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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 gray 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 sensorimotor 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.

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; 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 gray 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, 2003; Peterson, 2003; Mewes et al., 2006; Thompson et al., 2007; Clark and Woodward, 2010; Hutchinson et al., 2013). Further, these structural abnormalities have been associated with cognitive and behavioral defects during childhood and adolescence (Peterson et al., 2000, 2003; Peterson, 2003; Thompson et al., 2007; 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, 2008; Soria-Pastor et al., 2008, 2009; Giménez et al., 2006a,2006b; Nagy et al., 2009; Nosarti et al., 2008, 2009; 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., 2011; Frye et al., 2010; Skranes et al., 2013; Bjuland et al., 2013). Studies of cortical folding, which undergoes rapid development during 28–40 week gestation, suggest reduced cortical folding and delayed gyral development in preterm infants (Battin et al., 1998; Ajayi-Obe et al., 2000; 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 week gestation who underwent MRI at 7 years of age. These were compared with data from 24 age-matched term control (TC) children born >37 week gestation. In addition, regions of abnormal cortical folding were further analyzed using a combination of qualitative and quantitative approaches.

Abbreviations: VPT, very preterm; TC, term control; MRI, magnetic resonance imaging; GM, gray matter; WM, white matter; CC, corpus callosum; cGMC, cortical gray 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

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Methods

Subject recruitment and MRI scanning

The subjects were drawn from an initial cohort of 203 VPT infants born prior to 30 week gestation, and 46 TC (>37 week 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 week 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 week gestation) and 24 TC (37 to 42 week 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 Fig. 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 T MRI scanner (Siemens Magnetom Tim Trio system) at the Royal Children's Hospital. Sagittal three-dimensional rapid gradient-echo T_1-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 mm^3, and bandwidth = 200 Hz/Px.

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 periventicular leukomalacia n (%)	0 (0)	0 (0)
White Matter Abnormality score[a] (Grades 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)

[a] 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).
* $p < 0.05$.

Parameters for sagittal three-dimensional turbo spin-echo T_2-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 mm^3, 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 gray and white matter boundaries. The relative differences of total cortical gray 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; Hill et al., 2010a) were automatically drawn on each individual surface and 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 gray 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 excluded from all the measurements. Thirty-four sub-regions in each hemisphere were automatically parcellated by Freesurfer using the Desikan-Killiany 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