Prefrontal Cortical Folding of the Preterm Brain: A Longitudinal Analysis of Preterm-Born Neonates

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Abstract. Very preterm birth (less than 32 weeks completed gestation) coincides with a rapid period of brain growth and development. Investigating the changes of certain brain regions may allow the development of biomarkers for predicting neurological outcome. The prefrontal cortex, associated with the executive function, undergoes major changes during the last 10 weeks of pregnancy, and therefore its development may be altered by very-preterm birth. In this paper we use surface-based spectral matching techniques to analyse how the prefrontal cortex develops between 30 weeks and 40 weeks equivalent gestational age in 5 infants born preterm. Using this method, we can accurately map the regions where the secondary and tertiary sulci and gyri of the prefrontal cortex will form. Additionally, measurements of cortical curvature can be used to estimate the local bending energy required to generate the observed pattern of cortical folding. Longitudinal measurement of the cortical folding change can provide information about the mechanical properties of the underlying tissue and may be useful in discriminating mechanical changes during growth in this vulnerable period of development.

1 Introduction

Infants that were born prematurely are at higher risk of developing cognitive and neurologic impairment from an early age, despite the advances in neonatal intensive care [1]. During the last 10 weeks of pregnancy, major changes occur in the appearance and connectivity of the fetal brain. During this relatively short period of time, the cortex develops from a lissencephalic state and dramatically increases in volume and surface area [2]. Following premature birth the structural development of the brain takes place under the altered conditions of the extrauterine environment. Recently, there has been much interest in understanding changes in brain development during the preterm period [3]. Accurate measurements of the preterm brain during this early post-natal period may yield predictive biomarkers of neurological outcome.

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Of particular interest, the prefrontal cortex (PFC) is situated in the anterior part of the frontal lobes of the brain, inferior to the motor and premotor areas. This neocortical region is thought to play an important role in cognitive control, executive function and habituation [4]. Because of its anatomical connections with the cortical and subcortical centres, important for movement control, the PFC plays a role in coordinating motor function. Thus, accurate measurements in this region, in particular its volume and shape change, might be predictive of early delays in motor control. The development of the superior, middle and inferior gyri of the PFC takes place mostly during the last trimester of pregnancy, later than the parietal and occipital cortex, making it possible to study it using longitudinal data of infants aged between 30 and 40 weeks estimated gestational age. The superior frontal gyrus of the PFC becomes defined by 25 weeks of gestation [5]. The inferior frontal sulcus is visible by 28 weeks gestational age (GA), followed by the delineation of the middle and inferior gyri [5]. All three main gyri shows secondary gyri at about 32 weeks GA, while tertiary gyri are distinctive by 40 weeks GA [5]. Due to its development timing, of the PFC may be affected by preterm birth.

Matching of cortical surfaces is a challenging process and most methods that address this problem are are based on either optimising flows, such as LDDMM [6], or on inflating surfaces to a common template which is usually a sphere, such as FreeSurfer [7] and Spherical Demons [8]. However, both of these methods are computationally expensive. Spectral graph methods offer a fast alternative to matching shapes in the spectral domain [9].

In this paper we use Joint-Spectral Matching techniques [9] to measure the longitudinal change in the cortical folding patterns of the same preterm-born infants between 30 weeks equivalent gestational age (EGA) and term equivalent age. Determining such correspondence yields information about the dynamics of cortical folding, shape change, surface areas and volume growth rates of different regions. This type of longitudinal correspondence will enable the understanding of the development of the PFC during this crucial period, how it is affected by preterm birth and how it might influence neurological outcome. Furthermore this type of research might begin to illuminate the debate on the mechanical role of tissue growth on the observed cortical folding pattern, information that is only measurable in feral and neonatal cohorts of this type.

2 Methods

Subjects. Volumetric T_1-weighted images were acquired for five infants (Mean Gestational Age at Birth (GAB) of 26.0 ± 0.9 weeks) acquired on a Philips Achieva 3T MRI machine. T_1-weighted data was acquired at a resolution of $0.82 \times 0.82 \times 0.5mm$ at TR/TE $=17/4.6ms$, acquisition duration $462s$. The infants were scanned at first at around 30 weeks EGA (33w+1d, 31w+3d, 31w, 29w+6d, 31w+6d) and then at around 40 weeks EGA (40w+1d, 42w, 42w, 46w+2d, 40w+2d).

Infant Brain Segmentation. Brain masks and priors for automated segmentation of the 40 week EGA scans were propagated from a publicly available

neonate brain atlas [10]. Brain masks for the early 30 week EGA scan were propagated from the 40 week EGA mask. All masks were checked and manually corrected to exclude any non-brain tissue that can generate mislabelled voxels.

We segmented each infant brain into six different parts: grey matter, white matter, cerebrospinal fluid (CSF), deep gray matter, cerebellum and brainstem, using a preterm specific Expectation-Maximization (EM) segmentation with prior relaxation [11].

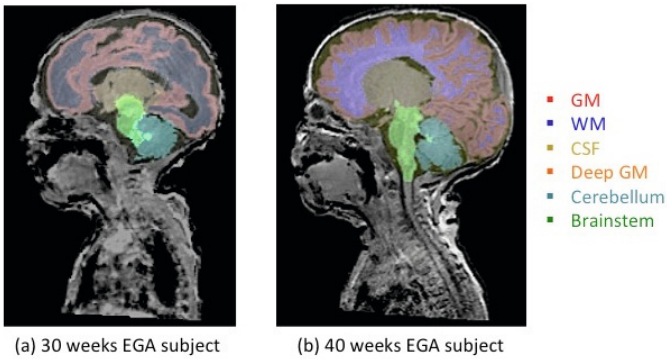

Fig. 1. Brain segmentation into grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), deep grey matter, cerebellum and brainstem of the same infant for the two different time points: 30 and 40 weeks EGA respectively

In order to separate the prefrontal cortex from the rest of the brain, we used a multi-contrast human neonatal brain atlas [12] registered to the space of the early and late scans using non-rigid registration. The corresponding regions of the prefrontal cortex were grouped by hemisphere: left and right PFC.

The white matter segmentation was then combined with the delineation of the PFC. Any segmentation errors were corrected by morphological operations (largest component and filling of the holes) to ensure a topologically correct surface. The processed left and right white matter PFC segmentation were used to create smooth triangle-based meshes of each surface.

Joint-Spectral Matching of the Cortical Surface. A rigid Coherent Point Drift (CPD) algorithm (translation and rotation) was used to find an initial correspondence for the intra-subject prefrontal cortex at the two different time-points [13]. Since the two paired meshes are very different in shape, size and morphology, the CPD is preferable to the Feature Oriented Correspondence using Spectral Regularization (FOCUSR) [14], a conventional spectral method that requires a robust eigenvector reordering, which is challenging with our meshes. After initial correspondence was established, Joint-Spectral Matching (JSM) was used to find the correspondence for the intra-subject prefrontal cortex at 30 week EGA and term equivalent age for each subject [9]. The use of a joint-spectral

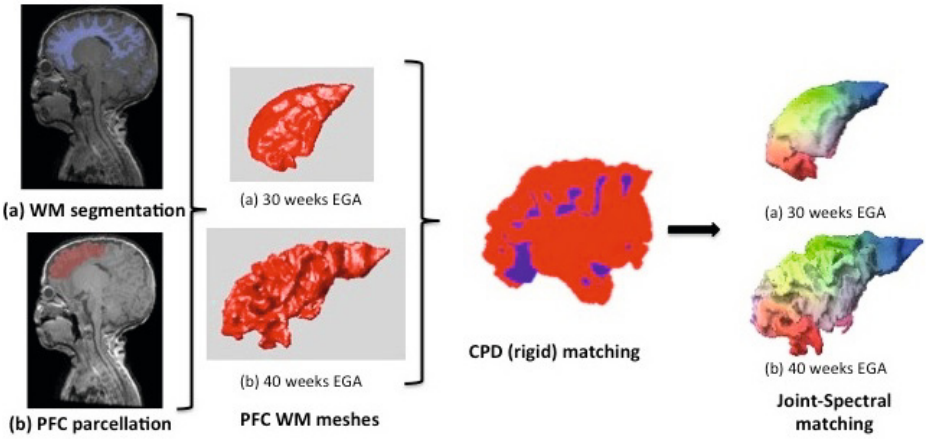

Fig. 2. The spectral matching algorithm. After preterm-specific segmentation, meshes are defined for the 30 and 40 week timepoints. After Coherent Point Drift initialisation, a mesh correspondence is defined by Joint-Spectral Matching (spectral matching colour-coded anterior-posterior).

matching technique is important for data of this type due to the longitudinal nature of the change being measured. The algorithm is summarised in Figure 2.

Application of this technique also allows us to find correspondence between all the 30w meshes in order to carry out a group analysis of cortical change in this preterm period.

Measurement of Longitudinal Development. To quantify the early cortical folding we computed the principal curvatures κ_1 and κ_2 for each vertex of the surface mesh from which we derived the mean and Gaussian curvatures, $M = \frac{1}{2}(\kappa_1 + \kappa_2)$ and $G = \kappa_1\kappa_2$, respectively. Because of the uniqueness of the application, we decided to choose well-known measures of curvature for the measurement of longitudinal change in each individual.

Additionally, we computed the bending energy (E) [15], which is intuitively dependent on the local surface area change. The change in the bending energy, over time and over area, describes the energy needed to deform that area over the corresponding period of time, thus providing information about the mechanical properties of the underlying tissue:

$$\frac{\partial E}{\partial t} = \frac{\partial}{\partial t} \int ({\kappa_1}^2 + {\kappa_2}^2) dA \tag{1}$$

To investigate the longitudinal development of the prefrontal cortex for each subject, we mapped the 40 week PFC to the 30 week PFC using the JSM and computed the change of the surface parameters at each vertex of the mesh. The longitudinal change in all the parameters (M, G, E) can be computed by measuring the change between the parameter value at any given point on one surface and its corresponding point on the other surface given the local volume and area change. The surface area of the 30 and 40 week meshes may be estimated

by calculating the sum of the triangle areas of each region. The correspondence between the areas can be estimated and thus this defines a local measurement of surface area change. Additionally, the volume enclosed in the triangular surface mesh is computed using the divergence theorem.

The values for the mean and Gaussian curvature were corrected for brain volume by dividing each value by the cube root of the ratio of the subject's PFC white matter volume and mean PFC white matter volume of the 30 and 40 week EGA. The difference in total curvature (sum of squared principal curvatures) was corrected by taking into account the local area change between the 30 and 40 week subjects to obtain the bending energy. The total curvature value of each vertex in the 40 week mesh was divided by the local area change at that vertex and then mapped into the space of the 30 week mesh, where it was multiplied by the local area change in the 30 week mesh.

We also carried out a group analysis, using JSM, by mapping all changes into the space of one subject at 30 week and computed the surface parameters at each vertex of the mesh. Again, we took into account the different volumes of each 30 week subject and corrected the mean and Gaussian curvature by dividing them by the cube root of the ratio of the subject's PFC white matter volume and mean PFC white matter volume of all 30 week subjects.

3 Results

FOCUSR and CPD Correspondence. We found a very good point qualitative correspondence between all 5 pairs of 30 and 40 week meshes of both hemispheres for all subjects. Finding an initial correspondence was challenging due to differences in shape, size and morphology of the meshes, but using a rigid CPD for initialisation (Figure 3 B) improved the initial result (Figure 3 A).

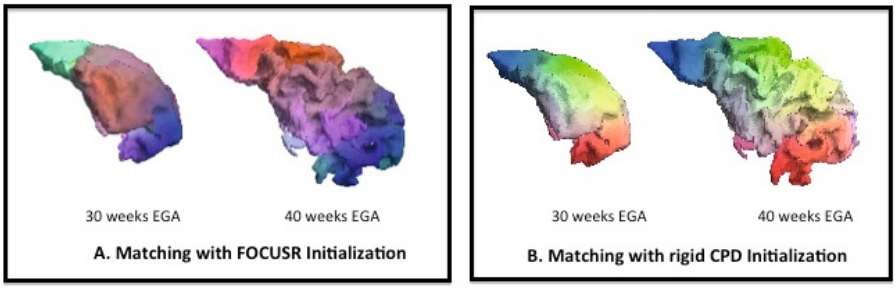

Fig. 3. Initialization using FOCUSR with a wrong eigenvector ordering gives poor correspondence (A). We use a method not prone to such issues, such as rigid CPD (B).

Longitudinal Correspondence Between 30 and 40 Weeks. Figure 4 and 5 shows an example of maps of mean curvature changes and Gaussian curvature changes, respectively, for the prefrontal cortex white matter of a subject scanned

at 31 weeks and 42 weeks EGA. The maps of mean and Gaussian curvature change in 30 week space (Figure 4 (d) and Figure 5 (d)) show the locations where the secondary and tertiary sulci and gyri will be formed, as well as how the primary sulci and gyri will develop. These changes are commensurate with [5].

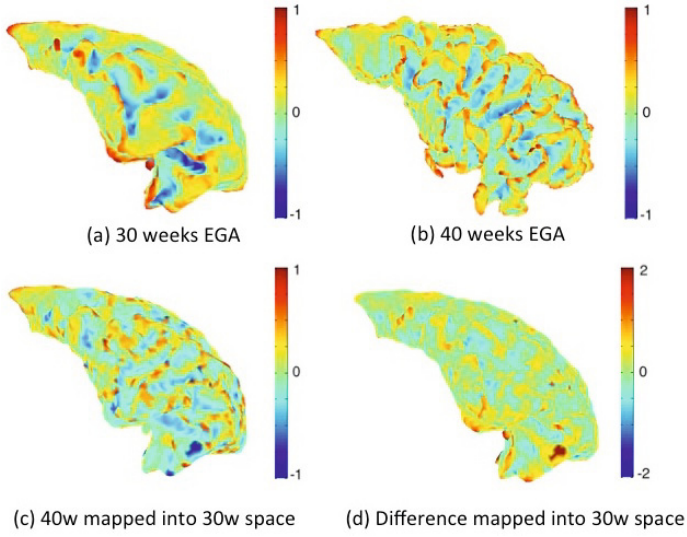

Fig. 4. Maps of mean curvature changes for one subject scanned at 31 and 42 weeks EGA

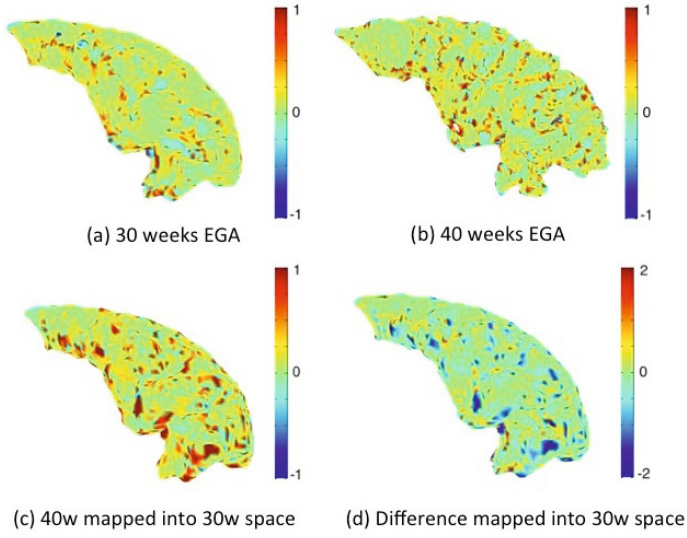

Fig. 5. Maps of Gaussian curvature changes for one subject scanned at 31 and 42 weeks EGA

It can be observed however that the Gaussian curvature is very sensitive to the geometric errors on the surface and thus not as reliable and useful feature for cortical surface analysis like the mean curvature.

From the maps of change in bending energy (Figure 6 (d)), we can notice the amount of energy required for the folding gyri and sulci between the two time points, as anticipated. As mentioned before, the bending energy depends on both the total curvature difference and the change in local surface area. The map of local surface area change (Figure 6 (c)) shows that the inferior prefrontal cortex undergoes more changes than the superior prefrontal cortex and expands the most overall. The superior cortex undergoes almost no change, which is expected since it develops and folds mostly before 30 week and only minor changes happen after [5].

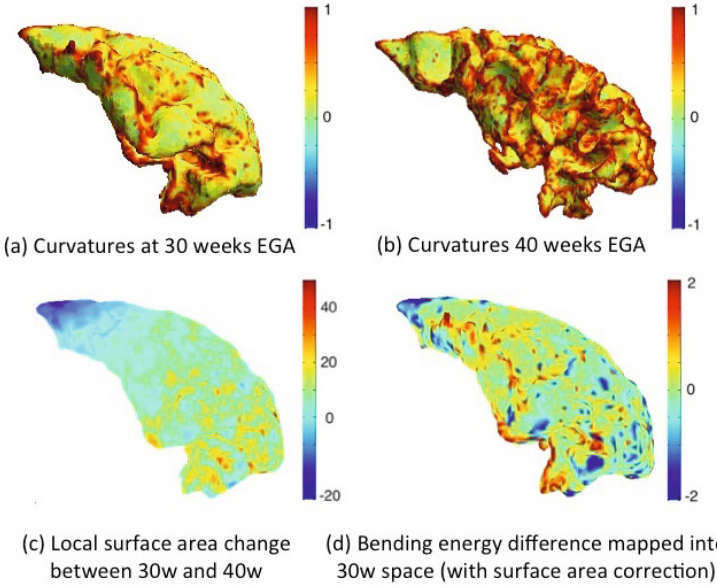

Fig. 6. Total curvature shown for 31w (a) and 42w (b) EGA, local surface area change (c) and bending energy required (d) for one subject

Group-Based Analysis at 30 Week GA. A group analysis was performed by mapping all the the changes into the space of a 30 week EGA and maps of average change in mean curvature, Gaussian curvature and local area change were obtained over the cohort.

From the maps of mean and Gaussian curvature (Figure 7, (a) and (b)), we notice the same folding trend as in the individual results, i.e. the same sulci and gyri are developing, however the overall changes are smaller than in the one particular case shown above, probably due to the variation of each individual subject and their gestation age at birth.

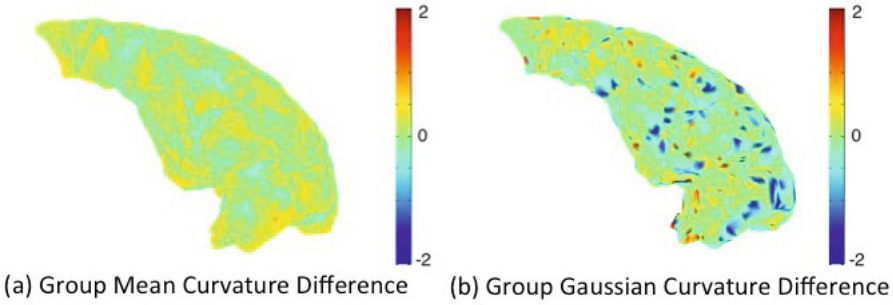

Fig. 7. Maps of average mean and Gaussian curvature change for 5 infants

The map of local area change (Figure 8, (a)) shows that the inferior PFC expands the most, while the surface of the superior PFC undergoes almost no change, as before. We computed the total surface area of the each hemisphere of the prefrontal cortex for all 5 subjects and plotted them as a function of estimated gestational age in order to compute the rates of change. By using a linear fit, we can estimate the surface area increase rate of the left hemisphere of the PFC to be $5.21cm^2$ ($R^2 = 0.94$) and the slightly higher increasing rate for the right hemisphere to be $5.67cm^2$ ($R^2 = 0.92$).

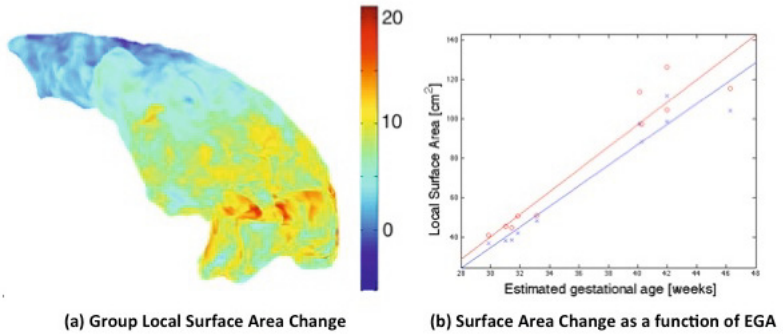

Fig. 8. Surface area change for all 5 subjects. A. The average local surface area change; B. The total surface area change of each PFC hemisphere as a function of EGA for all 5 infants: blue represents the left hemisphere and red the right hemisphere.

4 Discussion

In this work, we used joint spectral matching techniques to find the correspondence between the prefrontal cortex of the same 5 preterm infants at 30 and 40 weeks EGA, a quite novel method that has much potential for assessment of preterm development. The dataset we have is quite unique and although it

would be ideal to have more time points for a longitudinal study, this is not achievable because the infants are extremely preterm and receiving intensive medical support. Another issue is introduced by the fact that many subjects in the study could not undergo both sets of scans due to healthcare complications, which again limits the number of subjects part of a longitudinal study.

Although qualitatively we obtained a very good correspondence for the intra-subject and inter-subject prefrontal cortex, it is very difficult to validate this cortical matching, since the data is quite novel and there is no proper way of establishing a ground truth. The prefrontal cortex undergoes major changes during this period of time [5]. We mapped the folding of the PFC occurring in this rapid period of development by investigating the change of the mean and Gaussian curvatures as well as the bending energy required for the folding. The uniqueness of the application motivated us to choose well-known measures of curvature and cast these as a measurement of longitudinal change in the individual. This is appropriate for a new application of the technique such as here in contrast to new and unfamiliar measures of curvature. As stated, we have a particular interest in the bending energy because it can provide information about the underlying tissue deformation and can be interpreted directly as a measurement of change in the infant folding pattern. The maps of mean and Gaussian curvature over the entire cohort provide us with information about gyrification of normal preterm development, and therefore can be used as baseline for further subjects and identify these infants that do not follow this trend.

This work will be extended to finding correspondences for the whole brain. However, the folding pattern of the parietal and occipital cortex is much more advanced than the frontal and pre-frontal region, thus differences may be more difficult to quantify. Furthermore, the correspondence between the 30 and 40 week scans can be correlated with diffusion imaging in order to determine the relationship between the mechanism of the surface cortical folding and underlying changes in connectivity, particularly the establishment of associative cortico-cortical connections which occurs over this 30-40 week period. Combined measurements of this type have the potential to investigate the mechanical and cellular processes leading to gyrogenesis. Our immediate future work will investigate correlations between the rates of cortical folding and neuropsychological outcomes during infancy and childhood.

Generating accurate correspondences between the intra-subject prefrontal cortex at multiple time points enables us to measure the longitudinal changes that take place in this region in preterm infants. These measures may contribute to early biomarkers for predicting executive and motor development.

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