Region-specific growth restriction of brain following preterm birth

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Regional brain sizes of very-preterm infants at term-equivalent age differ from those of term-born peers, which have been linked with later cognitive impairments. However, dependence of regional brain volume loss on gestational age has not been studied in detail. To investigate the spatial pattern of brain growth in neonates without destructive brain lesions, head MRI of 189 neonates with a wide range of gestational age (24–42 weeks gestation) was assessed using simple metrics measurements. Dependence of MRI findings on gestational age at birth (Age\textsubscript{birth}) and the corrected age at MRI scan (Age\textsubscript{MRI}) were assessed. The head circumference was positively correlated with Age\textsubscript{MRI}, but not Age\textsubscript{birth}. The bi-parietal width, deep grey matter area and the trans-cerebellar diameter were positively correlated with both Age\textsubscript{birth} and Age\textsubscript{MRI}. The callosal thickness (positive), atrial width of lateral ventricle (negative) and the inter-hemispheric distance (negative) were exclusively correlated with Age\textsubscript{birth}. The callosal thickness and cerebral/cerebellar transverse diameters showed predominant dependence on Age\textsubscript{birth} over Age\textsubscript{MRI}, suggesting that brain growth after preterm-birth was considerably restricted or even became negligible compared with that \textit{in utero}. Such growth restriction after preterm birth may extensively affect relatively more matured infants, considering the linear relationships observed between brain sizes and Age\textsubscript{birth}.

During the last decade, magnetic resonance imaging (MRI) scans at term-equivalent age have been established as a reliable prognostic biomarker of motor, verbal and cognitive outcomes in preterm infants\textsuperscript{1–3}. In addition to the detection of overt destructive brain injury, evaluation of subtle brain injury, represented by diffuse-excessive high signal intensity and mild brain atrophy, has been established using a composite assessment scale for both white matter and grey matter\textsuperscript{4}. For more objective assessment of regional brain sizes, quantitative analysis of brain MRI has been developed. Three-dimensional volumetric analysis gives direct measures of regional brain volume\textsuperscript{4,5}, where reduced brain volume in preterm infants is indicative of adverse neurodevelopmental outcomes up to 2 years of age\textsuperscript{6,7}. A more recent study using the same technique demonstrated that low brain volumes observed in very-preterm infants are associated with long-term functional outcomes of up to 7 years old\textsuperscript{8}. Even without specialised software and expertise, reliable regional brain sizes can be obtained using simple biometric analysis\textsuperscript{9}. Although a relatively greater inter-observer variability was noted for the measurement of fluid spaces\textsuperscript{9}, Kidokoro and colleagues reported that the predictive value of cognitive development may be improved by incorporating one-dimensional measurements of regional brain sizes into the aforementioned composite MRI scoring system\textsuperscript{10}.

Brain sizes obtained using simple metric analysis in the parietal and frontal lobes, and cerebellum show consistent dependences on the corrected age of preterm infants at the MRI scan (dependence on gestational age at birth not assessed)\textsuperscript{9}. This finding suggests that brain growth after preterm birth at least mimics that within the uterus. However, previous comparative studies showed a significant reduction of regional brain volume in very-preterm infants compared with their full-term peers when assessed at term-equivalent age, suggesting a difference between intra- and extra-uterine patterns of brain growth\textsuperscript{11–13}.

Important questions are raised whether regional brain volume loss is specific to very-preterm infants or is extensively observed in a gestational-age dependent manner, and whether smaller regional brain sizes at term represent the consequence of permanent brain injury or a temporary delay in growth that can eventually catch up.
However, the spatial patterns of altered regional brain growth and their mechanism have not been fully elucidated especially in moderately- and late-preterm infants.

To investigate spatial growth patterns of the brain in preterm infants, we performed an MRI study using simple metrics measurement. Instead of comparing MRI findings between several groups of preterm and term infants, we assessed the dependences of regional brain sizes on the gestational age at birth (Agebirth) and corrected age at the MRI scan (AgeMRI) in a single cohort of newborn infants spanning a wide range of gestational ages. This was based on an assumption that, in specific brain regions, where brain growth following preterm birth is substantially restricted, regional brain sizes may depend on Agebirth rather than AgeMRI.

Results

Clinical characteristics. Five newborn infants were diagnosed with congenital cerebral anomalies (congenital hydrocephaly, n = 1; major chromosomal abnormality, n = 2; and congenital cytomegalovirus infection, n = 2), and 11 newborn infants showed severe, destructive cerebral lesions (intra-ventricular haemorrhage ≥ grade 3, n = 5; cerebral venous or arterial infarction, n = 3; and cystic encephalomalacia due to severe neonatal encephalopathy, n = 3). Of these 16 newborn infants, moderate to severe brain injury in white matter, cortical grey matter, deep grey matter, cerebellum and the whole brain was observed in 10 (62.5%), 2 (12.5%), 7 (43.8%), 7 (43.8%) and 10 (62.5%) newborn infants, respectively. These subjects were excluded from further analysis.

Subsequently, MRI findings were assessed for 189 preterm and term infants, whose Agebirth and AgeMRI were 31.8 ± 4.1 (range, 22.6–42.0) weeks and 38.9 ± 1.6 (range, 36.3–44.3) weeks, respectively (Table 1). AgeMRI was positively correlated with Agebirth ($p = 0.021$). Antenatal and/or postnatal glucocorticoids were used in 43.3% and 15.3% of the population, respectively; 66.1% of the newborn infants were born via caesarean section; mechanical ventilation was required in 49.7%.

MRI findings. Moderate to severe brain injury in white matter, cortical grey matter, deep grey matter, cerebellum and the whole brain was observed in 15 (7.9%), 1 (0.5%), 0 (0.0%), 8 (4.3%), and 4 (2.1%) newborn infants, respectively. These subjects were excluded from further analysis.

Subsequently, MRI findings were assessed for 189 preterm and term infants, whose Agebirth and AgeMRI were 31.8 ± 4.1 (range, 22.6–42.0) weeks and 38.9 ± 1.6 (range, 36.3–44.3) weeks, respectively (Table 1). AgeMRI was positively correlated with Agebirth ($p = 0.021$). Antenatal and/or postnatal glucocorticoids were used in 43.3% and 15.3% of the population, respectively; 66.1% of the newborn infants were born via caesarean section; mechanical ventilation was required in 49.7%.

MRI findings. Moderate to severe brain injury in white matter, cortical grey matter, deep grey matter, cerebellum and the whole brain was observed in 15 (7.9%), 1 (0.5%), 0 (0.0%), 8 (4.3%), and 4 (2.1%) newborn infants, respectively (Supplemental Table 1). Moderate to severe injury in the whole brain was exclusively observed in very-preterm infants <28 weeks gestation.

Dependence of MRI findings on gestational and corrected age. The bi-parietal width, deep grey matter area and the trans-cerebellar diameter showed positive linear correlations with both AgeMRI (all $p < 0.001$), but not Agebirth (Supplemental Table 2). The severity of brain injury for the white matter ($p < 0.001$), cortical grey matter ($p = 0.002$), cerebellum ($p < 0.001$) and the whole brain ($p < 0.001$) was linearly associated with AgeMRI, but not Agebirth. The bi-parietal width, deep grey matter area and the trans-cerebellar diameter showed positive linear correlations with both AgeMRI (all $p < 0.001$), which were most prominent between the bi-parietal width and AgeMRI (Table 2, Fig. 1 and Supplemental Fig. 1; see Supplemental Table 3 for findings from exploratory analysis, which assessed the dependence of regional brain sizes on other clinical variables). The callosal thickness for all three regions (positive) (all $p < 0.001$), atrial width of lateral ventricle (negative) ($p = 0.001$) and the

| Variables                                    | Mean ± SD, or number (%) |
|----------------------------------------------|--------------------------|
| Gestational age at birth (week)              | 31.8 ± 4.1               |
| <28                                          | 29 (15.3)                |
| 28 ≤ <32                                     | 58 (30.7)                |
| 32 ≤ <36                                     | 73 (38.6)                |
| 37 ≤                                         | 29 (15.3)                |
| Birth weight (g)                             | 1537 ± 709               |
| Male sex                                     | 91 (48.1)                |
| Antenatal glucocorticoid                     | 82 (43.3)                |
| Multiple pregnancy                           | 50 (26.5)                |
| Caesarean delivery                           | 125 (66.1)               |
| Intrauterine growth restriction              | 71 (37.6)                |
| Apgar score <7                               | 90 (47.6)                |
| 5 min.                                       | 29 (15.3)                |
| Duration of mechanical ventilation (day)     | 9.8 ± 17.5               |
| Chronic lung disease                         | 45 (23.8)                |
| Symptomatic patent ductus arteriosus         |                          |
| Indomethacin                                 | 49 (25.9)                |
| ligation                                     | 10 (5.3)                 |
| Enteral feeding >100 ml/kg (day)              | 7.6 ± 5.5                |
| Postnatal glucocorticoid                     | 29 (15.3)                |
| Corrected age at MRI scan (week)             | 38.9 ± 1.6               |
| Head circumference at MRI scan (cm)           | 34.2 ± 1.6               |

Table 1. Clinical characteristics of the study population. Abbreviation: SD, standard deviation.
### Table 2. Relationships between simple brain metrics and age.

| Variables                         | Mean  | SD   | r   | (95% CI) | p     | r   | (95% CI) | p     |
|-----------------------------------|-------|------|-----|----------|-------|-----|----------|-------|
| Age<sub>birth</sub>               |       |      |     |          |       |     |          |       |
| Head circumference (cm)           | 34.2  | 1.6  | 0.120 | (−0.223, 0.258) | 0.100 | 0.447 | (0.325, 0.554) | <0.001 |
| Cerebral hemisphere              |       |      |     |          |       |     |          |       |
| Bi-parietal width (mm)            | 75.4  | 6.5  | 0.611 | (0.513, 0.693) | <0.001 | 0.348 | (0.216, 0.468) | <0.001 |
| Fronto-occipital diameter (mm)    | 100.3 | 5.3  | −0.004 | (−0.147, 0.147) | 0.957 | 0.067 | (−0.076, 0.208) | 0.358 |
| Corpus callosum (thickness in [mm]) |       |      |     |          |       |     |          |       |
| Genu                              | 4.4   | 0.8  | 0.332 | (0.199, 0.453) | <0.001 | 0.139 | (−0.004, 0.276) | 0.056 |
| Body                              | 2.5   | 0.5  | 0.328 | (0.194, 0.450) | <0.001 | 0.078 | (−0.065, 0.218) | 0.287 |
| Splenium                          | 3.5   | 0.7  | 0.515 | (0.402, 0.613) | <0.001 | −0.058 | (−0.199, 0.085) | 0.426 |
| Deep grey matter                  |       |      |     |          |       |     |          |       |
| Deep-grey-matter area (cm<sup>2</sup>) | 10.9 | 0.8  | 0.252 | (0.113, 0.381) | <0.001 | 0.364 | (0.233, 0.482) | <0.001 |
| Cerebellum                        |       |      |     |          |       |     |          |       |
| Trans-cerebellar diameter (mm)    | 50.2  | 2.8  | 0.561 | (0.455, 0.652) | <0.001 | 0.483 | (0.365, 0.585) | <0.001 |
| Antero-posterior cerebellar diameter (mm) | 16.4 | 1.4  | 0.105 | (−0.038, 0.244) | 0.151 | 0.367 | (0.237, 0.484) | <0.001 |
| Fluid measures                    |       |      |     |          |       |     |          |       |
| Atrial width of Lateral ventricle (mm) | 5.1 | 1.6 | 0.123 | (0.263, 0.092) | 0.001 | 0.061 | (−0.082, 0.202) | 0.404 |
| Right                             | 6.4   | 2.1  | 0.430 | (0.207, 0.653) | <0.001 | 0.483 | (0.365, 0.585) | <0.001 |
| Mean                              | 5.8   | 1.7  | −0.232 | (−0.363, −0.092) | 0.001 | 0.061 | (−0.082, 0.202) | 0.404 |
| Thalamo-occipital distance (mm)   | 25.5  | 4.3  | −0.165 | (−0.301, −0.023) | 0.024 | −0.043 | (−0.185, 0.100) | 0.552 |
| Inter-hemispheric distance (mm)   | 1.9   | 1.1  | −0.628 | (−0.707, −0.533) | <0.001 | 0.006 | (−0.137, 0.149) | 0.936 |

### Discussion

Previous MRI studies have highlighted the poor regional brain growth of preterm infants compared with their term-born peers<sup>8,11,12</sup>. In the current study, instead of comparing brain sizes between preterm- and term-born cohorts, we assessed the dependence of brain size on Age<sub>birth</sub> and Age<sub>MRI</sub> in a single cohort of newborn infants with a spectrum of maturation stages. This was based on an assumption that, in regions where postnatal brain growth mimics that in utero, regional brain sizes primarily depend on Age<sub>MRI</sub> but not Age<sub>birth</sub>. However, we found that measures such as deep-grey-matter area and transverse diameters of the cerebrum and cerebellum depended on both Age<sub>birth</sub> and Age<sub>MRI</sub>, whereas the thickness of the corpus callosum depended exclusively on Age<sub>birth</sub>. This suggests that brain growth in these regions after preterm-birth is significantly restricted or is even negligible compared with that in utero. Considering that abnormal size of the corpus callosum and lateral ventricles are good indicators of cognitive impairment in children and adolescents born prematurely<sup>11–18</sup>, the region-specific growth patterns of the immature brain observed in our study may represent the irreversible consequence of adverse extra-utero conditions for the brain of preterm infants. In addition, given the linear relationships observed between brain sizes and Age<sub>birth</sub> in some regions, growth restriction of the brain is a continuum, which is not specific to extremely- and very-preterm infants, but may affect even more matured newborn infants.

Despite the established relationship between callosoal size and neurodevelopmental outcomes following preterm birth<sup>11–18</sup>, the mechanism of altered callosal growth remain largely unknown. Volume loss in the corpus callosum of preterm-born children is most evident in the posterior region<sup>14,15,17,19</sup>. The rudimentary corpus callosum originates in the anterior body at the end of the first trimester, and expands towards remaining parts during development<sup>20</sup>. Similarly, the genu and the body show a consistent increase in thickness during pregnancy<sup>21,22</sup>,
Figure 1. Relationships between regional brain sizes and age. Regional brain sizes are plotted against gestational age at birth (Age\textsubscript{birth}) (A,C,E,G) and corrected age at MRI scan (Age\textsubscript{MRI}) (B,D,F,H) with 95% confidence ellipse. The bi-parietal width (A,B) and deep-grey-matter area (E,F) were positively correlated with both Age\textsubscript{birth} and Age\textsubscript{MRI}. The thickness of the splenium of the corpus callosum and inter-hemispheric distance were correlated with Age\textsubscript{birth}, but not Age\textsubscript{MRI} (C,D,G,H).
whereas the splenium shows the maximum growth in thickness between 18 and 26 weeks gestation, which slows down after 28 weeks gestation\(^2^2\). Preterm infants, even with their favourable clinical course, experience dramatic environmental changes at birth, which are followed by a prolonged period with stressful procedures, malnutrition, and separation from the mother. The burden of such adverse events, experienced just when the splenium is supposed to grow most rapidly, might be responsible for altered callosal growth after preterm birth.

In preterm infants, increased cerebrospinal fluid space is persistently observed even in adolescence\(^1^7,2^3\). Ventriculomegaly without preceding severe intra-ventricular haemorrhage is known as an independent predictive marker for adverse neurodevelopmental outcomes in preterm infants\(^1^8,2^4,2^5\). Interestingly, the thalamo-occipital distance of the lateral ventricle, suggesting that the brain size along the longitudinal axis might be determined by both physiological postnatal growth and pathological dilatation of ventricles. This characteristic balance of cerebral growth between the longitudinal and transverse axes may explain the scaphocephalic head shape commonly observed in preterm infants. It is widely accepted that scaphocephaly in healthy preterm infants does not influence deep brain structures\(^2^9\). However, the current findings suggest that excessive scaphocephaly might be indicative of altered brain volume and structure subsequent to preceding brain injury. In addition, given that approximately 51% of the head circumference can be explained by the fronto-occipital diameter (based on

|                         | BPW       | FOD       | gCC       | bCC       | sCC       | DGMA      | TCD       | APCD      | AWLV      | TOD       | HHD       |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Head circumference      | 0.418     | 0.713     | 0.025     | 0.154     | 0.279     | 0.574     | 0.585     | 0.560     | 0.183     | 0.397     | 0.029     |
| (0.293, 0.529)         | (0.635, 0.777) | (0.012, 0.290) | (0.142, 0.406) | (0.470, 0.662) | (0.488, 0.672) | (0.454, 0.651) | (0.041, 0.317) | (0.270, 0.511) | (0.114, 0.171) |
| Bi-parietal width       | −0.043    | 0.176     | 0.201     | 0.336     | 0.355     | 0.674     | 0.193     | −0.231    | −0.173    | −0.207    |           |
| (−0.185, 0.100)        | (0.034, 0.311) | (0.060, 0.334) | (0.203, 0.457) | (0.324, 0.474) | (0.588, 0.745) | (0.052, 0.327) | (−0.362, −0.091) | (−0.308, −0.031) | (−0.340, −0.066) |
| Fronto-occipital diameter | (−0.144, 0.142) | (−0.082, 0.202) | (0.049, 0.324) | (0.205, 0.459) | (0.107, 0.376) | (0.361, 0.582) | (0.158, 0.419) | (0.562, 0.583) | (0.190, 0.409) |
| Thalamo-occipital       | 0.448     | 0.329     | 0.172     | 0.232     | 0.018     | −0.049    | −0.010    | −0.174    |           |           |           |
| distance (TOD)          | (0.326, 0.555) | (0.195, 0.451) | (0.030, 0.307) | (0.092, 0.363) | (−0.125, −0.160) | (−0.190, −0.094) | (−0.153, 0.133) | (−0.309, −0.032) |           |           |
| Genu of the corpus callosum (gCC) | 0.453     | 0.173     | 0.253     | 0.084     | −0.065    | 0.043     | −0.272    |           |           |           |           |
| (0.332, 0.560)         | (0.031, 0.308) | (0.114, 0.382) | (−0.059, 0.224) | (−0.078, 0.078) | (−0.066, 0.078) | (−0.066, 0.100) | (−0.399, −0.134) |           |           |           |
| Body of the corpus callosum (bCC) | 0.255     | 0.363     | 0.153     | −0.084    | 0.057     | −0.384    |           |           |           |           |           |
| (0.117, 0.384)         | (0.232, 0.481) | (0.010, 0.289) | (−0.224, −0.059) | (−0.086, 0.198) | (−0.499, −0.255) |           |           |           |           |           |
| Splenium of the corpus callosum (sCC) | 0.506     | 0.352     | 0.178     | 0.237     | 0.048     |           |           |           |           |           |           |
| (0.392, 0.605)         | (0.220, 0.471) | (0.036, 0.313) | (0.098, 0.367) | (−0.189, 0.095) |           |           |           |           |           |           |
| Deep-grey-matter area (DGMA) | 0.356     | −0.034    | 0.064     | −0.164    |           |           |           |           |           |           |           |
| (0.225, 0.475)         | (−0.176, 0.109) | (−0.079, 0.205) | (−0.030, −0.022) |           |           |           |           |           |           |           |
| Trans-cerebellar diameter (TCD) | 0.105     |           |           |           |           |           |           |           |           |           |           |
| Antero-posterior cerebellar diameter (APCD) | 0.065     | 0.143     | 0.011     |           |           |           |           |           |           |           |           |
| (0.078, 0.206)         | (0.000, 0.280) | (0.132, 0.153) | (0.002, 0.282) |           |           |           |           |           |           |           |
| Atrial width of Lateral ventricle (AWLV) | 0.533     | 0.145     |           |           |           |           |           |           |           |           |           |
| (0.422, 0.628)         | (0.002, 0.282) |           |           |           |           |           |           |           |           |           |
| Thalamo-occipital distance (TOD) | 0.103     |           |           |           |           |           |           |           |           |           |           |
|                         | (−0.040, 0.242) |           |           |           |           |           |           |           |           |           |           |

Table 3. Correlation coefficient and 95% confidence interval between regional brain sizes. Associations between regional brain sizes were assessed with Pearson correlation, using the Fisher Transformation to calculate the 95% confidence intervals. Abbreviation, IHD, inter-hemispheric distance.
the observed \( r^2 = 0.51 \) between these variables), careful interpretation is required to assess the brain growth using the head circumference in preterm infants.

Although no correlation was observed between the bi-parietal width and the fronto-occipital diameter, the longitudinal and transverse diameters of the cerebrum were tightly correlated with those of the cerebellum. The transverse diameters of the cerebrum and the cerebellum both showed predominant correlations with \( A\text{ge}_{\text{birth}} \) despite significant differences in the environment between the supra- and infra-tentorial spaces. This suggests the presence of a common mechanism causing the growth restriction of the cerebrum and cerebellum along the transverse axis in preterm infants. Considering that the sideways head position is generally preferred for preterm infants during intensive care, gravity may predominantly affect brain growth towards the transverse axis of the brain after birth. This may influence the growth pattern of the immature brain, as studies in developing rat demonstrated that exposure to hyper-gravity environment causes various types of cerebellar injury, including Purkinje cell loss and subsequent reduction in cerebellar volume.

In the current study, the severity of brain injury assessed using the composite MRI scores depended on \( A\text{ge}_{\text{MRI}} \), where \( A\text{ge}_{\text{MRI}} \) is already incorporated within the scoring system. Given that we did not include newborn infants with major cerebral lesions in the current cohort, preterm birth itself was likely to be the primary independent variable of non-destructive brain injury at term. Recently, the incidence of moderate to severe neurodevelopmental impairments in preterm infants has decreased, in part due to the reduced incidence of destructive brain lesions such as intra-ventricular haemorrhage and periventricular leukomalacia. Hence, early diagnosis of non-destructive brain lesions would be important for the prevention of subsequent cognitive impairment. Comprehensive assessment of brain growth and maturation at term using qualitative measures, regional brain size and other quantitative markers may allow more precise detection of injury.

We excluded newborn infants with apparent destructive brain lesions. This led to uncertainty regarding typical brain growth in extremely-preterm infants, who often develop severe cerebral lesions. We did not use volumetric analysis in our current study. While volumetric data are easy to translate, their use in clinical practice remains limited because of additional requirements for software and expertise for data processing. The present study and others suggest the benefit of a simple metric approach, which is reliable, reproducible and readily available in clinical practice. Future studies should incorporate other quantitative magnetic resonance biomarkers including apparent diffusion coefficients, fractional anisotropy and T2-relaxation time.

We found that the size of specific brain regions, including the thickness of the corpus callosum and the transverse diameter of the cerebrum, depended on \( A\text{ge}_{\text{birth}} \), but not \( A\text{ge}_{\text{MRI}} \), suggesting a difference between intra- and extra-uterine brain growth after preterm birth. The linear relationships observed between brain sizes and \( A\text{ge}_{\text{birth}} \) in these regions suggested that regional brain growth restriction is not specific to very-preterm infants, but is likely to affect even more matured infants in a gestational-age dependent manner. Further studies are required to elucidate the mechanism and direct consequence of brain growth patterns specific to preterm infants. Serial cranial ultrasound sonography might help delineate the temporal process of region-specific growth pattern in these infants.

**Methods**

This study was conducted in compliance with the Declaration of Helsinki under the approval of the Ethics Committee of Kurume University School of Medicine. Informed parental consent was obtained for each participating newborn infant before enrolment into this study.

**Study population.** Two hundred and five newborn infants, who were admitted to a tertiary neonatal intensive care unit of Kurume University Hospital (Kurume, Fukuoka, Japan) immediately after birth and underwent MRI scans between 36 and 44 weeks corrected age during the period from September 2007 to March 2012, were enrolled into the study. In this unit, head MRI is routinely obtained (i) for preterm infants <34 weeks gestation, and (ii) for near term- and term-born infants with either neurological abnormality, clinical details suggestive of perinatal hypoxia–ischaemia, respiratory failure, major congenital anomaly, chromosomal aberration, or metabolic disease, after the clinical condition is stabilised.

**MRI study.** A 3-Tesla Signa HDxt scanner (GE Medical Systems, Milwaukee, WI, USA) was used to obtain head MRI with a three-dimensional brain volume imaging (BRAVO) for T1-weighted images (TR 11 ms; TE 5 ms; slice thickness 1 mm; matrix 384 x 224, interpolated 512 x 512; field of view 200 x 200 mm; both coronal and sagittal sections reconstructed from axial slices) and a fast spin echo imaging for T2-weighted images (TR 5000 ms; TE 87 ms; slice thickness 4 mm; matrix 384 x 224, reconstruction matrix 512 x 512; field of view 200 x 200 mm). Diffusion-tensor imaging was also obtained, information of which was not used in the current study. MRI was visually inspected for its quality, and was assessed using an established MRI scoring system for brain maturation, growth, and injury. This system gives 0–4 stepwise scores over 13 items, according to the qualitative and quantitative findings of the brain on T1- and T2-weighted images, so that composite scores are calculated for the white matter (range, 0–17), cortical grey matter (0–9), deep grey matter (0–7) and cerebellum (0–7). The MRI was categorised as having no, mild, moderate, or severe injury according to the regional and global composite scores (Supplemental Fig. 2). Simple metric measures were obtained for T2-weighted coronal images (bi-parietal width, trans-cerebellar diameter, interhemispheric distance, and atrial width of the lateral ventricle), T1-weighted sagittal images (thalamo-occipital distance of the lateral ventricle, thickness of the corpus callosum at the genu, mid-portion of the body, and splenium, and antero-posterior cerebellar diameter) and T2-weighted axial images (fronto-occipital diameter and deep-grey-matter area) sections (Fig. 2).
Clinical information. Clinical information for the newborn infants was obtained including intrauterine growth restriction, gestational age and body weight at birth, delivery mode, use of antenatal and postnatal glucocorticoid, duration of mechanical ventilation, postnatal age when enteral feeding exceeded 100 mL/kg, symptomatic patent ductus arteriosus requiring treatments with intravenous indomethacin (excluding prophylactic administration within 72 h of life) or surgical ligation, chronic lung disease (oxygen dependence on Day 28 and/or 36 weeks corrected age), and the body weight and head circumference on the day of the MRI scan.

Data analysis. To further understand the extra-uterine brain growth of newborn infants without major anomalies and destructive brain injury, newborn infants with congenital cerebral anomalies or destructive brain lesions (intra-ventricular haemorrhage ≥ grade 3, cerebral infarction and cystic encephalomalacia due to severe neonatal encephalopathy) were excluded from the analysis. Correlations between brain metrics, head circumference on the day of the MRI scan, severity of MRI findings on composite scores, Age\(_{\text{birth}}\) and Age\(_{\text{MRI}}\) were assessed using either Pearson's correlation coefficient or Spearman's correlation coefficient when applicable. For multiple comparisons over 11 simple brain metrics and 18 items of the composite scoring system, statistical significance was assumed for \(p < 0.0045\) and \(0.0028\), respectively (Bonferroni correction).

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Author Contributions

S.I., T.A. and O.I. designed the study protocol. S.I., R.K., M.K., M.S. and O.I. recruited study subjects and performed the MRI assessment. Y.A., S.I. and O.I. performed the statistical analyses. S.I., S.T. and O.I. contributed to interpretation of findings. S.I. drafted the initial manuscript. Y.A., R.K. and T.A. drafted the technical part of the manuscript related with MRI, and Y.A., M.K., M.S. and O.I. revised the manuscript. All authors have seen and approved the final version of this manuscript.

Additional Information

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