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Cortical Structural Abnormalities in Very Preterm Children at 7 Years of Age

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Abstract

We analyzed long-lasting alterations in brain morphometry associated with preterm birth using volumetric and surface-based analyses applied to children at age 7 years. Comparison of 24 children born very preterm (VPT) to 24 healthy term-born children revealed reductions in total cortical grey matter volume, white matter volume, cortical surface area and gyrification index. Regional cortical shape abnormalities in VPT children included the following: shallower anterior superior temporal sulci, smaller relative surface area in the inferior sensori-motor cortex and posterior superior temporal cortex, larger relative surface area and a cingulate sulcus that was shorter or more interrupted in medial frontoparietal cortex. These findings indicate a complex pattern of regional vulnerabilities in brain development that may contribute to the diverse and long-lasting neurobehavioral consequences that can occur after very premature birth.

Keywords

Very Preterm; MRI; cortical surface; volume; folding; relative surface area; structural abnormality

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Introduction

Up to 50% of very preterm (VPT) children develop neurodevelopmental disabilities, including low IQ, specific cognitive impairments, as well as behavior and socialization problems (Rickards et al., 1988, Bos and Roze, 2011, Van Noort-van der Spek et al., 2012, Amin et al., 2009, Briscoe et al., 1998, Foster-Cohen et al., 2010, Saigal et al., 1991, Treyvaud et al., 2012, Rogers et al., 2012, Hack et al., 2002 and D'Angio et al., 2002). Research using magnetic resonance imaging (MRI) has revealed a variety of region-specific volumetric abnormalities in preterm infants and children. These include reductions in grey matter (GM) volume in sensorimotor, frontal and temporal cortex and abnormalities of white matter (WM) in the corpus callosum (CC), occipital and sensorimotor regions (Inder et al., 1999a, Peterson et al., 2000, Peterson et al., 2003a and b, Mewes et al., 2006, Thompson et al., 2007, Clark and Woodward, 2010 and Hutchinson et al., 2013). Further, these structural abnormalities have been associated with cognitive and behavioral defects during childhood and adolescence (Peterson et al., 2000, Peterson, 2003, Peterson et al., 2003, Thompson et al., 2007 and Clark and Woodward, 2010). These reductions in the volumes of GM and WM appear to persist as they have also been documented into adolescence and adulthood (Kesler et al., 2004, Kesler et al., 2008, Soria-Pastor et al., 2008, Soria-Pastor et al., 2009, Gimenez et al., 2006a and b, Nosarti et al., 2008, Nosarti et al., 2009, and Bjuland et al. 2014).

Surface-based analyses in preterm born adolescents have also been reported, indicating reduced cortical thickness and surface area in portions of parietal and temporal cortex (Martinussen et al., 2005, Nagy et al., 2010 and Frye et al., 2010, Skranes et al., 2013 and Bjuland et al. 2013). Studies of cortical folding, which undergoes rapid development during 28-40 weeks gestation, suggest reduced cortical folding and delayed gyral development in preterm infants (Battin et al., 1998, Ajayi-Obe et al., 2000 and Ramenghi et al., 2007), though one study of regional cortical gyrification index (GI) suggested an increase in cortical folding in the temporal lobes of preterm children (Kesler et al., 2006).

In this study, we characterized global and regional structural alterations in volume and cortical folding in 24 very preterm children born <27 weeks gestation who underwent MRI at 7 years of age. These were compared with data from 24 age-matched term control (TC) children born > 37 weeks gestation. In addition, regions of abnormal cortical folding were further analyzed using a combination of qualitative and quantitative approaches.

Methods

Subject recruitment and MRI scanning

The subjects were drawn from an initial cohort of 203 VPT infants born prior to 30 weeks gestation, and 46 TC (>37 weeks gestation) infants recruited at the Royal Women's Hospital in Melbourne, Australia between July 2001 and December 2003. MRI images were acquired at term equivalent postmenstrual age (40 ± 1.7 weeks) (Thompson et al., 2007). The 46 healthy term control born infants were recruited from the postnatal wards of the Royal Women's Hospital and via response to advertisements in the recruiting hospitals. The selection criteria were that these infants had an unremarkable antenatal course, labor and delivery at >37 weeks gestation, and were in good health with no parental or medical

concerns at the time of study. Subsequently, 143 of the VPT subjects plus 36 TC individuals were rescanned at 7 years of age. To study the impact of very preterm birth on the brain structure, we selected the first 24 VPT (<27 weeks gestation) and 24 TC (37 to 42 weeks gestation) individuals matched for gender, whose scan quality was high enough to enable accurate surface reconstructions with at most modest manual editing after FreeSurfer reconstruction (table 1). None of the selected subjects had severe (grade 4) white matter injury (WMI) or were small for gestational age (SGA). Additional cohort details are provided in the Supplemental Material, including a consort flow chart (Supplemental Figure 1); for gestational ages and white matter abnormality scores for each subject (supplementary table 1); and mean neurobehavioral performance for each group (supplementary table 2). All subjects' parents had completed informed consent during infancy and again at age 7 years along with assent from the children. The study protocol was approved by the Human Research Ethics Committees at the Royal Women's and Children's Hospitals.

MRI Data Acquisition and Processing

Structural neuroimaging data were obtained using a 3 Tesla MRI scanner (Siemens Magnetom Tim Trio system) at the Royal Children's Hospital. Sagittal three-dimensional rapid gradient-echo T₁-weighted imaging parameters were as follows: T_R = 1900 ms, T_E = 2.27 ms, matrix = 256 × 256, field of view = 210 × 210 mm, section thickness = 0.85 mm, isotropic voxels = 0.8 mm³, and bandwidth = 200 Hz/Px. Parameters for sagittal three-dimensional turbo spin-echo T₂-weighted images were as follows: T_R = 3200 ms, T_E = 447 ms, matrix = 256 × 230, field of view = 240 × 215 mm, section thickness = 0.90 mm, isotropic voxels = 0.9 mm³, and bandwidth = 610 Hz/Px. FreeSurfer 4.4.0 software was used to convert DICOM files into MGZ format, resample to 1-mm isotropic voxels, segment cortical gray matter, and generate pial and white matter surfaces for each subject. Manual editing was performed to correct for inaccuracies in cortical grey and white matter boundaries. The relative differences of total cortical grey matter volume (cGMV) and white matter volume (WMV) before and after manual editing were less than 2.0%. To provide a more balanced representation of sulcal and gyral regions (Van Essen, 2005), cortical midthickness surfaces were generated by averaging the edited pial and white matter surfaces using Caret 5.61 software.

PALS-TA24 atlas and surface-based registration

To quantitatively compare the cortical surfaces of VPT and TC children, we used an existing infant-adult hybrid atlas (PALS-TA24) based on 12 TC infants and 12 healthy adults (Hill et al., 2010a). The midthickness cortical surfaces of the 48 subjects (24 VPT and 24 TC children) were registered from FreeSurfer to the PALS-TA24 atlas using an automatic landmark identification algorithm in Caret (Anticevic et al., 2012). Six anatomical landmarks including central sulcus, Sylvian fissure, anterior half of the superior temporal gyrus, calcarine sulcus, dorsal and ventral medial wall segments ("Core-6"), previously shown to be highly consistent in location and extent from infancy to adulthood (Van Essen, 2005 and Hill et al., 2010a), were automatically drawn on each individual surface and were manually corrected as needed by a single rater (YZ). The corrected landmarks were used as constraints for registering the individual's spherical mesh to the population-average spherical

landmarks. This registration process yielded resampled surface meshes (73,730 vertices) for each individual subject that were in geographic correspondence with one another.

Volumetric and Surface Based Calculations

Total cerebral grey matter and white matter volumes were calculated from the pial and white matter surfaces using FreeSurfer 4.4.0. The total cortical surface area (CSA) for each hemisphere was generated from the native-space, native-mesh midthickness cortical surface using Caret. The non-cortical region along the medial wall was identified (by fusing two landmark contours running along this transition and identifying vertices enclosed within this region) and was excluded from all the measurements. Thirty-four sub-regions in each hemisphere were automatically parcellated by FreeSurfer using the Desikan-Killian Atlas (Desikan et al., 2006). To reduce concerns about Type I errors, we a-priori analyzed a reduced number of regions of the brain by combining some contiguous regions in an anatomically appropriate manner that would be of greater regional significance. See Supplemental Table 3 for details on how these regions were combined.

Relative cGMV was calculated by dividing the GMV of these regions by the total GMV of the corresponding hemisphere. All p-values presented were Bonferroni-corrected for 36 regional analyses (counting both hemispheres). Using the parcellation label files generated from FreeSurfer, we also calculated the regional CSA of the midthickness surface in several regions located in the medial frontoparietal region where cortical folding abnormalities were observed.

GI was used to evaluate the global degree of cortical convolution in each individual hemisphere. The GI was calculated by measuring the ratio of the surface area of the cortical midthickness surface and that of the cerebral hull in native space. The cerebral hull surface (enclosing the entire hemisphere but not dipping into sulci) was generated using Caret software (Van Essen, 2005). To identify and exclude the medial wall from the cerebral hull, the medial wall border contour was unprojected from the midthickness surface and projected onto the cerebral hull mesh.

Reliability tests

Scans of five subjects randomly selected from the 24 TC and 24 VPT children in this study were used to test the consistency of our analysis methods. Volumes (cGMV, WMV), CSA, and surface folding measures of the midthickness surface, including mean curvature index (MCI), intrinsic curvature index (ICI), and folding index (FI), were used to calculate the intraclass correlation coefficient (ICC) between repeated measures. Results were compared for: values from each individual subject generated from two independent runs by FreeSurfer 4.4.0 applied to the same scan without manual editing; values from manually-edited cortical surfaces edited by the same operator at time points six months apart; and values from of cortical surfaces that were manually edited by two different operators independently. The ICC of all the six measurements without manual editing exceeded 0.998 (Test 1 in Table 2), indicating very high reliability. The ICC of the 6 cortical measurements with manual editing by one operator all exceeded 0.990 (Test 2 in Table 2), indicating high consistency of the

same operator. The ICC of the 6 cortical measurements of two operators all exceeded 0.984 (Test 3 in Table 2), indicating high consistency between different operators.

Population-average midthickness surfaces and sulcal depth maps

To characterize the structural difference of population-averaged cortical surfaces between VPT and TC children, average midthickness cortical surfaces and sulcal depth maps were generated for each group. The population-average (VPT/TC) midthickness cortical surfaces were created by averaging the 3D coordinates of each vertex for the resampled midthickness cortical surface of the children in each group using Caret. Sulcal depth at each vertex was defined as the distance from the vertex on the midthickness surface to the nearest point in the cerebral hull surface (Van Essen, 2005). Sulcal depth maps for each surface were generated by calculating sulcal depth at each surface vertex on the registered individual surfaces. Population-average sulcal depth maps were then created by averaging the sulcal depth maps of the 24 individuals in that population.

Relative surface area

A map of relative surface area was computed by normalizing the surface area associated with each tile relative to the total CSA of the hemisphere. Since each vertex is associated with multiple tiles and each tile contains three vertices, the surface area assigned to each vertex was one-third the sum all tiles associated with that vertex. The relative surface area map was computed using the resampled individual surface in the atlas space. Absolute CSA depends upon overall brain size as well as the pattern and complexity of cortical convolutions. Because it normalizes for total CSA, the relative surface area map provides a measure that depends on local shape features and not on the absolute size of each hemisphere.

Statistical analysis

To determine the statistical significance of shape feature differences between populations, we first assigned each individual a group membership (i.e. VPT or TC) and generated a t-statistic map by computing two-sample t-test at each vertex between the 24 VPT and 24 TC subjects for relative surface area and sulcal depth. Randomization tests were performed by randomly permuting the group membership at least 1,000 times and calculating the t-statistic map for each permutation (Nichols and Holmes, 2002; Hill et al., 2010b). To identify statistically significant clusters on the t-map, we used the threshold-free cluster enhancement (TCFE) method (Smith and Nichols, 2009). This entailed applying a TFCE transform to the t-statistic at each surface vertex. The TFCE value corresponding to the 95th percentile of this TFCE maximum value distribution was set as the cutoff, and significant clusters on the final t-map were identified at a $p < 0.05$ level.

Asymmetry analysis

To determine whether VPT subjects had altered asymmetry at seven years, we computed left minus right depth differences for each subject. For each group (VPT and TC), a paired t-test was performed (Hill et al., 2010a). To determine whether one group was significantly more asymmetric than the other, we performed a two-sample t-test on the left-right depth

differences (VPT vs TC). The statistical analysis (e.g., TFCE thresholding) was performed as described above in the Statistical analysis section.

Analysis of sulcal trajectories

We analyzed the trajectories of individual sulci in an objectively defined ROI of medial cortex identified from other analyses (see Results). The skeleton of sulci within this ROI was generated for each individual hemisphere using a semi-automated method. The Caret-generated folding (mean curvature) map was thresholded at < -0.2 to identify surface vertices near sulcal fundi. On mean curvature maps, negative values are associated with sulcal regions (concave) and positive values are gyral (convex). Empirically, we determined that for both groups in this study, a threshold of -0.2 represented a suitable cutoff for successfully identifying sulci and avoiding undesirable interruptions in the sulcal trajectory. The start and end points of each sulcus were manually selected, and an automated process in Caret computed a trajectory running along the curvature minimum between these endpoints. Sulcal contours shorter than 8 mm were excluded. The operator was blind to the group identity (VPT vs TC) when drawing the sulcal skeletons for each individual surface. To visually compare sulcus patterns between VPT and TC children, contours of all the sulci within the medial frontoparietal cortex from the VPT and TC children were projected onto the average mean midthickness cortical surface of the VPT and TC children, respectively. The surfaces were then hidden so the skeletonized sulci could be seen. The longest sulcus in the ROI for each subject was selected and used for a two-sample t-test between populations.

Results

Our analysis revealed no statistically significant differences in demographic and health characteristics (GA, illness, social risk etc) for the infants followed at 7 years in this cohort versus the entire cohort or the infants who were not followed. Notably, 85% of eligible infants were followed up at 7 years of age. No infant in this series had motor performance at 2 years or 7 years that was categorized as significantly delayed performance. When examining the performance of the 24 VPT children in this study, their average performances in all tests were poorer than the 24 control children, especially in visual skills, language, IQ and behavioral functions which were particularly vulnerable in preterm children. However, only the IQ scores reached statistical significance (see supplementary table 2).

In terms of brain morphology, marked differences between VPT and TC children were observed, with reductions in cGMV, WMV, CSA and GI (Table 3). On average, cGMV, WMV and CSA in very VPT children were approximately 10% less than in TC children. We also found that GI was approximately 4% smaller in VPT children ($P < 0.0001$). All the global measures were calculated in native space and the surface measures were based on native mesh cortical surfaces. Group differences in overall brain dimensions have greater effect on cGMV, WMV and CSA than on GI, which was normalized by the area of the convex hull.

Absolute and relative regional GMV alteration in VPT children

In a preliminary analysis, we also compared the cGMV and relative cGMV of 18 regions between VPT and TC children (Table 4). VPT children had lower cGMV in lateral parietal cortex, orbital frontal cortex, middle temporal cortex, and insular cortex of both hemispheres ($p < 0.05$). Smaller volumes in VPT children were also found in the inferior frontal region of the left hemisphere and postcentral region of the right hemisphere (Table 4). In contrast, larger relative cGMV was found in VPT children in the lateral occipital lobe of left hemisphere and medial parietal lobe of right hemispheres (Table 4).

The medial parietal region displays a similar absolute volume between TC and VPT, with an increased relative proportion in the VPT children. This is in contrast to most cerebral regions, which have a reduced absolute cerebral volume and, in some regions, relative volumes in VPT vs TC children. The next section describes surface-based analyses that better characterize the structural differences between VPT and TC children.

Population-averaged surfaces and sulcal depth maps

Qualitatively, the VPT and TC mean midthickness surfaces are similar in most regions (Figure 1). By visual inspection, the most obvious difference between VPT and TC children was in the anterior portion of the superior temporal sulcus in both hemispheres, where the sulcus appeared shallower in VPT children (arrows in Figure 1). This impression was confirmed by a quantitative analysis of sulcal depth (Fig. 2). Figures 2A and 2B show sulcal depth t-maps for VPT children vs TC children on lateral views of inflated (left column) and average midthickness (middle column) surfaces and on medial views of the average midthickness (right column) surfaces. The lateral aspect of each hemisphere contained two large clusters. One is centered on the superior temporal sulcus, with a deeper sulcus in TC children (red/orange), especially in the right hemisphere (yellow arrow in the middle panel). This sulcal depth abnormality in the superior temporal sulcus is evident when comparing the individual inflated surfaces of TC and VPT children, as shown on three exemplar pairs of right hemispheres that sample the range of total brain volumes in each group (Figure 2C and 2D). The second cluster includes the inferior precentral and inferior postcentral sulcus plus a large region of opercular and insular cortex (yellow arrow in the left panel of Figures 2A and B). These differences are also illustrated in Supplemental Figure 2, which shows average midthickness surfaces of TC and VPT children overlaid on average coronal slice of the MNI305 population-average atlas volume.

Sulcal Depth Asymmetries in VPT and TC children

Both the VPT and TC groups showed regions of significant sulcal depth asymmetry between left and right hemispheres (Fig. 3). The largest region showing significant asymmetry in both groups is in the superior temporal sulcus. This region was markedly larger for the TC group (7742 mm^2 , Fig. 3A) than for the VPT group (2345 mm^2 , Fig. 3B). However, this group difference in hemispheric asymmetry was not statistically significant insofar as no vertices survived the TFCE threshold in a two sample t-test of the VPT left-right vs control left-right group differences (Fig. 3C).

Relative surface area abnormalities in VPT children

Relative cortical surface area was larger in term-born children (Figure 4, orange/yellow) in lateral regions of both hemispheres, including the posterior superior temporal and angular gyri bilaterally, the inferior precentral and inferior postcentral cortex in the left hemisphere, and the ventral sensori-motor cortex in the right hemisphere. In medial cortex, the relative surface area was larger in VPT children (blue/green) in parietal and frontal regions of the right hemisphere and in parieto-occipital and parahippocampal cortex of the left hemisphere. Because the area of each surface tile was normalized to total cortical surface area, a larger relative surface area suggests relatively greater folding complexity in that region. To illustrate the regional population characteristics of cortical folding, we examined all of the individual surfaces in both groups. The most obvious folding abnormalities were found in cingulate cortex and the precuneus, where surfaces of VPT children have a larger relative surface area (yellow arrow in Figure 4B). The cortex appears visibly more convoluted in VPT children (Figures 4C and 4D). In addition, inspection of these individual surfaces suggested that cingulate sulcus has a more interrupted trajectory in VPT children.

In these examples (Figures 4C and 4D), the callosal gyrus is wider in the 3 exemplar TC children than in the 3 exemplar VPT children. However, inspection of medial views of the left and right hemispheres for all subjects each group indicated that this was not a consistent pattern. Many VPT children had a wide callosal gyrus on one or both sides, and many TC children had a narrow callosal gyrus on one or both sides.

Comparison of the absolute and relative surface area of this region of interest in TC and VPT children revealed that the absolute surface area of these regions in VPT children was close to TC, despite their significantly smaller total cortical surface area (Table 5; see also Supplemental Figure 3 for scatter plots showing the dispersion of subjects' mean relative surface area within the left and right hemisphere ROIs analyzed in table 5).

Abnormal sulcal configurations in medial frontoparietal cortex in VPT children

In the medial frontoparietal region identified as having greater relative surface area in VPT children, we visually inspected the folding pattern in each individual. To quantify our impression that sulci in this region tended to be more abbreviated in VPT children, we used a semi-automated method to generate the skeleton of every sulcus in this region for all subjects. Figure 5 shows the superimposed skeletons of all sulci exceeding 8 mm in length for TC (Figure 5B) and VPT (Figure 5C) children after alignment to stereotaxic space. Differences were apparent in the sulci of the medial cingulate cortex and precuneus (red arrow in Figure 5C). To quantify this difference, we identified the longest sulcus in each subject in this ROI (see Methods). The longest sulcus was shorter in VPT children in both the right hemisphere (TC = 146mm $\pm$ 32; VPT = 107mm $\pm$ 32; $p=0.0001$) and left hemisphere (TC = 131mm $\pm$ 26; VPT = 116mm $\pm$ 22; $p=0.04$). Additionally, VPT children have two branches of the cingulate sulcus more frequently than TC children (Supplemental Table 4).

Discussion

We report here on abnormalities of brain morphology in children born preterm, especially patterns of cortical folding, that represent long-term influences of premature birth combined with extended periods in a neonatal intensive care unit. Some of these abnormalities may have arisen in the early postnatal period and have been established by term equivalence (Ajayi-Obe et al., 2000; Dubois et al., 2008; Engelhardt et al., 2014). This period (i.e., the third trimester for term-born infants) is after cortical neurogenesis and neuronal migration are largely complete (Dubois et al., 2008), and instead is a time of massive expansion of subcortical white matter, formation of long-distance connections, and extensive cortical folding. It has been proposed that mechanical tension generated by axons within the white matter may be a major factor that contributes to cortical folding during normal maturation (Van Essen, 1997) and to abnormalities of cortical folding in developmental disorders such as Williams Syndrome (Van Essen et al., 2006). While this hypothesis remains unproven, it provides a useful conceptual framework when considering the folding abnormalities reported in the present study.

We identified global reductions in brain volume and cortical surface area of VPT children at school age compared to TC children. This was accompanied by specific regional patterns of cortical morphological changes, including shallower sulcal depth in the superior temporal sulcus, more convoluted medial frontoparietal cortex and abbreviated cingulate sulci in VPT children. The global brain volumetric and surface area reductions documented in VPT children are consistent with previous studies in preterm born children and adolescents (Kesler et al., 2004, Kesler et al., 2008, Soria-Pastor et al., 2008, Soria-Pastor, 2009, Gimenez et al., 2006a and b, Nosarti et al., 2008 and Nosarti et al., 2009). Our analysis provides a more detailed characterization of these morphological differences.

Global volume and folding reduction

The ~10% reduction in global cortical volume and surface area we found exceeds the previously reported volumetric reduction of brain tissue in preterm children (Kesler et al., 2004 and Soria-Pastor et al., 2009). This difference may reflect our sample of VPT children had a lower gestational age (mean gestational age is 25.3 weeks) than the preterm samples reported in other studies. We also found a ~4% global reduction of cortical convolution (GI) bilaterally in VPT children. Previous studies indicate slower cortical development with reduced cortical folding and delay of gyral formation in preterm infants compared with term born infants (Battin et al., 1998, Ajayi-Obe et al., 2000 and Ramenghi et al., 2007). Our data indicate that this reduction of global cortical complexity persists into their early childhood.

Regional patterns of cortical folding abnormalities

Most previous studies of cortical folding abnormalities in VPT children are limited to global measures of folding or examination of cortical shape in individual subjects. Here, we registered each individual hemisphere to a surface-based atlas to identify regional cortical shape abnormalities without parcellation of the cerebral cortex into predetermined sub-regions. We used relative surface area as a measurement of regional cortical complexity. Because surface area is related to both cortical volume and folding, normalization relative to

the total surface area provides a measure that is more closely related to cortical folding. In addition, we used sulcal depth measurements to complement the information from the relative surface area measurements. Sulcal depth and relative surface area are sensitive to different features, even though they are not orthogonal measures. Differences in sulcal depth (distance from the midthickness surface to closest node on the hull surface) can arise from differences in folding patterns that have little or no effect on total or relative cortical surface area. Differences in relative surface area (the proportion of an ROI's surface area to total hemispheric area) are not necessarily associated with a consistent difference in folding or in mean sulcal depth.

Temporal cortex—We demonstrated abnormal cortical folding in the superior temporal and angular gyri in VPT children, with a shallower superior temporal sulcus. This is consistent with previous studies indicating that the temporal lobe is vulnerable in preterm subjects, as manifest by reductions in cortical volume, surface area, WM integrity and cortical thickness (Kesler et al., 2004, Norsarti et al., 2008, Norsarti et al., 2010, Nagy et al., 2010 and Frye et al., 2010, Skranes et al., 2013 and Bjuland et al. 2013). It has been previously suggested that both the anterior and posterior temporal lobe have lower gyrification values in VPT infants, consistent with our findings (Battin et al., 1998). However, one study that examined cortical complexity in the temporal lobe suggested a higher GI in this region in preterm children (Kesler et al., 2006). One potential explanation for this discrepancy may be the measures used, because Kesler *et al.* used only one measure (GI) on a large predetermined subcortical region (temporal lobe), while we used multiple measures of differences in regional cortical folding. Functionally, the superior temporal cortex has been implicated in language processing and social cognition, both of which have been reported to be areas of concern for preterm children (Röder et al., 2002, Scott et al., 2006, Jellema and Perrett, 2003, Narumoto et al., 2001 and Bigler et al., 2007). The pattern of abnormal cortical folding in this region might serve as a biomarker for these functional abnormalities in preterm individuals.

The mechanism(s) underlying the vulnerability of the temporal lobe and alterations in the formation of the temporal sulcus remain unknown. Our laboratory has previously identified alterations in temporal lobe microstructure and resting state functional connectivity in preterm infants exposed to greater procedural pain and stress (Smith et al., 2011). Further, abnormalities in the superior temporal region in Williams syndrome were reported by Sampaio *et al.* (Sampaio et al., 2008), based on a reduction in regional volume, though these were not observed in a surface-based analysis (Van Essen et al., 2006). In Down's syndrome, morphological abnormalities, including widening of the superior temporal sulcus, have been associated with impaired pruning of neurons after 22 weeks gestation that is hypothesized to result from impaired axonal and/or dendritic connectivity (Golden and Hyman, 1994). Immature oligodendroglia are well recognized as a primary target for injury from ischemia and/or inflammation in the preterm brain. In addition, neuronal abnormalities may result from either primary neuronal injury or secondary deafferentation, producing a combined lesion of white, cortical and deep nuclear gray matter injury coined “encephalopathy of prematurity” (Volpe, 2009). Distinctive maturational changes in fractional anisotropy in superior temporal cortex revealed by diffusion tensor imaging (Aeby et al., 2012) might

underlie this regional vulnerability, but additional factors, such as metabolism or distribution of neurotransmitter receptors, may also contribute. Further histological evaluation of this region in the immature brain, particularly from autopsy of preterm infants, may aid in characterizing this regional vulnerability.

With regard to the superior temporal sulcus, it is notable that the most significant cluster of difference was located on the right, rather than left, hemisphere. Previous studies have reported that the superior temporal sulcus is largely developed between 31 to 36 weeks gestation and matures earlier in the right hemisphere (Chi et al., 1977 and Dubois et al., 2008). This is consistent with the hypothesis that abnormalities in the development of this sulcus arise during the period that preterm infants are within the neonatal intensive care unit. While no asymmetry differences across the VPT and TC groups survived significance thresholding, the left-right sulcal depth asymmetry in the STS appeared less pronounced in VPT children and may warrant further analysis in future studies.

Medial frontoparietal cortex—We found that VPT children have a larger relative surface area in the medial frontoparietal cortex and that this is associated with greater cortical folding. A previous surface-based study of preterm infants (mean gestational age 31 weeks) with white matter abnormalities showed a trend for a globally increased sulcation index (Dubois et al., 2008). Moreover, preterm infants having white matter lesions sometimes demonstrate polymicrogyria in the region of injury (Inder et al., 1999b). The white matter within the corpus callosum is significantly altered by preterm birth (Thompson et al., 2010, van Pul et al., 2011 and Ball et al., 2012). Therefore, one possible explanation for our finding of the more convoluted medial frontoparietal cortex may relate to a disturbance of white matter development in this region.

The pattern of excessive cortical folding in the medial frontoparietal cortex of VPT children drew our attention to the morphology of the sulci in this region. The major sulcus is the cingulate sulcus, which showed morphological differences between VPT and TC groups. Previous studies have reported that the cingulate sulcus is continuous and uninterrupted in ~60-80% of hemispheres in healthy individuals (Paus et al., 1996 and Ono et al., 1990). An interrupted cingulated sulcal pattern in adults is associated with a higher genetic risk of schizophrenia (Meredith et al., 2012). Further, more people in a high risk of psychosis group had an interrupted left cingulated sulcus when compared with controls (Yücelet et al., 2003).

Finally, a study of prematurely born adolescents demonstrated greater cortical thickness in the cingulate cortex (Frye et al., 2010). Our study demonstrated that the cingulate sulcus of VPT children was on average shorter and less continuous than that of TC children, especially in the right hemisphere. The cingulate sulcus appears around 27 weeks gestational age and is largely developed by 37 weeks gestational age (Dubois et al., 2008), consistent with the hypothesis that these cortical folding abnormalities present in childhood may arise during the period in the neonatal intensive care unit. The mechanism responsible for this alteration in cingulate sulcal structure remains unknown, but if cortical folding is driven by mechanical tension along long-distance axons (Van Essen, 1997), folding abnormalities may reflect altered patterns of connectivity in VPT children. This is consistent with the observation that hypoxia-ischemia, a known risk factor for brain injury in preterm infants

(Dammann and Leviton, 1997 and Greisen and Vannucci, 2001), produces an increased number of apoptotic cingulate neurons in piglets (Mehmet et al., 1994). The asymmetry of sulcal abnormalities in our findings are consistent with previous reports of anatomical asymmetries in medial cortical regions (Paus et al. 1996; Thompson et al., 2010).

We also found that the pattern of an interrupted cingulate sulcus was more pronounced in the right hemisphere of VPT children, but not in TC children. This rightward interrupted cingulate asymmetry has been observed in healthy young adults (Ono et al., 1990 and Paus et al., 1996) along with increased volume in the right cingulate sulcus, suggestive of a more convoluted cortical surface (Leonard et al., 2009, Watkins et al., 2001 and Paus et al., 1996). The cingulate cortex has been associated with emotional and behavioral regulation, including the assessment of complex information, reaction to pain and selection of appropriate responses (McCrory et al., 2012, Rushworth and Behrens, 2008, Vogt et al., 2003 and Passingham, 1996). These are common areas of impairment in preterm children.

In conclusion, this study provides insights into the long-lasting disruptions of cortical morphology in very preterm infants, including evidence for regional vulnerability in the superior temporal and cingulate regions, with greater impact within the right hemisphere. These findings suggest lines of future research that may elucidate the underpinnings of this regional vulnerability. In addition, the relationship between alterations in cortical morphology and childhood neurodevelopmental outcomes will be important to characterize.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

VPT	Very Preterm
TC	Term Control
MRI	Magnetic Resonance Imaging
GM	Grey Matter

WM	White Matter
CC	Corpus Callosum
cGMC	cortical Grey matter Volume
WMV	White Matter Volume
CSA	Cortical Surface Area
GI	Gyrification Index
FI	Folding Index
ICI	Intrinsic Curvature Index
MCI	Mean Curvature Index
ICC	Intraclass Correlation Coefficient
TCFE	Threshold-free Cluster Enhancement

Highlights

- We compared brain morphometry at 7 years in children born prematurely vs at term.
- Very preterm (VPT) children had reduced cortical folding in lateral temporal cortex.
- VPT children showed more complex cortical folding in medial frontoparietal cortex.
- Premature birth is associated with complex and long-lasting cortical abnormalities.

Figure 1.

Average midthickness surfaces of left (A) and right (B) hemispheres for TC and VPT children with average sulcal depth maps overlaid. The color bar shows the scale of the sulcal depths in mm. The most obvious structural differences based on visual inspection were found in the anterior portion of the superior temporal sulcus in both hemispheres (red arrows), which are shallower in VPT-born children.

Figure 2.

Group differences in sulcal depth. The top two rows show sulcal depth t-maps of the left (A) and right (B) hemispheres generated by a two-sample t-test comparing the surfaces of 24 VPT and 24 TC children. In the left panels of these two rows, the t-maps are overlaid on the inflated average surfaces of the 48 subjects in this study. In the middle and right panels, the t-maps are overlaid on the average midthickness cortical surfaces. The black contours outline regions that are statistically different ($p < 0.05$) using TFCE. The bottom two rows show lateral views of the inflated right hemispheres of individuals from the TC (C) and VPT (D) groups. In each of these two rows, the left panel shows the individual with the largest total brain volume in its population, the middle panel shows the individual closest to the population mean, and the right panel shows the individual with the smallest total brain volume (total brain volume is labeled on the right corner of each surface). White boxes delineate the approximate region having a visible sulcal depth difference between groups.

Figure 3.

Sulcal Depth Asymmetry Analysis. A. Lateral (top) and medial (bottom) sulcal depth t-maps (left-right) for the TC group. Red=right deeper; blue=left deeper. White borders encircle vertices that exceeded the 95th percentile on the paired t-test (TFCE). B. Corresponding panels for the VPT infants. There are more significant clusters in the TC group than the VPT group. The cluster in the superior temporal sulcus of TC (7742 mm²) is larger than that of VPT (2345 mm²), but this difference is not statistically significant C. The t-map resulting from a two sample t-test between the VPT and TC left-right differences. Red=VPT.left-right>TC.left-right; blue=TC.left-right>VPT.left-right. No vertices survived TFCE thresholding.

Figure 4.

Relative surface area t-maps of the left (A) and right (B) hemispheres generated by a two-sample t-test comparing the cortical surfaces of 24 VPT and 24 TC children. The t-maps are overlaid on the inflated surface of the average cortical surfaces of the 48 subjects (left panel) and the average midthickness cortical surface of the 48 subjects in this study (middle and right panels). The black contours outline regions that are statistically different ($p < 0.05$) using TFCE. The bottom two rows show the medial cortex of the right hemispheres of TC (C) and VPT (D) children. Surfaces from the individuals in each group with the lowest CSA are shown in the left panel, surfaces from those with CSA closest to the mean are shown in the center panel, and surfaces from those with the highest CSA are shown in the right panel (CSA is labeled on the bottom of each surface). White boxes show the approximate region of visible differences between TC and VPT subjects.

Figure 5.

Abnormal sulcal patterns in medial fronto-parietal cortex. (A) The medial fronto-parietal region of interest is highlighted (green) on the average fiducial surface of the TC and VPT children. (B and C) Skeletons of all sulci (left) and the longest sulcus (right) within the medial fronto-parietal cortex of surfaces from TC (panel B) and VPT (panel C) children were projected onto their respective average midthickness surfaces (surfaces not shown). Red arrows indicate regions that show discernible group differences.

Table 1

Demographics of VPT and TC children selected for the study.

	VPT Children	TC Children
Gestational Age (weeks) Mean (range)	25.(22-26)	39 (37-41)
Age at MRI (years) Mean (SD)	7.4 (0.4)	7.4 (0.4)
Male n (%)	12 (50)	12 (50)
Birth weight (g) Mean (SD)	776 (156)	3317 (467)
Cystic Periventricular leukomalacia n (%)	0 (0)	0 (0)
White Matter Abnormality Score ** (Grade 2/3)	12/4	0
Intraventricular Hemorrhage Grade 1/2	5/3	0
Dexamethasone postnatal corticosteroids n (%)	0 (0)	0 (0)
Wechsler Abbreviated Scale of Intelligence Full IQ	97.9 (10.7) *	110.3 (12.7)
Movement Assessment Battery for Children 2 Score	9.0 (2.8)	10.4 (2.1)
Behavior Rating Inventory of Executive Function (BRIEF)	53.6 (12.8)	47.0 (10.7)
Conners 3 Attention Deficit Hyperactivity Deficit Index	62.8 (17.6)	50.1 (13.3)

* P < 0.05.

** WM Abnormality was graded from 1–4 where Grade 1 was normal, Grade 2 was mild abnormality, Grade 3 was moderate abnormality based on loss of white matter volume, thinning of the corpus callosum (Inder et al., 2003).

Table 2

Intraclass correlation coefficient (ICC) for analysis reliability tests.

	cGMV		WMV		CSA		MCI		ICI		FI	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
ICC												
Test 1 (Freesurfer consistency)	1.000	0.998	1.000	1.000	1.000	1.000	1.000	1.000	0.998	0.998	1.000	1.000
Test 2 (Intra-operator consistency)	0.997	0.990	0.995	0.997	0.990	0.995	0.995	0.993	0.998	0.989	0.998	0.998
Test 3 (Inter-operator consistency)	0.995	0.995	0.991	0.996	0.990	0.986	0.984	0.994	0.997	0.993	0.998	0.997

Table 3

Two sample t-test of the average cGMV, WMV, CSA and GI of VPT and TC children at 7 years of age.

	TC (n=24) Mean (std)	VPT (n=24) Mean (std)	Mean Percentage difference	P value
cGMV (cm³)				
Left	312 (24)	285 (24)	9.1%	0.0003
Right	312 (25)	284 (22)	9.1%	0.0002
WMV (cm³)				
Left	225 (22)	201 (22)	11.3%	0.0004
Right	226 (22)	202 (21)	11.2%	0.0003
CSA (cm²)				
Left	1011 (68)	923 (71)	9.1%	<0.0001
Right	1016 (70)	926 (66)	9.3%	<0.0001
GI				
Left	2.73 (0.06)	2.63 (0.08)	3.7%	<0.0001
Right	2.76 (0.06)	2.65 (0.07)	4.1%	<0.0001

Table 4

T-test comparison of the regional absolute and relative cortical grey matter volume between VPT and TC children. The 18 regions in the list are based on the 34 sub-regions automatically parcellated by Freesurfer using Desikan-Killian Atlas (refer to supplementary table 3). All p-values have been Bonferroni-corrected for multiple comparisons for 36 regions. The p-value highlighted in light blue indicates the relative GM volume is significantly larger in VPT than that in TC.

	Left Hemisphere						Right Hemisphere					
	GM Volume (cm ³)		P Value	Relative GM Volume (%)		P Value	GM Volume (cm ³)		P Value	Relative GM Volume (%)		P Value
	TC	VPT		TC	VPT		TC	VPT		TC	VPT	
Lateral Occipital	15.8±2.7	16.6±2.6	X	5.0±0.6	5.8±0.6	0.006	16.4±2.9	16.7±2.5	X	5.2±0.7	5.9±0.8	X
Lateral Parietal	36.8±3.5	31.8±3.2	0.006	11.8±0.8	11.1±1.1	X	41.0±3.7	35.2±4.0	<0.001	13.2±1.1	12.4±1.4	X
SupraMarginal	15.9±2.5	14.0±2.3	X	5.1±0.7	4.9±0.6	X	14.4±2.6	12.6±1.9	X	4.6±0.7	4.4±0.5	X
PostCentral	13.0±1.6	12.4±1.7	X	4.2±0.4	4.3±0.5	X	12.4±1.7	10.8±1.3	0.036	4.0±0.4	3.8±0.3	X
Precentral	16.5±1.6	15.4±2.4	X	5.3±0.5	5.4±0.7	X	16.3±1.8	15.4±2.0	X	5.2±0.5	5.4±0.7	X
SuperiorFrontal	29.7±3.3	28.6±3.3	X	9.5±0.8	10.0±0.8	X	28.3±3.9	27.1±3.7	X	9.0±0.7	9.5±0.8	X
MiddleFrontal	31.7±4.0	30.1±3.3	X	10.2±0.9	10.5±0.9	X	31.7±4.2	29.6±3.9	X	10.2±1.1	10.4±1.0	X
InferiorFrontal	12.2±1.8	10.1 ± 1.2	<0.001	3.9±0.5	3.5±0.3	X	10.9±1.5	9.8±1.3	X	3.5±0.4	3.5±0.4	X
OrbitalFrontal	19.0±1.9	16.9±1.8	0.006	6.1±0.5	5.9±0.5	X	19.8±1.6	17.8±1.9	0.006	6.4±0.4	6.3±0.5	X
SuperiorTemporal	17.6±2.6	16.2±1.9	X	5.6±0.6	5.7±0.5	X	16.4±1.5	15.0±1.8	X	5.3±0.3	5.3±0.5	X
MiddleTemporal	19.2±2.7	16.0±2.4	<0.001	6.2±0.7	5.6±0.6	X	21.2±2.6	17.3±2.0	<0.001	6.8±0.6	6.1±0.8	0.072
InferiorTemporal	27.5±3.0	24.8±2.7	X	8.8±0.7	8.7±0.8	X	27.0±3.9	25.0±3.7	X	8.6±0.9	8.8±1.0	X
MedialTemporal	7.4±1.0	7.0±1.4	X	2.4±0.3	2.5±0.4	X	6.8±0.8	6.3±1.1	X	2.2±0.2	2.2±0.3	X
MedialOccipital	11.4±1.6	10.6±1.8	X	3.7±0.4	3.7±0.5	X	11.6±1.7	10.8±1.6	X	3.7±0.6	3.8±0.5	X
MedialParietal	22.1±2.7	21.4±1.7	X	7.1±0.7	7.5±0.4	X	23.3±3.0	23.0±2.1	X	7.5±0.7	8.1±0.5	0.012
CingulateLobule	10.0±1.6	8.5±1.5	0.072	3.2±0.3	3.0±0.4	X	9.3±1.3	8.2±1.2	X	3.0±0.4	2.9±0.4	X
Isthmus	3.5±0.7	3.4±0.6	X	1.1±0.2	1.2±0.2	X	3.1±0.4	2.9±0.5	X	1.0±0.1	1.0±0.2	X
insula	7.4±0.8	6.6±0.7	0.036	2.4±0.1	2.3±0.1	X	7.4±0.8	6.6±0.8	0.036	2.4±0.2	2.3±0.2	X

X: p > 0.1.

Table 5

T-test of the total cortical surface area, surface area of an ROI 1 and 2 (red, shown on an individual midthickness surface) and relative surface area of the same ROI in native space. Values in parentheses represent standard deviations (see supplementary figure 3).

	Left Hemisphere			Right Hemisphere		
	Total SA (cm ²)	SA of ROI 1 (cm ²)	Relative SA of ROI 1	Total SA (cm ²)	SA of ROI 2 (cm ²)	Relative SA of ROI 2
TC	1011 (68)	92 (10)	0.091 (0.007)	1016 (70)	154 (16)	0.152 (0.008)
VPT	923 (71) **	90 (10)	0.098 (0.008) *	926 (66) **	147 (15)	0.159 (0.008) **

* p< 0.005,
** p < 0.0001