

# Dynamic Development of Regional Cortical Thickness and Surface Area in Early Childhood

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**Cortical thickness (CT) and surface area (SA) are altered in many neuropsychiatric disorders and are correlated with cognitive functioning. Little is known about how these components of cortical gray matter develop in the first years of life. We studied the longitudinal development of regional CT and SA expansion in healthy infants from birth to 2 years. CT and SA have distinct and heterogeneous patterns of development that are exceptionally dynamic; overall CT increases by an average of 36.1%, while cortical SA increases 114.6%. By age 2, CT is on average 97% of adult values, compared with SA, which is 69%. This suggests that early identification, prevention, and intervention strategies for neuropsychiatric illness need to be targeted to this period of rapid postnatal brain development, and that SA expansion is the principal driving factor in cortical volume after 2 years of age.**

**Keywords:** brain development, cerebral cortex, gray matter, human, magnetic resonance imaging

## Introduction

Cortical thickness (CT) and surface area (SA) are important components of cortical structure and are related to normal development and aging, cognitive functioning, as well as to neuropsychiatric disease. Abnormalities of CT and SA are commonly observed in neurodevelopmental disorders, including schizophrenia (Rapoport et al. 2012; Rimol et al. 2012), autism (Courchesne et al. 2007; Hazlett et al. 2012), and attention deficit hyperactivity disorder (Shaw et al. 2007, 2012). CT has been positively linked to IQ as well as the general factor of intelligence (*g*) in healthy individuals in late childhood, adolescence, and adulthood (Narr et al. 2007; Karama et al. 2011). Developmental trajectories of CT in frontal regions have been shown to be predictive of cognitive outcomes in typically developing children and adolescents (Shaw et al. 2006).

The first 2 years of life are an exceptionally dynamic period of structural and functional development in the human brain. The infant brain reaches 80% of adult volume by age 2 years, with a doubling of cortical gray-matter volume in the first year of life (Knickmeyer et al. 2008; Gilmore et al. 2011). Increasing evidence suggests that many neurodevelopmental and psychiatric disorders are the result of abnormal brain development in this stage of rapid cortical growth in early childhood, though very little is known about CT growth and SA expansion in this important period. Previous studies of childhood development of CT have been limited to late childhood and adolescence, and find that CT generally peaks around puberty and thins thereafter, exhibiting a regionally heterogeneous pattern in which association cortices reach peak values after sensory or motor cortices (Sowell 2004; Shaw et al. 2008). Studies of SA have found a 2- to 4-fold expansion between infancy and adulthood (Hill et al. 2010), with regionally heterogeneous

expansion in the first 2 years of life (Li et al. 2013). Peak overall SA is reached in late childhood, similar to CT (Raznahan et al. 2011). The trajectory of CT in later childhood is less clear as some studies find CT peaks around puberty at age 8 or later (Shaw et al. 2006; Raznahan et al. 2011), though others indicate that CT peaks earlier (Sowell 2004; Brown et al. 2012).

This study is the first comprehensive investigation of longitudinal development of CT growth and SA expansion from birth to 2 years of age using 3-T magnetic resonance imaging (MRI) scans. We employed a novel image analysis approach that utilized subject-specific atlases that allowed for longitudinal registration and segmentation of scans in this challenging period of rapid growth and changing tissue contrasts. Our primary aim was to characterize the healthy developmental trajectories of regional CT and SA in the first 2 years of life and to determine the proportion of lifetime cortical growth that occurs in the first 2 years of life by comparing 2 year olds to healthy adults. We also studied the relationship between CT growth and SA expansion during infant brain development and explored gender differences in longitudinal growth patterns.

## Methods

The Institutional Review Board of the University of North Carolina at Chapel Hill approved this study. Subjects were part of large prospective studies of early childhood brain development in healthy singletons and twins (Gilmore et al. 2007, 2010, 2011; Knickmeyer et al. 2008). Subjects were recruited prenatally and scanned shortly after birth, and at ages 1 and 2 years, and assessed with the Mullen Scales of Early Learning at 1 and 2 years of age (Mullen 1995). Children with a complete sets of successful longitudinal scans were included in this study; exclusion criteria were 1) gestational age at birth <32 weeks, 2) stay in the neonatal intensive care unit for more than 1 day, 3) abnormality on MRI other than a minor intracranial hemorrhage, common in the neonatal period (Looney et al. 2006), 4) major medical or neurologic illness after birth, or 5) Mullen Early Learning Composite score of <71 (Mullen 1995).

The primary study population consists of 40 typically developing singletons and a replication population consisting of 31 typically developing “single” twins randomly selected from pairs. Thirty-seven subjects (20 singletons; 17 twins) were included in a previous analysis of regional gray-matter development (Gilmore et al. 2011) and vertex-based analyses of SA expansion and structural cortical asymmetries (Li, Nie, Wang, Shi, Lin et al. 2013; Li, Nie, Wang, Shi, Lyall et al. 2013). Adult subjects ( $n=44$ ) were part of a previous study of adult brain development (Bullitt et al. 2005). Demographic information for the 2 infant cohorts and the adult cohort can be found in Supplementary Table 1.

## Image Acquisition

Image were acquired on a Siemens head-only 3T scanner (Allegra, Siemens Medical Systems, Erlangen, Germany). Children were scanned unsedated while asleep, fitted with ear protection and with their heads

secured in a vacuum-fixation device.  $T_1$ -Weighted structural pulse sequences were a 3D magnetization prepared rapid gradient echo (MP-RAGE TR = 1820 ms, inversion time = 1100 ms, echo time = 4.38 ms, flip angle =  $7^\circ$ , resolution =  $1 \times 1 \times 1 \text{ mm}^3$ ). Proton density and  $T_2$ -weight images were obtained with a turbo-spin echo sequence (TSE, TR = 6200 ms, TE1 = 20 ms, TE2 = 119 ms, flip angle =  $150^\circ$ , resolution =  $1.25 \times 1.25 \times 1.95 \text{ mm}^3$ ). For neonates who failed or were deemed likely to fail due to difficulty sleeping, a “fast”  $T_2$  sequence was done with a 15% decreased TR, smaller image matrix and fewer number of slices (5270 ms,  $104 \times 256 \text{ mm}$ , 50 slices); 28  $T_2$  fast scans (14 singleton; 14 twin) were performed. Potential differences resulting from the  $T_2$  scan sequences were controlled using a covariate in the statistical modeling.

Adult scans were performed on the same 3T scanner and were provided by the CASILab at The University of North Carolina at Chapel Hill and were distributed by the MIDAS Data Server at Kitware, Inc. (Bullitt et al. 2005).  $T_1$ -Weighted structural imaging used a 3D spoiled gradient echo pulse sequence, fast low angle shot (FLASH TR = 14 ms, echo time = 7.7 ms, flip angle =  $25^\circ$ , resolution =  $1 \times 1 \times 1 \text{ mm}^3$ ).  $T_2$ -Weighted images were obtained with a turbo-spin echo sequence (TSE, TR = 7780 ms, TE = 80 ms, flip angle =  $180^\circ$ , resolution =  $1 \times 1 \times 1 \text{ mm}^3$ ).

### Image Analysis

All images in this study were visually checked and rated for motion artifacts using a 4-point visual scale [none 1), mild 2), moderate 3), severe 4)] based on Blumenthal et al. (2002). Of the 213 pediatric scans in the study, 150 (70.5%) had no motion artifacts, 47 (22%) had mild motion artifacts, 16 (7.5%) had moderate motion artifacts, and no scans had severe motion artifacts. Our average motion artifact rating for this study was 1.37 for both samples and 1.41 and 1.31 for singletons and twin cohorts, respectively.

Images were resampled into  $1 \times 1 \times 1 \text{ mm}^3$  resolution, skull-stripped, and then had the cerebellum and brain stem removed (Shi et al. 2012). Automated segmentation of neonatal brain images remains a challenging problem due to low tissue contrast, low spatial resolution, and high within tissue intensity variability. Segmentation of neonatal images is specifically challenging due to image signal contrast changing dramatically from birth to 2 years of age (Dietrich et al. 1988; Prastawa et al. 2005). In order to overcome these challenges, a novel longitudinally guided level-set-based method specifically designed for consistent image segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) during infancy was jointly applied on  $T_2$ -weighted images from neonates and  $T_1$ -weighted images from 1 and 2 years olds (Wang et al. 2013). Major steps include: 1) performing an adaptive fuzzy c-means segmentation algorithm on both the neonate/1-year and 2-year-old images of the same subject, which integrates both bias correction and tissue classification into a single framework; 2) using of coupled level sets for initial neonatal segmentation; and 3) applying longitudinal information from later time points using non-linear HAMMER registration (Shen and Davatzikos 2002) to guide the neonatal/1-year image segmentation. Utilization of later time point images to guide neonatal segmentation provides increased accuracy and produced more longitudinally consistent results. Subject-specific priors allow for less anatomical variability with the to-be-segmented image than previously employed methods utilizing atlases generated from randomly selected images (Wang et al. 2013).

Inner and outer cortical surfaces were first constructed using the process described in Li et al. (2012) with the inner cortical surface defined by the interface between white matter and gray matter, and the outer cortical surface is defined by the interface between gray matter and CSF (Li et al. 2012). The surface reconstruction includes the following steps: 1) performing topology-correction of white matter to ensure a spherical topology; 2) utilizing the Marching cubes method to convert the boundary of the corrected white matter to an explicit surface representation; 3) applying the deformable surface method driven by a force derived from the Laplace's equation to obtain the refined inner surface and outer surface. CT and SA were measured after the surface reconstruction. The CT for each vertex was computed as the average value of the minimum distance from inner to outer surfaces and the minimum distance from outer to inner surfaces.

A prior 90-region parcellation atlas (76 cortical and 14 subcortical regions; Tzourio-Mazoyer et al. 2002) was transformed to infant space (Shi et al. 2011) and used to generate surface-based regions of interest (ROIs). The neonate, 1-year, and 2-year parcellation atlas images were registered to individual subjects with nonlinear HAMMER registration and atlas label maps were transformed accordingly. Cortical ROIs were first projected onto the inner cortical surface and then mapped to the outer cortical surface to obtain surface-based ROIs. The average CT and SA were calculated within each ROI. All adult images were processed with the same algorithm using the original atlas on adult space without the temporal constraint. Total cortical volume is defined as the volume of the cerebrum, as the cerebellum and the brain stem were removed during processing.

To validate the cortical surface measure computation results, a single rater (AEL) performed 14 manual segmentations (5 at neonate, 5 at 1 year, and 4 at 2 years). CT and SA values and were compared with those generated from the automated segmentation. Intraclass correlations (ICC) were calculated for whole brain and regional CT and SA. Whole-brain ICC for CT and SA were 0.975 and 0.986, respectively. ICCs for all 76 cortical regions averaged 0.87 for CT (range 0.40–0.98) and 0.91 for SA (range 0.39–0.99). Heat maps of ICCs across cortical brain regions are presented in Supplementary Figure 1. One region had no correlation between manual segmentations for CT measurements: the left middle temporal pole.

### Statistical Analysis

All statistical analyses were performed using SAS statistical software, version 9.3. For demographic variables, frequency distributions were calculated for categorical variables, and means (standard deviations) were calculated for continuous variables. The least-squared means (standard error) were also calculated for the 76 ROIs for cortical surface measures, CT, and SA. Mixed models were used to calculate the least-squared means for CT and SA in the 76 ROIs at years 0, 1, and 2, and corresponding percent changes for years 1 and 2. An autoregressive covariance structure was used, as data were longitudinal. The mixed models included neonatal total cortical volume, year, gender, neonatal  $T_2$  scan status (fast vs. routine), and the interaction between gender and year as covariates. Neonatal total cortical volume is the sum of all gray, white, and cerebrospinal fluid labels from the segmentation subtracting the cerebellum. All statistical hypothesis tests were two-tailed and conducted at a significance level of 0.05. *P* values were not corrected for multiple comparisons, as this study is primarily hypothesis generating; all comparisons were analyzed in the replication sample of single unpaired twins.

Linear relationships between SA and CT growth rates were analyzed by calculating correlations between growth rates for each year. For the comparison of CT and SA values between 2 year olds and adults, least-squared means were calculated in a model, which included age at MRI, and gender. Rates of change between genders were compared using a longitudinal model that included gender, year, total neonatal cortical volume, and the interaction between gender and year as covariates. Intraclass correlations were calculated for the validation analysis between the automated segmentation algorithm and the manual segmentations and can be seen in Supplementary Figure 1 (Shrout and Fleiss 1979; Simpson et al. 1998).

## Results

### CT Growth

CT growth was studied in 40 typically developing children (22 males, 18 females) with longitudinal MRI scans done at ~3 weeks, 1, and 2 years of age (Supplementary Table 1). We confirmed our results in a second cohort of 31 children (15 males, 16 females) from a related study of twin brain development (Supplementary Table 1). Plots of average global CT and total global SA for all children included in both cohorts can be seen in Supplementary Figure 2.

There are marked regional differences in CT in neonates; these regional variations are generally consistent from birth to 2 years (Fig. 1A, Supplementary Table 2). Thinnest cortices include primary sensory and motor cortices such as the precentral gyrus, postcentral gyrus, paracentral lobule, olfactory gyrus, Heschl's gyrus, and many regions in the occipital lobe (Fig. 1A, Supplementary Table 2). Thicker cortices include the medial superior frontal gyrus; the superior, medial, middle, and inferior orbitofrontal gyrus; the superior and middle temporal poles and the insula (Fig. 1A).

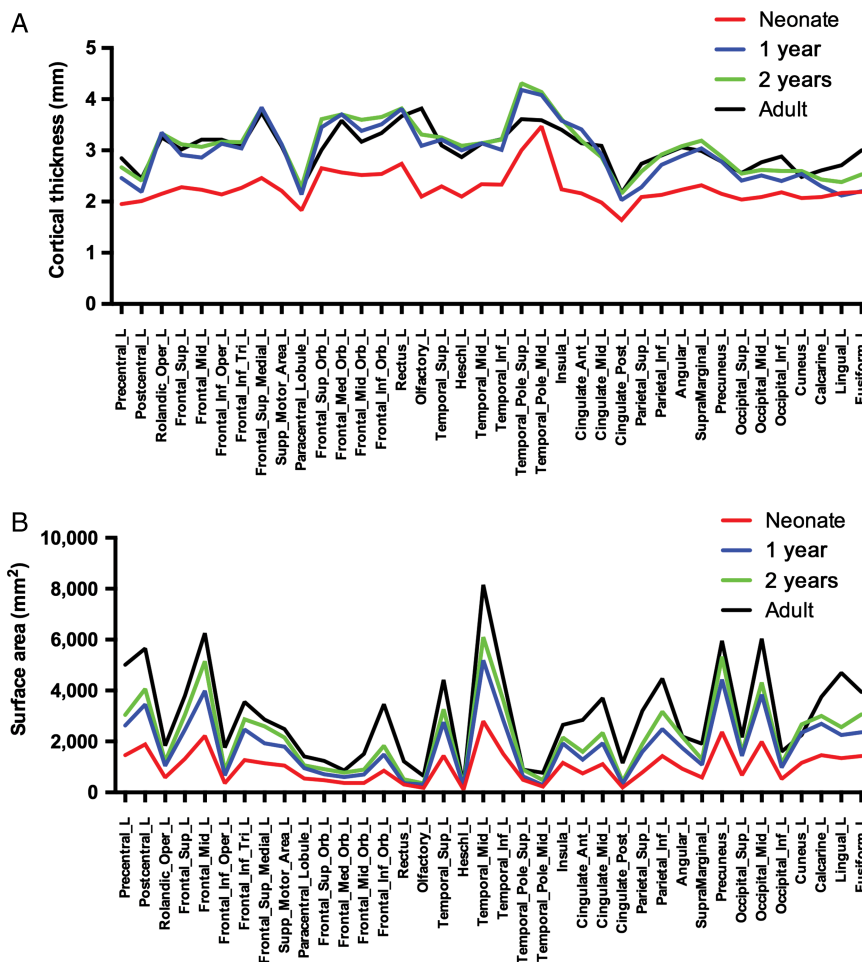
There is robust and regionally heterogeneous growth of CT averaging 31% per ROI in the first year (range -2.50–65.83%), and 4.3% in the second (range -6.83–17.78%) (Fig. 2A,B, Supplementary Table 2). Overall, from birth to 2 years, CT increases an average of 36.08% (range 6.04–68.11%) (Fig. 2C, Supplementary Table 2). To better highlight the distinct regional differences in CT occurring during the second year of life, a supplementary figure was generated with a heat map more suitable for the range of growth occurring in this developmental time period (Supplementary Fig. 3).

In the first 2 years of life, regions experiencing the greatest degree of CT growth (top 25%) include primary auditory cortex (Heschl's gyrus, R superior temporal gyrus) and the Rolandic operculum, regions involved with speech and language

development, as well as higher order association areas such as the inferior frontal operculum, medial superior frontal gyrus. The insula and anterior and middle cingulate gyrus, components of the limbic system, were also among the fastest growing regions. Regions experiencing the least amount of CT growth (bottom 25%) include primary sensory (postcentral gyrus) and sensory association (superior parietal gyrus) areas, multiple primary and secondary visual areas in the occipital lobe, and the middle temporal pole. Six regions experienced significant cortical thinning in the second year of life, including the left and right anterior cingulate gyrus, left and right middle cingulate gyrus, right gyrus rectus, and the left Rolandic operculum. Regional patterns of CT growth were very similar in our replication sample (Supplementary Table 3). ROI percent change comparisons between the singleton and twin cohorts show high correlations for both age ranges (birth to 1 year:  $r^2=0.93$ ; 1–2 years:  $r^2=0.88$ ) and are presented in Supplementary Figure 4.

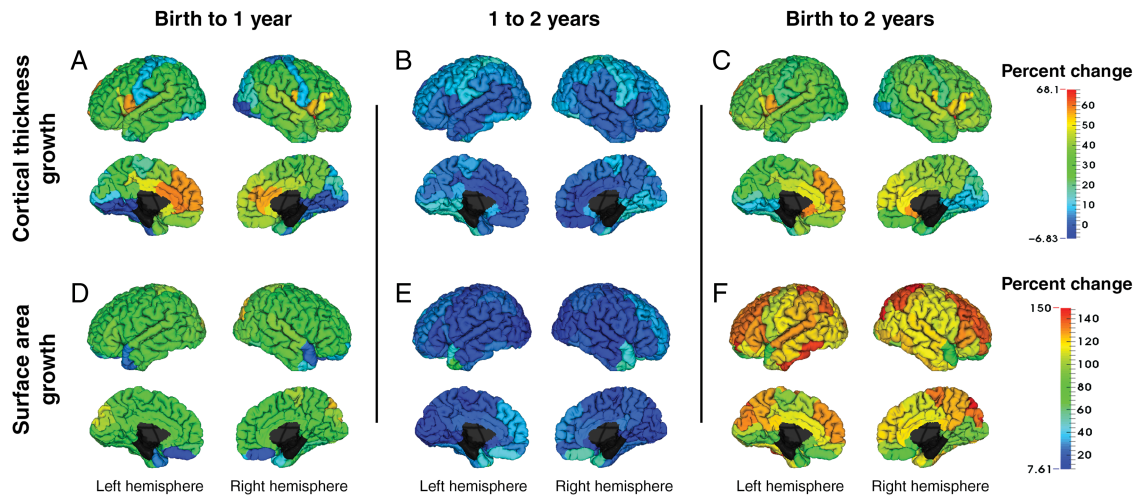
### Cortical Surface Expansion

There is also robust and regionally heterogeneous expansion of SA, averaging 76.35% per ROI in the first year (range 15.46–120.50%) and 22.51% in the second (range 7.61–66.73%) (Figs 1B, 2D, and 3E; Supplementary Table 4). Overall, cortical

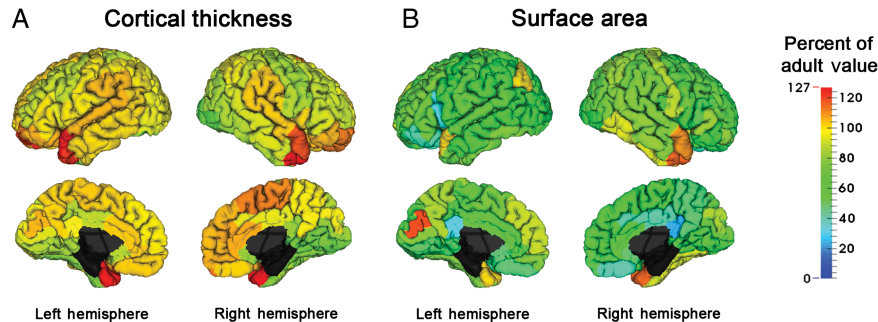


**Figure 1.** Regional growth of CT and SA over time. (A) CT anatomical LS means at neonate (blue), 1 year (red), 2 years (green), and adult (black); (B) SA anatomical LS means at neonate (blue), 1 year (red), 2 years (green), and adult (black). Only left hemispheric ROIs are shown; ROIs for both CT and SA exhibited symmetry. Quantitative results can be found in Supplementary Table 2 (CT), Supplementary Table 4 (SA), Supplementary Table 8 (Adult CT), and Supplementary Table 9 (Adult SA). (Note: SA values are determined by the size of the ROI as defined by the parcellation atlas).





**Figure 2.** Early cortical surface measures development from birth to 2 years. Regional percent change for CT (A–C) and SA (D–F) from birth to 1 year (A, D), 1 to 2 years (B, E), and birth to 2 years (C, F). Warmer colors indicate larger percent changes than cooler colors. Quantitative results can be found in Supplementary Tables 2–5.



**Figure 3.** Comparison of 2 year old to adult cortical surface measure values. Percent of adult values for CT (A) and SA (B). For each ROI, we calculated the percent of adult value at 2 years of age. Warmer colors indicate larger percent of adult values than cooler colors. Quantitative results can be found in Supplementary Tables 8 and 9.

SA increases an average of 114.56% in the first 2 years of life (range 64.55–149.57%) (Fig. 2F and Supplementary Fig. 3 and Table 4). Supplementary Figure 3 presents regional differences of 1- to 2-year change with a heat map that provides better visualization of the regional differences. High-expanding regions (top 25%) in the first 2 years of life include regions in the lateral frontal lobes (superior, mid, and inferior operculum), lateral parietal (superior parietal and angular gyrus), mid orbital frontal, and occipital lobes (cuneus and superior occipital gyrus), as well as left Heschl's and left inferior temporal gyri. Low-expanding regions (bottom 25%) include multiple regions of the orbital surface of the frontal lobes, superior temporal poles, occipital regions (lingual, R calcarine, R fusiform), and the insula. Overall SA expansion in the first 2 years of life reflects growth rates in the first year in which the majority of expansion takes place. Regional patterns of SA expansion were very similar in our replication sample (Supplementary Table 5). ROI percent change comparisons between the singleton and twin cohorts show high correlations for both age ranges (birth to 1 year:  $r^2 = 0.88$ ; 1–2 years:  $r^2 = 0.84$ ) and can be visualized in Supplementary Figure 4.

### Gender Differences

While this study is not adequately powered to detect sexual dimorphism, we explored gender differences in CT growth and

SA expansion. At birth, the left fusiform gyrus was the only region with replicated significant differences in CT between males and females when controlling for neonatal total cortical volume (Supplementary Table 6). There were no significant replicated differences in SA (Supplementary Table 6). There were no significant gender differences in CT growth rates between birth and 2 years of age for any ROI (Supplementary Table 6). For SA, males had a significantly faster rates of SA expansion compared with females in 7 ROIs: the left precentral gyrus, left superior frontal gyrus, left middle frontal gyrus, left olfactory gyrus, left insula, left superior parietal gyrus, and right calcarine gyrus (Supplementary Table 6). In the second year, males had a faster rate of growth in the right middle temporal gyrus. Our findings are consistent with a study by Raznahan et al. (2011) that found gender differences in late childhood and adolescence were primarily driven by changes in SA and not thickness.

### Comparison Analysis: 2 years to Adult

Figure 1 clearly shows the spatial variation across the cortex tends to be generally set at birth and remains consistent through infancy into adulthood. Figures 1 and 3 also indicate that by 2 years of age, CT has generally reached adult-like values while SA continues to grow into adulthood. To demonstrate the proportion of lifetime cortical growth that occurs



in first 2 years of life, we compared cortical surface measures at 2 years of age to those of 44 healthy adults (21 males, 23 females, mean age at scan 29.44 years). As the adult cohort is different from the infant cohort and scanned with a different sequence, results from this analysis have limitations, however, do provide a general comparison of infant and adult brain structure. Average ROI CT at 2 years of age was 97.1% of adult values (range 75.48–126.84%) (Fig. 3A, Supplementary Table 7). Only 4 regions had CT values significantly greater in 2 year olds than adults (temporal poles and left superior orbital gyri), while 16 2-year-old regions had significantly thinner CT than adult values, including many regions of the occipital lobe, the bilateral pre- and right post-central gyri, and right inferior temporal gyrus and bilateral middle lateral frontal gyri. In contrast to CT, SA at 2 years of age averages 69.1% of adult values (range 22.5–116.7%) (Fig. 3B, Supplementary Table 8). In 2 year olds, 57 of 76 cortical regions had significantly smaller SA compared with adults; no 2-year-old regions had significantly larger SAs. These findings suggest that CT develops earlier than SA and that overall cortical growth after age 1 is principally driven by increases in SA.

### Relationships of Cortical Measures During Early Development

The relationship of how CT and SA relates to overall cortical volume has not been studied in this developmental window. In Figure 4, log–log plots demonstrate there is little to no relationship between CT and cortical volume. Conversely, there is a strong and significant relationship between total SA and total cortical volume for both singleton and twin cohorts (Fig. 4B). The similarity between the 3 cohorts of unrelated individuals across multiple time points suggests a fixed and constant relationship in healthy individuals between total cortical volume and total SA. The relationship of  $\log(\text{CV})$  to  $\log(\text{total SA})$  and  $\log(\text{mean CT})$  was compared with predicted scaling exponents— $1/3$  power of ICV for CT and  $2/3$  power of ICV for SA—as outlined in Im et al. (2008). In the combined sample, we found significant differences from the predicted scaling relationships for CT at all time points. There were also

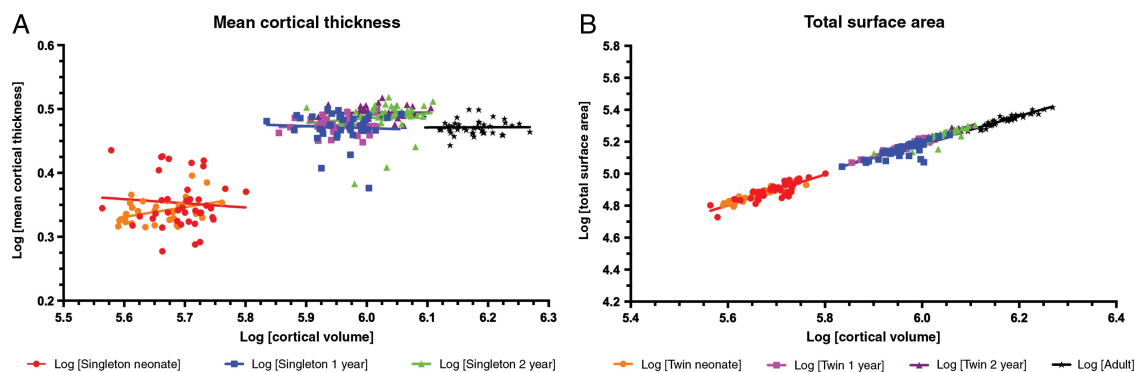
significant differences from the predicted scaling relationship for SA at neonate, 2 years, and adult and a trend-level significance at 1 year ( $P = 0.06$ ; data not shown).

Similarly, the relationship between CT and SA growth has not been studied in the first 2 years of life. The correlation between CT and SA growth rates were calculated for each ROI (Supplementary Table 9). Correlations of CT and SA growth were nonuniform and highly variable across the cortex. Overall, there were few regions with significant correlations and little replication in our twin sample, suggesting that CT growth and SA expansion in the first years of life are not related (Supplementary Table 9).

### Discussion

Our results show that CT and SA have distinct and regionally heterogeneous patterns of development that are exceptionally dynamic, especially in the first year of life. SA expansion is more robust compared with CT growth, with an average expansion of 114.6% compared with 36.1% for CT. By age 2, CT is roughly 97.1% of adult values, compared with 69.1% for SA. This suggests that CT is relatively more established than SA at birth. Our study also suggests that the majority of CT growth is complete by age 2, while cortical surface expansion accounts for most of cortical volume growth after 1 year of age. Regional patterns of CT and SA growth were different from one another. The lack of clear regional correlations between CT and SA growth indicates that different genetic, environmental, and experience-dependent processes likely drive the development of these 2 components of cortical volume. These results provide an improved framework for understanding abnormalities of CT and SA observed in neurodevelopmental disorders as well as their potential relationship to cognitive and functional development.

Overall regional patterns of CT in early postnatal life are similar to those observed in older children and adults. Sensory and primary visual processing areas tended to have thinner cortices whereas thicker cortices tended to be in the medial frontal, temporal, and orbital regions. Similarities between our findings and previous postmortem (Economo and Koskinas 1925) and imaging studies (Fischl and Dale 2000; Sowell 2004)



**Figure 4.** Relationship of CT and SA to cortical volume. Raw data values for each cohort are plotted at each time point. (A) The log–log relationship of mean CT to cortical volume is shown for neonate singletons (red), neonate twins (orange), 1-year singletons (blue), 1-year twins (pink), 2-year singletons (green), 2-year twins (purple), and adults (black). Regression analysis  $r^2$  values at neonate (singleton:  $r^2 = 0.0061$ ; twin:  $r^2 = 0.1327$ ), 1 year (singleton:  $r^2 = 0.0033$ ; twin:  $r^2 = 0.0099$ ), 2 years (singleton:  $r^2 = 0.0196$ ; twin:  $r^2 = 0.0001$ ), as well as in the adult cohort ( $r^2 = 5.98E-5$ ) are not significantly different from zero. (B) The log–log relationship of total cortical SA to cortical volume is shown for neonate singletons (red), neonate twins (orange), 1-year singletons (blue), 1-year twins (pink), 2-year singletons (green), 2-year twins (purple), and adults (black). Linear regression  $r^2$  values at neonate (singleton  $r^2 = 0.7177$ ; twin  $r^2 = 0.8691$ ), 1 year (singleton  $r^2 = 0.5924$ ; twin  $r^2 = 0.9324$ ), 2 years (singleton  $r^2 = 0.8395$ ; twin  $r^2 = 0.9558$ ), and adult ( $r^2 = 0.8907$ ) are each significantly different from zero ( $P < 0.0001$ ).

indicate that the overall pattern of CT is established within the first year of life. Growth rates observed for CT in the first 2 years of life dwarf those observed later in childhood, with CT growing 31% in the first and 4.3% in the second year of life. Maximal annual rates of change in late childhood are about 0.5% (Raznahan et al. 2011). Imaging studies in older children and adolescents indicate that CT displays regionally heterogeneous patterns of development with association cortices reaching peak values later than sensory or motor cortices (Sowell 2004; Shaw et al. 2008; Brown et al. 2012). From birth to age 2 years, primary and secondary sensory cortices tended to be slower growing, while regions involved with speech and language, some higher order association areas, and the insula and cingulate cortex were faster growing. We found that the left and right anterior cingulate gyrus, left and right middle cingulate gyrus, right gyrus rectus, and the left Rolandic operculum exhibited significant cortical thinning in the second year of life in both cohorts, suggesting that these regions may experience an early childhood wave of synaptic pruning prior to that already described in adolescence.

Less is known about SA expansion in childhood. Hill et al. (2010) found nonuniform 2- to 4-fold expansion between birth and adulthood; low-expanding regions included occipital, insular and medial temporal regions, while high-expanding regions included lateral temporal, lateral parietal, and medial prefrontal regions. Our results are generally consistent with these findings, with the exception of the occipital lobe, in which we found areas of both high and low expansion. A vertex-based analysis of cortical SA expansion from birth to 2 years of age in a sample that overlaps with this sample found similar patterns of cortical SA expansion, including differential rates in the occipital lobe, supporting this ROI-based analysis (Li et al. 2013). Mismatch between results for the temporal pole and caudal prefrontal cortices from this study and the previous analysis by Li et al. (2013) could be due to the decreased reliability of segmentations for the bilateral temporal poles and orbitofrontal cortices, 2 regions that are difficult to segment in young children (Kim et al. 2013); regions that we found have low correlations between manual and automatic segmentations (Supplementary Fig. 1). Very little is known about region-specific SA growth rates between age 2 and adulthood. Overall SA has been shown to peak at 9.7 years in males and 8.1 years in females (Raznahan et al. 2011), suggesting that SA expansion from the 69% of adult values we found at age 2, must occur between 2 years and 8–9 years of age at a considerably slower annual rate. Previous research has found that interindividual variation in adult brain size is almost exclusively due to SA rather than CT (Pakkenberg and Gundersen 1997), and our results demonstrate that these differences likely emerge very early in development. The appearance of early postnatal interindividual differences within our study cohorts can be seen in Figure 4B, which clearly shows that individuals with larger total cortical volume have larger total cortical SA at birth. Visual inspection of Supplementary Figure 2 shows that individuals with larger SA at birth continue to have relatively larger SA at age 1 and 2.

It has been estimated that adult human cortical gray-matter volume is composed of 30% dendrites and 29% axons, while neuronal cell bodies, synapses, and glial cells contribute only 7.8, 6, and 14%, respectively (Bennett 2011). At birth, neurogenesis, cortical lamination, and gyrification are largely complete, and the rapid postnatal CT growth and SA expansion are

likely the result of increases in dendritic arborization, axonal elongation and thickening, synaptogenesis, and glial proliferation. Synapse densities increase rapidly after birth with regional variability (Huttenlocher and Dabholkar 1997). Spine density in prefrontal cortex increases rapidly in early childhood, peaking at over 200% of adult values in later childhood (Petanjek et al. 2011). The complexity of the basal dendritic tree of pyramidal neurons in prefrontal cortex also increases rapidly after birth, with segment numbers reaching adult values by 1 month of age, and dendrite elongation reaching adult values by 12–15 months for layer V neurons and 2.5 years for layer IIIC neurons (Petanjek et al. 2008). Maturation of dendritic arborization and synapse and spine development are likely significant contributors to the increased CT and SA observed on our study. Other contributors would include glia cell proliferation and cortical axon development and myelination, though developmental studies in postnatal human cortex are lacking.

The principal element of cortical architecture is the cortical minicolumn (Buxhoeveden and Casanova 2002; Rakic 2009). CT has been found to be evolutionarily conserved, exhibiting only a ~2-fold increase compared with a mouse while cortical SA exhibits a ~1000-fold increase (Rakic 2009). In humans, this dramatic cortical SA expansion compared with other species is due to the addition of minicolumns within the cortical surface (Buxhoeveden and Casanova 2002; Rakic 2009). At birth, the width of the cortical minicolumn is approximately one-third adult size (Buxhoeveden and Casanova 2002), which is consistent with our results that find a 111% expansion of SA to 69% of adult values by age 2.

Previous studies of scaling relationships in the adult human brain have demonstrated that human cortices are not scaled versions of each other (Im et al. 2008; Toro et al. 2008). Brains with increased cortical volume have been shown to have greater numbers of neuronal and glial cells as well increased SA, increased sulcal depth, and increased region-specific cortical folding complexity (Pakkenberg and Gundersen 1997; Rilling and Insel 1999; Im et al. 2008; Toro et al. 2008). However, it has not been known whether this relationship is present during the earliest stages of development. Our study shows that a strong and “adult-like” scaling relationship between total cortical volume and total cortical SA is already present at birth and persists through the period of rapid postnatal development. Mean CT, on the other hand, appears to have little relationship to total cortical volume at any age.

We found very different and noncorrelated growth patterns for CT and SA. A variety of studies indicate that CT and SA have distinct genetic underpinnings. Twin studies have shown high, though somewhat inconsistent, regional heritability for both SA and CT with apparently unrelated genetic correlation (Panizzon et al. 2009). A recent twin study utilizing a data-driven genetic clustering algorithm showed very little overlap between estimated genetic correlations for CT and SA (Chen et al. 2013). Most importantly, this study showed that even if clusters were anatomically overlapping that the underlying genetic influences appeared to be quite distinct (Chen et al. 2013). Differences in regional SA have been linked to polymorphisms of MECP2 and microcephaly genes in humans (Joyner et al. 2009; Rimol et al. 2010). In animal models, manipulation of transcription factors Ngn1/2 and Tlx in intermediate progenitor cells results in changes to thickness, but not to SA (Pontious et al. 2008). Alternatively, beta-catenin overexpression in rodent models leads to

increased cortical SA but unchanged CT (Chenn and Walsh 2003). Arealization and expansion of specific cortical areas such as primary visual or sensory areas are also affected by specific genetic mutations of early developmental regulatory genes *Emx2* and *Pax 6* in rodents (Bishop et al. 2002). Recent studies in monozygotic healthy twins suggest that differences in birth weight can influence SA but not CT indicating that pre- and perinatal environmental influences may also have a different effects (Raznahan et al. 2012).

Comparison with genetic regionalization in human brain as evidenced in twin and transcriptome studies suggests that factors other than gene expression, such as functional circuit activity, may account for the observed differences in regional cortical growth rates in the first 2 years of life. Recent studies using a twin design have found that SA and CT have up to 12 measure-specific regional clusters of genetic correlations (Chen et al. 2011, 2012, 2013). While direct comparison is difficult due to different methodology, SA expansion rates in the first 2 years of life appear to reflect some of the observed genetic regional clusters (Chen et al. 2012), with some exceptions, such as the occipital cortex and perisylvian cortex which show genetic correlation, though have locally heterogeneous rates of SA expansion. Evidence from human transcriptome analyses also demonstrates regionalization of gene expression in the cortex, with related expression in primary sensorimotor cortices, including the pre- and postcentral cortices, Heschl's gyrus, and primary and secondary visual areas (Hawrylycz et al. 2012). In the first 2 years of life, these regions with similar gene expression profiles have variable growth rates for both CT and SA.

CT and SA are differentially affected in neurodevelopmental disorders. Children with ADHD show a developmental lag in CT and SA maturation compared with typically developing children (Shaw et al. 2007, 2012). Studies in schizophrenia have primarily seen patterns of cortical thinning in both childhood-onset and adult-onset cases (Rapoport et al. 2012; Rimol et al. 2012), though marginal reductions in SA have also been described (Gutiérrez-Galve et al. 2010; Rapoport et al. 2012). Brain overgrowth in autism is one of the most consistent findings in children between the ages of 2 and 4, and this cerebral enlargement is not present at birth yet emerges between 9 and 18 months (Courchesne et al. 2007). It is unclear whether or not overgrowth is due to aberrant increases in CT or SA, as studies have provided evidence for both (Hazlett et al. 2011; Mak-Fan et al. 2012). However, a recent study has called this into question, suggesting that the early brain overgrowth may not be a disease-specific biomarker but instead due to head circumference population norm biases in previous studies (Raznahan et al. 2013), at least with head circumference studies.

An interesting finding in this study was that sensory-specific association cortices, such as the superior occipital gyrus (visual association), superior/middle temporal gyrus (auditory association), and superior parietal gyrus (sensory/tactile association/spatial correspondence) all exhibited large growth in cortical SA. Evidence exists that each of these areas house topographic or representative maps for each corresponding sense (Romani et al. 1982; Silver and Kastner 2009). Rapid growth of SA in early childhood may reflect expansion of topographic maps, which are highly plastic and reorganized and refined with increased experience (Pienkowski and Eggermont 2011). Remarkably, many of these regions do not experience large amounts of CT growth, suggesting that topographic map plasticity may be regulated primarily by SA expansion. An exception to this general

pattern is the insula, which houses a topographic map for viscerosensation, thermosensation, and nociception, important functions to a developing infant (Stephani et al. 2011) but does not experience rapid SA growth in early development. A potential hypothesis for this contradictory behavior could be that the insular cortex, due to its location, experiences growth restrictions and is therefore potentially limited to growth in a singular direction. There are 2 potential explanations: 1) due to the apparent structural importance of cortical lamination, the insula may grow predominantly in thickness as opposed to SA or 2) it is possible that the insula may increase in SA later in development. Future study on this important structure, which has been implicated in a variety of functions and neurodevelopmental disorders, is necessary to understand its role in cortical development and cortical networks (Nagai et al. 2007; Takahashi et al. 2009; Uddin and Menon 2009).

Image signal contrast changes dramatically from neonates to 1 or 2 year olds, which presents a challenge for tissue segmentation (Prastawa et al. 2005) and poses a potential limitation for this work. CT is defined by the segmentation's definition of the white-gray-matter boundary and the gray-pial surface boundary and is thus potentially sensitive to these changing contrasts. However, to address this issue, we employed a longitudinally guided segmentation algorithm (Wang et al. 2013) that we show is highly consistent with our manual segmentations (Supplementary Fig. 1). In this algorithm, the white-gray-matter boundary is defined by myelinated white matter at 1 and 2 years of age and by unmyelinated white matter at neonate, both of which have distinctly different intensity profiles from gray matter at each age (Dietrich et al. 1988).

Our study indicates that there is rapid development of the cortex in the first 2 years of life, with CT approaching 97% of adult values and SA approaching 70% of adult values. Periods of rapid growth are considered to be highly susceptible to genetic and environmental insults; the first years of life may be a period of high vulnerability. Interestingly, white-matter maturation follows a similar pattern, with rapid and tract-specific development of white-matter tract microstructure in the first 2 years of life (Geng et al. 2012) with much more slow and gradual maturation thereafter (Faria et al. 2010). Recent studies also indicate that most resting-state functional networks, including the default and attention control are established by age 2 years (Gao et al. 2011). These clinical studies, combined with postmortem studies of neuronal dendritic complexity and synapse development (Huttenlocher and Dabholkar 1997; Petanjek et al. 2008, 2011) suggest that by age 2 years, the fundamental structural and functional stage is largely set for future learning and neuroplasticity that will occur later in childhood. It is also likely that abnormal structural and functional networks associated with neuropsychiatric disorders are established in the first 2 years of life, and that interventions to modify abnormal development will need to be targeted to this period of rapid postnatal brain development.

### Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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## Notes

*Conflict of Interest:* None declared.

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