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Prematurity Affects Cortical Maturation in Early Childhood

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Abstract

Cortical development in the first years of life in children born at very low birth weight (VLBW) has not been well characterized. We obtained high resolution structural MRI scans from children age 18–22 months (16 VLBW/7 term) and 3–4 years (12 VLBW/8 term). Cortical surface area and thickness of the brain were assessed using the FreeSurfer data analysis program and manually inspected for accuracy. Within the group of VLBW children, there was a negative correlation between birth weight and cortical thickness at 18–22 months ($p=0.04$) and a positive correlation with cortical surface area at 3–4 years ($p=0.02$). Between groups there was a consistent trend in VLBW children for thicker cortex and reduced surface area compared to control term children, (18–22 month surface area $p=0.08$ & thickness $p=0.11$, 3–4 year surface area $p=0.73$ & thickness $p=0.14$). The normal processes of cortical thinning and surface area expansion in the first several years of life may be delayed by premature delivery, an effect which might be more prominent with greater degrees of prematurity.

Introduction

Neuropathology associated with premature birth has been characterized recently as an “encephalopathy of prematurity,” involving injury to both gray and white matter structures¹. This is consistent with neuroimaging studies identifying smaller gray and white matter volumes in the neonatal period^{2, 3}, as well as in adolescence^{4–6}. The impact of prematurity on normal dynamic changes in regional structure is less clear. In the only longitudinal report of former premature children with repeated neuroimaging, Ment et al showed that, between 8 and 12 years of age, there is a change in the proportion of gray and white matter in VLBW children that is significantly different than the change shown by age matched term controls⁵.

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However it is not clear how brain structures change during *early* childhood in VLBW infants.

Characterizing the effect of prematurity on early cortical development is a necessary step toward suggesting new approaches to early identification of children who will manifest later cognitive/behavioral problems. Because there have been no studies evaluating cortical structure including thickness and surface area after premature birth in early childhood, we conducted a follow up study of VLBW children at two ages in the preschool years, between 18 and 22 months and between 3 and 4 years, comparing cortical thickness and surface area to age and gender matched term born control children. Our hypothesis was that compared to controls, VLBW children would demonstrate delayed cortical expansion as well as delayed cortical thinning. Furthermore, we hypothesized that the differences between VLBW and control children would be more prominent in the later developing frontal brain regions as has been suggested by prior neuropathology reports ^{7, 8}.

Methods

Subjects

This investigation is part of a larger ongoing study of developmental follow up after prematurity being conducted at the University of New Mexico. Enrollment criteria include birth weight less than 1500 grams with no known history of neonatal stroke, meningitis, grade IV intraventricular hemorrhage, hyperbilirubinemia requiring exchange transfusion, other major medical illness or prenatal drug exposure. Children were identified from a registry in a newborn follow up clinic. Those between 18–22 months or 3–4 years were invited to participate. Of 98 total children that qualified for enrollment, 39 enrolled and attempted an MRI scan of which 28 VLBW children successfully provided imaging datasets (16 were between 18 – 22 months, 12 were 3 – 4 years old). Control children were formerly born at term, currently healthy without known developmental disorders, and were recruited through community advertisements. Out of 30 attempted MRI scans, 18 successfully provided imaging datasets (10 were between 18 – 22 months, and 8 were between 3 – 4 years old). In both preterm and term groups, the main reason for failed scans was excessive motion artifact or inability to fall asleep for the MRI scan. Informed consent was obtained from parents of all participants.

Developmental Assessments

All assessments were conducted at the Mind Research Network by doctoral level graduate students or a senior diagnostician. Parents were allowed to remain with their child during the testing session, which routinely took one to two hours. For children in the 18–22 month cohort, age was adjusted for prematurity. The younger children completed the Bayley Scales of Infant Development-III (BSID-III), which includes a cognitive composite scale⁹. Chronologic age was used for premature children in the 3–4 year old cohort. These older children completed the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III), which provides a measure of global cognitive functioning (Full Scale IQ), combining scores from verbal and performance-based sub-tests¹⁰. An additional goal of the larger study is to explore early development of executive function in premature children. A measure of response of inhibition and self control was administered to both groups. For the younger children (18–22 month olds), the Snack Delay was used; children were presented with a small snack and told to wait. The score on Snack Delay was the time in seconds before the child touched the snack. The Gift Delay was used for the older group (3–4 year olds); children were asked to turn around while the examiner noisily wrapped a package for them. The Gift Delay task was scored by the number of seconds it took the child to “peek” at the present ¹¹.

MRI Data Acquisition

Imaging was performed on a Siemens 3-tesla TrioTIM magnetic resonance scanner using the 12-channel radiofrequency head coil provided with the system (Erlangen, Germany). T₁-weighted images were collected in the sagittal plane using a five-echo 3D Magnetization Prepared Rapid Gradient Echo sequence (repetition time (TR)=2530, TE (echo time) =1.64, 3.5, 5.36, 7.22, 9.08, TI=1200, flip angle = 7°, field of view = 256 × 256 mm, matrix = 256 × 256, 1 mm thick slice, 192 slices, GRAPPA acceleration factor 2). Most VLBW children were sedated with chloral hydrate using a low oral dose of 50 mg/kg.

MRI data was processed using FreeSurfer, an automated data processing tool which reconstructs the brains cortical surface from T1 images (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures have been described previously^{12–22}. The method consisted of removal of non-brain tissue images using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. In order to ensure accuracy of the FreeSurfer segmentation, each scan was hand traced to check the delineation of gray and white matter differentiation. FreeSurfer provides separate measures of volume, surface area, and cortical thickness. Total volume reported in this manuscript is cortical volume only, eliminating ventricles and white matter tissue.

Statistical analysis

There were several outliers in the imaging data, therefore the Mann-Whitney-Wilcoxon test was used to compare cortical thickness and surface area in the two groups; where no outliers were present, independent samples t-tests (not reported) gave comparable results. Because of multiple comparisons, we include effect sizes in addition to p-values. P-values for Pearson correlation coefficients between birth weight and cortical structure were performed using standard t-tests for significance of correlation. Because of ties in the developmental data and given our relatively small sample size, Mann-Whitney-Wilcoxon exact p-values were calculated using the *coin* package in the statistical program R to compare the two groups on the cognitive test variables and measures of executive function.

Results

Subjects

Characteristics of the study participants are shown in Table 1. There were no differences in age at testing between the VLBW and term born children at either age group, nor were there differences in anthropometric measures including frontal-occipital circumference between VLBW and term born children (data not shown). All children underwent a neurologic examination and only one had cerebral palsy (mild diplegia).

Structural data

Table 2 summarizes structural data. A neuroradiologist reviewed all scans and no parenchymal abnormalities were noted on high resolution Magnetization Prepared Rapid Gradient Echo images, with the exception of one VLBW subject who likely had asymmetric periventricular leukomalacia. Total cortical thickness of one control 3–4 year old subject was several standard deviations lower than others, and because this was felt to be biologically implausible, this data point was omitted (if retained, this would have accentuated the group differences we found between 3–4 year old VLBW and term born children). At both ages VLBW children had less total cortical volume and surface area and

greater cortical thickness than term born children, although differences did not reach statistical significance (see boxplots, Figure 1). Within each group, older children had greater surface area and thinner cortex than younger children.

Analysis of within group relationships between birth weight and brain structure was performed. As demonstrated in Figure 2, the average cortical thickness of VLBW children was inversely related to birth weight at both ages, which was most evident at 18 months ($p < 0.038$, $r = -0.52$). Total surface area was positively related to birth weight at both ages, particularly in the 3–4 year age group ($p < 0.02$, $r = 0.66$).

In addition to assessing total cortical structure, 4 specific regions of interest were evaluated including 2 primary sensory areas (transverse temporal gyrus and occipital pole) and 2 higher association areas (orbital frontal and dorsolateral prefrontal cortex). As noted in Table 2, results were mixed. Term born participants had larger surface areas for each of the 4 ROIs at 18–22 months, with the greatest differences observed for the orbital frontal ($p < 0.036$, effect size=0.87) and transverse temporal ($p < 0.037$, effect size=0.91) gyri. However in the 3–4 year group, in 3 of these 4 ROIs (all except the transverse temporal gyrus) the VLBW children trended towards larger surface area. Average cortical thickness for VLBW children was greater in all ROIs at 18–22 months and also at 3–4 years except for the transverse temporal gyrus, the largest difference was found for the 18–22 month occipital pole ($p < 0.002$, effect size=1.33). No results reached statistical significance at the $p < 0.05$ level after Bonferroni correction for multiple comparisons.

Developmental data

As expected, differences were found between VLBW children and term born children at both ages, with executive function most affected (snack delay and gift delay). See Table 1.

Discussion

Prior reports suggest that prematurity is associated with smaller brain volume at term^{3, 23} as well as later in childhood^{4, 24} and adolescence^{25–28}. However there has been no investigation of brain volume in the preschool years. Additionally, with a single exception²⁹, there have been no reports that explore the impact of premature delivery on cortical surface area and thickness at any age. Our study begins to address this gap in the literature. When compared to term born controls, our cross-sectional study of premature preschool children at 2 ages did not find statistically significant differences between groups, however there was a consistent trend at both ages for thicker cortex and decreased surface area in VLBW children compared to term born children. Moreover, within our group of VLBW children there was a negative correlation between birth weight and cortical thickness at 18–22 months ($p = 0.038$, $r = -0.52$) and a positive correlation with surface area at 3–4 years ($p = 0.020$, $r = 0.66$). Taken together, our results suggest that the normal processes of cortical thinning and surface area expansion in the preschool years may be delayed after premature delivery, an effect which might be directly proportional to the degree of prematurity.

Cortical development during childhood is a dynamic process. In healthy term born children over 4 years of age, volumetric cross sectional MRI reports³⁰ and longitudinal studies^{31, 32} suggest that an initial increase in cortical volume occurs, followed by a decrease in volume that appears initially in the primary sensorimotor areas and later in higher order association regions. Changes in cortical thickness through development are similar, following a general pattern of initial thickening then thinning, which varies by location and developmental trajectory^{31, 33, 34} (for review see Giedd et al³⁵), occurring first in primary sensorimotor regions. Although published MRI studies of children between approximately 4 years old and

early adulthood suggest regionally-specific changes that occur in both cortical volume and in cortical thickness, there are few MRI studies of normal development that include children under 4 years of age,^{36, 37} none of which are longitudinal.

Several neuropathology reports characterize cortical development in children under 4 years of age. Huttenlocher demonstrated an increase in synaptogenesis followed by synaptic loss, occurring earlier in primary sensory regions (the auditory cortex demonstrating maximal synaptic density at 3 months) and later in higher association regions such as the middle frontal gyrus (not until 15 months)^{8, 38}. These studies also suggest that, at least in part, changes in gray matter volume and thickness may be related to synaptic density³⁹. The largest neuropathology study of normal development in the first years of life was published in a series of book chapters from 1939 to 1967 by Conel^{40–47}. This data was reanalyzed by Shankle⁷ who reported an increase in neuronal density in the first several months of life, then a decrease to 24 months, followed by a final increase from 2 to 6 years of life. In general, primary sensory and motor regions changed first followed by later maturing multimodal association areas of the cortex such as the prefrontal and dorsolateral occipital cortex. It is of interest that the pattern of primary sensorimotor regions maturing earlier than higher association regions was identified by Conel and Shankle⁷ regarding neuronal number, Huttenlocher for synaptic density^{8, 38}, and by Gogtay³¹ and Shaw³⁴ using neuroimaging of cortical thickness.

A number of publications describe differences in cortical volume after prematurity. During adolescence there are reductions in size of hippocampus^{48, 49}, orbitofrontal cortex²⁵, and other cortical regions^{6, 50}. In the first several years of life, the only published study of premature children (average gestational age 33 weeks) suggests that regional gray matter volumes increase generally in an inferior to superior and posterior to anterior direction. However no control subjects were included, therefore direct comparisons to term children are not possible⁵¹. Ment et al⁵ compared 55 former premature children to 20 age-matched controls in a longitudinal study between 8 and 12 years of age, and found group differences in gray and white matter changes over time. Finally, in the only publication evaluating cortical *thickness* after prematurity, Martinussen et al reported on 50 former preterm and 58 term born healthy controls who were imaged at 15 years of age and found significant regional differences in cortical thickness²⁹. We are aware of no reports characterizing cortical structure (including thickness and surface area) in VLBW children compared to age matched healthy controls under 4 years of age. This is an important gap in the neuroimaging literature that may have treatment implications. If one goal of imaging is to lead to earlier and more accurate identification of children at risk for global cognitive delays or behavioral problems, studies must include these first several years of life, when developmental interventions might have the greatest impact.

Strengths of our current study are that age and gender matched controls were included, and both cortical thickness and surface area were assessed in children at 2 different ages in early childhood. As may be expected from prior neuropathology reports, in both premature and control groups the surface area was smaller and cortical thickness greater in 18–22 month old children compared to 3–4 year old children. There was a difference between VLBW children and term born children, however. At both 18–22 months and 3–4 years, we found a trend for thickness to be greater and surface area smaller in the VLBW children that was consistent at both ages. Furthermore, within group analysis showed an inverse correlation between birth weight and cortical thickness at 18–22 months ($p=0.038$, $r=-0.52$), and a direct correlation between birth weight and surface area at 3–4 years ($p=0.020$, $r=0.66$). We speculate that it is possible the thicker cortex in VLBW children reflects a gestational age-dependent maturational delay. Longitudinal studies, with larger numbers of participants, are required to confirm this finding.

Because prior reports suggest that cortical structure changes in a regionally specific manner in the first years of life, in addition to assessing total average thickness and surface area we also sampled 4 individual regions of interest that included 2 primary sensory regions (occipital pole and transverse temporal cortex) and 2 later developing regions (the orbital frontal cortex and the dorsolateral prefrontal cortex). Our hypothesis was that the later developing frontal cortex would show greater group differences than the primary sensory regions. This was not substantiated by our findings, as noted in Table 2.

There are several shortcomings of this study. As a cross-sectional investigation, structural data cannot be used to predict behavioral outcome. Also, our low subject numbers limit statistical power and therefore we could not perform correlations between behavioral assessments and neuroimaging. Indeed, although our analyses failed to reach statistical significance after Bonferroni correction, trends were in the predicted direction, suggesting that small sample size may have limited our ability to identify group differences. Finally, most VLBW children received low dose chloral hydrate for MRI scanning, which is not ethically permissible in the term born children. Although it is very unlikely that this affected the structural data, it does imply that only children capable of being scanned during natural sleep were able to participate as controls. Despite this possible selection bias, our control population was well matched to VLBW participants in gender and family demographics, and scored as expected on our behavioral assessments.

Clearly, longitudinal studies with adequate power are required to fully characterize the effect of prematurity on normal cortical development in the first years of life. These studies are inherently difficult, as they involve scanning young control children without sedation and require multidisciplinary teams capable of performing appropriate developmental assessments over time. However these are important studies to pursue, as a better understanding of brain development in VLBW children during the first years of life may lead to earlier and more accurate characterization of the impact of prematurity on individual children.

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Figure 1.

Boxplots of total volume, surface area and cortical thickness at 18–22 months (above) and at 3–4 years (below). Although group differences fail to meet statistical significance after correction for multiple comparisons (see table #2), there is a consistent trend for very low birth weight children to have reduced surface area and greater cortical thickness at both ages. In both very low birth weight and term born children the 18–22 month group had reduced surface area and increased cortical thickness compared to the 3–4 year group. Parameters of cortical structure are on the Y axis, and the X axis represents very low birth weight (VLBW) or term born (Term) subject groups.

Figure 2.

Birth weight vs cortical thickness (figures a and b) and surface area (figures c and d) at 18–22 months and at 3–4 years. The very low birth weight children are ≤ 1500 grams. Note negative correlation between cortical thickness and birth weight of VLBW children, and the positive correlation between surface area and birth weight of VLBW children.

Table 1

Subject characteristics and developmental test results

	18–22 month VLBW (n = 16)	18–22 month Term (n = 10)	3–4 year VLBW (n = 12)	3–4 year Term (n = 8)
Gestational age (weeks, +/- SD)	28.12 +/- 1.48	39.39 +/- 1.14	29.75 +/- 1.30	38.82 +/- 1.94
Birth weight (grams, +/- SD)	1082 +/- 195	3116 +/- 360	1187 +/- 237.21	3286 +/- 514.47
Gender (Male/female)	8/8	6/4	11/1	7/1
Age (months, +/- SD)	20.17 +/- 1.47	21.40 +/- 1.46	42.45 +/- 3.63	43.43 +/- 3.22
IVH: grade I/grade II/grade III	5/1/2	0	0	0
BSID Cognitive SS	93.44 +/- 12.07	101.50 +/- 8.83		
WPPSI FSIQ*			88.50 +/- 12.06	106.38 +/- 10.47
Snack Delay (seconds)*	3.81 +/- 3.85	34.40 +/- 36.22		
Gift Delay Peek (seconds)*			17.75 +/- 18.45	39.88 +/- 21.59

BSID - Bayley Scales of Infant Development-III, IVH – intraventricular hemorrhage, WPPSI - Wechsler Preschool and Primary Scale of Intelligence-III

Table 2

Group average cortical surface area and cortical thickness

Region	18 mo Control	18 mo VLBW	18 mo p value/effect size (VLBW vs Control)	3-4 year Control	3-4 year VLBW	3-4 year p value/effect size (VLBW vs Control)
Surface Area						
Total Surface Area (mm ²)	146,949 (+/- 17,341)	131,838 (+/- 22,608)	0.077/0.73	167,744 (+/- 21,851)	164,226 (+/- 9,440)	0.734/0.23
DLPFC SA	11,728 (+/- 3,140)	10,483 (+/- 2,951)	0.484/0.41	12,951 (+/- 4,241)	13,288 (+/- 2,430)	0.624/0.1
Orbital Frontal SA	2,550 (+/- 559)	2,063 (+/- 559)	0.036/0.87	2,758 (+/- 680)	2,784 (+/- 345)	0.792/0.05
Transverse temporal gyrus SA	622 (+/- 507)	332 (+/- 86)	0.037/0.91	497 (+/- 241)	441 (+/- 96)	0.97/0.33
Occipital Pole SA	3,096 (+/- 322)	3,086 (+/- 663)	0.938/0.02	3,313 (+/- 808)	3,732 (+/- 357)	0.047/0.73
Thickness						
Total Thickness, average (mm)	3.33 (+/- 0.08)	3.42 (+/- 0.17)	0.108/0.55	3.11 (+/- 0.12)	3.20 (+/- 0.17)	0.135/0.59
DLPFC Thickness	3.69 (+/- 0.17)	3.75 (+/- 0.24)	0.76/0.25	3.39 (+/- 0.12)	3.54 (+/- 0.28)	0.181/0.66
Orbital Frontal Thickness	3.74 (+/- 0.26)	3.85 (+/- 0.32)	0.388/0.35	3.46 (+/- 0.29)	3.62 (+/- 0.32)	0.263/0.50
Transverse temporal gyrus Thickness	3.21 (+/- 0.55)	3.45 (+/- 0.33)	0.141/0.58	3.26 (+/- 0.46)	3.05 (+/- 0.46)	0.418/0.47
Occipital Pole Thickness	2.87 (+/- 0.28)	3.28 (+/- 0.33)	0.002/1.33	2.61 (+/- 0.16)	2.72 (+/- 0.25)	0.334/0.52

DLPFC – dorsolateral prefrontal cortex (superior and middle frontal gyrus and pars triangularis of the inferior frontal gyrus), SA – surface area, VLBW – very low birth weight