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Abnormal Ventricular Development in Preterm Neonates with Visually Normal MRIs

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Abstract

Children born preterm are at risk for a wide range of neurocognitive and neurobehavioral disorders. Some of these may stem from early brain abnormalities at the neonatal age. Hence, a precise characterization of neonatal neuroanatomy may help inform treatment strategies. In particular, the ventricles are often enlarged in neurocognitive disorders, due to atrophy of surrounding tissues. Here we present a new pipeline for the detection of morphological and relative pose differences in the ventricles of premature neonates compared to controls. To this end, we use a new hyperbolic Ricci flow based mapping of the ventricular surfaces of each subjects to the Poincaré disk. Resulting surfaces are then registered to a template, and a between group comparison is performed using multivariate tensor-based morphometry. We also statistically compare the relative pose of the ventricles within the brain between the two groups, by performing a Procrustes alignment between each subject's ventricles and an average shape. For both types of analyses, differences were found in the left ventricles between the two groups.

Keywords

brain; image analysis; magnetic resonance imaging; prematurity

1 Introduction

Infants born pre-term have increased risk of long-term cognitive and behavioral problems. There is growing evidence of significant anatomical brain abnormalities in premature neonates, that may predispose them to these long-term neurodevelopmental deficits.

Factors used in the clinic such as gestational age at birth, birth weight and visual evaluation of injury on conventional MRI correlate strongly with overall neurodevelopmental outcome [16–18]. However, these measures have poor specificity with regards to outcome for specific cognitive neural domains. Hence, more refined measures are urgently needed to accurately pinpoint abnormalities to particular brain regions at neonatal ages, to help determine at risk patients which could benefit from targeted treatment. However, despite major advances in brain imaging methods to understand cortical changes, there is still a lack of sensitive, reliable, and accessible brain imaging algorithms capable of characterizing the influence of prematurity on the anatomy of neonatal brain subcortical structures.

In our earlier work [17, 9], we designed a pipeline to localize abnormalities to specific subcortical structure regions in preterm neonates, and found regional surface morphological and pose differences in the preterm neonatal ventral striatum, and in the thalamus.

Here, we design a new pipeline for the analysis of the ventricles in neonates, and apply it to investigate the differences in ventricular anatomy and pose in preterm vs. term born infants. In many disorders, ventricular expansion occurs due for example to atrophy of the surrounding tissues. Using structural MRI, [2] performed a tensor-based morphometry analysis and found a volume increase in the posterior horn of the ventricles in premature children compared to controls. In addition, in [13], children born preterm had increases in lateral ventricular volume in adolescence. In our previous prematurity study [9], the left thalamus was the most affected; hence, we hypothesize that the adjacent left ventricle will also have the greatest changes.

2 Method

2.1 Neonatal Data

Our dataset comprises 17 premature neonates (gestational ages 25–36 weeks, 41.12 ± 5.08 weeks at scan time) prospectively recruited with normal MR scans and 19 healthy term born infants (gestational ages 37–40 weeks, 45.51 ± 5.40 weeks at scan time). T1- weighted MRI scans were acquired using a dedicated neonatal head coil on a 1.5T GE scanner using a coronal three-dimensional (3D) spoiled gradient echo (SPGR) sequence. The inclusion criteria for our preterm subjects were the following: 1) prematurity (less than 37 gestational weeks at birth), and 2) visually normal scans on conventional MR imaging. All subjects with visible injuries were excluded from the dataset. Structural MR images were qualitatively classified as normal by 2 board certified neonatal neuroradiologists. Preterm subjects were excluded based on abnormal neurological exam, or if they exhibited brain lesions including: (1) focal or diffuse white matter injury (2) ventriculomegaly and (3) significantly increased subarachnoid space and sulcal enlargement. The institutional review board at our medical center approved the study protocol.

2.2 Ventricular Analysis

Lateral ventricle volumes are manually labeled using ITK-SNAP. Surface models of ventricular surfaces are built by using a topology-preserving level set method [7], and then applying the marching cube algorithm [10] to construct triangular surface meshes. Mesh simplification and refinement are done for smoothing. Next, to construct a conformal grid for the ventricular structure, we automatically locate three cuts: 1) the superior horn, 2) the inferior horn, and the 3) occipital horn on each ventricular surface, a process which we call topology optimization. We use the Ricci flow method to compute conformal mappings from ventricular surfaces to the hyperbolic space. Since a hyperbolic space cannot be realized in $\mathbb{R}^3$, we use the Poincaré disk model to visualize it. The process is detailed in [18]. and illustrated in Figure 1.

We compute four transformations that map the fundamental domain of the ventricular surface to four different positions in the Poincaré disk and glue the four fundamental domains with the original fundamental domain to tile a finite portion of the universal covering space. The new ventricle boundaries, i.e., the hyperbolic lines connecting the endpoints of existing geodesic curves are uniquely determined and consistent. We obtain the canonical fundamental domain of the ventricular surface by slicing the universal covering space along the new geodesic curves. Next, we convert the Poincaré disk model to the Klein model, where all hyperbolic lines become Euclidean. This is used as the canonical parameter space for surface registration. We call this process geodesic curve lifting. After surface registration, we used multivariate tensor-based morphometry (mTBM) as a local shape change measure. MTBM measures directional changes in local area at each surface vertex. The mTBM feature was smoothed with heat kernel method [5] and controlled for age and gender by the GLM in [18].

2.3 Pose Analysis

Pose analysis is performed in a structure-wise, which completes the above vertex-wise analysis in a global point of view. The relative pose of a structure is its rotation, translation and scale with respect to an average template. The average template is a population based mean shape that minimizes the Procrustes distances of our subjects' point distribution models [3, 4]. A detailed description of our relative pose analysis can be found in [9]. Here we compute the relative pose of the left and right ventricles for the preemies vs. term-born groups. In short, the relative pose is found through a Procrustes transform between each subject's image and a mean shape [6, 3, 4]:

$$T = \begin{bmatrix} sRX & d \\ T & 1 \end{bmatrix} \quad (1)$$

where s is the scalar scaling factor, R is a 3×3 rotation matrix, and d is the translation vector $(x, y, z)^T$. Computations are performed in the simpler log-Euclidean space as in [1, 3]. The mean pose is then calculated iteratively [8, 4, 14], and subtracted from each subject's pose. Convergence typically occurs within 5 iterations. The 7 relative pose parameters (1 scale, 3 rotations, 3 translations) are then used as measures in the statistical analysis.

3 Results

3.1 Results of the mTBM analysis

The group differences detected between the premature (n=17) and term born (n = 19) groups is shown in Figure 3. Widespread significant areas are seen on most of the left ventricle, with the exception of the temporal horn. The right ventricular surface is mostly spared. This result is consistent with our previous findings on the thalamus and putamen, showing changes primarily on the left in these structures. However, it is to be noted that ventricular surfaces are highly variable in neonates, which may prevent detection of subtle changes on the right given our current sample size.

3.2 Results of the pose analysis

Differences in relative pose between the two groups are shown in Figure 4. Significantly different values are found for rotations on the left side, but not the right, consistent with the surface analysis. The left panel shows the mean relative pose of premature subjects' ventricles overlaid on that of the term born controls, and shows rotation of the left ventricle, with little difference in the other parameters.

4 Discussion

Studies reveal that enlarged ventricles are important indicators of prematurity [22, 23]. However, previous findings focus on extreme preterm population with various degrees of brain abnormalities or premature complications[22, 25, 24, 23]. Here, significant results were detected between the premature and term-born groups even in our relatively small and 'healthy preterm' dataset. These results are also in line with our previous results showing that both relative pose and surface thalamic changes in the preterm group that are primarily located on the left. Our results confirms the prematurity associated lateral ventricular alterations in a relative healthy preterm population, and may help to separate the influence of prematurity itself from its associated complications.

The work described here inscribes itself as part of our larger study on subcortical structures morphometry and relative pose in preterm neonates. Results for the putamen and thalamus studies are in [9, 16]. The next steps will involve: 1) Combining all structures to detect correlations between structures which may indicate affected brain networks. For the ventricles in particular, this will also allow us to understand the relationship between the results found here and associated injury of surrounding tissues. 2) Correlating results with long term neurodevelopmental scores, in order to determine a set of early biomarkers of development in premature children.

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Fig. 1.

A flowchart showing the algorithm pipeline. First, we manually segment the ventricle volume from MR images. Then ventricular surfaces are reconstructed and smoothed. Second, we introduce 3 cuts on each ventricular surface with the topology optimization process. Then the global conformal parameterization of each ventricular surface is computed by hyperbolic Ricci flow and the surface is embedded onto the fundamental domain in the Poincaré disk. Third, a finite portion of the universal covering space of the ventricular surface is tiled by the Möbius transformation. With geodesic curve lifting, we introduce consistent boundaries on the ventricular surfaces. By slicing the universal covering space with the consistent geodesic curves, we construct consistent ventricular surface registration across subjects. Finally, mTBM is computed on each vertex and smoothed to conduct the group difference analysis.

Fig. 2.

A flowchart showing the pipeline of the relative pose analysis. First, outputs from in Figure 1(A) are procrustes aligned to an average template shape (B), which results in a set of 7 pose parameters for each of the subjects (C). Then group analysis results (D) are obtained through univariate and multivariate tests, and detailed explanations can be found in Figure 4.

Fig. 3. Results of the mTBM analysis

The statistical p -map of group differences detected by our method between the premature ($n=17$) and term-born ($n=19$) groups, using the smoothed and covaried mTBM statistic as the measure of local surface area changes and the pre-defined significance level at each surface vertex is 0.05. The non-blue colors illustrate areas with statistically significant differences between the two groups. The overall significance p -value of the p -map is 0.0050.

Fig. 4. Results of the pose analysis
Left: Superposition of average ventricles of preemies vs. term-born controls. Table: P-value of statistical analyses on pose parameters: 13 sets of parameters characterizing relative pose of left ventricle (LVent) and right ventricle (RVent) are investigated here using univariate and multivariate analyses. Parameters are categorized as $\log S$, $\log R$, $\log d$, θ_x , θ_y , θ_z , x , y , and z for univariate tests, and as $(\theta_x, \theta_y, \theta_z)$, (x, y, z) , $(\log S, \log R, \log d)$, and a combination of 7 parameters for multivariate tests. All the p -values are obtained after permutation testing. Significant p -values ($p < 0.05$) are highlighted in light cyan, while p -values that are interestingly low but failed to reach significance are highlighted in light grey.