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Individualized characterization of volumetric development in the preterm brain

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Abstract

Objective: Preterm birth carries a significant risk for atypical development. While studies comparing group means have identified a number of early brain correlates of prematurity, they may 'average out' effects significant in a single individual. To understand better the cerebral consequences of prematurity, we created normative 'growth curves' characterizing neonatal brain development and explored the effect of preterm birth and related clinical risks in *individual* infants.

Methods: We used Gaussian process regression to map typical volumetric development in 275 healthy term-born infants, modelling for age at scan and sex. We compared magnetic resonance images of 89 preterm infants (born 28.7–34 weeks gestational age) scanned at term-equivalent age to these normative charts and related deviations from typical volumetric development to both perinatal clinical variables and neurocognitive scores at 18 months. We then tested if this approach can be generalized to an independent dataset of 253 preterm infants (born 28–31.6 weeks gestational age) also scanned at term-equivalent age but using different acquisition parameters and scanner, who were followed-up at 20 months.

Results: In both preterm cohorts, cerebral atypicalities were widespread and often multiple, but varied highly between individual infants. Deviations from normative brain volumetric development were associated with perinatal factors including respiratory support, nutrition and postnatal growth, as well as with later neurocognitive outcome.

Conclusion: Group-level understanding of the preterm brain might disguise a large degree of individual differences. We provide a method and a normative dataset for clinicians and researchers to profile the individual brain. This will allow a more precise characterization of the cerebral consequences of prematurity and improve the predictive power of neuroimaging.

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Introduction

Preterm birth (before 37 weeks gestational age, GA) affects approximately 10% of pregnancies worldwide[1]. While recent advances in neonatal medicine have greatly improved survival rates, preterm born children are at a significant risk of atypical brain development and lifelong cognitive difficulties[2] including a higher incidence of neurodevelopmental and psychiatric disorders[3,4].

Although early brain correlates of preterm birth have been identified at a group level in preterm infants[5], this vulnerable population is highly heterogenous, with individuals following diverse clinical and neurocognitive trajectories[6,7]. This variability poses a significant challenge for the statistical techniques adopted by studies that explore mean or median effects to describe the *average* abnormality observed within a group[8,9]. Despite providing valuable insights about how the vulnerable brain develops, these approaches struggle to capture atypical development fully due to their limited capacity to characterize heterogeneity and their inability to infer at the level of the individual.

To understand brain development at an individual level, offer accurate prognosis of later outcome, and study the effects of clinical risks and interventions, it is necessary to provide a personalized assessment of cerebral maturation[10]. Indeed, an unwarranted assumption that preterm birth has a homogenous effect on brain development might account for the relatively poor predictive power of neonatal MRI for later outcome, especially in the absence of major focal lesions[11,12]. Comparing individuals against robust normative data avoids the requirement to define quasi-homogenous groups in a search for effects common to the group, and offers a powerful alternative to investigate brain maturation with high sensitivity to pathology at an individual infant level[10,13,14].

In this study, we used Gaussian process regression (GPR) to create 'growth curves' of normative volumetric development using a large sample of healthy term-born infants scanned cross-sectionally within the first month of life. Analogous to the widely employed paediatric height and weight growth charts, this technique allows the local imaging features of individuals to be referred to typical variation in term-born infants while simultaneously accounting for confounds and variables such as age and sex[9]. Having established normative values for brain growth in a large group of healthy term-born infants, we quantified deviations from typical development in individual preterm infants. We investigated the heterogeneity of these deviations, and the association between individual deviations, perinatal clinical variables and later neurocognitive abilities. To test generalizability, we repeated these assessments in infants from a second large independent dataset acquired on a different MR scanner using different imaging parameters.

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Methods

Participants

This study utilised data from two neonatal cohorts. Informed written consent was given by parents prior to imaging. Pulse oximetry, temperature and heart rate were monitored throughout, and ear protection was used for each infant (President Putty, Coltene Whaledent, Mahwah, New Jersey, USA; MiniMuffs, Natus Medical, San Carlos, California, USA). All images were inspected by experienced neonatal neuroradiologists.

Developing Human Connectome Project

Infants were participants in the developing Human Connectome Project (dHCP), approved by the National Research Ethics Committee (REC: 14/Lo/1169) and were scanned during natural unsedated sleep at the Evelina London Children's Hospital between 2015 and 2019. Full details regarding the preparation of infants prior to scanning have been previously described[15]. The initial dataset consisted of 323 term-born and 100 preterm infants scanned at term-equivalent age (TEA: 37-45 weeks postmenstrual age, PMA). Exclusion criteria for the term-born infants included admission to neonatal intensive care unit or significant intracranial abnormality detected on neonatal MRI scan (including acute infarction and parenchymal haemorrhage), but not punctate white matter lesions (PWMLs), small subependymal cysts/haemorrhages in the caudothalamic notch, mildly prominent ventricles or widening of the extra-axial CSF (within normative variation). Seventeen term-born infants were excluded due to incidental findings. There were no exclusion criteria for the preterm infants, except for major congenital malformations.

Evaluation of Preterm Imaging Project

We used the data from a second preterm cohort consisting of 511 infants from the Evaluation of Preterm Imaging (EPrime, REC:09/H0707/98). Details regarding infant characteristics and preparation prior to scanning have been previously described[12]. In brief, infants born before 33 weeks GA underwent MRI between 37 and 45 weeks PMA at the neonatal intensive care unit in Hammersmith Hospital between 2010 and 2013. Infants with major congenital malformations were excluded.

MRI acquisition and preprocessing

MRI data for the dHCP were collected on a Philips Achieva 3T (Philips Medical Systems, Best, The Netherlands) using a dedicated 32-channel neonatal head coil[15]. T_2-weighted scans were acquired with TR/TE of 12s/156ms, SENSE=2.11/2.58 (axial/sagittal) with in-plane resolution of 0.8x0.8mm, slice thickness of 1.6 and overlap of 0.8mm. Images were motion corrected and super-resolution reconstructed resulting in 0.5mm isotropic resolution (full details in Makropoulos et al.[16]). MRI data collected for EPrime were acquired on a Philips 3T system using an eight-channel phased array head

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coil. T_2-weighted turbo spin echo was acquired with TR/TE of 8670/160ms, in plane resolution 0.86×0.86mm, slice thickness of □2mm with 1mm overlap.

Both datasets were preprocessed using the dHCP structural pipeline[16]. In brief, motion-corrected, reconstructed T_2-weighted images were corrected for bias-field inhomogeneities, brain extracted and segmented into 9 tissue classes using the Draw-EM algorithm[17]. Tissue labels included cerebrospinal fluid (CSF), white matter (WM), cortical grey matter (cGM), deep grey matter (dGM), ventricles (including the cavum), cerebellum, brainstem, hippocampus and amygdala. dGM was further parcellated into left/right caudate, lentiform and thalamus. Total tissue volume (TTV) incorporated all brain GM and WM volumes; total brain volume (TBV) included TTV and ventricles; and intracranial volume (ICV) included TBV and CSF (Table 1). Given the high correlation between TTV and TBV (ρ=0.98), we reported only TTV.

The quality of the preprocessing was visually evaluated to ensure no images severely affected by head motion or with poor segmentation were included. This was achieved using a scoring system detailed in Makropoulos et al[16]. In brief, we excluded images of poor quality due to severe (score 1) or significant motion (score 2) and included images with negligible motion (score 3) and no visible effects of motion (score 4) (*Suppl. Fig. 1*). The quality of the segmentation was examined in the same fashion. Images were excluded due to unsuccessful (score 1) or poor (regional errors – score 2; *Suppl. Fig. 2*) segmentation and included if there were small localised segmentation errors (score 3) or no visible errors (score 4). Following quality control, 31 term and 11 preterm dHCP infants were excluded from further analysis. In the Eprime cohort, 253 infants had MRI data not severely affected by motion and with successful preprocessing.

Table 1. Brain regions of interest, the structures they include and what global brain measures they are taken as a proportion from when calculating relative brain volumes.

Brain regions	**Brain structures included**	**Relative volume** (% from)
cortical Grey Matter (cGM)	-	TTV
White Matter (WM)	-	TTV
Cerebellum	-	TTV
Brainstem	-	TTV
Cerebrospinal fluid (CSF)	-	ICV
Ventricles	Lateral ventricles + cavum	TBV
Caudate (left/right)	-	TTV
Lentiform (left/right)	Pallidum + Putamen	TTV
Thalamus (left/right)	-	TTV
Total tissue volume (TTV)	All brain GM + WM tissue	-
Total brain volume (TBV)	All brain GM + WM tissue + ventricles	-
Intracranial volume (ICV)	All brain GM + WM tissue + ventricles + CSF	-

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Modelling volumetric development using Gaussian Process Regression

To characterize neonatal volumetric development we used GPR, a Bayesian non-parametric regression, implemented in GPy (https://sheffieldml.github.io/GPy/). GPR simultaneously provides both point estimates and coherent measures of predictive confidence for every observation which represent the distance of each individual observation from the normative group mean at that point on the developmental curve accounting for modelled covariates[9]. A Z-score was derived for every individual by estimating the difference between the predicted and the observed value normalized by the prediction uncertainty.

GPR was estimated separately for 14 brain structures (ICV, TTV, cGM, WM, cerebellum, brainstem, CSF, ventricles and left/right caudate, lentiform and thalamus; Table 1). To characterize volumetric development, we used PMA at scan and sex as predictors. Following image quality control (31 infants excluded) and exclusion of infants with incidental findings (17 infants), the final training sample comprised of 275 term-born infants. To assess the effects of preterm birth on brain volumetric development, we applied this model to 89 dHCP preterm infants scanned at TEA. To assess generalizability, we applied the same model to 253 EPrime preterm infants imaged using a different scanner and imaging parameters.

Accuracy was tested under 5-fold cross-validation stratified to cover the whole PMA range (37 to 45 weeks). The association between brain volumes and the model predictors was estimated with a combination of radial basis function, linear and white noise covariance kernels (sum kernel). Model hyperparameters were optimized using log marginal likelihood. Prediction performance was evaluated using the mean absolute error and the correlation (Spearman ρ) between the observed and the predicted values from the 5-fold cross-validation.

We characterized normative development in absolute (cm^3) and relative (%) volumes. To calculate relative volumes, we estimated the proportion of each tissue volume from TTV, the ventricles from TBV and CSF from ICV (Table 1). To investigate the effects of preterm birth, we chose to look at relative instead of absolute volumes to (i) ensure results are not driven by extreme individual differences in non-brain intracranial volume, often seen in preterm infants, (ii) partially alleviate differences in data acquisition. Furthermore, to quantify the effect of the difference in imaging spatial resolution between the dHCP and EPrime datasets, we reran the GPR models with dHCP data downsampled to 1mm isotropic resolution prior to tissue segmentation and examined the difference in (i) model means and (ii) the number of EPrime infants who deviated significantly from the predicted model mean.

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Association between perinatal clinical risks and deviations from normative development

Individual Z-scores were computed for every region and infant. To quantify extreme deviations, prior to analyses, we chose a threshold of $|Z|>2.6$ (corresponding to $p<0.005$) following the convention adopted in previous GPR analyses modelling adult brain development[8,18]. We examined the proportion of infants with volumes lying more than 2.6 standard deviations (sd) above or below the model mean (indicating the top and bottom 0.5 percent of the typical group values described hereafter as extreme *positive* or *negative* deviations).

We tested the association between these deviations and recognized perinatal clinical risks[19]. These included GA at birth, postnatal growth, birth weight Z-score, days receiving mechanical ventilation, days receiving continuous positive airway pressure (CPAP) and days receiving total parenteral nutrition (TPN, available only for EPrime). Postnatal growth was estimated as the difference between birth and scan weight Z-score calculated using the population data from the *uk90* growth charts implemented in *sitar* R package[20].

Association between deviations from normative development and later neurocognition

Bayley III Scales of Infant Development (BSID-III)[21] assessment was carried out by trained developmental paediatricians/psychologists at 18 months for the dHCP and at 20 months for EPrime. We used the composite scores for motor, cognitive and language development (mean(sd)=100(15)). Socio-economic status was defined by the Index of Multiple Deprivation (IMD), based on parents' postal address, which accounts for 38 factors including income, employment, education, health and crime, with a higher score indicating greater deprivation.

Statistical testing

Associations were examined using Spearman rho (ρ) or Mann-Whitney U test combined with Cliff's delta (*d*, ranging from -1 to 1). Statistical testing was done under Bonferroni-Holm multiple comparison corrections. Data analyses and visualization were performed in R 3.6.1 (www.r-project.org) and python 3.7 (www.python.org).

Data availability

The data collected for the dHCP will be publicly available at http://developingconnectome.org/.

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Results

The perinatal characteristics, demographics and neurocognitive outcome of the sample are presented in Table 2. On average EPrime infants were born earlier ($p<0.05$, $d=0.28$) and had lower birth weight ($p<0.05$, $d=0.19$) compared to dHCP preterm infants. They also had poorer motor ($p<0.05$, $d=0.22$) but not language ($p=0.1$) nor cognitive ($p=0.12$) skills at follow-up. There were no differences in days on CPAP between the two preterm cohorts ($p=0.57$), but on avarage dHCP preterm infants required mechanical ventilation for longer ($p<0.05$, $d=0.16$). The two preterm cohorts did not differ in PWMLs incidence ($p=0.09$) or proportion of infants with intrauterine growth restriction (IUGR, $p=0.15$).

Characterizing typical brain volumetric development during the neonatal period

First, we characterized the development of absolute brain volumes during the neonatal period. The data showed an increase in all volumes except ventricles, where no change was detected (Fig. 1A, *Suppl. Fig. 3A*). The increase was greatest in the cGM (10.4% per week, pw) and the cerebellum (9.9% pw) compared to ICV (6.1% pw), TTV (6% pw) and CSF (7% pw). Subcortical structures increased between 4 and 6% pw (caudate L:4.1%, R:4.3%; lentiform L:6.6%, R:5.3%; thalamus L:4.1%, R:4.7% pw) with smaller increases in brainstem (3.9% pw) and WM (2% pw). Mean absolute error ranged between 0.48 (cerebellum) and 0.74 (ventricles) in units of sd (*Suppl. Table 1*). Correlation between observed and predicted values was highest in cGM ($\rho=0.72$) and cerebellum ($\rho=0.77$), and lowest in CSF ($\rho=0.33$).

The greatest changes in relative volumes were observed in cGM and WM (Fig. 1B, *Suppl. Fig. 3B*). cGM represented 36% of TTV at 37 weeks PMA, and increased to 44% at 44 weeks PMA, while the relative WM volume decreased from 48% to 38% of TTV. The relative cerebellar volume increased from 6% to 7%. The model showed an increase in the relative volume of the lentiform, a subtle decrease in caudate and no change in thalamus. We observed a slight increase in the CSF proportion of ICV and a steady decrease in the proportion that ventricles contributed to TBV. Mean absolute error ranged between 0.43 (cGM and WM) and 0.78 (CSF) in units of sd (*Suppl. Table 1*). Correlation between observed and predicted values was highest for cGM ($\rho=0.81$) and WM ($\rho=0.83$), and lowest for left/right lentiform ($\rho=0.10$ for both).

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Table 2. Perinatal, demographic and neurocognitive characteristics of the study sample.

	Term (dHCP) *n = 275*	**Preterm (dHCP)** *n = 89*	**Preterm (EPrime)** *n = 253*
GA at birth (wks), *median (IQR)*	40.3 (39.1 – 41)	31.6 (28.7 – 34)	30.3 (28 – 31.6)
PMA at scan (wks), *median (IQR)*	40.7 (39.4 - 41.4)	41.3 (40.1 - 42.7)	42.4 (41 – 43.4)
Female, No. (%)	129 (47%)	43 (46%)	115 (45%)
HC at scan (cm) *median (IQR)*	35 (33.5 - 36)	35 (33.7 - 36.1)	36.3 (35 – 37.2)
Weight at scan (kg) *median (IQR)*	3.4 (3 – 3.8)	3.1 (2.7 – 3.7)	3.4 (2.8 – 3.8)
Weight at birth (kg), *median (IQR)*	3.4 (3 – 3.7)	1.6 (1 - 2)	1.3 (1 – 1.59)
Days of ventilation, No. infants, (%) *median (IQR)**	-	45 (51%) 6 (2.5 - 20)	116 (46%) 2 (1 - 5)
Days of TPN, No. infants, (%) *median (IQR)**	-	-	160 (63%) 10 (6 - 15)
Days of CPAP, No. infants, (%) *median (IQR)**	-	63 (71%) 7 (1 - 30)	204 (81%) 11 (4 - 30)
IUGR, No. infants, (%)	-	22 (25%)	43 (17%)
PWMLs, No. infants, (%)	34 (12%)	27 (30%)	52 (21%)
Haemorrhagic Parenchymal Infarction (HPI), No. infants, (%)	-	-	11 (4%)
Periventricular leukomalacia (PVL), No. infants, (%)	-	-	8 (3%)
BSID-III, No infants (%)	222 (81%)	65 (73%)	237 (94%)
Motor, *median (IQR)*	103 (97 - 107)	100 (94 – 107)	95 (85 - 100)
Language, *median (IQR)*	97 (88 - 106)	97 (86 - 106)	91 (79 - 103)
Cognition, *median (IQR)*	100 (95 - 105)	100 (90 - 105)	95 (88 - 103)
IMD, *median (IQR)*	28.2 (17.6 – 36.8)	17.5 (8.9 – 29.6)	17.7 (10.8 – 29)

GA – Gestational age at birth; IQR – interquartile range; PMA – Postmenstrual age at scan; HC – head circumference; TPN – total parenteral nutrition; CPAP – continuous positive airway pressure; IURG – intrauterine growth restriction; PWMLs – punctate white matter lesions; BSID-III – Bayley Scales of Infant Development III; IMD – Index of Multiple Depreivation. Missing data: Birth HC – 11 preterm infants; birth weight - 1 preterm. TPN data were not available for dHCP preterm infants. *median (IQR) calculated only for infants on ventilation/CPAP/TPN.

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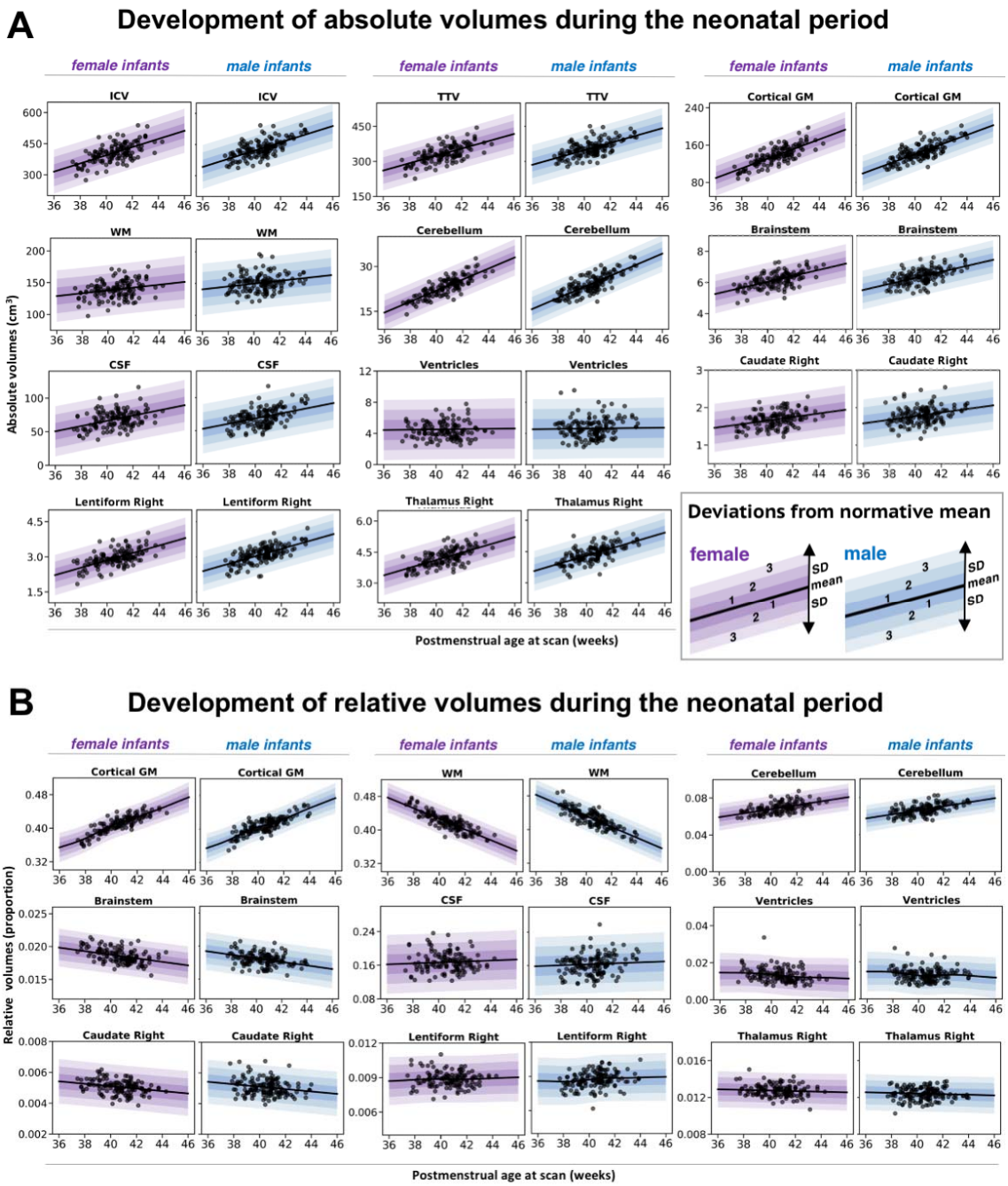

Figure 1. Normative modelling of volumetric development during the neonatal period. The model means for both female and male term infants are shown in purple and blue respectively, together with ±1, ±2 and ±3 standard deviations from the model means for absolute (A) and relative (B) volumes (tissue volumes represented as a proportion from TTV, ventricles from TBV and CSF from ICV). For subcortical structures we show growth curves only for right structures (left structures are shown in *Suppl. Fig. 3*).

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Image resolution and volumetric development

Overall, the majority of observations in both dHCP and EPrime preterm infants fit within 2.6 sd of the term-born model mean with good agreement between the two studies (Fig. 2A). Differences were most profound in fluid-filled structures, likely attributable to partial voluming of high T_2 signal CSF. In agreement, when compared to the models built using the original dHCP resolution of 0.5mm, the matched 1mm resolution GPR models showed a mean shift (increase) *only* for the CSF and ventricular volumes (Fig. 2B; *Suppl. Fig. 4 and 5*). As a result, when using the lower resolution growth charts the proportion of extreme positive deviations in the EPrime decreased from 53% to 29% for CSF and from 44% to 32% for ventricles (Fig. 2C). Changes in the proportion of extreme deviations associated with image resolution for the rest of the brain structures were more subtle. Unless stated otherwise, data were presented for the 0.5mm resolution models.

Infants with reduced total tissue volumes suffered more extreme prematurity

Six dHCP preterm infants (7%) and eight EPrime (3%) infants showed extreme negative deviations in TTV (Fig. 2), all of which (except one EPrime infant) were born at GA<30 weeks and weighed less than 1 kg at birth. Significantly reduced TTV was accompanied by enlarged CSF and ventricles (dHCP: 3/6; EPrime: 7/8). Four infants (dHCP: 1/6; EPrime 3/8) also had associated reduction in cerebellar volumes. Further three preterm infants (dHCP: 1/6; EPrime 2/8) had associated reduction in the thalami, bilaterally. All infants required oxygen support after birth. Infants who had TTV 2.6 sd above the model mean (dHCP: 4 (5%); EPRIME: 18 (7%)), were born GA>30 weeks and had no incidental findings, other than PWMLs, and short need for oxygen support and TPN after birth.

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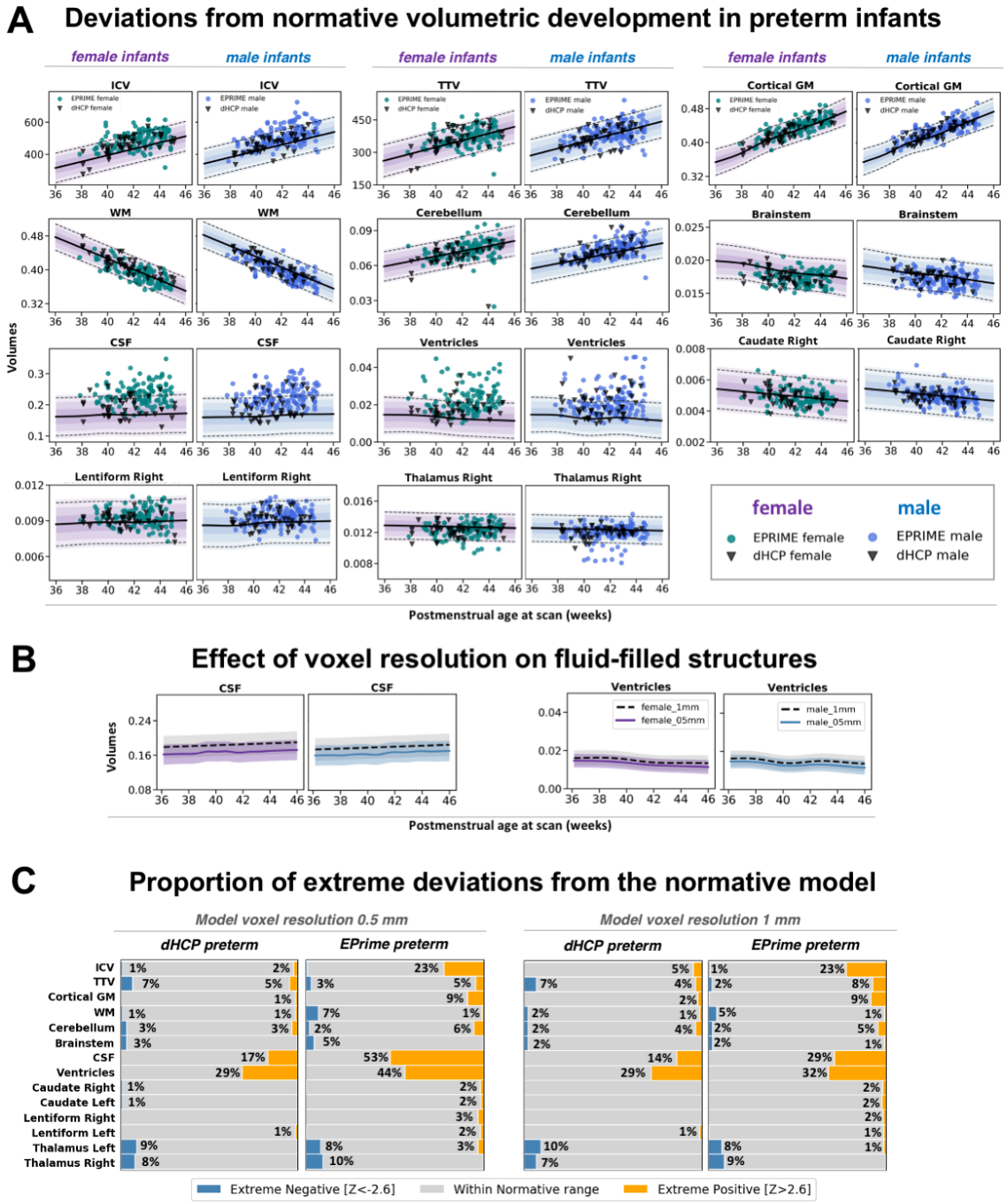

Figure 2. Characterizing the effects of preterm birth on the developing brain. (A) Deviations from normative volumetric development in preterm infants. Observations for individual preterm infants from both dHCP and EPrime cohorts are shown with model means for both female and male term-born infants together with ±1, ±2 and ±3 standard deviations. Intracranial brain volume (ICV), total brain volume (TBV) and total tissue volume (TTV) are in cm^3; cGM, WM, cerebellum, brainstem and subcortical structures shown as a proportion from TTV; CSF from ICV and ventricles from TTV. Horizontal --- lines show Z > |2.6|, the threshold used to define extreme deviations. The growth curves for the ventricles show data within 10 sd from the mean, full range is shown in Fig 5 and discussed below. **(B)** Mean differences in fluid filled structures between GPR models build using 0.5mm and 1mm

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imaging resolution. **(C)** Proportion (%) of extreme deviations from the normative model in preterm infants. Extreme negative deviations (Z < -2.6) are depicted in blue, while extreme positive deviations (Z > 2.6) are shown in orange.

Infants who showed deviations in thalamic volume also had PWMLs

In the dHCP preterm sample, all eight infants with extreme negative thalamic deviations had PWMLs, seven out of eight had multiple lesions. Four out of these seven infants had lesions involving the corticospinal tract (Fig. 3). Seven out of the eight infants were on CPAP, but none of them for a long period of time (five infants<4 days; one infant 11 days; one infant 18 days) and all seven did not require ventilation. In six out of the eight cases, extreme deviations in thalamic volumes were isolated findings with no other deviations in brain volumes. In one infant this was accompanied by overall brain alterations including reduced TTV and cerebellar volume and increased CSF. This infant had bilateral cystic lesions in the thalamus and was on ventilation for 6 days and CPAP for 11 days. In one infant, reduced thalamic volumes were accompanied by increased CSF. None of these infants had a birthweight of less than 1kg.

In the EPrime cohort 17 infants had bilateral reduced thalamic volume and 10 had unilateral extreme deviations (with structure in the other hemisphere close to but not reaching Z<-2.6). 78% of these infants had PWMLs compared to 16% incidence in the rest of the sample. Furthermore, overall across the whole cohort, infants with PWMLs had significantly reduced left (Cliff's d=0.56) and right (Cliff's d=0.53) thalamic volumes, compared to infants without (both $p<0.05$). In the EPrime study, infants with reduced thalamic volumes, often had CSF or ventricular volumes significantly bigger than the normative values for their age. In seven infants, this was associated with periventricular leukomalacia and in a further two, with haemorrhagic parenchymal infarction.

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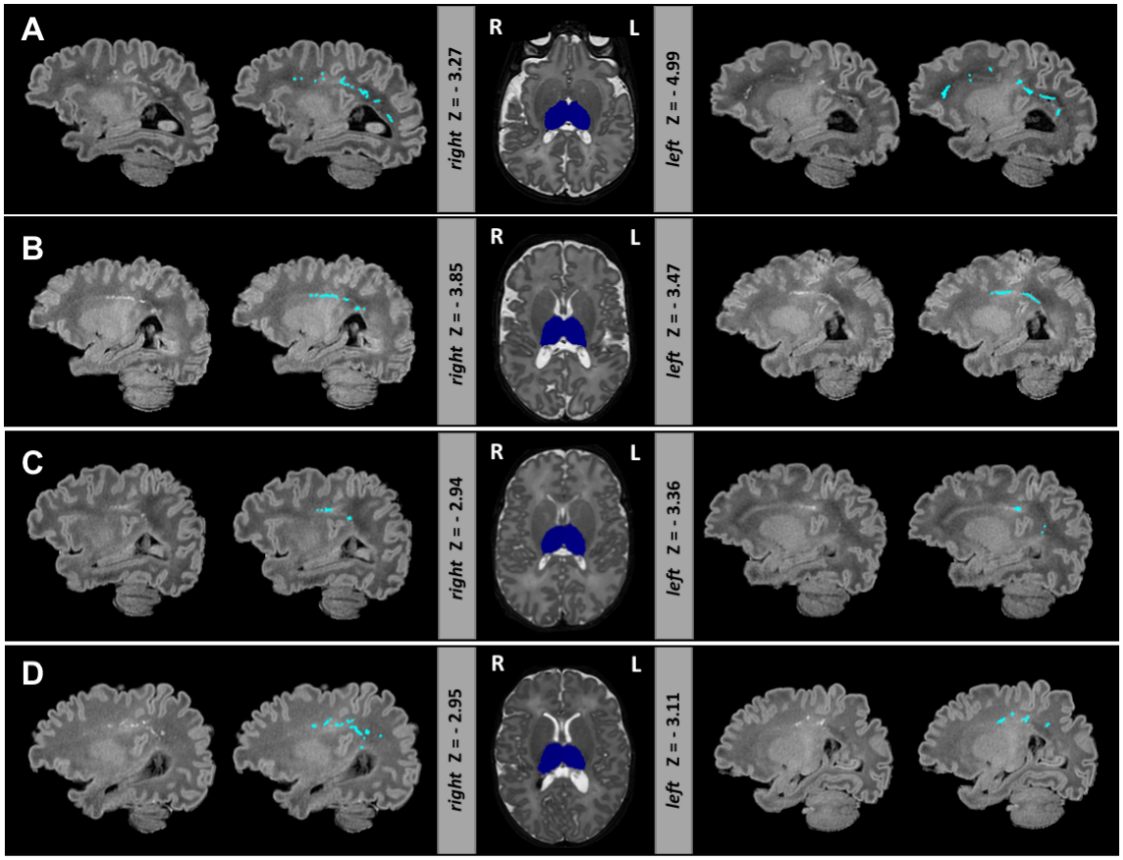

Figure 3. Extreme negative deviations in thalamic volume were often accompanied by punctate WM lesions in the preterm brain. Depicted are four infants (A-D) with bilateral thalamic volumes significantly below the model mean. Thalamic segmentation (dark blue) is overlaid onto the T_2-weighted images. Raw T_1-weighted images are shown with and without the manual outlined punctate WM lesions (light blue). Note T_1-weighted images were not used in the preprocessing but are shown here due to better contrast for detecting PWMLs.

Infants with extreme deviations in cerebellar volume have poor outcome

Significant reductions in cerebellar volumes (Z<-2.6) were accompanied by increased ventricular volume in all infants and by CSF widening in the majority of infants (dHCP: 2/3; EPrime: 4/5). In two infants, we observed significant cerebellar injury resulting in deviations lying more than 10 sd below the predicted mean for their age and sex. The first infant had bilateral cerebellar haemorrhage with marked parenchymal damage, resulting in atrophic brainstem and substantial cerebellar tissue loss (infant 1, Fig 4). The second infant had imaging features suggestive of likely underlying genetic condition (infant 2, Fig 4). Both infants were born extremely preterm with very low birth weight (infant 1: GA=24^{+3}, 800 grams; infant 2: GA=27^{+3}, 550 grams). Where follow-up data were available (dHCP: 1/3; EPrime: 3/5), they indicated poor cognitive outcome, more than two sd lower than the populational means. Bayley scores for the infants with marked cerebellar injury, shown in Fig 4, were 55, 71, 85 for infant 1 and 55, 59, 46 for infant 2 in the cognitive, language and motor domains, respectively, indicative of severe impairment in all domains (except the motor domain in infant 1).

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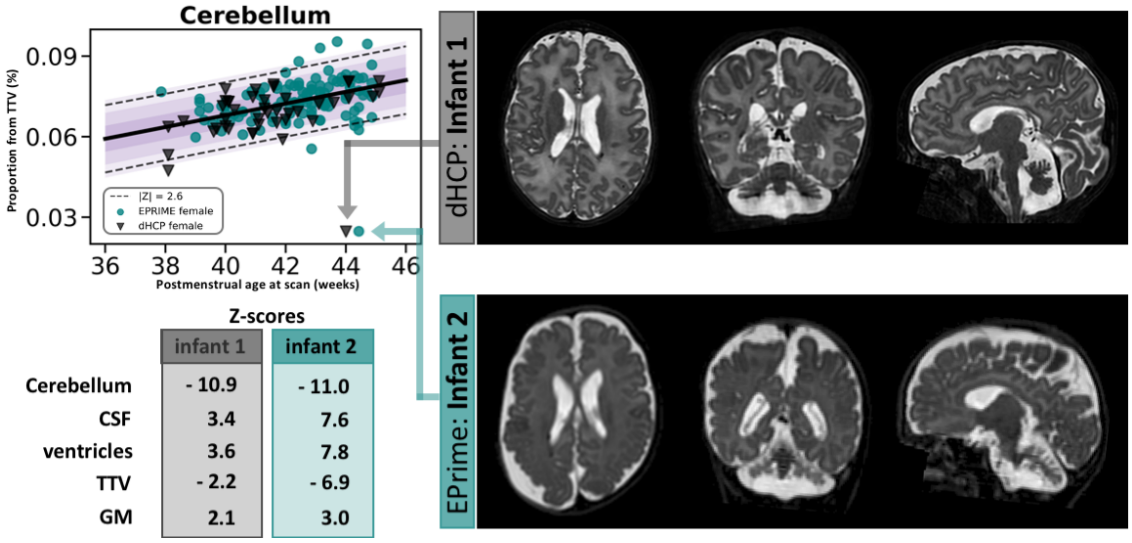

Figure 4. **Extreme deviations in cerebellar development in two preterm infants with marked cerebellar injury.** Extreme reduction in cerebellum volume during the perinatal period is associated with widespread alterations across the neonatal brain. In both cases, reduced cerebellar volume was accompanied by widening of the CSF, dilation of the ventricles and reduction in TTV. Both of these infants had poor neurocognitive follow-up.

Atypical ventricular development in preterm infants – frequent but highly heterogeneous

Widening of the fluid-filled brain structures was the most frequently observed deviation from normative development in both studies. In the dHCP 29% and 17% of the preterm infants showed extreme deviations in ventricular and CSF volumes, respectively. This number was higher in the EPrime where increased ventricles and CSF were seen in 44% and 53% of the sample with the original 0.5mm dHCP resolution and in 29% and 32% when the downsampled 1mm resolution was used. Figure 5 shows the most extreme cases where infants' ventricles were 10 sd above the model mean. These extreme deviations in ventricular volume were associated with overt focal brain injuries including haemorrhagic parenchymal infarction in infants 1,2,4 and 6, and periventricular leukomalacia in infants 5 and 7. In all these infants we also observed extreme negative deviations in TTV or thalamus and increased CSF. These infants had poor neurocognitive performance later in life (Fig 5). The figure also depicts the marked variability in ventricular development observed in preterm cohorts.

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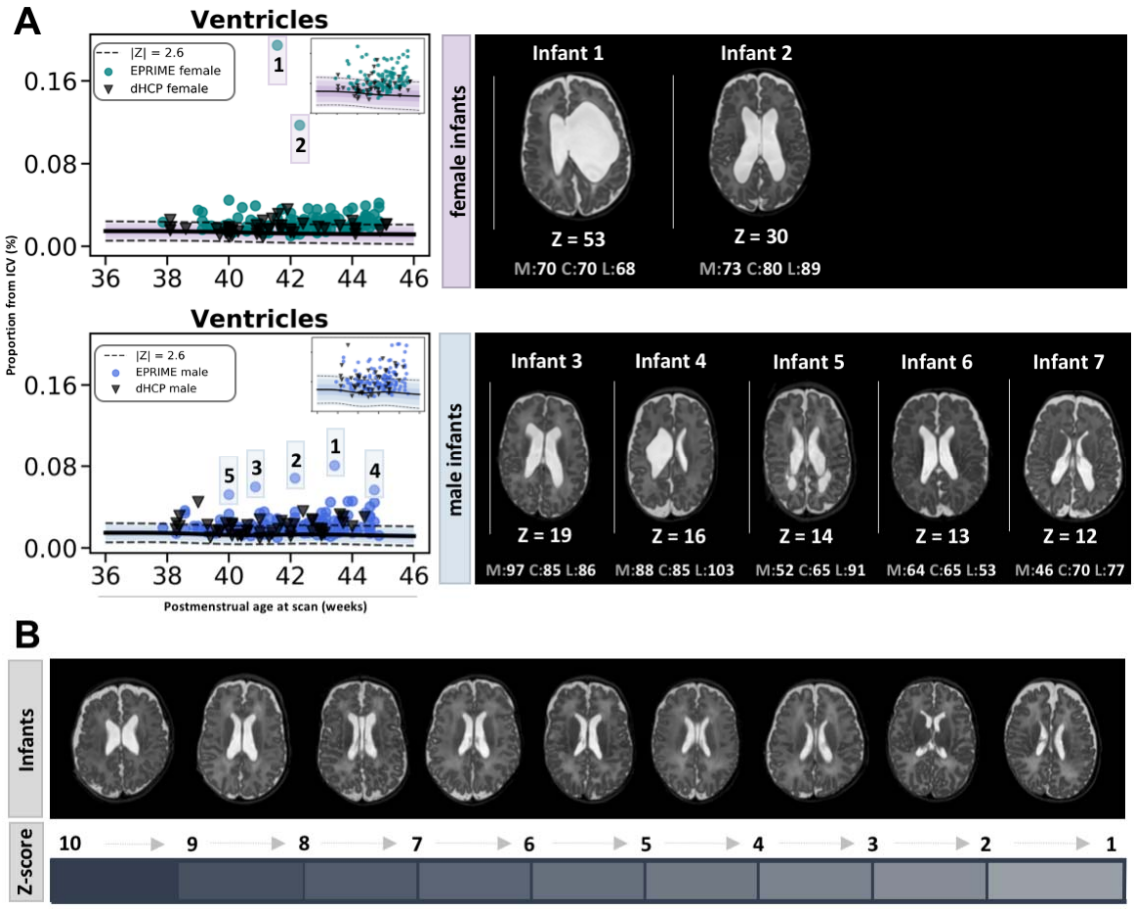

Figure 5. Capturing heterogeneity and extreme deviations in ventricular development in the preterm brain at term equivalent age. (A) Growth curves are shown for both female and male infants (in upper right corner – curves excluding the outliers, also shown in Fig 2A). The figure also depicts the T_2-weighted images for infants with ventricular volume lying 10 sd above the mean, separate for females (top) and males (bottom), together with their neurocognitive scores (M – motor, C – cognitive, L – language). Ventricular development in EPrime preterm infants is highly heterogeneous both in shape and size as illustrated in **(B)** showing ventricular volumes of various Z-scores.

Association between perinatal clinical risks and deviations from normative development

Next, we sought to replicate previous findings describing the relationship between preterm birth, related clinical risks and brain volumetric development.

In the dHCP cohort, decreased GA at birth related to reduced TTV (ρ=0.45) and increased CSF (ρ=-0.44), while in EPrime to reduced TTV (ρ=0.27) and increased ventriclar volumes (ρ=-0.26) (all at p_{corr}<0.05) (Fig 6; *Suppl. Table 2*). These associations remained even after excluding outliers (CSF Z>10). In both preterm cohorts, greater birth weight Z-score was related to bigger ICV (dHCP: ρ=0.41, EPrime: ρ=0.36) and TTV (ρ=0.40, ρ=0.37) at TEA and in EPrime alone, to reduced brainstem (ρ=-0.26) and bilateral thalamic volumes (right: ρ=-0.28, left: ρ=-0.25) (all p_{corr}<0.05, *Suppl. Table 3*). Furthermore, in EPrime, increased postnatal growth was related to increased ICV

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(ρ=0.21), CSF (ρ=0.30) and cerebellum (ρ=0.21) and reduced WM (ρ=-0.21) and left caudate (ρ=-0.18) (all p_{corr}<0.05, *Suppl. Table 3*).

In the dHCP preterm sample, longer requirement for CPAP related to smaller TTV (ρ=-0.47), and ICV (ρ=-0.37) as well as to increased CSF (ρ=0.39) and ventricles (ρ=0.37). Longer need for mechanical ventilation was associated with reduced TTV (ρ=-0.44), left caudate volume (ρ=-0.34) and enlarged CSF (ρ=0.39) and ventricles (ρ=0.42) (all p_{corr}<0.05). Consistent with this, in EPrime, longer requirement for both CPAP and mechanical ventilation were related to reduced TTV (ρ=-0.30, ρ= -0.38, respectively) and increased ventricular volume (both at ρ=0.22) (all p_{corr}<0.05). Increased number of days requiring TPN were related to reduced TTV (ρ=-0.43) and ICV (ρ=-0.35) and increased ventricles (ρ=0.25, p_{corr}<0.05) (*Suppl. Table 4*).

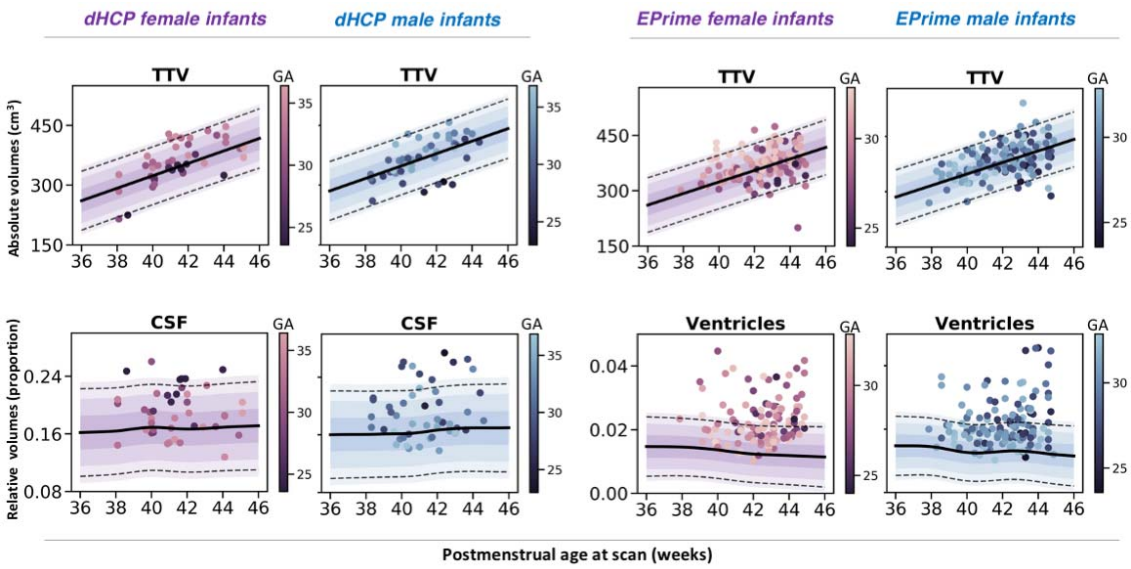

Figure 6. Association between GA at birth and deviations from normative brain growth. In the dHCP preterm sample, decreased GA at birth was related to reduced TTV and increased CSF. In EPrime, decreased GA at birth was associated with reduced TTV and increased ventricular volume. Individual preterm observations are plotted against the normative model mean for female (purple) and male (blue) term infants. The plots also show ±1, ±2 and ±3 sd from the normative model means together with --- lines indicating Z > |2.6|, the threshold used to define extreme deviations. Ventricular data are shown only for infants with volume ±10 sd from the model mean.

Association between deviations from normative development and later neurocognition

In the dHCP preterm sample, increased ventricular volume was related to poorer motor (ρ=-0.40) and language (ρ=-0.37) scores at 18 months (all p_{corr}<0.05). In EPrime, increased CSF (ρ=-0.22) and GM (ρ=-0.21), and reduced WM (ρ=0.20) were associated with poorer language abilities, while

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reduced TTV (ρ=0.20), increased CSF (ρ=-0.25) and GM (ρ=-0.20) were linked to poorer cognitive performance (all p_{corr}<0.05). While most of these association were of similar effect size in the dHCP preterm sample (language: CSF (ρ=-0.23); cognition: TTV (ρ=0.20), CSF (ρ=-0.20); cGM (ρ=-0.18)), they did not survive multiple comparison correction (*Suppl. Table 5*). Higher deprivation was linked to poorer cognitive (EPrime: ρ=-0.29, p_{corr}<0.05) and language (dHCP: ρ=-0.33; EPrime: ρ=-0.26, p_{corr}<0.05) scores but was not associated with motor outcome (*Suppl. Table 6*).

Discussion

The diverse cerebral consequences of preterm birth create significant challenges for understanding pathogenesis or predicting later neurocognitive outcomes. Focusing on individuals and their unique cerebral development can offer new insights. Here, we charted normative volumetric development during the neonatal period using a large sample of healthy term-born infants. We then characterized the effect of prematurity at an *individual* infant level, showing deviations from the normative curves consistent with previous studies but with marked variability among individuals. These individual deviations were associated with perinatal clinical risks and later neurocognition.

We previously demonstrated that GPR could be used to detect subtle white matter injury with high sensitivity[10], and to characterise the heterogeneous cerebral consequences of prematurity on the developing brain microstructure[7]. However, the present application of GPR to volumetric data offers more straightforward clinical translation. GPR provides growth curves describing normative volumetric growth and can detect and quantify atypical development[22–24]. The GPR approach generalized to a cohort of infants with brain images collected on a different MR scanner with different acquisition parameters. This information could be integrated into automatic tools that complement radiological decisions regarding infant development, and in the future it might aid personalized intervention choices[24]. GPR allows an inclusion of further covariates within the model framework, for example genetic or demographic data, and our methods and normative dataset will be freely available for clinicians and researchers to develop further personalized approaches to understanding pathogenesis, trialling interventions and defining neurocognitive prognosis for vulnerable preterm infants.

We quantified rapid postnatal brain growth consistent with previous imaging and post-mortem studies which have described dynamic changes in the size, organisation and complexity of the human brain during the perinatal period[17,25–31]. Abrupt preterm extrauterine exposure represents a significant stressor leading to widespread deviations from the normative trajectory of brain growth with a wide range of neurodevelopmental consequences[32–36]. However, these alterations are not a result of loss of

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intrauterine environment alone, but are a product of the cumulative effects of clinical and genetic factors creating individualized circumstances for every infant. GPR applied to a large normative dataset offers a powerful approach to study how prematurity shapes the brain at an individual infant level, and offers the means to capture important differences in single infants that may be missed by analysis of the means or medians of quasi-homogenous groups which 'averages-out' personal effects.

By quantifying this inter-individual variability, our analysis clarified the relationship between reduced global brain growth and preterm birth. Many but not all studies show group-level differences in total brain volume between preterm and term-born infants[33]. We report a subset of infants in both preterm cohorts that deviated significantly from normative brain tissue volumes. These infants were born very early, very small and had prolonged need for supplemental oxygen. Consistent with this, lower GA at birth, birth weight Z-score, longer requirement for respiratory support and TPN were related to reduced TTV and enlarged CSF/ventricles in both preterm cohorts. Not all extremely preterm infants had TTV deviations significantly below the model mean, which could explain the discrepancies found between previous group analyses. A personalized approach is now possible to address the important question of which protective factors or lack of adverse perinatal risks, lead to typical global brain growth in these at-risk infants.

Brain growth is neither uniform nor uniformly affected by preterm birth. The thalamus is particularly vulnerable following preterm birth[37,38]. In agreement with group mean studies reporting reduced thalamic size at TEA[38–40], we showed a subset of preterm infants with thalamic volumes significantly below the model mean ($Z<-2.6$). These infants had a high load of PWMLs, further supporting previous suggestions of a close link between thalamic development and white matter abnormalities, including a previous group analysis of the EPrime dataset[38,41,42]. The cerebellum is one of the most rapidly growing structures during the perinatal period, but altered cerebellar development in preterm infants and its relation to supratentorial brain injury is complex and poorly characterized[43–46]. We observed significant deviations in cerebellar volume in the absence of structural supratentorial injury in a small proportion of infants in both preterm cohorts. Yet, infants furthest from the normative mean had substantial cerebellar injury. These infants were extremely preterm and low-birth-weight, consistent with reports of highest incidence of cerebellar haemorrhages/infarcts in this risk subgroup[47]. The cerebellum plays a crucial role in motor and cognitive development[46], and cerebellar injury during the last trimester, especially in these extreme cases, had an adverse effect on later neurocognitive abilities.

Compared to the dHCP preterm cohort, the EPrime study comprised extremely preterm infants (GA<33 weeks), that were overall sicker during clinical care, had poorer motor outcomes, and were imaged using different acquisition parameters. These factors in combination likely underlie some of

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the differences in associations between extreme deviations and later neurocognitive scores observed between the two datatsets. The lower spatial resolution in EPrime in particular, contributed to the mean shift (increase) in CSF and ventricular volumes observed in the EPrime. With all this in mind, it was reassuring that deviations in brain development and their association with perinatal risks found in the dHCP broadly replicated in EPrime. We chose to use absolute and relative brain volumetric measures that are easy to calculate in research studies or routine clinical examinations. This offers a direct clinical application, though given the regional heterochrony of early life brain development[48], future work should focus on more finely-parcellated regions and take advantage of more sophisticated MRI-derived features, including cortical thickness and surface area.

Some associations were only observed in the larger EPrime cohort, which comprised earlier preterm born infants compared to the dHCP preterm sample. Specifically, an association between bigger birth weight Z-score and reduced proportion of brainstem and bilateral thalamic volumes, as well as increased postnatal growth and reduced TTV proportion of WM and left caudate volumes. Given that the proportion these structures represent from TTV *decreased* with age, these findings are intuitive, suggesting that for preterm infants, being born bigger and showing good postnatal growth is related to more mature or robust volumetric development of these subcortical structures and WM by TEA.

The argument that essentially every brain is different is not novel, and the expectation that the effects of preterm birth are homogeneous and exactly alike in every infant is equally untenable[7,10]. Personalized methodologies have been successfully applied in other fields (e.g. neuropsychology[14]) and may hold significant promise for the preterm infant. A target for future personalized analysis could be the marked variability in ventricular size. This is likely to be important given that ventricular enlargement has been broadly but imprecisely linked to poorer outcome in group-wise studies[49,50]. Although a group-mean difference may be detected using the conventional case-control approach, the significant heterogeneity would not be captured and effects of possible clinical significance to individual infants would be averaged out[6]. Effects that might appear visually subtle on their own might have prognostic significance when combined with other deviations from normative brain growth, for example reduced thalamic volume, and further analytic power may be gained by including covariates in the GPR model.

By focusing on the individual rather than the average atypicality within a group, our approach offers more precise understanding of the cerebral consequences of preterm birth and in future might improve the predictive power of neuroimaging.

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