Brain Growth Gains and Losses in Extremely Preterm Infants at Term

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Premature exposure to the extraterine environment negatively affects the brains’ developmental trajectory. Our aim was to determine whether extremely preterm (EPT) infants, with no evidence of focal brain lesions, show morphological brain differences when compared with term-born infants. Additionally, we investigated associations between perinatal factors and neuroanatomical alterations. Conventional magnetic resonance imaging was acquired at term-equivalent age (TEA) from 47 EPT infants born before 27 weeks of gestation, and 15 healthy, term-born controls. Automatic segmentation and voxel-based morphometry-Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) were used. Compared with controls, EPT infants displayed global reductions in cortical and subcortical gray matter, brainstem, and an increased cerebrospinal fluid volume. Regionally, they showed decreased volumes of all brain tissues, in particular cortical gray matter. Increased volumes of cortical gray and white matter were observed in regions involved in visual processing. Increasing prematurity, intraventricular hemorrhage grade I–II, and patent ductus arteriosus ligation were associated with decreased volumes and had a particular effect on the cerebellum. Concluding, EPT infants without focal brain lesions had an altered brain growth at TEA that particularly affected the gray matter, and varied when it came to the presence of perinatal risk factors. Brain growth gains in EPT infants may be related to a longer extrauterine experience.

Keywords: brain growth, extremely preterm birth, perinatal risk factors, voxel-based morphometry

Introduction

The brain of the extremely preterm (EPT) infant grows and develops in a completely different way than it would in the womb. In addition, these babies are exposed to extrauterine stimuli, which may affect the processes of brain maturation, and as a result, how the brain gets wired (Lubsen et al. 2011). Altered connectivity of the developing brain may result in cognitive and neuropsychiatric impairment (Skiold et al. 2012; Marret et al. 2013; Serenius et al. 2013). It is, therefore, very important to develop a greater understanding of the structural mechanisms responsible for neurodevelopmental problems, so that effective early intervention programs can be devised.

Most of the earlier studies have focused on infants born later than 27 weeks of gestation, and information on the structural consequences of EPT birth is scarce. Moreover, most of the studies in the field report altered the brain development of preterm children in childhood, whereas our study focuses on the early brain development of EPT infants up to their term-equivalent age (TEA; term age). Similar studies have previously reported significant reductions in deep gray matter volumes (Inder et al. 2005), gray matter structures, and prominent compromise of the white matter (Parikh et al. 2013) in the presence of several clinical complications. Using diffusion magnetic resonance imaging (MRI), we have previously described altered white matter organization in the centrum semiovale and the corpus callosum of EPT infants with diffuse excessive high signal intensities (DEHSIs; Skiold et al. 2010) and a specific pattern of functional connectivity at term age (Fransson et al. 2007, 2011). Taken together, the body of literature suggests different patterns of early brain development in the anatomy and function of the EPT infant. However, brain injuries such as high-grade intraventricular hemorrhage (IVH) and periventricular white matter lesions are very common in these infants, and the relative contribution of prematurity itself is unclear. We therefore studied EPT infants without evidence of focal brain lesions at TEA, based on neonatal ultrasound or MRI, by employing complementary techniques in order to extend previous findings in this population.

Voxel-based morphometry (VBM; Ashburner and Friston 2000) is an automated procedure for quantifying changes from a voxel-by-voxel analysis of MRI data. It has been used to examine the effects of preterm birth during childhood (Kesler et al. 2008; Padilla et al. 2011), adolescence (Nosarti et al. 2008; Nagy et al. 2009), and early adulthood (Allin et al. 2004). Only one study including preterm infants at term age has used a VBM approach to detect gray matter volume differences of the hippocampus (Lodygensky et al. 2008). We aimed to investigate volumetric differences in brain tissues, on a whole-brain level, by using VBM in EPT infants examined at term age. We hypothesized that EPT infants at term age would show differences in brain morphology on a global and regional level when compared with term infants, even without evidence of focal brain lesions being detected by neonatal ultrasound or conventional MRI. We used automated segmentation and VBM improved by a Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) algorithm (Ashburner 2007), respectively. Our secondary objective was to examine the effect of potentially adverse perinatal factors on brain volumes.

Materials and Methods

Subjects

Eligible subjects for this study were all EPT infants (<27 weeks of gestation) born in the Stockholm region between 1 January 2004 and 31 December 2008, who successfully underwent T1- and T2-weighted (w) MRI at term age. We excluded infants with any grade of periventricular leukomalacia (PVL) or IVH grade III and IV on neonatal ultrasound...
and focal brain lesions (e.g. cysts and infarctions), moderate and severe white matter abnormalities (defined qualitatively) (Inder et al. 2003), or persistent ventricular dilatation on MRI examination at term age. A group of healthy, term-born infants was recruited from the maternity ward and was also scanned at term age. At term age, 190 EPT infants successfully underwent imaging. Of these infants, 19 (9.7%) did not have structural MRI acquisition, meaning that 171 MRI cases were assessed for good quality assurance. The most common reasons for poor quality studies were: the presence of motion artifacts in 62 (35.02%) patients, incomplete coverage of the brain in 38 (21.46%) patients, and blurring of the gray and white matter interfaces in 15 (8.47%) patients. Fifteen (8.47%) MRI cases were excluded for clinical reasons. Two of these patients had noncystic PVL, one had cystic PVL, seven had IVH grades III and IV (six had qualitatively defined white matter abnormalities, with one categorized as severe and five as moderate) (Inder et al. 2003), and five had posthemorrhagic ventriculomegaly. Two of the 15 infants who were excluded were classified as small for gestational age. A control group of 21 healthy, term-born infants underwent MRI, and six (28.57%) of these were excluded due to motion artifacts. Our final sample comprised 47 EPT infants of 177 (26.55%), who all had MRI images suitable for segmentation and volumetric analyses, together with 15 term infants of 21 (71.4%). The regional ethical review board in Stockholm granted ethical approval for the study and written consent was obtained from the parents of the infants.

MRI Data Acquisition
All imaging was performed on a Philips Intera 1.5-T MRI system (Philips International, Amsterdam, The Netherlands). The conventional MRI protocol consisted of a sagittal T1-w turbo spin-echo sequence, an axial inversion recovery sequence, and an axial T2-w sequence. Details of the sequence parameters have previously been published (Skiodl et al. 2012). The 3-dimensional T1-w gradient-echo images were acquired with an echo time of 4.6 min, a repetition time of 40 min, a flip angle of 30°, a voxel size of 0.7 × 0.7 × 0.1 mm, and an field of view of 180 mm.

Qualitative Assessment of the MRI Studies
Structural scans (T1- and T2-w images) were assessed by a neuroradiologist to ensure that they were free of gross abnormalities. Qualitative white matter abnormalities were defined based on a previously published scoring system (Inder et al. 2003). This system assessed 5 separate items: Abnormal white matter signal, reduced white matter volume, cystic changes, myelination/thinning of the corpus callosum, and ventricular dilatation. White matter abnormalities were further classified by the composite scores of these 5 categories (ranging from 5 to 15) into: No white matter abnormalities (score 5–6), mild white matter abnormalities (score 7–9), moderate white matter abnormalities (score 10–12), or severe white matter abnormalities (score 13–15).

Automatic Brain Segmentation and Voxel-Based Morphometry
The prior manual steps included reorientation of the original T1-w images in the plane of anterior–posterior commissures and removal of nonbrain tissue components using the Brain Extraction Tool (Smith 2002). Structural images were then segmented into tissue classes using unified segmentation (Ashburner and Friston 2005), as implemented in the “new segment” option of the SPM v8 software, Wellcome Department, University College (London, UK), running on MATLAB v7.5 (MathWorks, Natick, MA, USA). For guiding segmentation, we used tissue probability maps from preterm infants scanned at term age (Kuklisova-Murgasova et al. 2011). A quantitative evaluation of the segmentations was performed, and the Dice coefficient (Dice 1945) was calculated showing an agreement of 0.87 ± 0.02 for cortical gray matter, 0.86 ± 0.02 for white matter, 0.79 ± 0.05 for deep gray matter, 0.84 ± 0.02 for cerebellum, and 0.83 ± 0.01 for brainstem (see Supplementary Material for further details on automatic brain segmentation and validation).

The segmented brain tissues (see Supplementary Fig. 1) were spatially normalized by using DARTEL. Finally, all images were modulated and smoothed with a full width at half-maximum of 3-mm Gaussian kernel. We used these smoothed brain tissue images to conduct the statistical analyses, as outlined below (see Supplementary Material for further details on VBM). Global brain tissue volumes (in cm³) were extracted from the segmented/normalized/modulated images of each subject with the Easy Volume toolbox (Pernet et al. 2009).

Neonatal Complications and Brain Tissue Volumes
To investigate the effect of the neonatal variables on brain tissue volumes within the preterm group, 2 subgroups were formed based on the presence or absence of the following neonatal variables: Qualitatively defined mild white matter abnormalities; DEHSI; IVH grades I–II; patent ductus arteriosus (PDA); PDA with medical treatment (ibuprofen); retinopathy of prematurity grade ≥2; and bronchopulmonary dysplasia, defined as the need of oxygen at 36 weeks of gestation and clinical diagnosis of sepsis, with or without positive blood culture. Additional analyses were performed based on: the degree of immaturity (≤25th and ≥26th–26th weeks); any use of mechanical ventilation versus nasal continuous positive airway pressure (nCPAP), and PDA litigation versus PDA with medical treatment. We also studied correlations between brain tissue volumes and days on ventilatory support (mechanical ventilation and nCPAP) in the EPT group.

Statistical Analysis
Variables were tested for normality and homogeneity before each analysis. Quantitative data were analyzed with Student’s t-test, and qualitative data with Pearson’s χ² or Fisher’s exact test. The Mann–Whitney U-test was applied for non-normally distributed data. The statistical significance level was set at P < 0.05. All statistical analyses were computed using the SPSS, version 20.0 (SPSS, Inc., Chicago, IL, USA).

Global Brain Volumes
To assess differences in global volumetric measures between the groups, a general lineal model analysis (multivariate) was performed with all brain volumes as dependent variables and group status as the independent factor. The data were tested to ensure that no data assumptions were violated. The covariates used were total intracranial volume (TIV = all brain tissues, including cerebrospinal fluid (CSF), to control for generalized scaling effects, and postmenstrual age at the time of the scan. Owing to the fact that variations in CSF volumes could affect the TIV in the EPT infants, we also conducted analyses controlling for the total volume of the cerebral parenchyma (CPAR), including all the brain tissues, but excluding CSF, in addition to postmenstrual age at imaging. For the model, we used a Type III sum of squares, which is invariant with respect to unequal samples. The same model was used to investigate the effect of the neonatal variables on brain tissue volumes between the preterm groups. In this case, analyses were adjusted for gestational age at birth and days on mechanical ventilations as appropriate.

Voxel-Based Morphometry Analysis
For VBM analysis, t-test group comparisons were performed to evaluate the brain volume differences between groups. In the EPT group, a multiple regression analysis was performed to evaluate the relationship between brain tissue volumes and days on ventilatory support (mechanical ventilation and nCPAP). We restricted the statistical analyses to areas with a minimum probability value of 0.25 (absolute threshold masking), avoiding possible edge effects around tissue borders. We analyzed the following contrasts: Patients greater than controls and controls greater than patients. Analyses were adjusted for CPAR. TIV, age at MRI, and gender did not account significantly for variations in the model and were not included in subsequent analyses. We used the same previously defined covariates in the VBM analyses between preterm groups. Only clusters >10 voxels are reported. All statistical images were subjected to family-wise error correction for multiple comparisons. For visualization purposes, the significant clusters were
displayed at uncorrected *P* < 0.001 in order to identify the affected structures and networks.

**Results**

Table 1 summarizes the neonatal characteristics of the preterm and term cohorts. The neonatal morbidity of the preterm group is reported in Table 2.

**Global Volume Data**

Global brain volume measurements are summarized in Table 3. Overall, EPT infants had lower brain volumes than term infants, and we specifically found that cortical gray matter, deep gray matter, and brainstem volumes were significantly lower. The CSF volume was significantly higher in the preterm group. It is noteworthy that the differences in deep gray matter and brainstem volumes remained significant after adjustment for CPAR and the exclusion of infants with mild white matter abnormalities.

**Whole-Brain Voxel-Based Morphometry Analysis**

The results of this section are presented in Supplementary Table 1. Compared with the term group, EPT infants exhibited significantly reduced global and regional brain volumes (Supplementary Table 4). Of note, areas of increased cortical gray matter were detected in the medically PDA treated group, also showed a decreased volume. The results were not altered when infants treated with postnatal steroids (*n* = 5) were excluded from the analysis. Smaller clusters of white matter decrements were observed in areas adjacent to the gray matter decreases, primarily affecting the temporal cortex and, to a minor extent, the angular gyrus and perirlandic area bilaterally (Fig. 1B). Notably, larger gray matter and white matter volumes were detected bilaterally in the occipital, parietal, and frontal cortices (Fig. 1C,D). The preterm group also displayed areas of decreased volume in the deep gray matter, cerebellum, and brainstem (Fig. 2).

**Perinatal Risk Factors: Global and Regional Brain Volumes**

The most immature infants, those with low-grade IVH and also with PDA who needed surgical ligation, had significant reduced global and regional brain volumes (Supplementary Tables 2 and 3) in several regions (Fig. 3). Notably, cerebellar growth was affected in the presence of all of these perinatal risk factors. The neonatal variables that significantly differed between preterm groups were used as covariates in all analyses (Supplementary Table 4). Of note, areas of increased cortical gray matter were detected in the medically PDA treated group.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the study groups</th>
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</thead>
<tbody>
<tr>
<td>Perinatal</td>
<td>Term (n = 15)</td>
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<tr>
<td>Gestational age at delivery</td>
<td>25.67 (1.09)</td>
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<tr>
<td>Male/female ratio</td>
<td>21/26</td>
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<tr>
<td>Birth weight (g)</td>
<td>838.96 (152.83)</td>
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<tr>
<td>Range</td>
<td>528–1161</td>
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<tr>
<td>Corrected age at scan (weeks)</td>
<td>40.05 (1.02)</td>
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<tr>
<td>Range</td>
<td>38.14–43.28</td>
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Note: Results are expressed as mean (SD) or median (range). *U*, Mann–Whitney *U*-test; *t*, Student’s *t*-test.
when compared with the group without PDA ($P<0.005$). Although we could not find global brain volume differences between infants on mechanical ventilation in comparison with those using nCPAP, a cluster of decreased cortical gray matter volume in the left primary motor cortex (cluster = 475 voxels, $P=0.04$) was identified on a regional level (not shown). Significant negative correlations were observed between days on mechanical ventilation and brain volumes in deep gray matter ($r=0.51$, $P<0.001$), cerebellum ($r=0.57$, $P<0.001$), and brainstem ($r=0.53$, $P<0.001$) (Supplementary Fig. 2). With respect to other medical conditions, we could not find any differences in global or regional level brain volumes between the preterm groups.

**Discussion**

The main findings of this study are that when the EPT infants were compared with the term infants, they showed significant global reductions in brain tissue, accompanied by a significant increase in CSF volume. On a regional level, the preterm infants showed decreased volumes of all brain tissues, in particular cortical gray matter. An unexpected finding of the study is that the EPT infants displayed increased cortical gray matter and white matter involving vision-related brain areas. Finally, increasing prematurity, low-grade IVH, and PDA ligation were associated with different patterns of brain volume reductions and had a particular effect on the cerebellum. Our study extends previous findings and supports the notion that EPT birth induces deviations in the developmental trajectory of the brain at term age, even in the absence of focal brain pathology.

**Global Brain Volumes**

We found decreased global volumes of cortical gray matter, deep gray matter, and brainstem. This is similar to a previous report (Parikh et al. 2013), which also found smaller global brain volumes, but with a major involvement of the white matter.
matter. However, this might be due to the fact that their study population had more clinical complications than ours. Moreover, 25% of the infants in that study were small for their gestational age, a condition that is known to affect white matter maturation in preterm infants at term age (Lepomaki et al. 2013). In the current study, major volume reductions were found in the deep gray matter and brainstem of the EPT infants. The volumetric differences in the deep gray matter persisted even when conventional MRI sequences failed to identify any white matter abnormality in infants. Our results confirm previous findings that the deep gray matter is specifically vulnerable after preterm birth and is particularly affected in more immature infants (Inder et al. 2005). In this study, EPT infants had significant reductions in the whole-brainstem volume. At this early age, the brainstem is part of a vertical-integrative hierarchical system, along with the limbic and cortical systems, and is involved in the process of regulatory functions, such as arousal, attention, and emotion (Geva and Feldman 2008).

The global volume reductions found in our study were probably not due to acute or hypoxic injury, as there were no signs of brain abnormalities caused by these conditions. It is more than likely that the present results can be explained by the extreme preterm infants (mean gestational age of 25.6 weeks) being born during a critical period of brain development, when synaptic density neuronal wiring is increasing in all the cortical regions (Zecevic 1998), and the thalamo-cortical projections are waiting within the subplate zone to reach the cortical plate (Kostovic and Judas 2010). In addition, at the time of EPT birth, the many cortical interneurons in the human fetus are been generated in the proliferative zones and are still migrating to the cerebral cortex (Letinic and Rakic 2001). Altogether, the EPT birth per se probably leads to altered connections at multiple anatomical levels, from the cortex to the deep gray matter and brainstem, with subsequent developmental disturbances and trophic consequences reflected by volume alterations (Volpe 2009a, 2009b; Kostovic and Judas 2010; Ball et al. 2012).

Regional Analyses: Voxel-Based Morphometry

We found that when we compared the EPT infants with the term infants in the control group, they showed extensive regions of reduced gray matter in several brain areas that have previously been described in more mature infants studied in childhood and adolescence. These areas included: the cortical temporal lobe bilaterally (Kesler et al. 2008; Nosarti et al. 2008; Nagy et al. 2009), precentral and postcentral gyrri (Peterson et al. 2003; Allin et al. 2004; Kesler et al. 2008); orbito-frontal cortex (Thompson et al. 2007; Nagy et al. 2009; Ball et al. 2012); amygdala (Peterson et al. 2000; Kesler et al. 2008); para-hippocampal gyrus (Kesler et al. 2008); hippocampus (Peterson et al. 2000; Kesler et al. 2008; Nagy et al. 2009), and left insula (Nosarti et al. 2008). The additional involvement of subcortical gray matter sites, including the deep gray matter (an interface between neocortical and lower-level systems), cerebellum, and brainstem, confirms the increase susceptibility of the gray matter in the preterm brain (Dean et al. 2013; Malik et al. 2013).
Structures involved in auditory, language, and somatosensory processing were recognized. We also identified a structure that has not previously been reported in EPT infants at term age, namely the entorhinal cortex, a gateway between neocortical association areas and the hippocampal system (Fransen 2005). In adolescents born preterm, entorhinal thinning has been associated with impaired cognitive function as a result of aberrant cortical maturation (Skranes et al. 2012). Further studies should focus on the entorhinal cortex and its correlation with cognition in EPT samples. The decreased regional volumes found in our study may be due to compromised neurogenesis (Malik et al. 2013), disturbances of the dendritic arbor, and synapse formation of cortical neurons (Dean et al. 2013).

Increased volumes were detected in regions known to be involved in visual processing, contrary to previous studies (Peterson et al. 2003; Shah et al. 2006; Thompson et al. 2007). However, the infants in these studies were more mature than the preterm infants included in our study and experienced several clinical complications. The nature of the increase in gray and white matter volumes may reflect an abnormal or delayed pruning program, as has been previously suggested (Nosarti et al. 2008). However, the visual cortex represents a particular region of the brain that matures earlier than other areas of the cortex (Tzarouchi et al. 2009) and has a functional relevance in EPT infants at term age (Fransson et al. 2007, 2011). In this respect, increased volumes in our preterm cohort may correspond to advanced maturational aspects in the visual regions, due to longer extraterine visual experiences during a critical period, compared with term infants. In fact, both classic (Wiesel 1982; Bourgeois et al. 1989) and modern studies (Tsunenishi and Casar 2000; Gimenez et al. 2008) support the theory that neural activity driven by visual experience is essential for shaping the early rudimentary cortical connectivity patterns (Penn and Shatz 1999). Further studies that follow up functional aspects are needed to define the developmental correlates of these findings.

Perinatal Risk Factors

In addition to the degree of immaturity, the presence of IVH grade I–II and surgically ligated PDA were associated with
reduced brain growth. The regional gray matter was also affected by the severity of respiratory illness. Overall, brain volume reductions preferentially affected gray matter structures and, in particular, the cerebellum, as mentioned above. The other perinatal factors that were studied had no significant effect on cerebral structure at term age.

In this study, we included infants with IVH grade I–II as these hemorrhages are usually considered to be benign. Our findings of reduced brain volumes are in agreement with previous MRI studies (Vasileiadis et al. 2004) and may reflect the influence of the low-grade IVH on developmental processes related to suppression of cell proliferation (Del Bigio 2011) and microglia activation (Supramaniam et al. 2013). These findings may help to explain the impaired developmental outcomes reported in preterm infants with low-grade IVH at different ages (Klebermass-Schrehof et al. 2012).

The adverse effect of PDA ligation may be due to disturbed cerebral circulation. Infants who needed surgical ligation faced a higher risk of affected brain growth than those who only received medical treatment. There seem to be adverse effects of the PDA ligation per se, where intraoperative or postoperative physiological alterations may affect cerebral hemodynamics (El-Khuffash et al. 2013), potentially causing further injury to an already vulnerable brain. It is, however, surprising to note that the infants in our cohort who only received medical treatment (ibuprofen) for PDA had preserved brain volumes compared with those without. We speculate that the anti-inflammatory effect of ibuprofen might be protective for brain growth, which is in line with previous findings where ibuprofen showed neuroprotective effects attenuating neuronal damage (Wixey et al. 2012).

The neuropathological basis of the decreased regional cerebellar volume in our study still needs to be elucidated. Of note, the gestational age of the EPT neonates included in our research corresponds to a phase of rapid cerebellar development, representing a period of particular vulnerability. It is, therefore, likely that the suppression of neuronal proliferation (Volpe 2009a, 2009b), trophic interactions (Tam et al. 2011), and a compromised cerebellar perfusion (Limperopoulos et al. 2005) might specifically affect the growth of the cerebellum. Impaired cerebellar growth accounts for subsequent developmental problems, which indicate the need for heightened clinical surveillance and early target interventions. Remarkably, the presence of DEHSI detected in 48.9% of our preterm cohort at term age was not associated with brain volume alterations. We have previously found that the presence of DEHSI in EPT infants at term age was not related to abnormal neurologic outcome at 30 months (Skiold et al. 2012). These results suggested that DEHSI is a prematurity-related transient phenomenon.

Our study benefits from including a unique cohort of EPT infants without major brain alterations on neonatal ultrasound or MRI at term age and a mean gestational age lower than previously published cohort studies. However, some methodological concerns must be considered. We are aware that tissue segmentation in preterm infants at term is a challenging task, owing to the developmental characteristics of the preterm brain. Furthermore, the segmentation is limited in smaller cerebral structures, owing to the smaller volumes and a lower signal-to-noise ratio than in older infants. To minimize these limitations, we only used good quality $T_1$-w images. For guiding segmentation, we used a larger number of tissue probability maps, together with an extraclass tissue map for background, to provide better modeling of CSF and other non-brain voxels and further to improve the tissue classification. Additionally, the tissue probability maps used here were based on a sample of preterm neonates scanned at term age. We also used the DARTEL algorithm to provide a better intersubject registration.

In conclusion, we have shown that at TEA, and in the absence of focal brain lesions, EPT infants have an altered global and regional brain growth pattern, involving decreases and increases of brain tissue volumes. Gray and white matter gains in regions known to be involved in visual processing suggest maturational brain changes driven by precocious visual experiences in EPT infants. The degree of immaturity, IVH grade I–II, and surgically ligated PDA were associated with global and regional decreased brain growth that preferentially affected gray matter structures, in particular the cerebellum. Our study suggests that structural alterations may be used as structural markers to identify children at risk earlier, and that this may prevent adverse outcomes following EPT birth. Longitudinal studies, including functional follow-up data, would help to determine the significance of the volumetric brain alterations found in the EPT infants in our study.

Supplementary Material

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

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Notes

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References


