Spatio-Temporal Modelling of Laminar Neurodevelopment from Fetal MRI

Ernst Schwartz[1], Gregor Kasprian[1], András Jakab[1,2], Veronika Schöpf[3], Daniela Prayer[1] and Georg Langs[1⋆]

[1] Computational Imaging Research Lab and Division of Neuroradiology and Musculoskeletal Radiology, Department of Biomedical Imaging and Image-guided Therapy, Medical University Vienna ernst.schwartz@meduniwien.ac.at
[2] Center for MR-Research, University Children's Hospital Zürich
[3] Institute of Psychology, University of Graz
veronika.schoepf@uni-graz.at

Abstract. Brain development in the fetal stage is characterized by differential growth of both transient and preserved cell layers between the proliferative subventricular zones and the expanding cortical sheet. The time-courses and regionalization patterns of these processes determine brain morphology and function and are therefore at the root of crucial neuroscientific questions such as genetic determinants of brain development and disease mechanisms. Studies of the cortical lamination process are to date mostly limited to ex-vivo histological methods, studies on model organisms or in vivo studies of short periods of gestation. Notably, analysis of local cortical development in large cohorts is lacking due to challenges in establishing reliable corrrespondences between surfaces of the cerebral cortex during gestation. In this paper, we propose a first step towards linking knowledge about micro- and macroscopic cerebral brain development. Applying recently developed methods from differential geometry on a dataset of more than 300 fetal MRI acquisitions allows us to model the progression of cerebral lamination between the 20th gestational week and term. In doing so, we find significant inter-hemispheric differences in these models with interesting links to structural and functional lateralization in children and adults.

1 Introduction

The human cerebrum undergoes rapid expansion during the fetal period, growing from a smooth lissencephalic shape to its highly convoluted form conserved until adulthood. Due to efforts in imaging and genetics research, knowledge about the developing fetal brain has increased considerably in the last decades [1–3]. Fetal brain growth relies on histogenic processes occuring in transient layers between the ventricular and pial surfaces [4]. The dynamic laminar cytoarchitectonic structure of the developing brain parenchyma is visible both in histological preparations and magnetic resonanace imaging (MRI) [5].

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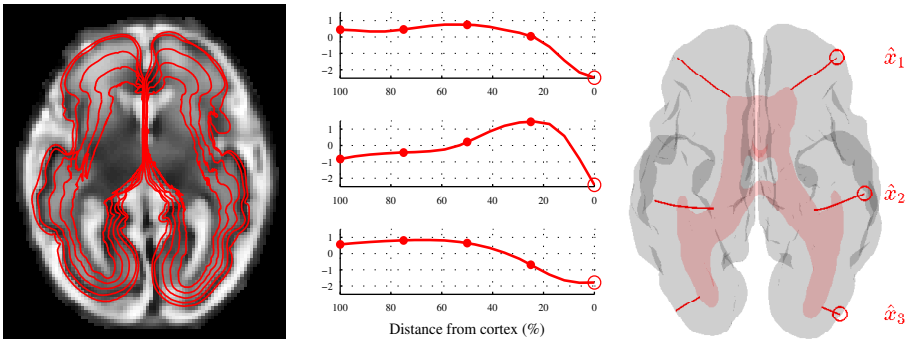
At the macroscopic level, both pre- [6–8] and post-natal [9] MR imaging studies have revealed distinctive patterns of development during gestation as well as regional differences in growth, notably in perisylvian areas. By manually delineating proliferative and migratory layers in the developing cortex, various groups were able to establish the time-course of parenchymal development in the whole brain [10] or anatomically defined subregions [11].

Largely due to the challenging problem of establishing comparative surface models between morphologically different cortical surfaces and the limited availability of healthy in utero data, a gap remains between the understanding of localized brain development and the underlying microscopic processes. Recently, methods based on the spectral decomposition of differential geometric operators have been successfully applied to the matching between cortical surfaces at comparable morphological maturity [8]. In this paper, we extend these methods to establish spatio-temporal models of laminar neurogenesis in the fetal brain as observed in in utero MRI. In contrast to previous work, the proposed method does not require manual annotation of brain layers and allows to model brain development over the whole course of gyrification at consistent locations on the cerebral cortex. After evaluating the proposed model in terms of repeatability on independent datasets, we show that it can be used to establish a potential link between radial progression of neural development and local morphological brain lateralization.



(a) Illustration of radial sampling locations $p(x_{r_1}) \dots p(x_{r_5})$

(b) Radial intensity profiles $I(p(x_{r_1}), \dots, p(x_{r_5}))$ (z-scores)

(c) Tracks $p(\hat{x}_i)$ between cortex (gray) and ventricles (red)

Fig. 1: Radial intensity profiles $I(p(x))$ are sampled at corresponding locations $\hat{x}_i$ at a fixed number of levels m (5 for illustration) between cortex and ventricles.

2 Method

We use a sequence of established methods for processing fetal MRI data to obtain normative spatio-temporal models of brain tissue maturation during gestation, related to the microstructural development of the fetal brain.

2.1 Tissue Segmentation in Fetal MRI

In order to limit the influence of maternal and fetal motion, in utero acquisitions of fetal anatomy are performed using fast Rapid Acquisition with Refocused Echoes (RARE) T2 sequences [13] with increased slice thickness. Combined registration and slice-wise motion correction followed by super-resolution reconstruction [14] is then applied to axial, coronal and sagittal slice stacks to establish an isotropic volume $I : \Omega \rightarrow \mathbb{R}$, $\Omega \subset \mathbb{R}^3$ containing the fetal brain.

We use a publicly available atlas [12] to segment the fetal brain from in utero MRI. Specifically, we manually annotate the most frontal and occipital points of the lateral ventricles to initialize a sequence of affine and non-rigid intensity-based registration steps relying on the consistent contrast between cerebrospinal fluid (CSF), developing white matter and cortex. We use the resulting deformation fields to map tissue probability maps onto the patient anatomy, which serve as priors to a second-order Markov Random Field (MRF) segmentation procedure [15] and provide an initial delineation of ventricular and subarachnoid CSF, the cortical zone and remaining brain parenchyma.

Ventricle Segmentation MRF-based segmentation of the ventricles contains errors originating from various sources such as MR signal inhomogeneities due to field bias or CSF flow as well as artifacts in the motion correction or super-resolution procedures. These can be alleviated via a second segmentation step of the ventricles using level-sets [16], resulting in an estimate for the volume $V \subset \Omega$ occupied by ventricular CSF.

Cortical Segmentation Especially in older fetuses, image resolution is insufficient to allow for an accurate delineation of the convoluted cortical sheet using MRFs. We therefore apply morphological operations to enhance the constrast of the cortical sheet in the volumetric image I [17] and preform surface-based segmentation. We initialize the procedure with models for each cerebral hemisphere obtained from the MRF segmentation that have been mapped to the sphere to enable inter-hemispheric matching [18] and denote the final estimate of the cortex ∂C.

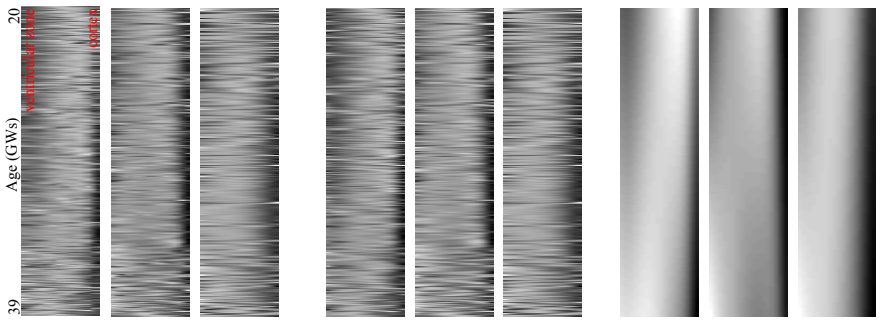
2.2 Tracing Potential Radial Cell Migration Paths

Brain growth during gestation is driven by successive waves of neuronal proliferation, migration and cytoarchitectonic changes [3]. In order to approximate the paths travelled by the different types of neural cells during growth, we establish a

distance map in the parenchymal layer between the border ∂V of the ventricular region and the cortical sheet ∂C by solving for f in the Eikonal equation

$$|\nabla f(x)| = 1 \; \forall x \in \Omega, \quad f(x) = 0 \; \forall x \in \partial V \tag{1}$$

The Eikonal equation is commonly used to approximate problems of propagation in a medium and can be solved efficiently using the Fast Marching Method [19]. By performing particle tracking starting at cortical surface model vertices $\partial C(x)$ in ∇f using Euler integration we can then trace non-intersecting paths $p(x)$ between the cortical sheet and the ventricular zone, and sample corresponding radial intensity profiles $I(p(x))$. In practice, we evaluate $p(x)$ at a fixed number of locations $x_{r_1} \dots x_{r_m}$ resulting in m concentric surface models (Figure 1a) and normalize their intensities to z-scores.



(a) Original radial profiles at 3 exemplary locations $\hat{x}_{(n,1\dots3)}$ sorted by gestational age $t(n)$.

(b) Radial intensity profiles reconstructed from low-rank approximations $U^n(p(\hat{x}_{1\dots3}))$.

(c) Longitudinal intensity profiles reconstructed from $(a_{1\dots3}, b_{1\dots3})$ for $t \in (20, 39)$

Fig. 2: Normative models of radial intensity $I(p(\hat{x}_i))$ development over time can be established from point-wise correspondences at locations $\hat{x}_i$ (sampling locations matching Figure 1).

2.3 Establishing Models of Spatio-Temporal lamination

Inter-patient surface matching Accurate matching of cortical surface models is required for inter-patient comparison of lamination patterns. In contrast to adults, the surfaces of fetal brains appear smooth on in utero MRI until approximately the 20th gestational week (GW), when first sulci and gyri can be discriminated [20]. Thus, geometrical features required for establishing correspondences between surfaces are not consistently available over the whole observed period. We proceed in a two-step fashion to establish a common reference frame for all cases and GWs. First, surface models of the cerebral hemispheres

at consecutive GWs obtained from the atlas images of [12] are matched using the spectrum of the Laplace operator of the cortical surface models [21]. Then, joint embedding [8] of atlas models at GWs 19-37[1] is performed. The models ∂C_n of an individual case n can then be resampled at corresponding surface locations $\{\hat{x}_{(n,i)}\}, \hat{x}_{(n,i)} \in \partial C_n$ by matching with the closest time-point in this spatio-temporal surface atlas using the same method.

Spatio-temporal modelling We aim at establishing models of change in appearance of the laminar intensity profiles $I(p(\hat{x}_i))$ (Figure 2a) over time. In order to distinguish important information from measurement errors and noise, we perform low-rank approximation using principal component analysis (PCA) such that $I(p(\hat{x})) = U(\hat{x})\Sigma W + \epsilon$, $U(\hat{x}) \in \mathbb{R}^{k \times l}$, $l < m$. We then fit linear models to the components U at each surface location $\hat{x}_i$ by solving

$$\sum_{n=1}^{N} \left\| U_n(\hat{x}_i) - (a_i + b_i t(n)) \right\|_2^2 \tag{2}$$

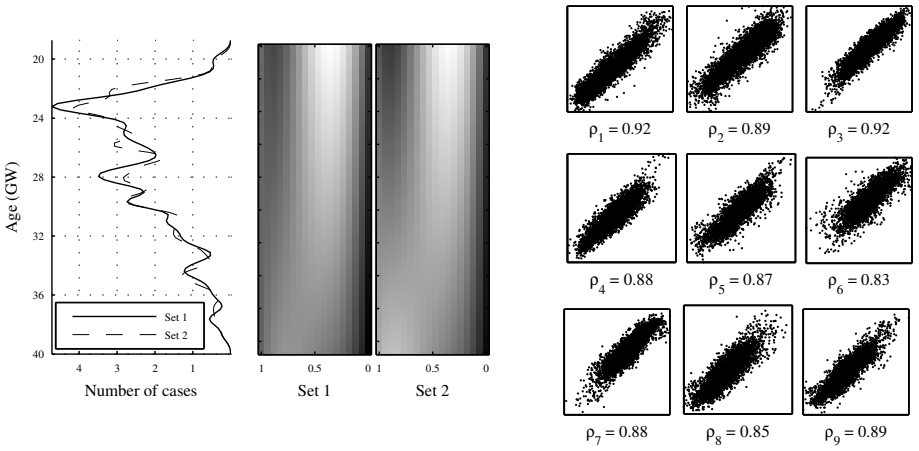
for N surface models observed at gestational weeks $t(n)$. Progression of changing intensities between a point $\hat{x}_i$ on the cortical surface and its associated location in the ventricular zone in terms of the solution to Equation 1 is then represented by the tuple (a_i, b_i), whereas normative longitudinal intensity models for specific locations can be reconstructed as $I(p(\hat{x}_i)) \approx (a_i + b_i t(n))\Sigma W$ (Figure 2c).

2.4 Dataset and Parameter Settings

The dataset used for evaluation consists of 311 in utero fetal MRIs acquired between 2012 and 2015 at Vienna General Hospital during clinical examinations indicated from maternal ultrasound. Imaging was performed on a 1.5T Philips Gyroscan unit without any maternal or fetal sedation. Consecutive T2-weighted scans were acquired in approximate axial, coronal and sagittal planes of the fetal brain with an in-plane resolution of 0.78-0.9mm and slice thickness of 3-4.4mm and reconstructed as described in Section 2 to isotropic volumes with voxel dimension 1mm^3.

Cortical surface segmentations result in surface models with $|\{x_i\}| = 40962$ sampling points and are consequently resampled at $|\{\hat{x}_i\}| = 2562$ matching locations. Paths p between cortical and ventricular zones were initially sampled at 20 concentric layers, but the 2 closest to the ventricles had to be removed from the analysis due to partial voluming and segmentation artifacts, resulting in a representation $I(p(\hat{x})) \in \mathbb{R}^{2562 \times 18}$ for each cortical hemisphere in each case. PCA was then performed on the concatenation of the representations of all cases and hemispheres. In order to retain 99% of the variability in this dataset, the 5 largest principal components U in Equation 2 were kept.

[1] We extended the atlas of [12] to GWs 19-22 using additional data.



(a) Kernel density estimate of GW distribution and average intensity profiles in sets S_1 and S_2

(b) Correlation between individual PCA modes of sets S_1 and S_2

Fig. 3: The repeatability of the method was evaluated on two disjoint datasets S_1 and S_2. The obtained model coefficients showed high correlation (ρ) in all dimensions.

3 Results

We evaluate the proposed method on a large dataset of fetuses with unaffected brain development. By comparing the results obtained on two disjoint subsets we show that the method is repeatable and accurately captures the developing intensity profiles of changing cortical lamination during gestation. Analysis of the inter-hemispheric asymmetry of development signatures U shows interesting relationships with established knowledge about the micro- and macroscopic lateralization of brain morphology and function.

3.1 Repeatability

To evaluate the repeatability of the method, we split the dataset into two disjoint sets S_1 and S_2 of cases with matching distributions of gestational age (Figure 3). Qualitative comparison of the resulting average intensity profiles serves as quality control and shows little variability between the experiments (Figure 3a). We then computed separate linear models for $U_n(\hat{x}_i)$ and $U_m(\hat{x}_i)$, $I_n \in S_1$, $I_m \in S_2$, resulting in two sets of 10 (one constant and one linear term for each of the 5 principal components) values per surface sampling point $\hat{x}$. Correlation plots for the first 9 parameters[2] are shown in Figure 3b, with the average correlation between all dimensions reaching 0.93. As expected, correlation decreases with

[2] Correlation of the last parameter - the linear factor of the model of the 5th component - was $\rho_{10} = 0.66$.

component number, as higher components represent less stable properties of the observed data. However, it remains very strong, indicating that the proposed model is useful in capturing a measureable process of tissue development.

3.2 Developmental asymmetry

Figure 4 shows the t-values of regions exhibiting asymmetry in terms of the model parameters (a_i, b_i) at a vertex level. Observations have been thresholded at significance level of 0.01 after correction for false discovery rate (FDR).

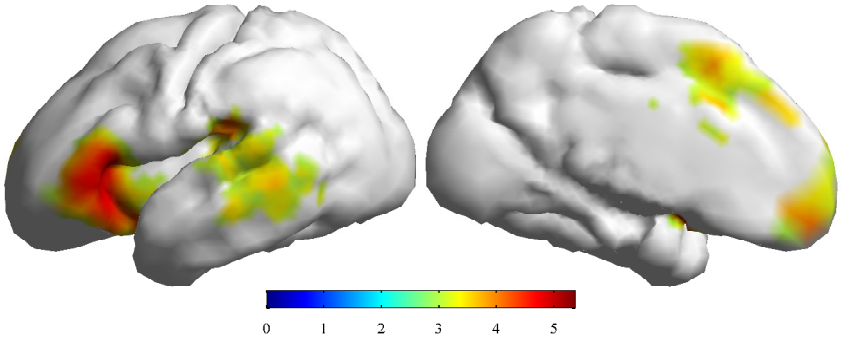
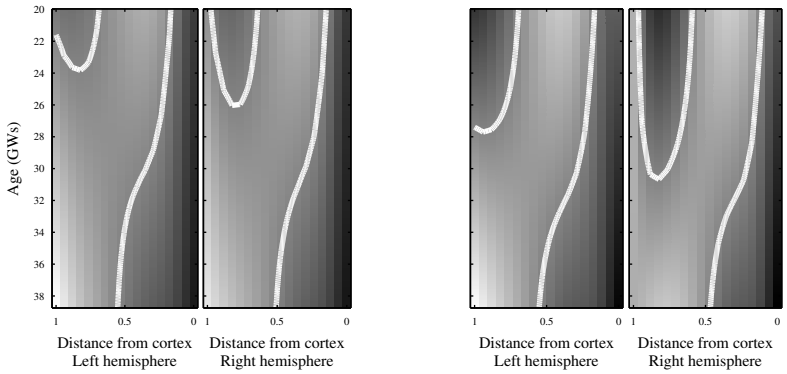


Fig. 4: T-values of regions showing significant (corrected for FDR at threshold of 0.01) different model parameters (a, b) of developing intensity profiles, rendered on the average surface model of the left cerebral hemisphere of 311 cases in this study indicate lateralization in perisylvian, temporal and medio-frontal areas.

We observe that regions known for their morphological lateralization such as the planum temporale or the superior temporal region also show significant hemispheric asymmetry in terms of tissue development as captured by the proposed method. Additionally, regions such as the pars opercularis and pars triangularis of the inferior frontal gyrus that are structurally and functionally related to the tempo-parietal region due to their role in language processing also exhibit large inter-hemispheric asymmetry. Similar peri-sylvian regions were also found to exhibit lateralization of brain development as quantified using voxel-based morphometry in premature neonates [9], whereas both manual measurements of cortical morphology [11] and deformation-based morphometry in fetuses [22] also revealed developmental asymmetries at the level of the superior temporal sulcus (STS). Finally, developmental asymmetry could also be observed in the medial aspect of the superior frontal sulcus.



(a) Average profile in symmetric regions (b) Average profile in asymmetric regions.

Fig. 5: Normative models of radial image intensity in symmetricly and asymmetricly developing brain regions, the white line indicating the zero-crossing of the associated z-scores. Dark regions corresponding to the cortex (right) and germinal matrix (upper left) are clearly visible.

4 Discussion

Previous image-based studies on the development of the laminar cortical and subcortical structure of the fetal brain were mainly based on manual delination of specific layers and lacked point-wise comparability of measurements [23] or were performed in a volumetric fashion on a cohort of fetuses at similar gestational age [10, 6]. The proposed method allows for the first time to investigate the possible basis of the observed lateralization between GW 20 and up to term (GW 39). Figure 5 shows the average profiles in the regions showing significantly lateralized brain development (Figure 5b). Comparison with the normative model of the remaining regions of the brain (Figure 5a) reveals a longer persistence of the dense subventricular layer in the reported asymmetric regions, noticeable as a hypo-intense region in the upper left part of the profile images. While undoubtedly influenced by partial voluming at older gestational ages, these results nonetheless indicate a link between the timing of cytostructural processes such as cell proliferation and specialization occuring in the inner layers and the later migratory behaviour affecting the surface morphology of the developing brain. One possible explanation for the larger size of the planum temporale in the left hemisphere is a longer "waiting period" [4] of migrating cortical neurons as observable in the right hemisphere in Figure 5b or also a relationship between conical expansion of radial glia cells [24] and cell density.

The shape of the human cortex at birth is determined by a sequence of cytoarchitectural events such as cell proliferation, differentiation and migration. There are some inherent limitations to analysing these processes from the data available in this study. For one, image resolution in clinical fetal MR is too low to consistently discriminate between subtle transient compartments during the whole fetal period. Necessary image contrast could only be achieved either at

higher field strengths ex-vivo or using much longer scan times under sedation, a procedure that cannot be applied to the study of healthy human fetuses for ethical reasons. Also, the radial sampling of image intensities used in this paper can only be considered an approximation to true radial migratory pathways and inherently ignores tangential migration in the subcortical layers.

The models presented in this paper should thus not be interpreted as perfect correlates of histogenetic events in the fetal cerebrum. Rather, we have presented highly repeatable results on the regionalization of laminar organization during fetal brain development on a large dataset of standard clinical fetal MRI acquisitions. The proposed method allowed for the observation of developmental lateralization in language-associated areas in the fronto-orbital region associated to Broca's area and tempo-parietal regions around the planum termporale and Wernicke's area as well as surrounding the STS. The development of language is considered a hallmark in human brain evolution [25] and the STS has recently been shown to be a distinctive landmark in human brain morphology [26]. In this paper, we have presented evidence that these distinctively human traits can be linked to locally modulated histogenic processes in the proliferative layers of the cerebrum during gestation. We hope that these results motivate further research into the origins of our observations and help in assembling the puzzle of human brain evolution and development.

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