Using Ventricular Modeling to Robustly Probe Significant Deep Gray Matter Pathologies: Application to Cerebral Palsy

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Abstract: Understanding the relationships between the structure and function of the brain largely relies on the qualitative assessment of Magnetic Resonance Images (MRIs) by expert clinicians. Automated analysis systems can support these assessments by providing quantitative measures of brain injury. However, the assessment of deep gray matter structures, which are critical to motor and executive function, remains difficult as a result of large anatomical injuries commonly observed in children with Cerebral Palsy (CP). Hence, this article proposes a robust surrogate marker of the extent of deep gray matter injury based on impingement due to local ventricular enlargement on surrounding anatomy. Local enlargement was computed using a statistical shape model of the lateral ventricles constructed from 44 healthy subjects. Measures of injury on 95 age-matched CP patients were used to train a regression model to predict six clinical measures of function. The robustness of identifying ventricular enlargement was demonstrated by an area under the curve of 0.91 when tested against a dichotomised expert clinical assessment. The measures also showed strong and significant relationships for multiple clinical scores, including: motor function ($r^2 = 0.62$, $P < 0.005$), executive function ($r^2 = 0.55$, $P < 0.005$), and communication ($r^2 = 0.50$, $P < 0.005$), especially compared to using volumes obtained from standard anatomical segmentation approaches. The lack of reliance on accurate anatomical segmentations and its resulting robustness to large anatomical variations is a key feature of the proposed automated approach. This coupled with its strong correlation with clinically meaningful scores, signifies the potential utility to repeatedly assess MRIs for clinicians diagnosing children with CP. *Hum Brain Mapp* 37:3795–3809, 2016. © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

Cerebral palsy (CP) is the most common cause of physical disability in children worldwide [Kuban and Leviton, 1994; Towsley et al., 2011]. It describes a heterogeneous group of nonprogressive disturbances in the developing brain [Korzeniewski et al., 2008], which lead to varied functional and motor impairments, and further symptoms related to cognition, language, behavior and sensation [Himmelman et al., 2006]. Magnetic resonance imaging (MRI) allows for visualization of these disturbances [Krägeloh-Mann and Horber, 2007], which can provide important insights into the structure-function relationship of the brain. While the clinical assessment of cerebral injury is mainly performed using qualitative approaches [Fiori et al., 2014; Kidokoro et al., 2013], automated image analysis techniques are needed to develop large scale quantitative relationships between observed injury and clinical outcomes. Such analyses can facilitate the tailoring of treatment strategies of individual children and could enable some prediction of functional outcomes.

The challenge for implementing automated image analysis tools for detecting injuries observed in children with CP is the large heterogeneity in the appearance and location of injury. Segmentation of white and gray matter tissues is often complicated by the presence of gross injury and the variations in intensity indicating injury can be subtle. In contrast, the ventricles have a clearly defined boundary, which assists the segmentation of these structures. Their proximity to key deep gray matter structures, and the fact that ventricular enlargement occurs in up to 70% of CP cases [Kulakowski and Larroche, 1980; Sööt et al., 2008; Truwit et al., 1992], suggests that surrogate markers of deep gray matter injury based on ventricular enlargement are likely to be relevant to the clinical assessment of children with CP.

The ventricles are spaces filled with cerebrospinal fluid (CSF) in the centre of the brain that transport nutrients to the brain and act as a cushion to movement. They may enlarge due to an abnormal accumulation of CSF in the brain, or following a hypoxic-ischemic event in the periventricular white or gray matter. As this expansion of the ventricles is caused by developmental disturbances, it is fundamentally different from degenerative pathologies like Alzheimer's disease (AD) where there is a global expansion of the ventricular space [Gado et al., 1983]. Instead, this enlargement is typified by the local, irregular, or angular appearance of the lateral ventricles and ventricular trigones, and may impact one or both hemispheres of the brain [Truwit et al., 1992]. Expansion of the ventricles into

the adjacent white matter and key subcortical gray matter structures of the brain has been shown to provide an indirect measure of tissue loss [Hoon and Vasconcellos Faria, 2010] and has been shown to correlate with the degree of impairment [Maunu et al., 2011; Melhem et al., 2000].

Several techniques for assessing ventricular enlargement have been proposed, albeit in the context of degenerative diseases, rather than developmental, such as AD [Horga et al., 2011; Nestor et al., 2008] and schizophrenia [Kemp-ton et al., 2010]. Of these, global ventricular volume is the most common biomarker extracted from structural MR images, which have been computed using automatic edge-detection [Shenton et al., 1991], fuzzy tissue segmentation [Barra et al., 2002], and region growing techniques [Nestor et al., 2008]. Less frequently, this biomarker has also been measured in children with CP, [Melhem et al., 2000]. Although straight forward to measure, ventricular volume varies significantly among the healthy population [Wright et al., 2002], complicating the identification of subtle ventricular enlargement due to injury.

More complex biomarkers based on the shape of ventricles have been developed in other studies. Several studies have reported linear measures of ventricular dilation [Maunu et al., 2011; Northam et al., 2011]. The distance between the approximate centroid of the ventricle, to the surface, was found to be sensitive to local atrophy [Apostolova et al., 2012]. A common technique used to model ventricular shape is called statistical shape models (SSM), which provides a more detailed description of how the shape of ventricles varies. These models have been used to identify the pathological enlargement of ventricles due to AD [Chou et al., 2007; Ferrarini et al., 2006, 2008b; Thompson et al., 2004] and schizophrenia [Graham et al., 2006; Narr et al., 2001; Styner et al., 2003]. The extent of atrophy can thus be identified as the distance of the ventricle surface from corresponding points on a healthy SSM. These measures were correlated to measures of cognition in the context of AD [Ferrarini et al., 2008a]. Although this local shape-based analysis would allow for a more informative assessment of ventricular enlargement in children with CP, there has been little focus on applying these methods in this setting. This is due to the large variability in the appearance and severity of brain injury observed in children with CP, leading to technical difficulties obtaining vertex-wise correspondences between meshes of enlarged ventricles.

In this article, a novel biomarker of deep gray matter injury is presented. This marker is extracted from an automated method for identifying and quantifying the extent of ventricular enlargement observed in structural MRIs of

Figure 1.

The computed brain mask obtained from an MR image of a 5-year old male, clinically diagnosed with CP, using the in-house developed brain masking algorithm. This MRI shows severe ventricular enlargement, particularly in the right hemisphere. (a) Axial, (b) sagittal, and (c) coronal views are shown.

children with CP. The key contribution of this work is to use local deformation as a surrogate marker for ventricular impingement on adjacent surrounding anatomy. The relationship between the proposed measure and several functional outcomes is examined to evaluate the extent to which the proposed method can assist clinicians in identifying injury indicative of CP, and hence guide the selection of treatment strategies.

MATERIALS AND METHODS

Subjects

A total of 139 patients were included in this study: 95 patients with clinically diagnosed CP (50 male, 45 female, mean age 11.7, age range 5–17), and 44 healthy subjects with no observed diagnosis of injury (15 male, 29 female, mean age 12.3, age range 7–16), were included. Of the 95 children with CP, 68 exhibited ventricular enlargement while the remaining 27 did not. Image data was obtained from The University of Queensland Cerebral Palsy and Research Rehabilitation Centre, Brisbane and the Stella Maris Fondazione, Pisa. Study participants included children who were recruited as part of ongoing studies of children with unilateral CP [Boyd et al., 2013a,b]. Diagnoses were made based on clinical assessment by experienced practitioners in the field of CP. The University of Queensland and Children's Health Queensland ethics committees granted ethics approval. Informed parental consent was obtained for all participants.

MRI Acquisition and Preprocessing

MR images were acquired on a 3T MR-system (Siemens, Germany) using the following pulse sequences: spin-echo (T_1 -weighted): time to echo (TE) 2.32 ms, repetition time

(TR) 1,900 ms, 192 contiguous 0.90 mm slices, matrix 256×256 , field of view 230 mm.

Several preprocessing steps for the MR images were implemented to assist downstream SSM methods. An affine transform was used to register the MR images to the Colin 27 Average Brain Atlas (The McConnell Brain Imaging Centre) using a block-matching registration approach [Rivest-Hénault et al., 2015]. Anisotropic diffusion [Perona and Malik, 1990] was performed on the images in MATLAB 2013a (Mathworks, Natick, MA) to minimize the effect of Rician-distributed noise in the MR image while attempting to preserve high resolution features within the image. Skull stripping was performed using an in-house algorithm, which identifies intradural CSF using thresholding and morphological operations, implemented in MATLAB. The preprocessing pipeline is capable of accurately segmenting the brain in cases of large lesions, which may be present in children with CP. An example of a MR image with a large injury is shown in Figure 1.

For most of the children with CP in this study ($n = 89$), several clinical scores of patient function were measured around the time of MRI scanning. To evaluate patient motor function, the Assisted Hand Assessment (AHA) score [Krumlinde-Sundholm et al., 2007] was measured. This is a score between 0 and 100 that measures how much the patient's impaired hand is used as an assisting hand during bimanual tasks, with larger scores indicating greater assistance from the impaired hand during these tasks. Both the Behavior Rating Inventory of Executive Function (BRIEF) [Gioia et al., 2002] and strengths and difficulties questionnaire (SDQ) [Bourdon et al., 2005] were used to questionnaires score patients' emotional and behavioral function in daily life. Visual acuity, including the ability to discriminate and memorize visual cues, was measured using the test of visual perception skills (TVPS) measure [Frostig et al., 1961]. Communicative ability was assessed using the vocabulary (VOC) and word reasoning

Figure 2.

The pipeline of the (a) healthy ventricular shape model construction, (b) multivariable linear regression model construction relating image-derived marker of injury to outcome, and (c) computing image derived measures of injury from a target image.

(WR) subtests of the Wechsler Preschool and Primary Scale of Intelligence [Wechsler, 1967].

Overview of Scoring Method

The surrogate marker of brain injury is generated in two steps as outlined in Figure 2. In the first step, a set of impingement volumes are generated using a SSM, shown in Figure 2a. In the second step, the impingement volumes are converted into a scalar estimate of clinical function using a linear regression model, shown in Figure 2b.

The SSM describes the typical shape and variability of the lateral ventricles in healthy subjects. The SSM was constructed from the available cohort of 44 healthy subjects. The constructed SSM was subsequently fitted to the ventricles of individual unhealthy patients to generate an estimate of the volume of (atypical) enlargement. The volume of enlargement is partitioned into a set of volumes associated with nearby anatomical regions, referred to as impingement volumes.

The regression model was constructed using the cohort of unhealthy patients. The impingement volumes, patient age and patient gender were used as the independent variables in the regression model, with the dependent variables consisting of the clinical scores. A separate regression model was constructed for each clinical score. Correlations between the estimated clinical function from the regression model and the actual (measured) clinical functions were measured to test the accuracy of the entire method.

Finally, for new data, ventricular enlargement is computed. After alignment with the normative atlas, impingement of subcortical gray matter structures is computed. The values are combined with age and gender and weighted by the coefficients of the regression model, to obtain a predictive image score, shown in Figure 2c.

Ventricle Segmentation

The automated segmentation of the ventricles was performed in MATLAB using Otsu thresholding [Otsu, 1975]

to identify all regions of CSF. This segmentation includes the third ventricle and the cerebral aqueduct, however only the lateral ventricles were retained for the subsequent analysis using several atlas-derived seed points, and morphological opening was utilized to ensure that any connections of ventricular CSF to the subarachnoid space due to injury were contained. Subsequent morphological closing operations were applied to ensure that internal gaps in the segmented ventricles that were left out due to partial volume effects were filled in, and to ensure that if a ventricle appeared as a number of disconnected pieces, they were connected into a single structure. The segmented ventricles were divided into the left and right lateral ventricles based on the position of the third ventricle segmentation, and the right lateral ventricle was mirrored to align it to the left lateral ventricle yielding 88 (single) lateral ventricles for statistical analysis and training. The aligned lateral ventricles were used to generate a single SSM, which was flipped to test for enlargement in each lateral ventricle independently. This, as opposed to constructing two separate SSMs for each lateral ventricle, ensures the same statistical assessment of enlargement can be applied to either lateral ventricle, of which one or both may be enlarged.

Mesh Point-Correspondences

The segmented ventricles were converted to meshes using the marching cubes algorithm [Lorensen and Cline, 1987]. Decimation was then performed on the meshes, removing 65% of the triangles [Knapp, 2002]. Smoothing was subsequently performed on these meshes using a windowed sinc filter [Gabriel et al., 1996]. Each ventricle surface is represented by the coordinates of its n landmarks, concatenated into a $3n$ -vector. Note that initially the number n of landmarks in each ventricle surface is not necessarily the same for each mesh. The median reference ventricle was selected from the subset of 88 healthy lateral ventricles by selecting the ventricle with the minimum row sum from the matrix of residuals between each mesh pair. This shape surface was then registered to the remaining 87 healthy lateral ventricles using the Expectation Maximisation – Iterative Closest Point (EM-ICP) method [Combès and Prima, 2010]. This method interleaves estimating the nonrigid transformation between two surfaces that minimizes the sum of squared surface distance between corresponding points, and updating the expected correspondence between surface points using the EM algorithm. A symmetric term and a regularization term were added in the cost function to ensure inverse consistency and regularity of the transformation. This method allows the points corresponding to each vertex on the reference mesh to be located on every other mesh. The point correspondences allow the remaining meshes to be represented by vectors of the same size as the reference mesh.

SSM Construction

The meshes of the registered healthy lateral ventricles with point correspondences were represented by concatenating the landmark points into vectors of equal length. The mean shape, $\bar{x}$, and covariance matrix, Σ , were computed from the s shapes in the sample. A principal component analysis [Jolliffe, 2002] was performed to obtain eigenvectors ϕ_m , and their corresponding eigenvalues λ_m . The eigenvectors capture the principal modes of variation in the sample of shapes. Only the first c eigenvectors were used, such that the largest c eigenvalues described more than 90% of the total variance. Each individual shape x_i can be represented by both the mean shape $\bar{x}$, and a c -length vector describing the projection of the shape along each of the main modes of variation using the shape descriptor b :

$$x_i \approx \bar{x} + \sum_{m=1}^c b_{i,m} \phi_m \quad (1)$$

To accurately describe the high degree of healthy variation in shape of the ventricles, an iterative method was used [Hufnagel et al., 2009], in which the current estimated SSM was registered back to the original 87 healthy ventricles using the EM-ICP-based shape estimation method [Shen et al., 2012], which is formulated in the Bayesian setting, producing an updated SSM at each iteration, for five iterations. In this Bayesian framework, Tikhonov regularization was used on the estimator to penalize large deviations from the mean shape, that is, the objective function included a regularization term consisting of the weighted sum of square parameters. The default regularisation parameter ($\beta=1$), equivalent to a Bayesian estimation informed by the shape priors, was used here. Previous results show robustness of regularizing the hippocampal shape parameters (provided it is non-zero) in estimating the shape of the hippocampus. The process of iteratively corresponding the SSM back to the original shapes reduces the residual error of the fit of the SSM to the original healthy shapes, making the computed eigenvectors more representative of the majority of the population.

The mean shape and the first three modes of variation, within two standard deviations, of the final SSM are illustrated in Figure 3. The first mode approximately describes variations along the lateral aspect of the ventricle and the second describes anterior to posterior shifts while the third defines changes in size of the anterior horn. Note that care should be taken not to assign too much meaning to the principle components by conflating them with physical effects.

Identifying Age-Related Changes in Ventricular Shape

To identify any changes in ventricle shape due to patient age, and potentially account for this in the SSM,

Figure 3.
Mean shape and first three modes of variation (± 2 S.D.) of the SSM.

we isolated two groups of corresponding meshes, those belonging to patients between 5 and 9 years ($n = 8$, 4 male, 4 female), and between 12 to 17 years of age ($n = 8$, 5 male, 3 female), respectively. Following initial ICP matching, Procrustes analysis was performed [Gower, 1975], that is, the ventricles were uniformly scaled to obtain an optimal match, followed by discriminant analysis between the ventricle shapes of both groups. From this analysis, a map of significance was generated which illustrates the statistical significance of the difference of each corresponding point between the two groups. In addition, the first three shape descriptors of the constructed SSM corresponding to these meshes were analyzed using Hotelling's T -squared test [Styner et al., 2007], providing a shape descriptor comparison for each age group with a Hotelling's T -squared statistic [Shen et al., 2011].

Multiple SSM Construction

To account for the deviation of ventricle shapes observed from the healthy subjects, three additional SSMs were constructed, using subsets of the 88 cases, with the aim of using the most appropriate SSM to fit to a given unclassified ventricle. To identify the separate groups of shapes, the initially constructed SSM was transformed to fit the original healthy ventricles, providing a vector of shape descriptors. Fuzzy c-means (FCM) [Bezdek et al., 1984] clustering was performed on the first two shape descriptors, whose eigenmodes explain approximately 90% of the variance in the SSM, identifying three groups of shapes. Individual SSMs were constructed for each of these groups, as detailed in SSM construction section.

To determine the differences between these three groups, the meshes were Procrustes aligned and discriminant analysis was performed between the three possible pairs. This generates a map of the statistical significance of the difference between the corresponding points between the compared groups. Additionally, the SSM constructed from all healthy ventricles was transformed to the remaining 87 ventricles, and the first three shape descriptors from the transformation were obtained and grouped based on the shape

grouping of the target healthy ventricle. Shape descriptors were again analyzed using the Hotelling's T -squared test between the different shape groups, correcting for multiple comparisons using Bonferroni correction.

Measuring SSM Correspondence

The EM shape estimation method [Shen et al., 2012] was further used to transform the iteratively improved single and multiple SSMs to the remaining ventricles obtained from the MRIs of the 95 children with CP. In this step, the SSM transforms along the six largest eigenvectors to best fit the target ventricle. Tikhonov regularization was used to constrain the shape descriptors fitting the SSM to a given lateral ventricle, x_i , which can be described as:

$$x_i = \bar{x} + b\phi + \epsilon = \bar{x} + (b_{\text{constrained}} + b_{\text{remainder}})\phi + \epsilon, \quad (2)$$

where $\bar{x}$ is the mean SSM shape, ϕ contains the SSM eigenvectors, $b_{\text{constrained}}$ contains the constrained shape parameters obtained from the SSM fitting process, $b_{\text{remainder}}$ contains the difference between unconstrained and constrained shape descriptors, and ϵ contains the residual that cannot be described by the eigenvectors of the model. As a result, the SSM provides the closest healthy shape to a target (healthy or injured) ventricular shape, with regions of ventricular enlargement caused by injury not modeled by the SSM. Hence, for the function, $V(x)$, that converts a mesh model x into its volumetric representation, the enlarged volume mask, V_{enlarged} , is:

$$V_{\text{enlarged}} = V(x_i) - V(\bar{x} + b_{\text{constrained}}\phi) = V(b_{\text{remainder}}\phi + \epsilon) \quad (3)$$

Here, the term $V(\bar{x} + b_{\text{constrained}}\phi)$ represents the assumed maximum natural variation in ventricle shape. The remaining volume $V(b_{\text{remainder}}\phi + \epsilon)$ is assumed to represent the atypical shape variation arising from injury. We term the volume mask V_{enlarged} as the volume of enlargement.

This approach along with its inherent assumptions was taken because the parameters obtained from fitting (i.e., $\phi_{\text{constrained}}$), which represent the distance from the mean,

Figure 4.

(a) The frequency of correspondence errors observed among the healthy ventricles used to construct the SSM. (b) The corresponding atlas weights used to down weight regions with high correspondence errors. (c) The frequency of ventricular enlargement observed in the set of unclassified ventricles (containing both healthy and enlarged ventricles), weighted by the atlas weights in (b). [Color figure can be viewed at wileyonlinelibrary.com]

may not adequately describe the magnitude of injury due to the efforts of the model to fit the data and the high dimensionality of the parameters. Even so, for completeness, the utility of distance from the mean, $\sum \phi_{\text{constrained}}^2$ was tested as another potential measure of injury.

A receiver operator characteristic (ROC) analysis was performed to determine the performance of both the volume of enlargement and sum of squares of the constrained shape parameters to correctly identify cases of ventricular enlargement caused by disturbances during development, compared to the gold standard diagnosis of ventricular enlargement obtained from a medical expert. From these ROC analyses for each measure of enlargement, the area under the curve (AUC) and the standard error (SE) were computed using the trapezoidal integration approach [Bradley, 1997]. In addition, at the optimal location, the positive and negative predictive values (NPVs) were computed. ROC analyses were performed using a single SSM, constructed from all healthy ventricles, for correspondence, as well as for multiple SSMs, each representing a specific subgroup of ventricular shape in the healthy population. In the latter case, the SSM that most closely matched the target ventricle was used to obtain correspondence.

Measuring Anatomical Biomarkers of Injury

From the ventricles classified as enlarged by the SSM, the volume of enlargement was identified from the correspondence of the SSM, and impingement volumes quantifying the extent of deep gray and white matter impact was measured. This was computed as the overlap of the enlarged ventricular volume, and the labeled deep gray matter structures obtained from the automated anatomical labeling atlas registered to the Colin 27 atlas. The overlap with the posterior limb of the internal capsule (PLIC) and the anterior limb of the internal capsule (ALIC) were also computed,

which was achieved by manually labeling the respective limbs of the internal capsule on the Colin 27 atlas.

A voxel-wise weighting was applied to these labeled anatomies, to down-weight voxels in regions where correspondence errors were observed among the healthy ventricles. Figure 4a shows the frequency and location of correspondence errors among the set of healthy ventricles used to construct the SSM. Figure 4b shows the corresponding weights of this region in the atlas, illustrating the down weighting regions with high correspondence errors. Figure 4c shows a cumulative map of ventricular enlargement, identified from the set of children with CP having either healthy or enlarged ventricles, using the multiple healthy SSMs. This map shows the frequency of injury at locations in the adjacent deep white and gray matter anatomies, scaled by the weights from Figure 4b.

Statistical Methodology

Statistical analysis was performed using R statistical software Version 3.1.1 [The R Development Core Team, 2008]. Multivariable linear regression was used to quantify the relationship between the computed impingement volumes into five key structures, as well as patient age and gender, to several clinical scores of function. The structures analyzed comprised of the thalamus, lenticular nucleus, caudate nucleus, PLIC and ALIC. The regression coefficients for the independent variables were standardized to a variance of one to allow for more intuitive comparisons between coefficients. The covariance between the measured impingement volumes for each anatomy was also computed, to observe the extent to which these measures co-vary. Measures of statistical significance were corrected for multiple comparisons using Bonferroni correction, comparing the calculated *P*-values against the adjusted alpha ($\alpha = 0.05/6, 0.008$).

Comparison to Direct Measure of Injury

To address concerns that the volume of local ventricular enlargement is an indirect measure of injury to subcortical anatomies, we additionally compute a set of regression models using the volumes of these anatomies as a direct measure of possible injury to these structures, for comparison. Deep gray matter anatomies were segmented using the FMRIB's Integrated Registration and Segmentation Tool (FIRST) [Patenaude et al., 2011], providing volumes of the lenticular nucleus, caudate nucleus and thalamus for 70 out of the 95 CP patients.

RESULTS

Age Comparisons

We considered the possibility that age was a factor in the shape of the lateral ventricles, even if scale had been removed. Hotelling's T -squared statistic, which quantifies the difference in the shape descriptors obtained from the two age groups, was 5.31 ($P = 0.746$). The low T -squared value implies that the effect of age was not a significant factor influencing ventricular shape. Hence, subject age was not controlled for in the SSM. The significance map of the point-wise comparison between the two age groups is provided in the supplementary material.

Shape Subpopulation Comparisons

Significant shape differences were observed between the three shape groups, with the significance map of the point-wise comparison between the first and second identified shape groups, as well as the first and third shape groups, is illustrated in Figure 5. These maps highlight extensive regions along the ventricle shape that are statistically significantly different between the three shape groups. Furthermore, the Hotelling's T -squared statistic showed statistically significant differences between the first and second shape groups ($T = 142.5$, $P < 0.0001$), the second and third shape groups ($T = 68.1$, $P < 0.0001$), and then first and third groups ($T = 56.6$, $P < 0.0001$), motivating for the use of multiple SSMs. The three SSMs were observed to have a similar variation in healthy ventricle shape, that is, eigenvectors, including the global lateral widening, and anterior/posterior thickening, and mainly differed in their mean shape.

ROC Analysis

The results of the ROC analysis are illustrated in Table I. Two measures of SSM correspondence were computed, the sum of squares of the shape descriptors and the volume of enlargement, to identify the optimal biomarker for the classification of ventricular enlargement compared to the manual gold standard. In this table, the top row shows the ROC results using measures computed from the single

Figure 5.

The p -map of statistical significance between corresponding points between the (a) first and second shape, and (b) first and third shape groups, which were identified from fuzzy c-means clustering, obtained from the discriminant analysis. The comparison between the second and third shape groups is not shown. [Color figure can be viewed at wileyonlinelibrary.com]

SSM transformed to the unclassified ventricles, and the bottom row shows the ROC results from using the three SSMs constructed from each shape group. In the latter case, only the SSM that was most similar to the unclassified shape, as determined by the Dice overlap [Dice, 1945], and the correspondence measures obtained from this transformation were used. The computed performance measures include the AUC, SE, positive predictive value (PPV), and NPV for both measures. These performance measures quantify how closely the classification of ventricular enlargement by the SSM agrees with the gold standard classification obtained from a medical expert, with the AUC measure representing the probability of correctly classifying ventricles as healthy or enlarged. As expected, the SSM shape descriptors showed reduced performance compared to the volume of enlargement, hence only the volume of enlargement was used to measure the magnitude of injury in individual anatomical regions.

TABLE I. The computed area AUC, SE, PPV, and NPV for each of the three measures of model correspondence, obtained from the ROC analysis

ROC measure	Sum of squares of the shape descriptors		Volume of enlargement (mm ³)
Single SSM	AUC ± SE	0.680 ± 0.050	0.889 ± 0.029
	PPV	0.629	0.798
	NPV	0.629	0.800
Multiple SSMs	AUC ± SE	0.545 ± 0.057	0.925 ± 0.023
	PPV	0.489	0.830
	NPV	0.486	0.829

Key: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SE, standard error; SSM, statistical shape model.

Performance of Biomarkers

The linear regression models of the impingement volumes in the periventricular white and gray matter structures with the multiple clinical scores are detailed in Table II. The variables incorporated into each regression model, which include the impingement volumes into each labeled anatomy as well as subject age and gender, are shown in the rows of Table II. Each column of this table describes the standardized regression coefficients of each variable with the AHA, BRIEF, SDQ, TVPS, WR, or VOC clinical scores respectively. The amount of variation in each clinical measure explained by the regression models is described by the R-squared value. In addition, the amount of variation explained by the two covariates, age and gender, alone were computed from regression models constructed using only these variables. The likelihood of the

regression coefficients being erroneously found to have a non-zero relationship with the outcome variable is shown by the associated *P*-value.

All deep gray and white matter structures, except the caudate nucleus, were significantly associated with the clinical scores for motor function (AHA). The PLIC was significantly associated with both scores of executive function (BRIEF and SDQ), while the ALIC was also associated with the SDQ score. No significant anatomical associations were observed for the TVPS score for visual perception or the VOC score for VOC. The caudate nucleus, ALIC, and lenticular nucleus were strongly associated with the WR score.

Females performed significantly better than males on both the BRIEF and SDQ measures of executive function (*P* < 0.008), while age was strongly associated with the AHA, SDQ, and WR scores (*P* < 0.008). We note that this

TABLE II. The standardized regression coefficients and associated *P*-value for each of the linear models, which show the relationship between the volume biomarkers of enlargement into key structures surrounding the ventricle, and the AHA, BRIEF, SDQ, TVPS, WR, and VOC clinical scores of outcome

	AHA	BRIEF	SDQ	TVPS	VOC	WR
Variable	Regression coefficient	Regression coefficient	Regression coefficient	Regression coefficient	Regression coefficient	Regression coefficient
Caud	−0.20	0.14	0.49	0.20	−0.09	0.59^a
Thal	1.15^c	0.40	−0.45	0.10	−0.08	0.18
PLIC	− 1.77^c	− 0.78^a	1.06^a	0.02	0.59	−0.47
ALIC	0.76^a	0.19	− 1.13^a	−0.32	0.03	− 0.99^a
Lnt	− 0.48^a	0.03	−0.03	0.24	−0.42	0.78^b
Age	0.25^a	−0.06	0.42^b	−0.21	0.33	0.49^c
Gender	−0.01	0.49^b	0.46^a	0.08	−0.08	−0.21
Multiple <i>r</i> -squared	0.62^c	0.33^a	0.55^c	0.09	0.20	0.50^c
Multiple <i>r</i> -squared of covariates (age, gender)	0.08	0.24^b	0.24^a	0.05	0.10	0.28^c

Superscripted correlations found to be statistically significant.

^a*P* < 0.008.

^b*P* < 0.0016.

^c*P* < 0.00016. Correlations in bold have a statistical significance of *P* < 0.08.

The resulting *r*-squared of the complete linear models, as well as linear models of just the covariates (patient age, in years, and gender) are shown at the bottom. AHA, Assisted Hand Assessment; ALIC, Anterior limb of the internal capsule; BRIEF, Behavior Rating Inventory of Executive Function; Caud, Caudate nucleus; Lnt, Lenticular nucleus; PLIC, Posterior limb of the internal capsule; SDQ, Strengths and Difficulties Questionnaire; Thal, Thalamus; TVPS, Test of Visual Perception Skills; VOC, Vocabulary; WR, Word Reasoning.

Figure 6.

A visual illustration of the regression coefficients of the linear models computed between the impingement volumes, and the (a) AHA, (b) BRIEF, (c) SDQ, (d) TVPS, (e) VOC, and WR. Blue colors indicate a larger negative regression coefficient and red represents a larger positive regression coefficient. Nonsignificant regression coefficients ($P > 0.05/6$) are indicated in white. [Color figure can be viewed at wileyonlinelibrary.com]

latter observation of age being strongly associated with these functional scores is expected from the literature [Henry and Millar, 1991; Morris et al., 1982], even though age was not found to be associated to lateral ventricle shape and hence not incorporated into the SSM. Overall, these covariates explained relatively less variation in the AHA score than the measured impingement volumes. They did, however, explain most of the variance in the BRIEF measure, and explained roughly half of the variation in the SDQ, TVPS, VOC, and WR measures.

Regression models explained between 9% of the variance in the clinical score (for the TVPS measure) to 62% (for the AHA measure). Four of the regression models (for the AHA, BRIEF, SDQ, and WR scores) reached significance ($P < 0.008$). A visual representation of the regression coefficients from the regression models in Table II is illustrated in Figure 6. In this figure, the deep gray matter structures, and the ALIC and PLIC, are illustrated adjacent to the outlined lateral ventricles.

Performance of Anatomical Volumes

The regression models constructed with the deep gray matter anatomical volumes obtained from FIRST are detailed in Table III. These regressions explained between 5 and 25% of the variance in the six clinical measures, with only the regression model of the AHA score of motor

function reaching clinical significance following Bonferroni correction. The thalamus and lenticular nucleus volumes were found to be significant in the BRIEF measure, however no other anatomical volumes were found to be significant in any of the other regression models. The age of the child was found to be a significant factor for three of the six clinical scores. Overall, these regression models explained less of the variance in the clinical scores compared to the corresponding regression models containing the identified volume of local ventricular enlargement, shown in Table II.

DISCUSSION

This study has developed an automated tool to quantify ventricular enlargement and demonstrated its correlation to clinical function. The proposed automated method uses SSMs to model the healthy variation in ventricular shape, which provide as a surrogate marker of subcortical gray matter tissue damage that can be measured robustly. The robustness of measuring ventricular was demonstrated with an ROC analysis, with showed the healthy SSM was frequently able to identify the regions of ventricular enlargement symptomatic of injury ($AUC = 0.9$). Additionally, significant correlations were observed between the computed anatomical impingement volumes and multiple clinical scores of function. This demonstrates the clinical

TABLE III. The standardized beta coefficients and associated *P*-value for the linear models which show the relationship between the anatomical volumes and the AHA, BRIEF, SDQ, TVPS, WR, and VOC clinical scores

	AHA	BRIEF	SDQ	TVPS	VOC	WR
Variable	Regression coefficient	Regression coefficient	Regression coefficient	Regression coefficient	Regression coefficient	Regression coefficient
Caud	−0.18	−0.08	0.22	−0.28	−0.28	0.22
Thal	−0.30	−0.95^a	0.05	0.13	0.13	0.05
Lnt	0.35	1.07^b	−0.46	0.29	0.29	−0.46
Age	−0.43^a	0.24	−0.43	0.47	0.47^a	−0.43^a
Gender	0.93	0.15	0.09	−0.08	−0.08	0.09
Multiple <i>r</i> -squared	0.25^a	0.16	0.13	0.05	0.15	0.13

Superscripted correlations found to be statistically significant.

^a*P* < 0.008.

^b*P* < 0.0016.

^c*P* < 0.00016. Correlations in bold have a statistical significance of *P* < 0.08.

The resulting *r*-squared of the model, and of the covariates (patient age and gender) alone are shown at the bottom. AHA, Assisted Hand Assessment; BRIEF, Behavior Rating Inventory of Executive Function; Caud, Caudate nucleus; Lnt, Lenticular nucleus; SDQ, Strengths and Difficulties Questionnaire; Thal, Thalamus; TVPS, Test of Visual Perception Skills; VOC, Vocabulary; WR, Word Reasoning.

utility of these predictive regression models of function using the proposed impingement volumes to predict patient outcome from MR images alone, and subsequently tailor patient-specific treatment. Furthermore, these regression models provide a tool to elucidate the relationship between observable injury and clinically observed symptoms, which can help improve the understanding of the brain's structure-function relationship.

The high variability in the shape of healthy ventricles presents a technical challenge in the modeling and correspondence of the SSM approach, so several additional steps were included in the methodology. First, to avoid errors in obtaining correspondences between healthy ventricles and the highly variable shapes of enlarged ventricles, a healthy SSM was constructed, which allows injured areas to be identified as the volume of enlargement outlined by the transformed SSM. To further account for the high variability in shape of healthy ventricles, point correspondences between the constructed SSM and the training data were iteratively recomputed to further reduce the reconstruction error of the SSM, resulting in a better representation of these healthy ventricle shapes. Second, multiple diverse SSMs were generated, to describe subpopulations of healthy ventricle shapes. The utilization of multiple SSMs led to improvements in the binary classification of ventricular enlargement compared to the manual gold standard from 0.889 to 0.925 (Table I). Although using multiple SSMs requires greater computational resources, it minimizes errors in the SSM construction and transformation processes, which critically rely on an accurate correspondence match between shapes.

A Bayesian approach based on representing injured and healthy ventricles as separate classes could be performed to assist classification. For this approach, a careful trade-

off must be made between the dimensionality of the shape descriptor and the number of samples. Additionally, the sum of squares of the shape descriptors was not predictive of enlargement whether one or multiple references were used (respective AUCs of 0.680 and 0.545). The greater than random classification performance of this measure reflects that enlarged ventricles are typically larger than the mean; however, its reduced performance compared to enlargement arises as instances of ventricular enlargement do not lead to the ventricles extending significantly along healthy eigenmodes, but rather this enlargement typically occurs along eigenmodes not contained within the healthy SSM. For instance, in cases where small ventricles were locally enlarged due to injury, appearing as a subtle irregularity, the computed shape descriptors would be small as the global ventricle size is small; however, the subtle irregular enlargement is still captured by the volume mismatch measure. Finally, the likelihood output of a Bayesian detector will not necessarily vary linearly with the magnitude of injury, which is what we sought to quantify in this study.

The impingement volumes quantifying the extent to which deep gray and white matter structures adjacent to the ventricle were impacted by the change in shape were found to be significantly associated with four of the six measured clinical scores of patient outcome. The known importance of the thalamus, PLIC and basal ganglia (which includes the putamen of the lenticular nucleus) in relaying motor information [Hoon et al., 2009; Rose et al., 2011; Rutherford et al., 1996] is reflected in the strong association of all structures with the AHA score, and the explanation of over 60% of variance in the AHA score in the regression model. White matter abnormalities in the PLIC and ALIC were strongly associated with both scores

of executive function (BRIEF and SDQ), which is consistent with the literature [Edgin et al., 2008; Kurowski et al., 2009]. However, the known role of the thalamus and caudate nucleus in executive function [Grahm et al., 2008; Van der Werf et al., 2003] has not been identified in these regression models. There were few significant associations between impacted periventricular anatomies and the clinical scores for visual perception and communication (TVPS and VOC respectively), which may be due to the larger role the cortical gray matter plays in both visual processing as well as the comprehension and production of language. Despite this, the second score for communication (WR) showed a significant association with the caudate nucleus, ALIC, and lenticular nucleus. The association between these anatomies with language comprehension has been demonstrated in the literature [Giroud et al., 1997; Watkins et al., 2002]. Gender was observed to be a factor for both scores of executive function, indicating that females performed better than males in these tasks within the age range of 5–17, which was expected. Similarly, age was found to have a positive association with several scores including AHA, SDQ, and WR, indicating that older patients performed better in these tasks. The strong relationship to several clinical outcomes highlights that the impact of ventricular enlargement on adjacent structures plays an important role in influencing patient outcome.

There was a positive covariance observed between the computed impingement volumes for all pairs of anatomical structures. This was expected as injury to one anatomy due to ventricular enlargement is likely to lead to greater impact to adjacent structures as well. These associations between anatomies explain why there are positive regression coefficients in the constructed regression models, as shown in Table II. In all the regression models, the largest regression coefficient was negative, and the association of injury measures in adjacent regions caused other coefficients to have smaller positive values to maximize the fit to the clinical score. Including interaction effects into the regression was considered to help minimize this effect and will produce regression models with better correlations to clinical outcomes; however, the risk of over-fitting by including too many interaction terms was deemed to outweigh the potential benefit. Although the positive regression coefficients imply that there is a positive relationship between extent of injury and patient function, it is important to note that these positive coefficients should be considered as part of the regression model, with all anatomies included, and not in isolation with the clinical score.

The volume of ventricular enlargement, identified using multiple SSMs, was found to explain a greater percentage of variance in all of the clinical scores compared to the computed volume of the entire subcortical structures obtained from FIRST. The regression models constructed using the volume of these anatomies was not strongly indicative of any measure of patient function, with patient age being the only significant variable identified across

multiple regression models. This suggests either that anatomical volume does not represent injury or that the estimation of anatomical volumes is too error prone in the presence the large anatomical injuries typical of CP. As a result, the proposed method of identifying a volume of enlargement using healthy ventricular SSMs provides measures that are more representative of the underlying injury due to ventricular enlargement, and yields regression models that can more accurately predict patient function given this type of injury. This performance benefit stems directly from the method's use of ventricle segmentations, lending it robustness in the face of extensive anatomical malformation.

The limitation of this study was that the proposed method only analyses the shape of the ventricles, so the measure is fundamentally a surrogate measure of injury, albeit one that can be reliably characterized. Although this is a common type of injury in children with CP, it does not consider lesions and cortical malformations that do not influence ventricular shape. Consequently, this automated method cannot quantify the whole range of brain injury that may occur, and additional methods are required to fully explore the link between structure and function in the brain. Another limitation is that the areas labeled as deep gray and white matter anatomies were only defined from the Colin 27 atlas, and not identified individually for each patient. Therefore, there may be inaccuracy in the computed impingement volumes as it does not account for the translation of these anatomies due to ventricular enlargement.

The main strength of this study of the proposed surrogate biomarker is that it avoids quantifying deep gray matter volumes directly, an error prone approach when injuries are large. This is an important consideration, as extreme anatomical variations which are commonly observed in children with CP are a critical limitation of atlas-based approaches for segmenting anatomical structures for subsequent estimations of volume. Additionally, the proposed method only requires one structural MR image, and does not require additional modalities such as diffusion or functional MRI, which facilitates the potential translation of such automated techniques to clinical practice. The advantages of this approach for assessing children with CP are highlighted by the improved correlations compared to the more sophisticated approach used in FIRST. Future work will involve devising methods for robustly segmenting the subcortical anatomies for each patient, allowing more accurate measures of enlargement to be derived.

CONCLUSION

This article presents an automated method for robustly detecting and quantifying a subset of CP associated injuries, by quantifying ventricular enlargement and its impingement on local anatomical structures. Using the

SSM method, a model describing the variability in the shape of healthy ventricles was used to identify regions of enlargement related to developmental disturbances in ventricles segmented from structural MR images. A ROC analysis showed that this SSM accurately classifies ventricles as enlarged or healthy. Quantifications of the effect of ventricular enlargement on adjacent deep gray and white matter structures were shown to have a strong correlation with multiple clinical scores, including motor, executive, and communicative function, especially in comparison to more standard atlas-based segmentation approaches. These results show that SSMs are an effective method for identifying cases of ventricular enlargement due to injury in the CP setting, and the potential in translating these image findings to patient function. The validity of quantifying ventricular enlargement in the clinical assessment of CP patients is demonstrated by the strong correlation with clinically meaningful scores. It also illustrates the potential for quantification of MR images for further elucidating the relationship between observable physical brain injury and clinically observed symptoms, with potential to better tailor treatments for patients. Future work will investigate the segmentation of other types of injury observed in children with CP, including cortical malformations and periventricular white matter injury, and quantifying their impact on clinical outcomes.

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