Lateral ventricle morphology analysis via mean latitude axis

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ABSTRACT

Statistical shape analysis has emerged as an insightful method for evaluating brain structures in neuroimaging studies, however most shape frameworks are surface based and thus directly depend on the quality of surface alignment. In contrast, medial descriptions employ thickness information as alignment-independent shape metric. We propose a joint framework that computes local medial thickness information via a mean latitude axis from the well-known spherical harmonic (SPHARM-PDM) shape framework. In this work, we applied SPHARM derived medial representations to the morphological analysis of lateral ventricles in neonates. Mild ventriculomegaly (MVM) subjects are compared to healthy controls to highlight the potential of the methodology. Lateral ventricles were obtained from MRI scans of neonates (9-144 days of age) from 30 MVM subjects as well as age- and sex-matched normal controls (60 total). SPHARM-PDM shape analysis was extended to compute a mean latitude axis directly from the spherical parameterization. Local thickness and area was straightforwardly determined. MVM and healthy controls were compared using local MANOVA and compared with the traditional SPHARM-PDM analysis. Both surface and mean latitude axis findings differentiate successfully MVM and healthy lateral ventricle morphology. Lateral ventricles in MVM neonates show enlarged shapes in tail and head. Mean latitude axis is able to find significant differences all along the lateral ventricle shape, demonstrating that local thickness analysis provides significant insight over traditional SPHARM-PDM. This study is the first to precisely quantify 3D lateral ventricle morphology in MVM neonates using shape analysis.

Keywords: Statistical shape analysis, pediatric imaging, magnetic resonance image biomarkers, mild ventriculomegaly, lateral ventricles

1. INTRODUCTION

Quantitative morphologic assessment of individual brain structures is often based on volumetric measurements. Volume changes can intuitively explain atrophy or dilation due to illness but changes at specific locations are not sufficiently reflected in global volume measurements. Statistical shape analysis has emerged as a way of evaluating location and magnitude of morphology in brain structures. One of the first and most influential research in shape analysis was presented by D'Arcy Thomson [1] in his groundbreaking book "On Growth and Form". In more recent years, several researchers proposed shape analysis via deformable registration to a template [2,3,4,5] where inter-subject comparisons are made by analyzing the individual deformable transformations. Bookstein et al.[6] and Dryden et al.[7] presented some of the first mathematical methods for 3D shape analysis based on sampled descriptions. Cootes and Taylor [8] first investigated the shape analysis of densely sampled 3D Point Distribution Models (PDM) and their deformations. Inspired by their experiments, Gerig et al.[9] proposed shape analysis based on a parametric boundary description called SPHARM [10]. The SPHARM shape analysis approach was extended by Styner et al. to use the implied PDM [11], a method recently also used by Shen et al.[12]. Since shape frameworks that are surface based directly depend on the quality of surface alignment, some of those shape methodologies are very dependent on aligment and are not able to differentiate shape changes from positional differences [13]. In contrast, medial axis descriptions employ thickness information as alignment-independent shape metric. The first works in shape analysis on medial shape descriptions in 2D and 3D were proposed by Pizer et al.[14,15] and Golland et al.[16]. Since then, medial model methodology is a widely used technology for solving problems of the medical image analysis community [17], such as segmentation or shape analysis [18][19].

We propose a quasi-medial representation model to independently analyze volume and positioning that inherits the shape-constrained point correspondence of the well-known spherical harmonic (SPHARM-PDM) shape framework. One

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of the main advantages of the proposed framework is that it is and end-to-end free open source software (FOSS) solution, as part of Slicer [20]. The SPHARM-PDM toolbox module in Slicer intends to bridge the gaps between the experimental science made by computer scientists and the clinical research science, making it available to a bigger audience that does not need to have a big computer expertise or deep understanding of the underlying basic science to operate the tool.

We validated our integrated shape and mean latitude axis analysis framework by assessing pathological variations of mild vetriculomegaly (MVM) pediatric lateral ventricles (see figure 1) by applying our method to a large database of neonatal scans. Enlargement of the cerebral lateral ventricle has been observed in many psychiatric disorders, including schizophrenia, and has been recognized as a potential biomarker for identifying early abnormal brain development [21]. Biomarkers for detecting lateral ventricle enlargement are especially relevant be-cause establishing a normal trend and a diseased deviation of it would provide tools for early diagnosis and early intervention in psychiatric developmental diseases.

The database used for this study included a cohort of Mild ventriculomegaly (MVM) subjects that we decided to compare to healthy controls in order to highlight the potential of the methodology. MVM is characterized as the prenatal enlargement of the cerebral lateral ventricles and identified by ultrasound measurement of the atrial width of the fetal lateral ventricle in-utero [22]. The cause of MVM is unknown, and to date there are no studies that analyze MVM morphology compared to healthy morphology.

To this end, the paper is structured as follows: section 2 "Data" describes the data used in this study, in section 3 "Methods" the methodological framework is described, consisting in: SPHARM-PDM and statistical analysis. Section 4 "Results" describes the results obtained in the quantification of both mean latitude axis and boundary shape result comparison of MVM and healthy lateral ventricles, while section 5 "Discussion" presents the conclusions, discussion points and future directions of this study.

2. DATA

Ninety pairs of lateral ventricles were used for this study, 30 MVM and 60 age- and sex-matched control obtained from MRi scans. Images were acquired on a Siemens 3T scanner (Allegra, Siemens Medical System, Erlangen, Germany). Infants were scanned unsedated while asleep, fitted with ear protection and had their heads secured in a vacuum fixation device at both 1 and 2 year follow up sessions. T1-weighted, proton density and T2-weighted images were obtained. Spatial resolution was 1x1x1 mm for T1-weighted images, 1.25x1.25x1.5 mm with .5 mm gap for PD/T2-weight images.

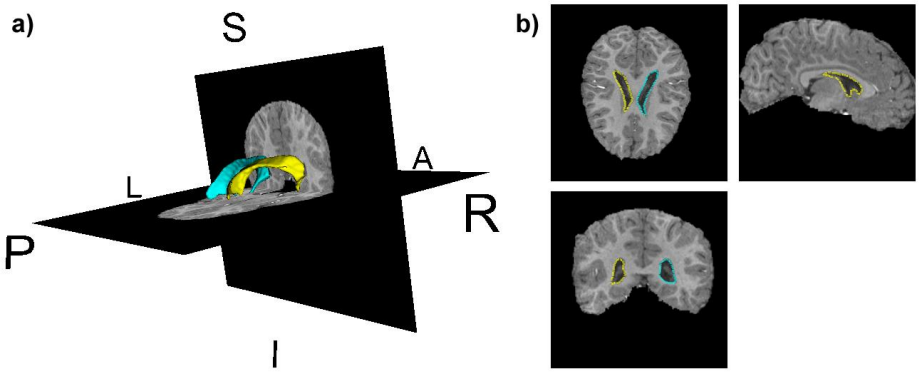

Figure 1. Pediatric lateral ventricle segmented in a 2-year-old MRI scan. a) 3D rendering of the right (yellow) and left (cyan) lateral ventricles displayed in coronal and axial cross-sections of the brain for anatomical reference b) Axial (top-left), sagittal (top-right) and coronal (bottom-left) cross-sections of the brain with lateral ventricle slice intersections visible.

For all datasets, the lateral ventricle segmentation was performed manually, i.e., outlining the lateral ventricle visible in the cross-sections of the MRi scans, via InsightSNAP [23]. The correspondence obtained from lateral ventricle segmentations and computed using SPHARM-PDM were quality controlled. From the 90 initial pairs of lateral ventricle, 78 lefts (26 MVM and 52 sex- and age-matched controls) and 75 right (25 MVM and 50 sex- and age-matched controls) lateral ventricles were selected for the study.

3. METHODS

3.1 SPHARM-PDM

We performed a local shape analysis on the lateral ventricle segmentations via the UNC SPHARM-PDM (Spherical HARMonics Point Distribution Models) shape analysis toolbox. The SPHARM-PDM toolbox presents a comprehensive set of tools for the computation of 3D structural statistical shape analysis. The SPHARM-PDM description is a sampled boundary description with object-inherent correspondence that can only represent objects of spherical topology [10]. The input of SPHARM-PDM toolbox is our set of lateral ventricle segmentations. These segmentations are first processed to ensure spherical topology and then converted to surface meshes. Next, a spherical parameterization is computed from the surface meshes using an area-preserving, distortion minimizing spherical mapping. Further, the SPHARM description is computed from the mesh and its spherical parameterization [24]. The correspondence is determined by aligning the principal curves of first order ellipsoid representation with the standard coordinate frame, so that the north pole of the first order ellipsoid aligns with the positive z axis, and its 0° meridian aligns with the x–z plane. This description is then sampled into triangulated surfaces via an icosahedron subdivision of the spherical parameterization. Lateral ventricle surfaces are well represented (local representation error is smaller than 0.1 mm on average) by a subdivision of level 10 resulting in 1002 surface points. Alignment of triangulated surfaces was finally performed using rigid body, Generalized Procrustes alignment that iteratively aligns the surfaces to the population mean. Equally parameterized locations in Phi and Theta parameters means correspondent locations (figure 2).

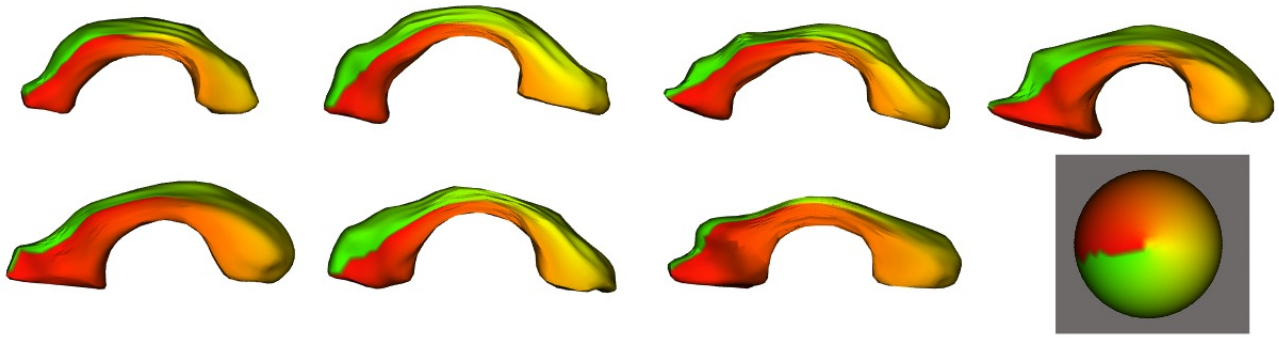

Figure 2. Visualization of the SPHARM-PDM correspondence using the Phi-attribute file shown on seven randomly selected lateral ventricle cases. Same color represents the same φ parameter value of the spherical parametrization.

By following these set of steps SPHARM-PDM performs a boundary shape analysis that allows discovering the local lateral ventricle areas that are consistently affected by an enlargement. However the reliability of these results depends on the quality of the alignment of the 3D correspondent point distribution models.

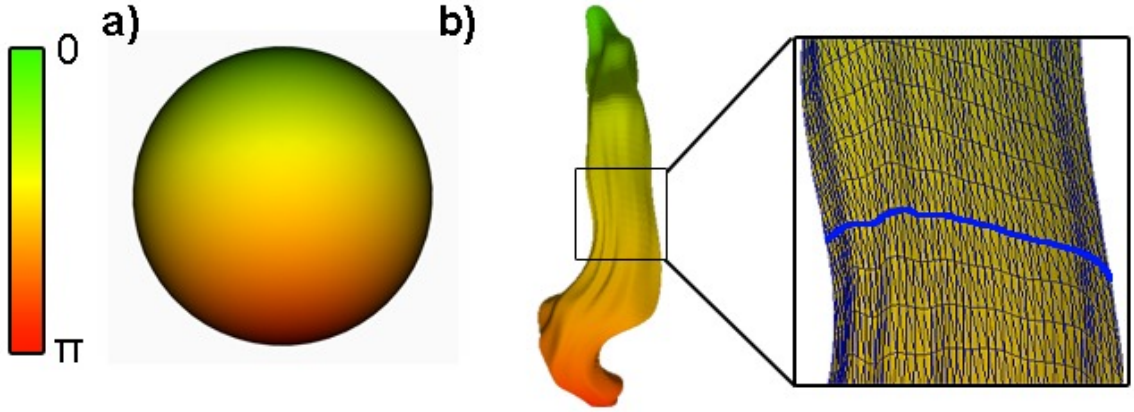

Figure 3. a) Theta parametric field where north pole = 0 and south pole = π. b) Superior view of the SPHARM medial mesh of a left lateral ventricle. The close up shows the iso-latitude lines (one of the lines, highlighted bold blue line).

3.2 Mean Latitude Axis

As an alignment-independent alternative shape analysis, we propose a quasi-medial representation model to analyze independently volume and positioning that inherits the shape-constrained point correspondences from SPHARM-PDM computed models. Mean latitude axis is not a full medial representation but its computation is straightforward and easily to compute from the boundary descriptions already provided by SPHARM-PDM. This idea was initially proposed by Kim et al. [1], however our proposal differs in the way the mean medial axis is computed (see figure 3): after calculating a parameterization of all points of the initial 3D voxel mesh, a medial mesh is computed by dividing the theta (θ) parametric field with values between [0, π] a fixed number of times specified by the user (in SPHARM-PDM, this parameter is called theta_iterations). A theta_iterations number of iso-latitude lines will then placed at equally valued latitudes in the new SPHARM Mesh. A number of points also specified by the user (in SPHARM-PDM, this parameter is called phi_iterations) will be then placed along each iso-latitude lines. The new medial mesh will have then theta_iterations x phi_iterations number of vertices. The 3D locations of the mean latitude axis will be then calculated by averaging all points along each iso-latitude line. The number of points of the medial mesh will be theta_iterations. This idea is different from the original icosahedron subdivision surface reconstruction from the spherical harmonic coefficients information. Using a linear, uniform icosahedron subdivision (figure 4.a.), it is possible to gain a good approximation of a homogeneous sampling of the spherical parameter space and thus also of the object space. The subdivision is linear in the number of subdivisions along each edge of the original icosahedron, rather than the commonly used recursive subdivisions. Any recursive subdivision has a corresponding linear subdivision, but most linear subdivisions have no corresponding recursive subdivision. Mean latitude axis reconstruction (figure 4.b.) object reconstruction follows the steps described before in the section.

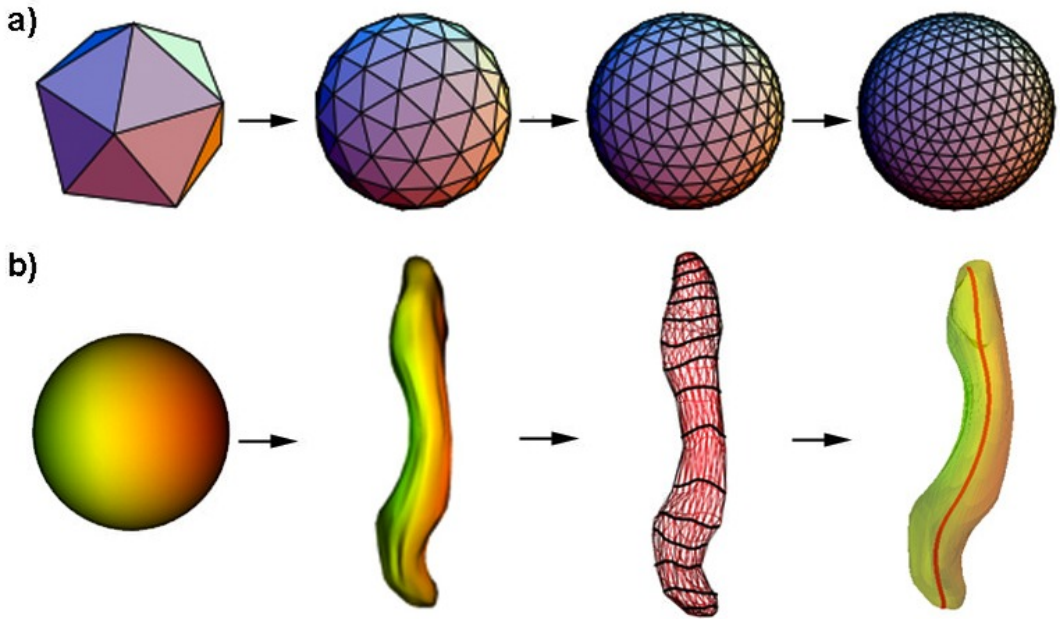

Figure 4. SPHARM-based object reconstruction. a) Icosahedron subdivision for different levels of sampling. From left to right: Base icosahedron, subdivision factors 2, 4 and 6, respectively. b) Mean latitude axis surface reconstruction. From left to right: Base parametric field with theta coloring, example lateral ventricle with theta coloring, subdivisions in parametric fields, medial axis reconstruction.

3.3 Statistical shape analysis

Both surface and mean latitude axis descriptors will be used to analyze lateral ventricle morphology, and differentiate between MVM and healthy subjects at neonatal stage in a cross-sectional groupwise study.

- Surface metrics: The point-based models are analyzed using multivariate analysis of covariance (MANCOVA) [25]. shapeAnalysisMANCOVA is provided as an extension of UNC SPHARM-PDM to perform statistical shape analysis based on a parametric boundary description. The number of variates being tested is the dimensionality of our observations. Each point of these observations is a 3-D displacement vector from the

mean. The number of contrasts is the number of equations involved in the null-hypothesis. In order to encompass varying numbers of variates and contrasts, and to account for independent variables, a matrix computation is performed. This matrix represents the multidimensional aspects of the correlation significance and it can be transformed into a scalar measure by manipulation of its eigenvalues. For this study, age and gender will be used as covariates. Point-wise p-value maps of group differences displayed over the whole surface will be provided as results.

- Mean latitude axis metrics: Two alignment-independent metrics calculated from mean latitude axis are proposed. Mean radius across each iso-latitude line (figure 5.a.), and area of each iso-latitude cross-section (figure 5.b.). Point-wise p-value for the difference in group least-squares means displayed over the mean latitude axis will be provided as results for both radius and area.

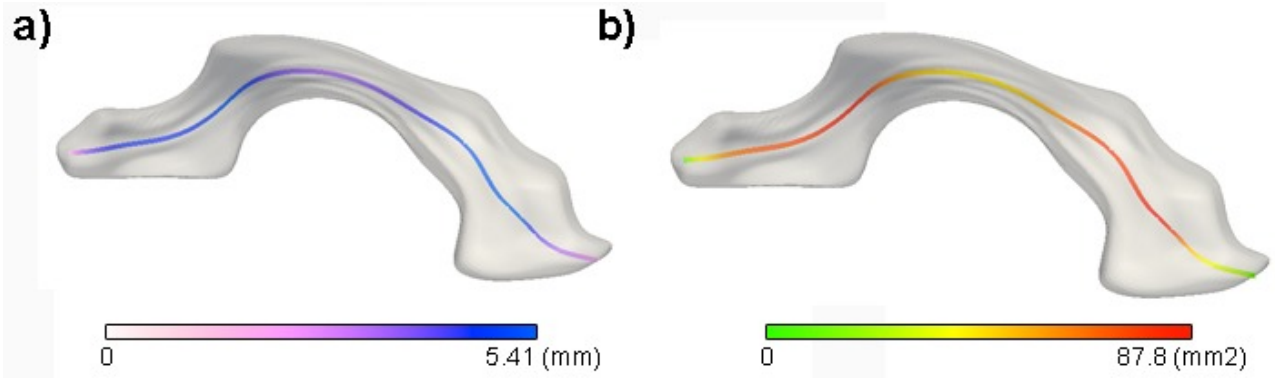

Figure 5. Mean latitude axis metrics, sagittal view of an example neonatal lateral ventricle a) Radius b) Area.

3.4 Technology dissemination

UNC SPHARM-PDM toolbox was implemented as command-line and a stand-alone 3DSlicer module [20], which works as an input to end shape correspondence module. This is an open-source free software available in NITRC (Neuroimaging Informatics Tools and Resources Clearinghouse) [26].

4. RESULTS

Shape results (figure 6) are presented via color coded p-values maps, visualized over a mean lateral ventricle surface. In the map, highly significant correlations ($p < 0.001$) are color-coded with red and green ($0.01 > p > 0.05$) and non-significant correlations are color-coded with blue. The main areas of significance in our comparison analysis for the left lateral ventricle are primarily located on the lateral aspects of the anterior and posterior sections. The right lateral ventricle exhibits fewer clusters of significance than seen in the left, but significance is also primarily located in the posterior and anterior aspects of the main body of the ventricle. This suggests that the enlargements seen in our MVM cohort tend to occur in the anterior and posterior sections of the lateral ventricle more often than in the medial sections. Mean latitude axis results are presented via color coded p-values maps, visualized over the mean latitude axis of a lateral ventricle that is used as template. Mean latitude axis disentangles shape and position, and therefore both area and radius are able to differentiate successfully lateral ventricle morphology between MVM and healthy age- and sex-matched controls. Mean latitude axis, therefore, is an excellent method to detect abnormal lateral ventricle morphology in neonates.

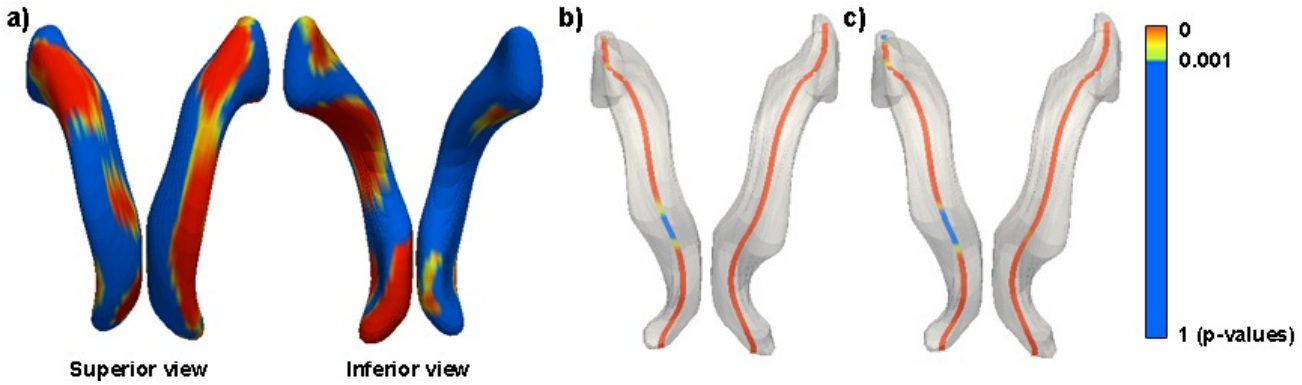

Figure 6. P-values of a) surface and b) axis differences between MVM and healthy control cross-sectional group analysis displayed over a) mean lateral ventricle surfaces (superior and inferior views) and b) radius mean latitude axis p-value maps in a template ventricle, c) area mean latitude axis p-value maps in a template ventricle mean latitude axis.

5. CONCLUSIONS

By using inherent correspondences of SPHARM-PDM, mean latitude axis allowed shape-constrained correspondence without a registration step. Disentangling shape from positioning anomalies may provide new insights in the pathogenesis of a variety of other brain disorders in which these morphometric characteristics coexist. We previously quantified local volume changes to differentiate MVM and healthy controls in neonatal age [27]. To date, this is the first study that has analyzed shape morphology in an MVM cohort. We have successfully identified that the regions of enlargement are primarily located in the anterior and posterior sections of the lateral ventricle. Interestingly, in a recent study analyzing longitudinal shape morphology changes in healthy individuals, we also found that the anterior and posterior regions of the lateral ventricle experienced the highest growth rates in the first two postnatal years [28]. This suggests that it is possible enlargement of the cerebral lateral ventricles in MVM could be a result of potential accelerated expansion of these dynamic areas during the prenatal stages of development. We have shown here that assessing lateral ventricle morphology at the early stages of brain development provides useful information for locating and quantifying shape changes between MVM subjects and sex- and age-matched controls. Mean latitude axis successfully differentiates abnormal lateral ventricle morphology of MVM in neonates and provides a more detailed picture of the structural changes that lead to pathogenesis in MVM.

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