et al. 2016).

Current theories of cortical development also point to the prenatal period as a foundational period in the emergence of individual differences in CT and SA. According to the radial unit hypothesis, differences in global and regional surface area are driven by the number of cortical columns generated during the early embryonic period, while differences in CT are attributed to the number and size of cells within a column, packing density, and numbers of neuronal processes, glial processes, and synapses, features which arise primarily during the fetal

and perinatal periods (Rakic 1995; 2009). More recently, a supragranular layer expansion hypothesis has been proposed which posits that outer radial glial cells play a critical role in radial and tangential expansion of supragranular layers in primates with potential implications for individual differences in CT and SA (Nowakowski et al. 2016). Throughout the prenatal and early postnatal developmental window, these processes are influenced by tightly regulated patterns of gene expression and environmental signals (Kandel 2013). How these factors influence individual variation in early CT and SA is not well understood.

In this chapter, we report the first large scale neuroimaging study of environmental influences on CT and SA during infancy. Our aim was to understand how 17 major demographic and medical history variables affect neonatal CT and SA. Studying infants allows us to determine pre- and perinatal variables of interest with a high degree of accuracy and reduces potential confounding effects that can arise when studying children or adults, where pre- and perinatal variables of interest may be correlated with later environmental exposures. Previous work by our group (Knickmeyer et al. 2016) revealed that age, sex, gestational age at birth, and birth weight are highly significant predictors of neonatal brain volumes, but did not assess CT and SA. Based on the theories of cortical development reviewed in this report, we hypothesized that different sets of environmental factors would impact CT and SA. Additionally, based on previous findings relating birth weight, sex, and socioeconomic status (SES) to cortical structure in later childhood/adulthood (Raznahan et al. 2011; 2012; Walhovd et al. 2012; Wierenga et al. 2014; Noble et al. 2015), we hypothesized that these environmental influences would determine individual variation in SA to a greater extent than CT. Given that many complex psychiatric diseases are the result of altered neurodevelopmental trajectories that commence in prenatal and early postnatal life (Wolff and Piven 2014; Birnbaum et al. 2015), our investigation of

environmental influences on neonatal CT and SA represents a fundamental step in developing public health interventions to optimize early cortical development and reduce risk for later mental illness.

MATERIALS AND METHODS

Subjects

Our study included 805 neonates (434 twins, 371 singletons; 429 males, 376 females) between the ages of 6 and 144 days post birth, drawn from two prospective longitudinal studies of early brain development being carried out at the University of North Carolina (UNC) at Chapel Hill (Gilmore, Kang, et al. 2010; Gilmore, Schmitt, et al. 2010; Gilmore et al. 2012). Pregnant mothers were recruited from outpatient obstetrics and gynecology clinics in central North Carolina. Women with major medical illnesses or abnormal fetal ultrasounds were excluded at enrollment. Maternal reports were used to determine parental demographic information such as maternal age, paternal age, maternal education, paternal education, paternal ethnicity, maternal ethnicity, total household income, maternal psychiatric history, and paternal psychiatric history. Psychiatric history variables were also determined using medical record review. Both maternal and paternal psychiatric history were categorized and binarized such that individuals were considered positive for psychiatric history if they reported a diagnosis in any of the following DSM-V categories, or if medical record review indicated such a diagnosis: schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, attention-deficit hyperactivity disorders, Tourette's syndrome, or autism-spectrum disorders. Maternal smoking during pregnancy was also collected using maternal reports. Labor, delivery, and pediatric medical records were used to collect medical history variables such as birth weight, gestational

age at birth, 5 minute APGAR scores, stay in neonatal intensive care unit over 24 hours, gestation number, and delivery method. Detailed demographic information can be viewed in Table 2.1. After complete description of the study to subjects' parent(s), written informed consent was obtained. Study protocols were approved by the Institutional Review Board of the UNC School of Medicine.

Image Acquisition

MRI images were obtained using either a Siemens Allegra head-only 3T scanner (N=673) or a Siemens TIM Trio 3T scanner (N=132) (Siemens Medical System, Inc., Erlangen, Germany) during unsedated natural sleep. Subjects were fitted with earplugs and secured into a vacuum-fixed immobilization device prior to the scan. Heart rate and oxygen saturation were monitored using a pulse oximeter. 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 = 287, sequence name = Type1). For neonates who were deemed unlikely to sleep through the scan session, 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=386, sequence name = Type2). For the Trio, subjects were initially scanned using a TSE protocol (TR=6200ms, TE1=17, TE2=116ms, flip angle=150°, spatial resolution= 1.25mm x1.25mm x1.95 mm, N = 12, sequence name = Type3) while the rest were scanned using a 3-D T2 SPACE protocol (TR=3200ms, TE=406, flip angle=120°, spatial resolution= 1mm x 1mm x 1mm, N=120, sequence name = Type4). We determined that sequence parameters had a

significant influence on both cortical thickness and surface area and therefore included T2 sequence name (Type1-Type4) as a covariate in all of the analyses described in this study.

Image Analysis

Cortical thickness and surface area measures were derived for all subjects using a pipeline previously described by 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 (Shi et al. 2011). Gray matter (GM), 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, et al. 2014) was applied to the tissue segmentation 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 inner, middle, and outer surfaces for the left and right hemisphere were visually examined for accurate mapping.

The inner surface was defined as the boundary between grey and white matter and the outer surface as the boundary between the grey matter and CSF. A third, 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 surfaces and the minimum distance from the outer to the inner surfaces. SA

was computed based on the central cortical surface. The cortical surface was parcellated into 78 regions of interest based on an infant-specific 90 region parcellation atlas (Tzourio-Mazoyer et al. 2002; Gilmore et al. 2012) as shown in in Figure 2.1. Twelve regions represent subcortical structures and were therefore not examined. The average CT and total SA were calculated for each ROI based on corresponding values at each vertex.

Statistical Analysis

Parental demographic and medical history variables included maternal age, paternal age, maternal education, paternal education, maternal ethnicity, paternal ethnicity, maternal psychiatric history, paternal psychiatric history, total household income, and maternal smoking during pregnancy. Infant demographic variables included sex, birth weight, gestational age at birth, postnatal age at MRI, 5 min APGAR scores, stay in neonatal intensive care unit over 24 hours, gestation number, and delivery method. See Table S2.1 for a correlation matrix of predictor variables (continuous and binary). See Table S2.2 for a comparison of demographic variables between Caucasian and African American subjects. See Table S2.3 for a comparison of demographic variables by income. To examine the effects of these variables on individual differences in neonatal cortical thickness and surface area, we applied a moment-based method to select fixed effects in a linear mixed effects model (Ahn et al. 2012; Knickmeyer et al. 2016). For the selection of fixed effects, an adaptive lasso penalty was applied with all twin pairs treated as repeated measures. Results were bootstrapped 1,000 times. Variables were considered to be significant predictors if they were selected more than 800 times. T2 sequence type was included as a fixed variable when model selection was run for all surface area and cortical thickness measures. To account for overall brain size, total surface area was also fixed for all regional surface area model selections and the cubed root of intracranial volume (a sum of gray matter,

white matter and cerebrospinal fluid) was fixed in the model selection for average and regional cortical thickness. As a sensitivity analysis, model selections were also run without adjusting for overall brain size.

After variable selection, linear mixed effects models were run using the selected variables for each region independently. These selected models were used to perform significance testing and to generate effect sizes and r^2 values. Mixed effects models were also run including all variables for comparison. To account for familial relatedness within monozygotic (MZ) and dizygotic (DZ) twins, we used a standard ACE model described in Xia et al. (2014), which includes additive genetic effects (A), common environmental effects (C) and random environmental effects (E). For all regional analyses, adjustments for multiple comparisons were made using Benjamini & Hochberg method. FDR <0.05 was considered significant for each region of interest.

RESULTS

Average CT

Postnatal age at MRI, paternal education, and maternal ethnicity emerged as significant predictors of average neonatal cortical thickness (Table 2.2). Postnatal age at MRI showed a positive relationship, with average cortical thickness (Figure 2.2a) increasing 0.09% every day. Paternal education was negatively associated with average CT. With every additional year of paternal education, there was a 0.13% decrease in average CT. Significant associations between CT and maternal ethnicity were largely driven by differences between Caucasian and African American mothers. Compared to offspring of Caucasian mothers, offspring of African American mothers showed 1.4% larger average CT, offspring of Asian mothers showed 0.45% larger average CT, and offspring of Native American mothers showed 0.29% smaller average CT.

Regional CT

Postnatal age at MRI, gestational age at birth, maternal ethnicity, and paternal education emerged as significant predictors of regional CT in at least 10% of regions examined (Table S2.4). Postnatal age at MRI showed positive associations with regional CT (Figure 2.3, Table S2.5). Specifically, older babies had thicker cortices in the pre- and postcentral gyri, right supplementary motor area, right middle cingulate gyrus, insula, and portions of the lateral frontal, occipital, and parietal lobes. Gestational age at birth showed negative associations with regional CT (Figure 2.3, Table S2.6). Earlier born babies had thicker cortices in the medial and lateral frontal lobe, superior and middle temporal poles, right hippocampal gyrus, and postcentral gyrus. Paternal education also showed a negative association with regional CT (Figure 2.4, Table S2.7). Higher paternal education was associated with thinner cortices in superior frontal, middle frontal, and middle orbital frontal gyri as well as in the right inferior frontal pars triangularis, right medial superior frontal gyrus, right olfactory region, and right middle temporal gyrus.

Associations between maternal ethnicity and CT were largely driven by differences between infants of Caucasian and African American mothers (Figure 2.5, Table S2.8). Compared to offspring of Caucasian mothers, offspring of African American mothers had thicker cortices in bilateral postcentral gyri, superior parietal lobules, precuneus, and the supramarginal gyri, as well as the right precentral gyrus, insula, inferior parietal lobule, supplementary motor area, and rolandic operculum. Compared to offspring of Caucasian mothers, offspring of Asian mothers had thicker cortices in the right precentral gyrus, rolandic operculum, supramarginal gyrus, insula, and precuneus as well as the left superior parietal lobule. Offspring of Asian mothers had thinner cortices in the postcentral gyrus, right superior parietal lobule, right inferior parietal lobule, right supplementary motor area, left supramarginal gyrus, and left precuneus. Compared

to offspring of Caucasian mothers, offspring of Native American mothers had thicker cortices in the precuneus, left postcentral gyrus, right rolandic operculum, right supramarginal gyrus, right supplementary motor area, and right insula, and thinner cortices in the right precentral and postcentral gyri, superior parietal lobule, right inferior parietal lobule, and right supramarginal gyrus. Sex, birth weight and gestational number were also significant predictors of average CT in a small number of cortical regions. These results can found in Table S2.9.

Total SA

Birth weight, gestational age at birth, postnatal age at MRI, and sex emerged as the most significant predictors of total surface area (Table 2.2). Birth weight showed a strong positive association with total SA. For every 500g increase in birth weight, there was a 3.6% increase in overall cortical SA. Gestational age at birth and postnatal age at MRI also showed strong positive associations with total SA (Figure 2.2b-c). Total surface area increased 0.35% for every additional day in the womb and 0.51% for every postnatal day. Additionally, sex was a significant predictor of total SA, with males having 3.9% larger cortical surfaces than females.

Regional SA

We found postnatal age at MRI, birth weight, paternal ethnicity, maternal ethnicity, sex and gestational age at birth to be significant predictors of regional SA in a small number of ROIs. These results can found in Table S2.10.

The following were not significant predictors of neonatal CT and SA at either the global or regional level: Apgar scores at 5 minutes, delivery method, maternal education, total household income, maternal age, paternal age, maternal psychiatric history, paternal psychiatric history, and NICU stay over 24 hours. Results of mixed effects models containing all possible predictors (Table S2.11) were highly similar to results using the adaptive lasso. Exceptions

included birth weight and maternal ethnicity, which did not emerge as significant predictors of regional CT in the full mixed models. Additionally, gestational age at birth, sex, and birth weight were significant predictors of regional SA in the full model but did not appear in the adaptive lasso.

Secondary Analyses

In a secondary analysis, model selection was performed without adjusting for overall brain size. For regional CT, significant predictors were similar to those in the primary analysis. For regional SA, we identified postnatal age at MRI, gestational age at birth, birth weight, gestation number, and sex as significant predictors in widespread regions of the cortex (Table S2.12).

DISCUSSION

To our knowledge, this study is the first to examine environmental influences on cortical thickness and surface area in a large normative sample of neonates. Our findings build on our previous work examining the influences of obstetric, demographic, and socioeconomic factors on neonatal brain volumes (Knickmeyer et al. 2016) and provide a more refined account of how these factors impact early cortical development.

We found that the cortical surface expanded 0.51% and cortical thickness increased 0.09% daily between the ages of 6 and 144 days post birth. These results capture extremely rapid expansion and growth of the cortex during early postnatal development, likely driven by dendritic development, synaptogenesis, and, gliogenesis, as well as complex patterns of cortical connectivity and cortical folding (Stiles 2008). By comparison, annual growth rates during middle and late childhood reach maximum values of only 0.005% and 0.015% for CT and SA respectively (Raznahan et al. 2011). We also found that CT growth patterns were regionally

heterogeneous, with primary visual, motor, and auditory regions representing some of the fastest growing cortices after birth. This is consistent with longitudinal studies of CT, SA, (Li, Lin, et al. 2015; Lyall et al. 2015) and cortical volume during early brain development (Gilmore et al. 2012) that also show heterogeneous patterns of growth across the cortex. Specifically, sensory and motor regions are shown to mature earlier during development compared to regions involved with higher-order integrative functions. Similar hierarchical organization is observed in older children and adolescents, with sensory and motor regions reaching their peak thickness values earlier than association cortices (Sowell et al. 2004; Shaw et al. 2008). While our results were in line with these reports, faster growing cortices also included association regions within orbitofrontal and prestriate cortex. This suggests there are complex patterns of CT growth after birth in both primary sensory and association regions. Given minimal regional differences in gene expression during infancy (Pletikos et al. 2014), heterogeneous patterns of CT growth observed in our sample may reflect post-transcriptional processes and activity-dependent mechanisms sensitive to environmental input. Interestingly, we observed nominal regional heterogeneity in surface area growth during this time period.

We found that gestational age at birth had opposing effects on surface area and cortical thickness (positive and negative associations respectively). In keeping with published studies showing reduced cortical SA during infancy (Engelhardt et al. 2015) and childhood (Lax et al. 2013; Rogers et al. 2014; Zhang et al. 2015) in infants born preterm, total SA was larger in later born babies. During the late fetal stage, there is rapid growth in brain size driven by the accelerated development of cortical surface area relative to cortical volume (Kapellou et al. 2006). This is likely influenced by the development of sulci, gyri, and cortico-cortical connectivity. Our results suggest that being born early disrupts these processes, even in children

that are not technically premature (> 37 weeks). In contrast to SA, later born babies had thinner cortices in widespread regions of the frontal lobe as well as the postcentral gyrus, precuneus, and the temporal poles. This finding suggests that exposure to the postnatal environment in earlier born babies may alter the growth of the cortical mantle in these regions. Compared to the intrauterine environment, the extra-uterine environment is rich in sensory information and could promote synaptogenesis and complex dendritic morphology, leading to the accelerated growth of the cortex. Alternatively, thicker cortices in earlier born babies may reflect cortical overgrowth resulting from disrupted apoptotic mechanisms which normally take place late in gestation. Thicker cortices in earlier born babies compared to later born babies may also reflect a lack of maturation of the underlying white matter (Keunen et al. 2016) which would influence tissue classification during automated MRI segmentation protocols. The intrauterine environment is critical for the organization of axonal pathways and the processes of premyelination and myelination that begin during the second half of pregnancy and are likely interrupted as a result of preterm birth (Qiu, Mori, et al. 2015). Additional studies assessing white matter microstructure and myelination would help clarify the biological mechanisms underlying these findings.

Overall, the opposing effects of gestational age at birth on CT and SA reaffirm the conceptualization of CT and SA as relatively independent phenotypes. This conceptualization is further supported by our finding that individual variation in infant CT and SA is explained by different sets of environmental factors. Sex and obstetric history variables (especially birth weight) had a strong influence on neonatal SA whereas variables related to SES and ethnic disparities (paternal education and maternal ethnicity) had a strong influence on CT. Observed differences are in keeping with twin studies which consistently report CT and SA to be

genetically independent (Jansen et al. 2015), and with current theories of prenatal cortical development. In particular, the radial unit hypothesis (Rakic 2009) suggests that the number of cortical minicolumns determines the size of the cortical surface and that the number of minicolumns depends on the rate of cell proliferation and/or programmed cell death within symmetrically-dividing radial glial cells of the ventricular zone (VZ). Differences in CT are ascribed to changes in proliferation kinetics of asymmetrically dividing neural progenitor cells, as well as to changes in the size of neurons and the amount of tissue situated between neuronal cell bodies, which is itself composed of neuronal and glial processes including dendrites, dendritic spines, axon terminals and synapses (Rakic 1995; 2009). Additionally, the recently proposed supragranular layer expansion hypothesis suggests that at mid-neurogenesis, radial glial scaffolds become discontinuous (Nowakowski et al. 2016). During this discontinuous phase, self-renewing divisions of oRG cells increase the surface area of supragranular layers, while neurogenic divisions of oRG cells increase the thickness of these layers.

Our findings regarding birth weight and sex are similar to studies in older children and adults, which reveal males and heavier born babies have larger surface area but not cortical thickness (Raznahan et al. 2011; 2012; Walhovd et al. 2012; Wierenga et al. 2014; Walhovd, Fjell, et al. 2016). Our results indicate that these relationships are established during prenatal brain development and remains stable throughout childhood and into adulthood, confirming the importance of prenatal factors during early development. Keeping the above neurodevelopmental hypotheses in mind, the positive association of birth weight with SA may reflect the influence of genetic potential for growth, maternal nutrition and metabolism, endocrine factors, and placental perfusion and function on proliferation and apoptosis of radial glial cells, as well as on self-renewing divisions of oRG cells, and, in late pregnancy, the

development of corticocortical connectivity. Larger total SA in males may reflect the influence of gonadal steroids on these same processes. It is notable that testosterone secretion in male fetuses is highest between weeks 14 and 18 (Prince 2001), encompassing the latter portion of the continuous scaffold stage and the early portions of the discontinuous scaffold stage.

The association between paternal education and CT may reflect the father's ability to provide psychosocial resources during pregnancy and the early postpartum period, support healthy maternal behaviors, reduce stress, and provide greater cognitive stimulation in the home (Blumenshine et al. 2011; Shapiro et al. 2016). All of these factors may influence asymmetrically dividing neural progenitor cells, neurogenic divisions of oRG cells, synaptogenesis, and the formation/elaboration of neuronal and glial processes during development. Alternatively, associations between neonatal CT and paternal education could be driven by genetic influences. Given the rapid rates of CT growth observed in our study, it is somewhat surprising that this association is negative such that infants of more educated fathers have thinner cortices, especially in the frontal lobes. With that said, our findings are in keeping with previous work showing negative correlations between CT and intelligence during early childhood (Shaw et al. 2006). These findings have led to the hypothesis that children with higher IQs have more prolonged maturation of higher order regions. Thus, we hypothesize that infants born to more educated fathers may experience a slower, more extended developmental window of the frontal lobe that may be advantageous to later cognitive outcomes. It is also possible that thinner cortices in offspring of highly educated fathers reflect changes in image contrast caused by the myelination of underlying white matter (Sowell et al. 2004). Notably, environmental enrichment and social interactions promote oligodendrocyte lineage development and myelination (Tomlinson et al. 2016). Supporting this hypothesis, we previously found that higher paternal

education is associated with larger overall white matter volume in neonates (Knickmeyer et al. 2016).

We observed that offspring of African American mothers had thicker cortices in parietal regions involved in somatosensory processes and sensory integration compared to offspring of Caucasian mothers. However, we note that these associations were not significant in the full mixed effects models. Associations between maternal ethnicity and CT may reflect genetic differences and/or the influences of environmental factors associated with the sociocultural construct of race/ethnicity on the cellular processes described above. Additional studies are needed to determine whether these associations are robust and if they are temporary or represent persistent alterations with functional consequences. Furthermore, to effectively develop interventions aimed at optimizing infant brain development, future studies must delineate specific mechanisms underlying these associations. Specific variables that may be of importance include psychosocial stress, exposure to environmental pollutants, and reduced access to/utilization of prenatal care, which may be more common among racial and ethnic minorities (Grobman et al. 2016; Lorch and Enlow 2016). These variables were not assessed in the current study, but when comparing infants of Caucasian and African American (AA) mothers, we did observe significant differences in birth weight, maternal and paternal education, and maternal age (all lower in AA), in NICU stay greater than 24 hours, maternal psychiatric history, and maternal smoking (all more common in AA), and in paternal psychiatric history (less common in AA).

We note that Apgar scores at 5 minutes, delivery method, maternal education, total household income, maternal age, paternal age, maternal psychiatric history, paternal psychiatric history, and NICU stay over 24 hours were not selected as significant predictors of neonatal CT

and SA. In some cases, this may reflect high correlations between predictor variables (e.g. between paternal and maternal education). In such a situation, the moment-based method selects the best predictive variable. With specific regard to psychiatric history, the lack of associations may reflect the fact that our psychiatric history variables include multiple disorders with depression being the most common. Previous work by our group has shown that a maternal history of severe mental illness (specifically schizophrenia) does influence brain development (Gilmore, Kang, et al. 2010).

In conclusion, CT and SA both exhibit rapid growth during the first postnatal month but show distinct relationships with environmental factors. Gestational age at birth is positively associated with SA, but negatively associated with CT. Birth weight and sex influence SA, potentially through cellular processes active during early pregnancy and midgestation, while maternal ethnicity and paternal education influence CT, possibly through cellular processes active in the perinatal period. Strengths of this study include the use of detailed medical, obstetric, and demographic data, the collection of a large representative imaging dataset, and the application of cutting-edge pediatric image analysis methods. Limitations reflect inherent difficulties in imaging infant subjects. Age-related changes in signal intensities and contrast may affect CT and SA measures (Walhovd, Fjell, et al. 2016). In addition, compared to SA measurements at this age, CT measurements are much smaller, show less variation, and more prone to partial volume errors. Despite these limitations, our results highlight the importance of obstetric, demographic, and socioeconomic factors in explaining individual variation in neonatal CT and SA. Ultimately, this line of research will allow the development and optimal application of interventions to support prenatal/perinatal cortical development, ensuring a strong foundation for a long, healthy, and productive life.

Table 2.1. Descriptive Statistics for Demographic and Medical History Variables

Continuous Variables		**Average**	**SD**	**Min**	**Max**
Birth weight		2843.511	706.544	790	4820
Gestational Age at Birth		261.195	19.082	192	295
Postnatal Age at MRI		30.64	16.871	6	144
5 Minute APGAR Score		8.72	0.693	3	10
Maternal Education		15.05	3.464	0	26
Paternal Education		14.86	3.488	0	26
Maternal Age		29.858	5.585	16	47
Paternal Age		32.379	6.553	17	64
Categorical Variables		**N**		**%**	
NICU Stay > 24 hours	No	635		79%	
	Yes	170		21%	
Sex	Male	429		53%	
	Female	376		47%	
Delivery Method	Vaginal	382		47%	
	C-section	423		52%	
Household Income	High	238		30%	
	Mid	217		27%	
	Low	299		37%	
	Missing	51		6%	
Maternal Ethnicity	Caucasian	612		76%	
	African American	173		21%	
	Asian	17		2%	
	Native American	3		< 1%	
Paternal Ethnicity	Caucasian	588		73%	
	African American	184		23%	
	Asian	26		3%	
	Native American	7		1%	
Gestational Number	Singleton	371		46%	
	Twin	434		54%	
Maternal Psychiatric History	No	508		63%	
	Yes	297		37%	
Paternal Psychiatric History	No	714		89%	
	Yes	91		11%	
Maternal Smoking	No	738		92%	
	Yes	67		8%	
T2 Sequence Type	Type 1	287		36%	
	Type 2	386		48%	
	Type 3	12		1%	
	Type 4	120		15%	

Table 2.2. Significant Associations with Global Cortical Thickness and Surface Area

Region of Interest	R^2	Predictors	Beta	r^2	q- value	Relative Difference
Average Thickness	0.52	Intercept	1.14E+00			
		Postnatal Age at MRI	1.64E-03	1.77E-01	6.67E-44	0.09%
		Paternal Education	-2.44E-03	1.67E-02	3.26E-06	-0.13%
		Maternal Ethnicity - Asian	8.66E-03	3.58E-04		0.45%
		Maternal Ethnicity - African American	2.74E-02	2.91E-02	3.39E-08	1.40%
		Maternal Ethnicity - Native American	-5.44E-03	2.53E-05		-0.29%
		$ICV^{1/3}$	9.59E-03	1.87E-01	4.24E-49	0.50%
		T2 Sequence (Type1 vs Type2)	3.62E-03	7.53E-04		0.19%
		T2 Sequence (Type1 vs Type3)	2.73E-03	2.52E-05	8.12E-01	0.14%
		T2 Sequence (Type1 vs Type4)	-1.86E-03	1.01E-04		-0.10%
Total Surface Area	0.51	Intercept	-2.11E+02			
		Birth Weight	5.70E+00	1.89E-01	3.98E-24	3.6%*
		Gestational Age at Birth	2.78E+02	3.29E-01	1.78E-26	0.35%
		Postnatal Age at MRI	4.08E+02	5.52E-01	1.16E-67	0.51%
		Sex	-3.06E+03	2.71E-02	1.69E-10	3.90%
		T2 Sequence (Type1 vs Type2)	7.39E+02	1.59E-03		0.93%
		T2 Sequence (Type1 vs Type3)	-1.26E+03	2.72E-04	3.76E-01	-1.59%
		T2 Sequence (Type1 vs Type4)	4.33E+02	2.73E-04		0.55%

* per 500g for birth weight

Figure 2.1. The 78 cortical regions of interest from the AAL atlas projected onto a representative neonatal brain

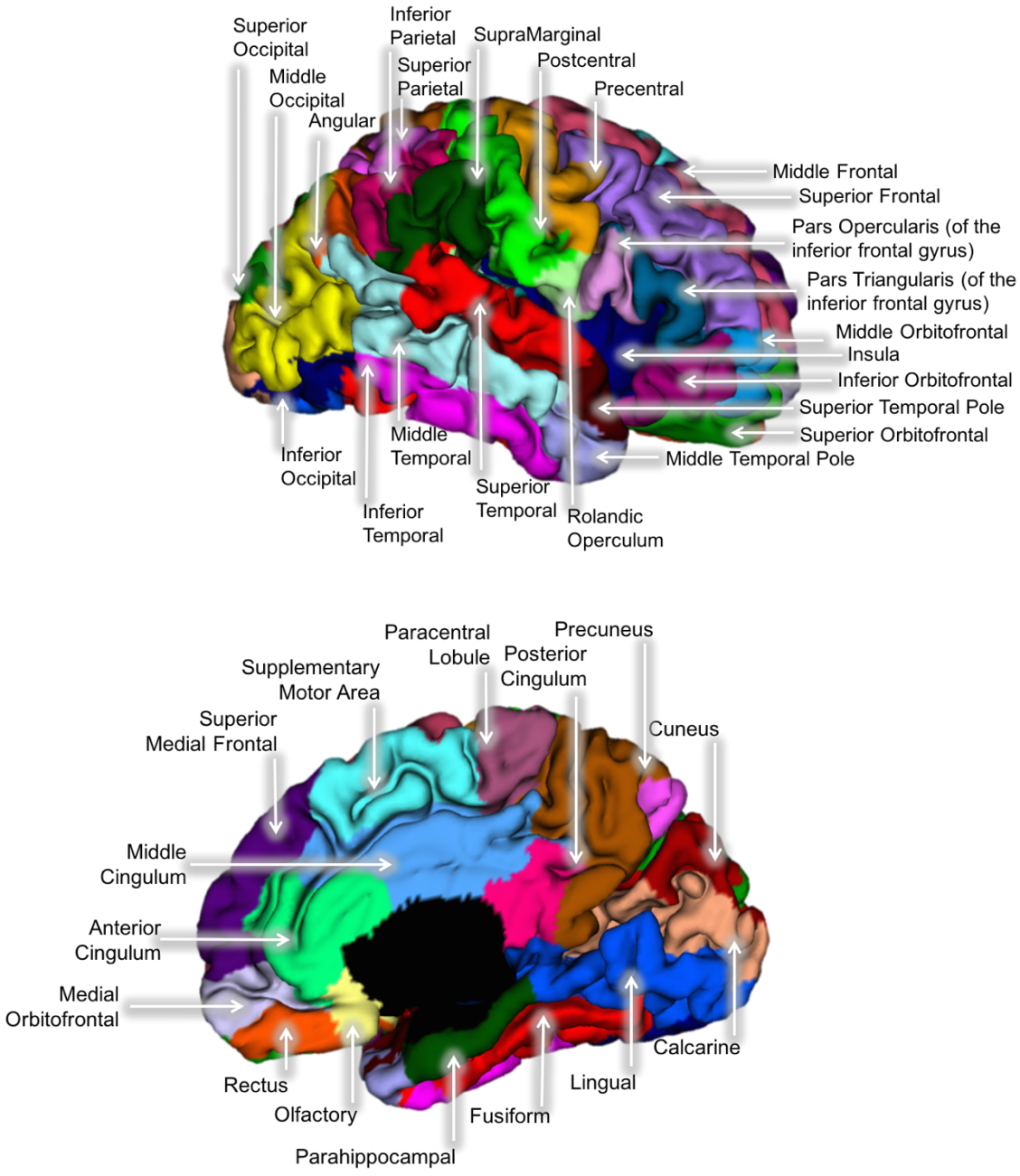


Figure 2.2. Age at MRI plotted against average CT (a), age at MRI plotted against total SA (b), and gestational age at birth plotted against total SA (c) for all individual subjects.

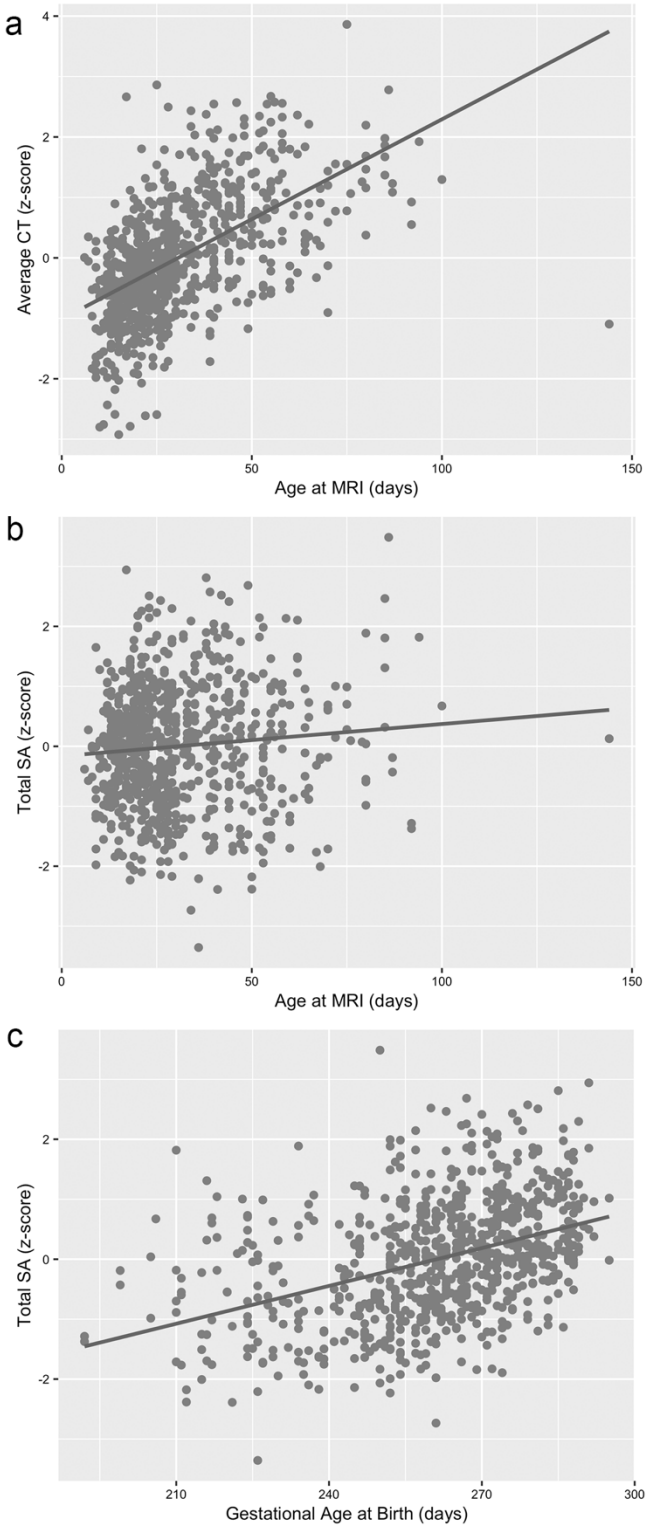


Figure 2.3. Significant associations between regional CT and postnatal age at MRI and gestational age at birth shown as percent change by day. Regions in white were not deemed significant after correction for multiple comparisons. Subcortical regions are in gray and were not analyzed.

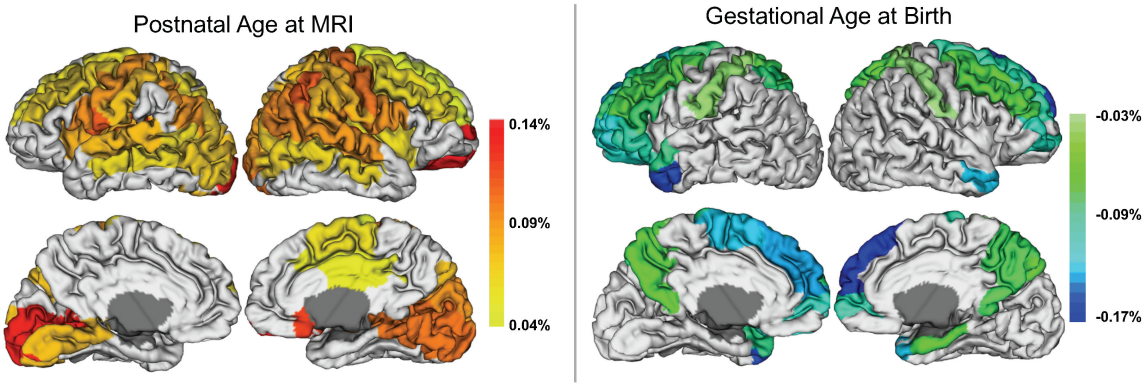


Figure 2.4. Significant associations between regional CT and paternal education are projected onto the cortical surface. Regions in white were not significant and regions in gray were not analyzed.

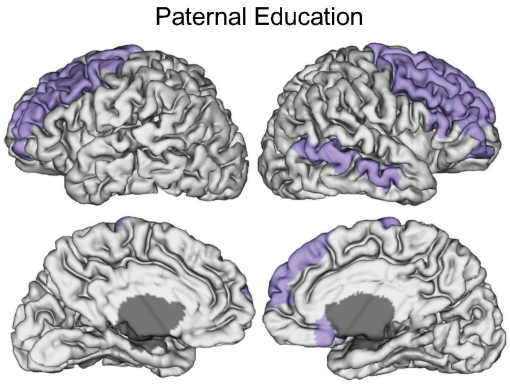


Figure 2.5. Significant associations between regional CT and maternal ethnicity are projected onto the cortical surface. Regions in dark pink show thinner cortices in infants of Caucasian mothers and regions in light pink show thicker cortices in infants of Caucasian mothers. Regions in white were not significant and regions in gray were not analyzed.

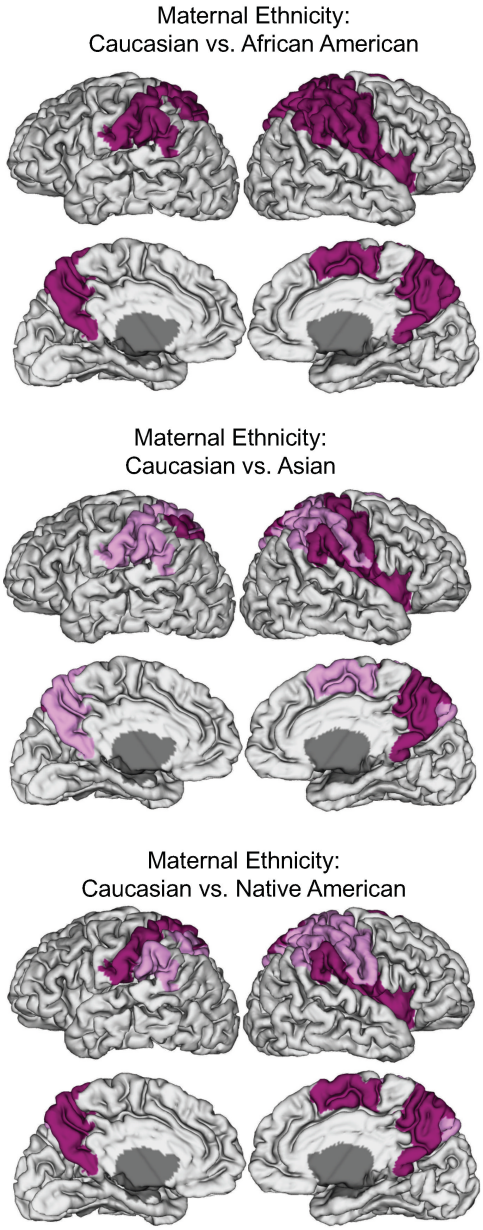


Table S2.1. Correlation Matrix of Predictor Variables

	Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9	Var10	Var11	Var12	Var13	Var14	Var15
Var1	1.00														
Var2	0.83	1.00													
Var3	-0.61	-0.71	1.00												
Var4	-0.60	-0.70	0.55	1.00											
Var5	-0.03	0.05	0.00	-0.01	1.00										
Var6	0.30	0.37	-0.31	-0.39	-0.02	1.00									
Var7	-0.32	-0.38	0.27	0.28	-0.05	-0.16	1.00								
Var8	0.15	0.14	-0.15	-0.10	-0.05	0.03	-0.02	1.00							
Var9	0.11	0.12	-0.10	-0.08	-0.03	0.05	-0.06	0.70	1.00						
Var10	0.01	-0.01	-0.02	-0.03	0.00	0.00	0.12	0.41	0.31	1.00					
Var11	-0.06	-0.09	0.05	0.03	0.00	-0.04	0.12	0.27	0.19	0.68	1.00				
Var12	-0.67	-0.65	0.43	0.34	-0.05	-0.18	0.43	-0.03	-0.01	0.13	0.10	1.00			
Var13	-0.01	-0.04	0.03	0.03	-0.03	-0.12	0.03	-0.20	-0.22	-0.15	-0.08	-0.11	1.00		
Var14	0.01	0.00	0.01	0.03	-0.05	-0.05	-0.01	0.05	-0.01	0.03	-0.03	-0.04	0.19	1.00	
Var15	-0.11	-0.06	0.03	0.12	-0.03	-0.04	0.06	-0.27	-0.20	-0.14	-0.08	-0.06	0.21	0.03	1.00

Var1- Birth Weight, Var2 – Gestational Age at Birth, Var3 – Postnatal Age at MRI, Var4 – NICU stay > 24 hours, Var5 – Sex, Var6 – 5 Minute APGAR Score, Var7 – Delivery Method, Var8 – Maternal Education, Var9 – Paternal Education, Var10 – Maternal Age, Var11 – Paternal Age, Var12 – Gestational Number, Var13 – Maternal Psychiatric History, Var14 – Paternal Psychiatric History, Vary15 – Maternal Smoking

Table S2.2. Demographic Characteristics of Neonates with Caucasian and African American Mothers

		Caucasian (n = 612)		African American (n = 173)		
Continuous Variables		**Average**	**SD**	**Average**	**SD**	**P-value**
Birth weight (grams)		2910.941	695.798	2610.613	727.922	**< 0.001**
Gestational Age at Birth (days)		261.882	18.644	258.572	21.128	0.063
Postnatal Age at MRI (days)		30.092	16.878	32.601	17.153	0.089
5 Minute APGAR Score		8.740	0.696	8.642	0.706	0.105
Maternal Education (years)		15.428	3.513	13.569	2.771	**< 0.001**
Paternal Education (years)		15.204	3.633	13.420	2.230	**< 0.001**
Maternal Age (years)		30.361	5.326	27.994	6.236	**< 0.001**
Paternal Age (years)		32.379	6.068	32.237	8.249	0.833
Categorical Variables		**N**	**%**	**N**	**%**	**P-value**
NICU Stay > 24 hours	No	493	81%	125	72%	**0.026**
	Yes	119	19%	48	28%	
Sex	Male	321	52%	92	53%	> 0.999
	Female	291	48%	81	47%	
Delivery Method	Vaginal	298	49%	78	45%	0.388
	C-section	314	51%	95	55%	
Gestational Number	Singleton	286	47%	75	43%	0.489
	Twin	326	53%	98	57%	
Paternal Ethnicity	Caucasian	564	92%	17	10%	**< 0.001**
	African American	31	5%	152	88%	
	Asian	13	2%	1	1%	
	Native American	4	1%	3	2%	
Maternal Psychiatric History	No	403	66%	90	52%	**0.001**
	Yes	209	34%	83	48%	
Paternal Psychiatric History	No	527	86%	169	98%	**< 0.001**
	Yes	85	14%	4	2%	
Maternal Smoking	No	569	93%	149	86%	**0.008**
	Yes	43	7%	24	14%	

Table S2.3. Demographic Characteristics of Neonates by Total Household Income

		High (n = 238)		Middle (n = 217)		Low (n = 299)		
Continuous Variables		**Average**	**SD**	**Average**	**SD**	**Average**	**SD**	**P-value**
Birth weight (grams)		2920.231	678.033	2887.76	781.669	2761.137	677.829	**0.022**
Gestational Age at Birth (days)		263.122	18.503	260.834	19.517	259.786	19.434	0.13
Postnatal Age at MRI (days)		29.769	17.052	29.433	15.485	32.144	17.636	0.128
5 Minute APGAR Score		8.769	0.624	8.728	0.642	8.682	0.788	0.358
Maternal Education (years)		17.466	2.6	15.871	2.775	12.793	2.85	**< 0.001**
Paternal Education (years)		16.911	2.736	15.452	3.053	12.785	3.26	**< 0.001**
Maternal Age (years)		32.882	3.868	31.014	5.227	26.732	5.523	**< 0.001**
Paternal Age (years)		35.075	5.386	33.598	5.427	29.192	6.93	**< 0.001**
Categorical Variables		**N**	**%**	**N**	**%**	**N**	**%**	
NICU Stay > 24 hours	No	205	86%	162	75%	225	75%	**0.002**
	Yes	33	14%	55	25%	74	25%	
Sex	Male	124	52%	117	54%	157	53%	0.921
	Female	114	48%	100	46%	142	47%	
Delivery Method	Vaginal	110	46%	95	44%	151	51%	0.298
	C-section	128	54%	122	56%	148	49%	
Gestational Number	Singleton	112	47%	99	46%	134	45%	0.873
	Twin	126	53%	118	54%	165	55%	
Maternal Ethnicity	Caucasian	220	92%	165	76%	199	67%	**< 0.001**
	African American	12	5%	45	21%	95	32%	
	Asian	6	3%	7	3%	2	1%	
	Native American	0	< 1%	0	< 1%	3	1%	
Paternal Ethnicity	Caucasian	214	90%	159	73%	186	62%	**< 0.001**
	African American	14	6%	47	22%	104	35%	
	Asian	9	4%	9	4%	5	2%	
	Native American	1	< 1%	2	1%	4	1%	
Maternal Psychiatric History	No	170	71%	146	67%	163	55%	**< 0.001**
	Yes	68	29%	71	33%	136	45%	
Paternal Psychiatric History	No	213	89%	188	87%	267	89%	0.56
	Yes	25	11%	29	13%	32	11%	
Maternal Smoking	No	236	99%	206	95%	257	86%	**< 0.001**
	Yes	2	1%	11	5%	42	14%	

Table S2.4. Bootstrapping Results from Variable Selection

Variable of Interest	Cortical Thickness		Surface Area		Total SA
	# ROIs > 800	% ROIs > 800	# ROIs > 800	% ROIs > 800	> 800
5 Minute Apgar	0	0%	0	0%	No
Postnatal Age at MRI	41	52%	3	4%	Yes
Birth weight	4	5%	2	3%	Yes
Delivery Method	0	0%	0	0%	No
Gestational Age at Birth	24	30%	1	1%	Yes
Gestational Number	2	3%	0	0%	No
Income (low vs high)	0	0%	0	0%	No
Income (low vs mid)	0	0%	0	0%	No
income (low vs missing)	0	0%	0	0%	No
Maternal Age	0	0%	0	0%	No
Maternal Education	0	0%	0	0%	No
Maternal Ethnicity (Caucasian vs Native American)	0	0%	0	0%	No
Maternal Ethnicity (Caucasian vs Asian)	0	0%	0	0%	No
Maternal Ethnicity (Caucasian vs African American)	14	18%	1	1%	No
Maternal Psychiatric History	0	0%	0	0%	No
Maternal Smoking	0	0%	0	0%	No
NICU Stay > 24 hours	0	0%	0	0%	No
Paternal Age	0	0%	0	0%	No
Paternal Education	11	14%	0	0%	No
Paternal Ethnicity (Caucasian vs Native American)	0	0%	0	0%	No
Paternal Ethnicity (Caucasian vs Asian)	0	0%	0	0%	No
Paternal Ethnicity (Caucasian vs African American)	0	0%	2	3%	No
Paternal Psychiatric History	0	0%	0	0%	No
Sex	7	9%	1	1%	Yes
T2 Sequence Type (Type1 vs Type2) *	79	100%	78	100%	Yes
T2 Sequence Type (Type1 vs Type3) *	79	100%	78	100%	Yes
T2 Sequence Type (Type1 vs Type4) *	79	100%	78	100%	Yes
$ICV^{1/3}$ *	79	100%	---	---	---
Total Surface Area *	---	----	78	100%	---

*Variables are fixed in the model

Table S2.5. Significant Associations of Postnatal age at MRI with Cortical Thickness from Selected Models

Region of Interest	Beta	r^2	q- value	Relative Difference
Angular_L	1.69E-03	0.05	1.57E-10	0.091%
Angular_R	1.72E-03	0.08	1.43E-15	0.094%
Calcarine_L	2.42E-03	0.08	1.36E-16	0.130%
Calcarine_R	1.98E-03	0.05	1.70E-05	0.102%
Cingulum_Mid_R	9.81E-04	0.03	1.07E-07	0.051%
Cuneus_R	1.68E-03	0.05	1.01E-09	0.092%
Frontal_Inf_Oper_L	1.80E-03	0.08	2.12E-15	0.093%
Frontal_Inf_Oper_R	1.77E-03	0.06	5.04E-14	0.091%
Frontal_Mid_L	1.21E-03	0.04	1.77E-05	0.065%
Frontal_Mid_R	1.12E-03	0.04	1.91E-05	0.061%
Frontal_Sup_L	1.06E-03	0.02	8.62E-04	0.056%
Frontal_Sup_Orb_R	2.51E-03	0.09	8.97E-17	0.139%
Frontal_Sup_R	8.12E-04	0.01	8.84E-03	0.043%
Heschl_L	2.08E-03	0.06	1.96E-13	0.103%
Heschl_R	2.47E-03	0.07	1.61E-14	0.117%
Insula_L	1.65E-03	0.10	4.77E-23	0.082%
Insula_R	1.25E-03	0.06	9.70E-14	0.061%
Lingual_L	1.43E-03	0.06	3.55E-06	0.076%
Lingual_R	1.91E-03	0.08	4.98E-16	0.101%
Occipital_Mid_L	1.21E-03	0.05	3.47E-10	0.069%
Occipital_Mid_R	1.17E-03	0.04	1.11E-08	0.066%
Occipital_Sup_L	1.29E-03	0.04	1.19E-08	0.074%
Occipital_Sup_R	1.52E-03	0.06	5.28E-12	0.086%
Olfactory_R	2.71E-03	0.04	1.56E-08	0.120%
Parietal_Inf_L	1.66E-03	0.08	5.39E-16	0.090%
Parietal_Inf_R	1.96E-03	0.09	1.10E-18	0.108%
Parietal_Sup_L	1.06E-03	0.02	7.03E-03	0.059%
Parietal_Sup_R	1.32E-03	0.04	1.28E-04	0.074%
Postcentral_L	1.38E-03	0.07	3.40E-07	0.074%
Postcentral_R	1.43E-03	0.07	1.88E-08	0.078%
Precentral_L	1.72E-03	0.11	1.58E-25	0.091%
Precentral_R	1.91E-03	0.12	8.31E-29	0.101%
Rolandic_Oper_L	2.18E-03	0.14	4.03E-26	0.109%
Rolandic_Oper_R	1.83E-03	0.10	1.81E-21	0.093%
Supp_Motor_Area_R	1.25E-03	0.03	3.65E-04	0.060%
SupraMarginal_R	1.45E-03	0.05	2.79E-09	0.077%
Temporal_Mid_L	1.15E-03	0.04	8.33E-08	0.061%
Temporal_Mid_R	1.22E-03	0.05	4.18E-10	0.063%
Temporal_Sup_L	1.57E-03	0.08	7.57E-15	0.077%
Temporal_Sup_R	1.84E-03	0.12	4.49E-22	0.091%

Table S2.6. Significant Associations of Gestational Age at Birth with Cortical Thickness from Selected Models

Region of Interest	Beta	r^2	q-value	Relative Difference
Frontal_Inf_Orb_L	-2.07E-03	0.12	1.38E-24	-0.10%
Frontal_Inf_Tri_L	-1.64E-03	0.08	1.62E-18	-0.09%
Frontal_Med_Orb_L	-2.35E-03	0.06	5.53E-13	-0.12%
Frontal_Med_Orb_R	-2.13E-03	0.07	4.29E-14	-0.11%
Frontal_Mid_L	-1.16E-03	0.05	2.01E-06	-0.06%
Frontal_Mid_Orb_L	-2.49E-03	0.08	4.04E-18	-0.13%
Frontal_Mid_Orb_R	-2.16E-03	0.07	2.20E-14	-0.12%
Frontal_Mid_R	-1.18E-03	0.05	2.44E-07	-0.06%
Frontal_Sup_L	-1.67E-03	0.08	2.17E-09	-0.09%
Frontal_Sup_Medial_L	-2.97E-03	0.22	4.06E-49	-0.14%
Frontal_Sup_Medial_R	-3.56E-03	0.23	4.80E-50	-0.17%
Frontal_Sup_Orb_L	-2.24E-03	0.08	8.28E-16	-0.12%
Frontal_Sup_R	-1.96E-03	0.11	1.05E-12	-0.10%
ParaHippocampal_R	-1.59E-03	0.02	4.01E-03	-0.07%
Parietal_Sup_L	-1.58E-03	0.06	4.22E-06	-0.09%
Parietal_Sup_R	-1.07E-03	0.03	3.42E-04	-0.06%
Postcentral_L	-5.96E-04	0.02	1.08E-02	-0.03%
Postcentral_R	-5.06E-04	0.01	2.06E-02	-0.03%
Precuneus_L	-1.28E-03	0.09	2.65E-19	-0.07%
Precuneus_R	-1.57E-03	0.11	4.34E-23	-0.08%
Supp_Motor_Area_L	-2.93E-03	0.17	8.21E-33	-0.14%
Temporal_Pole_Mid_L	-3.46E-03	0.13	9.18E-23	-0.16%
Temporal_Pole_Mid_R	-2.94E-03	0.11	1.24E-19	-0.14%
Temporal_Pole_Sup_L	-2.05E-03	0.10	1.69E-17	-0.09%

Table S2.7. Significant Associations of Paternal Education with Cortical Thickness from Selected Models

Region of Interest	Beta	r^2	q-value	Relative Difference
Frontal_Inf_Tri_R	-5.05E-03	0.03	3.80E-07	-0.27%
Frontal_Mid_L	-4.41E-03	0.02	7.63E-08	-0.24%
Frontal_Mid_Orb_L	-6.97E-03	0.02	3.72E-06	-0.37%
Frontal_Mid_Orb_R	-6.70E-03	0.02	6.00E-06	-0.36%
Frontal_Mid_R	-4.59E-03	0.03	1.98E-09	-0.25%
Frontal_Sup_L	-4.10E-03	0.02	1.15E-05	-0.22%
Frontal_Sup_Medial_R	-5.04E-03	0.02	1.15E-05	-0.25%
Frontal_Sup_R	-5.46E-03	0.03	3.65E-09	-0.29%
Olfactory_R	-7.59E-03	0.01	5.57E-04	-0.34%
Temporal_Mid_R	-4.34E-03	0.03	1.27E-06	-0.23%

Table S2.8. Significant Associations of Maternal Ethnicity with Cortical Thickness from Selected Models

Region of Interest	Beta	r^2	q-value	Relative Difference
Insula_R				
African American	3.06E-02	0.02		1.5%
Asian	6.49E-03	< 0.01	4.04E-05	0.006%
Native American	5.80E-02	< 0.01		2.82%
Parietal_Inf_R				
African American	3.46E-02	0.02		1.9%
Asian	-1.43E-02	< 0.01	7.12E-04	0.020%
Native American	-7.87E-04	< 0.01		-0.04%
Parietal_Sup_L				
African American	5.20E-02	0.03		2.9%
Asian	2.74E-03	< 0.01	3.11E-06	0.001%
Native American	-4.93E-02	< 0.01		-2.76%
Parietal_Sup_R				
African American	6.09E-02	0.05		3.4%
Asian	-2.48E-02	< 0.01	1.55E-11	0.058%
Native American	-2.55E-02	< 0.01		-1.43%
Postcentral_L				
African American	3.41E-02	0.02		1.8%
Asian	-6.40E-03	< 0.01	8.29E-06	0.005%
Native American	1.35E-02	< 0.01		0.72%
Postcentral_R				
African American	3.05E-02	0.02		1.7%
Asian	-1.11E-02	< 0.01	8.18E-06	0.018%
Native American	-4.51E-02	< 0.01		-2.47%
Precentral_R				
African American	4.23E-02	0.04		2.2%
Asian	5.70E-03	< 0.01	5.96E-09	0.004%
Native American	-1.98E-02	< 0.01		-1.05%
Precuneus_L				
African American	3.20E-02	0.03		1.7%
Asian	-1.17E-02	< 0.01	9.15E-06	0.023%
Native American	2.46E-02	< 0.01		1.29%
Precuneus_R				
African American	3.55E-02	0.03		1.8%
Asian	1.23E-03	< 0.01	1.04E-05	0.000%
Native American	4.27E-02	< 0.01		2.20%
Rolandic_Oper_R				
African American	4.12E-02	0.03		2.1%
Asian	1.67E-02	< 0.01	8.68E-07	0.032%
Native American	4.62E-02	< 0.01		2.34%
Supp_Motor_Area_R				
African American	5.23E-02	0.03		2.5%
Asian	-9.05E-03	< 0.01	1.58E-06	0.005%
Native American	9.58E-02	< 0.01		4.58%
SupraMarginal_L				
African American	5.67E-02	0.04		2.9%
Asian	-1.15E-02	< 0.01	1.36E-06	0.010%
Native American	-2.82E-02	< 0.01		-1.46%
SupraMarginal_R				
African American	4.06E-02	0.02		2.2%
Asian	4.08E-03	< 0.01	4.84E-04	0.001%
Native American	3.20E-02	< 0.01		1.70%

Table S2.9. Significant Associations of Sex, Gestational Number, and Birth Weight with Cortical Thickness from Selected Models

Region of Interest	Beta	r^2	q-value	Relative Difference
Sex				
Calcarine_L	4.62E-02	0.03	7.36E-07	2.48%
Heschl_L	4.02E-02	0.02	1.57E-05	2.00%
Lingual_R	3.54E-02	0.03	2.32E-06	1.87%
Parietal_Inf_L	2.50E-02	0.02	1.62E-04	1.36%
Parietal_Inf_R	2.66E-02	0.02	1.69E-04	1.47%
Precentral_L	2.54E-02	0.02	8.61E-07	1.34%
Temporal_Mid_R	2.44E-02	0.02	9.28E-05	1.27%
Gestational Number				
ParaHippocampal_R	1.09E-01	0.06	1.31E-07	4.78%
Fusiform_R	-3.77E-02	0.02	4.31E-05	-2.34%
Birth Weight*				
Frontal_Inf_Tri_R	-4.65E-05	0.09	4.93E-19	-1.25%
Lingual_L	-1.82E-05	0.02	1.25E-02	-0.47%
Supp_Motor_Area_R	-4.23E-05	0.06	5.11E-07	-1.12%

* relative difference is based per 500g for birth weight

Table S2.10. Significant Associations with Surface Area from Selected Models

Region of Interest	Beta	r^2	q-value	Relative Difference
Birth Weight				
Frontal_Mid_L	-0.05	0.01	8.98E-06	1.20%
Rectus_R	0.01	0.03	1.59E-05	1.10%
Postnatal age at MRI				
Frontal_Sup_Medial_R	0.52	0.01	1.05E-07	0.07%
Occipital_Mid_R	-1	0.01	1.10E-06	0.10%
Temporal_Pole_Sup_L	0.46	0.01	2.31E-06	0.08%
Gestational Age at Birth				
Rectus_R	-0.68	0.06	1.04E-08	0.15%
Sex				
Temporal_Pole_Mid_L	-14.92	0.02	4.49E-06	3.78%
Paternal Ethnicity				
Frontal_Mid_R				
African American	102.84	0.01		4.96%
Asian	26.29	< 0.01	1.19E-07	1.27%
Native American	5.99	< 0.01		0.29%
Temporal_Sup_R				
African American	48.24	0.01		2.64%
Asian	6.92	< 0.01	2.21E-05	0.38%
Native American	-9.33	< 0.01		0.51%
Maternal Ethnicity				
Rectus_R				
African American	14.2	0.01		3.13%
Asian	1.08	< 0.01	2.79E-05	0.24%
Native American	-33.19	< 0.01		7.32%

** relative difference is based per 500g for birth weight*

Table S2.11. Summary of Results from Mixed Effects Models Containing All Possible Predictors

Variable of Interest	Cortical Thickness		Surface Area		Total SA
	# Significant ROIs	% Significant ROIs	# Significant ROIs	% Significant ROIs	Significant
5 Minute Apgar	0	0%	0	0%	No
Postnatal Age at MRI	42	53%	5	6%	Yes
Birth weight	0	0%	7	9%	Yes
Delivery Method	0	0%	0	0%	No
Gestational Age at Birth	18	23%	2	3%	Yes
Gestational Number	2	3%	1	1%	No
Income	0	0%	0	0%	No
Maternal Age	0	0%	0	0%	No
Maternal Education	0	0%	0	0%	No
Maternal Ethnicity	1	1%	1	1%	No
Maternal Psychiatric History	0	0%	0	0%	No
Maternal Smoking	0	0%	0	0%	No
NICU Stay > 24 hours	0	0%	0	0%	No
Paternal Age	0	0%	0	0%	No
Paternal Education	10	13%	0	0%	No
Paternal Ethnicity	0	0%	1	1%	No
Paternal Psychiatric History	0	0%	1	1%	No
Sex	41	52%	13	17%	Yes
T2 Sequence Type	27	34%	11	14%	Yes
$ICV^{1/3}$	78	99%	---	---	---
Total Surface Area	---	----	78	100%	---

Table S2.12. Bootstrapping Results from Variable Selection – Without Adjustments for Global Measures

Variable of Interest	Cortical Thickness		Surface Area	
	# ROIs > 800	% ROIs > 800	# ROIs > 800	% ROIs > 800
5 Minute Apgar	0	0%	0	0%
Postnatal Age at MRI	69	87%	78	99%
Birth weight	9	11%	77	97%
Delivery Method	0	0%	1	1%
Gestational Age at Birth	13	16%	78	99%
Gestational Number	3	4%	29	37%
Income (low vs high)	0	0%	0	0%
Income (low vs mid)	0	0%	0	0%
Income (low vs missing)	0	0%	0	0%
Maternal Age	0	0%	0	0%
Maternal Education	0	0%	0	0%
Maternal Ethnicity (Caucasian vs Native American)	0	0%	0	0%
Maternal Ethnicity (Caucasian vs Asian)	0	0%	1	1%
Maternal Ethnicity (Caucasian vs African American)	6	8%	2	3%
Maternal Psychiatric History	0	0%	0	0%
Maternal Smoking	0	0%	0	0%
NICU Stay > 24 hrs	0	0%	0	0%
Paternal Age	0	0%	0	0%
Paternal Education	2	3%	1	1%
Paternal Ethnicity (Caucasian vs Native American)	0	0%	0	0%
Paternal Ethnicity (Caucasian vs Asian)	0	0%	2	3%
Paternal Ethnicity (Caucasian vs African American)	1	1%	1	1%
Paternal Psychiatric History	0	0%	1	1%
Sex	3	4%	53	67%
T2 Sequence Type (Type1 vs Type2) *	79	100%	79	100%
T2 Sequence Type (Type1 vs Type3) *	79	100%	79	100%
T2 Sequence Type (Type1 vs Type4) *	79	100%	79	100%

**Variables are fixed in the model*

CHAPTER 3: GENETIC INFLUENCES ON INFANT CORTICAL THICKNESS AND SURFACE AREA

INTRODUCTION

Individual variations in cortical thickness and surface area are associated with complex psychiatric and neurodevelopmental conditions, intellectual ability, and aging (Shaw et al. 2006; Wolosin et al. 2009; Long et al. 2012; Janssen et al. 2014). Current evidence suggests CT and SA are independent phenotypes with distinct genetic underpinnings. Twin and family studies have revealed that overall total SA and average CT are highly heritable, with genetic factors accounting for up to 89% and 81% of total phenotypic variance respectively (Panizzon et al. 2009; Winkler et al. 2010). Regionally, heritability measures are found to be distinct across the cortex, ranging from 17% to 76% for SA and from 6% to 73% for CT, after correcting for global measures (Winkler et al. 2010). These studies also reveal small and nonsignificant genetic correlations between CT and SA, suggesting that these phenotypes are driven by different sets of genetic factors. At present, the majority of this research has been performed in children, adolescents, and adults. There are no investigations that focus on genetic contributions to CT and SA during infancy.

This is an important unanswered question given that the prenatal and early postnatal periods represent the foundational phase of cortical development. The radial unit hypothesis and the supragranular layer expansion hypothesis suggest that the number of cortical columns generated during the early embryonic period drive SA development and the number and size of cells within a column, packing density, and numbers of neuronal processes, glial processes, and synapses drive CT development (Rakic 1995; 2009). Additionally, CT and SA development are

also regulated by outer radial glial (oRG) cells which play a critical role in radial and tangential expansion of supragranular layers (Nowakowski et al. 2016). These processes are marked by dynamic patterns of gene expression. Indeed, the majority of brain-expressed genes show strong temporal changes (Kang et al. 2011) and large regional differences in expression during the prenatal period (Pletikos et al. 2014). In contrast, during the early postnatal period, there is a shift in temporal and spatial gradients resulting in relatively stable levels of gene expression over time and minimal regional differences across the cortex (Kang et al. 2011; Pletikos et al. 2014; Silbereis et al. 2016). Genes expressed at high levels midgestation are likely involved in proliferation and migration of neuronal cell types while genes expressed at high levels during late fetal and early postnatal development likely reflect the robust growth of dendrites and synapses, as well as myelination. (Stiles and Jernigan 2010). Postmortem brain transcriptomic studies have also shown that many genes associated with autism, schizophrenia, intellectual disability, and syndromic neurodevelopmental disorders exhibit elevated expression during these developmental windows (Birnbaum et al. 2015; Chen et al. 2015). Investigating genetic influences during this period is therefore crucial to our understanding of typical and atypical brain development.

In this chapter, we report findings from the first twin study of cortical thickness and surface area during infancy. We examine the genetic, shared environmental, and unique environmental contributions to individual differences in neonatal CT and SA using both global CT and SA as well as CT and SA measures in 78 cortical regions. We also assess genetic correlations among ROIs for CT and SA measures to identify regions with shared genetic architecture. Given the dynamic patterns of gene expression and the robust cortical growth within the prenatal and early postnatal period, we hypothesize that heritability estimates will be

higher for neonatal SA compared to CT. Moreover, based on the radial unit hypothesis, we predict that we will observe CT and SA to have independent genetic origins. Outcomes from this study fill a critical gap in our understanding of how genetic influences shape cortical structure during early development and provide key insight for future imaging genetic studies of cortical structure.

MATERIALS AND METHODS

Subjects

This study included 246 dizygotic and 130 monozygotic twins between the ages of 9 and 85 postnatal days, drawn from UNC's Early Brain Development Program (Gilmore, Schmitt, et al. 2010). Mothers with twin pregnancies were recruited during the second trimester of pregnancy from outpatient OB-GYN clinics in central North Carolina. Exclusion criteria included major medical illnesses in the mother or abnormal fetal ultrasounds. Zygosity was determined by polymerase chain reaction-short tandem repeat (PCR-STR) analysis of 14 loci on DNA extracted from buccal cells (BRT Laboratories, Baltimore, MD). Detailed subject demographics can be viewed in Table 3.1. After complete description of the study to subjects' parent(s), written informed consent was obtained. Study protocols were approved by the Institutional Review Board of the UNC School of Medicine.

Image Acquisition

All MRI images were collected at UNC's Biomedical Research Imaging Center using a Siemens Allegra head-only 3T scanner (N=309) or a Siemens TIM Trio 3T scanner (N=67) (Siemens Medical System, Inc., Erlangen, Germany). Infants were scanned at 37.22 ± 16.82 days post birth on average. All neonate subjects were fitted with earplugs, secured into a vacuum-fixed immobilization device, and scanned during unsedated natural sleep. Heart rate and oxygen

saturation were monitored using a pulse oximeter. On the Allegra scanner, proton density and T2 weighted structural images were acquired 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, sequence name = Type1, N = 124). For neonates who were deemed unlikely to sleep through the scan session, a "fast" turbo-spin echo sequence was collected 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, sequence name = Type2, N=185) On the Trio, subjects were initially scanned using a TSE protocol (TR=6200ms, TE1=17, TE2=116ms, flip angle=150°, spatial resolution= 1.25mm x1.25mm x1.95 mm, sequence name = Type3, N = 11) while the rest were scanned using a 3DT2 SPACE protocol (TR=3200ms, TE=406, flip angle=120°, spatial resolution= 1mmx1mmx1mm, sequence name = Type4, N=56). Because sequence parameters could have a significant influence on cortical measures, we used T2 sequence (Type1-Type4) as a covariate in all of the analyses described in this study.

Image Analysis

Cortical thickness and surface area measures were derived for all subjects using an image analysis pipeline previously described by Li et al (2016). First, all T2-weighted images were preprocessed for tissue segmentation using a standard infant-specific pipeline (Li et al. 2013). This included skull stripping and manual editing of non-brain tissue, removal of the cerebellum and brain stem, corrections for intensity inhomogeneity, and finally, a rigid alignment of all the images into an average atlas space (Shi et al. 2011). Thereafter, an infant-specific path-driven coupled level sets method (described in Wang et al. 2014)) was applied to segment gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Non-cortical regions were masked,

and tissues were divided into left and right hemispheres. A deformable surface method (Li et al. 2012; Li, Nie, et al. 2014) was then applied to the tissue segmentations to reconstruct the inner, middle, and outer cortical surfaces. The inner surface was defined as the boundary between grey and white matter and the outer surface was defined as the boundary between the grey matter and CSF. A third, middle cortical surface, was defined as the layer lying in the geometric center of the inner and outer surfaces of the cortex. The deformable surface method involved a topological correction of the WM 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 inner, middle, and outer surface.

All cortical surfaces for the left and right hemisphere were visually examined for accurate mapping. In order to generate a regional parcellation, all inner cortical surfaces were smoothed, inflated, and mapped to a standard sphere (Fischl et al. 1999). The cortical surface was parcellated into 78 regions of interest based on an infant-specific 90 region parcellation atlas (Tzourio-Mazoyer et al. 2002; Gilmore et al. 2012). Twelve regions represent subcortical structures and were therefore not examined. CT was computed for each vertex as the average value of the minimum distance from the inner to the outer surfaces and the minimum distance from the outer to the inner surfaces. SA was computed based on the central cortical surface. The average CT and total SA were calculated for each ROI based on corresponding values at each vertex. Overall total SA was computed as the total of the regional SA values and overall average CT was computed by weighting regional CT values by the corresponding surface size.

Statistical Analysis

All statistical analyses were performed in R using OpenMx, a matrix-based structural equation modeling package (Neale and Cardon 1992; Boker et al. 2011; Neale and Cardon

2013). Phenotypes of interest included: 1) overall average CT, 2) total SA, 3) regional CT in 78 ROIs, and 4) regional SA in 78 ROIs. Univariate analyses were performed using a classical ACE model, which allows for the decomposition of the observed phenotypic variance into variance explained by additive genetic (a^2), shared environmental (c^2), and unique environmental (c^2) components. Maximum likelihood was used to generate estimates of model parameters and to perform hypothesis testing (Schmitt et al. 2008). The significance of genetic and shared environmental effects was assessed by removing a parameter of interest and comparing the resulting change in the fit of the submodel against the original model. The difference in maximum likelihood asymptotically follows a χ^2 distribution, with degrees of freedom equal to the difference in the number of free parameters (Neale and Cardon 1992)

Bivariate Cholesky decomposition models were used to identify common genetic and environmental determinants between global CT, SA, and ICV, between regional CT measures, and between regional SA measures. The Cholesky decomposition model allows for the covariance between two phenotypes to be segregated into covariance resulting from either genetic or environmental sources (Neale and Cardon 1992). Covariance estimates were used to calculate genetic and environment correlations between phenotypes. These correlations represent the degree of genetic overlap between two phenotypes and are calculated as the genetic covariance of two phenotypes divided by the square root of the heritabilities of both phenotypes.

In both univariate and bivariate analyses, models for regional and total average CT were adjusted for birth weight, gestational age at birth, age at MRI, sex, paternal education, and maternal ethnicity. Models for regional SA were adjusted for birth weight, age at MRI and sex. The model for total SA was adjusted for birth weight, gestational age at birth, age at MRI, and gender. Covariates were chosen based on output from variable selection and linear mixed effects

model results for CT and SA in a large sample of neonates (see chapter 2). To account for overall brain size, total surface area was fixed for all regional surface area models and the cubed root of intracranial volume (a sum of gray matter, white matter and cerebrospinal fluid) was fixed in the models for average and regional cortical thickness. As a sensitivity analysis, univariate variance decomposition and bivariate Cholesky decomposition models were also run without adjusting for overall brain size. An additional sensitivity analysis was also performed controlling for age at MRI and sex as the main covariates. For regional analyses of CT and SA, adjustments for multiple comparisons were made using Benjamini & Hochberg method. FDR <0.05 was considered significant for each region of interest.

RESULTS

Cross-twin correlations for CT and SA are presented in Table 3.2. In general, MZ twin pairs had increased correlations when compared to DZ twin pairs.

Global CT and SA

Parameter estimates and tests of significance for global CT and SA are presented in Table 3.3. Overall, shared environmental influences had very small and nonsignificant impacts on global CT/ SA variation. Total SA was highly heritable, with genetic influences accounting for a large portion of the observed variance (0.79). For average CT, genetic influences accounted for a small (0.2) and nonsignificant proportion of the phenotypic variance. The observed genetic correlation between average CT and total SA was strong and significant ($r_G = 0.78$, see Table 3.4). To understand the impact of overall brain size on CT and SA, we also examined the heritability of intracranial volume (ICV). Genetic influences on ICV accounted for a significantly large amount of the total phenotypic variance (0.64). Significantly high genetic correlations were found between ICV and total SA ($r_G = 0.95$) and between ICV and overall

average CT (r_G = 0.69). Phenotypic (rP), common environmental (rC), and unique environmental (rE) correlations for global measures can be found in Table 3.4.

Regional CT and SA

Parameter estimates and tests of significance for regional CT and SA are presented in Tables 3.5 and 3.6 respectively. For CT, regional heritability estimates ranged from < 0.01 to 0.55 with significant genetic effects in 6 of the 78 regions. After correcting for multiple comparisons however, no regional significance was observed. Genetic correlations of regional CT ranged from -1 to 1 (Figure S3.1), with 79 significant relationships. No significant correlations were found across regions after correcting for multiple comparisons. Heritability estimates for regional SA ranged from < 0.01 to 0.76 with significant genetic influences in 20 of the 78 regions. Of these, genetic influences remained significant in 4 regions after a correction for multiple comparisons (see Table 3.6). Genetic correlations of regional SA also ranged from -1 to 1 (Figure S3.2) with 128 significant relationships. One significant correlation (between the left and right insula, r_G = 0.90) remained after FDR correction. Overall, shared environmental influences had very small and nonsignificant impacts on regional CT/ SA variation.

Secondary analyses

In the first secondary analysis, genetic influences on CT and SA were examined without adjusting for overall brain size. For regional CT, heritability estimates ranged from < 0.01 to 0.58 and were significant in 7 of the 78 ROIs (Table S3.1). No significant genetic influences remained after FDR correction. For regional SA, heritability estimates ranged from < 0.01 to 0.83 and were significant in 60 of the 78 ROIs. After correction for multiple comparisons, estimates were significant in 54 of the 78 ROIs (Table S3.2). Genetic correlations for regional CT and regional SA ranged from -1 to 1(Figures S3.3 and S3.4). For regional CT, 187 significant

correlations were found and one (between the left and right insula, $r_G = 0.94$) remained after FDR correction. For regional SA, there were 2,283 significant correlations across various regions of interest and 2,167 survived FDR correction. Shared genetic influences remained small and nonsignificant for both regional CT and SA.

Most twin studies of CT and SA are performed during childhood, adolescence, and adulthood, and often do not have access to detailed prenatal demographics that may serve as important covariates. Therefore, we performed an additional sensitivity analysis controlling for variables most often used as covariates in studies performed at later ages: brain size, age, sex, and scanner parameters. We observed significant genetic and common environmental influences on total SA (0.32 and 0.60 respectively) and on ICV (0.42 and 0.48 respectively). There were no significant genetic or common environmental influences on CT (Table S3.3). Genetic correlations were 0.72 between CT and SA, 0.95 between total SA and ICV, and 0.73 between average CT and ICV (Table S3.4). For regional CT, heritability estimates ranged from < 0.01 to 0.60 and were significant in 6 of the 78 ROIs (Table S3.5). One significant genetic influence remained after FDR correction. For regional SA, heritability estimates ranged from < 0.01 to 0.73 and were significant in 19 of the 78 ROIs (Table S3.6). After correction for multiple comparisons, estimates were significant in 4 of the 78 ROIs. Genetic correlations for regional CT and regional SA ranged from -1 to 1 but no significant correlations remained after FDR correction (Figures S3.5 and S3.6).

DISCUSSION

Utilizing a sample of 376 twin neonates, we performed the first quantitative genetic study of infant CT and SA. Our results revealed strong genetic influences on total SA and significant genetic overlap between CT and SA. Overall, findings provide a deeper understanding of CT and

SA development and contribute critical insight into how genetic influences shape cortical structure across the human lifespan.

We found that that genetic influences determine a significant portion of individual differences in neonatal total SA. Specifically, when controlling for obstetric history variables, we observed a high heritability estimate of 0.79. When controlling for variables most often used in adult studies (age, sex, and scanning protocol) the heritability estimate remained significant but was greatly reduced. Compared to adult twin and family studies, which report high estimates of 0.89 and 0.71 respectively (Panizzon et al. 2009; Winkler et al. 2010), genetic influences seem to play a significant but smaller role in explaining individual differences in total SA at birth. During early development, genetic influences driving total SA may control the tangential expansion of the cortex by impacting symmetric divisions of ventricular radial glia during early neurogenesis and outer radial glia during late neurogenesis (Rakic 2009; Nowakowski et al. 2016). Genes involved in the development of sulci, gyri, and cortico-cortical connectivity may also impact individual differences in total SA observed in our study (Lewitus et al. 2013).

In contrast to total SA, genetic influences did not explain a significant proportion of the variation observed in neonatal average CT. However, similar to total SA, the observed heritability in our neonatal sample (0.20) was smaller compared to higher heritability estimates (0.81and 0.69) reported in adults (Panizzon et al. 2009; Winkler et al. 2010). Our findings suggest that genetic influences on average CT and total SA may increase between the neonatal period and adulthood. In adults, individual differences in average CT and total SA may be related to genes impacting the number and size of neurons, glia, and synaptic machinery (de Graaf-Peters and Hadders-Algra 2006; Rakic 2009) and pathways controlling processes of synaptic pruning, myelination, and aging (Stiles and Jernigan 2010). A potential increase in heritability for total SA and average CT between

neonates and adults may also be reflective of canalization, (Lenroot and Giedd 2008; Gilmore, Schmitt, et al. 2010) the concept that heritability of a phenotype will increase as various genetic influences act over development under expected environmental conditions. To best understand how early postnatal genetic influences compare to genetic influences during later ages however, heritability studies of total SA and average CT should be performed during late childhood and adolescence.

Our most interesting and unexpected finding regarding total SA and average CT was the strong genetic overlap between these global measures. We found that variation in neonatal average CT and total SA was largely determined by the same set of genetic factors (rG = 0.78). Thus far, studies comparing CT and SA in adults have found little to no genetic associations between the two phenotypes (Panizzon et al. 2009; Winkler et al. 2010). Such reports argue that CT and SA are driven by two distinct sets of genetic influences related to distinct developmental events during early prenatal life. In contrast to these findings, our twin neonate study reveals that early genetic influences driving the columnar organization of the cortex are actually similar and overlapping. The association we observe between total SA and average CT is likely reflective of broad ranging genetic influences that control general molecular mechanisms involved in cortical development and those which coordinate the tangential and radial expansion during the fetal and early postnatal periods (Silbereis et al. 2016). In fact, developmental studies in rodents reveal that many genes involved in cortical patterning or the proliferation of founder cells also play a role in determining the thickness of the cortex by controlling neuron number and size (Korada et al. 2002; Georgala et al. 2011). Our assessment of neonatal CT and SA serves as the earliest snapshot of genetic effects on brain structure and provides evidence of a dynamic genetic relationship between these two features across different periods of development. To better understand the genetic relationship between CT and SA

during the prenatal period, comparable fetal MRI studies of global cortical structure are critical. Moreover, longitudinal studies of global cortical structure from infancy to adulthood will also provide insight into the genetic association of CT and SA across the lifespan.

At the regional level, genetic influences accounted for < 1% to 76% of variation in SA and < 1% to 55% of the variation in CT across the cortex. In adult samples, Panizzon and colleagues (2009) found genetic influences ranging from 3% to 74% for regional SA and from 20% to 76% for regional CT and Winkler et al. (2010) found genetic influences ranging from 17% to 76% regional SA and from 6% to 73% for regional CT. When comparing our findings to these studies, we note that genetic influences during infancy explain a smaller percent of the total phenotypic variation in CT and SA. Moreover, while we observe considerable heterogeneity in regional heritability estimates, genetic influences remain largely nonsignificant in our sample. The exceptions are the heritability estimates for SA in the insular cortex and precuneus, which are similar to those found in adults.

Furthermore, when examining heritability estimates across all 78 ROIs, we did not observe clear regional patterns based on structural, functional, or maturational organization. Nor did we observe meaningful patterns of regionalization when examining the genetic correlations among regions of CT and SA. Together, these results suggest that individual differences in CT and SA are likely driven by a common set of underlying genetic factors influencing cortical structure at the global level. This is in contrast to twin studies of regional CT in older populations which reveal that regional heritability estimates align with maturational patterns. Specifically, in early childhood, CT in primary sensory and motor regions is highly heritable and at older ages, heritability is higher in dorsal prefrontal and temporal lobes (Lenroot et al. 2009). Moreover, twin studies of genetic regionalization in older adults have found up to 12 genetically similar

clusters. Genetic divisions of SA follow an anterior- posterior division with spatially contiguous regions being genetically correlated. Genetic divisions of CT follow a basic dorsal-ventral pattern and are driven by similarities of maturational timing (Chen et al. 2011; 2012; 2013). The lack of significant regional genetic patterns in our sample is in keeping with studies of cortical gene expression which suggest that there are minimal interareal differences in gene expression across the cortex during infancy (Kang et al. 2011; Pletikos et al. 2014; Silbereis et al. 2016). This period is characterized by general neuronal and glial proliferation transcriptional programs (Pletikos et al. 2014) that are involved in the construction and maturation of neuronal circuitry and are sensitive to experience and external inputs from the environment. Significant regional differences in genetic studies of CT and SA observed in studies of older populations are likely reflections of increasing interareal differences across the cortex during later time periods.

By performing the first twin study of infant CT and SA, we show genes are important determinants of individual differences in neonatal cortical structure. Our findings provide important data points previously unavailable for the understanding of genetic contributions to CT and SA across the lifespan. Strengths of this study include a unique sample, extensive demographic data, and the application of cutting-edge infant image analysis methods. Limitations of this study are largely centered around the challenges of infant neuroimaging. While offering many unprecedented opportunities to study neurodevelopment, our pediatric population may be underpowered to detect significant shared environmental effects. Additionally, our use of predefined cortical regions may limit our ability to find genetic relationships across regions of the cortex, if those relationships do not adhere to classic anatomical boundaries. However, it should be noted that cortical parcellations based on genetic data do reveal genetic divisions that largely correspond to anatomical divisions similar to those

used in the current study (Chen et al. 2012). Future studies should focus on pursuing a non-biased approach of using vertex-based analysis to generate continuous maps of genetic influences on CT and SA. Moreover, because results from our analysis are based on one infant dataset, they may not be generalizable to other pediatric populations. However, because there are no genetic investigations of CT or SA in young typically developing infants, results from this study are highly informative. Findings provide cortical regions to prioritize for future imaging genetic studies and valuable targets to better understand genetic processes that contribute to psychiatric and developmental disorders.

Table 3.1. Demographics for Neonate Twin Sample

Continuous Variables		Average	SD
Birth weight		2409.82	534.84
Gestational Age at Birth		249.67	16.86
Postnatal Age at MRI		37.22	16.82
5 Minute Apgar		8.62	0.75
Maternal Education		14.99	3.39
Paternal Education		14.77	3.52
Maternal Age		30.49	5.6
Paternal Age		32.89	6.83
Categorical Variables		**N**	**%**
Zygosity	Monozygotic	130	35%
	Dizygotic	246	65%
NICU Stay > 24 hours	No	249	66%
	Yes	127	34%
Sex	Male	214	57%
	Female	162	43%
Delivery Method	Vaginal	104	28%
	C-section	272	72%
Household Income	High	106	28%
	Mid	108	29%
	Low	142	38%
	Missing	20	5%
Maternal Ethnicity	Caucasian	284	76%
	African American	84	22%
	Asian	6	2%
	Native American	2	1%
Paternal Ethnicity	Caucasian	276	73%
	African American	84	22%
	Asian	14	4%
	Native American	2	1%
Maternal Psychiatric History	No	254	68%
	Yes	122	32%
Paternal Psychiatric History	No	338	90%
	Yes	38	10%
Maternal Smoking	No	356	95%
	Yes	20	5%
T2 Sequence Type	Type 1	124	33%
	Type 2	185	49%
	Type 3	11	3%
	Type 4	56	15%

Table 3.2. Co-twin Correlations for MZ and DZ pairs

Region of Interest	Cortical Thickness		Surface Area	
	DZ	MZ	DZ	MZ
Total SA	--	--	0.74	0.93
Average Thickness	0.66	0.77	--	--
Precentral_L	0.52	0.54	0.54	0.77
Precentral_R	0.48	0.64	0.56	0.82
Frontal_Sup_L	0.54	0.7	0.59	0.55
Frontal_Sup_R	0.62	0.71	0.63	0.76
Frontal_Sup_Orb_L	0.46	0.53	0.44	0.63
Frontal_Sup_Orb_R	0.45	0.6	0.61	0.65
Frontal_Mid_L	0.54	0.63	0.56	0.82
Frontal_Mid_R	0.55	0.58	0.66	0.83
Frontal_Mid_Orb_L	0.25	0.18	0.4	0.72
Frontal_Mid_Orb_R	0.29	0.53	0.55	0.79
Frontal_Inf_Oper_L	0.24	0.44	0.49	0.6
Frontal_Inf_Oper_R	0.17	0.44	0.4	0.64
Frontal_Inf_Tri_L	0.35	0.58	0.4	0.6
Frontal_Inf_Tri_R	0.3	0.36	0.39	0.73
Frontal_Inf_Orb_L	0.46	0.5	0.55	0.88
Frontal_Inf_Orb_R	0.36	0.56	0.55	0.85
Rolandic_Oper_L	0.39	0.51	0.48	0.79
Rolandic_Oper_R	0.26	0.38	0.55	0.75
Supp_Motor_Area_L	0.41	0.6	0.57	0.69
Supp_Motor_Area_R	0.42	0.48	0.6	0.78
Olfactory_L	0.23	0.19	0.18	0.56
Olfactory_R	0.3	0.29	0.23	0.69
Frontal_Sup_Medial_L	0.37	0.55	0.5	0.61
Frontal_Sup_Medial_R	0.31	0.53	0.62	0.79
Frontal_Med_Orb_L	-0.03	0.27	0.28	0.4
Frontal_Med_Orb_R	0.21	0.43	0.56	0.77
Rectus_L	0.13	0.51	0.32	0.62
Rectus_R	0.12	0.36	0.51	0.71
Insula_L	0.39	0.71	0.59	0.83
Insula_R	0.45	0.72	0.62	0.85
Cingulum_Ant_L	0.27	0.36	0.36	0.67
Cingulum_Ant_R	0.39	0.2	0.62	0.85
Cingulum_Mid_L	0.39	0.58	0.47	0.72
Cingulum_Mid_R	0.44	0.48	0.59	0.89
Cingulum_Post_L	0.05	0.31	0.29	0.71
Cingulum_Post_R	0.23	0.17	0.38	0.58
ParaHippocampal_L	0.22	0.59	0.2	0.54
ParaHippocampal_R	0.04	0.45	0.38	0.74
Calcarine_L	0.44	0.39	0.45	0.67
Calcarine_R	0.32	0.35	0.32	0.69
Cuneus_L	0.18	0.29	0.34	0.61
Cuneus_R	0.24	0.05	0.33	0.69
Lingual_L	0.42	0.24	0.54	0.73
Lingual_R	0.47	0.27	0.69	0.82
Occipital_Sup_L	0.42	0.2	0.42	0.67
Occipital_Sup_R	0.21	0.19	0.46	0.63
Occipital_Mid_L	0.47	0.46	0.59	0.74
Occipital_Mid_R	0.24	0.33	0.57	0.67
Occipital_Inf_L	0.18	0.32	0.45	0.55

Occipital_Inf_R	0.33	0.51	0.48	0.61
Fusiform_L	0.29	0.52	0.51	0.55
Fusiform_R	0.39	0.47	0.5	0.71
Postcentral_L	0.42	0.65	0.47	0.71
Postcentral_R	0.41	0.58	0.62	0.81
Parietal_Sup_L	0.48	0.51	0.41	0.49
Parietal_Sup_R	0.37	0.28	0.67	0.86
Parietal_Inf_L	0.31	0.4	0.51	0.65
Parietal_Inf_R	0.31	0.43	0.53	0.71
SupraMarginal_L	0.17	0.3	0.35	0.55
SupraMarginal_R	0.33	0.31	0.54	0.78
Angular_L	-0.01	0.19	0.31	0.6
Angular_R	0.36	0.5	0.54	0.69
Precuneus_L	0.22	0.48	0.53	0.84
Precuneus_R	0.23	0.26	0.71	0.88
Paracentral_Lobule_L	0.27	0.55	0.3	0.62
Paracentral_Lobule_R	0.09	0.38	0.45	0.69
Heschl_L	0.11	0.36	0.09	0.62
Heschl_R	0.31	0.59	0.28	0.59
Temporal_Sup_L	0.25	0.48	0.51	0.81
Temporal_Sup_R	0.17	0.54	0.66	0.84
Temporal_Pole_Sup_L	0.16	0.4	0.56	0.81
Temporal_Pole_Sup_R	0.24	0.25	0.65	0.75
Temporal_Mid_L	0.3	0.42	0.59	0.76
Temporal_Mid_R	0.41	0.58	0.61	0.86
Temporal_Pole_Mid_L	0.11	0.32	0.37	0.72
Temporal_Pole_Mid_R	0.3	0.49	0.5	0.75
Temporal_Inf_L	0.24	0.68	0.45	0.74
Temporal_Inf_R	0.34	0.55	0.64	0.85

Table 3.3. Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Global Measures

Region of Interest	Variance Components			Hypothesis test (P values)		
	a^2	c^2	e^2	A	C	A and C
Total SA	0.79	0.11	0.10	***< 0.001***	0.401	***< 0.001***
Average CT	0.20	0.23	0.57	> 0.999	> 0.999	***< 0.001***
ICV	0.64	0.19	0.17	***< 0.001***	0.199	***< 0.001***

A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

Table 3.4. Bivariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Global Measures

Region of Interests		Correlation Coefficient				Hypothesis test (P values)				
1	**2**	**rP**	**rG**	**rC**	**rE**	**A**	**C**	**E**	**A and C**	**A, C, and E**
Total SA	Average CT	0.29	0.78	0.13	-0.22	***0.005***	0.840	0.091	***< 0.001***	***< 0.001***
Total SA	ICV	0.85	0.95	0.8	0.51	***< 0.001***	0.611	***< 0.001***	***< 0.001***	***< 0.001***
Average CT	ICV	0.56	0.69	0.77	0.37	***0.029***	0.383	***0.003***	***< 0.001***	***< 0.001***

A= test of genetic covariance; C = test of shared environmental covariance; A and C = test of familial covariance (genetic + environmental); A, C, and E = test of all and any covariance

Table 3.5. Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Regional CT Measures

Region of Interest	Variance Components			Hypothesis test P values			Hypothesis test Q values		
	a^2	c^2	e^2	A	C	A and C	A	C	A and C
Precentral_L	0.04	0.19	0.77	0.896	0.356	***0.012***	1.000	1.000	***0.030***
Precentral_R	0.38	< 0.01	0.62	0.200	0.995	***0.002***	0.698	1.000	***0.009***
Frontal_Sup_L	0.03	0.29	0.68	0.915	0.139	***< 0.001***	1.000	1.000	***0.001***
Frontal_Sup_R	< 0.01	0.38	0.62	1.000	***0.028***	***< 0.001***	1.000	1.000	***< 0.001***
Frontal_Sup_Orb_L	< 0.01	0.25	0.75	1.000	0.196	***0.003***	1.000	1.000	***0.010***
Frontal_Sup_Orb_R	0.36	< 0.01	0.64	0.100	1.000	***0.001***	0.668	1.000	***0.007***
Frontal_Mid_L	< 0.01	0.20	0.80	1.000	0.192	***0.022***	1.000	1.000	0.050
Frontal_Mid_R	< 0.01	0.21	0.79	1.000	0.109	***0.017***	1.000	1.000	***0.040***
Frontal_Mid_Orb_L	< 0.01	< 0.01	1.00	1.000	0.964	0.999	1.000	1.000	1.000
Frontal_Mid_Orb_R	0.29	< 0.01	0.71	0.200	1.000	***0.041***	0.698	1.000	0.083
Frontal_Inf_Oper_L	0.14	< 0.01	0.86	0.433	1.000	0.345	1.000	1.000	0.454
Frontal_Inf_Oper_R	0.04	< 0.01	0.96	0.732	1.000	0.943	1.000	1.000	0.993
Frontal_Inf_Tri_L	0.26	< 0.01	0.74	0.115	1.000	***0.016***	0.685	1.000	***0.040***
Frontal_Inf_Tri_R	0.14	< 0.01	0.86	0.531	1.000	0.360	1.000	1.000	0.466
Frontal_Inf_Orb_L	< 0.01	0.18	0.82	1.000	0.295	***0.049***	1.000	1.000	0.096
Frontal_Inf_Orb_R	0.12	< 0.01	0.88	0.495	1.000	0.568	1.000	1.000	0.680
Rolandic_Oper_L	0.20	0.14	0.66	0.461	0.490	***0.001***	1.000	1.000	***0.003***
Rolandic_Oper_R	0.16	< 0.01	0.84	0.407	1.000	0.305	1.000	1.000	0.408
Supp_Motor_Area_L	0.20	0.14	0.66	0.515	0.485	***0.001***	1.000	1.000	***0.006***
Supp_Motor_Area_R	< 0.01	0.22	0.78	1.000	0.153	***0.009***	1.000	1.000	***0.026***
Olfactory_L	< 0.01	0.14	0.86	1.000	0.443	0.169	1.000	1.000	0.258
Olfactory_R	< 0.01	0.07	0.93	1.000	0.501	0.632	1.000	1.000	0.713
Frontal_Sup_Medial_L	< 0.01	0.07	0.93	1.000	0.524	0.601	1.000	1.000	0.698
Frontal_Sup_Medial_R	0.13	< 0.01	0.87	0.379	1.000	0.424	1.000	1.000	0.531
Frontal_Med_Orb_L	< 0.01	< 0.01	1.00	1.000	1.000	1.000	1.000	1.000	1.000
Frontal_Med_Orb_R	0.21	< 0.01	0.79	0.395	1.000	0.138	1.000	1.000	0.219
Rectus_L	0.24	< 0.01	0.76	0.086	1.000	***0.035***	0.668	1.000	0.074
Rectus_R	0.11	< 0.01	0.89	0.564	1.000	0.578	1.000	1.000	0.682
Insula_L	0.41	< 0.01	0.59	***0.006***	1.000	***< 0.001***	0.248	1.000	***0.003***
Insula_R	0.55	< 0.01	0.45	***0.001***	1.000	***< 0.001***	0.076	1.000	***< 0.001***
Cingulum_Ant_L	0.32	< 0.01	0.68	0.271	0.990	***0.008***	0.793	1.000	***0.022***
Cingulum_Ant_R	< 0.01	0.20	0.80	1.000	0.117	***0.022***	1.000	1.000	0.050
Cingulum_Mid_L	0.43	< 0.01	0.57	0.065	1.000	***< 0.001***	0.668	1.000	***< 0.001***
Cingulum_Mid_R	0.02	0.20	0.78	0.943	0.367	***0.011***	1.000	1.000	***0.030***
Cingulum_Post_L	0.02	< 0.01	0.98	0.875	1.000	0.988	1.000	1.000	1.000
Cingulum_Post_R	< 0.01	0.10	0.90	1.000	0.495	0.370	1.000	1.000	0.472
ParaHippocampal_L	0.44	< 0.01	0.56	***0.014***	1.000	***< 0.001***	0.283	1.000	***0.002***
ParaHippocampal_R	0.28	< 0.01	0.72	***0.048***	1.000	0.064	0.638	1.000	0.116
Calcarine_L	< 0.01	0.19	0.81	1.000	0.369	***0.036***	1.000	1.000	0.075
Calcarine_R	0.13	0.08	0.79	0.658	0.717	0.069	1.000	1.000	0.121
Cuneus_L	0.13	0.05	0.83	0.664	0.837	0.174	1.000	1.000	0.259
Cuneus_R	< 0.01	0.13	0.87	1.000	0.293	0.189	1.000	1.000	0.276
Lingual_L	< 0.01	0.24	0.76	1.000	0.057	***0.005***	1.000	1.000	***0.016***
Lingual_R	< 0.01	0.28	0.72	1.000	0.094	***< 0.001***	1.000	1.000	***0.003***
Occipital_Sup_L	< 0.01	0.24	0.76	1.000	0.097	***0.005***	1.000	1.000	***0.016***
Occipital_Sup_R	< 0.01	0.12	0.88	1.000	0.402	0.272	1.000	1.000	0.377
Occipital_Mid_L	0.01	0.20	0.78	0.962	0.330	***0.013***	1.000	1.000	***0.032***
Occipital_Mid_R	0.08	< 0.01	0.92	0.407	1.000	0.710	1.000	1.000	0.789
Occipital_Inf_L	0.11	< 0.01	0.89	0.519	1.000	0.618	1.000	1.000	0.708
Occipital_Inf_R	0.37	< 0.01	0.63	0.156	1.000	***0.002***	0.698	1.000	***0.009***

Fusiform_L	0.33	< 0.01	0.67	0.130	1.000	***0.005***	0.685	1.000	***0.016***
Fusiform_R	0.03	0.33	0.64	0.904	0.085	***< 0.001***	1.000	1.000	***< 0.001***
Postcentral_L	0.38	< 0.01	0.62	0.127	1.000	***0.001***	0.685	1.000	***0.004***
Postcentral_R	0.17	< 0.01	0.83	0.271	1.000	0.226	0.793	1.000	0.319
Parietal_Sup_L	< 0.01	0.28	0.72	1.000	0.185	***0.001***	1.000	1.000	***0.004***
Parietal_Sup_R	< 0.01	0.14	0.86	1.000	0.154	0.170	1.000	1.000	0.258
Parietal_Inf_L	0.23	< 0.01	0.77	0.243	1.000	0.056	0.793	1.000	0.108
Parietal_Inf_R	0.03	0.10	0.87	0.940	0.666	0.286	1.000	1.000	0.389
SupraMarginal_L	0.04	0.06	0.90	0.889	0.787	0.478	1.000	1.000	0.581
SupraMarginal_R	0.16	0.07	0.77	0.623	0.748	0.063	1.000	1.000	0.115
Angular_L	< 0.01	< 0.01	1.00	1.000	1.000	1.000	1.000	1.000	1.000
Angular_R	0.26	< 0.01	0.74	0.203	1.000	***0.025***	0.698	1.000	0.054
Precuneus_L	0.22	< 0.01	0.78	0.188	1.000	0.095	0.698	1.000	0.156
Precuneus_R	0.13	< 0.01	0.87	0.560	1.000	0.443	1.000	1.000	0.547
Paracentral_Lobule_L	0.33	< 0.01	0.67	0.141	1.000	***0.003***	0.696	1.000	***0.010***
Paracentral_Lobule_R	0.04	< 0.01	0.96	0.711	1.000	0.933	1.000	1.000	0.993
Heschl_L	0.05	< 0.01	0.95	0.712	1.000	0.876	1.000	1.000	0.961
Heschl_R	0.43	< 0.01	0.57	***0.014***	1.000	***< 0.001***	0.283	1.000	***0.003***
Temporal_Sup_L	0.36	< 0.01	0.64	0.088	1.000	***0.003***	0.668	1.000	***0.010***
Temporal_Sup_R	0.22	< 0.01	0.78	0.101	1.000	0.138	0.668	1.000	0.219
Temporal_Pole_Sup_L	0.09	0.07	0.84	0.762	0.760	0.194	1.000	1.000	0.278
Temporal_Pole_Sup_R	< 0.01	0.16	0.84	1.000	0.385	0.092	1.000	1.000	0.155
Temporal_Mid_L	0.23	< 0.01	0.77	0.175	1.000	0.058	0.698	1.000	0.110
Temporal_Mid_R	0.35	< 0.01	0.65	0.100	1.000	***0.002***	0.668	1.000	***0.008***
Temporal_Pole_Mid_L	0.04	< 0.01	0.96	0.646	1.000	0.900	1.000	1.000	0.974
Temporal_Pole_Mid_R	0.31	< 0.01	0.69	0.186	1.000	***0.005***	0.698	1.000	***0.016***
Temporal_Inf_L	0.37	< 0.01	0.63	***0.022***	1.000	***< 0.001***	0.347	1.000	***0.003***
Temporal_Inf_R	0.24	< 0.01	0.76	0.253	1.000	0.073	0.793	1.000	0.126

A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

Table 3.6. Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Regional SA Measures

Region of Interest	Variance Components			Hypothesis test P values			Hypothesis test Q values		
	a^2	c^2	e^2	A	C	A and C	A	C	A and C
Precentral_L	0.25	0.13	0.62	0.353	0.498	***< 0.001***	0.521	1.000	***0.001***
Precentral_R	0.14	0.20	0.66	0.605	0.319	***< 0.001***	0.705	1.000	***0.001***
Frontal_Sup_L	0.02	0.18	0.79	0.937	0.384	***0.021***	1.000	1.000	***0.034***
Frontal_Sup_R	0.18	0.15	0.67	0.508	0.455	***0.001***	0.647	1.000	***0.002***
Frontal_Sup_Orb_L	0.32	< 0.01	0.68	0.081	1.000	***0.009***	0.221	1.000	***0.015***
Frontal_Sup_Orb_R	0.03	0.01	0.97	0.927	0.982	0.942	1.000	1.000	0.966
Frontal_Mid_L	0.38	< 0.01	0.62	***0.017***	1.000	***0.002***	0.127	1.000	***0.004***
Frontal_Mid_R	0.27	0.20	0.53	0.265	0.256	***< 0.001***	0.445	1.000	***< 0.001***
Frontal_Mid_Orb_L	0.20	< 0.01	0.80	0.264	1.000	0.158	0.445	1.000	0.190
Frontal_Mid_Orb_R	0.29	< 0.01	0.71	***0.035***	1.000	***0.016***	0.169	1.000	***0.026***
Frontal_Inf_Oper_L	0.07	< 0.01	0.93	0.607	1.000	0.772	0.705	1.000	0.824
Frontal_Inf_Oper_R	0.05	< 0.01	0.95	0.674	1.000	0.915	0.761	1.000	0.951
Frontal_Inf_Tri_L	0.08	< 0.01	0.92	0.575	1.000	0.723	0.689	1.000	0.793
Frontal_Inf_Tri_R	0.31	< 0.01	0.69	0.172	1.000	***0.011***	0.332	1.000	***0.019***
Frontal_Inf_Orb_L	0.56	< 0.01	0.44	***< 0.001***	1.000	***< 0.001***	***0.005***	1.000	***< 0.001***
Frontal_Inf_Orb_R	0.51	< 0.01	0.49	***0.020***	1.000	***< 0.001***	0.133	1.000	***< 0.001***
Rolandic_Oper_L	0.33	< 0.01	0.67	0.054	1.000	***0.006***	0.169	1.000	***0.012***
Rolandic_Oper_R	0.44	< 0.01	0.56	0.056	1.000	***< 0.001***	0.169	1.000	***0.001***
Supp_Motor_Area_L	0.38	0.02	0.60	0.160	0.906	***< 0.001***	0.332	1.000	***0.001***
Supp_Motor_Area_R	0.17	0.15	0.68	0.558	0.458	***0.001***	0.687	1.000	***0.003***
Olfactory_L	0.10	< 0.01	0.90	0.384	1.000	0.685	0.532	1.000	0.762
Olfactory_R	0.26	< 0.01	0.74	***0.045***	1.000	***0.040***	0.169	1.000	0.055
Frontal_Sup_Medial_L	0.28	< 0.01	0.72	0.140	1.000	***0.040***	0.316	1.000	0.055
Frontal_Sup_Medial_R	0.08	< 0.01	0.92	0.460	1.000	0.761	0.596	1.000	0.824
Frontal_Med_Orb_L	< 0.01	0.05	0.95	1.000	0.490	0.788	1.000	1.000	0.830
Frontal_Med_Orb_R	0.27	0.06	0.67	0.356	0.761	***0.004***	0.521	1.000	***0.008***
Rectus_L	0.24	< 0.01	0.76	0.134	1.000	0.110	0.314	1.000	0.141
Rectus_R	0.09	0.09	0.83	0.783	0.690	0.138	0.871	1.000	0.173
Insula_L	0.76	< 0.01	0.24	***< 0.001***	1.000	***< 0.001***	***0.001***	1.000	***< 0.001***
Insula_R	0.64	< 0.01	0.36	***< 0.001***	1.000	***< 0.001***	***0.005***	1.000	***< 0.001***
Cingulum_Ant_L	0.23	< 0.01	0.77	0.149	1.000	0.141	0.328	1.000	0.174
Cingulum_Ant_R	0.31	< 0.01	0.69	***0.045***	1.000	***0.032***	0.169	1.000	***0.047***
Cingulum_Mid_L	0.34	< 0.01	0.66	0.191	1.000	***0.008***	0.342	1.000	***0.014***
Cingulum_Mid_R	0.38	< 0.01	0.62	***0.024***	1.000	***0.003***	0.136	1.000	***0.006***
Cingulum_Post_L	0.29	< 0.01	0.71	0.055	1.000	***0.030***	0.169	1.000	***0.045***
Cingulum_Post_R	0.12	< 0.01	0.88	0.565	1.000	0.537	0.687	1.000	0.606
ParaHippocampal_L	0.21	< 0.01	0.79	0.135	1.000	0.163	0.314	1.000	0.193
ParaHippocampal_R	0.24	0.14	0.62	0.392	0.468	***< 0.001***	0.534	1.000	***0.001***
Calcarine_L	0.25	0.28	0.48	0.273	0.114	***< 0.001***	0.450	1.000	***< 0.001***
Calcarine_R	0.49	0.01	0.50	0.054	0.971	***< 0.001***	0.169	1.000	***< 0.001***
Cuneus_L	0.26	< 0.01	0.74	0.321	1.000	***0.041***	0.507	1.000	0.055
Cuneus_R	0.27	< 0.01	0.73	0.107	1.000	0.055	0.273	1.000	0.073
Lingual_L	0.53	0.02	0.45	***0.039***	0.899	***< 0.001***	0.169	1.000	***< 0.001***
Lingual_R	0.17	0.38	0.45	0.402	***0.023***	***< 0.001***	0.539	1.000	***< 0.001***
Occipital_Sup_L	0.45	< 0.01	0.55	***0.010***	1.000	***< 0.001***	0.100	1.000	***< 0.001***
Occipital_Sup_R	0.47	< 0.01	0.53	***0.036***	1.000	***< 0.001***	0.169	1.000	***0.001***
Occipital_Mid_L	0.48	< 0.01	0.52	***0.018***	1.000	***< 0.001***	0.127	1.000	***< 0.001***
Occipital_Mid_R	< 0.01	0.26	0.74	1.000	0.168	***0.002***	1.000	1.000	***0.004***
Occipital_Inf_L	< 0.01	0.12	0.88	1.000	0.529	0.267	1.000	1.000	0.306
Occipital_Inf_R	0.25	< 0.01	0.75	0.383	1.000	***0.035***	0.532	1.000	0.051

Fusiform_L	0.30	< 0.01	0.70	0.190	1.000	***0.006***	0.342	1.000	***0.011***
Fusiform_R	0.27	< 0.01	0.73	0.300	1.000	***0.025***	0.484	1.000	***0.038***
Postcentral_L	0.37	< 0.01	0.63	0.053	1.000	***0.001***	0.169	1.000	***0.002***
Postcentral_R	0.34	< 0.01	0.66	0.117	1.000	***0.006***	0.288	1.000	***0.011***
Parietal_Sup_L	< 0.01	< 0.01	1.00	1.000	1.000	1.000	1.000	1.000	1.000
Parietal_Sup_R	0.50	0.04	0.46	0.050	0.827	***< 0.001***	0.169	1.000	***< 0.001***
Parietal_Inf_L	< 0.01	0.29	0.71	1.000	0.112	***< 0.001***	1.000	1.000	***0.001***
Parietal_Inf_R	0.27	< 0.01	0.73	0.342	1.000	***0.020***	0.521	1.000	***0.032***
SupraMarginal_L	< 0.01	< 0.01	1.00	1.000	1.000	1.000	1.000	1.000	1.000
SupraMarginal_R	0.37	< 0.01	0.63	***0.010***	1.000	***0.001***	0.100	1.000	***0.003***
Angular_L	0.20	< 0.01	0.80	0.163	1.000	0.158	0.332	1.000	0.190
Angular_R	0.21	0.10	0.69	0.430	0.657	***0.001***	0.566	1.000	***0.003***
Precuneus_L	0.50	< 0.01	0.50	***0.004***	1.000	***< 0.001***	0.067	1.000	***< 0.001***
Precuneus_R	0.61	< 0.01	0.39	***0.001***	1.000	***< 0.001***	***0.026***	1.000	***< 0.001***
Paracentral_Lobule_L	0.41	< 0.01	0.59	***0.022***	1.000	***0.004***	0.136	1.000	***0.008***
Paracentral_Lobule_R	0.31	< 0.01	0.69	0.078	1.000	***0.008***	0.221	1.000	***0.014***
Heschl_L	0.40	< 0.01	0.60	***0.010***	1.000	***0.002***	0.100	1.000	***0.005***
Heschl_R	0.19	< 0.01	0.81	0.210	1.000	0.174	0.368	1.000	0.202
Temporal_Sup_L	0.44	< 0.01	0.56	0.096	1.000	***< 0.001***	0.252	1.000	***0.001***
Temporal_Sup_R	0.44	< 0.01	0.56	0.052	1.000	***< 0.001***	0.169	1.000	***< 0.001***
Temporal_Pole_Sup_L	0.24	0.09	0.66	0.366	0.656	***0.001***	0.526	1.000	***0.002***
Temporal_Pole_Sup_R	0.17	0.10	0.72	0.542	0.627	***0.007***	0.680	1.000	***0.012***
Temporal_Mid_L	0.34	< 0.01	0.66	***0.018***	1.000	***0.006***	0.127	1.000	***0.011***
Temporal_Mid_R	0.31	< 0.01	0.69	0.181	1.000	***0.023***	0.340	1.000	***0.035***
Temporal_Pole_Mid_L	0.12	0.20	0.67	0.639	0.330	***< 0.001***	0.732	1.000	***0.001***
Temporal_Pole_Mid_R	0.23	< 0.01	0.77	0.170	1.000	0.095	0.332	1.000	0.123
Temporal_Inf_L	0.24	< 0.01	0.76	0.170	1.000	0.082	0.332	1.000	0.108
Temporal_Inf_R	0.44	0.08	0.48	0.061	0.648	***< 0.001***	0.178	1.000	***< 0.001***

A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

Table S3.1. Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Regional CT Measures Without Adjustments for Brain Size

Region of Interest	Variance Components			Hypothesis test P values			Hypothesis test Q values		
	a^2	c^2	e^2	A	C	A and C	A	C	A and C
Precentral_L	0.08	0.26	0.66	0.752	0.18	***< 0.001***	1	1	***< 0.001***
Precentral_R	0.38	0.07	0.55	0.143	0.693	***< 0.001***	0.51	1	***< 0.001***
Frontal_Sup_L	0.18	0.26	0.55	0.438	0.157	***< 0.001***	0.804	1	***< 0.001***
Frontal_Sup_R	0.11	0.4	0.49	0.598	***0.019***	***< 0.001***	0.942	0.952	***< 0.001***
Frontal_Sup_Orb_L	0.06	0.23	0.71	0.825	0.251	***0.001***	1	1	***0.002***
Frontal_Sup_Orb_R	0.4	< 0.01	0.6	0.087	1	***< 0.001***	0.51	1	***0.001***
Frontal_Mid_L	0.07	0.27	0.66	0.782	0.166	***< 0.001***	1	1	***< 0.001***
Frontal_Mid_R	< 0.01	0.29	0.71	1	0.124	***< 0.001***	1	0.952	***0.001***
Frontal_Mid_Orb_L	< 0.01	0.07	0.93	1	0.486	0.624	1	1	0.657
Frontal_Mid_Orb_R	0.31	< 0.01	0.69	0.124	1	***0.017***	0.51	1	***0.032***
Frontal_Inf_Oper_L	0.2	0.04	0.76	0.48	0.854	***0.029***	0.822	1	***0.048***
Frontal_Inf_Oper_R	0.14	< 0.01	0.86	0.363	1	0.465	0.796	1	0.511
Frontal_Inf_Tri_L	0.39	< 0.01	0.61	0.097	1	***< 0.001***	0.51	1	***< 0.001***
Frontal_Inf_Tri_R	0.25	< 0.01	0.75	0.381	0.983	***0.026***	0.796	1	***0.043***
Frontal_Inf_Orb_L	0.07	0.26	0.67	0.805	0.192	***< 0.001***	1	1	***< 0.001***
Frontal_Inf_Orb_R	0.29	< 0.01	0.71	0.14	1	***0.02***	0.51	1	***0.036***
Rolandic_Oper_L	0.18	0.19	0.64	0.489	0.349	***< 0.001***	0.822	1	***< 0.001***
Rolandic_Oper_R	0.2	< 0.01	0.8	0.432	1	0.145	0.804	1	0.188
Supp_Motor_Area_L	0.35	0.11	0.54	0.185	0.561	***< 0.001***	0.542	1	***< 0.001***
Supp_Motor_Area_R	< 0.01	0.31	0.69	1	0.105	***< 0.001***	1	0.952	***< 0.001***
Olfactory_L	< 0.01	0.14	0.86	1	0.468	0.179	1	1	0.224
Olfactory_R	< 0.01	0.1	0.9	1	0.396	0.382	1	1	0.431
Frontal_Sup_Medial_L	0.25	0.01	0.74	0.404	0.952	***0.036***	0.804	1	0.057
Frontal_Sup_Medial_R	0.23	< 0.01	0.77	0.238	1	0.065	0.606	1	0.09
Frontal_Med_Orb_L	0.02	< 0.01	0.98	0.839	1	0.98	1	1	0.992
Frontal_Med_Orb_R	0.21	< 0.01	0.79	0.365	1	0.144	0.796	1	0.188
Rectus_L	0.27	< 0.01	0.73	0.067	1	***0.016***	0.482	1	***0.03***
Rectus_R	0.18	< 0.01	0.82	0.347	1	0.211	0.796	1	0.257
Insula_L	0.55	< 0.01	0.45	***0.001***	1	***< 0.001***	0.07	1	***< 0.001***
Insula_R	0.58	< 0.01	0.42	***0.002***	1	***< 0.001***	0.07	1	***< 0.001***
Cingulum_Ant_L	0.33	< 0.01	0.67	0.232	1	***0.005***	0.606	1	***0.011***
Cingulum_Ant_R	< 0.01	0.21	0.79	1	0.104	***0.015***	1	0.952	***0.03***
Cingulum_Mid_L	0.35	0.13	0.53	0.15	0.501	***< 0.001***	0.51	1	***< 0.001***
Cingulum_Mid_R	0.15	0.21	0.64	0.565	0.314	***< 0.001***	0.91	1	***< 0.001***
Cingulum_Post_L	0.11	< 0.01	0.89	0.31	1	0.586	0.742	1	0.625
Cingulum_Post_R	< 0.01	0.14	0.86	1	0.319	0.164	1	1	0.209
ParaHippocampal_L	0.47	< 0.01	0.53	***0.012***	1	***< 0.001***	0.192	1	***< 0.001***
ParaHippocampal_R	0.3	< 0.01	0.7	***0.037***	1	***0.045***	0.42	1	0.069
Calcarine_L	0.03	0.21	0.76	0.929	0.316	***0.008***	1	1	***0.016***
Calcarine_R	0.13	0.11	0.76	0.655	0.586	***0.019***	0.962	1	***0.035***
Cuneus_L	0.19	0.01	0.8	0.516	0.962	0.123	0.848	1	0.168
Cuneus_R	< 0.01	0.13	0.87	1	0.334	0.2	1	1	0.246
Lingual_L	< 0.01	0.26	0.74	1	***0.038***	***0.001***	1	0.952	***0.003***
Lingual_R	< 0.01	0.29	0.71	1	0.133	***< 0.001***	1	0.952	***0.001***
Occipital_Sup_L	< 0.01	0.24	0.76	1	0.093	***0.004***	1	0.952	***0.01***
Occipital_Sup_R	< 0.01	0.12	0.88	1	0.374	0.271	1	1	0.315
Occipital_Mid_L	0.01	0.22	0.77	0.979	0.292	***0.008***	1	1	***0.017***
Occipital_Mid_R	0.08	< 0.01	0.92	0.383	1	0.683	0.796	1	0.71
Occipital_Inf_L	0.13	< 0.01	0.87	0.48	1	0.48	0.822	1	0.52
Occipital_Inf_R	0.38	< 0.01	0.62	0.162	1	***0.002***	0.51	1	***0.004***

Fusiform_L	0.37	< 0.01	0.63	0.148	1	***0.001***	0.51	1	***0.003***
Fusiform_R	0.1	0.31	0.59	0.698	0.093	***< 0.001***	0.985	0.952	***< 0.001***
Postcentral_L	0.51	< 0.01	0.49	***0.008***	1	***< 0.001***	0.192	1	***< 0.001***
Postcentral_R	0.31	< 0.01	0.69	0.138	1	***0.006***	0.51	1	***0.013***
Parietal_Sup_L	< 0.01	0.38	0.62	1	0.064	***< 0.001***	1	0.952	***< 0.001***
Parietal_Sup_R	< 0.01	0.17	0.83	1	0.121	0.06	1	0.952	0.086
Parietal_Inf_L	0.32	< 0.01	0.68	0.144	1	***0.004***	0.51	1	***0.01***
Parietal_Inf_R	0.26	0.03	0.71	0.412	0.888	***0.024***	0.804	1	***0.041***
SupraMarginal_L	0.15	0.01	0.84	0.62	0.974	0.296	0.942	1	0.339
SupraMarginal_R	0.16	0.09	0.75	0.615	0.68	***0.034***	0.942	1	0.055
Angular_L	< 0.01	< 0.01	1	1	1	1	1	1	1
Angular_R	0.26	< 0.01	0.74	0.197	1	***0.022***	0.556	1	***0.039***
Precuneus_L	0.35	< 0.01	0.65	0.054	1	***0.002***	0.478	1	***0.004***
Precuneus_R	0.05	0.09	0.87	0.884	0.687	0.265	1	1	0.313
Paracentral_Lobule_L	0.41	< 0.01	0.58	0.113	0.987	***< 0.001***	0.51	1	***< 0.001***
Paracentral_Lobule_R	0.18	< 0.01	0.82	0.223	1	0.25	0.606	1	0.299
Heschl_L	0.13	< 0.01	0.87	0.425	1	0.426	0.804	1	0.474
Heschl_R	0.48	< 0.01	0.52	***0.012***	1	***< 0.001***	0.192	1	< 0.001
Temporal_Sup_L	0.38	< 0.01	0.62	0.062	1	***0.001***	0.482	1	***0.003***
Temporal_Sup_R	0.26	< 0.01	0.74	0.054	1	0.053	0.478	1	0.08
Temporal_Pole_Sup_L	0.12	0.06	0.81	0.689	0.773	0.126	0.985	1	0.169
Temporal_Pole_Sup_R	0.14	0.08	0.78	0.657	0.717	0.062	0.962	1	0.088
Temporal_Mid_L	0.24	< 0.01	0.76	0.154	1	0.059	0.51	1	0.086
Temporal_Mid_R	0.36	< 0.01	0.64	0.142	1	***0.001***	0.51	1	***0.003***
Temporal_Pole_Mid_L	0.07	< 0.01	0.93	0.449	1	0.751	0.806	1	0.77
Temporal_Pole_Mid_R	0.32	< 0.01	0.68	0.168	1	***0.004***	0.51	1	***0.01***
Temporal_Inf_L	0.38	< 0.01	0.62	***0.02***	1	***< 0.001***	0.268	1	***0.001***
Temporal_Inf_R	0.25	< 0.01	0.75	0.286	1	0.05	0.706	1	0.075

A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

Table S3.2. Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Regional SA Measures Without Adjustments for Brain Size

Region of Interest	Variance Components			Hypothesis test P values			Hypothesis test Q values		
	a^2	c^2	e^2	A	C	A and C	A	C	A and C
Precentral_L	0.56	0.13	0.31	***0.003***	0.43	***< 0.001***	***0.007***	1	***< 0.001***
Precentral_R	0.7	0.03	0.27	***< 0.001***	0.849	***< 0.001***	***0.001***	1	***< 0.001***
Frontal_Sup_L	< 0.01	0.4	0.6	1	***0.024***	***< 0.001***	1	0.58	***< 0.001***
Frontal_Sup_R	0.35	0.3	0.35	0.054	0.066	***< 0.001***	0.067	0.724	***< 0.001***
Frontal_Sup_Orb_L	0.55	< 0.01	0.45	***0.014***	1	***< 0.001***	***0.023***	1	***< 0.001***
Frontal_Sup_Orb_R	0.3	0.24	0.46	0.204	0.157	***< 0.001***	0.229	0.934	***< 0.001***
Frontal_Mid_L	0.64	0.07	0.29	***0.001***	0.643	***< 0.001***	***0.003***	1	***< 0.001***
Frontal_Mid_R	0.48	0.29	0.23	***0.002***	***0.044***	***< 0.001***	***0.004***	0.58	***< 0.001***
Frontal_Mid_Orb_L	0.6	< 0.01	0.4	***0.001***	1	***< 0.001***	***0.003***	1	***< 0.001***
Frontal_Mid_Orb_R	0.59	0.08	0.33	***0.003***	0.648	***< 0.001***	***0.007***	1	***< 0.001***
Frontal_Inf_Oper_L	0.41	0.05	0.54	0.104	0.811	***< 0.001***	0.119	1	***< 0.001***
Frontal_Inf_Oper_R	0.57	< 0.01	0.43	***0.001***	1	***< 0.001***	***0.004***	1	***< 0.001***
Frontal_Inf_Tri_L	0.28	0.15	0.57	0.283	0.437	***< 0.001***	0.302	1	***< 0.001***
Frontal_Inf_Tri_R	0.56	< 0.01	0.44	***0.018***	1	***< 0.001***	***0.028***	1	***< 0.001***
Frontal_Inf_Orb_L	0.83	< 0.01	0.17	***< 0.001***	1	***< 0.001***	***< 0.001***	1	***< 0.001***
Frontal_Inf_Orb_R	0.57	0.16	0.27	***0.001***	0.294	***< 0.001***	***0.003***	1	***< 0.001***
Rolandic_Oper_L	0.69	< 0.01	0.31	***< 0.001***	1	***< 0.001***	***0.002***	1	***< 0.001***
Rolandic_Oper_R	0.64	0.08	0.28	***0.001***	0.603	***< 0.001***	***0.003***	1	***< 0.001***
Supp_Motor_Area_L	0.47	0.13	0.4	***0.032***	0.427	***< 0.001***	***0.045***	1	***< 0.001***
Supp_Motor_Area_R	0.37	0.3	0.32	***0.039***	***0.045***	***< 0.001***	0.052	0.58	***< 0.001***
Olfactory_L	0.39	< 0.01	0.61	***0.023***	1	***0.001***	***0.034***	1	***0.001***
Olfactory_R	0.47	< 0.01	0.53	***0.004***	1	***< 0.001***	***0.008***	1	***< 0.001***
Frontal_Sup_Medial_L	0.61	< 0.01	0.39	***0.007***	1	***< 0.001***	***0.013***	1	***< 0.001***
Frontal_Sup_Medial_R	0.69	0.02	0.29	***< 0.001***	0.92	***< 0.001***	***0.002***	1	***< 0.001***
Frontal_Med_Orb_L	0.27	< 0.01	0.73	0.265	1	***0.037***	0.29	1	***0.037***
Frontal_Med_Orb_R	0.59	0.03	0.39	***0.009***	0.881	***< 0.001***	***0.016***	1	***< 0.001***
Rectus_L	0.53	< 0.01	0.47	***0.003***	1	***< 0.001***	***0.007***	1	***< 0.001***
Rectus_R	0.55	0.02	0.44	***0.023***	0.924	***< 0.001***	***0.034***	1	***< 0.001***
Insula_L	0.72	0.13	0.15	***< 0.001***	0.32	***< 0.001***	***< 0.001***	1	***< 0.001***
Insula_R	0.62	0.2	0.18	***< 0.001***	0.154	***< 0.001***	***< 0.001***	0.934	***< 0.001***
Cingulum_Ant_L	0.53	< 0.01	0.47	***0.007***	1	***< 0.001***	***0.013***	1	***< 0.001***
Cingulum_Ant_R	0.78	< 0.01	0.22	***< 0.001***	1	***< 0.001***	***< 0.001***	1	***< 0.001***
Cingulum_Mid_L	0.67	< 0.01	0.33	***0.001***	1	***< 0.001***	***0.003***	1	***< 0.001***
Cingulum_Mid_R	0.82	< 0.01	0.18	***< 0.001***	1	***< 0.001***	***< 0.001***	1	***< 0.001***
Cingulum_Post_L	0.49	< 0.01	0.51	***0.004***	1	***< 0.001***	***0.008***	1	***< 0.001***
Cingulum_Post_R	0.46	< 0.01	0.54	***0.02***	1	***< 0.001***	***0.03***	1	***< 0.001***
ParaHippocampal_L	0.38	< 0.01	0.62	***0.041***	1	***0.003***	0.054	1	***0.003***
ParaHippocampal_R	0.57	< 0.01	0.43	***0.01***	1	***< 0.001***	***0.017***	1	***< 0.001***
Calcarine_L	0.43	0.19	0.38	***0.038***	0.235	***< 0.001***	0.052	1	***< 0.001***
Calcarine_R	0.6	< 0.01	0.4	***0.002***	1	***< 0.001***	***0.005***	1	***< 0.001***
Cuneus_L	0.45	0.02	0.54	0.084	0.933	***< 0.001***	0.1	1	***< 0.001***
Cuneus_R	0.57	< 0.01	0.43	***0.001***	1	***< 0.001***	***0.004***	1	***< 0.001***
Lingual_L	0.63	0.08	0.28	***0.001***	0.582	***< 0.001***	***0.003***	1	***< 0.001***
Lingual_R	0.29	0.44	0.27	***0.044***	***0.003***	***< 0.001***	0.057	0.176	***< 0.001***
Occipital_Sup_L	0.64	< 0.01	0.36	***0.002***	1	***< 0.001***	***0.004***	1	***< 0.001***
Occipital_Sup_R	0.57	0.06	0.37	***0.013***	0.729	***< 0.001***	***0.023***	1	***< 0.001***
Occipital_Mid_L	0.7	0.02	0.28	***< 0.001***	0.904	***< 0.001***	***0.001***	1	***< 0.001***
Occipital_Mid_R	0.51	0.13	0.36	***0.018***	0.411	***< 0.001***	***0.028***	1	***< 0.001***
Occipital_Inf_L	0.26	0.15	0.58	0.329	0.415	***< 0.001***	0.346	1	***< 0.001***
Occipital_Inf_R	0.16	0.26	0.58	0.54	0.156	***< 0.001***	0.554	0.934	***< 0.001***

Fusiform_L	0.18	0.23	0.58	0.48	0.206	***< 0.001***	0.499	1	***< 0.001***
Fusiform_R	0.39	0.17	0.44	0.073	0.346	***< 0.001***	0.09	1	***< 0.001***
Postcentral_L	0.64	< 0.01	0.36	***0.001***	1	***< 0.001***	***0.004***	1	***< 0.001***
Postcentral_R	0.71	0.03	0.26	***< 0.001***	0.858	***< 0.001***	***0.001***	1	***< 0.001***
Parietal_Sup_L	< 0.01	0.27	0.73	1	0.097	***0.001***	1	0.934	***0.001***
Parietal_Sup_R	0.53	0.29	0.19	***< 0.001***	***0.037***	***< 0.001***	***0.001***	0.58	***< 0.001***
Parietal_Inf_L	0.47	0.12	0.41	***0.039***	0.463	***< 0.001***	0.052	1	***< 0.001***
Parietal_Inf_R	0.26	0.26	0.48	0.241	0.148	***< 0.001***	0.268	0.934	***< 0.001***
SupraMarginal_L	0.4	< 0.01	0.6	0.098	1	***0.001***	0.115	1	***0.001***
SupraMarginal_R	0.68	< 0.01	0.32	***0.001***	1	***< 0.001***	***0.002***	1	***< 0.001***
Angular_L	0.37	< 0.01	0.63	***0.017***	1	***0.001***	***0.028***	1	***0.001***
Angular_R	0.39	0.16	0.45	0.078	0.391	***< 0.001***	0.094	1	***< 0.001***
Precuneus_L	0.8	< 0.01	0.2	***< 0.001***	1	***< 0.001***	***< 0.001***	1	***< 0.001***
Precuneus_R	0.75	0.15	0.11	***< 0.001***	0.275	***< 0.001***	***< 0.001***	1	***< 0.001***
Paracentral_Lobule_L	0.56	< 0.01	0.44	***0.002***	1	***< 0.001***	***0.004***	1	***< 0.001***
Paracentral_Lobule_R	0.43	0.15	0.42	***0.045***	0.389	***< 0.001***	0.058	1	***< 0.001***
Heschl_L	0.47	< 0.01	0.53	***0.002***	1	***< 0.001***	***0.005***	1	***< 0.001***
Heschl_R	0.44	< 0.01	0.56	0.053	1	***< 0.001***	0.067	1	***< 0.001***
Temporal_Sup_L	0.56	0.12	0.31	***0.003***	0.44	***< 0.001***	***0.007***	1	***< 0.001***
Temporal_Sup_R	0.58	0.2	0.23	***< 0.001***	0.189	***< 0.001***	***0.001***	1	***< 0.001***
Temporal_Pole_Sup_L	0.51	0.16	0.33	***0.007***	0.364	***< 0.001***	***0.013***	1	***< 0.001***
Temporal_Pole_Sup_R	0.19	0.45	0.36	0.269	***0.005***	***< 0.001***	0.291	0.189	***< 0.001***
Temporal_Mid_L	0.69	0.02	0.29	***< 0.001***	0.887	***< 0.001***	***0.002***	1	***< 0.001***
Temporal_Mid_R	0.73	0.08	0.18	***< 0.001***	0.567	***< 0.001***	***< 0.001***	1	***< 0.001***
Temporal_Pole_Mid_L	0.37	0.14	0.48	0.101	0.436	***< 0.001***	0.118	1	***< 0.001***
Temporal_Pole_Mid_R	0.64	< 0.01	0.36	***< 0.001***	1	***< 0.001***	***0.002***	1	***< 0.001***
Temporal_Inf_L	0.56	< 0.01	0.44	***0.019***	1	***< 0.001***	***0.03***	1	***< 0.001***
Temporal_Inf_R	0.56	0.24	0.2	***< 0.001***	0.11	***< 0.001***	***0.001***	0.934	***< 0.001***

A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

Table S3.3. Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Global Measures Controlling for Age, Sex, Brain Size, and T2 Type

Region of Interest	Variance Components			Hypothesis test (P values)		
	a^2	c^2	e^2	A	C	A and C
Total SA	0.32	0.60	0.08	***< 0.001***	***< 0.001***	***< 0.001***
Average CT	0.16	0.33	0.51	0.963	0.578	***< 0.001***
ICV	0.42	0.48	0.10	***< 0.001***	***< 0.001***	***< 0.001***

A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

Table S3.4. Bivariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Global Measures Controlling for Age, Sex, Brain Size, and T2 Type

Region of Interests		Correlation Coefficient				Hypothesis test (P values)				
1	**2**	**rP**	**rG**	**rC**	**rE**	**A**	**C**	**E**	**A and C**	**A, C, and E**
Total SA	Average CT	0.32	0.72	0.36	-0.23	**0.012**	0.057	0.065	**< 0.001**	**< 0.001**
Total SA	ICV	0.92	0.95	0.96	0.62	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Average CT	ICV	0.53	0.73	0.58	0.28	**0.012**	**0.027**	**0.035**	**< 0.001**	**< 0.001**

A= test of genetic covariance; C = test of shared environmental covariance; A and C = test of familial covariance (genetic + environmental); A, C, and E = test of all and any covariance

Table S3.5 Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Regional CT Measures Controlling for Age, Sex, Brain Size, and T2 Type

Region of Interest	Variance Components			Hypothesis test P values			Hypothesis test Q values		
	a^2	c^2	e^2	A	C	A and C	A	C	A and C
Precentral_L	< 0.01	0.26	0.74	1	0.158	***0.001***	1	0.862	***0.005***
Precentral_R	0.28	0.10	0.62	0.334	0.603	***< 0.001***	0.851	1	***0.002***
Frontal_Sup_L	0.04	0.33	0.64	0.879	0.088	***< 0.001***	1	0.578	***< 0.001***
Frontal_Sup_R	< 0.01	0.45	0.55	1	***0.004***	***< 0.001***	1	0.295	***< 0.001***
Frontal_Sup_Orb_L	0.12	0.20	0.68	0.651	0.318	***< 0.001***	1	1	***0.002***
Frontal_Sup_Orb_R	0.39	< 0.01	0.61	0.075	1	***< 0.001***	0.506	1	***0.001***
Frontal_Mid_L	< 0.01	0.24	0.76	1	0.161	***0.005***	1	0.862	***0.011***
Frontal_Mid_R	< 0.01	0.23	0.77	1	0.072	***0.007***	1	0.578	***0.015***
Frontal_Mid_Orb_L	< 0.01	0.06	0.94	1	0.468	0.706	1	1	0.764
Frontal_Mid_Orb_R	0.37	< 0.01	0.63	0.135	1	***0.003***	0.59	1	***0.008***
Frontal_Inf_Oper_L	0.18	< 0.01	0.82	0.476	1	0.166	0.963	1	0.208
Frontal_Inf_Oper_R	0.07	< 0.01	0.93	0.627	1	0.848	1	1	0.893
Frontal_Inf_Tri_L	0.30	< 0.01	0.70	0.107	1	***0.004***	0.556	1	***0.01***
Frontal_Inf_Tri_R	0.09	0.06	0.86	0.764	0.8	0.26	1	1	0.307
Frontal_Inf_Orb_L	< 0.01	0.26	0.73	0.988	0.196	***0.001***	1	0.862	***0.004***
Frontal_Inf_Orb_R	0.20	< 0.01	0.80	0.276	1	0.164	0.808	1	0.208
Rolandic_Oper_L	0.23	0.13	0.64	0.381	0.511	***< 0.001***	0.861	1	***0.001***
Rolandic_Oper_R	0.19	< 0.01	0.81	0.392	1	0.189	0.861	1	0.23
Supp_Motor_Area_L	0.29	0.15	0.56	0.289	0.408	***< 0.001***	0.815	1	***< 0.001***
Supp_Motor_Area_R	< 0.01	0.28	0.72	1	0.086	***< 0.001***	1	0.578	***0.002***
Olfactory_L	< 0.01	0.16	0.84	1	0.398	0.102	1	1	0.139
Olfactory_R	< 0.01	0.11	0.89	1	0.367	0.328	1	1	0.376
Frontal_Sup_Medial_L	< 0.01	0.14	0.86	1	0.461	0.18	1	1	0.222
Frontal_Sup_Medial_R	0.22	< 0.01	0.78	0.387	1	0.094	0.861	1	0.133
Frontal_Med_Orb_L	0.03	< 0.01	0.97	0.786	1	0.964	1	1	0.976
Frontal_Med_Orb_R	0.26	< 0.01	0.74	0.272	1	***0.044***	0.808	1	0.07
Rectus_L	0.27	< 0.01	0.73	0.068	1	***0.014***	0.506	1	***0.027***
Rectus_R	0.13	< 0.01	0.87	0.508	1	0.414	1	1	0.461
Insula_L	0.44	< 0.01	0.56	***0.004***	1	***< 0.001***	0.148	1	***0.001***
Insula_R	0.60	< 0.01	0.40	***0.001***	1	***< 0.001***	***0.041***	1	***< 0.001***
Cingulum_Ant_L	0.29	0.04	0.67	0.323	0.834	***0.004***	0.851	1	***0.01***
Cingulum_Ant_R	< 0.01	0.23	0.77	1	0.075	***0.006***	1	0.578	***0.013***
Cingulum_Mid_L	0.44	< 0.01	0.56	0.066	1	***< 0.001***	0.506	1	***< 0.001***
Cingulum_Mid_R	< 0.01	0.25	0.75	0.997	0.253	***0.003***	1	1	***0.007***
Cingulum_Post_L	0.03	< 0.01	0.97	0.787	1	0.964	1	1	0.976
Cingulum_Post_R	< 0.01	0.11	0.89	1	0.462	0.326	1	1	0.376
ParaHippocampal_L	0.45	< 0.01	0.55	***0.014***	1	***< 0.001***	0.239	1	***0.001***
ParaHippocampal_R	0.34	< 0.01	0.66	***0.029***	1	***0.017***	0.388	1	***0.03***
Calcarine_L	< 0.01	0.22	0.78	1	0.187	***0.011***	1	0.862	***0.021***
Calcarine_R	0.09	0.13	0.78	0.774	0.545	***0.039***	1	1	0.064
Cuneus_L	0.13	0.07	0.80	0.66	0.727	0.076	1	1	0.111
Cuneus_R	< 0.01	0.15	0.85	1	0.191	0.115	1	0.862	0.154
Lingual_L	< 0.01	0.25	0.75	1	***0.046***	***0.002***	1	0.578	***0.006***
Lingual_R	< 0.01	0.30	0.70	1	***0.044***	***< 0.001***	1	0.578	***0.001***
Occipital_Sup_L	< 0.01	0.26	0.74	1	0.054	***0.001***	1	0.578	***0.004***
Occipital_Sup_R	< 0.01	0.15	0.85	1	0.313	0.136	1	1	0.179
Occipital_Mid_L	< 0.01	0.25	0.75	1	0.18	***0.002***	1	0.862	***0.006***
Occipital_Mid_R	0.10	< 0.01	0.90	0.392	1	0.59	0.861	1	0.647
Occipital_Inf_L	0.15	< 0.01	0.85	0.432	1	0.351	0.922	1	0.396
Occipital_Inf_R	0.42	< 0.01	0.58	0.113	1	***< 0.001***	0.556	1	***0.001***

Fusiform_L	0.35	< 0.01	0.65	0.115	1	***0.002***	0.556	1	***0.005***
Fusiform_R	0.04	0.34	0.62	0.876	0.062	***< 0.001***	1	0.578	***< 0.001***
Postcentral_L	0.41	0.01	0.58	0.113	0.969	***< 0.001***	0.556	1	***0.001***
Postcentral_R	0.24	< 0.01	0.76	0.232	1	0.05	0.763	1	0.076
Parietal_Sup_L	< 0.01	0.40	0.60	1	***0.009***	***< 0.001***	1	0.339	***< 0.001***
Parietal_Sup_R	< 0.01	0.21	0.79	1	0.072	***0.015***	1	0.578	***0.027***
Parietal_Inf_L	0.27	< 0.01	0.73	0.265	1	***0.019***	0.808	1	***0.033***
Parietal_Inf_R	0.07	0.10	0.83	0.835	0.665	0.156	1	1	0.202
SupraMarginal_L	0.17	0.01	0.82	0.574	0.971	0.214	1	1	0.256
SupraMarginal_R	0.15	0.08	0.77	0.632	0.707	***0.049***	1	1	0.076
Angular_L	< 0.01	< 0.01	1.00	1	1	1	1	1	1
Angular_R	0.27	0.03	0.70	0.332	0.881	***0.006***	0.851	1	***0.013***
Precuneus_L	0.32	< 0.01	0.68	0.175	1	***0.006***	0.693	1	***0.012***
Precuneus_R	0.02	0.14	0.84	0.952	0.504	0.101	1	1	0.139
Paracentral_Lobule_L	0.35	< 0.01	0.64	0.191	0.988	***0.001***	0.72	1	***0.003***
Paracentral_Lobule_R	0.08	< 0.01	0.92	0.547	1	0.788	1	1	0.842
Heschl_L	0.05	< 0.01	0.95	0.714	1	0.873	1	1	0.907
Heschl_R	0.44	< 0.01	0.56	***0.013***	1	***< 0.001***	0.239	1	***0.001***
Temporal_Sup_L	0.37	< 0.01	0.63	0.077	1	***0.002***	0.506	1	***0.006***
Temporal_Sup_R	0.25	< 0.01	0.75	0.069	1	0.069	0.506	1	0.103
Temporal_Pole_Sup_L	0.26	0.03	0.71	0.359	0.871	***0.008***	0.861	1	***0.016***
Temporal_Pole_Sup_R	0.16	0.08	0.76	0.612	0.687	***0.036***	1	1	0.061
Temporal_Mid_L	0.25	< 0.01	0.75	0.175	1	***0.04***	0.693	1	0.065
Temporal_Mid_R	0.38	< 0.01	0.62	0.12	1	***< 0.001***	0.556	1	***0.002***
Temporal_Pole_Mid_L	0.21	< 0.01	0.79	0.218	1	0.091	0.763	1	0.131
Temporal_Pole_Mid_R	0.40	< 0.01	0.60	0.076	1	***< 0.001***	0.506	1	***0.001***
Temporal_Inf_L	0.39	< 0.01	0.61	***0.015***	1	***< 0.001***	0.239	1	***0.001***
Temporal_Inf_R	0.26	< 0.01	0.74	0.228	1	***0.037***	0.763	1	0.062

A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

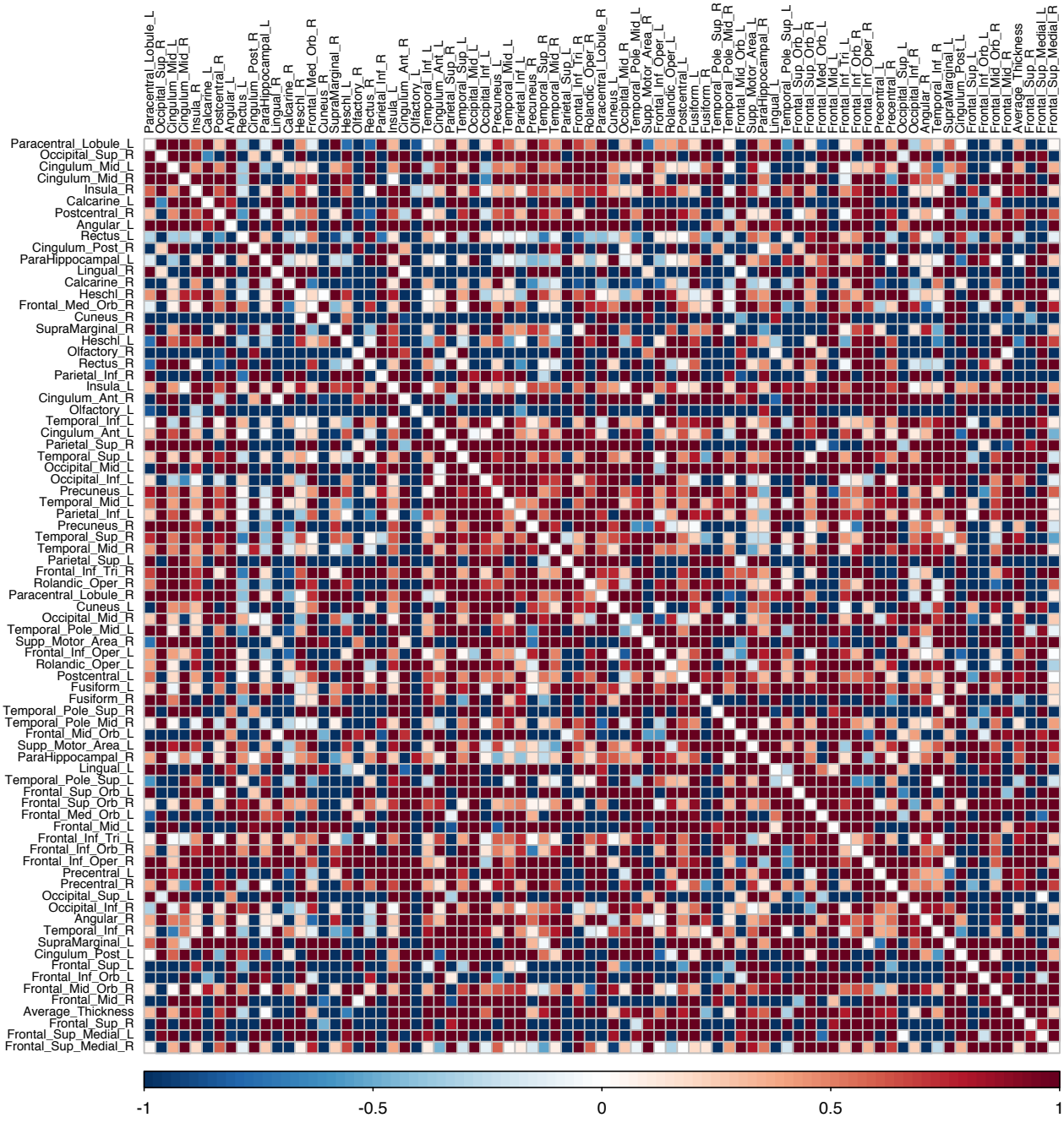
Table S3.6. Univariate ACE Model Maximum Likelihood Parameter Estimates and P-values for Regional SA Measures Controlling for Age, Sex, Brain Size, And T2 Type

Region of Interest	Variance Components			Hypothesis test P values			Hypothesis test Q values		
	a^2	c^2	e^2	A	C	A and C	A	C	A and C
Precentral_L	0.26	0.13	0.61	0.338	0.511	***< 0.001***	0.509	1	***0.001***
Precentral_R	0.13	0.21	0.66	0.622	0.299	***< 0.001***	0.72	1	***0.001***
Frontal_Sup_L	0.03	0.19	0.79	0.926	0.381	***0.019***	0.999	1	***0.03***
Frontal_Sup_R	0.18	0.15	0.67	0.512	0.45	***0.001***	0.664	1	***0.002***
Frontal_Sup_Orb_L	0.32	< 0.01	0.68	0.072	1	***0.007***	0.215	1	***0.013***
Frontal_Sup_Orb_R	0.03	< 0.01	0.96	0.923	0.984	0.939	0.999	1	0.989
Frontal_Mid_L	0.35	< 0.01	0.65	***0.03***	1	***0.005***	0.18	1	***0.01***
Frontal_Mid_R	0.26	0.22	0.52	0.276	0.224	***< 0.001***	0.459	1	***< 0.001***
Frontal_Mid_Orb_L	0.21	< 0.01	0.79	0.228	1	0.137	0.403	1	0.169
Frontal_Mid_Orb_R	0.28	< 0.01	0.72	***0.042***	1	***0.018***	0.185	1	***0.03***
Frontal_Inf_Oper_L	0.07	< 0.01	0.93	0.624	1	0.783	0.72	1	0.841
Frontal_Inf_Oper_R	0.02	< 0.01	0.98	0.858	1	0.984	0.963	1	1
Frontal_Inf_Tri_L	0.08	< 0.01	0.92	0.572	1	0.767	0.698	1	0.841
Frontal_Inf_Tri_R	0.31	< 0.01	0.69	0.169	1	***0.011***	0.326	1	***0.019***
Frontal_Inf_Orb_L	0.55	< 0.01	0.45	***< 0.001***	1	***< 0.001***	***0.008***	1	***< 0.001***
Frontal_Inf_Orb_R	0.51	< 0.01	0.49	***0.014***	1	***< 0.001***	0.127	1	***< 0.001***
Rolandic_Oper_L	0.33	< 0.01	0.67	0.056	1	***0.007***	0.185	1	***0.012***
Rolandic_Oper_R	0.42	< 0.01	0.58	0.077	1	***< 0.001***	0.221	1	***0.001***
Supp_Motor_Area_L	0.37	0.03	0.6	0.164	0.88	***< 0.001***	0.324	1	***0.001***
Supp_Motor_Area_R	0.16	0.16	0.68	0.593	0.421	***0.001***	0.714	1	***0.003***
Olfactory_L	0.11	< 0.01	0.89	0.348	1	0.644	0.516	1	0.727
Olfactory_R	0.26	< 0.01	0.74	***0.045***	1	***0.04***	0.185	1	0.055
Frontal_Sup_Medial_L	0.28	< 0.01	0.72	0.134	1	***0.039***	0.317	1	0.055
Frontal_Sup_Medial_R	0.07	< 0.01	0.93	0.48	1	0.779	0.643	1	0.841
Frontal_Med_Orb_L	< 0.01	0.05	0.95	1	0.734	0.788	1	1	0.841
Frontal_Med_Orb_R	0.27	0.06	0.67	0.357	0.753	***0.003***	0.519	1	***0.007***
Rectus_L	0.23	< 0.01	0.77	0.15	1	0.136	0.324	1	0.169
Rectus_R	0.09	0.09	0.82	0.777	0.687	0.129	0.884	1	0.164
Insula_L	0.73	< 0.01	0.27	***< 0.001***	1	***< 0.001***	***0.003***	1	***< 0.001***
Insula_R	0.61	< 0.01	0.39	***< 0.001***	1	***< 0.001***	***0.008***	1	***< 0.001***
Cingulum_Ant_L	0.23	< 0.01	0.77	0.151	1	0.14	0.324	1	0.17
Cingulum_Ant_R	0.29	< 0.01	0.71	0.056	1	***0.046***	0.185	1	0.062
Cingulum_Mid_L	0.36	< 0.01	0.64	0.197	1	***0.005***	0.363	1	***0.01***
Cingulum_Mid_R	0.38	< 0.01	0.62	***0.027***	1	***0.003***	0.172	1	***0.007***
Cingulum_Post_L	0.29	< 0.01	0.71	0.054	1	***0.03***	0.185	1	***0.045***
Cingulum_Post_R	0.12	< 0.01	0.88	0.567	1	0.549	0.698	1	0.629
ParaHippocampal_L	0.2	< 0.01	0.8	0.132	1	0.164	0.317	1	0.194
ParaHippocampal_R	0.24	0.14	0.62	0.392	0.467	***< 0.001***	0.551	1	***0.001***
Calcarine_L	0.25	0.28	0.48	0.272	0.11	***< 0.001***	0.459	1	***< 0.001***
Calcarine_R	0.49	0.01	0.5	0.054	0.946	***< 0.001***	0.185	1	***< 0.001***
Cuneus_L	0.26	< 0.01	0.74	0.33	1	***0.037***	0.509	1	0.054
Cuneus_R	0.28	< 0.01	0.72	0.085	1	***0.035***	0.228	1	0.052
Lingual_L	0.54	0.01	0.45	***0.036***	0.951	***< 0.001***	0.184	1	***< 0.001***
Lingual_R	0.16	0.38	0.45	0.426	***0.022***	***< 0.001***	0.59	1	***< 0.001***
Occipital_Sup_L	0.45	< 0.01	0.55	***0.01***	1	***< 0.001***	0.107	1	***< 0.001***
Occipital_Sup_R	0.47	< 0.01	0.53	***0.033***	1	***< 0.001***	0.183	1	***0.001***
Occipital_Mid_L	0.47	< 0.01	0.53	***0.026***	1	***< 0.001***	0.172	1	***< 0.001***
Occipital_Mid_R	< 0.01	0.26	0.74	1	0.173	***0.002***	1	1	***0.004***
Occipital_Inf_L	< 0.01	0.11	0.89	1	0.54	0.317	1	1	0.368
Occipital_Inf_R	0.25	< 0.01	0.75	0.374	1	***0.035***	0.535	1	0.052

Fusiform_L	0.3	< 0.01	0.7	0.201	1	***0.007***	0.363	1	***0.012***
Fusiform_R	0.27	< 0.01	0.73	0.261	1	***0.024***	0.452	1	***0.038***
Postcentral_L	0.37	< 0.01	0.63	0.055	1	***0.001***	0.185	1	***0.002***
Postcentral_R	0.35	< 0.01	0.65	0.118	1	***0.004***	0.306	1	***0.009***
Parietal_Sup_L	< 0.01	< 0.01	1	1	1	1	1	1	1
Parietal_Sup_R	0.49	0.05	0.47	0.054	0.792	***< 0.001***	0.185	1	***< 0.001***
Parietal_Inf_L	< 0.01	0.3	0.7	1	0.095	***< 0.001***	1	1	***0.001***
Parietal_Inf_R	0.27	< 0.01	0.73	0.323	1	***0.019***	0.509	1	***0.03***
SupraMarginal_L	< 0.01	< 0.01	1	1	1	1	1	1	1
SupraMarginal_R	0.37	< 0.01	0.63	***0.01***	1	***0.001***	0.107	1	***0.003***
Angular_L	0.2	< 0.01	0.8	0.162	1	0.146	0.324	1	0.175
Angular_R	0.19	0.12	0.69	0.479	0.58	***0.001***	0.643	1	***0.003***
Precuneus_L	0.49	< 0.01	0.51	***0.005***	1	***< 0.001***	0.075	1	***< 0.001***
Precuneus_R	0.61	< 0.01	0.39	***0.001***	1	***< 0.001***	***0.026***	1	***< 0.001***
Paracentral_Lobule_L	0.4	< 0.01	0.6	***0.023***	1	***0.005***	0.172	1	***0.01***
Paracentral_Lobule_R	0.31	< 0.01	0.69	0.08	1	***0.007***	0.222	1	***0.012***
Heschl_L	0.4	< 0.01	0.6	***0.009***	1	***0.002***	0.107	1	***0.004***
Heschl_R	0.2	< 0.01	0.8	0.184	1	0.111	0.347	1	0.144
Temporal_Sup_L	0.42	0.01	0.56	0.132	0.945	***< 0.001***	0.317	1	***0.001***
Temporal_Sup_R	0.44	< 0.01	0.56	0.059	1	***< 0.001***	0.187	1	***< 0.001***
Temporal_Pole_Sup_L	0.27	0.07	0.65	0.312	0.723	***0.001***	0.507	1	***0.002***
Temporal_Pole_Sup_R	0.17	0.11	0.72	0.549	0.612	***0.006***	0.698	1	***0.011***
Temporal_Mid_L	0.34	< 0.01	0.66	***0.017***	1	***0.005***	0.138	1	***0.01***
Temporal_Mid_R	0.32	< 0.01	0.68	0.15	1	***0.016***	0.324	1	***0.026***
Temporal_Pole_Mid_L	0.15	0.17	0.68	0.562	0.421	***< 0.001***	0.698	1	***0.001***
Temporal_Pole_Mid_R	0.24	< 0.01	0.76	0.156	1	0.067	0.324	1	0.09
Temporal_Inf_L	0.25	< 0.01	0.75	0.159	1	0.069	0.324	1	0.091
Temporal_Inf_R	0.47	0.07	0.46	***0.044***	0.708	***< 0.001***	0.185	1	***< 0.001***

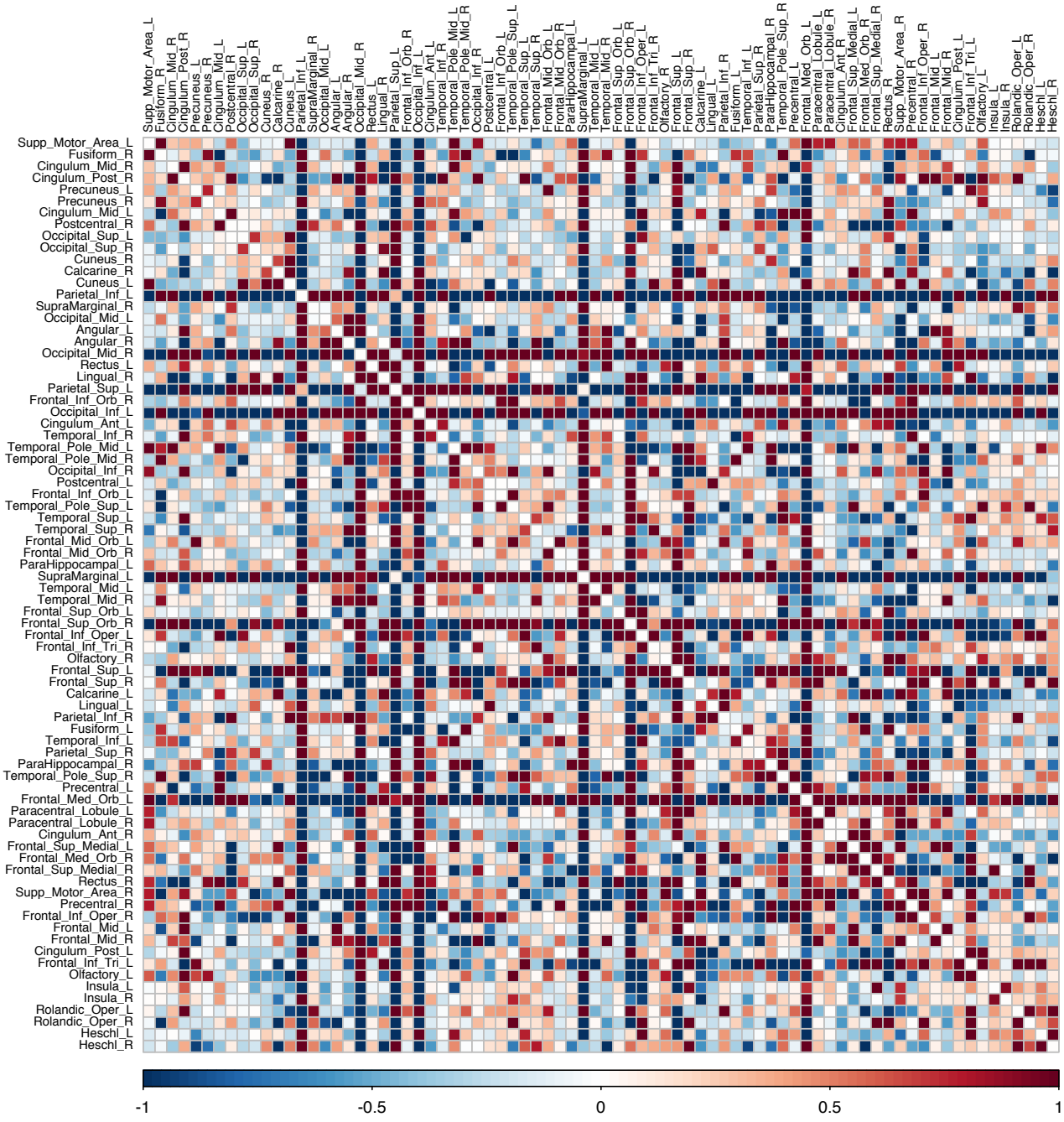
A= test of genetic effects; C = test of shared environmental effects; A and C = test of familial effects (genetic + environmental).

Figure S3.1. Genetic Correlation Matrix of Regional CT Measures



Adjusting for birth weight, gestational age at birth, age at MRI, sex, paternal education, maternal ethnicity, $ICV^{1/3}$, and T2Type

Figure S3.2. Genetic Correlation Matrix of Regional SA Measures



Adjusting for birth weight, age at MRI, sex, total surface area, and T2 type

Figure S3.3. Genetic Correlation Matrix of Regional CT Measures Without Adjustments for Brain Size

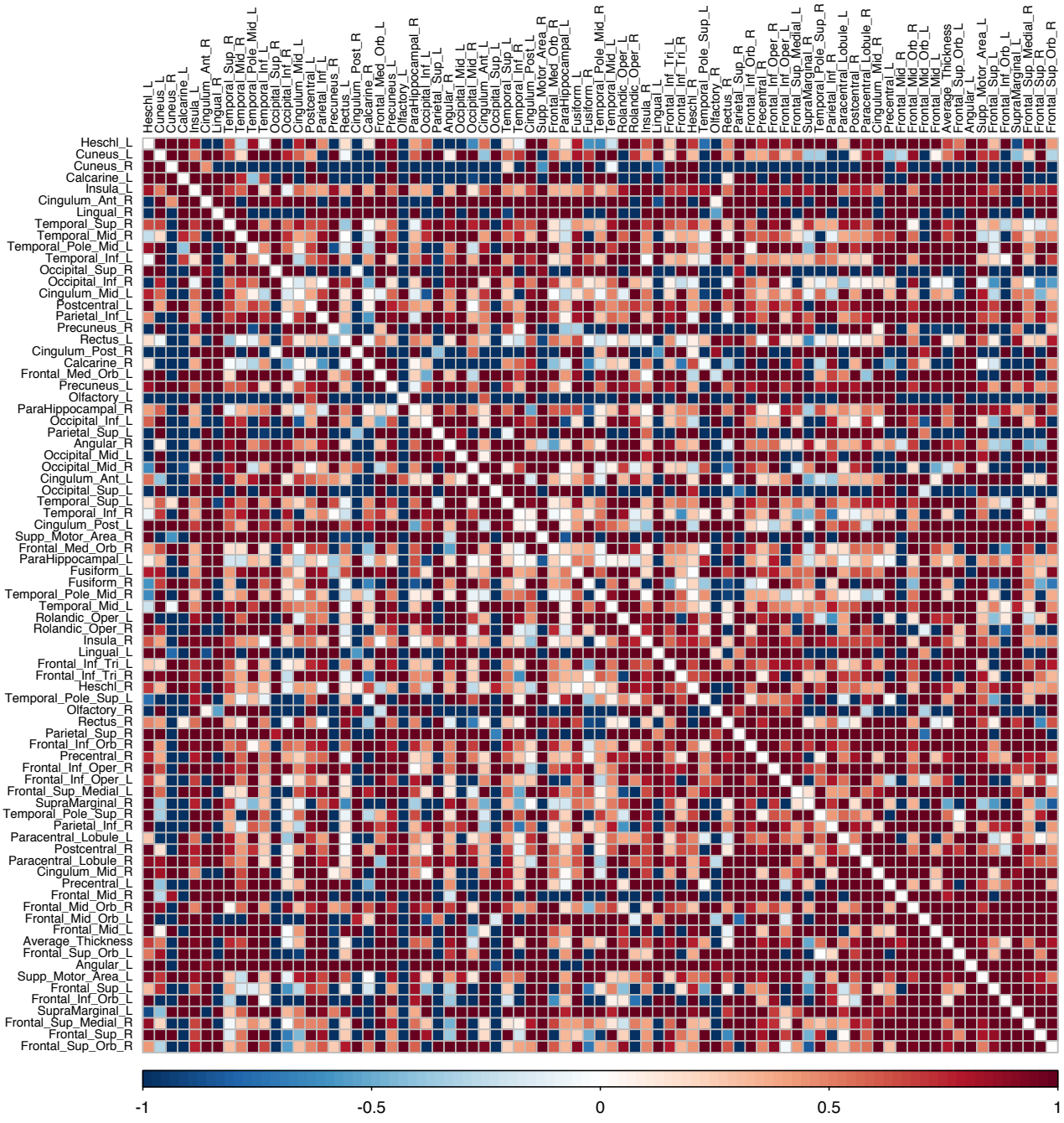


Figure S3.4. Genetic Correlation Matrix of Regional SA Measures Without Adjustments for Brain Size

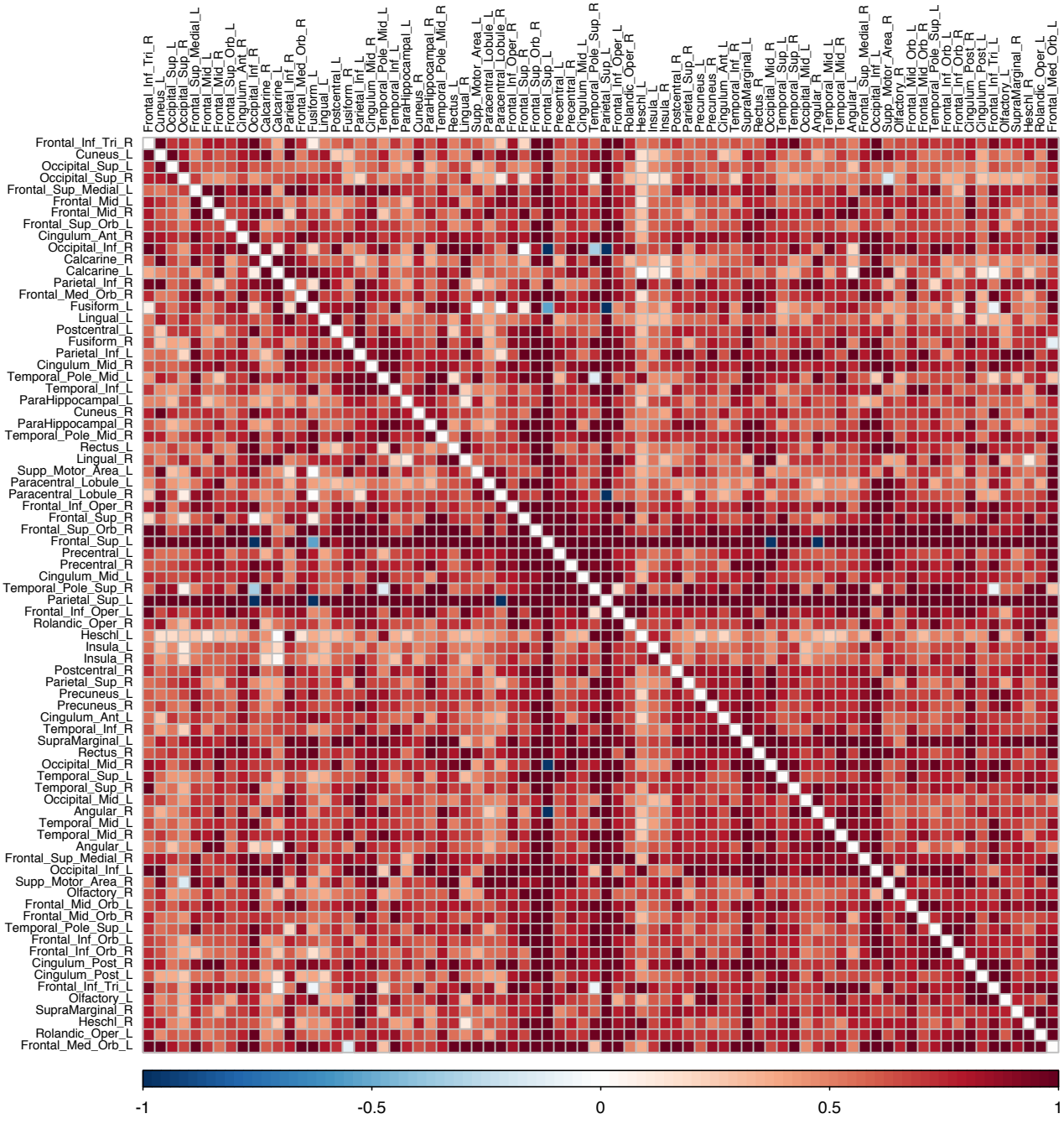


Figure S3.5. Genetic Correlation Matrix of Regional CT Measures Controlling For Age, Sex, Brain Size, and T2 Type

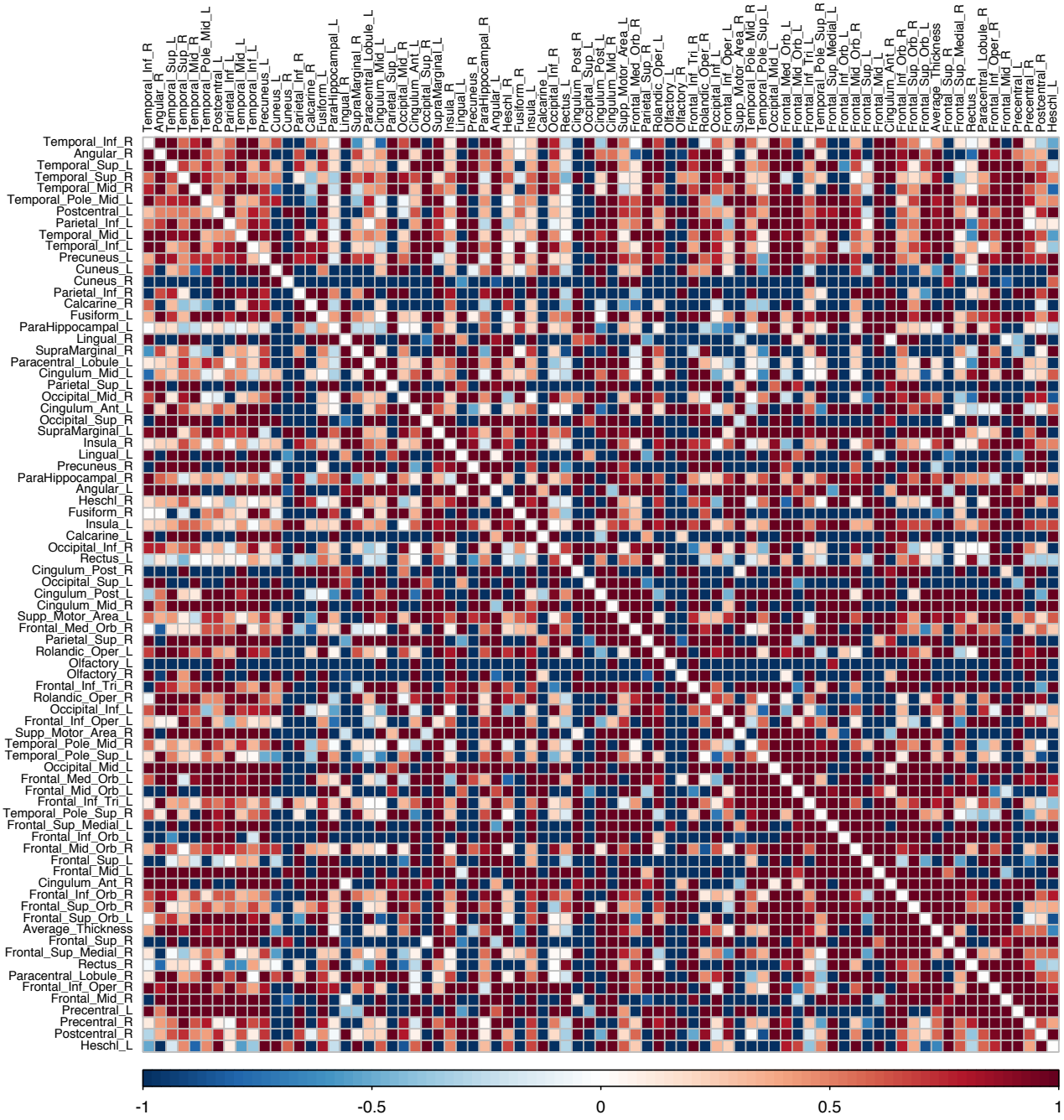
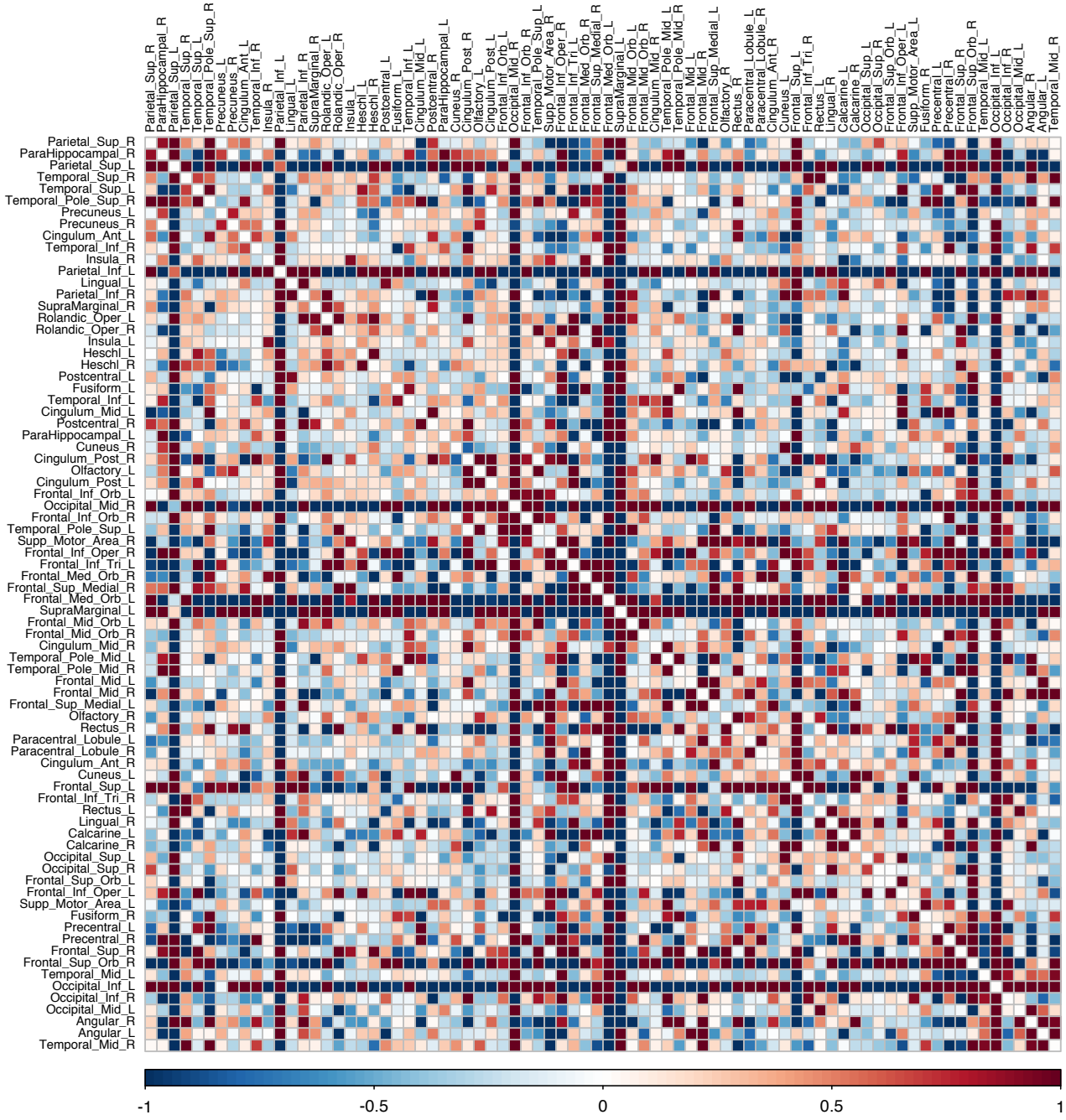


Figure S3.6: Genetic Correlation Matrix of Regional SA Measures Controlling for Age, Sex, Brain Size, and T2 Type



CHAPTER 4: CONCLUSIONS

SUMMARY OF FINDINGS

In the first large-scale population-based neuroimaging study of infant cortical structure, we sought to understand how environmental and genetic factors contribute to individual differences in neonatal CT and SA. In **Aim 1 (Chapter 2)**, we examined the impact of 17 major demographic, obstetric, and socioeconomic variables on inter-individual variation in global and regional CT and SA. Our findings suggested that individual differences in infant CT and SA are explained by different sets of environmental factors likely acting on different cellular processes. Sex and obstetric history variables had a strong influence on neonatal SA whereas variables related to SES and ethnic disparities (paternal education and maternal ethnicity) had a strong influence on CT. In **Aim 2 (Chapter 3),** we used a classical twin model to identify genetic contributions to global and regional CT and SA variation. Our results indicated that genetic influences explained a large degree of the individual differences in total SA and revealed a substantial genetic overlap between total SA and average CT. Heritability estimates and genetic correlations at the regional level were not significant and did not reveal meaningful organizational patterns. Outcomes from these studies provide a unique addition to the existing understanding of how environmental and genetic factors influence CT and SA development during the lifespan.

CONTRIBUTIONS TO THE FIELD

This research provides the following contributions to the field of pediatric neuroimaging and to the understanding of cortical thickness and surface area:

A normative reference for future studies of neurodevelopmental disorders

Overall, our research addresses high priority areas identified by the National Institutes of Mental Health by focusing on normative development during a sensitive and highly malleable period of neurodevelopment. For many neurodevelopmental disorders, abnormalities in CT and SA are not only observed in diagnosed patients but are also evident in at-risk populations as early as the first two years of life (Li et al. 2016; Hazlett et al. 2017). To better understand these pathological conditions, it is crucial to understand how normal neurodevelopmental trajectories are established, how they are influenced by environmental and genetic factors, and how they are altered in mental illness. By investigating the environmental and genetic influences on early brain structure, we made progress toward identifying brain regions which might show heightened genetic vulnerability to later dysfunction and ultimately allow early identification and intervention for these devastating disorders.

An unprecedented CT and SA sample

Our dataset is comprised of a large infant sample with detailed medical, obstetric, and demographic information. It is currently the largest collection of cortical data spanning the early postnatal period. Moreover, CT and SA measures in this report are generated using well-established infant imaging protocols and cutting-edge image analysis methods developed precisely for this age range. Specifically, tissue segmentation, image registration, and cortical surface construction tools used are designed to address the rapid changes in tissue contrast during the first years of life. Unlike many emerging pediatric samples which span several critical years

of development (Remer, Croteau-Chonka, Dean, D'Arpino, Dirks, Whiley, and Deoni 2017), our sample is focused on an early window into prenatal development by targeting the first month of life. Moving forward, there is enormous potential for additional informative studies in our dataset. Neonatal subjects in the EBDS were followed up throughout infancy and early childhood and will be studied longitudinally. Moreover, additional measures have been acquired from these subjects by using diffusion tensor imaging, and cognitive, genetic, and microbiome assessments.

New insights into prenatal and perinatal environmental factors

By applying an epidemiological approach to studying environmental influences on early brain structure, we revealed the first detailed snapshot of perinatal cortical development. Our analysis revealed that daily growth rates of CT and SA dwarf annual growth rates measured in childhood and adolescence (Raznahan et al. 2011). Using a neonatal sample, we were also able to confirm that robust effects of birth weight and sex on total surface area during childhood and adolescence (Raznahan et al. 2011; Walhovd et al. 2012; Wierenga et al. 2014) are similar at birth. Continuous impacts of these variables across the lifespan follow the same pattern, with males and heavier born babies having larger total surface area. Based on previous reports and results from our study, it is likely that in utero influences are particularly important for explaining these relationships.

Very little research has examined how SES and ethnicity contribute to normative trajectories of brain development. For the first time, we show that individual differences in infant CT but not SA are influenced by parental socioeconomic and ethnicity variables. Specifically, we show that it is paternal education and not household income that drives the individual differences in CT observed in our sample. No studies to date have examined paternal education as a stand-alone variable yet our findings highlight just how critical it may be for shaping early

cortical trajectories. Findings from both ethnicity and SES variables highlight the potential role of prenatal care and psychosocial stress (Blumenshine et al. 2011; Grobman et al. 2016; Mutambudzi et al. 2017) on brain development during a period of heightened plasticity and vulnerability. For the first time, we show that variables such as parental ethnicity and education may have direct effects on cellular processes such as those controlling the radial expansion of the developing cortex during both prenatal and early postnatal time periods.

Addition of critically needed genetic insight into cortical development

Our studies fill an important gap in the understanding of how genetic influences shape cortical thickness and surface area during a critical yet understudied period of development. In contrast to the heritability studies performed in childhood, adolescence, and adulthood, we show that during infancy, genetic influences on CT and SA reveal virtually no regional significance or meaningful associations. Instead, our twin model suggests that neonatal genetic influences act through general mechanisms, influencing global measures such as total SA. We also provide novel insights into the genetic relationship between CT and SA. Adult studies of CT and SA suggest that average CT and total SA are genetically independent (Panizzon et al. 2009; Winkler et al. 2010), and it has generally been assumed that this independence reflects different neural mechanisms occurring during prenatal brain development. For the first time, we reveal that the genetic relationship between these two features is significantly strong during infancy and is likely dynamic throughout the lifespan. This finding has immense implications on our current understanding of how underlying genetic and cellular processes influence cortical development. Primarily, it suggests that differences in CT and SA observed in adult studies may not be reflective of fetal differences in radial and tangential expansion as explained by the radial unit hypothesis. Moreover, it suggests that CT and SA independence may be driven by differences in

cellular and genetic processes that are implicated in synaptic pruning and neuronal degeneration. Additional genetic studies of CT and SA are needed to better understand how neurobiological processes are involved. Overall, we demonstrate that during the early perinatal window into brain development, genetic mechanisms contributing to CT and SA are largely overlapping and likely act in coordination to produce a properly functioning cortex.

An avenue for data reduction in large-scale imaging genetic studies

Our quantitative genetic approach allows us to examine genetic contributions to early cortical structure without the need to focus on specific genes or mechanisms (Lenroot and Giedd 2011). For this reason, it serves as a crucial first step for examining the genetic influences on imaging phenotypes like CT and SA (Blokland et al. 2012). Promising findings highlighted in our report enable researchers to prioritize cortical regions for future candidate gene studies and further GWAS analyses (van Dongen et al. 2012). Our results indicate that total SA, as well as regional SA in the bilateral insula should be the focus of genetic studies moving forward. Our results provide an important data reduction and selection approach for additional studies in typically developing cohorts and identify potential endophenotypes for future neurodevelopmental studies.

FUTURE DIRECTIONS

Replication is an important avenue for follow-up research. With the establishment of the Baby Connectome Project and a growing number of infant imaging datasets across the world (Broekman et al. 2014; Grewen et al. 2014; Holland et al. 2014; Spann et al. 2014; Deoni et al. 2015), it is feasible to investigate the role of environmental and genetic factors on cortical structure in other independent samples. Replication of our findings would greatly fortify our

current understanding of prenatal and perinatal influences on the brain and provide critical information about the generalizability of the current results. Additional proposed future studies are as follows:

Extension of the current environmental and genetic analyses to 1 and 2 year olds subjects

Cross-sectional and longitudinal follow-up studies are needed to address the stability of findings across the postnatal period. Pediatric imaging studies consistently demonstrate that the first two years of life are an extremely rapid and dynamic time of cortical brain growth. As reviewed in the introductory chapter, postnatal growth is driven by large increases in dendritic processes, elongation of axons, the proliferation of glial cells, and formation of synapses across the brain (Stiles 2008). At the structural level, these processes are reflected in complex regional patterns of volumetric growth and CT and SA change at ages 1 and 2 (Gilmore et al. 2012; Li, Lin, et al. 2015; Lyall et al. 2015). Concurrent with rapid structural growth, there is an emergence of early cognitive functions, with infants reaching many sensory, motor, and language milestones during this time (Luby 2017). All of these processes are heavily regulated by genetic and molecular mechanisms and are influenced by the ever-growing infant environment. Thus, as a feasible next step to the research outlined in this report, I propose environmental and genetic influences should continue to be examined during the first two years of life.

Many neonate subjects recruited through UNC's Early Brain Development Studies program have received follow-up structural MRI scans at ages 1 and 2. Specifically, there are 462 subjects at age 1 (189 singletons, 273 twins, 238 males, and 224 females) and 353 subjects at age 2 (162 singletons, 191 twins, 197 males, and 156 females) that can be used to assess the genetic and environmental predictors of CT and SA. Preliminary data regarding total SA and

overall average CT has been collected and provides interesting results regarding both environmental and genetic influences.

Regarding obstetric and demographic influences, sex is a significant predictor of total SA at ages 1 and 2. Compared to females, males have 7.21% larger SA at age 1 and 6.79% larger SA at age 2. Sex differences between males and females have also been observed in studies of total SA from childhood through adulthood (Raznahan et al. 2011; Walhovd et al. 2012; Wierenga et al. 2014) and were found in our neonate sample as well. Differences likely reflect the presence of androgens and other sex-chromosome related processes (Lentini et al. 2013; Knickmeyer, Wang, Zhu, Geng, Woolson, Hamer, Konneker, Styner, et al. 2014) influencing cortical growth during both prenatal and postnatal periods as well as effects of cultural and parental expectations (Luby 2017).

Regarding socioeconomic factors, we found paternal education is a significant predictor of total SA at the 2-year time point. With every additional year of paternal education, there is a 0.64% increase in total SA. In chapter 2, we discuss the negative relationship between average CT and paternal education in our neonate sample. Paternal education appears to be an important predictor of early cortical development, showing differential effects during early and late infancy. During early infancy, paternal education likely captures father's ability to provide psychosocial resources during pregnancy and the early postpartum period, support healthy maternal behaviors, and reduce stress (Blumenshine et al. 2011; Shapiro et al. 2016) and influences the cellular mechanisms governing CT. During late infancy and into toddlerhood, paternal education likely captures the father’s ability to provide cognitive stimulation in the home and reflects the quality and quantity of language exposure (Cabrera et al. 2007) and

influences neurodevelopmental processes involved in SA expansion. We found no significant environmental predictors of average CT at ages 1 and 2.

Additionally, univariate and bivariate ACE models were applied to assess the genetic influences driving variation in total SA and average CT at ages 1 and 2. Total SA was significantly heritable, with genetic influences accounting for a large portion of the observed variance (0.56 at age 1 and 0.92 at age 2). For average CT, genetic influences accounted for a moderate (0.45) and non-significant proportion of the total variance at age 1 but accounted for a large and significant portion of variance at age 2 (0.68). Results regarding total SA suggest that genetic influences remain significant determinants of individual differences in the surface area throughout the lifespan. Moreover, results regarding CT and SA at ages 1 and 2 support the notion that genetic influences increase with age from infancy to toddlerhood and likely into adulthood. Increasing heritability estimates may also reflect decreasing environmental influences or effects of canalization with age (Lenroot et al. 2009; Gilmore, Schmitt, et al. 2010; Douet et al. 2014). Most interestingly, while we observed a strong and positive genetic correlation between neonatal average CT and total SA, at ages 1 and 2 the genetic overlap between these variables was small and negative (-0.29 at age 1 and -0.29 at age 2). These outcomes are similar to those observed in adult studies (Winkler et al. 2010) suggesting that CT and SA relationships at birth are unique and may represent prenatal-specific cellular processes.

Preliminary outcomes from our cross-sectional analyses of 1 and 2-year-old samples provide a strong impetus for performing longitudinal analyses of CT and SA. Longitudinal studies will be critical in understanding whether there are significant differences in environmental effects or heritability estimates between neonates, one-year-olds, and two-year-olds. Assessments will also provide insight into how environmental and genetic factors influence

CT and SA growth trajectories across the first two years of life. Studies from our lab have revealed extensive growth in both cortical features in the first two years of life (Li, Lin, et al. 2015; Lyall et al. 2015) but have not explored the underlying influences.

Based on longitudinal studies of CT and SA in children, adolescents, and adults, and our cross-sectional results reviewed in this dissertation, I expect that we will find significant effects of sex (Raznahan et al. 2011; Wierenga et al. 2014; Vijayakumar et al. 2016) and birth weight (Raznahan et al. 2012; Walhovd et al. 2012) on global SA trajectories. Moreover, studies of intelligence reveal that general cognitive function is associated with trajectories of CT and SA during childhood, showing positive associations with SA and negative associations with CT(Shaw et al. 2006; Schnack et al. 2015). This is in keeping with our cross-sectional findings of paternal education and suggests that paternal and/or maternal education many also be significant contributors to cortical developmental trajectories in the first two years of life. Regarding genetic influences, I expect higher heritability estimates of total SA expansion compared to average CT growth. Additionally, because gene expression studies suggest increased synchronization of areal transcriptomes during postnatal development(Pletikos et al. 2014), I expect genetic factors will be significant drivers of global CT and SA trajectories and regional heritabilities over the first two years will be small. Overall, proposed longitudinal analyses would identify which obstetric, demographic, and genetic features contribute to the expansion of the cortex and how they differ from results observed at older ages.

Assessment of potential genetic variants associated with neonatal CT and SA

In this dissertation, we discuss the potential role of complex neurodevelopmental processes in shaping prenatal and postnatal CT and SA development. However, our results cannot directly address these relationships. To identify exact developmental processes and

whether they contribute to CT and SA development, I propose imaging genetic studies be performed during this period. Specifically, two feasible approaches for our pediatric dataset include candidate gene and genome-wide association analyses. Genetic activity in the embryonic and early fetal neocortex is imperative to the proliferation and migration of neuronal cell types. Conversely, during late fetal development, and continuing into perinatal development, gene expression patterns are reflective of neurodevelopmental processes such as synaptogenesis, dendritic development, gyrogenesis, and myelination (Kang et al. 2011; Tebbenkamp et al. 2014). What remains largely unexplored is how these early gene expression patterns contribute to the ultimate macrostructure of the cortex and more specifically to CT and SA growth. Investigating how genetic mechanisms govern the development of CT and SA might provide important implications into the distinct biological nature of these clinical endophenotypes.

Using a candidate gene approach, we can test whether variants in pre-specified genes of interest are associated with global and regional CT and SA measures. Genes would be selected based on biological and functional relevance. A few candidate gene studies in healthy adult and clinical populations have shown that genes related to brain development drive CT and SA growth in distinct ways. Variations in the *MECP2* region have been associated with SA but not CT in two independent adult populations (Joyner et al. 2009). In patients with schizophrenia, the effects of *COMT* on gray matter volumes are found to be driven largely by CT rather than SA (Li, Xiang, et al. 2015). No candidate gene studies of CT and SA have been performed in a normative population within the first few years of life.

This is a promising avenue for follow up research given that a previous study in our cohort (Knickmeyer, Wang, Zhu, Geng, Woolson, Hamer, Konneker, Lin, et al. 2014) revealed variations in neonatal local gray matter volumes were associated with polymorphisms in putative

psychiatric risk genes including *DISC1, COMT, NRG1, APOE, ESR1,* and *BDNF*. As a follow up, these candidate genes should also be studied in relation to CT and SA in our sample. Proposed candidates should also include biologically plausible genes based on gene expression analyses performed by Kang et al (2011). Specifically, these genes are linked to neuronal migration (*DCX*), dendritic development (*MAP1A, MAPT, CAMK2A*), neuronal differentiation (*MAP1B, MAP2, TUBB*), synaptogenesis (*SYP, SYPL1, SYPL2, SYN1*) and axonal development (*CNTN2*). Overall, I hypothesize that genes related to synaptogenesis and dendritic development will be most predictive of CT and SA. Additionally, I hypothesize that candidate gene associations will be the strongest for total surface area. This candidate gene approach would allow us to investigate genetic variants of known relevance to brain development and psychiatric and neurodevelopmental outcomes.

While the candidate gene approach enables us to investigate how genetic variants of known biological and clinical relevance impact cortical structure, current research in the field of imaging genetics has shifted toward GWAS. GWAS can provide an unbiased assessment of millions of markers across the genomes to identify novel variants associated with CT and SA development. GWA studies of CT and SA are extremely limited. Thus far, such analyses have identified common genetic variants that contribute to SA in the adult visual cortex (Bakken et al. 2012) and auditory cortex (Cai et al. 2014) but GWA studies aimed at identifying genes influencing cortical development are greatly lacking. By performing genome-wide assessments in infants, it is possible to capture individual differences in fetal and early postnatal neurodevelopmental processes such as neuron proliferation, migration and differentiation, axonal growth, dendritic arborization, synaptogenesis, myelination and programed cell death. Recently, our group performed the first GWAS of infant brain volumes and identified a significant genetic

variant in *IGFBP7* (rs114518130) associated with neonatal GM. Compared to imaging genetic studies in adolescents and adults, genetic determinants of neonatal brain volumes were highly distinct (Xia et al. 2017). Thus, genome-wide association studies of CT and SA during infancy would provide a unbiased approach to finding novel variants associated with foundational prenatal and perinatal developmental processes. I hypothesize that genes related to the development of neuronal and glial processes and synapses will be significant for neonatal CT development and genes related to radial glial proliferation, cortical folding, and programmed cell death will be most significant for explaining neonatal SA. Understanding the relationship between specific genes and CT and SA development will provide critically needed evidence regarding the origins of these morphometric features.

Investigation of links between SES, ethnicity/race, and brain structure

In our report, we examined the impacts of maternal and paternal ethnicity and SES variables like maternal education, paternal education, and total household income on inter-individual variation in global and regional CT and SA. Our results revealed meaningful relationship between SES and ethnic disparities, specifically paternal education and maternal ethnicity, and neonatal CT. To date, studies examining SES have focused on maternal education or have used an average or sum of educational attainment from all parents in the home (Lawson et al. 2013; Noble et al. 2015). To our knowledge, there are no neuroimaging studies which report contributions of paternal education to neurodevelopmental outcomes. Similarly, neuroimaging studies assessing maternal and paternal ethnicity in the context of healthy brain development are also greatly lacking. As a whole, imaging and behavioral studies of infant and childhood neurodevelopment should include parental education and ethnicity as important variables of interest moving forward. Additionally, future studies should focus on dissecting the

causal mechanisms underlying our findings of thinner cortices in infants of more educated fathers and infants of Caucasian mothers.

Important variables likely include levels of psychosocial stress and access and utilization of quality health care before, during and after pregnancy. To tackle these questions infant imaging studies should set specific goals for evaluating SES and ethnic disparities on brain structure using economically and ethnically diverse families. These studies should not only collect detailed infant medical and obstetric history variables but should also place a large focus on assessing prenatal stress and variables related to personalized prenatal care. Prenatal stress should be measured using a variety of instruments aimed at assessing anxiety, depression, socio-environmental stressors, stressors related to pregnancy and parenting, and daily hassles and life events (Nast et al. 2013). Quality of prenatal care should be assessed through parent reports and prenatal medical records to gage the initiation and frequency of medical visits and the quality of health care facilities, health care providers, and educational resources provided (Phillippi 2009; Phillippi et al. 2014).

Existing studies of psychosocial stress during pregnancy suggest that mothers who experience high levels of prenatal stress report higher incidences of gastrointestinal and respiratory illnesses and higher rates of urgent care and emergency department visits for infants in the first year of life (Phelan et al. 2015). Similarly, access to adequate antenatal care during pregnancy is associated with infant health outcomes such as preterm birth (Fernandez Turienzo et al. 2016). Studies of maternal well-being during pregnancy also show associations with brain structure, including cortical thickness in infants (Buss et al. 2010; Qiu, Tuan, et al. 2015). By collecting structural MR images and detailed prenatal data in a diverse population of infants,

researchers can assess whether relationships between brain structure and SES or ethnicity are mediated by variables reflecting antenatal stress and access to prenatal care.

Recently, randomized control trials have also become a potential avenue of future SES and brain development research. A current research study funded by the National Institutes of Child Health & Human Development has proposed to understand the relationship between SES and child development by conducting a randomized control trial to determine whether unconditional cash payments have causal effects on brain development in infants from low-income families in the first three years of life (HD087384). Similar approaches may be taken to study the mechanisms of prenatal stress and access to adequate health care during pregnancy and to evaluate the influences on structural phenotypes like CT and SA. By facilitating early and adequate access to prenatal care through monetary incentives and education approaches and assessing psychosocial burdens through home-based interventions and prenatal counseling, researchers can study how these mechanisms vary among diverse populations of parents and assess the impacts on neurodevelopmental outcomes in infants.

Importantly, future studies should also determine whether SES and ethnicity variables are associated with cognitive and functional outcomes during early development. Performing the studies above will allow public health and policy experts to develop interventions aimed at optimizing infant brain development and overall infant health outcomes.

OVERALL CONCLUSION

In summary, our findings suggest that CT and SA exhibit extremely rapid growth during the first month of life. These results also reveal genetic, obstetric, demographic, and socioeconomic factors are important determinants of cortical development during infancy. Both genetic and environmental influences, especially sex and birth weight, are central to individual

differences in neonatal SA while variation in neonatal CT is largely explained by environmental factors such as paternal education and maternal ethnicity. These influences likely impact key prenatal and early postnatal cellular processes responsible for the formation, differentiation, and organization of neurons and the establishment and refinement of neuronal circuits (Stiles and Jernigan 2010). Results are also particularly meaningful because the neonatal brain is highly plastic and thus a period for both intervention and potential injury. Overall, our findings highlight the important environmental and genetic influences on CT and SA development

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