Early Growth in Brain Volume Is Preserved in the Majority of Preterm Infants

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Objective: Preterm infants have reduced cerebral tissue volumes in adolescence. This study addresses the question: Is reduced global brain growth in the neonatal period inevitable after premature birth, or is it associated with specific medical risk factors?
Methods: Eighty-nine preterm infants at term equivalent age without focal parenchymal brain lesions were studied with 20 full-term control infants. Using a deformation-based morphometric approach, we transformed images to a reference anatomic space, and we used the transformations to calculate whole-brain volume and ventricular volume for each subject. Patterns of volume difference were correlated with clinical data.
Results: Cerebral volume is not reduced compared with term born control infants ($p = 0.765$). Supplemental oxygen requirement at 28 postnatal days is associated with lower cerebral tissue volume at term ($p < 0.001$), but there were no significant differences in cerebral volumes attributable to perinatal sepsis ($p = 0.515$) and quantitatively defined diffuse white matter injury ($p = 0.183$). As expected, the ventricular system is significantly larger in preterm infants at term equivalent age compared with term control infants ($p < 0.001$).
Interpretation: Cerebral volume is not reduced during intensive care for the majority of preterm infants, but prolonged supplemental oxygen dependence is a risk factor for early attenuation of global brain growth. The reduced cerebral tissue volume seen in adolescents born preterm does not appear to be an inevitable association of prematurity, but rather caused by either specific disease during intensive care or factors operating beyond the neonatal period.

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Children and adolescents who were born with very low birth weight (VLBW) appear to have reduced total cerebral tissue volumes compared with age-matched control subjects,[1–3] and alterations in the distribution of gray matter, white matter, and ventricular cerebrospinal fluid (CSF) persist into the third decade of life.[4,5] Many of the morphological abnormalities identified in this population are associated with adverse neurodevelopmental outcomes (see Counsell and Boardman[6] for review). However, an understanding of the causes, nature, and temporal evolution of this abnormal growth pattern remains elusive.

In particular, it is unclear to what degree the growth failure leading to reduced brain volume in adolescence takes place in the perinatal period or in later childhood. In a study of preterm infants at term equivalent age, brain volume was reduced compared with infants born at term,[7] but this cohort included infants with risk factors for abnormal brain development such as postnatal steroid exposure or cerebral lesions (periventricular leukomalacia and intraventricular hemorrhage). In a smaller study that excluded infants with known risk factors, we found a reduction in cortical complexity with no apparent reduction in whole-brain volume[8]; and Zacharia and coworkers[9] report no reduction in brain volume in "low-risk" preterm infants, although these infants were relatively mature at birth and the study group was small. It is thus unclear whether whole-brain growth failure is an inevitable consequence of preterm delivery or the result of specific and potentially preventable adverse events during the period of intensive care. The answer to this question is important in understanding the causes of neurodevelopmental impairment and in planning therapeutic strategies for these vulnerable infants.

To investigate this, we used a deformation-based morphometric approach to compare a large group of preterm infants who did not have focal brain lesions

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with a group of healthy infants born at term. The deformation-based morphometric procedure uses a high-dimensional, nonrigid registration algorithm to transform images from all subjects into a template anatomic space.[10] A region of interest (ROI) labeled in the template anatomy is propagated to all images using the transformations, so that the volume of the corresponding structure for each subject can be computed.[11]

We hypothesized that if global brain growth failure is an inevitable consequence of premature birth, there would be a significant difference between the preterm group and control subjects. Alternatively, if no overall difference was found, specific medical conditions might be associated with reduced brain growth. Because bronchopulmonary dysplasia (BPD) is associated with increased rates of neurodevelopmental impairment,[12,13] and is a risk factor for structural cerebral abnormalities,[7,14] we hypothesized that preterm infants with prolonged respiratory illness (defined as needing supplemental oxygen administration at 28 days of postnatal life) might be particularly vulnerable to attenuated global brain growth. We also explored whether other putative risk factors for brain injury in preterm infants are associated with reduced brain growth in the neonatal period: quantitatively defined diffuse white matter injury, perinatal infection, and intrauterine growth restriction (IUGR).

Because this is the first use of a deformation-based morphometric approach for calculating ROI volumes from neonatal magnetic resonance (MR) images, we evaluated the reliability of the approach by measuring the agreement in ROI volume values obtained when different anatomic templates are used.

Subjects and Methods

Ethical permission was granted by the Hammersmith Hospital Research Ethics Committee, and informed parental consent was obtained for each infant.

Subjects

The MR images of 89 preterm infants at term equivalent age (37 male and 52 female infants), together with 20 term born control infants (12 male and 8 female infants), were analyzed. The infants were recruited from Queen Charlotte's and Chelsea Hospital between February 2001 and November 2003, and patient characteristics are described in Table 1. Preterm infants were eligible for recruitment if they were born at less than 33 completed weeks of gestation, had no congenital malformation, and survived to discharge. Preterm infants with focal parenchymal lesions or posthemorrhagic ventricular dilation (defined as ventricular index >97th centile after a germinal matrix hemorrhage-intraventricular hemorrhage [GMH-IVH]) on cranial ultrasound or MR imaging were excluded.

During this period, 666 infants were born or transferred in and fulfilled the gestational age criterion: 592 survived to discharge; of these, 48 were excluded because of congenital malformation, and 17 of the remaining infants were excluded because of focal parenchymal lesions or posthemorrhagic ventricular dilation, leaving 527 eligible. A total of 109 infants were recruited; 89 had images that were free of motion artefact and suitable for volumetric analysis. No infant received postnatal steroids.

Preterm infants were sedated with chloral hydrate, and

Table 1. **Summary of Patient Characteristics**

Characteristics	Preterm Infants at Term Equivalent Age (n = 89)	Term Control Subjects (n = 20)
Median PMA at birth (range), wk	29.86 (24-34.43)	39.14 (35.57-42)
Median birth weight (range), gm	1,290 (610-2,250)	3,280 (2,448-4,780)
Median corrected PMA at scan (range), wk	40.57 (37.86-44.57)	40.43 (36.57-43.14)
Mean weight at time of image acquisition (range), gm	2,980 (1,686-4,380)	3,381 (2,448-4,780)
Mean occipitofrontal head circumference at scan (range), cm	34.91 (32.0-38.0)	34.94 (33.0-38.0)
Diffuse white matter injury, n	66[a]	—
IUGR, n	26	—
Perinatal sepsis, n	27	—
Persistent oxygen requirement at 28 days postnatal life, n	26	—

Intrauterine growth restriction (IUGR) was defined as birth weight <10th centile for age; prolonged oxygen dependence was defined as a persistent supplemental oxygen requirement at postnatal day 28; and perinatal sepsis was defined as positive blood cultures or viral isolation in the infant, or a clinical diagnosis of maternal infection together with increased maternal C-reactive protein and/or white blood cell count. The control group weighed significantly more than the preterm group at the time of image acquisition ($p = 0.006$).

[a]Diffuse white matter injury was defined quantitatively using apparent diffusion coefficient values, available for 80 of 89 preterm infants at term equivalent age.

PMA = postmenstrual age.

control infants were examined in natural sleep. Pulse oximetry and electrocardiographic and televisual monitoring were used throughout the examination. Ear protection was used (Natus MiniMuffs; Natus Medical, San Carlos, CA).

Image Acquisition

A 1.5-Tesla MR Eclipse system (Philips Medical Systems, Best, the Netherlands) was used to acquire high-resolution, T1-weighted (TR = 30 milliseconds, TE = 4.5 milliseconds, flip angle = 30 degrees) volume data sets in contiguous slices with a voxel size of 1.0 × 1.0 × 1.6mm, as well as transverse T1-weighted conventional spin-echo (TR 500/TE 15 milliseconds) and T2-weighted fast-spin echo (TR 4,500/TE_{eff} 210 milliseconds) images. Diffusion-weighted images were acquired using a single-shot echo planar imaging sequence with the following parameters: TR 6,000 milliseconds; TE 100 milliseconds; 100 × 100 matrix, field of view 24cm, slice thickness 5mm. A reference image was obtained with a b value of 0 (nominal value), and diffusion-weighted images were obtained with a b value of 1,000sec/mm^2 in the read, phase, and slice directions. To measure apparent diffusion coefficient values, we positioned ROIs in frontal, central, and posterior white matter at the level of the centrum semiovale on the reference image ($b = 0$) and on the read, phase, and slice diffusion-weighted images. The apparent diffusion coefficient values for each ROI were calculated using previously described methods.[15] Infants were classified as having white matter disease if one or more white matter region had an apparent diffusion coefficient value greater than two standard deviations above the mean of that measured in a group of normal term control subjects (values published previously[16]).

Deformation-Based Morphometry

NONRIGID IMAGE REGISTRATION. The MR image of a term born control subject was chosen as the reference coordinate system to which all other images were aligned. To model the anatomic variability of subjects, we used a high-dimensional nonrigid registration algorithm that is ideal for neonatal studies because it can capture wide anatomic variability and is robust to differences in signal intensity between images.[10,16–18] The goal of the registration process is to achieve precise spatial correspondence between all subjects and the anatomy of the reference subject. This is achieved using a three-dimensional registration with normalized mutual information as the maximized similarity measure. An affine registration models global differences, and local registration is achieved using a free-form deformation represented by displacements on a grid of control points using cubic B-splines.[10]

The output of the registration process is a geometric transformation, or deformation field, which allows spatially resolved measurement of volume change. This can be achieved by calculating all first derivatives of the transformed coordinates with respect to the native coordinates in the template space. For a three-dimensional space, these can be written as a 3 × 3 matrix, the Jacobian operator. The determinant of the Jacobian provides a scalar measure summarizing the point-wise volume change at each voxel.[19,20] A qualitative evaluation of the accuracy of anatomic alignment of the transformed images with the template was made before deformation fields were used to calculate volume changes.

The transformations were used to propagate ROIs segmented in the reference coordinate system to the corresponding structure in all subjects, and the volume increase/decrease for these structures relative to the reference was computed. In this way, volumes for the lateral and third ventricular system and whole cerebral tissue were calculated for each subject.

Region-of-Interest Labels

Contours including the boundaries of the ventricular system were drawn manually on contiguous slices. A mean signal intensity threshold for CSF was calculated, and this was used to extract voxels labeled as CSF within the manually defined contours. Ventricular volumes were calculated by multiplying the number of labeled voxels by the voxel volume.

To segment whole-brain tissue, we used an automatic contour-following algorithm to extract brain tissue (including cerebellum but excluding brainstem) from bone and soft tissue.[21] Signal from CSF was excluded using the signal intensity thresholding technique described earlier. Brain tissue volume was calculated by multiplying the number of voxels labeled as tissue by voxel volume. All segmentations were checked for anatomic accuracy and edited as required (Fig 1).

Statistical Analyses

Statistical analyses were performed using SPSS 11.0 (SPSS, Chicago, IL). For group comparisons of ROI measurements, data were tested for normality using Shapiro–Wilk W test. If values in both groups conformed to a Gaussian distribution, the groups were compared using Student's t test for independent samples. A natural log transform was performed before parametric analysis if the data did not have a Gaussian distribution.

We estimated that with 89 infants in the preterm group and 20 in the control group, a 10% difference in whole cerebral tissue volume would be detected with 80% power at a significance level of $p = 0.05$.[22]

The general linear model analysis of variance procedure was used to investigate the effect of the following dichotomous variables on brain tissue volume at term: IUGR, prolonged supplemental oxygen dependence, perinatal sepsis, and diffuse white matter injury. For each factor in the model, a simple contrast was applied to compare preterm infants with (level 1) and without the condition (level 2) to the control group (level 3). This allows a priori specification of t-statistic calculations and limits the number of multiple comparisons. Postmenstrual age (PMA) at scan was controlled for because this has a significant relation with brain volume ($p < 0.001$) over the age range of the group at the time of image acquisition (36.57–44.57 weeks).

Effect of the Template on Region-of-Interest Measurements

Images from all subjects were registered to a second template, $R_{\#2}$, and the transformations were used to propagate segmentations of whole-brain tissue and the lateral and third ventricular system made in $R_{\#2}$ to the corresponding structure in all subjects. The agreement between measurements derived from $R_{\#1}$ and $R_{\#2}$ for each ROI was assessed using methods that Bland and Altman[23] described.

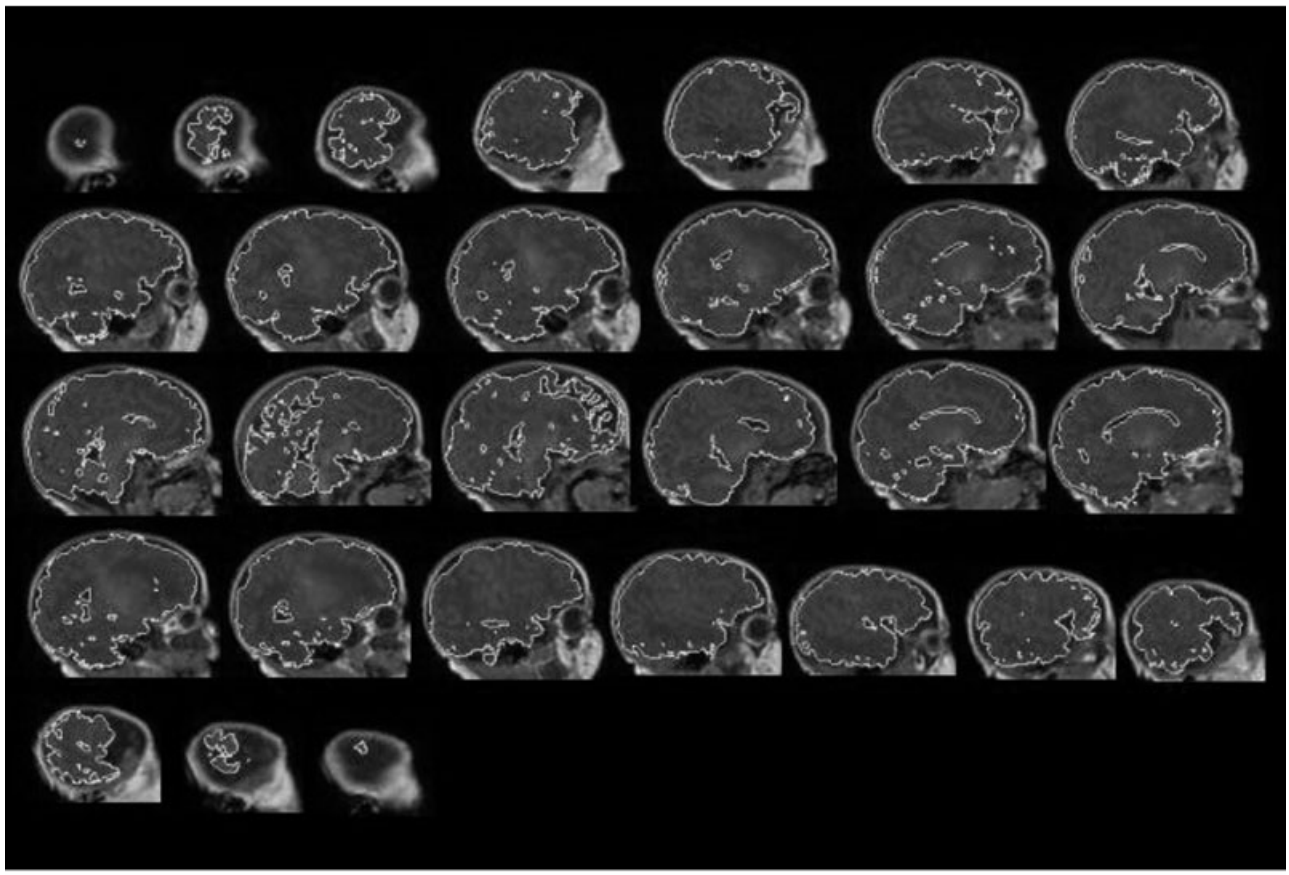

Fig 1. Whole-brain segmentation. The segmentation includes all cerebral tissue, and selected sagittal slices are displayed. The lateral and third ventricular system was segmented in a separate procedure (see Subjects and Methods). Transformations from the registration process were used to propagate both segmentations to all registered images, enabling calculation of the volume of the corresponding structure for all subjects in the group.

Results

Brain Compartment Volumes

There was no significant difference in whole-brain tissue volume between preterm infants at term equivalent age compared with term control subjects ($p = 0.765$), controlling for PMA at time of image acquisition, and there is no linear relation between PMA at birth and brain volume at term equivalent age ($p = 0.363$) (Fig 2).

The need for supplemental oxygen at 28 days of postnatal life accounted for significant variance in whole cerebral tissue volume of preterm infants at term equivalent age ($p < 0.001$), and IUGR approached significance ($p = 0.056$) (Table 2). By applying a simple contrast, we identified that the effect of prolonged oxygen requirement in the model was due to the reduction in brain tissue volume in preterm infants with this problem compared with those without (Fig 3). The mean gestational age at birth of the group requiring supplemental oxygen at 28 days (n = 26) was 27.29 weeks, and that of the group breathing air was 30.86 weeks ($p < 0.001$); infants with this requirement (mean weight, 2,737gm) weighed less at the time of image acquisition compared with preterm infants (mean weight, 3,098gm) without this problem ($p = 0.007$). Neither quantitatively defined diffuse white matter injury nor perinatal sepsis accounted for significant variance within the group.

The volume of the lateral and third ventricular system was significantly larger among preterm infants at term equivalent age compared with term control infants (Fig 4). There is a linear relation between PMA at birth and log ventricular volume at term equivalent (regression coefficient = −0.037; 95% confidence interval, −0.051 to −0.023; $p < 0.001$), and IUGR, diffuse white matter injury, prolonged supplementary oxygen requirement, and perinatal sepsis did not account for significant variance in the model.

Effect on Volume Measurements When Different Template Images Are Used

We measured the agreement in cerebral tissue volumes and ventricular system volumes based on the calculations from transformations of the whole study group to two different templates (Fig 5). The mean difference in

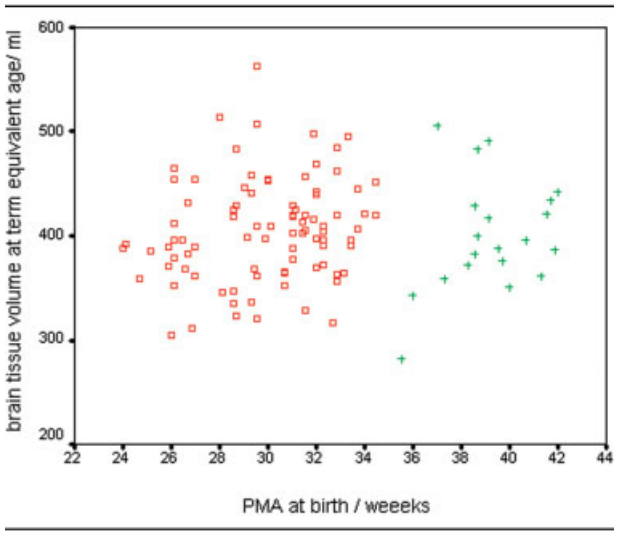

Fig 2. Cerebral tissue volume measurements at term equivalent age. Squares *represent brain volume for each preterm infant at term equivalent age (n = 89), and* crosses *represent brain volume for control subjects (n = 20). There is no significant difference between the mean brain volume of the preterm infants at term equivalent age (404.9ml) and term control infants (401.1ml)* (p = *0.765, two-tailed test). PMA = postmenstrual age. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]*

brain tissue volumes is 18.34ml (95% confidence interval, 1.3–35.37ml), and the mean difference in ventricular volumes is 0.19ml (95% confidence interval, −0.68–1.07ml).

Discussion

Cerebral tissue volume is similar in preterm infants at term equivalent age compared with infants born at term. This is consistent with our previous smaller study that reported aberrant cortical development without early changes in global brain volume after preterm birth,[8] with the finding of similar head circumference measurements in both groups (see Table 1), and with anthropometric data that show accelerated head growth during neonatal intensive care.[24] This is striking in light of the global growth failure reported among survivors of preterm birth in later life,[1–3] and it suggests that global cerebral maldevelopment does not result from a fixed injury incurred during the period of neonatal intensive care, but could be a process that is programmed in the antenatal or neonatal period and is modified by postnatal events.

Mammalian brain morphology alters with environmental manipulation,[25] the acquisition of new skills,[26,27] genetic influences,[28] and sex chromosome and hormonal effects.[29,30] Premature delivery could predispose to an attenuated response to one or more of these processes so that the normal linear increase in white matter volume[31] and/or complex cortical growth patterning that takes place over the first two decades of life is disrupted.[32] These data suggest that factors in early childhood may modify brain growth after preterm birth. If so, the potential window for therapeutic interventions designed to ameliorate the neurocognitive impairments commonly seen among VLBW children[33] may be wider than current understanding suggests.

Thompson and colleagues[7] report a mean 6% reduction in whole cerebral tissue volume among preterm infants at term equivalent age, although the confidence of this estimate is unclear. The study group had a younger median gestational age than that of the group studied in this article, and it included infants with independent risk factors for abnormal brain growth. However, the data from Thompson and colleagues,[7] together with our own power calculation, mean that we cannot exclude the possibility that 23 and 24 weeks gestation infants are susceptible to attenuated whole-brain growth in the neonatal period, whereas slightly less premature infants are not. Studying larger numbers of infants with this gestational age and/or more term born control infants would clarify this issue. The older cohorts of patients with long-term cerebral volume reduction may have contained a greater proportion of subjects with parenchymal lesions, which might not have been detected with the imaging technology available at that time; and postnatal steroid exposure was more common. We studied a selected group of infants who are representative of the majority of survivors of modern neonatal intensive care.

A requirement for supplemental oxygen at 28 days of postnatal life was associated with reduced brain volume at term compared with preterm infants without this complication. The finding is consistent with clinical, imaging, and experimental data that implicate respiratory illness in the pathogenesis of preterm brain injury. VLBW infants with BPD have a greater prevalence of neurocognitive and motor impairment at school age than VLBW infants without BPD, and respiratory illness accounts for a greater proportion of the variance in performance than birth weight or gestational age.[13,34] The anatomic correlates of this phenomenon are poorly understood, but BPD was associated with reductions in all brain regions in Thompson and colleagues' study[7]; and in a group of adolescents with VLBW, the length of supplemental oxygen requirement was a significant predictor of dyscalculia, which was associated with abnormal parietal gray matter structure.[35]

From experimental studies, hyperoxia induces cell death in the newborn rat brain,[36] and in a baboon model of preterm birth, wide fluctuations in the fraction of inspired oxygen is associated with adverse outcome in all measures of cerebral injury at autopsy, regardless of the type of assisted ventilation.[37] These points are pertinent because hyperoxia is a risk while

Table 2. **Summary of Analysis of Variance for Effects on Brain Tissue Volume**

Source	Type III Sum of Squares	Degrees of Freedom	Mean Square	*F* Statistic	Significance
Corrected model	100,609.381	6	16,768.230	10.597	0.000
Intercept	19,513.639	1	19,513.639	12.332	0.001
IUGR	5,930.755	1	5,930.755	3.748	0.056
WMI	2,846.928	1	2,846.928	1.799	0.183
Supplemental oxygen requirement at 28 days	21,459.219	1	21,459.219	13.561	0.000
Sepsis	675.355	1	675.355	0.427	0.515
PMA at scan	68,702.537	1	68,702.537	43.417	0.000

$r^2 = 0.409$.

IUGR = intrauterine growth restriction; WMI = diffuse white matter injury; PMA = postmenstrual age at time of image acquisition.

the optimal target range for oxygen saturation is unknown, and preterm infants receiving assisted ventilation commonly have widely fluctuant transcutaneous oxygen levels.[38] Only five of the infants in this group developed BPD, so these data imply that relatively benign respiratory illness adversely affects brain development.

Infants with IUGR had smaller cerebral tissue volumes when compared with appropriately grown preterm infants, and this difference approached statistical significance in the model ($p = 0.056$). Given that IUGR has been identified as a specific risk factor for reduced intracranial and cortical gray matter volume at term equivalent age,[39] it is possible that a significant difference would be detected with larger numbers. Diffuse white matter injury was not associated with volume loss at term equivalent age. This may be because the diffuse white matter lesion represents increased water content in affected tissue, so although axonal/glial number or caliber may be reduced, affected tissue does not lose volume, at least in the perinatal period. Although perinatal sepsis is associated with focal brain lesions, there was no evidence of global growth failure in this group.[40]

Ventriculomegaly is common among preterm infants at term equivalent age,[14,41] so we expected to identify

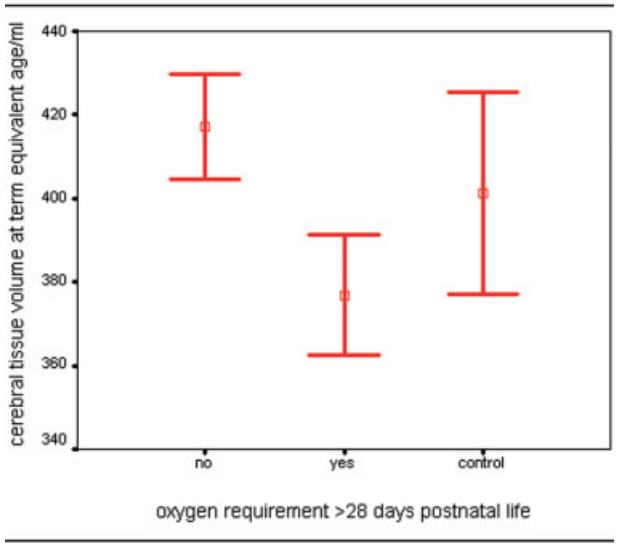

Fig 3. Prolonged oxygen requirement accounts for significant variance in brain tissue volume among preterm infants at term equivalent age. Preterm infants with a supplemental oxygen requirement at 28 days (n = 26) had smaller cerebral tissue volumes (mean, 376.02ml) than preterm infants breathing air at 28 postnatal days (mean, 417.02ml) (n = 63; p *< 0.001). Bars represent ±1 standard error of the mean. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]*

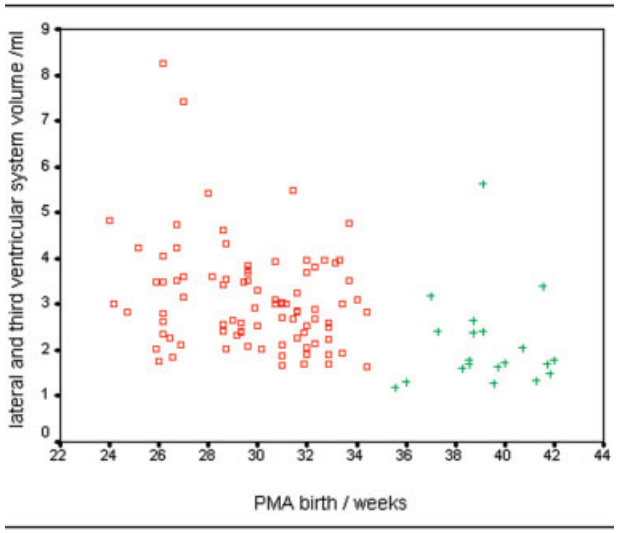

Fig 4. Prematurity and ventricular system volume at term equivalent age. Lateral and third ventricular system volumes of preterm infants at term equivalent age (squares) *and term control infants* (crosses). [*Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com*]

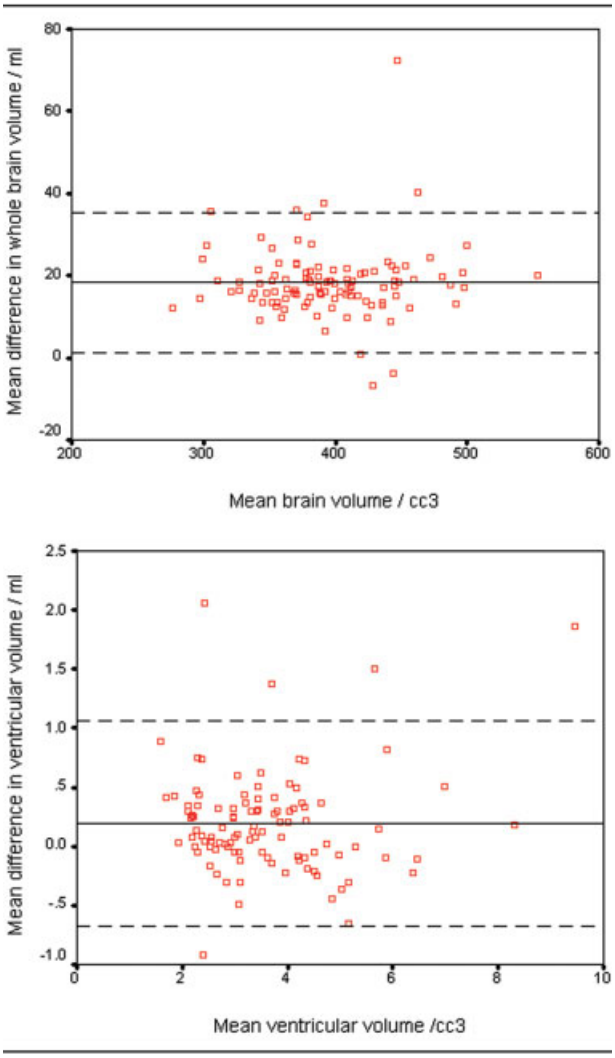

Fig 5. Agreement between region-of-interest measurements calculated from different templates. The solid line *is the mean difference, and the* hashed lines *are the limits of agreement (mean ± 2 standard deviations). For whole-brain tissue (A), the mean difference was 18.34ml with limits of agreement of 1.31 to 35.37ml, and for the ventricular system (B), the mean difference was 0.19ml with limits of agreement of −0.68 to 1.07ml. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]*

increased volume of the lateral and third ventricular system. The infants did not have cerebral lesions typically associated with impaired CSF dynamics; we speculate that this is a structural consequence of abnormal white matter development. There was no detectable increase in occipito-frontal circumference (OFC) among the preterm infants at term, which probably reflects the lower order of magnitude of change in this compartment relative to the entire intracranial and extracranial volume that contributes to the OFC measurement.

There are limitations to the approach that we used. A single image template has the advantage of enabling visualization of anatomic correspondence in a common coordinate system, but there is bias inherent to the template space, which is manifest as a dependence of volume calculations on the anatomy of the template image. We evaluated the magnitude of this effect for the ROIs studied (see Fig 5), and found the mean difference in brain volume attributable to performing the procedure using different templates was 18.34ml (95% confidence interval, 1.31–35.37ml). This could reflect differences in label definition between the two templates caused by normal structural variability between individuals, and/or error associated with the label propagation procedure that was not detectable on our qualitative assessment of segmentation and registration accuracy. We conclude that the principal utility of the technique lies in the analysis of population differences with respect to a common reference, rather than determining the volume of a ROI for an individual. Construction of the ideal template (representing the average shape of the population) is currently a subject of research, and in the absence of a published neonatal brain template, using a single representative subject is the best approach for defining a common coordinate system from which to make group comparisons.

The unambiguous tissue boundaries of the ROIs studied here facilitated visual assessment of the transformed label for accuracy. However, segmentation of ROIs with lower contrast between adjacent structures and the subsequent evaluation of propagated labels is challenging; the use of T2-weighted volume data could help to inform this process. Finally, there are errors associated with all registration processes, and these may vary in different regions of the brain volume,[18] so this approach cannot be applied to all brain structures without a stringent assessment of registration accuracy for the specific ROI.

Conclusions

We compared ROI volumes between groups and demonstrate that, in the absence of specific risk factors for abnormal brain growth, preterm birth per se is not associated with failure in global brain growth in the neonatal period. However, infants with prolonged supplementary oxygen requirements are susceptible to attenuated brain growth, as well as somatic growth.

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