Magnetic resonance (MR) imaging studies have demonstrated reduced global and regional brain volumes in infants with congenital heart disease (CHD). This study aimed to provide a more detailed evaluation of altered structural brain development in newborn infants with CHD compared to healthy controls using tensor-based morphometry (TBM). We compared brain development in 64 infants with CHD to 192 age- and sex-matched healthy controls. T2-weighted MR images obtained prior to surgery were analysed to compare voxel-wise differences in structure across the whole brain between groups. Cerebral oxygen delivery ($cDo_2$) was measured in infants with CHD ($n = 49$) using phase contrast MR imaging and the relationship between $cDo_2$ and voxel-wise brain structure was assessed using TBM. After correcting for global scaling differences, clusters of significant volume reduction in infants with CHD were demonstrated bilaterally within the basal ganglia, thalami, corpus callosum, occipital, temporal, parietal and frontal lobes, and right hippocampus ($p < 0.025$ after family-wise error correction). Clusters of significant volume expansion in infants with CHD were identified in cerebrospinal fluid spaces ($p < 0.025$). After correcting for global brain size, there was no significant association between voxel-wise brain structure and $cDo_2$. This study localizes abnormal brain development in infants with CHD, identifying areas of particular vulnerability.

Congenital heart disease (CHD) is the most common congenital abnormality, with a reported prevalence of over 9 per 1,000 live births worldwide. As advances in management of CHD lead to improved mortality rates, morbidity and long-term outcomes have become of increasing concern. Infants and children with CHD may have impaired neurodevelopmental outcomes compared to healthy peers, even in the absence of known genetic syndromes. Impaired neurodevelopment in CHD leads not only to short-term impact on early childhood development, but also long-term impact, including poorer school performance and academic achievement, and an increased need for special education services.

The neurodevelopmental abnormalities observed in survivors of CHD may be related to abnormal brain development. Magnetic resonance (MR) imaging studies have identified brain injury and abnormal brain development in infants with CHD including impaired cortical folding and white and grey matter microstructural abnormalities. In addition, foetuses and infants with CHD have impaired brain growth, including reductions...
in total and regional brain volumes, compared to healthy controls. These abnormalities are evident prior to surgery and have been associated with reduced cerebral oxygen delivery.

Tensor-based morphometry (TBM) is an MR analysis approach that enables the comparison of variation in shape and volume between the brains of individuals on a voxel-wise basis across the whole brain. This method enables increased precision in localizing structural variation between groups compared to methods that involve segmentation of pre-selected brain regions. Of note, TBM is able to identify structural differences that are independent of global scaling differences, ensuring observed differences do not merely reflect differences in global brain volume and head size.

The primary aim of this study was to assess differences in brain structure between infants with CHD and healthy controls using TBM in order to identify those areas at risk of abnormal development in infants with CHD. Our secondary aim was to assess the relationship between structural brain development at a voxel-wise level and cerebral oxygen delivery (CDO2) in infants with CHD.

Results
Demographics. We studied 64 infants with CHD (35 male) and 192 healthy controls (105 male). There were no significant differences in gestational age (GA) at birth, post-menstrual age (PMA) at scan, sex, birthweight, head circumference at birth, head circumference at scan, or mode of delivery between infants with CHD and healthy controls (Table 1).

The primary aim of this study was to assess differences in brain structure between infants with CHD and healthy controls using TBM in order to identify those areas at risk of abnormal development in infants with CHD. Our secondary aim was to assess the relationship between structural brain development at a voxel-wise level and cerebral oxygen delivery (CDO2) in infants with CHD.

| Variable                               | Infants with CHD (n = 64) | Healthy controls (n = 192) | p-value |
|----------------------------------------|----------------------------|----------------------------|---------|
| Gestational age at birth, weeks        | 38.57 (35.29–41.57)       | 38.86 (35.14–40.43)       | 0.06†   |
| Post-menstrual age at scan, weeks      | 39.29 (36.43–42.29)       | 39.43 (36.43–42.86)       | 0.23†   |
| Male, no. (%)                          | 35 (55)                   | 105 (55)                  | 1.00†   |
| Birth weight, kg                       | 3.11 (1.81–4.29)          | 3.11 (1.87–4.80)          | 0.37*   |
| Birth weight z-score                   | −0.83 (−4.32 to 1.58)     | −0.65 (−3.57 to 3.12)     | 0.23*   |
| Birth head circumference, cm           | 33.70 (29.00–38.50)       | 34.00 (30.00–37.00)       | 0.48†   |
| Birth head circumference z-score       | −0.60 (−4.92 to 3.09)     | −0.27 (−3.96 to 2.75)     | 0.24†   |
| Head circumference at scan, cm         | 34.00 (29.50–37.40)       | 34.00 (28.50–37.50)       | 0.35†   |
| Head circumference at scan z-score     | −0.81 (−4.60 to 2.15)     | −0.48 (−3.61 to 2.70)     | 0.30†   |
| Mode of delivery, no. (%)              |                           |                           |         |
| Spontaneous/induced vaginal delivery   | 24 (38)                   | 58 (30)                   |         |
| Instrumental delivery                  | 11 (17)                   | 38 (20)                   | 0.07†   |
| Elective C-section                     | 7 (11)                    | 48 (25)                   |         |
| Emergency C-section                    | 22 (34)                   | 48 (25)                   |         |
| Cardiac diagnosis, no. (%)             |                           |                           |         |
| Transposition of the great arteries    | 29 (45)                   | −                         |         |
| Coarctation of the aorta              | 15 (23)                   | −                         |         |
| Hypoplastic left heart syndrome        | 3 (5)                     | −                         |         |
| Pulmonary atresia                      | 2 (3)                     | −                         |         |
| Tricuspid atresia                      | 2 (3)                     | −                         |         |
| Tetralogy of Fallot                    | 7 (11)                    | −                         |         |
| Pulmonary stenosis                     | 4 (6)                     | −                         |         |
| Truncus arteriosus                     | 1 (2)                     | −                         |         |
| Large ventricular septal defect        | 1 (2)                     | −                         |         |

Table 1. Demographic details of infants with congenital heart disease (CHD) and healthy controls. Values shown are median (range), except where indicated. *Student’s t-test used. †Mann–Whitney U test used. #Chi-squared test used.
interpeduncular cistern, as well as bilaterally in the ambient cisterns, and extra-axial spaces around the sylvian fissures, frontal lobes, parietal lobes and inferior poles of the temporal lobes. Symmetrical clusters of significant expansions were also found in the third ventricle, fourth ventricle and in the caudothalamic notches bilaterally.

Figure 1. Map of t-statistic values of areas of significant (a) reductions and (b) expansions in volumes in infants with congenital heart disease compared to healthy controls (family-wise-error-corrected \( p < 0.025 \)). Images in 3 planes are shown: (i) axial, (ii) sagittal, (iii) coronal. t-statistic range is shown on the colour bars. Results are overlaid on the template image with post-menstrual age at scan of 40 weeks. Left–right orientation follows radiological convention. Sagittal views are presented from right to left.
On comparison of total brain and regional brain volumes, we found that infants with CHD had significantly smaller total brain, cortical grey matter, white matter, deep grey matter, and cerebellum volumes than controls (Supplementary Table S2). There was no significant difference in relative regional volumes between groups (Supplementary Table S2). The results of subgroup analysis of abnormal mixing cardiac lesions (n = 31), left-sided cardiac lesions (n = 18), and right-sided cardiac lesions (n = 15) compared to matched controls are included in Supplementary Figure S1.

**Brain development and cerebral oxygen delivery.** Forty-nine infants with CHD underwent phase contrast flow imaging and cerebral blood flow (CBF) was measured and used to calculate CDO₂. The median CBF was 84.58 mL/min with range 45.58–123.16 mL/min and the median CDO₂ was 1657 mL O₂/min with range 1,106–3,023 mL O₂/min. There were no significant differences between infants in whom CDO₂ was measured, and those in whom CDO₂ was not (Supplementary Table S3). No significant association between voxel-wise brain structure and CDO₂ or CBF was found on TBM analysis.

There were no significant differences in CBF or CDO₂ between cardiac subgroups (Supplementary Figure S2). A significant positive correlation was observed between CDO₂ and total brain, cortical grey matter, and deep grey matter volumes (Supplementary Table S4).

**Discussion**

This study identified regions of abnormal brain development on preoperative MR imaging in infants with CHD compared to healthy age- and sex-matched controls after taking into account differences in overall brain size between groups. However, after accounting for global scaling, we did not identify any significant associations between CDO₂ and structural brain development at a voxel-wise level.

Previous studies have shown reductions in total brain volume, regional brain volumes and biometric measurements of brain size, and expansions in extra-axial CSF volume in infants with CHD prior to surgery. Similar to our previous reports in a subsample of this cohort, we observed smaller total brain, white matter, deep grey matter and regional cortical grey matter volumes in infants with CHD compared to controls. However, we did not observe any significant differences in relative regional volumes between infants with CHD and controls, suggesting similar volume reductions across all brain regions at this coarse level of analysis. Our study used TBM to extend these analyses in order to identify specific locations of altered brain development in infants with CHD, taking into account global size differences, without the need for a priori definition of regions of interest or image segmentation.

In the analysis of different CHD subgroups, we observed different patterns of abnormal brain development in infants with different cardiac physiologies. However, there were no significant differences in measures of cerebral haemodynamics between cardiac subgroups. It is not clear whether the smaller regions of volume differences in the left- and right-sided lesion groups compared to controls are due to cardiac physiology or the small sample sizes of these 2 groups.

Assessing brain development may be useful in understanding the basis of impaired long-term neurodevelopment in survivors of CHD. Previous studies have demonstrated significant associations between brain volume and impaired neurodevelopment in this high-risk group. Reduced subcortical grey matter and increased CSF volumes in the neonatal period are associated with impaired behavioural state regulation and visual orienting in infants with CHD prior to surgery. In addition, smaller cortical grey matter, white matter, cerebellum, basal ganglia and thalami, and brainstem volumes in newborns with CHD after surgery are associated with poorer cognitive and language outcome scores and below-average IQ in later infancy and childhood. These relationships persist into adolescence where reduced white matter, cerebellum, and hippocampal volumes are associated with impaired total IQ and other measures of cognitive, motor and executive functions.

In this study, we identified significant clusters of reduced volume in regions that are important for cognitive, behavioural and motor function including the caudate nuclei, globus pallidus, thalami, posterior cingulate gyri, frontal lobes, and the hippocampus. The basal ganglia and thalami are associated with cognitive, affective, somatosensory and motor function, and reductions in volume within the thalami and basal ganglia have been linked to adverse neurodevelopment in CHD and prematurity. In particular, the anterior thalamus, where we localized volume reduction, have been associated with information processing and attention, memory, and spatial navigation. The hippocampi play a crucial role in intellectual function and memory, and significant correlations have been observed between hippocampal volume and verbal memory, verbal comprehension, perceptual reasoning, and total IQ in adolescents with CHD. In addition, we localized volume reductions to the posterior cingulate gyri, regions which are linked to memory, emotional response, attention, and spatial orientation. We also observed clusters of significant reductions in the frontal lobes. The frontal lobes are associated with many higher cognitive functions, including attention, executive function, impulse control, language, and memory, functions which may be impaired in children with CHD.

We localized significant volume expansions in CSF spaces, including the basal cisterns, third and fourth ventricles and caudothalamic notches bilaterally. Increased CSF volume has been found in children with specific language impairment compared to controls and has been linked to autism spectrum disorder in infants at high genetic risk, and to moderate-severe neurodevelopmental disability and decreased working memory performance in preterm infants.

There are a number of potential mechanisms underlying abnormal brain development in infants with CHD including altered cerebral haemodynamics, reduced substrate delivery to the brain, genetic factors, impaired placental development, and impaired cerebral haemodynamics. We previously reported a correlation between CDO₂ and preoperative neonatal total brain and cortical grey matter volumes in our CHD cohort. In this study, we also observed significant associations between CDO₂ and total brain, cortical grey matter, and deep grey matter volumes.
after controlling for global scaling, we did not identify additional clusters of altered development on a voxel-wise level associated with CDO₂. This suggests that either (i) reduced CDO₂ impairs growth across the whole brain and there are no regions that are specifically vulnerable to low CDO₂, or (ii) there was insufficient statistical power to assess voxel-wise differences after correcting for multiple comparisons. Of note, the measurement of CDO₂ at a single postnatal timepoint may not reflect the full burden of hypoxia experienced by these infants. Indeed, reduced cerebral oxygenation has been associated with reduced brain volume in utero56. While the reduction of CDO₂ is probably global, intrinsic vulnerabilities, such as high metabolic demand, could play a role in the impact on specific brain structures. In other at-risk populations of neonates, such as in those experiencing acute hypoxic-ischaemic events, patterns of injury involving structures with higher metabolic demand, including the basal ganglia and thalamus, and hippocampus, have been observed50,71.

However, in this study, we observed clusters of volume reductions, in regions including both the grey and white matter. This is presumably because the effect of chronic hypoxia differs from that of acute events, and different regions of the brain have varying metabolic demands at different stages of development72,73. Furthermore, cerebral autoregulatory mechanisms play an important role44, and different regions of the brain may be affected by different degrees of “brain sparing”74, particularly as the cerebral vasculature is itself developing during mid-late gestation75.

A limitation of this study is that, as yet, we do not have neurodevelopmental outcome data for all of the infants. Further studies are required to examine the relationship between regions of altered brain development identified on voxel-wise analyses and neurodevelopmental outcome.

Conclusions
Using tensor-based morphometry, this study identified clusters of localized volume alterations in regions important for subsequent cognitive, behavioural and motor function in infants with CHD compared to healthy control infants. Whilst cerebral oxygen delivery was significantly associated with total brain and regional brain volumes, no significant relationship was found between cerebral oxygen delivery and voxel-wise brain volume after controlling for global size differences. Assessing brain structural abnormalities using a voxel-wise approach, such as tensor-based morphometry, refines our understanding of abnormal brain development in infants with CHD.

Methods
The project was approved by the National Research Ethics Service West London committee (CHD: 07/H0707/105; Controls: 14/LO/1169). Informed written parental consent was obtained before imaging. All methods and experiments were carried out in compliance with relevant guidelines and regulations.

Participants. A prospective cohort of 74 infants born with critical or serious CHD requiring surgery within one year, based on previously published UK classification76,77, was recruited for MR neuroimaging from the Neonatal Intensive Care Unit at St Thomas’ Hospital, London. Exclusion criteria were known or suspected genetic syndromes, major abnormalities on MR imaging and GA at birth < 35 weeks. Sixty-four infants were included in the analysis (Fig. 2). Healthy controls were obtained from the Developing Human Connectome Project (dHCP) database78 and were matched for GA at birth, PMA at scan, and sex, to each infant in the CHD group in a ratio of three healthy controls per one infant with CHD. Matching of healthy controls to infants with CHD was carried out in R, version 3.2.379, using an automated method based on the daisy dissimilarity matrix calculation85,86.

MR imaging. High-resolution MR imaging was performed on a Philips Achieva 3-T system (Best, The Netherlands) using a 32-channel neonatal head coil and neonatal positioning device47. T2-weighted, T1-weighted, and diffusion-weighted MR images were acquired using the dHCP protocol optimized for neonatal scanning78,81,82.

Phase contrast flow imaging was also acquired for the CHD cases83.

T2-weighted images were used for TBM analysis and were acquired using a multi-slice turbo spin echo sequence in 2 stacks of 2-dimensional slices in sagittal and axial planes, with pulse repetition time 12 s, echo time 156 ms, flip angle 90°, slice thickness 1.6 mm with 0.8 mm overlap, in-plane resolution 0.8 mm × 0.8 mm. Quantitative flow imaging was acquired using velocity-sensitive phase contrast imaging, with a single-slice spoiled gradient echo sequence, with field of view 100 mm × 100 mm, acquisition resolution 0.6 mm × 0.6 mm × 4.0 mm, repetition time 6.4 ms, echo time 4.3 ms, flip angle 10°, 20 cardiac phases, maximal encoding velocity 140 cm/s, and scan time 71 s84. Other imaging parameters have been previously described85. Infants were scanned in natural sleep without sedation, in the presence of a paediatrician experienced in MR imaging procedures. All images were reviewed for abnormalities by a paediatric neuroradiologist.

Infants had physiological monitoring (electrocardiography, respiratory rate, oxygen saturations and temperature) throughout the scan. Ear protection was used to minimize impact of scanner noise: ear plugs moulded from putty (President Putty, Coltene Whaledent, Mahwah, NJ, USA) placed in the external auditory meatus and covered with neonatal earmuffs (MiniMuffs, Natus Medical Inc., San Carlos, CA, USA), with an acoustic foam hood for noise absorption positioned over the infant in the scanner.

Structural image processing. Motion-correction and slice-to-volume image reconstruction were carried out retrospectively using a dedicated algorithm to obtain 0.8 mm³ isotropic T2-weighted images84,85. These were segmented into tissue type (white matter, grey matter, cerebrospinal fluid (CSF), cerebellum, deep grey matter) using a multi-structure expectation–maximization-based segmentation technique in a neonatal-specific automated pipeline described previously86–88.
Cerebral oxygen delivery. For infants with CHD, cerebral blood flow (CBF) was calculated from phase contrast MR imaging acquired in a plane perpendicular to both internal carotids and basilar arteries at the level of the sphenoid bone, using a previously described method. Haemoglobin (Hb) measurements were performed as part of routine clinical care, at a median (range) of 2 (−1 to 10) days before the scan. Arterial oxygen saturation (SaO₂) was measured at the time of scan using a Masimo Radical-7 monitor (Masimo Corp, Irvine, CA) applied to the right hand. Cerebral oxygen delivery (CDO₂) was calculated using the following formula:

\[
\text{CDO}_2 = \text{SaO}_2 \times [\text{Hb}] \text{ (g/dL)} \times 1.36 \times \text{[CBF]} \text{ (mL/min)}
\]

where 1.36 is the amount of oxygen bound per gram of haemoglobin at 1 atmosphere (Hüfner's constant).

Tensor-based morphometry. Neonatal templates constructed for each week of gestation created from the dHCP neuroimaging database were used as templates for registration. Subject T2-weighted images were registered to an age-at-scan-matched template image using the Symmetric Normalization (SyN) algorithm from tensor-based morphometry.
Advanced Normalization Tools (ANTS), version 3.0\cite{32}. Segmented T2-weighted images were included in the algorithm to improve the quality of registration.

Following rigid and affine transformations of the image, the non-linear transformations from the SyN algorithm were used to create deformation tensor fields within the template space. By using only non-linear transformations, global volume differences are factored out. The resulting tensor fields describing the voxel-wise shape and volume change from the template to each subject image were used to calculate scalar Jacobian determinants, which were subject to logarithm transformation, using ANTs\cite{33}.

and volume change from the template to each subject image were used to calculate scalar Jacobian determinants, which were subject to logarithm transformation, using ANTs\cite{33}.

Log-Jacobian determinant maps were smoothed with a sigma of 3.5 mm full width at half maximum Gaussian filter. To facilitate processing, the log-Jacobian determinant maps were re-sized to a voxel size of 1 mm\(^3\) isotropic prior to statistical analysis.

Statistical analysis. Clinical data were compared between groups using Student’s \(t\)-test or Mann–Whitney \(U\) for continuous variables, with prior normality testing using the Shapiro–Wilk test. Chi-squared test was used for categorical variables. A \(p\)-value of less than 0.05 was taken as significant. Missing values for clinical data were dealt with through pairwise deletion. Statistical analysis was performed with IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Z-scores for birth weight and head circumference were calculated using the GrowthCharts\cite{13}–WHO application, version 2.0.1\cite{14}, based on UK–WHO 2006 population reference data\cite{15}.

For TBM analysis, the 64 infants with CHD were first compared to age- and sex-matched healthy controls. Voxel-wise \(t\)-tests of log-Jacobian determinants between CHD and control groups were carried out using FSL Randomise (FSL, version 6.0.1)\cite{16,17}. Threshold-free cluster enhancement was used with a random permutation method with 10 000 permutations, based on a General Linear Model (GLM) matrix\cite{18,19}. Additionally, for CHD infants with successful phase contrast flow imaging (\(n = 49\)), voxel-wise regression analyses of log-Jacobian determinants with CDO\(_2\) and CBF were performed. A brain mask for the template image at a PMA of 40-weeks was created using the GrowthCharts\cite{13}–WHO application, version 2.0.1\cite{14}, based on UK–WHO 2006 population reference data\cite{15}.

Further supplementary methods are included within the supplementary information.

Data availability
Anonymised data pertaining to the Developing Human Connectome Project have been made publicly available at the Developing Human Connectome Project repository and can be accessed at https://www.developingconnectome.org/. The remaining data, analytic methods, and study materials will be available to other researchers for the purposes of reproducing the results or replicating the procedure on reasonable request.

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Competing interests
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