Feature similarity gradients detect alterations in the neonatal cortex associated with preterm birth

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Feature similarity gradients detect alterations in the neonatal cortex associated with preterm birth

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Abstract
The early life environment programmes cortical architecture and cognition across the life course. A measure of cortical organisation that integrates information from multimodal MRI and is unbound by arbitrary parcellations has proven elusive, which hampers efforts to uncover the perinatal origins of cortical health. Here, we use the Vogt-Bailey index to provide a fine-grained description of regional homogeneities and sharp variations in cortical microstructure based on feature gradients, and we investigate the impact of being born preterm on cortical development at term-equivalent age. Compared with term-born controls, preterm infants have a homogeneous microstructure in temporal and occipital lobes, and the medial parietal, cingulate, and frontal cortices, compared with term infants. These observations replicated across two independent datasets and were robust to differences that remain in the data after matching samples and alignment of processing and quality control strategies. We...
conclude that cortical microstructural architecture is altered in preterm infants in a spatially distributed rather than localised fashion.

**KEYWORDS**

feature similarity gradients, MRI, neonatal brain, neonatal cortex, preterm birth

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## 1 | INTRODUCTION

The cortex undergoes dramatic changes in the last trimester of pregnancy and early postnatal life as a result of concurrent cellular and molecular processes including synaptogenesis, axonal growth, dendritic arborisation and myelination (Kostović et al., 2019; Ouyang et al., 2018; Volpe, 2019). Disruption of normal gestation during this period of rapid growth can have long-lasting consequences on neurodevelopment (Fleiss et al., 2020; Kersbergen et al., 2016; Kline et al., 2020; Zhang et al., 2015). Imaging of the preterm brain at term-equivalent age has characterised dysmaturatation following preterm birth as a global phenomenon (i.e. encompassing the whole brain), with generalised dysconnectivity and atypical topology of developing neural networks, increased water diffusivity, altered white matter microstructure and reduced brain volume and cortical surface area (Batalle et al., 2018; Blesa et al., 2021; Boardman & Counsell, 2020; Telford et al., 2017; Vahe et al., 2022). Motivated by the search for neural antecedents of cognitive impairment observed in some preterm-born individuals, studies focusing on the neonatal cortex have demonstrated that prematurity impacts cortical growth and microstructural development in a dose-dependent fashion (Ball, Srinivasan, et al., 2013; Kapellou et al., 2006) and that preterm birth alters cortical folding (Dubois et al., 2019; Neil & Smyser, 2018; Shimony et al., 2016), thalamo-cortical connectivity (Ball, Boardman, et al., 2013; Boardman et al., 2006) and different regional MRI metrics with varying spatial distribution, including water diffusion measures, markers of myelination and cortical morphology metrics (Ball et al., 2020; Bouyssi-Kobar et al., 2018; Dimitrova et al., 2021; Ouyang et al., 2019).

Parcellation of the brain into spatially contiguous and non-overlapping regions with a locally homogeneous profile is a useful abstraction to study cerebral function and organisation. However, there is no consensus on the optimal delineation of brain parcels, whether they are defined cytoarchitectonically, on the basis of function, or on a combination of features (Arslan et al., 2018; Bohland et al., 2009; Cloutman & Lambon Ralph, 2012; Eickhoff et al., 2018; Glasser et al., 2016). Individual variability in brain shape and organisation further complicates the definition of a universal brain map, as reference templates might not adapt well to the signal of individual acquisitions (Eickhoff et al., 2018). One of the main challenges in defining parcels is the arbitrary assignment of sharp boundaries between regions that may only show graded differences in local structure or function. Feature similarity gradients provide a unified approach to studying graded differences in brain organisation (Bajada et al., 2017; Bajada et al., 2020; Bernhardt et al., 2022). A gradient is defined as an axis of variance in cortical features, along which different areas are positioned to reflect their similarity (Huntenburg et al., 2018). This technique has been used to investigate multiple aspects of cortical organisation of the adult brain, including morphology, microstructure and structural and functional connectivity (Bernhardt et al., 2022). Studies based on functional connectivity have found a whole-brain gradient with primary sensory and motor regions at one end of the spectrum and multimodal association regions at the opposite end (Huntenburg et al., 2018; Margulies et al., 2016). This functional gradient is already detectable during adolescence (Dong et al., 2021), while closely after birth and through childhood the principal axis of variance spans between sensorimotor and visual areas (Dong et al., 2021; Larivière et al., 2020). Whole-brain gradients derived from microstructure describe a similar hierarchy to functional gradients, but they become increasingly dissociated from their functional counterparts in multimodal regions (Paquola et al., 2019). A neonatal study using principal component analysis on measures of cortical morphology and microstructure showed that cortical regions were ordered along a principal axis, with the primary cortex clearly separated from the association cortex (Ball et al., 2020). Using local rather than global gradients, Glasser et al. (Glasser et al., 2016) proposed a method to detect boundaries in the cortex in correspondence of spatial transitions in multiple brain maps describing different brain features: myelin-sensitive features (derived from T1/T2 contrasts), cortical thickness, cortical folding and functional activity patterns and connectivity. They did however rely on expert knowledge and priors from the neuroanatomical literature in the absence of sharp transitions.

Here, we introduce a framework for a local gradient analysis of the microstructural organisation of the neonatal cortex based on six microstructural metrics: fractional anisotropy, mean, axial and radial diffusivities, neural density index and orientation dispersion index. These metrics are known to share a substantial amount of variance, but at the same time, they carry specific information which differs between preterm and term infants, and their covariance structure varies across the brain (Vahe et al., 2022). We investigate the impact of being born preterm on cortical microstructure using the Vogt-Bailey index (VB) (Bajada et al., 2020). By integrating information from multiple features computed at each point of the cortical mantle, this index measures the extent of discontinuity in cortical intra-areal relationships, summarising in a single metric the information contained in a feature similarity gradient. Compared with previous approaches based on parcels or whole-brain gradients, this method works on a more
TABLE 1 Summary of acquisition parameters and processing steps for TEBC and dHCP datasets.

<table>
<thead>
<tr>
<th></th>
<th>TEBC</th>
<th>dHCP</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Image resolution</td>
<td>1 mm³</td>
<td>0.5 mm³</td>
<td>No</td>
</tr>
<tr>
<td><strong>Preprocessing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain extraction</td>
<td>BET</td>
<td>BET</td>
<td>Yes</td>
</tr>
<tr>
<td>T1 - T2 registration</td>
<td>Rigid alignment, BBR</td>
<td>Rigid alignment, BBR</td>
<td>Yes</td>
</tr>
<tr>
<td>Bias correction</td>
<td>N4</td>
<td>N4</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Segmentation/surface extraction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performed on</td>
<td>T2-weighted images</td>
<td>T2-weighted images</td>
<td>Yes</td>
</tr>
<tr>
<td>Tissue segmentation</td>
<td>Draw-EM</td>
<td>Draw-EM</td>
<td>Yes</td>
</tr>
<tr>
<td>White and pial surface extraction</td>
<td>Using tissue segmentation (no edge-based correction)</td>
<td>Using tissue segmentation (no edge-based correction)</td>
<td>Yes</td>
</tr>
<tr>
<td>Surface inflation</td>
<td>FreeSurfer re-implementation</td>
<td>FreeSurfer re-implementation</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Diffusion MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Image resolution</td>
<td>2 mm³</td>
<td>1.17 * 1.17 * 1.5 mm</td>
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<td>Bvalues (directions)</td>
<td>0 (16), 200 (3), 500 (6), 750 (64), 2500 (64)</td>
<td>0 (20), 400 (64), 1000 (88), 2600 (128)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Preprocessing</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Brain extraction</td>
<td>BET</td>
<td>BET</td>
<td>No</td>
</tr>
<tr>
<td>EPI correction</td>
<td>Topup</td>
<td>Topup</td>
<td>No</td>
</tr>
<tr>
<td>Eddy distortion correction</td>
<td>Eddy</td>
<td>Eddy</td>
<td>No</td>
</tr>
<tr>
<td>Bias correction</td>
<td>N4</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>DTI fitting</td>
<td>dtifit</td>
<td>dtifit</td>
<td>No</td>
</tr>
<tr>
<td>NODDI fitting</td>
<td>Noddi-Bingham cuDIMOT</td>
<td>Noddi-Bingham cuDIMOT</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Diffusion to structural registration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter modality registration</td>
<td>T2 to b = 0 Rigid Alignment, BBR</td>
<td>T2 to b = 1000 Rigid Alignment, BBR</td>
<td>No</td>
</tr>
<tr>
<td>Registration to 40-week cortical template</td>
<td>40</td>
<td>MSM</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: BBR, boundary-based registration age (Greve & Fischl, 2009); BET, brain extraction tool (Smith, 2002); cuDIMOT, CUDA diffusion modelling toolbox (Hernandez-Fernandez et al., 2019); draw-EM, draw expectation-maximization (Makropoulos et al., 2014); dtifit (Jenkinson et al., 2012); eddy (Andersson & Sotiropoulos, 2016); FreeSurfer (Fischl, 2012); MSM, multimodal surface matching (Robinson et al., 2014); N4, N4 bias field correction (Tustison et al., 2010); sMDS, spherical multi-dimensional scaling (Elad et al., 2005); topup (Andersson et al., 2003).

2 | MATERIALS AND METHODS

In the following, we detail data acquisition and processing strategies for the two datasets. Table 1 provides a side-by-side comparison of the pipelines for structural and diffusion processing and cortical registration.

2.1 | Data acquisition and processing

2.1.1 | Theirworld Edinburgh birth cohort (TEBC)

Participants were recruited as part of a longitudinal study on the long-term effects of preterm birth on neurodevelopment (Boardman et al., 2020) between 2016 and 2021. Ethical approval was obtained from the National Research Ethics Service, South East Scotland Research Ethics Committee (11/SS/0061, 13/SS/0143 and 16/SS/0154). Cohort exclusion criteria included major congenital malformations, chromosomal abnormalities, congenital infection, overt parenchymal lesions (cystic periventricular leukomalacia, haemorrhagic parenchymal infarction) or post-haemorrhagic ventricular dilatation.

A Siemens MAGNETOM Prisma 3T MRI clinical scanner (Siemens Healthcare, Erlangen, Germany) and 16-channel phased-array...
paediatric head receive coil were used to acquire a three-dimensional T2-weighted (T2w) SPACE (Sampling Perfection with Application-optimized Contrasts by using flip angle Evolution) structural images with 1-mm isotropic resolution, repetition time (TR) of 3.2 s and echo time (TE) of 409 ms; and a multi-shell axial diffusion MRI (dMRI) scan \((16 \times b = 0 \; \text{s/mm}^2, \; 3 \times b = 200 \; \text{s/mm}^2, \; 6 \times b = 500 \; \text{s/mm}^2, \; 64 \times b = 750 \; \text{s/mm}^2, \; 64 \times b = 2500 \; \text{s/mm}^2)\) with optimal angular coverage (Caruyer et al., 2013). Diffusion MRI images were acquired in two separate acquisitions to reduce the time needed to re-acquire data lost to motion artifacts. In addition, an acquisition of 3 b=0 volumes with an inverse phase encoding direction was performed. All dMRI images were acquired using single-shot spin-echo echo planar imaging (EPI) with twofold simultaneous multislice and twofold in-plane parallel imaging acceleration and 2-mm isotropic voxels; all three diffusion acquisitions had the same parameters (TR/TE 3.4 s/78 ms). Images affected by motion artifacts were re-acquired multiple times as required; dMRI acquisitions were repeated if signal loss was seen in three or more volumes. Infants were fed and swaddled and allowed to sleep naturally in the scanner. Pulse oximetry, electrocardiography and temperature were monitored. Flexible ear-plugs and neonatal earmuffs (MiniMuffs, Natus) were used for acoustic protection. All scans were supervised by a doctor or nurse trained in neonatal resuscitation. Full details on the protocol are provided in (Boardman et al., 2020).

Diffusion MRI processing was performed as follows: for each subject, the first two dMRI acquisitions were concatenated and then denoised using a Marchenko-Pastur-PCA-based algorithm (Tournier et al., 2019; Veraart et al., 2016); eddy current, head movement and EPI geometric distortions were corrected using outlier removal and slice-to-volume registration (Andersson et al., 2003; Andersson et al., 2016; Andersson et al., 2017; Andersson & Sotiropoulos, 2016); bias field inhomogeneity correction was performed by calculating the bias field of the mean b0 volume and applying the correction to all volumes (Tustison et al., 2010). Structural T2w images (1 mm isotropic) were processed using a modified version of the dHCP minimal processing pipeline (Makropoulos et al., 2018), detailed below. Finally, the mean b0 EPI volume of each subject was co-registered to their structural T2w volume using boundary-based registration (Greve & Fischl, 2009).

### 2.1.2 The developing human connectome project (dHCP)

Participants were scanned at the Evelina Newborn Imaging Centre, Evelina London Children’s Hospital between 2015 and 2019; the study was approved by the National Research Ethics Committee (REC: 14/Lo/173); Subjects were excluded if their scans had incidental findings with possible significance for both clinical and imaging analysis (e.g., destructive white matter lesions). To build a sample that matched as closely as possible the characteristics of the TEBC dataset, we included only preterm infants that had their MRI scans acquired at term-equivalent age and we selected term controls with matching age at scan, age at birth and sex distribution using the nearest neighbour method of the R package MatchIt (Ho et al., 2011).

Pre-processed data from the third dHCP data release were used. In brief, images were acquired using a 3T Philips Achieva system (Philips Medical Systems, Best, The Netherlands). All neonates were scanned without sedation in a scanner environment optimised for neonatal imaging, including a dedicated 32-channel neonatal coil. MR-compatible ear putty and earmuffs were used to provide noise attenuation. Neonates were fed, swaddled and positioned in a vacuum jacket prior to scanning to promote natural sleep (without sedation). All scans were supervised by a neonatal nurse and/or paediatrician who monitored heart rate, oxygen saturation and temperature throughout the scan (Hughes et al., 2017). T2w images were obtained using a Turbo Spin-Echo (TSE) sequence, acquired in two stacks of 2D slices (in sagittal and axial planes), using parameters: TR = 12 s, TE = 156 ms, SENSE factor 2.11 (axial) and 2.58 (sagittal) with overlapping slices (resolution 0.8 × 0.8 × 1.6 mm). Motion correction and super-resolution reconstruction techniques were employed resulting in isotropic volumes of resolution 0.5 mm\(^3\) (Cordero-Grande et al., 2018; Kuklisova-Murgasova et al., 2012). Diffusion MRI data were acquired over a spherically optimised set of directions on three shells (\(b = 400, 1000\) and 2600 s/mm\(^2\)). A total of 300 volumes were acquired per subject, including 20 with \(b = 0\) s/mm\(^2\). For each volume, 64 interleaved overlapping slices were acquired (in-plane resolution = 1.5 mm, thickness = 3 mm, overlap = 1.5 mm). The data were then super-resolved along the slice direction to achieve isotropic resolution of 1.5 mm\(^3\).

Structural T2w images (0.5-mm isotropic) were processed using the minimal processing pipeline of the dHCP (Makropoulos et al., 2014; Makropoulos et al., 2018). Diffusion image preprocessing was carried out according to the dHCP diffusion processing pipeline (Bastiani, Andersson, et al., 2019). This includes motion correction and distortion correction (Andersson et al., 2003; Andersson et al., 2016; Andersson et al., 2017; Andersson & Sotiropoulos, 2016).

### 2.2 Cortical surface reconstruction

The surface reconstruction from T2w images was carried out using a modified version of the dHCP surface processing pipeline (Makropoulos et al., 2018). The standard pipeline works by fitting an initial surface to the boundary of the white and cortical grey matter tissue segmentation; this is subsequently refined by using T2w image intensity values to detect the closest edges with cortical grey matter or cerebrospinal fluid and ‘pushing’ the surface towards these edges (Schuh et al., 2017). For the dHCP cohort this has been shown to correct segmentation errors and improve surface reconstruction but the parameters of the optimisation are cohort-specific and challenging to tune, often leading to failure on data with low resolution or intensity contrast. To avoid this issue and to align the processing of the two datasets, all surfaces were extracted by running the pipeline with this...
feature turned off (available through version 1.1.1), thus using only the tissue segmentation for the surface reconstruction.

2.3 Derivation of microstructural tissue maps

DTI maps were calculated from the dMRI processed images to obtain fractional anisotropy (FA) and mean, axial and radial diffusivities (MD, AD and RD, respectively). To calculate the DTI maps, only the shells of $b = 750$ s/mm$^2$ (TEBC) and $b = 1000$ s/mm$^2$ (dHCP) were used. NODDI maps were calculated for both datasets using the Bingham distribution to obtain the neurite density index (NDI), orientation dispersion index (ODI) and the isotropic water fraction (ISO) (Tariq et al., 2016; Zhang et al., 2012). The ISO map was used to obtain the tissue fraction (1-ISO), which was used to modulate the NDI and ODI maps (Parker et al., 2021). All diffusion metric maps were propagated to the T2w image in each subject’s native space, z-scored and then concatenated to obtain for each voxel a vector comprising all six microstructural metrics.

2.4 Registration to a common template

Cortical surfaces were registered to the 40-week symmetric dHCP cortical template (Williams et al., 2023) using multimodal surface mapping (Robinson et al., 2014; Robinson et al., 2018). For this, the script works by registering each subject to its age-specific template and then concatenating the subject-to-template registration with a registration which maps the age-specific template to the 40-week template (Williams et al., 2023). The configuration parameters were optimised for this study by including an additional regularisation level. The configuration file is available in the project repository (https://git.ecdf.ed.ac.uk/jbrl/neonatal-vbi).

2.5 Quality control

We used the eddy qc tool (Bastiani, Cottaar, et al., 2019) to measure in-scanner motion for dMRI acquisitions. For each volume, motion is quantified by averaging voxel displacement across all voxels (computed as 3 translations and 3 rotations around the x, y and z axes). We report the average relative motion (w.r.t. the previous volume) across all volumes. Note that the motion estimates are not directly comparable across datasets due to differences in resolution and parametrisation of input sequences and eddy correction. To check the quality of the registration of cortical surfaces to the template space, individual sulcal depth maps were overlaid onto template surfaces and visually inspected by three independent raters (PG, MBC and KV). Subjects were included in the analyses if five anatomical landmarks were clearly identifiable and correctly registered: central sulcus, superior temporal sulcus, lateral fissure, parieto-occipital fissure and calcarine sulcus. An example is shown in Figure 1. Inter-rater agreement was 94%. The quality check was performed separately for the left and right hemispheres, resulting in two different samples, one per hemisphere.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Participant characteristics for the TEBC by group. Mean, minimum and maximum values are reported for continuous variables and ratios for binary variables. The last column reports the $p$-values of the group differences computed with the Wilcoxon rank-sum test for continuous variables and with the chi-squared test for binary variables.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preterm (N = 147)</td>
</tr>
<tr>
<td>PMA at birth (weeks)</td>
<td>29.48 (22.14–32.86)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>1318 (370–2510)</td>
</tr>
<tr>
<td>PMA at scan (weeks)</td>
<td>40.71 (36.57–45.86)</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>85.62</td>
</tr>
<tr>
<td>In-scanner motion (mm)</td>
<td>0.24 (0.10–1.04)</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; PMA, postmenstrual age.

FIGURE 1 Sulcal map of an exemplar 38-week subject (left) compared with the 40-week sulcal template from dHCP (right). White dots demarcate five anatomical landmarks used for visual inspection: central sulcus, superior temporal sulcus, lateral fissure, parieto-occipital fissure and calcarine sulcus.

TABLE 2 Participant characteristics for the TEBC by group. Mean, minimum and maximum values are reported for continuous variables and ratios for binary variables. The last column reports the $p$-values of the group differences computed with the Wilcoxon rank-sum test for continuous variables and with the chi-squared test for binary variables.
2.6 | Vogt-Bailey index

Given a set of features computed at each vertex of a cortical surface, the Vogt-Bailey index measures the extent of homogeneity in cortical intra-areal relationships. Using a searchlight approach, at each vertex an affinity graph is built measuring affinity between each vertex and its neighbours; the affinity is calculated using a modified Pearson correlation (Bajada et al., 2020) computed over the features used to describe the vertices (in this case the six microstructural metrics); only positive correlations are retained. The VB index is then computed as the (scaled) algebraic connectivity of the affinity graph, that is the second smallest eigenvalue of the unnormalised Laplacian matrix of the graph. The index assumes values close to 0 when there are sharp changes in the cortical features in an area, and values close to 1 if the changes are graded. Compared with the original implementation (Bajada et al., 2020), where the neighbourhood was selected as the set of adjoining vertices on the cortical surface, in this work we used a hybrid approach where the neighbourhood is reconstructed in volumetric native space, in order to avoid spatial correlations induced by artefactual geometric patterns that follow cortical gyrification patterns (Ciantar et al., 2022; Farrugia et al., 2024). The coordinates of a given vertex and its neighbours are used to select the closest corresponding voxels in volumetric space, and the affinity graph is computed over the feature vectors of the matched brain tissue voxels that fall within a 27-voxel cube centred on the voxel corresponding to the input vertex, to guarantee that we only select voxel neighbours within a short radius from the central vertex, as vertices on the surface are not equally spaced.

2.7 | Statistical analysis

The PALM tool (Winkler et al., 2014) from the FSL suite (Jenkinson et al., 2012) was used to perform a surface-based, vertex-wise term vs. preterm comparison of the VB maps, controlling for PMA at scan and sex. An analysis comparing VB maps between datasets was also run, controlling for prematurity, PMA at scan, sex and vertex-wise cortical thickness and surface area, while sulcal depth was regressed out directly from the VB maps before running PALM as we hypothesised it to be the main contributor to between-dataset discrepancies as a consequence of the difference in image resolution (see also Appendix A and Appendix B). Separate analyses were run for each hemisphere, and independently for the two datasets. Prior to the analyses, Gaussian-weighted smoothing was applied to individual VB maps.

### TABLE 3

<table>
<thead>
<tr>
<th>Participant characteristics for the dHCP by group. Mean, minimum and maximum values are reported for continuous variables and ratios for binary variables. The last column reports the p-values of the group differences computed with the Wilcoxon rank-sum test for continuous variables and with the chi-squared test for binary variables.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm (N = 44)</td>
</tr>
<tr>
<td>PMA at birth (weeks)</td>
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<tr>
<td>Birth weight (grams)</td>
</tr>
<tr>
<td>PMA at scan (weeks)</td>
</tr>
<tr>
<td>M:F ratio</td>
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<tr>
<td>In-scanner motion (mm)</td>
</tr>
</tbody>
</table>

### TABLE 4

<table>
<thead>
<tr>
<th>Sample size (N) for each experiment, group and hemisphere.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hemisphere</td>
</tr>
<tr>
<td>Preterm</td>
</tr>
<tr>
<td>TEBC</td>
</tr>
<tr>
<td>dHCP</td>
</tr>
</tbody>
</table>
with a smoothing kernel with full-width at half-maximum set at 4 mm. Permutation p-values were computed over 10,000 random shuffles with threshold-free cluster enhancement (Smith & Nichols, 2009) and family-wise error rate corrections. Statistical significance was set at $p < .0253$ (equivalent to $\alpha = 0.05$, after Šidák correction over the two hemispheres, Šidák, 1967).

3 | RESULTS

In the TEBC sample, 254 infants had multimodal MRI data suitable for the proposed analysis. Quality control was performed separately for the left and right hemispheres. After visual inspection of the cortical surfaces, 221 subjects (147 preterm and 72 term-born infants) were included in either the left or right hemisphere analysis, or both (Table 2). Of the preterm infants, 36 had bronchopulmonary dysplasia (BPD), eight had necrotising enterocolitis (NEC) and six required treatment for retinopathy of prematurity (ROP). After quality control, the dHCP matching sample (matched on age at scan, age at birth and sex distribution) contained 43 preterm and 84 term-born infants (Table 3). None of the preterm infants in the dHCP sample had NEC or ROP; no information was recorded regarding BPD. In both datasets, there were no differences in in-scanner relative motion estimates of volume-to-volume displacement between the preterm and term groups (Table 2). The distributions of gestational age at birth and age at scan for the two datasets are shown in Figure 2. Table 4 reports the sample size for the preterm and term groups for each experiment. There were no statistically significant differences in postmenstrual age (PMA) distributions between the left and right hemisphere samples, or between any individual hemisphere and the whole sample, in either dataset (Wilcoxon rank-sum test, p-values > .43).

For each subject, VB maps were generated from six microstructural metrics (fractional anisotropy, mean, axial and radial diffusivities, neural density index and orientation dispersion index). Figure 3 shows two exemplar VB maps for one preterm and one term subject. Figure 3 shows two exemplar VB maps for one preterm and one term subject. Figure 4 shows the distribution of VB index (across both hemispheres) by group (preterm vs. term) for both datasets.

3.1 | The impact of preterm birth on cortical organisation

In both datasets, when comparing preterm and term infants controlling for age at scan and sex, we found more homogeneous
cortical microstructure (higher VB index) in the preterm group compared with the term group in widespread areas of the cortex including the right temporal lobe, occipital lobe, medial parietal cortex, right cingulate cortex and left frontal cortex. Figure 5 reports the standardised t-maps of the preterm vs. term comparisons for the two datasets, while the p-values maps in Figures 6 and 7 highlight regions where the VB index is significantly higher in the preterm group or in the term group, respectively. In the TEBC dataset only, the VB index is lower (decreased homogeneity) in the preterm group compared with term controls in the medial orbitofrontal cortex. There were no areas of lower VB index in the preterm group in the dHCP dataset.

3.2 | Replicability across datasets

We tested the replicability of our findings in two datasets, and we aimed to reduce avoidable variations in the samples, structural preprocessing and quality control strategies. However, some discrepancies remain, such as scanner differences, input resolution and variation in acquisition protocols; these had inevitable consequences on the down-stream processing, that are reflected in differences in cortical thickness (Appendix A) and single-metric maps between the two datasets (Appendix B) that were spread throughout the cortex.

With the exception of the temporal and occipital lobes, throughout the cortex the VB index was on average higher in the TEBC dataset, possibly as a consequence of lower image resolution, with the strongest effect size measured in the medial frontal lobe and right insular cortex (Figures 8–10). There was overlap in between-dataset differences in cortical thickness and between-dataset differences in VB maps in the temporal lobe and insular cortex and in medial parts of the occipital lobe and the frontal gyrus, but not in the rest of the frontal cortex. Single-metric difference maps also showed overlap with the cortical thickness differences but with variable patterns.

4 | DISCUSSION

In this work, we demonstrate that the VB index can be used to explore graded changes in the microstructural properties of the neonatal cortex. Consistent with previous descriptions of the dysmatura-tion following preterm birth as a substantially whole-brain phenomenon (Blesa et al., 2020; Telford et al., 2017; Vaher et al., 2022), across two independent datasets, we find that a
A significant proportion of cortical microstructure is consistently altered in association with preterm birth, in a spatially distributed rather than localised fashion.

The increased homogeneity measured by the VB index in preterm infants compared with term controls could reflect increased water content, potentially as a consequence of delayed maturation, as supported by previous findings (Ball, Srinivasan, et al., 2013; Dimitrova et al., 2021). In a previous study that used a region-based approach to investigate neuroanatomic variation associated with preterm birth, term infants showed less homogeneous microstructure throughout cortical grey matter regions compared with preterm infants, indicating a more advanced state of maturation (Galdi et al., 2020). Our results are also consistent with prior evidence that prematurity alters microstructural organisation throughout the cortex: Bouyssi-Kobar et al. (Bouyssi-Kobar et al., 2018) reported a higher diffusivity in preterm infants in the prefrontal, parietal, motor, somatosensory and visual cortices, and Dimitrova et al. (Dimitrova et al., 2021) reported increased cortical tissue water content and reduced neurite density index in posterior cortical regions, and greater cortical thickness in anterior cortex, in preterm compared with term-born infants. Sensory areas and posterior regions of the cortex have the largest maturational changes in microstructural and morphological profile around birth (Fenchel et al., 2020; Garcia et al., 2018), while the network of cortico-cortical connections involving sensory-motor and transmodal integration regions is characterised by a higher complexity in term compared with preterm infants (Blesa et al., 2021). Together with our findings, this suggests that cortical maturation in these regions is vulnerable to the impact of preterm birth.

Previous studies have characterised the maturation of microstructure in the preterm brain by measuring deviation from developmental trajectories estimated in term subjects (Dimitrova et al., 2020; Dimitrova et al., 2021) and have shown a high inter-individual heterogeneity in microstructure maturation throughout the cortex. Compared with these works, which examined each microstructural metric in isolation, we studied the joint variation of multiple microstructural properties to observe the impact of prematurity on cortical organisation. Our results complement these previous findings by showing that, overall, despite individual variability in deviation from normal development, prematurity results in locally homogeneous patterns of variation in a substantial portion of the cortex.

In the TEBC dataset, a region of the medial frontal lobe showed increased homogeneity of microstructure in the term subjects compared with the preterm group (Figure 7). We note that care must be taken when interpreting results along the midline sagittal plane, as they might be influenced by image processing artifacts (e.g., due to a
brain-size bias causing alignment errors in the preterm group) or cerebrospinal fluid contamination due to partial volume effects. The presence of diverging patterns of increased and decreased homogeneity could indicate that early exposure to the extra-uterine environment causes dysmaturity in a region-specific manner. Different cortical regions mature at different rates, with the insular cortex developing first, and the sensorimotor cortex maturing earlier than association cortices. This is reflected by increasing cortical anisotropy which occurs first in primary somatosensory regions and later in the frontal cortex (Bataille et al., 2019; Neil & Smyser, 2018). Prematurity can cause deviations from typical maturational trajectories, for example with primary and non-primary auditory cortices showing a delayed maturation in preterm infants at term-equivalent age (Monson et al., 2018). However, we did not observe decreased homogeneity of microstructure in any region in the dHCP dataset. The variation in results across datasets may be explained partly by unmodelled sample variability (e.g., in illness severity, ethnicity, socioeconomic factors and nutrition), and power differences, but any interpretation needs to be made in the context of the different experimental conditions. We investigated whether the observed variability was a consequence of differences in cortical metrics (Appendix A), that in turn might be driven by partial volume effects, and found that they could explain
only in part our results. We also compared single-metric cortical maps between datasets (Appendix B), finding differences in most part of the cortex, but with varying spatial patterns. In another experiment (results not shown), we regressed sulcal depth directly from VB maps, but it did not have any effect on the results. As our goal was to assess the replicability of VB index differences in independent datasets, we did not attempt any data harmonisation, but these results serve as a caveat for future retrospective multi-site studies. State-of-the-art harmonisation methods have the potential to minimise site-related differences especially in diffusion data (Ning et al., 2020), for which the processing was not harmonised in the current study. Allowing for these limitations, the existence of corresponding findings across the two datasets provides evidence of generalisability and indicates that the VB index is robust to scanner differences and methodological variation.

To conclude, the VB index is a promising metric for investigating upstream determinants of cortical development. In contrast to whole-brain gradient methods, this approach provides superior anatomical precision, enabling detailed analysis of specific brain regions or structures. Through the integration of multiple MRI features into a single localised metric, the VB index offers a comprehensive framework for evaluating how clinical and environmental variables impact the cortex in an integrated analysis. For example, future work could investigate whether the pattern described by the VB index underlies differences in cognitive and functional development observed in preterm infants. Elucidating the link between the widespread alterations in cortical microstructure observed in the preterm brain in the neonatal period and long-term outcomes will be important for study designs that would benefit from robust risk prediction in early life.

AUTHOR CONTRIBUTIONS
Conceptualisation, methodology, software, formal analysis, writing – original draft: PG. Methodology, software, formal analysis, data curation, writing – original draft: MBC. Methodology, software, writing – review and editing: CF. Investigation, data curation, writing – review and editing: KV. Software, writing – review and editing: LZJW. Investigation, data curation, writing – review and editing: GS. Investigation, writing – review and editing: DQS. Investigation, writing – review and editing: AJQ. Software, writing – review and editing: AM. Investigation, methodology, writing – review and editing: MJT. Investigation, methodology, writing – review and editing: MEB. Conceptualisation, writing – review and editing: HR. Conceptualisation, methodology, writing – review and editing: HW. Conceptualisation, writing – review and editing: ADE. Conceptualisation, methodology, software, writing – review and editing: CJB. Conceptualisation, methodology, software, writing – review and editing, supervision: ECR. Conceptualisation, writing – review and editing, supervision, resources, funding acquisition: JPB.

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CONFLICT OF INTEREST STATEMENT
The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT
Requests for TEBC anonymised data will be considered under the study’s Data Access and Collaboration policy and governance process (https://www.ed.ac.uk/centre-reproductivehealth/tbec/about-tbec/for-researchers/data-access-collaboration/). Any additional data supporting the findings of the study will be made available through the Edinburgh DataVault (https://doi.org/10.7488/e65499db-2263-4d3c-9335-55ae6d49af2b). Information on how to access dHCP data is available at the project homepage (https://biomedical.github.io/dhcp-release-notes/). The cortical template and the registrations for the dHCP dataset are available at https://brain-development.org/brain-atlas/atlases-from-the-dhcp-project/cortical-surface-template/. Code to reproduce the analyses presented in this paper is available at https://git.ecdf.ed.ac.uk/jbr/natali-vbi. The VB toolbox is available at https://github.com/VBIndex/py_vb_toolbox.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.