Cortical Structure and Cognition in Infants and Toddlers

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Abstract

Cortical structure has been consistently related to cognitive abilities in children and adults, yet we know little about how the cortex develops to support emergent cognition in infancy and toddlerhood when cortical thickness (CT) and surface area (SA) are maturing rapidly. In this report, we assessed how regional and global measures of CT and SA in a sample ($N = 487$) of healthy neonates, 1-year-olds, and 2-year-olds related to motor, language, visual reception, and general cognitive ability. We report novel findings that thicker cortices at ages 1 and 2 and larger SA at birth, age 1, and age 2 confer a cognitive advantage in infancy and toddlerhood. While several expected brain–cognition relationships were observed, overlapping cortical regions were also implicated across cognitive domains, suggesting that infancy marks a period of plasticity and refinement in cortical structure to support burgeoning motor, language, and cognitive abilities. CT may be a particularly important morphological indicator of ability, but its impact on cognition is relatively weak when compared with gestational age and maternal education. Findings suggest that prenatal and early postnatal cortical developments are important for cognition in infants and toddlers but should be considered in relation to other child and demographic factors.

Key words: brain development, cognitive development, neuroimaging, surface area, thickness

Introduction

Mounting evidence indicates that morphological features of the neocortex correlate with intelligence and cognitive ability in adolescents and adults. Regional and hemispheric cortical gray matter volumes have been positively correlated with cognitive ability from late childhood into adulthood (Posthuma et al. 2003; Narr et al. 2007). Studies have begun to break down cortical volume into its two main constituents: cortical thickness (CT) and surface area (SA), which have been independently (Shaw et al. 2006; Narr et al. 2007; Karama et al. 2009;

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

The first 2 years of postnatal brain development are marked by robust growth and dynamic cortical maturation (Knickmeyer et al. 2008; Gilmore et al. 2012, 2018) driven primarily by the expansion of SA, which increases at more than three times the rate of CT (Lyall et al. 2015). Interestingly, CT reaches 97% of adult values by age 2 and shows similar heterogeneous cortical patterns to those seen in adults (Lyall et al. 2015), indicating that CT is largely determined during this critical period of brain development. The differential developmental patterns of CT and SA are no surprise, as these two cortical components are differentially influenced by prenatal and perinatal child-level and environmental factors (Jha et al. 2018a). While neonatal SA is primarily influenced by sex and birth weight, neonatal CT is impacted by environmental variables including parental education level and maternal ethnicity (Jha et al. 2018a). Recent work has shown infant brain SA is highly heritable, while CT is markedly less so, though the genetic overlap is stronger than expected (Jha et al. 2018b), findings that have been replicated in a study of children, adolescents, and young adults (Schmitt et al. 2019). These studies further highlight the need to decompose volumetric studies of the cortex into CT and SA, which are distinctly influenced by environmental factors and both jointly and independently shaped by genetic factors that may in turn shape cognition.

During the early postnatal period, rapid gray matter growth coincides with the acquisition and refinement of sensorimotor, visual, and language skills that allow for information processing and the development of cognition (Kagan et al. 2005). Studies in older children and adults reveal that increased CT in a distributed network of cortical regions—including the dorsal lateral prefrontal cortex, anterior cingulate gyrus, inferior parietal cortex, and regions in the temporal and occipital cortices—is associated with better cognitive performance (Sowell et al. 2004; Shaw et al. 2006; Narr et al. 2007; Karama et al. 2009; Goh et al. 2011; Karama et al. 2011; Burgaleta et al. 2014). While less is known about the associations between SA and cognition, recent studies have shown positive correlations between regional SA and cognitive ability in areas spanning the frontal and prefrontal cortices in young adults (Colom et al. 2013), frontal, lateral temporal, and inferior parietal cortices in older adults (Vuoksimaa et al. 2016), and total SA across the lifespan (Schnack et al. 2015). However, little work has been done to confirm that these same relationships between cortical structure and cognition exist in early life, particularly in typically developing children. A recent study demonstrating that infant cortical structure, particularly SA, in the first year of life was highly predictive of later diagnosis of autism spectrum disorder (Hazlett et al. 2017) emphasizes the urgency of studying and understanding how cortical morphology relates to cognition during the early postnatal period.

In the present study, we sought to determine the association between CT, SA, and measures of general cognitive ability, language, motor, and visual reception skills in the first 2 years of life in a sample of 487 healthy children. Using this unique longitudinal data set, we tested cross-sectional relationships between CT and SA and cognition at ages 1 and 2, associations between preceding CT and SA and future cognitive performance at ages 1 and 2, and how changes in CT and SA across the first 2 years of life relate to cognitive performance at age 2. We hypothesized that CT and SA measures in the first 2 years of life would be related to present and future cognitive performance, that brain–cognition relationships would be similar to those found in older children and adults, and that trajectories of cortical maturation will be important for cognition at age 2. To our knowledge, this study is the first to investigate how CT and SA relate to cognitive ability in the early postnatal period in a large cohort of healthy young children. Herein we report a summary of our findings, along with results from several different analytical models in our supplemental materials, with the intention of providing others in the field with hypothesis-generating resources for future investigation into how cortical development is related to emerging cognition in infants and toddlers.

Materials and Methods

Participants

Participants were part of the University of North Carolina at Chapel Hill (UNC) Early Brain Development Study, an ongoing study of human brain development in singletons and twins (Knickmeyer et al. 2008; Gilmore et al. 2010; Knickmeyer et al. 2017) with multiple lines of research investigating normative brain development, genetic, and environmental contributions to brain development using twins, as well as neurodevelopmental trajectories in children born to mothers with a psychiatric illness. Pregnant women were recruited from outpatient obstetrics and gynecology clinics at UNC Hospitals and Duke University Medical Center. Mothers were excluded from the study for major illness or use of illegal drugs during pregnancy. Magnetic resonance images (MRIs) were collected for research purposes from all offspring shortly after birth (preterm infants were brought back for scans around term-age when possible) and at ages 1 and 2 years, and all scans were reviewed by a neuroradiologist. Cognitive assessments were also collected at 1- and 2-year visits. From the total 1135 infant participants followed up after prenatal recruitment, we retrospectively identified 487 participants with at least one structural MRI that produced usable CT and SA data and at least one cognitive assessment who met the following inclusion criteria: no diagnosis of a major psychiatric disorder in the mother (33% of total exclusions), born at $\geq$32 weeks gestation (moderately premature to full term; 10%), spent $\leq$24 h in the neonatal intensive care unit following birth (36%), had no major abnormalities (including Chiari malformations and mild ventriculomegaly) noted on any MRI (15%), and had no major medical issues or illnesses reported up to age 2 (4%). We additionally excluded three participants who scored in the range for developmental delay on their cognitive assessments. For additional information regarding participant follow-up and attrition, see Supplement S1 Figures.

We included both twin and single-born infants in this analysis to provide us with the largest possible data set of healthy participants to test hypotheses about brain–cognition

Table 1 Population demographics

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

[a]Reported at the time of the child's birth.

relationships. We acknowledge the potential implications of including twins and have performed sensitivity analyses to address these concerns (see Statistical Analysis). Table 1 outlines the demographic characteristics of the sample. Informed written consent and parental permission was obtained from at least one parent of all child participants, and all study protocols were approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

Image Acquisition

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

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

Proton density and T2-weighted structural images used for cortical reconstruction in neonates were acquired on the Allegra using a turbo-spin echo sequence (TSE, TR = 6200 ms, TE1 = 20 ms, TE2 = 119 ms, flip angle = 150°, spatial resolution = 1.25 mm × 1.25 mm × 1.95 mm, $N = 166$) or a "fast" TSE sequence using a decreased TR, a smaller image matrix, and fewer slices (TSE, TR range = 5270–5690 ms, TE1 range = 20–21 ms, TE2 range = 119–124 ms, flip angle = 150°, spatial resolution = 1.25 mm × 1.25 mm × 1.95 mm, $N = 189$). For the Trio, participants were initially scanned using a TSE protocol (TR = 6200 ms, TE1 = 17, TE2 = 116 ms, flip angle = 150°, spatial resolution = 1.25 mm × 1.25 mm × 1.95 mm, $N = 4$), while the remainder were scanned using a 3DT2 SPACE protocol beginning in mid 2011 when a higher-resolution 3D T2-weighted imaging protocol became available (TR = 3200 ms, TE = 406, flip angle = 120°, spatial resolution = 1 mm × 1 mm × 1 mm, $N = 58$). No differences were found in the average CT or total SA measurements collected on the Tim Trio using the lower and higher resolution T2 protocols (CT: $t = -1.04$, $df = 4.56$, $P = 0.343$, SA: $t = 1.27$, $df = 4.18$, $P = 0.270$).

All T1- and T2-weighted MRIs used in this study were visually inspected by two expert raters. Raters scored images based on motion artifacts on a scale from 1 to 4, with 1 being the highest quality images with no visible artifacts to slight artifacts in a few slices and 4 being the lowest quality images with moderate to heavy artifacts in a few to many slices. Each rater underwent an inter- and intra-reliability test (average inter-rater reliability = 97.5%, average intra-rater reliability = 87%), and each image was scored by two raters. Rater scores for each image were averaged, unless they differed by two or more points, in which case raters met to discuss the image and generate a consensus score. Raters also determined the usability of the image, where images of the poorest quality (category 4) were excluded if the artifacts spanned more than a few slices. The motion rating scale was based on a previously described method (Lyall et al. 2015) and is included as a nuisance variable in sensitivity analyses to determine the impact of relative motion on the associations between neuroimaging measures of CT and SA and cognitive abilities in infancy and toddlerhood. In the entire cohort (i.e. full sample from which the data in this study were obtained, $n = 1135$) 2.5% of neonatal, 5% of 1-year, and 3% of 2-year T1/T2 images were deemed unusable based on excessive motion, artifacts affecting image contrast and quality, and poor brain coverage (see Supplement S1 Figures) and were excluded from further image analysis.

Image Analysis

CT and SA measures were derived using a pipeline previously described by Li et al. (2016) and Jha et al. (2018a). All MRIs were preprocessed for tissue segmentation using a standard infant-specific pipeline (Li et al. 2013) that includes automated skull stripping and manual editing of non-brain tissue, removal of the cerebellum and brain stem, corrections for intensity inhomogeneity, and rigid alignment of T1- and T2-weighted images into an average atlas space (Shi et al. 2011). Gray matter, white matter, and cerebrospinal fluid 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, 2014) was applied to the tissue segmentations in order to reconstruct the inner, middle, and outer cortical surfaces. This method involved a topological correction of white matter volume to ensure spherical topology, a tessellation of the corrected white matter to generate a triangular mesh, and the deformation of the inner mesh towards the reconstruction of each cortical surface while preserving the initial topology. All surfaces for the left and right hemisphere were visually examined for accurate mapping. In the entire cohort of participants with usable images, 3% of neonatal, 2% of 1-year, and <1% of 2-year cortical surfaces were excluded (and were not included in our data set of 487 total participants) due to poor correspondence between the reconstructed cortical surfaces and cortical anatomy on the structural MRIs (see Supplement S1 Figures for study flow chart).

The inner surface was defined as the boundary between gray matter and white matter, and the outer surface as the boundary between the gray matter and cerebral spinal fluid. A third surface, the middle cortical surface, was defined as the layer lying in the geometric center of the inner and outer surfaces of the cortex. CT was computed for each vertex as the average value of the minimum distance from the inner to the outer and outer to the inner surfaces. SA was computed based on the central cortical surface. The cortical surface was parcellated into 78 cortical regions of interest (ROIs) based on an infant-specific parcellation atlas (Tzourio-Mazoyer et al. 2002; Gilmore et al. 2012), as shown in Jha et al. (2018a). The average CT (mm) and total SA (mm^2) for each ROI were calculated as a mean of the values at each vertex within the ROI. Global measures of total cortical SA and average CT across the whole cortex were also computed.

Cognitive Assessments

Cognitive ability was assessed at ages 1 and 2 using the Mullen Scales of Early Learning (MSEL). Child measures of gross motor (GM), fine motor (FM), visual reception (VR), expressive and receptive language (EL and RL, respectively) were collected by experienced testers. Performance on the MSEL cognitive scales were analyzed as raw scores, and for the latter four scales age-standardized *t*-scores were combined into an Early Learning Composite (ELC) standardized score [range: 49–155, mean = 100, standard deviation (SD) = 15]. The ELC has high internal consistency (median = 0.91) and reliability (median = 0.84 for the cognitive scales during these testing ages), and principal factor loadings of the scales lend support for the construct validity of the ELC as a general measure of cognitive ability (Mullen 1995), much like an intelligence quotient. The primary measure of interest for this study was the ELC, though we also investigated MSEL raw scale scores (not normalized for age) for each of the cognitive domains. We specifically chose to study raw scores because we were interested in within-subject relationships between cognitive performance and brain structure and not in the association between a child's brain structure and their cognitive performance relative to others, a rationale that has been previously described (Naigles et al. 2017). A subset of the MSEL assessments (4% and 6% of MSEL tests at ages 1 and 2, respectively) were conducted in Spanish to match the native language of the child, and a sensitivity analysis was conducted removing data from tests in Spanish to ensure this testing language difference had no impact on the main findings in this report. Prior to use in this project, MSEL scores were reviewed, and assessments that were incomplete or were deemed to not accurately reflect a child's ability were removed from the data set (see Supplement S1 Figures for information on exclusion rates). Descriptive statistics of the MSEL scores can be seen in Table 2.

Table 2 Descriptive statistics of cognitive scores

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

Note: ELC scores are calculated from age-standardized *t*-scores of FM, VR, EL, and RL scales. GM, FM, VR, EL, and RL scores presented here are raw scale scores that reflect points granted during test administration.

Statistical Analysis

The analytic approach for this project was conducted in five main steps. The first three steps involve correlation analyses where we (1) calculate brain–cognition correlations adjusted for age and sex to establish a baseline for comparison, (2) calculate brain–cognition correlations adjusted for a full set of covariates including age and sex that we compare to results from step (1) to determine the relative importance of cortical features as biomarkers of cognition, and (3) calculate correlations between cortical structure and the full covariate set to determine how covariates impact cortical structure. The final analyses involve testing (4) mediation hypotheses and (5) conducting longitudinal analyses. Detailed descriptions of each step are outlined below:

Step 1: We established the presence and strength of associations between regional and global CT and SA shortly after birth, age 1, and age 2 and emerging cognition by calculating within-subject partial Pearson's correlations that were adjusted for sex and age at scan and cognitive assessment (if comparing across ages). Correlations between neonatal cortical structure and later cognition were also adjusted for gestational age (GA) at birth given its impact on neonatal brain size (Knickmeyer et al. 2017). All possible cross-sectional and longitudinal relationships were assessed for both regional and global measures of cortical morphology: 1) CT and SA in neonates correlating with MSEL scores at ages 1 and 2, 2) CT and SA at age 1 correlating with MSEL scores at age 1 and 2, and 3) CT and SA at age 2 correlating with MSEL scores at age 2. We chose to explore regional and global measures because total SA has long been implicated in cognition, and average CT in infants is influenced by factors that also influence cognition in children, including GA at birth (Jha et al. 2018a; Bhutta et al. 2002).

Step 2: We determined the relative associations between cognition and regional and global CT and SA during early postnatal development by adjusting Pearson's correlations for additional covariates shown to be related to cognitive scores in this age range in an overlapping sample (Girault et al. 2018a). These variables included maternal education and gestational number (i.e. twin or singleton), as well as GA at birth (previously included in models with neonatal brain measures, now added to all models) and two nuisance variables: MRI scanner and MSEL

test date. MSEL test date accounts for the time elapsed since the start of MSEL data collection at each 1- and 2-year study visit; this variable was shown to have an impact on 1-year MSEL scores, possibly reflecting changes in personnel across the 10-year study period, though the effect was small (Girault et al. 2018a). We then compared the age-and-sex-adjusted correlations from Step 1 (termed "Age-Sex" in figures) from the first step to the correlations adjusting for the full covariate set in this step (termed "All Covariates" in figures), which allowed us to explore the usefulness of regional and global measures of CT and SA in early development as biomarkers of infant and toddler cognitive abilities.

Step 3: We sought to identify the nature of associations between the cortical structure, alone, and the full covariate set [sex, GA at birth, age at scan and MSEL testing (if comparing across ages), gestational number, maternal education level, scanner, and MSEL test date]. We used both unadjusted and partial Pearson's correlations to test for associations. This allowed us to test whether covariates that were previously shown to be associated with cognition were also correlated with cortical structure.

Step 4: A mediation analysis was performed to evaluate whether total neonatal SA mediates the effect of GA at birth on 2-year ELC scores and whether total SA at age 1 mediates the effects of maternal education on 2-year ELC scores—hypotheses that were generated based on findings in the previous analytic steps. The mediation analyses involved four stages: (1) show that the predictor (GA/maternal education) is correlated with the response (2-year ELC scores), (2) show that the predictor is correlated with the mediator (total neonatal SA or 1-year SA) treating the mediator as a response variable, (3) show that the mediator affects the response variable while controlling for the predictor, and (4) use a Sobel test to evaluate the significance of the mediation. All steps were tested using linear regression models.

Step 5: We performed a longitudinal analysis to determine if developmental trajectories of regional or global CT and SA in the first 2 years of life are associated with cognitive abilities at age 2. Specifically, we tested if neonatal CT and SA (as a reflection of prenatal brain development; CT_0, SA_0), the change in CT and SA in the first year of postnatal life ($dCT_{1,0}$, $dSA_{1,0}$; calculated as a subtraction of the measurement at the earlier age from that of the later age divided by the time elapsed in days between the two visits), or the change in CT and SA in the second year of life ($dCT_{2,1}$, $dSA_{2,1}$) related to MSEL 2-year scores. To do this, we used linear mixed effects models predicting 2-year scores including measures of cortical structure at all three time points/intervals (i.e. CT_0, $dCT_{1,0}$, and $dCT_{2,1}$) simultaneously while controlling for GA, maternal education (MEDUY), age at MSEL testing (Age_{MSEL}), age at the neonatal and 1-year MRI visits ($AgeMRI_0$, $AgeMRI_1$), sex and nuisance variables including MRI scanner at each age ($Scanner_0$ = neonatal scanner, $Scanner_1$ = 1-year scanner, $Scanner_2$ = 2-year scanner), and MSEL test date ($DATE_{MSEL}$). Only participants with complete longitudinal data—neonatal, 1-year and 2-year scans and cognitive data at age 2—were included in these analyses, and one twin from each pair was treated as a repeated measure (data from 94 participants were used, with 81 treated as unique subjects and 13 treated as repeated measures; Table 3). The statistical model for CT predicting ELC at age 2 (ELC_2) is shown below:

$$ELC_2 = \beta_{intercept} + \beta_{CT_0} CT_0 + \beta_{dCT_{1,0}} dCT_{1,0} + \beta_{dCT_{2,1}} dCT_{2,1} + \beta_{GA} GA + \beta_{Age_{MSEL}} Age_{MSEL} + \beta_{AgeMRI_0} AgeMRI_0 + \beta_{AgeMRI_1} AgeMRI_1 + \beta_{sex} sex + \beta_{MEDUY} MEDUY + \beta_{Scanner_0} Scanner_0 + \beta_{Scanner_1} Scanner_1 + \beta_{Scanner_2} Scanner_2 + \beta_{DATE_{MSEL}} DATE_{MSEL} + \varepsilon,$$

where ELC_2 is the dependent variable, and CT_0, $dCT_{1,0}$,$dCT_{2,1}$, GA, Age_{MSEL}, $AgeMRI_1$, $AgeMRI_2$, sex, $MEDUY$, $Scanner_0$, $Scanner_1$, $Scanner_2$, and $DATE_{MSEL}$ are the independent variables, and ε is the random error. The model for SA predicting any MSEL 2-year score was constructed in the same manner.

We performed several sensitivity analyses. To ensure our results were not impacted by including twins or infants born preterm, we re-ran primary analyses in singletons and full-term subjects only (≥37 weeks gestation), respectively. Additionally, we re-ran primary analyses removing data from participants tested in Spanish to ensure that testing language did not impact our findings. Finally, to ensure that our general findings were reproducible, we ran a 10-fold cross-validation analysis to test for the stability of results relating global CT and SA to cognition.

As a sensitivity check of our main findings from the adjusted Pearson's correlations between CT and SA and cognitive scores, we re-ran primary analyses using mixed effects models, which account for the relatedness of twins by treating one twin from each pair as a repeated measure with compound symmetric covariance structure. Due to the inclusion of twin pairs in our study, we additionally tested whether certain brain or behavioral traits were strongly influenced by genetics by comparing monozygotic (MZ) and dizygotic (DZ) twin-pair correlations using Fisher's z-transformation and z-tests (Fisher 1970). Finally, sensitivity analyses were also performed where we additionally corrected for cubic root of intracranial volume (ICV) or average CT (for regional CT results) and total SA (for regional SA results) to account for overall brain size and structural MRI motion rating to assess whether visual motion ratings impact associations between MRI measures of CT and SA and infant cognition. Sample sizes for all analyses are reported in Table 3. All results from regional CT and SA analyses are corrected for multiple comparisons using false discovery rate (FDR) (Benjamini and Hochberg 1995), such that each model using regional cortical measurements is corrected for the number of ROIs analyzed; all

Table 3 Sample sizes across analyses

	Pearson's correlations	
	N (% of entire sample)	
Neo CT/SA—1-yearr MSEL	402 (82.55%)	
Neo CT/SA—2-year MSEL	319 (65.50%)	
1-year CT/SA—1-year MSEL	269 (55.24%)	
1-year CT/SA—2-year MSEL	206 (42.30%)	
2-year CT/SA—2-year MSEL	183 (37.58%)	
	Mixed effect models[a]	
	Unique subs	Repeated Measures
	N (%)	N
Longitudinal model	81 (16.63%)	13

[a]For mixed effects models, one twin from each pair are treated as a repeated measure using compound symmetric covariance structure.

Table 4 Correlations between average CT and cognition

	Average CT											
	Adjusted for age and sex						Adjusted for all covariates					
	Neonate		Age 1		Age 2		Neonate		Age 1		Age 2	
1-year scores	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*
ELC	0.03	0.556	0.105	0.088	—	—	−0.020	0.69	0.038	0.543	—	—
GM	0.064	0.204	**0.137**	**0.025***	—	—	0.045	0.373	**0.132**	**0.033***	—	—
FM	−0.026	0.606	**0.186**	**0.002***	—	—	−0.054	0.279	0.11	0.076	—	—
EL	0.016	0.753	**0.147**	**0.016***	—	—	−0.036	0.474	0.107	0.084	—	—
RL	0.003	0.958	**0.12**	**0.049***	—	—	−0.039	0.438	0.055	0.373	—	—
VR	0.078	0.122	0.02	0.746	—	—	0.044	0.379	−0.088	0.157	—	—
2-year scores	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*
ELC	−0.024	0.673	0.111	0.117	0.076	0.307	0.009	0.869	0.074	0.304	0.088	0.247
GM	−0.057	0.319	0.124	0.078	0.073	0.332	−0.067	0.24	0.094	0.186	0.061	0.419
FM	−0.047	0.411	0.016	0.819	−0.142	0.056	−0.045	0.43	−0.032	0.657	−0.13	0.086
EL	0.016	0.779	0.122	0.084	**0.16**	**0.031***	0.039	0.488	0.092	0.199	**0.185**	**0.014***
RL	−0.048	0.398	**0.189**	**0.007**[a]	**0.169**	**0.023***	−0.017	0.76	**0.162**	**0.022***	**0.189**	**0.012***
VR	0.031	0.589	0.069	0.322	0.093	0.211	0.064	0.261	0.04	0.581	0.081	0.284

Note: *Significant at $P \leq 0.05$; [a]Significant after Bonferroni correction for evaluating six scores in the same comparison.

Table 5 Correlations between total SA and cognition

	Total SA											
	Adjusted for age and sex						Adjusted for all covariates					
	Neonate		Age 1		Age 2		Neonate		Age 1		Age 2	
1-year scores	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*
ELC	0.041	0.411	0.03	0.629	—	—	−0.006	0.91	0.008	0.897	—	—
GM	0.001	0.98	−0.05	0.416	—	—	−0.03	0.552	−0.055	0.373	—	—
FM	0.018	0.717	0	0.984	—	—	−0.023	0.645	−0.04	0.516	—	—
EL	0.017	0.733	0	0.996	—	—	−0.028	0.582	−0.021	0.734	—	—
RL	0.012	0.8	0	0.966	—	—	−0.021	0.68	−0.041	0.505	—	—
VR	0.064	0.204	0.091	0.14	—	—	0.033	0.514	0.042	0.496	—	—
2-year scores	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*	*r*	*P value*
ELC	**0.113**	**0.046***	**0.169**	**0.016***	**0.182**	**0.014***	0.064	0.264	0.027	0.702	0.083	0.272
GM	−0.049	0.386	−0.034	0.628	−0.042	0.573	−0.056	0.324	−0.057	0.427	−0.057	0.449
FM	0.063	0.261	**0.172**	**0.013***	**0.189**	**0.011***	0.037	0.207	0.079	0.271	0.111	0.142
EL	0.055	0.333	0.104	0.139	0.07	0.372	0.065	0.252	−0.021	0.765	−0.002	0.976
RL	0.083	0.142	**0.14**	**0.046***	0.013	0.093	0.043	0.454	0.008	0.91	0.03	0.695
VR	0.11	0.052	**0.188**	**0.007**[a]	**0.202**	**0.006**[a]	0.065	0.252	0.074	0.299	0.146	0.053

Note: *Significant at $P \leq 0.05$; [a]Significant after Bonferroni correction for evaluating six scores at a single age comparison.

regional results presented in the paper survive FDR correction unless otherwise noted. All statistical analyses were performed using SAS statistical software, version 9.4.

Results

Average CT

There were significant age-and-sex-adjusted positive correlations (Table 4, left panel) between average CT at age 1 and GM, FM, EL, and RL scores at age 1 ($r = 0.137$, $P = 0.025$; $r = 0.186$, $P = 0.002$; $r = 0.147$, $P = 0.016$; $r = 0.120$, $P = 0.049$, respectively), average CT at age 1 and RL scores at age 2 ($r = 0.189$, $P = 0.007$), and average CT at age 2 and EL ($r = 0.160$, $P = 0.031$) and RL scores ($r = 0.169$, $P = 0.023$) at age 2.

Many of these findings are also present after correction for the full covariate set (Table 4, right panel). Average CT at age 1 was positively correlated with GM scores at age 1 ($r = 0.132$, $P = 0.033$), average CT at ages 1 and 2 were positively correlated with RL scores at age 2 ($r = 0.162$, $P = 0.022$ and $r = 0.189$, $P = 0.012$, respectively), and average CT at age 2 was positively correlated with EL scores at age 2 ($r = 0.185$, $P = 0.014$).

Regional CT

ELC Scores

There were significant age-and-sex-adjusted positive correlations between ELC scores at age 2 and CT at age 1 in the bilateral middle frontal gyri, anterior cingulate, and bilateral middle temporal gyri (Fig. 1). None of these associations remain significant after adjusting for the full covariate set, and we found no significant correlations between regional neonatal CT and ELC scores at either age. However, at age 2, ELC scores were significantly positively correlated with CT in the right insula at the same age (Fig. 2) after adjustment for the full covariate set.

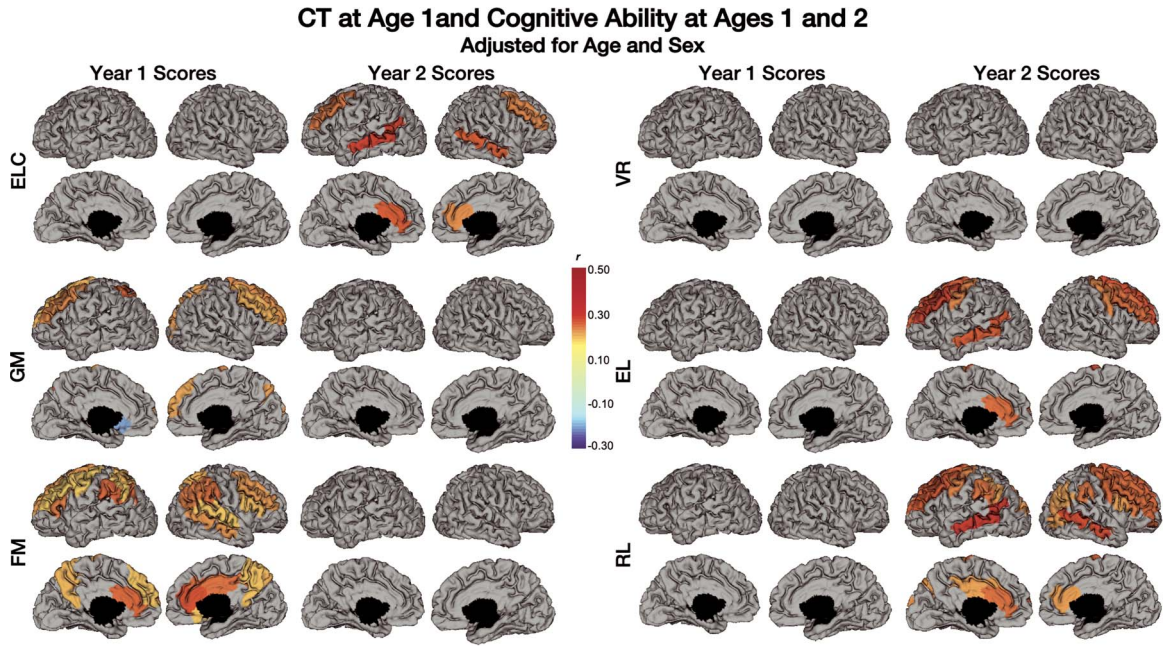

Figure 1. Significant age-and-sex-adjusted within-subject Pearson's correlations between CT at age 1 and cognitive abilities at ages 1 and 2. Correlations are shown in anatomical space for ELC (top left), GM (middle left), FM (bottom left), VR (top right), EL (middle right), and RL (bottom right) scores. All Pearson's correlations survive FDR correction ($q \leq 0.05$). Blue colors represent negative correlations, and yellow to red colors represent positive correlations; nonsignificant regions are shown in gray, and subcortical structures not analyzed are shown in black.

1-year Scale Scores

There were significant age-and-sex-adjusted positive correlations between GM scores and CT at age 1 in the bilateral superior frontal and middle frontal gyri, right medial superior frontal gyrus, right occipital superior gyrus, and the bilateral superior parietal cortices, while GM scores at age 1 were negatively correlated with CT in the left olfactory cortex at the same age (Fig. 1). Age-and-sex-adjusted positive associations were also found between FM scores at age 1 and CT at age 1 in the left primary motor cortex, bilateral regions in the frontal, prefrontal, and parietal cortices, bilateral anterior cingulate and precuneus, right middle cingulate, right superior and middle temporal cortices, right olfactory cortex, right medial superior frontal gyrus, and right frontal inferior operculum (Fig. 1). After adjusting for the full covariate set, all associations between GM and FM at age 1 and CT at age 1 were no longer present, except the relationship between 1-year GM scores and CT at age 1 in the left superior parietal cortex ($r = 0.21$, $q = 0.037$). A marginally significant association emerged after adjusting for the full covariate set between CT at birth in the right fusiform gyrus and EL scores at age 1 ($r = -0.171$, $q = 0.049$).

2-year Scale Scores

There were significant age-and-sex-adjusted positive correlations between EL scores at age 2 and CT at age 1 in the bilateral primary motor cortex, bilateral regions in the frontal cortex, right middle temporal gyri, and right anterior cingulate (Fig. 1). There were also significant age-and-sex-adjusted positive correlations between RL scores at age 2 and CT at age 1 in bilateral regions in frontal and parietal cortices, including regions overlapping with Wernicke's and Geschwind's areas, the bilateral middle temporal gyrus, regions overlapping with Broca's area in the right hemisphere, the right middle orbitofrontal gyrus, the bilateral anterior cingulate, and right middle cingulate, the left superior and right middle occipital gyri, and left inferior parietal cortex (Fig. 1). None of these associations remain significant after adjusting for the full covariate set.

EL scores at age 2 were positively correlated with CT at age 2 in the left primary motor and right middle orbitofrontal cortex. RL and VR scores at age 2 were positively correlated with CT in the right insula at the same age (Fig. 2). Each of these findings was significant after adjusting for the full covariate set. Significant correlations were also found between EL scores at age 2 and CT at age 2 in the left right frontal inferior operculum, bilateral rolandic operculum, right insula, right posterior cingulate, left heschl's gyrus, and left superior temporal gyrus.

A significant age-and-sex-adjusted negative correlation was found between 2-year FM scores and CT at age 2 in the left lingual gyrus ($r = -0.29$, $q = 0.0078$), though it did not survive adjustment for the full covariate set. All regional CT results can be viewed in table format in Supplement S2 Tables.

Total SA

Results from correlation analyses (Table 5) revealed significant age-and-sex-adjusted positive correlations between total SA shortly after birth, at age 1 and age 2, and ELC scores at age 2 ($r = 0.113$, $P = 0.046$; $r = 0.169$, $P = 0.016$; and $r = 0.182$, $P = 0.014$, respectively). Total SA at age 1 was also related to FM, RL and VR scores at age 2 ($r = 0.172$, $P = 0.013$; $r = 0.140$, $P = 0.046$; and $r = 0.188$, $P = 0.007$, respectively), and total SA at age 2 was correlated with FM and VR scores at age 2 ($r = 0.189$, $P = 0.011$ and $r = 0.202$, $P = 0.006$, respectively). No associations were significant after adjusting for the full covariate set.

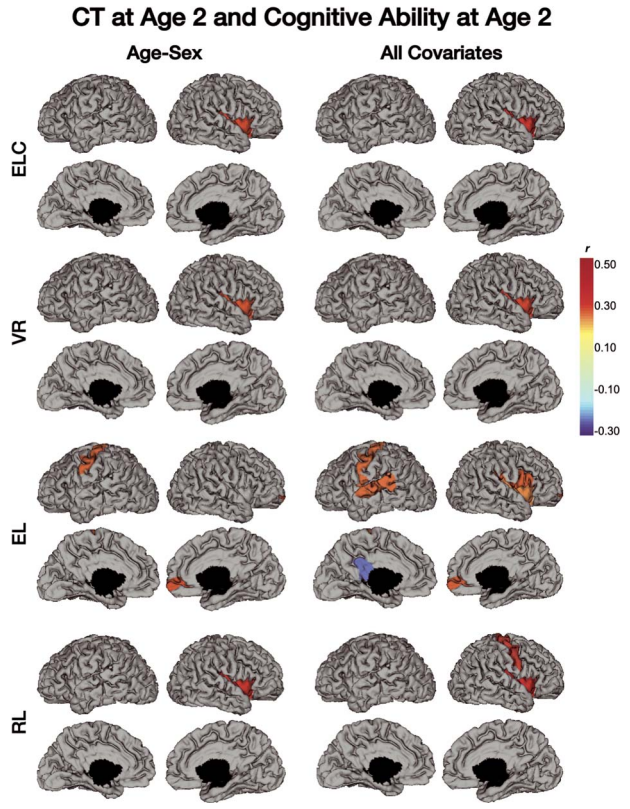

Figure 2. Comparison of age-and-sex-adjusted Pearson's correlations between CT at age 2 and cognitive scores at age 2 and those adjusted for all covariates (GA at birth, gestational number, sex, age at assessment, maternal education, and nuisance variables related to scanner and cognitive testing date). Correlations are shown in anatomical space for ELC, VR, EL, and RL scores. Age-and-sex-adjusted correlations are shown on the left side of each panel, and correlations adjusted for the full covariate set are shown the right. All Pearson's correlations survive FDR correction ($q \leq 0.05$). Blue colors represent negative correlations, and yellow to red colors represent positive correlations; nonsignificant regions are shown in gray, and subcortical structures not analyzed are shown in black.

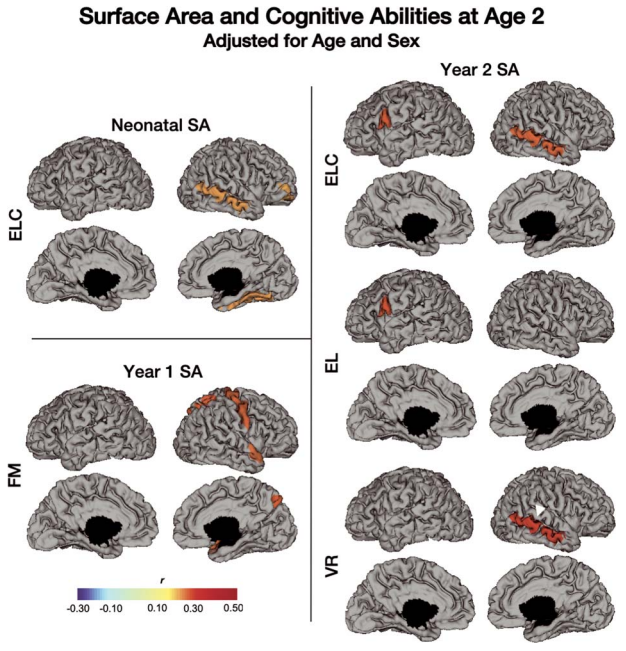

Figure 3. Significant age-and-sex-adjusted Pearson's correlations are shown between regional neonatal SA and the 2-year ELC (top left), 1-year SA and 2-year FM scores (bottom left), and 2-year SA and 2-year ELC, EL, and VR scores (right). The association between VR scores and SA in the right medial temporal lobe survives adjustment for the full covariate set ($r = 0.289$, $q = 0.008$; indicated by a white triangle). All Pearson's correlations survive FDR correction ($q \leq 0.05$). Blue colors represent negative correlations, and yellow to red colors represent positive correlations; nonsignificant regions are shown in gray, and subcortical structures not analyzed are shown in black.

Regional SA

ELC Scores

There were significant age-and-sex-adjusted positive correlations between neonatal SA and ELC scores at age 2 in the right middle temporal gyrus, right fusiform gyrus, and right middle orbitofrontal gyrus (Fig. 3). Larger SA at age 2 in the right middle temporal gyrus was also associated with higher 2-year ELC scores, along with larger SA in the left frontal inferior operculum overlapping with Broca's area. These associations, however, did not remain significant after adjusting for the full covariate set.

1-year Scale Scores

There were no significant relationships between regional SA at any age and cognitive scores at age 1.

2-year Scale Scores

Significant age-and-sex-adjusted associations were found between FM scores at age 2 and SA at age 1 in the right primary motor cortex, right superior temporal pole, and right superior parietal cortex (Fig. 3), though these associations do not survive adjustment for the full covariate set.

There was a significant age-and-sex-adjusted positive correlation between SA at age 2 in the left frontal inferior operculum overlapping with Broca's area and EL scores at the same age (Fig. 3). A significant age-and-sex-adjusted correlation was found between VR scores at age 2 and SA at age 2 in the right middle temporal gyrus (Fig. 3), which was also significant after adjustment for the full covariate set ($r = 0.289$, $q = 0.008$). All regional SA results can be viewed in table format in Supplement S3 Tables.

Covariates impacting CT and SA

We found that total and regional neonatal SA were correlated with GA at birth, as has been previously reported by our group using an overlapping sample (Jha et al. 2018a), such that longer gestation relates to larger total and regional SA, even after controlling for maternal education, gestational number, sex, age at MRI, and scanner ($r = 0.54$, $q < 0.0001$ for total SA; Fig. 4A). Associations between GA at birth and total SA at the neonatal scan are present across the range of postnatal age at scan (Fig. 4A). These effects of GA on SA are not present at ages 1 and 2. Gestational age at birth was positively associated with average CT ($r = 0.16$, $q = 0.0013$) after accounting for postnatal age at MRI, maternal education level, sex, gestational number, and MRI scanner. Total SA shortly after birth, at age 1, and at age 2 were positively correlated with maternal education level ($r = 0.10$, $q < 0.05$ for neonatal SA; $r = 0.29$, $q < 0.0001$ for SA at age 1; $r = 0.19$, $q < 0.05$ for SA at age 2), though only total SA at birth and age 1 remained significantly correlated with maternal education after adjusting for GA, gestation number, sex, age at MRI, and scanner ($r = 0.11$, $q = 0.022$ for neonatal SA; $r = 0.30$, $q < 0.0001$ for SA at age 1).

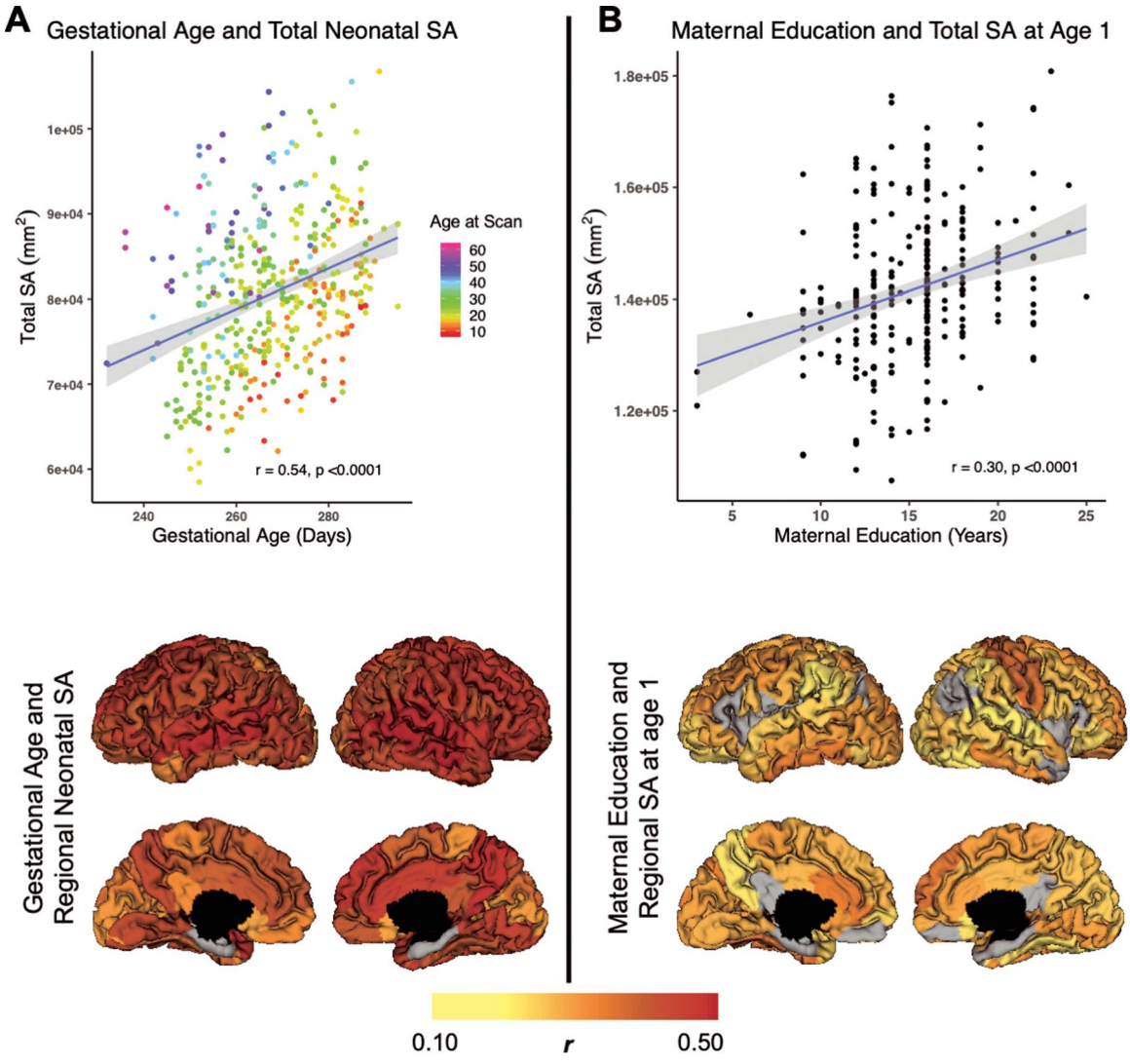

Figure 4. Significant correlations between global and regional neonatal SA and GA at birth (*A*) are presented for the sample; individual data points are colored by postnatal age at MRI in days. Significant correlations between global and regional SA at age 1 and maternal education level (*B*) are shown. Pearson's correlations after correction for covariates and significance level are shown for global associations. Pearson's correlation values for regional results that survived adjustment for covariates and FDR correction are shown in anatomical space ($q \leq 0.05$). Blue colors represent negative correlations, and yellow to red colors represent positive correlations; nonsignificant regions are shown in gray, and subcortical structures not analyzed are shown in black.

Regional associations between maternal education and SA are also present at age 1 across the cortex after adjusting for covariates (Fig. 4B). Few regional associations were found between maternal education and neonatal SA after adjusting for GA, gestation number, age at MRI, and scanner (right middle orbitofrontal gyrus: $r = 0.181$, $q = 0.011$; right olfactory gyrus: $r = 0.178$, $q = 0.011$).

Mediation Analyses

We found no significant mediating effect of total neonatal SA on the association between GA at birth and ELC scores at 2 years of age (Sobel test statistic = 1.13, $SE = 0.02$, $P = 0.26$). Total SA at age 1 was also not found to mediate the association between maternal education level and offspring 2-year ELC scores (Sobel test statistic = −1.16, $SE = 0.09$, $P = 0.25$).

Longitudinal Analyses

Longitudinal analyses revealed no significant relationships between the developmental change in regional CT or SA during the first or second year of life and cognitive scores at age 2. However, the change in total SA from age 1 to 2 was marginally significantly associated with FM scores at age 2 ($\beta = -0.036$, $P = 0.05$), such that slower SA expansion in the second year of life was associated with higher FM scores at age 2. This translates to very small impacts on FM scores; where the slowest to fastest rates of cortical SA expansion related to a decrease in expected FM scores at age 2 by 1.3 and 4.0 points, respectively.

Sensitivity Analyses

Analyses investigating the similarity of findings between our full sample and sub-samples of only full-term infants, singletons,

and participants tested only in English revealed highly similar results; similar trends were noted across all samples, though some correlations were weaker and did not reach statistical significance in the full-term and singleton-only samples, likely due to reduced sample size (Supplement S4 Tables). Results from the cross-validation analysis of global CT and SA replicated findings presented in Tables 4 and 5, further suggesting that the main findings in the manuscript are generalizable (Supplement S4 Tables). Additionally, results were highly similar between mixed effects models treating each twin from a twin-pair as a repeated measure and main findings from the adjusted Pearson's correlations (Supplement S5 Tables).

Comparing DZ ($n = 64$) and MZ ($n = 39$) twin correlations for brain and behavioral traits revealed that GM scores at age 1 (DZ: $r = 0.57$, MZ: $r = 0.92$, $z = -4.58$, $P < 0.0001$) and 2 (DZ: $r = 0.48$, MZ: $r = 0.80$, $z = -2.36$, $P = 0.0184$) and EL scores at age 2 (DZ: $r = 0.57$, MZ: $r = 0.64$, $z = -5.59$, $P < 0.0001$) were more strongly correlated in MZ pairs. Total SA at birth (DZ: $r = 0.81$, MZ: $r = 0.97$, $z = -3.53$, $P = 0.0004$) and age 1 (DZ: $r = 0.74$, MZ: $r = 0.96$, $z = -3.15$, $P = 0.0016$) were also more strongly correlated in MZ pairs; there were no significant associations between total SA at these ages, and cognitive measure found to be under strong genetic influence in this sample. Average CT at age 2 (DZ: $r = 0.62$, MZ: $r = 0.95$, $z = -3.18$, $P = 0.0015$) was more strongly correlated in MZ twins and was also found to be significantly correlated with EL at age 2 (Table 4), suggesting a notable role of genetic factors in this brain–cognition association. There was no overlap between regions with greater genetic influence (greater MZ vs. DZ correlations) and regions exhibiting CT–cognition associations. SA in the right middle temporal gyrus at birth was more strongly correlated among MZ pairs (DZ: $r = 0.61$, MZ: $r = 0.91$, $z = -3.36$, $q = 0.01$) and was also associated with ELC scores at age 2 (Fig. 3). However, this same region was implicated in brain–cognition associations at age 2, but there was no difference in the SA correlations between MZ and DZ pairs at this age. Taken together, our findings suggest that while brain measures and cognitive scores are under some level of genetic influence, results do not generally overlap with the main findings in this paper. This, coupled with sensitivity analyses demonstrating substantively similar results between twin and singleton subsamples and between mixed effects models and correlation analyses, suggests that the inclusion of twin pairs does not alter our primary findings.

Controlling for overall brain size (cubic root of ICV or average CT for regional CT results and total SA for regional SA results) or motion score in addition to other covariates did not substantially change the majority of results (Supplement S2 Tables, Supplement S3 Tables). Controlling for motion score did marginally rescue significant correlations between CT at age 1 and future RL scores at age 2 in regions overlapping with Broca's, Wernicke's, and Geschwind's areas and regions in the temporal lobe that were no longer significant after adjusting for the full covariate set (Fig. 5).

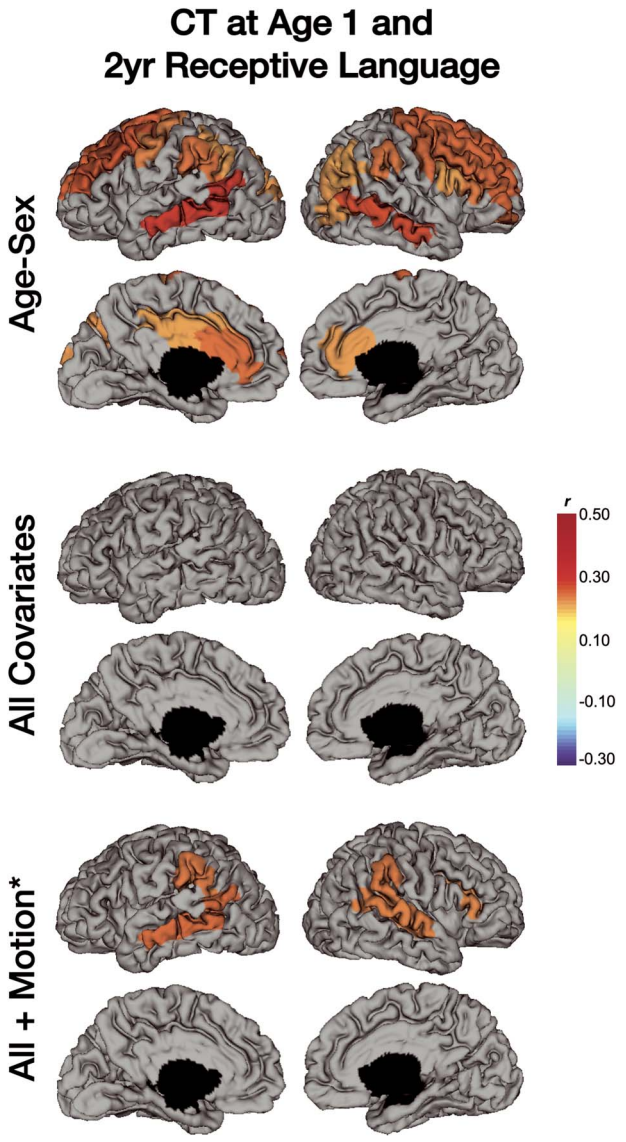

Figure 5. Comparison of age-and-sex-adjusted Pearson's correlations (top), those adjusted for all primary covariates (GA at birth, age at MRI, gestational number, sex, age at assessment, maternal education, and nuisance variables related to scanner and cognitive testing date; middle), and those adjusted for the full covariate set plus motion rater score (bottom) are displayed for associations between regional CT at age 1- and 2-year RL scores. Age-and-sex-adjusted Pearson's correlations survive FDR correction ($q \leq 0.05$), there are no significant associations surviving FDR for the full covariate set ($q > 0.09$), and correlations after adjustment for motion are marginally significant ($* = q < 0.06$). Blue colors represent negative correlations, and yellow to red colors represent positive correlations; nonsignificant regions are shown in gray, and subcortical structures not analyzed are shown in black.

Discussion

In the present study, we report the first associations between global and regional CT and SA and cognitive abilities in healthy infants and toddlers. We found that generally thicker, larger cortices across infancy related to better performance on cognitive tasks, suggesting that mechanisms governing cortical expansion play an important role in normative infant cognitive development. We found several expected brain–cognition relationships, with regions associated with motor planning and execution correlating with FM and GM scores and regions associated with language processing and production relating to EL and RL scores; though there was also a considerable overlap in cortical areas involved in early motor and language development. We generally found more significant relationships between CT and cognition than SA and cognition in infancy and toddlerhood. Analyses controlling for variables related to children's cognitive scores, including maternal education level, sex, GA, and

gestation number, reveal that correlations are greatly reduced after adding these variables in to the model. This suggests that while there are relationships between CT, SA, and cognition during this developmental period, the effect sizes are small when compared to other readily available child-level and environmental variables.

In general, we found that thicker, larger cortices related to better cognitive performance across domains in many regions that canonically support motor, language, and general cognition. CT at age 1 was correlated with future ELC scores at age 2 in a set of bilateral regions constrained to the middle frontal gyri spanning the dorsolateral prefrontal cortex and the anterior cingulate that have been implicated in cognitive control and attentional processes (Cai et al. 2016), as well as the middle temporal gyri that is responsible for processing sensory information (Jung and Haier 2007). Interestingly, these regions largely overlap with those implicated in the parieto-frontal integration theory of intelligence based on a review of human neuroimaging studies (Jung and Haier 2007), suggesting that the structural development of this cognitive network may begin during early infancy. We also found that CT in the right insula at age 2 was correlated with concurrent cognitive ability, which is interesting given the insula's role in integrating information across distinct cognitive and emotional networks (Chang et al. 2013). Our findings that cortical structure shortly after birth and at age 1 are associated with future cognition at age 2 and that cognition at age 2 is related to current cortical structure suggest that cognitive abilities are, at least in part, determined by preceding prenatal and postnatal brain development and related to present cortical structure in regions important for general cognition and network integration.

CT in several regions involved in sensory motor processing at age 1 were related to concurrent GM ability. These regions include the bilateral superior parietal cortex involved in motor planning and visuo-motor integration (Desmurget et al. 1999), bilateral frontal middle and frontal superior gyri that overlap with areas thought to relay goal-directed motor behavior (Corbetta and Shulman 2002), as well as the right occipital superior cortex involved in spatial visual processing (Haxby et al. 1991). Thicker cortices at age 1 also related to concurrent FM scores in several regions involved in motor behaviors including the left primary motor cortex, bilateral regions in the frontal and anterior cingulate cortices, and the bilateral superior and inferior parietal cortices that are thought to play a role in motor planning (Rizzolatti and Luppino 2001). Regions involved in language processing were also found to be related to FM scores at age 1, including regions overlapping Broca's, Wernicke's, and Geschwind's areas and the right superior and middle temporal cortices. Such an overlap in cortical areas is supporting by a growing body of work linking the development of motor and language skills (Iverson 2010, Bedford et al. 2016).

Language scores at age 1 were not related to regional cortical structure across infancy, though many associations between CT at age 1 and future language scores at 2 were found. CT in regions in the frontal, parietal, occipital, temporal, and midline association cortices at age 1 were associated with future RL and EL scores. Additionally, thicker right insular cortices at age 2 were significantly associated with higher RL and EL scores at the same age, while thicker cortex in regions overlapping Broca's area were related to EL. Additionally, larger SA in the right frontal inferior operculum overlapping Broca's area at age 2 was associated with higher EL abilities at the same age. Results appeared to be less domain specific with language scores, such that language regions (Broca's and Geschwind's areas and middle temporal gyri), sensory-motor regions (occipital cortices and primary motor cortex), and regions responsible for higher-order cognition (cingulate and prefrontal cortex) were found to associate with language scores at age 2. This could reflect a large-scale cortical network that is involved in early language learning that later becomes fine-tuned to adult-like regions through interactive specialization (Johnson 2000, 2011), as has been previously suggested (Redcay et al. 2008; Swanson et al. 2015).

Thicker cortices have often been linked to better cognitive performance in older children and adults (Sowell et al. 2004; Shaw et al. 2006; Narr et al. 2007; Luders et al. 2009; Karama et al. 2011; Burgaleta et al. 2014), and we have now extended these results to demonstrate early postnatal origins of such relationships starting around age 1. However, some regional CT findings were of the opposite direction, with thinner cortices associated with higher cognitive scores. These findings may suggest that some brain regions have a differential association between CT and cognition, which has been shown previously (Shaw et al. 2006; Choi et al. 2008; Goh et al. 2011; Burgaleta et al. 2014; Schnack et al. 2015). Fewer studies have focused on relationships between SA and cognition, but those that have demonstrate that larger SA is related to higher general intelligence (Colom et al. 2013; Yang et al. 2013; Fjell et al. 2015; Vuoksimaa et al. 2015) and that this association may be mediated by genetic factors (Schmitt et al. 2019). Our findings relating SA in neonates, 1-year-olds, and 2-year-olds, as well as the rate of SA expansion in the second year of life to cognitive abilities at age 2, are consistent with these findings and suggests that prenatal and early postnatal mechanisms driving SA expansion in infancy are important for emerging cognition.

The majority of significant results from these analyses were between CT, as opposed to SA, and cognition. While studies in adult male twins have reported CT and SA to be genetically distinct (Panizzon et al. 2009; Chen et al. 2013), more recent reports in neonates (Jha et al. 2018b) and children and adolescents (Schmitt et al. 2019) show that CT and SA have a strong genetic overlap. Genetic independence of CT and SA is supported by the radial unit hypothesis that posits that SA is determined by the number of cortical minicolumns, which is dependent upon the rate of cell proliferation and programmed cell death within symmetrically dividing radial glial cells of the ventricular zone (Rakic 2009), while CT is determined by changes in proliferation kinetics of asymmetrically dividing neural progenitor cells and changes in the size or number of neurons or glia and their processes (Rakic 1995, 2009). However, recent work has challenged this traditional model of cortical expansion (Kriegstein et al. 2006; Nowakowski et al. 2016), suggesting that it may not fully account for observed developmental patterns of CT (Kriegstein et al. 2006). Thus, it will be important moving forward to consider the genetic and environmental influences that shape the developmental trajectories of CT and SA and their associations with cognitive development.

While the genetic associations between CT and SA are likely much stronger than previously recognized, CT and SA still appear to follow different developmental trajectories across early infancy (Lyall et al. 2015) and adulthood (Schnack et al. 2015). We recently reported that neonatal CT and SA are impacted by different sets of environmental factors, with SA more strongly influenced by sex and obstetric history and CT more strongly influenced by socioeconomic and ethnic disparities (Jha et al. 2018a). This study also found that during

the neonatal period, heterogeneous growth patterns were observed in regional CT, while heterogeneity in regional SA growth was nominal (Jha et al. 2018a). We also recently reported significant additive genetic influences on total brain SA and small and nonsignificant genetic influences on average CT (Jha et al. 2018b). In light of the results reported here, this suggests that perhaps CT, shaped more by environmental experiences, is dynamically changing in early life to support experience-dependent learning and cognitive development in infancy and toddlerhood, whereas SA, shaped largely by genetic and obstetric factors, may set the stage for future cortical expansion and have a more global, brain-wide association with cognition thereafter.

In light of the environmental and demographic influences—which may have a genetic component—observed on both brain and cognitive development, it is no surprise that the majority of our results are no longer significant after adding these variables to the model. Regional CT and SA accounted for between roughly 2% and 9% of the variance in cognitive scores across models, highlighting that while there are correlations between cortical structure and cognition during these ages, they are modest. These correlations are of a similar magnitude to those previously reported in studies of older children and adults (Shaw et al. 2006; Narr et al. 2007; Karama et al. 2009; Burgaleta et al. 2014), suggesting that the strength of the associations between cortical structure and cognition are similar across development. In comparison, maternal education accounts for roughly 16% of the variance in children's 2-year cognitive scores, while GA at birth accounts for 12% of the variance in cognitive scores for twins and about 4% for singletons (Girault et al. 2018b). We also found influences of maternal education and GA at birth on cortical structure, with maternal education accounting for less than 2% of the variation in CT and SA in neonates, 9% of the variation in SA at age 1, and less than 4% of the variation in SA at age 2, echoing recent findings linking SA to socioeconomic factors in infancy (Jha et al. 2018a) and from childhood into early adulthood (Noble et al. 2015, McDermott et al. 2019). GA at birth only influenced neonatal cortical structure, accounting for roughly 2.5% of the variance in CT and 29% of the variance in SA after adjusting for other covariates including postnatal age at MRI, which is in line with reports from Jha et al. (2018a). Taken together, this suggests that maternal education and GA at birth exert influences on both brain and cognitive development that deserve further mechanistic study.

Interestingly, however, some results do survive adjustment for the full covariate set, indicating that these regions are perhaps informative neuroimaging biomarkers that account for individual differences in cognitive development in infancy and toddlerhood. The relationship between CT in the right insula at age 2 and concurrent VR, EL, RL, and ELC scores highlights a potentially interesting role for the insular cortex in general cognitive functioning in early life. Mounting evidence from functional MRI studies suggest that the insula is instrumental in integrating disparate functional systems involved in processing affect, sensorimotor information, and general cognition and is well suited to provide an interface between feelings, cognition, and action (Chang et al. 2013). Our findings suggest that by age 2, the insula may be structurally developing to support such a role in cognitive processing, which may be, at least partially, driven by the genetic heritability of CT in this region (Jha et al. 2018b). Other recent work suggests that the development of the insula may warrant further study, as the insula is a high-expanding cortical region during childhood and adolescence (Fjell et al. 2015), and disruptions in its regulation of central executive and default mode networks has been implicated in pathogenic states including schizophrenia (Namkung et al. 2017). Additional relationships that survived adjustment include expected brain–cognition relationships between 2-year CT in regions overlapping Broca's area and the superior temporal gyrus and EL scores at age 2, suggesting that by age 2, cortical areas responsible for speech production and language processing are organized to provide a foundation for burgeoning language abilities in toddlerhood. It is also important to note that a few brain–cognition associations between CT at age 2 and 2-year RL and EL scores emerged after adjusting Pearson's correlations for covariates; this suggests that after reducing between-subject variability in MSEL scores and CT values attributable to covariates, meaningful unique variation in residual MSEL values associated with the residual CT values are more detectable. These findings highlight the need to understand the unique and joint contribution of neuroimaging biomarkers and demographic characteristics to cognitive phenotypes.

From a developmental perspective, we identified that cortical structure was relevant for both concurrent and future cognitive performance. To our surprise, we found no significant associations between developmental changes in regional CT and SA across the first 2 years of life with cognitive abilities at age 2, though we did find a marginal association linking total SA expansion in the second year of life to FM scores at age 2. This finding that protracted rates of SA expansion from age 1 to 2 may relate to better toddler FM skills is in line with work demonstrating aberrant hyperexpansion of total SA from 6 to 12 months in infants later diagnosed with autism (Hazlett et al. 2017), though we caution over-interpretation of these findings as our sample sizes are small for the longitudinal analysis, and this result was marginally significant. The lack of regional findings may be a limitation of smaller sample sizes with full longitudinal data or a relatively low number of sampling points for the imaging data. Alternatively, it could suggest that the heterogeneous associations between the rates of local cortical maturation and cognition often reported in studies of older children and adults (Shaw et al. 2006; Schnack et al. 2015) may emerge later in development, especially given that these studies associated cortical thinning with cognition, while most of the cortex is still thickening across the first 2 years of life (Lyall et al. 2015). Our findings suggest that in infancy, thicker cortices, as a reflection of increased cortico–cortical connections via synaptogenesis and dendritic arborization, confer cognitive benefits. In later childhood and into adolescence, however, cortical thinning that occurs (Raznahan et al. 2011; Wierenga et al. 2014; Walhovd et al. 2016) via synaptic pruning and circuit refinement has been shown to reflect greater cognitive abilities (Shaw et al. 2006; Schnack et al. 2015). Finally, in adulthood, work suggests that thicker cortices, likely a reflection of slowed apoptotic mechanisms and conservation of neurons and their connections, confer benefits during aging (Schnack et al. 2015). This body of work highlights the importance of taking a developmental perspective in studying brain–cognition relationships that are reflective of different underlying neurodevelopmental mechanisms and thus adaptively fluctuate across ontogeny.

Strengths of this study include the use of a large, healthy sample including longitudinal neuroimaging and laboratory-based cognitive assessments and the implementation of cutting-edge pediatric image analysis methods. Limitations reflect the inherent difficulties of studying infants and toddlers, including shifts in image contrast that can affect cortical

surfaces measures (Walhovd et al. 2017), especially CT measurements in this age range that are prone to partial volume effects, and issues with testing young children including temperament and language abilities. Additionally, we found that controlling for motion in addition to other covariates marginally rescued some correlations between CT and cognition, particularly with language scores, suggesting that motion may contribute added noise to the imaging data that should be considered, as has been noted recently in the field (Reuter et al. 2015). This also highlights a need for a consensus on how to best capture and quantify motion in structural MRI data sets so that we may better understand how head motion not only impacts our imaging results but may also be inherently related to participant behavior. It is also possible that changes in imaging protocols and scanning platforms during this longitudinal study may have differential impacts on CT and SA measurements (Jha et al. 2018a), though we tried to statistically control for this possible confound by introducing nuisance variables controlling for scanner. Finally, including data from twins (which are not statistically independent) and premature infants may impact the generalizability of our study, though we performed several sensitivity analyses and found the same patterns of results. Despite these limitations, our study offers insights into how cortical structure across infancy and toddlerhood is related to cognition. An important future direction for this work is to use functional brain parcellations, as they become available for infants, in the study of brain–cognition associations; such an approach is better suited to linking structure with cognition. It will also be important to consider subcortical structures, which were unavailable as part of the image processing pipeline for this study.

This study is the first to investigate the relationships between CT, SA, and emerging cognitive abilities in a large, healthy sample. We report novel findings that thicker cortices at ages 1 and 2 and larger SA at birth, age 1 and age 2 confer a cognitive advantage in infancy and toddlerhood. We also found evidence that slower rates of total cortical SA expansion in the second year of life related to better motor skills. We found both expected brain–cognition results, and overlapping cortical areas implicated across cognitive domains that may suggest that infancy marks a period of plasticity and refinement in cortical structure to support burgeoning motor, language, and cognitive abilities. We also found that CT may be an important morphological indicator of ability, which is influenced by genetic and environmental variables that shape both brain and cognition. Taken together, this work highlights the importance of prenatal and early postnatal cortical development for cognition in infants and toddlers. Future studies will be needed to parse out the relative contributions of child and environmental factors to both cortical maturation and cognitive development.

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Author Contributions

JHG and JBG conceptualized this study. Statistical analysis was done by EC and JBG. Image analysis was done by JBG, MS, SCJ, VAM, GL, LW, and DS. Behavioral data were collected by BDG and quality controlled by JBG. The original manuscript was written by JBG and reviewed and edited by JHG, EC, BDG, SCJ, VAM, GL, LW, DS, RCK, and MS. Project supervision by JHG.

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