Revealing Regional Associations of Cortical Folding Alterations with In Utero Ventricular Dilation Using Joint Spectral Embedding

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Abstract. Fetal ventriculomegaly (VM) is a condition with dilation of one or both lateral ventricles, and is diagnosed as an atrial diameter larger than 10 mm. Evidence of altered cortical folding associated with VM has been shown in the literature. However, existing studies use a holistic approach (i.e., ventricle as a whole) based on diagnosis or ventricular volume, thus failing to reveal the spatially-heterogeneous association patterns between cortex and ventricle. To address this issue, we develop a novel method to identify spatially fine-scaled association maps between cortical development and VM by leveraging vertex-wise correlations between the growth patterns of both ventricular and cortical surfaces in terms of area expansion and curvature information. Our approach comprises multiple steps. In the first step, we define a joint graph Laplacian matrix using cortex-to-ventricle correlations. Next, we propose a spectral embedding of the cortex-to-ventricle graph into a common underlying space where their joint growth patterns are projected. More importantly, in the joint ventricle-cortex space, the vertices of associated regions from both cortical and ventricular surfaces would lie close to each other. In the final step, we perform clustering in the joint embedded space to identify associated sub-regions between cortex and ventricle. Using a dataset of 25 healthy fetuses and 23 fetuses with isolated non-severe VM within the age range of 26–29 gestational weeks, our results show that the proposed approach is able to reveal clinically relevant and meaningful regional associations.

Keywords: Joint spectral embedding · Ventriculomegaly · Fetal Cortical folding

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1 Introduction

During the intrauterine life, the fetal brain undergoes drastic maturational changes. Cortical folding is one of the major processes that occurs during this period, and any deviation from its normal developmental course might lead to adverse postnatal outcome [3]. In prenatal ultrasound examination, ventriculomegaly (VM) is the most frequent abnormal finding in the fetal brain. VM is a condition with dilation of one or both lateral ventricles, as shown in Fig. 1A. It is diagnosed as an atrial diameter larger than 10 mm at any gestational age [4]. Evidence of altered cortical folding associated with *in utero* VM has been shown by studies in the literature. Among their findings, cortical gray matter was significantly enlarged in fetuses with isolated VM [5]. Using curvature-based analysis, studies also found reduced cortical folding in the insula, the occipital lobe and the posterior part of the temporal lobe [2,9].

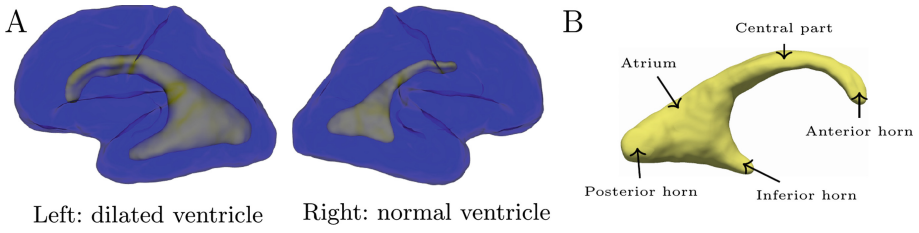

Fig. 1. A: Cortical and ventricular surfaces of a 28 gestational weeks fetus with left VM. B: Regions of the lateral ventricle.

To study the association between VM and the morphology of cortical folding, existing works either use diagnosis or ventricular volume to characterize this condition. Although ventricular volume captures the extent of enlargement and is more distinctive than the dichotomous information offered by diagnosis, a single scalar value might not be sufficient to provide all the information related to ventricular enlargement (e.g., spatial information about the dilated ventricular regions). In this work, we aim to find associations between ventricular regions (see Fig. 1B) and cortical folding by incorporating into our analysis the ventricular surfaces. For this purpose, we propose a novel approach to jointly analyze the cortical and ventricular shapes based on their growth patterns. The motivation of using growth patterns is their ability to reflect the underlying micro-structural brain changes. The main idea of our approach is to find a common underlying representation of the vertex-wise growth patterns of both cortical and ventricular surfaces such that vertices with associated patterns from both anatomical surfaces can lie close to each other. In this way, regional associations can be conveniently found by identifying clusters containing vertices from both surfaces in the new latent space. The contributions of our work are threefold:

– We propose a novel approach for joint analysis of different anatomical shapes based on their growth patterns.

– We identify, for the first time, spatially fine-scaled associations related to *in utero* VM between ventricular surfaces and alterations in cortical folding.
– We use fusion of similarity matrices to capture associations based on multiple cortical features.

2 Method

Given P subjects and their corresponding cortical and ventricular surfaces with N_c and N_v vertices respectively, for each subject, the growth patterns $\mathbf{x}_i$ for each vertex are represented by:

$$\mathbf{x}_i = [x_i^1, x_i^2, \cdots, x_i^P], \tag{1}$$

where x_i^k is the feature (e.g., local surface area) of the k-th subject at vertex i. In this study, growth patterns were built using a cross-sectional dataset. Although it is preferable to use longitudinal data, repeated *in utero* imaging is difficult due to ethical and practical issues.

Cortical and ventricular growth patterns are not necessarily to be represented using the same feature (e.g., we can use area for ventricles while curvature for cortices). We assume that there exists a common underlying representation for these heterogeneous growth patterns, $\mathbf{x}_i$, such that vertices of associated regions from both surfaces can lie close to each other and, most likely, form dense clusters. Thus, we propose to find a shared representation of cortical and ventricular growth patterns using joint projection onto a common space:

$$\begin{aligned} Y = \underset{Y}{\operatorname{argmin}} \sum_{i,j} \|Y_i^c - Y_j^c\|^2 S_c(i,j) + \sum_{i,j} \|Y_i^v - Y_j^v\|^2 S_v(i,j) \\ + \mu \sum_{i,j} \|Y_i^c - Y_j^v\|^2 S_{cv}(i,j), \end{aligned} \tag{2}$$

where $Y = [Y^c, Y^v]^T$ is the common latent representation with $N = (N_c + N_v)$ rows such that the first N_c rows correspond to the embedded cortical growth patterns (i.e., Y^c) and the remaining N_v rows belong to the ventricle (i.e., Y^v), T stands for matrix transpose, S_c and S_v are the intra-structure similarity matrices, S_{cv} is the similarity matrix between cortical and ventricular growth patterns, and μ is a tradeoff parameter. Given two similar (i.e., high $S_{cv}(i,j)$) growth patterns, $\mathbf{x}_i^c$ and $\mathbf{x}_j^v$ from cortex and ventricle respectively, the third term in Eq. (2) enforces their projections (i.e., Y_i^c and Y_j^v) to fall close to each other. This also occurs for similar growth patterns from the same surface (enforced by the first and second terms).

Since we are interested in identifying associations between the growth patterns of both structures, similarity between the growth patterns is defined in terms of correlation. First, we build the inter-structure similarity matrix based on the correlations between the growth patterns of both surfaces as follows:

$$S_{cv}(i,j) = \frac{1 + \rho(\mathbf{x}_i^c, \mathbf{x}_j^v)}{2}, \tag{3}$$

where ρ is Pearson's correlation coefficient. Similarly, intra-structure similarity matrices (S_c and S_v) are built to capture within surface correlations. The joint similarity matrix is constructed by filling its block-diagonal with the intra-structure matrices and the off-diagonal with the inter-structure matrix:

$$S = \begin{pmatrix} S_c & \mu S_{cv} \\ \mu S_{cv}^T & S_v \end{pmatrix}. \tag{4}$$

Then, we compute the normalized Laplacian of the joint similarity matrix:

$$L = I - D^{-1/2} S D^{-1/2}, \tag{5}$$

where D is the degree matrix of S (i.e., a diagonal matrix such that $D(i,i) = \sum_j S(i,j)$), and I is the identity matrix. Laplacian eigenmaps [1] can then be used to solve Eq. (2) based on the joint Laplacian and find the common underlying space Y.

To discover the regional relationships induced by ventricular enlargement, we cluster the embedded growth patterns using hierarchical clustering. Associated regions are identified by clusters containing vertices from both shapes.

Features for Cortical Growth Patterns

The area of ventricular surfaces increases dramatically with the enlargement and can be considered reliable in capturing the ventricular dilation. However, alterations in cortical folding can be characterized by multiple distinct features. Therefore, we extend our approach to include both area and curvedness (derived from curvature) as features for cortical surfaces by fusing the similarity matrices created for each of them with ventricular area: S_1 built using area for both structures, and S_2 using curvedness for cortices. For each similarity matrix, S_m, $m \in \{1, 2\}$, we derive two matrices [10]:

$$P_m(i,j) = \begin{cases} \frac{S_m(i,j)}{2\sum_{k \neq i} S_m(i,k)} & i \neq j \\ 1/2 & \text{otherwise.} \end{cases} \tag{6}$$

$$W_m(i,j) = \begin{cases} \frac{S_m(i,j)}{2\sum_{k \in \mathcal{N}_i} S_m(i,k)} & j \in \mathcal{N}_i \\ 0 & \text{otherwise,} \end{cases} \tag{7}$$

where $\mathcal{N}_i$ denotes the neighborhood of the i-th vertex in terms of the vertices with most correlated growth patterns. Fusion is then iteratively conducted:

$$P_1^{t+1} = W_1 P_2^t W_1^T, \qquad P_2^{t+1} = W_2 P_1^t W_2^T, \tag{8}$$

where P_m and W_m are the dense and sparse similarity matrices derived from S_m (i.e., S_1 and S_2). In this way, the reliable similarity information is diffused across matrices. Finally, the dense matrices are averaged to obtain the fused matrix:

$$P_f = (P_1 + P_2)/2. \tag{9}$$

The fused similarity matrix, P_f, is able to capture common and complementary associations, and remove spurious and isolated correlations. We use P_f (rather than S) to compute the joint Laplacian and project the growth patterns.

3 Experiments

3.1 Data and Preprocessing

In our experiments, we used a fetal brain MRI dataset of 25 controls and 23 subjects with isolated non-severe ventriculomegaly (INSVM) between 26 and 29 gestational weeks. The INSVM cohort was composed of fetuses with unilateral or bilateral ventricular width between 10–14.9 mm, with no abnormal karyotype, infections or malformations with risk of abnormal neurodevelopment. T2-weighted MR images were acquired on a 1.5T scanner (SIEMENS MAGNETOM Aera) with an 8-channel body coil. For each subject, multiple orthogonal 2D scans (i.e., 4 axial, 2 coronal, and 2 sagittal stacks) were collected, from which a high-resolution 3D image was reconstructed using the method in [7].

Tissue segmentation was performed on the reconstructed images using a learning-based method [8]. Then, cortical and ventricular surfaces were extracted for each hemisphere. In order to establish vertex-wise correspondences, for each structure, surfaces were co-registered and resampled to the same number of vertices [11].

3.2 Experimental Setup

Ventricular growth patterns were built with area information from each vertex, which was computed as one third of the total area of adjacent triangles [6]. For cortices, we used both area and curvedness. Thus, we conducted 3 different experiments, using: (1) correlations between ventricular area and cortical area, (2) ventricular area and cortical curvedness, and (3) fusing both similarity matrices (i.e., using both area and curvedness from the cortices and area for the ventricles). For clustering, we used 2 to 25 clusters to illustrate the number of correlated regions identified with different clusters. The optimal associations between ventricles and cortices were determined by finding the most appropriate number of cluster using the silhouette coefficient: $s(i) = (b(i) - a(i))/max(a(i), b(i))$, where i indexes vertices in the embedded space, $a(i)$ is the mean distance between the i-th vertex to the rest of vertices in its cluster, and $b(i)$ is the minimum average distance computed with the vertices in the rest of clusters.

3.3 Results

Although there may exist contralateral associations and unilateral ventricular enlargement may be associated with alterations in the opposite hemisphere, for this work, associations were only studied for each hemisphere independently. Figure 2 shows the associations identified by our approach in the left hemisphere between ventricular dilation and cortical folding. Surfaces are displayed such that cortical and ventricular regions found to be associated are depicted with the same color code. From these results, regardless of using area or curvedness to characterize the cortical growth patterns, we can observe that, with 3 clusters, the posterior part of the ventricular surface and the posterior part of the cortical

surface fall into the same cluster (blue for area and pink for curvedness). This pattern is replicated for the anterior part (green for area and cyan for curvedness) and further preserved with increasing clusters, as clusters emerge in the posterior/anterior parts of both surfaces. As the number of clusters increases, we obtain more localized and fine-grained associations (i.e., shared clusters), which emphasizes the strength of the maintained associations.

Comparing the associations found when using area expansion and curvature information for the cortex, we can see that, with 8 clusters, the anterior horn and part of the ventricular body are associated with a region nearby the anterior cingulate gyrus. This association is captured with cortical area (green) for a larger number of clusters than curvedness (cyan). The most important association found by curvedness is between the posterior (i.e., occipital) horn and the occipital lobe (pink). With 8 clusters, the association includes the calcarine and the parieto-occipital fissures, although only a small part of the latter fissure is preserved with 20 clusters. This association is also found by cortical area with 8 (blue) and 15 clusters (yellow).

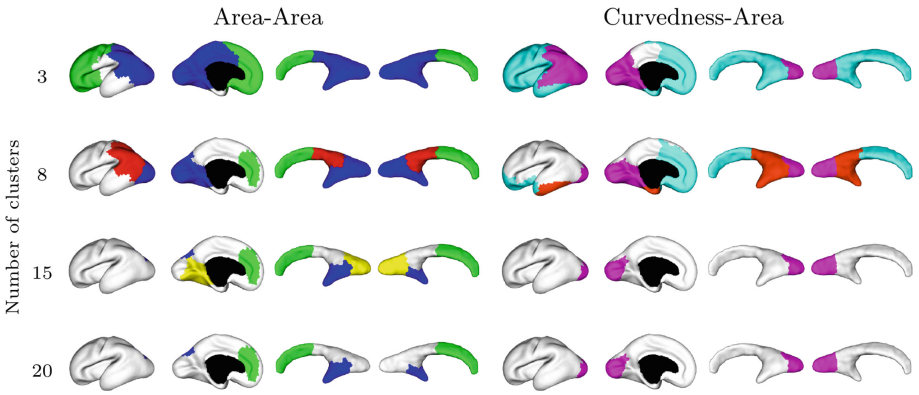

Fig. 2. Associations identified in left hemisphere using correlations between: (a) cortical area and ventricular area, and (b) cortical curvedness and ventricular area. Cortex-ventricle associations are color-coded, with white depicting no associations.

Still, using a single feature to describe the growth patterns might not be able to capture all putative associations or give rise to spurious ones. Results using the fused similarity matrix for different number of clusters are shown for both hemispheres in Fig. 3. Noteworthy is that associations found in both hemispheres are in large overlap, with the only difference being the correlation between the ventricular body and the anterior horn with the anterior cingulate gyrus (red) in the left cortex. Nonetheless, in both hemispheres, the posterior horn and the occipital lobe belonged in the same cluster (green in left hemisphere), and the inferior horn and the atrium (blue and cyan in left and right hemispheres, respectively) showed to be correlated with the superior part of the parietal lobe. Associations corresponding to the best clustering in terms of silhouette score are

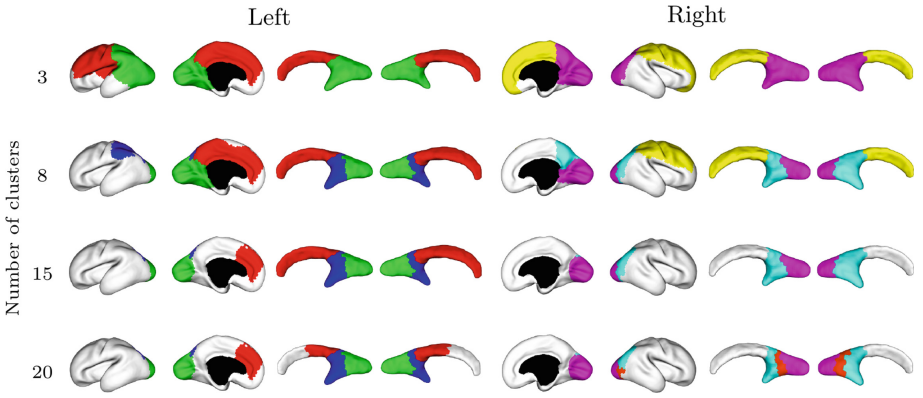

Fig. 3. Associations found using fused similarity matrix for each hemisphere separately. Cortex-ventricle associations are color-coded, with white depicting no associations.

shown in Fig. 4. The highest values of silhouette coefficient were found with 17 and 14 clusters for the left and right hemispheres, respectively. The atrium was identified bilaterally (blue and pink for left and right hemispheres, respectively). Since the atrium is the ventricular region used in clinical practice to diagnose VM, this highlights the clinic relevance of our results. In the cortex, the occipital lobe was found to be associated with the posterior horn (green and pink) in both hemispheres, which is consistent with findings in the literature [2,9]. In association with VM, our approach is able to identify meaningful cortical and ventricular regions. Furthermore, it provides the means to establish relationships between these regions and gain more insight into the fine-grained associations between ventricular enlargement and cortical development.

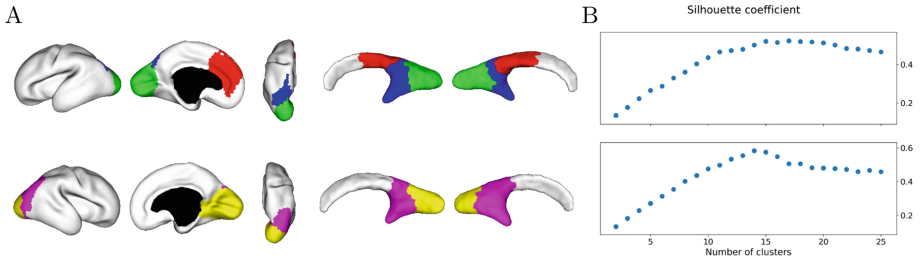

Fig. 4. A: Regional associations identified using fused similarity matrix with the optimal number of clusters in terms of silhouette coefficient for left (top) and right (bottom) hemispheres. B: Silhouette scores for different number of clusters for each hemisphere.

4 Conclusions

In this work, we have presented a novel approach to identify spatially fine-grained correlations between different shapes based on their growth patterns. This is the

first work that approaches the study of associations between fetal VM and cortical folding alterations by jointly analyzing cortical and ventricular shapes. Our results demonstrate that the proposed approach is able to identify clinically relevant regions (e.g., atrium in the ventricle and occipital lobe in the cortex) and further establish relationships between these regions. For future work, instead of fusing similarity matrices from different features prior to performing the embedding, multi-view approaches can be explored. Also, additional features (e.g., local gyrification index) can be used to identify other correlated regions.

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References

1. Belkin, M., Niyogi, P.: Laplacian eigenmaps for dimensionality reduction and data representation. Neural Comput. **15**(6), 1373–1396 (2003)
2. Benkarim, O.M., Hahner, N., Piella, G., et al.: Cortical folding alterations in fetuses with isolated non-severe ventriculomegaly. NeuroImage: Clin. **18**, 103–114 (2018)
3. Benkarim, O.M., Sanroma, G., Zimmer, V.A., et al.: Toward the automatic quantification of in utero brain development in 3D structural MRI: a review. Hum. Brain Mapp. **38**(5), 2772–2787 (2017)
4. Cardoza, J., Goldstein, R., Filly, R.: Exclusion of fetal ventriculomegaly with a single measurement: the width of the lateral ventricular atrium. Radiology **169**(3), 711–714 (1988)
5. Kyriakopoulou, V., Vatansever, D., Elkommos, S., et al.: Cortical overgrowth in fetuses with isolated ventriculomegaly. Cereb Cortex **24**(8), 2141–2150 (2014)
6. Li, G., Nie, J., Wang, L., et al.: Mapping region-specific longitudinal cortical surface expansion from birth to 2 years of age. Cereb Cortex **23**(11), 2724–2733 (2013)
7. Murgasova, M., Quaghebeur, G., Rutherford, M.: Reconstruction of fetal brain MRI with intensity matching and complete outlier removal. Med. Image Anal. **16**(8), 1550–1564 (2012)
8. Sanroma, G., Benkarim, O.M., Piella, G., Ballester, M.Á.G.: Building an ensemble of complementary segmentation methods by exploiting probabilistic estimates. In: Wang, L., Adeli, E., Wang, Q., Shi, Y., Suk, H.-I. (eds.) MLMI 2016. LNCS, vol. 10019, pp. 27–35. Springer, Cham (2016). https://doi.org/10.1007/978-3-319-47157-0_4
9. Scott, J., Habas, P., Rajagopalan, V., et al.: Volumetric and surface-based 3D MRI analyses of fetal isolated mild ventriculomegaly. Brain Struct. Funct. **218**(3), 645–655 (2013)
10. Wang, B., Mezlini, A.M., Demir, F., et al.: Similarity network fusion for aggregating data types on a genomic scale. Nat. Methods **11**, 333–337 (2014)
11. Xia, J., Zhang, C., Wang, F., et al.: Fetal cortical parcellation based on growth patterns. In: IEEE International Symposium on Biomedical Imaging (ISBI), pp. 696–699 (2018)