

Effects of Preterm Birth on Cortical Thickness Measured in Adolescence

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Despite the extensive research into brain development after preterm birth, few studies have investigated its long-term effects on cortical thickness. The Stockholm Neonatal Project included infants between 1988 and 1993 with birth weight (BW) \leq 1500 g. Using a previously published method, cortical thickness was estimated on T₁-weighted 3D anatomical images acquired from 74 ex-preterm and 69 term-born adolescents (mean age 14.92 years). The cortex was significantly thinner in ex-preterm individuals in focal regions of the temporal and parietal cortices as indicated by voxel-wise *t*-tests. In addition, large regions around the central sulcus and temporal lobe as well as parts of the frontal and occipital lobes tended also to be thinner in the ex-preterm group. Although these results were not significant on voxel-wise tests, the spatially coherent arrangement of the thinning in ex-preterm individuals made it notable. When the group of ex-preterm individuals was divided by gestational age or BW, the thinning tended to be more pronounced in the anterior and posterior poles in those born nearer term or with a BW closer to 1500 g. These results support the notion that preterm birth is a risk factor for long-term development of cortical thickness.

Keywords: brain, cerebral cortex, cortical thickness, MRI, preterm

Introduction

Neuroimaging studies of children born preterm have demonstrated a tendency for impaired cortical gray matter (GM) growth in infancy (Inder et al. 2005; Zacharia et al. 2006), which is still observable in childhood (Peterson et al. 2000) and adolescence (Nosarti et al. 2002; Nagy et al. 2009). However, it has become accepted that naturally occurring increases in brain volume are mainly due to the expansion of the cortical surface area (Rakic 1995) and an increase of the white matter (WM) volume (Zhang and Sejnowski 2000), whereas cortical thickness changes minimally. Therefore, one may not immediately conclude that the reduced GM volume observed in preterm-born individuals can be attributed to a reduction in cortical thickness. This question must be investigated independently.

The human neocortex is approximately 2–4 mm thick and consists of 6 layers (Amaral 2000). The layers develop in such a way that neurons migrating from the periventricular germinal zone toward the periphery will pass the deeper layers before settling into more superficial layers (Rakic 1974; Uylings 2008). Histological variations in this structure define cortical areas (Brodmann 1909) in which the constituent layers can vary in cell type, neurotransmitter receptor type, extent of myelination, and thickness. This specialization, together with the intrinsic connections between a given area and the rest of the brain, is thought to form the anatomical basis of functional

localization (Passingham et al. 2002; Thomson and Bannister 2003; Zilles et al. 2004; Uylings 2008). Recent longitudinal magnetic resonance imaging (MRI) investigations have demonstrated the dynamic nature of cortical thickness development during childhood and early adulthood (Shaw et al. 2008). Such dynamic changes seem to be intrinsically linked to functional ability (Shaw et al. 2006) or disability (Shaw et al. 2007). Consequently, variations in cortical thickness due to injury are important because they may interfere with the inherent specialization of cortical areas and thus hinder function.

One previous study found that the cortical thickness of ex-preterm adolescents differed from those born at term and those differences were most pronounced for the subgroups born after the shortest gestation or with smallest birth weight (BW) (Martinussen et al. 2005). However, because outcome can depend on the care received (Murphy et al. 2001; Gressens et al. 2002; Als et al. 2004) and care given can differ between centers (Van Reempts et al. 2007), it would be important to conduct similar investigations on cohorts that were cared for in different settings.

The Stockholm Neonatal Project (Katz-Salamon et al. 1997) was started with the aim to investigate a wide range of long-term effects associated with preterm birth and included preterm-born newborns between 1988 and 1993. Data from these individuals were used in a previous study to investigate differences in brain volume between preterm-born adolescents and controls (Nagy et al. 2009). The results showed that the formerly preterm individuals possessed smaller GM volumes. In the present study, the same data are used to investigate the hypothesis that the observed differences in GM volume in the preterm-born adolescents correspond to a thinner cortical mantle compared with those born at term. The results are also compared with those from a previous study of cortical thickness in ex-preterm adolescents (Martinussen et al. 2005) and with normal developmental dynamics (Salat et al. 2004; Sowell et al. 2004; Shaw et al. 2008).

Materials and Methods

Subjects

The Stockholm Neonatal Project is a prospective population-based study that included infants between 1988 and 1993 if born at or transferred to the Karolinska Hospital or Löwenströmska Hospital, and the BW was \leq 1500 g (Katz-Salamon et al. 1997). Of the 291 infants included at birth, 182 were available for follow-up at 5½ years of age (Bohm et al. 2004). The others had declined participation, died, or moved out of the Stockholm area. In order to form a control group, 125 children were selected from a population-based register according to birth date, birth hospital, gestational age (GA) of at least 37 weeks, and BW of at least 2500 g (Bohm et al. 2002). The initial contact of the participants and the MRI examination were performed with the

approval of the local ethics committee. Furthermore, both the participant who underwent the MRI examination and an accompanying adult signed a form of informed written consent. Of the 182 cases, 36 did not respond to the initial letter of invitation. A further 54 responded that they did not want to participate or initially were positive but declined on the day of the MRI examination. Sixteen subjects that otherwise would have participated were excluded because of surgical closure of ductus arteriosus with a clip of unknown composition. The remaining 76 of the cases had an MRI examination. One of these subjects could only tolerate the T_2 -weighted image, whereas the neonatal records were lost for another one. Of the 125 controls, 22 did not respond to the initial letter of invitation, whereas a further 34 responded negatively or declined on the day of the examination. The participants included in this study formed a representative sample of the total available group of individuals as there was no statistically significant difference between participants and nonparticipants with respect to GA, BW, gender distribution, and mother's age or level of education.

After the data collection was completed, there were useful data from 74 adolescents who were born preterm and 69 controls. These 2 groups did not differ with respect to age, height, weight, gender distribution on the day of the scan or mother's age, or level of education at birth (Table 1).

MRI Data Collection

The MRI examinations were performed in a random order of cases and controls between April 2005 and February 2006 on a 1.5-T GE scanner (Waukesha, WI) located at the MR center of the Karolinska University Hospital in Stockholm, Sweden. All but 2 of the examinations were performed by a single individual (Z.N.). The protocol included a 3D T_1 -weighted spoiled gradient echo anatomical image with repetition time = 24 ms, echo time = 6 ms, flip angle = 30°, and voxel size = 0.98 × 0.98 × 1.5 mm³.

Preprocessing of MR Images

As a first step, all the images were visually checked for artifacts and resampled to a voxel size of 1 mm³ using trilinear interpolation. Using the unified segmentation procedure (Ashburner and Friston 2005) implemented in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>), the images were segmented into GM, WM, and cerebrospinal fluid (CSF). For each subject, this resulted in a set of 3 images in the same space as the original T_1 -weighted image, in which each voxel was assigned a probability of being GM, WM, and CSF respectively. A voxel-based cortical thickness (VBCT) map (Hutton et al. 2008) was created for each subject using the GM, WM, and CSF segments created in the previous step. This method calculates an initial estimate of the GM/WM and GM/CSF boundaries from the input tissue probability maps and a transformed labeled brain atlas (<http://www.fil.ion.ucl.ac.uk/spm/ext/#IBASPM>) (Aleman-Gomez et al. 2006). Starting from the initial estimate of the GM/WM boundary, layers of 1 voxel in thickness are

successively added to surround the WM allowing voxels to be identified where the GM from different sides of a sulcus was in contact. Once all GM voxels have been processed in this way, Laplace's equation is solved for all voxels between the final GM/WM and GM/CSF boundaries resulting in a scalar field that makes a smooth transition from 1 boundary to the other (Jones et al. 2000). The gradient of this field at each point forms a unique trajectory connecting the 2 boundaries, and the thickness at each point is calculated by integrating along these trajectories. The resulting VBCT maps contain cortical thickness values within voxels identified as cortical GM and zeros outside the cortex and are in the space of the original input images with 1 mm³ resolution.

DARTEL (Ashburner 2007), an algorithm for diffeomorphic image registration which is implemented as a toolbox for SPM5, was used to warp the VBCT maps into a new group-specific reference space representing an average of all the subjects. This procedure uses the GM and WM segments estimated from the original T_1 -weighted images to calculate a group-specific template and the deformation fields required to warp data from each subject to the new template. Each VBCT map was warped to the new template using the corresponding subject-specific deformation field and was resampled to an isotropic voxel size of 1.5 mm³ using trilinear interpolation. The warped VBCT maps were scaled by the Jacobian determinant of the deformations to account for stretching and compression and subsequently smoothed with a 6-mm Gaussian kernel. A binary mask of each original VBCT map was generated which contained ones where there were nonzero values in the VBCT map. The warped, scaled, and smoothed VBCT maps were then divided by the corresponding warped, scaled, and smoothed mask. This procedure results in smoothed warped VBCT maps for which the Gaussian smoothing kernel applied in the warped space has been projected into the native space of the subject, and the cortical thickness values are preserved over a region the size of the smoothing kernel.

Statistical Analysis of MR Images

Regional effects of preterm birth were assessed by performing voxel-wise 2-sample *t*-tests on the smoothed warped VBCT maps in SPM5. Following the primary aim of the study, the first analysis compared 74 ex-preterm and 69 control adolescents. Subsequently, 2 separate sets of analyses were performed in which the group of ex-preterm individuals was subdivided either with respect to GA or with respect to BW, similar to analyses performed in a previous study (Martinussen et al. 2005). For the analysis of GA, the group with GA ≤ 28 weeks (*n* = 36) and the group with 28 weeks < GA ≤ 36 weeks (*n* = 38) were separately compared with the controls (*n* = 69) and were also compared with each other directly. The analysis of BW was performed analogously with groups where BW ≤ 1000 g (*n* = 36) or 1000 g < BW ≤ 1500 g (*n* = 38). Please see Table 2 for demographic details of the subgroups.

Previous MRI-based studies indicate that the cortical thickness undergoes dynamic changes during the period which subtends the ages of children and adolescents included in this study (Sowell et al. 2004;

Table 1

Description of the 2 groups compared in this study

	Case group	Control group
Number	74 (38 girls)	69 (34 girls)
Age (years) ^a	14.90 (12.38–17.7)	14.30 (12.18–16.47)
Weight (kg)	53.18 (25.60–83.80)	55.38 (32.40–88.90)
Height (cm)	163.94 (140.00–196.40)	165.60 (138.00–191.00)
GA (weeks)	28.54 (24–36)	39.72 (37–42)
BW (g)	1069.54 (645–1486)	3530 (2750–4655)
Mother's age at birth (years)	30.66 (20–42)	30.86 (22–44)
Mother's level of education	4 (2–6)	4 (2–6)

Note: Data are presented as mean (range) except the number of participants and mothers' level of education. The latter is on an ordinal scale and therefore displayed as median (range) as the mean value is not representative. There were no statistically significant differences between the groups with respect to age, weight, height, mother's age, and level of education.

^aAge, as given, was not corrected for GA. But after this correction is made, the mean age of the groups was not different.

Table 2

Description of the subgroups after division of ex-preterm individuals by GA or BW

	Division by GA		Division by BW	
	≤28 weeks	>28 weeks	≤1000 g	>1000 g
Number	36 (19 girls)	38 (19 girls)	36 (20 girls)	38 (18 girls)
Age (years)	14.92	14.89	14.76	15.04
Weight (kg)	51.46	54.8	49.42	56.7
Height (cm)	163.76	164.10	161.49	166.26
GA (weeks)	26.2	30.8	26.8	30.2
BW (g)	896	1234	844	1283
Mother's age at birth (years)	29.47	31.79	30.47	30.84
Mother's higher education	4	4	4	4

Note: Please see footnote for Table 1 for description of variables and statistical tests. The corresponding subgroups were not statistically significantly different in any of the variables when the division was made according to GA (except, as expected, BW). On the other hand, when the division is made according to BW (in addition to the expected difference in GA), the subgroups differed with respect to weight and height (bold).

Shaw et al. 2008). To avoid false positives resulting solely from developmental differences between the groups, the above analyses were repeated with age included as a covariate.

In all statistical tests, the results were considered statistically significant if the *P* value was less than 0.05 after family-wise error correction for multiple comparisons.

Statistical Analysis of Non-image Data

To compare the groups with respect to age, height, weight, and mother's age at birth, 2-tailed *t*-tests were employed assuming unequal variances. A 2-sample test for binomial proportions was used to compare the gender distribution of the 2 groups. The level of education of the mothers was categorized such that 0 = no schooling, 1 = 6 years of schooling, 2 = 9 years of schooling, 3 = less than 3 years of high school, 4 = more than 3 years of high school, 5 = less than 3 years university education, 6 = more than 3 years university education, and 7 = doctoral degree. The 2 groups were then compared using a Wilcoxon rank-sum test (a nonparametric analog of a 2-sample *t*-test) with respect to this variable. In all cases, a *P* value less than 0.05 was considered statistically significant.

Results

Surface projections of cortical thickness differences between ex-preterm and control adolescents are shown in Figures 1, 2, and 3. Thinner cortex was observed in widespread regions in ex-preterm adolescents compared with controls (Fig. 1*a*). After correcting for multiple comparisons, differences in the bilateral middle temporal regions and the posterior inferior parietal cortices were statistically significant (dotted lines) and in the order of 0.25 and 0.20 mm, respectively. Two small regions of significantly thicker cortex were observed in ex-preterm adolescents compared with controls in the right anterior inferior temporal gyrus and the left ventrolateral prefrontal cortex in the order of 2.0 mm (Fig. 1*b*).

When the ex-preterm group was divided into 2 subgroups by GA, regions of significantly thinner cortex compared with controls were the same for the subgroup born during or before the 28th week of gestation as those observed for the whole group of ex-preterm adolescents (Fig. 2*a*). However, the statistically significant clusters of voxels were less extensive, probably due to the reduced amount of data for this comparison. In the subgroup born after the 28th week of gestation, significantly thinner cortex was observed in a small region in the right dorsolateral prefrontal cortex in the order of 0.2 mm

(Fig. 2*b*). The regions where ex-preterm adolescents possessed a thicker cortex could be explained by the subgroup that was born during or before the 28th week of gestation (Fig. 2*c*). For completeness, Figure 2*d* displays a map of cortical thickening in those born preterm but after the 28th gestational week compared with controls, although no statistical significance was observed. Comparing the 2 GA subgroups directly did not result in statistically significant differences.

A very similar pattern of results was observed when the ex-preterm group was divided according to BW (Fig. 3). In the subgroup born with BW of less than or equal to 1000 g, the cortex was significantly thinner in the same regions as those found when considering the entire group of ex-preterm adolescents (Fig. 3*a*). When the subgroup of adolescents whose BW was more than 1000 g was compared with the controls, significantly thinner cortex was observed in the ex-preterm adolescents in the right dorsolateral prefrontal cortex, similar to the subgroup with the higher GA, and in the right anterior temporal lobe (Fig. 3*b*).

The cortex was found to be thicker in a small left ventral prefrontal region and in the right anterior temporal lobe in the subgroup with BW less than or equal to 1000 g (Fig. 3*c*) and in the right anterior temporal lobe in the subgroup whose BW was more than 1000 g (Fig. 3*d*) when compared with controls. Comparing the 2 BW subgroups directly did not result in statistically significant differences.

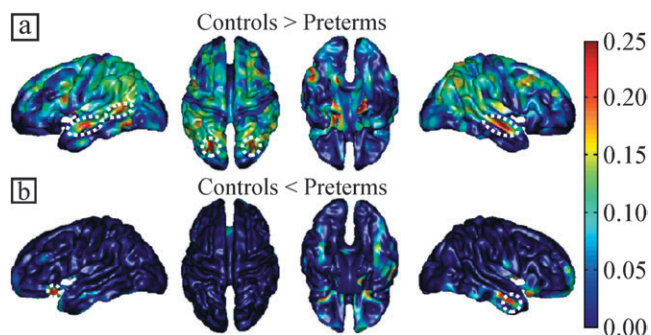


Figure 1. Maps of cortical thickness differences. Differences in thickness are displayed in millimeters. In a large set of regions, the ex-preterm adolescents possessed thinner cortex (*a*), whereas in a few specific areas, it was found to be thicker (*b*). Areas depicted with a dotted line were statistically significant ($P < 0.05$) after correction for multiple comparisons. All insets are in neurological convention (left is left) except the orbital view (third column), which is displayed in radiological convention (left is right).

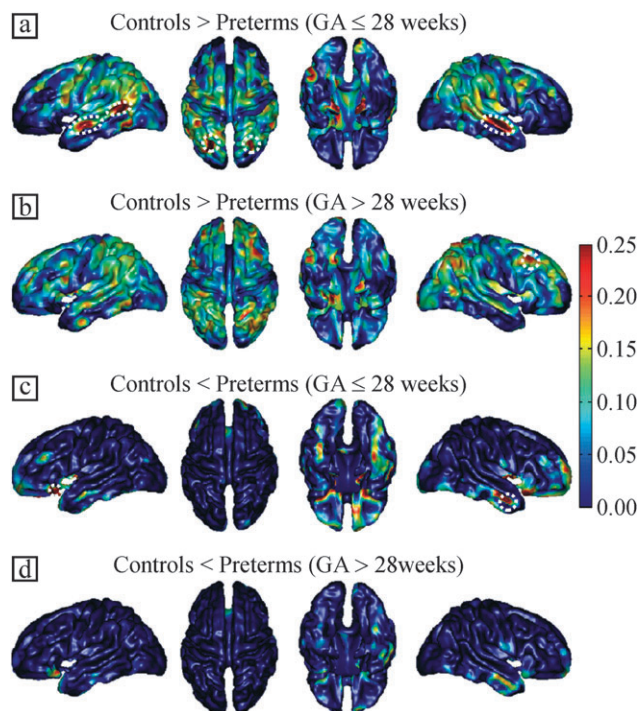


Figure 2. Maps of cortical thickness differences depending on GA. Differences in thickness are displayed in millimeters. The differences presented in Figure 1 are similar to those observed between the controls and preterm adolescents born before or during the 28th week (*a*, *c*). In addition, the dorsolateral prefrontal cortex was thinner in the subgroup born after the 28th week (*b*), whereas no statistically significant indication was found for thicker cortex in the older subgroup of ex-preterm adolescents (*d*). Areas depicted with a dotted line were statistically significant ($P < 0.05$) after correction for multiple comparisons. All insets are in neurological convention (left is left) except the orbital view (third column), which is displayed in radiological convention (left is right).

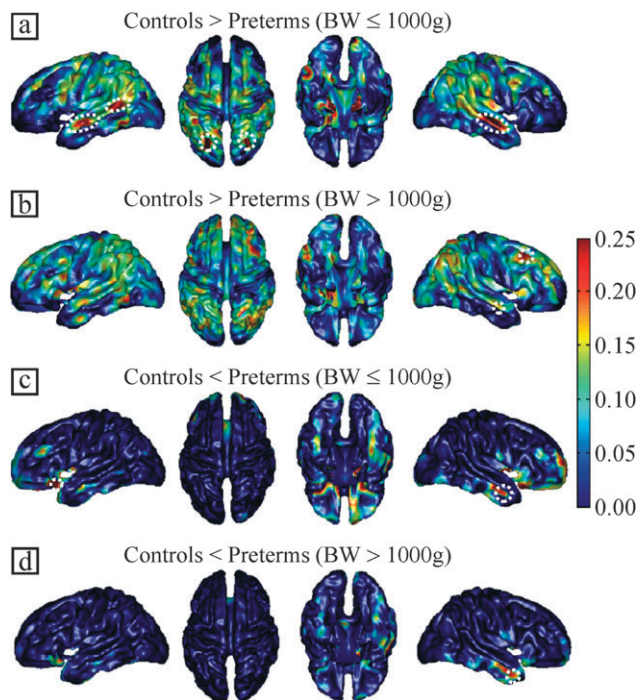


Figure 3. Maps of cortical thickness differences depending on BW. Differences in thickness are displayed in millimeters. The differences presented in Figure 1 are similar to those observed between the controls and preterm adolescents born with a BW of less than or equal to 1000 g (a, c). In addition, the cortical sheet was thinner in the dorsolateral prefrontal cortex (b) and thicker in the right anterior temporal lobe (d) in the subgroup born with a BW of more than 1000 g. Areas depicted with a dotted line were statistically significant ($P < 0.05$) after correction for multiple comparisons. All insets are in neurological convention (left is left) except the orbital view (third column), which is displayed in radiological convention (left is right).

The results of all the analyses above were unaffected when age was included as a covariate.

Discussion

In this study, we tested the hypothesis that preterm birth has a long-term effect on cortical thickness. Our main finding was a significant thinning within the temporal and parietal cortices in the ex-preterm adolescents. These regions are within those observed to have significantly smaller GM volumes in the same group of subjects (Nagy et al. 2009).

In the 2 additional analyses, the group of ex-preterm adolescents was divided into subgroups according to either GA or BW, and each subgroup was compared with the controls. The significantly thinner regions detected in the original analysis were only observed in the subgroups of adolescents born after a shorter GA and with smaller BW. In the adolescents born nearer term or with a BW closer to 1500 g, significantly thinner cortex was observed in the right dorsolateral prefrontal cortex and also in right anterior temporal lobe for the larger BW subgroup only. In the subgroups of adolescents born after a shorter gestation and with smaller BW, the overall pattern of thinning was most pronounced around the central sulcus and temporal lobes. In contrast, in the adolescents born nearer term or with a BW closer to 1500 g, the pattern of thinning was shifted toward the posterior regions of the parietal cortex and the prefrontal cortex. It is not surprising that these results were similar regardless of whether the grouping was according

to GA or BW. Although not identical, the subgroups were highly correlated because those born early tended also to be small. Therefore, these results are not sufficient to decide whether GA or BW is the more important predictor for localized cortical thinning. Furthermore, because the inclusion criteria for the study depended on BW but not GA, the older subjects were more likely to be small for GA (Fenton 2003), confounding the results. No significant differences were observed in the direct comparison between either pairs of GA or BW subgroups.

Similarities and differences exist between the results of this and a previous study of cortical thickness in ex-preterm adolescents (Martinussen et al. 2005). In particular, both studies found significantly thinner cortex in parietal and temporal regions in the ex-preterm adolescents compared with the controls, and these thickness differences could be mostly explained by the adolescents born after a shorter gestation and with a lower BW. In the study by Martinussen et al. (2005), significantly thinner regions in the ex-preterm adolescents were also identified in pre- and postcentral gyrus, more extended regions of the temporal lobes, the medial surface, and frontal regions. In the study presented here, a trend toward a similar pattern of cortical thinning can be observed but 2 additional regions reached statistical significance: one in the right dorsolateral prefrontal cortex in the adolescents born nearer term or with a BW closer to 1500 g and another in the right anterior temporal lobe for the larger BW subgroup only. In our study, small regions in the right anterior inferior temporal gyrus and left ventrolateral prefrontal cortex were found to be significantly thicker, whereas in the study of Martinussen et al. (2005), cortical thickening was detected in a more superior temporal region and in the occipital lobe.

The differences between the results of our study and that of Martinussen et al. (2005) can be attributed to differences in data acquisition, data processing and analyses, the cohort studied (in particular the gender and age distribution of the groups), or a mixture of these factors. For example, in this study, a voxel-based method was used for measuring cortical thickness, whereas a surface-based approach (Fischl and Dale 2000) was used in that of Martinussen et al. (2005). As a result, our analyses may have been more conservative as they involved voxel-wise statistical tests over all voxels in the GM involving the rather conservative family-wise error correction (Nichols and Hayasaka 2003) for multiple comparisons. For this reason, maps of cortical change in millimeters are shown, which include both significantly different regions and trends.

Dividing the ex-preterm group into GA and BW subgroups produced results that in general support the findings of Martinussen et al. (2005) in that the subgroup with lower GA and BW tended to explain most of the differences found when the entire group was used for the comparison. However, Martinussen et al. (2005) used 1250 g as the cutoff for dividing the subjects into 2 BW subgroups, whereas in this paper, we chose 1000 g, which is the weight commonly used as a division between “extremely” low and “very” low BW (Tucker and McGuire 2004). This may be significant because a general tendency exists that smaller BW leads to more severe outcome. Still, even though Martinussen et al. (2005) had only 9 subjects with BW <1000 g in their subgroup and we had 36 such individuals, the statistically significant differences found in this study were less extensive. Apart from methodological

differences, which are elaborated upon elsewhere in this discussion, this may be due to differences in the cohorts. For example, the overall mortality rate in the Stockholm Neonatal Project was 17.5%, rising to 25.0% for those born with a GA of 23–24 weeks (Katz-Salamon et al. 1997). Around the same time in the United Kingdom, the mortality rate was about 70% for those born with a GA of 23–24 weeks (Tucker and McGuire 2004), and in a review, it was reported that in a selection of economically developed countries, the survival rate in the 1990s was only 2–35% for infants born with a GA of 23 weeks (Hack and Fanaroff 1999). Also, over 50% of the subjects in this study needed only continuous positive airway pressure as respiratory support, and the incidences of bronchopulmonary dysplasia (Jonsson et al. 1997), intraventricular hemorrhage and periventricular leucomalacia (Hack et al. 1991; Hesser et al. 1997) tended to be lower than at other sites. Furthermore, although we do not yet have the long-term cognitive outcome of this cohort, the tests at 5 years of age showed that the mean IQ scores were 96 for the ex-preterm participants, whereas less than 5% had an IQ <70 and less than 10% had an IQ between 70–84 (Bohm et al. 2002). This may be comparatively less severe than that reported by Martinussen et al. (2005) where the mean IQ was 87, whereas out of 50 participants with very low BW, 10 (20%) had IQ <68 (2 standard deviations below control group mean).

It should also be noted that separating the ex-preterm group with respect to BW and GA can have 2 interacting effects. Because the number of individuals in the subgroups was smaller, the power of the statistical tests was reduced. On the other hand, if there is a difference in severity of effect between those born before or after the 28th week of gestation or between those weighing less or more than 1000 g, then including the less severely affected subgroups will reduce the sensitivity of the comparison. Furthermore, dividing the subgroups in this way means that the subgroups are no longer matched to the control group equivalently (e.g., see Tables 1 and 2). For example, in the subgroup with BW >1000 g, the mean age of the participants was 15.04 years, which was statistically significantly different from that of the control group (14.3 years).

No significant voxel-wise differences were found when the corresponding subgroups were compared directly. In addition to the suboptimal matching of the 2 groups, this may also be because statistical power was lower (i.e., in the analyses, we are comparing 2 ex-preterm subgroups of 36 vs. 38 members rather than 2 larger groups of 74 preterm adolescents and 69 controls).

A previous longitudinal study of the cortical thickness development of young healthy children found that the maximum rate of GM gain was located in the superior temporal lobes and dorsolateral prefrontal cortices (Sowell et al. 2004). The ex-preterm individuals in this study have statistically significantly thinner cortices in different regions than where natural thickening of the cortex occurs. Therefore, it is not a likely explanation that a slight impedance of the natural growth in childhood is the underlying reason for the thinning that we report. On the other hand, a large area of the cortex naturally and gradually thins starting in childhood and into adulthood (Salat et al. 2004; Sowell et al. 2004; Shaw et al. 2008). Many of these areas overlap with those we found to be thinner in adolescents that had been born preterm. And in this case, a possible explanation for our findings is that the gradual

thinning of the cerebral cortex is slightly exaggerated in preterm-born individuals.

From this cross-sectional observational study, it is not possible to discern the mechanism causing the cortical thinning. Neuronal proliferation has long finished, and migration has already mainly taken place by the time the ex-preterm adolescents in this study were born (Uylings 2008). It is notable that the transient structures like the cortical plate, ganglionic eminence, and thalamic reticular complex are highly prominent during the period between the time these participants were born and term equivalent age. The cortical plate and the thalamic reticular complex are thought to be waiting zones for neurons before they migrate into the cortex or thalamus to make their final connections, and thus, they are involved with properly connecting different regions of the cortex with each other and with the thalamus (Ulfig et al. 2000; Kostovic et al. 2002). Apoptosis is also tightly regulated in these transient regions. It is conceivable that the eventful extrauterine environment of preterm-born babies adversely affects the function of these important transient structures.

The stress of being born preterm and exposed to the extrauterine environment may increase the plasma level of corticosteroids, which indirectly has been found to reduce brain growth (Murphy et al. 2001; Spittle et al. 2009). Disturbances of cerebral blood flow, oxygen, and nutrient delivery, often seen in very preterm infants, may certainly harm the brain growth (Peterson et al. 2000). Some of the ex-preterm adolescents included have suffered periventricular leucomalacia and intraventricular hemorrhage (Katz-Salamon et al. 1997). Furthermore, preterm birth may affect the differentiation of neurons in the subplate, possibly disturbing laminar organization, axonal guidance, and proper connectivity (Judas et al. 2005). Previous studies have identified a reduction in the size of the corpus callosum (Stewart et al. 1999; Anderson et al. 2006) as well fractional anisotropy in this region (Nagy et al. 2009), which may adversely affect the development of the sensorimotor and parietal cortices (Peterson et al. 2000). Finally, our findings may be tightly coupled to the inverse relation between GA at birth and cognition at school age (Lagercrantz 2008).

One of the strengths of this study is the number of individuals included ($n = 143$). The groups of ex-preterm and control adolescents did not differ with respect to maternal education or maternal age at birth, nor weight, height, or gender distribution at the time of scanning in adolescence. Furthermore, the individuals who participated were good representatives of the total available groups on the above variables. Another asset is the coherence in data quality. All the examinations were carried out by the same individual within a 10-month period using the same scanner without any major hardware changes. This is an often overlooked factor, which is of great importance when trying to reduce unwanted variance in the data in order to increase the sensitivity of statistical tests.

Some limitations were also identified. Although the participants were good representatives of the total available group with regards to the neonatal and demographic data, a significant proportion of available individuals in both the ex-preterm and control groups chose not to participate. In addition, cohort studies are usually problematic from a statistical point of view. The individuals in the cohort were not chosen randomly (i.e., included because they were predisposed to some specific inclusion criteria), and hence the normal interpretation of

P values is difficult. This is especially relevant when considering the significant effect that neonatal care practices can have on the outcome of the individual (Murphy et al. 2001; Gressens et al. 2002; Als et al. 2004) and the differences that exist between sites (Van Reempts et al. 2007). For this limitation, we cannot offer a remedy. Multiple studies must be considered together in order to help strengthen the individual findings. The present work is a step in this direction. Finally, additional data would be required to investigate whether the observed differences in cortical thickness underlie differences in brain function. To this end, psychological assessments are currently underway in this cohort and are expected to be completed in 2011 when the youngest participants turn 18.

Conclusion

This study has demonstrated that preterm birth has a measurable long-term effect on cortical thickness in adolescents born prematurely with BW below 1500 g. This effect was particularly prominent in the temporal and parietal cortices. Consistently, thinner cortex was also observed in the prefrontal cortex within those subjects with BW less than or equal to 1000 g or GA below or including 28 weeks. These findings may explain deficient cognitive functions observed in individuals born preterm. The thinner prefrontal cortex may particularly affect executive functions.

The results correspond to differences in GM volume observed in a previous study involving the same cohort. The findings in temporal and parietal areas are also in agreement with a similar study of another cohort although differences also exist. Importantly, this indicates the difficulty in generalizing results obtained from specific cohorts of preterm children and hence motivates the performance of follow-up studies of preterm children from different settings.

Funding

Sällskapet Barnavård (Sweden); The Swedish Research Council; The Bank of Sweden Tercentenary Foundation; Wellcome Trust (UK).

Notes

Dr Birgitta Böhm spent countless hours compiling the neonatal database. Without her hard work, this project would not have been possible. Many thanks to Jessica Schiott for booking the subjects. Yords Österman and Marie Lundberg are experienced MRI radiographers who trained Z.N. extensively in data collection. Patient comfort and data quality were improved due to their involvement. Either Dr Anna-Karin Edstedt Bonamy (pediatrician) or Miss Jonna Karlen (medical student) attended each of the scans to provide support in case of medical emergency and to assist with the examinations. Their hard work and dedication was invaluable in the completion of this study. Many thanks also to the late Dr David Freedman from the Department of Statistics at University California Berkeley for patient and kind advice. *Conflict of Interest:* The authors have no financial relations or conflicts of interest to disclose in relation to this study.

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