An Investigation of Morphometric Changes in the Lateral Ventricles of Schizophrenic Subjects

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Abstract. We present results of morphometric analysis of the lateral ventricles of a group of schizophrenic and control subjects to investigate possible shape differences associated with schizophrenia. Our results show shape changes localised to three regions : the temporal horn (its tip near the amygdala, and along its body near the parahippocampal fissure), the central part of the lateral ventricles around the corpus callosum, and the tip of the anterior horn in the region of the frontal lobe. The differences in the temporal and anterior horns are in regions close to structures thought to be implicated in schizophrenia. The changes observed are the most significant changes ($p < 10^{-13}$) in shape parameters calculated using a 3D statistical shape descriptor (point distribution model). Corresponding points on the surface of the ventricles in the training set were obtained using an transportation-based method to match high curvature points.

1 Introduction

Schizophrenia is a serious brain disorder which is accompanied by altered brain structure. Interest in investigation of shape changes of the lateral ventricles due to schizophrenia can be attributed to the work of Johnstone et al. [7] who showed that schizophrenia is accompanied by an increase in the volume of the lateral ventricles. Several groups e.g. [5] [11], are currently developing methods to investigate whether specific localised shape changes occur in the lateral ventricles and other neuroanatomic structures due to schizophrenia and other brain diseases.

Because of the wide range of natural variability in the shape of structures in the human body, statistical approaches to measuring differences in shape are desirable. Statistical shape models (SSMs) use samples from control and/or disease populations, the training set, to learn the variability in the structures being modelled. They can therefore allow separation of shape changes due to disease in the presence of natural variation, and provide better characterisation

of differences between populations than volumetric techniques. A diverse number of SSMs have been described. However, these all need a method of representing shape, establishing correspondence across the training set and obtaining shape differences qualitatively and/or quantitatively.

The particular SSM we use here is the point distribution model (PDM) [3], which characterises shape by a small number of “modes of shape variation”, providing a compact parameterisation. We apply linear discriminant analysis (LDA - see e.g. [6]) to the shape parameters to characterise inter-group differences.

2 Related Work

Buckley et al. [2] use 48 manually defined landmarks corresponding to curvature extrema on the surface of the ventricles of 20 schizophrenic patients and 20 control subjects to investigate shape differences. They considered the whole ventricular system and reported no overall shape differences between the entire patient group and the entire schizophrenic group. However, when only the males of both groups were considered, significant shape differences were identified in the proximal juncture of the temporal horn and in the foramen of Monro.

Gerig et al. [5] performed shape analysis on the lateral ventricles of 5 pairs of monozygotic and 5 pairs of dizygotic twins. Ventricles were mapped to a unit sphere and decomposed into a summation of spherical harmonic functions. The first order harmonics were used to impose correspondence between points and the measure of shape differences was the mean squared distance between corresponding points on the surfaces. They showed that, without normalisation for ventricular size, no significant differences were seen between the two groups. However, after normalisation using the volumes of the ventricles, the right lateral ventricles of the two groups are significantly different. They concluded that shape measures reveal new information in addition to size or volumetric differences, which might assist in the understanding of structural differences due to neuroanatomical diseases.

Narr et al. [11] obtained average maps of anatomical differences based on voxel values of the limbic structures and the lateral ventricles of 25 schizophrenic and 28 control subjects. Their analysis showed that significant shape differences occurred in the left lateral ventricles. In particular, there was enlargement of the superior part of the lateral ventricle and the posterior horn. There were also noticeable differences in the part of the lateral ventricles in the vicinity of the caudate head.

Our approach has aspects in common with [2] and [5]. We build PDMs based on corresponding landmark points across a training set. The landmark points are used to generate a small number of shape parameters controlling the modes of variation of the shapes. The use of this parametric description distinguishes our approach from that of [2]. However, the parameters are devised from the training data, unlike those of [5].

3 Materials and Method

3.1 Data

Volumetric T2 MR scans of 30 controls (14-45 years, 13 female, 17 male) and 39 age and sex matched schizophrenics (14-45 years, 9 female, 30 male) were used in this study. The scans were independently acquired in the sagittal, coronal and axial orientations. Each slice had 256 x 256 voxels, with in-plane size of 0.86mm by 0.86mm for sagittal and axial orientations, and 0.78mm by 0.78mm for the coronal orientation. For all orientations the slice thickness was 5mm and the intra-slice gap was 1mm.

All images were corrected for MR inhomogeneity [15], and the three views of each subject were combined by rigid registration and interpolation to give 3D images with effective resolution of 0.78mm x 0.78mm x 0.78mm. The lateral ventricles were segmented using a 3D edge detector [9] to give edge segments which were manually linked to form closed contours in each slice with the guidance of a neuroradiologist. The contours of the left lateral ventricles were reflected to give the same pose as those of the right, resulting in an evaluation set of 138 ventricles for this study.

For each subject, brain size parameters were obtained as follows. Skull stripping was performed on each MR image [12], and ellipsoids were fitted to the resulting brains. The lengths of the three principal axes of the ellipsoids were stored as the brain size parameters. The ventricular surfaces were aligned to a canonical coordinate system using their centroids and the three principal axes obtained from the distribution of the coordinates of their surface points. The brain size parameters were then used to scale each object centred ventricle independently in the three orthogonal directions for normalisation for brain size with respect to the brain size of an arbitrarily chosen template brain. This was necessary to remove the influence of brain shape on ventricular shape.

3.2 Point Distribution Models

A PDM [3] reparameterises a shape described by surface landmark points to a smaller set of shape parameters using equation 1

$$\mathbf{x} = \bar{\mathbf{x}} + \mathbf{P}\mathbf{b} . \quad (1)$$

$\mathbf{x}$ is the vector of the coordinates of surface landmarks of a particular shape, $\bar{\mathbf{x}}$ is the average of these vectors over a training set. $\mathbf{P}$ is the matrix whose columns are the eigenvectors corresponding to the largest k eigenvalues of the covariance matrix of the shape vectors. $\mathbf{b}$ is a vector of weights of dimension k . Due to correlations in point positions, k can be much smaller than the number of landmark points. $\mathbf{b}$ then becomes a vector of k shape parameters which are equivalent to $\mathbf{x}$ as a description of the shape.

It is necessary to locate *corresponding* landmark points on all the surfaces in the training set. In the case of 2D PDMs this can be achieved by manual annotation. However, in 3D this becomes difficult and prohibitively labour-intensive.

Davies et al. [4] have shown that the specificity of a SSM depends critically on finding accurately corresponding landmark points. Several approaches have been made towards automatic landmark generation in 3D, including the use of spherical harmonic parameterisation [5] and optimisation of the shape models [4]. Here we identify landmarks from the set of “crest points” on the ventricle surface using a modification of the method due to Subsol et. al. [13]. Correspondence is established using non-rigid registration of the surfaces and minimisation of Euclidean distance expressed as a transportation cost.

3.3 Crest Lines on the Lateral Ventricle Surface

Crest points, which are curvature extrema on the ventricles, are used as anatomical landmarks here. According to the definition of [13] they are points where lines of principal maximal curvature on a surface have maximum values. Crest lines are the locus of crest points and impose an ordering on crest points, which is useful when using crest points to establish correspondence.

To extract the crest points of a ventricular surface, we use the marching lines algorithm [14]. This obtains crest lines directly from the segmented voxel images of the ventricles using the zero crossings of an extremality function of the principal maximal curvature. “Noisy” crest lines and crest points are removed by applying conservative smoothing during their extraction and thresholding using the curvature values at crest points. This results in a consistent set of crest lines across the training set.

3.4 Matching Crest Points as an Assignment Problem

To define correspondence across the training set, crest points and crest lines of the ventricles are matched between ventricles in a pair-wise manner. An ICP-based method for doing this is described in [13]. However, we use a method based on minimising “transportation” costs [1]. In the matching process “injectivity” and “monotonicity” have to be preserved. Injectivity refers to the requirement that in matching the crest points of two ventricles A and B , we create a one-to-one mapping between the crest points. The monotonicity constraint prevents crossovers in the mapping. Furthermore it is desirable to have symmetric matches, in that the matching of surfaces $A \rightarrow B$ and $B \rightarrow A$ give the same pairings.

The ICP-based method in [13] requires steps to impose injectivity and monotonicity, and in general the matches are not symmetric. The transportation method intrinsically enforces injectivity but not monotonicity. Furthermore, If the number of crest points on both examples are the same the matches are symmetric.

In general, the solution to the transportation problem is a global minimum of the transportation cost

$$z = \sum_i^m \sum_j^n D_{ij} x_{ij} . \quad (2)$$

where D_{ij} is a cost of transportation of one unit commodity from source i to destination j , and x_{ij} is the quantity transported, subject to the constraint that the sum of commodities generated at all (m) sources is equal to the sum consumed at all (n) destinations

$$\sum_{i=1}^m a_i = \sum_{j=1}^n b_j . \quad (3)$$

where a_i is the output of source i and b_j is the requirement at destination j .

In the present case D_{ij} is the Euclidean distance between point i on one surface and point j on the other (following registration). All a_i and b_j have unit value (each point can match to exactly one other point). In this case the problem reduces to an *assignment problem*. Here we make use of an efficient solution by Achatz et. al. [8]. A global minimum in z is guaranteed. Minimising the assignment cost results in matches that are more numerous and more evenly distributed than those that result from the ICP-based method. Figure 1 illustrates the application of both methods to a pair of synthetic lines.

Fig. 1. To illustrate the difference between the ICP-based and the transportation-based methods, both were applied to matching points on a pair of synthetic lines. The above shows initial results (before enforcement of monotonicity and injectivity constraints) for the ICP-based method in both directions (a and b). The initial results of the transportation-based method are always symmetric (c and d) when the number of points in A and B are the same, whereas those of the closest point method are not generally symmetric

3.5 Construction of the 3D PDM of the Lateral Ventricle

One ventricle $\mathbf{v}_t$ was used as a template and its surface represented by vertices and vertex faces defined by triangular triplets of the vertices. The initial triangulation produced about 10,000 vertices, but for computational reasons these were decimated to give about 1,000 vertices. Crest lines were obtained for each

ventricle and normalised with respect to the template as described in section 3.1.

The crest lines of each of the remaining 137 ventricles $\mathbf{v}_i \in \{\mathbf{v}_1, \dots, \mathbf{v}_{137}\}$ were matched in a pairwise manner to those of the chosen template, $\mathbf{v}_t$. The matches were in both directions i.e. $\mathbf{v}_t \rightarrow \mathbf{v}_i$ and $\mathbf{v}_i \rightarrow \mathbf{v}_t$, using the transportation method and a post-processing step to enforce monotonicity. Matching was performed over 30 iterations: ten iterations each of rigid alignment, affine alignment, and spline warping successively as described in [13].

Although the transportation-based method gives symmetric results for matches in both directions when the number of crest points are equal, the results are not guaranteed to be symmetric when the number of crest points are not equal, which in general is the case with matching ventricles. Therefore, from each matched pair ($\mathbf{v}_t \rightarrow \mathbf{v}_i$ and $\mathbf{v}_i \rightarrow \mathbf{v}_t$), a subset of matches occurring on parts of crest lines that were symmetrically matched in both directions were extracted. Although this decreases the number of matched points used in the subsequent transformation, it gives greater confidence that they are valid matches. For the present case, $1,586 \pm 167$ crest points (79% of the total number matched) were on symmetrically matched crest lines for the transportation-based method, and 964 ± 160 (70% of the total number matched) for the ICP-based method. The symmetric subset of matched points are used to obtain coefficients defining a final spline based warp allowing transformation of the vertex points of $\mathbf{v}_t$ onto the surface of each $\mathbf{v}_i$. The spline based warps are defined in [13].

3.6 Shape Analysis

The parameters of the $\mathbf{b}$ vectors are used to define a shape space using the first k eigenvalues in the PDM ($k=30$ in the present case, explaining over 99% of the observed variance). Each member of the training set is a point within this k -dimensional space, represented by a vector $\mathbf{b}_k$. To characterise shape differences between the groups we conducted linear discriminant analysis (LDA) using Fisher's criterion (see e.g. [6]). This provides a "discriminant vector" in shape space along which the difference between the groups is most marked. We can quantify the shape differences by projecting the individual shape vectors onto the discriminant vector to provide a scalar value representing the individual shapes. The nature of the shape differences between the groups can be visualised by reconstructing the shapes corresponding to the group means. Specific differences correspond to locations where large movements occur between the reconstructed shapes.

4 Results

Figure 2(a) shows the results of projection onto the discriminant vector. The difference in the means was statistically significant ($p < 10^{-13}$ by a Student's t test). Figure 2(b) shows the difference between the means of the schizophrenic group and that of the control group colour-mapped onto a ventricular surface.

The greatest differences were in the region of the tip of the anterior horn (8mm), in the region of the temporal horn (between 2mm and 6mm), around the central part of the main body of the ventricle in the region of the corpus callosum (between 4mm and 6mm).

(a) Projections of the points in 30-dimensional shape space onto the discriminant vector (group means in filled black)

(b) Colour mapped ventricle showing the areas of differences between the schizophrenic group and the control group

Fig. 2. Results of shape analysis

5 Discussion

The results of the morphometric analysis are similar to those of [11] in that they show differences localised to the temporal horn in the region of the parahippocampal fissure, and in the anterior part of the lateral ventricle near the frontal lobe. However, we also found differences in the central part of the lateral ventricle in the region of the corpus callosum. Although [2] also report differences in the temporal horn of male schizophrenics, they did not find differences in the pooled groups of male and females as we have reported here.

Schizophrenia is a complex disease and, as the results of the linear discriminant analysis shows, there is a considerable overlap in the ventricles of schizophrenics and normals. Hence we do not propose we have a method that allows the discrimination of lateral ventricles into schizophrenic and none

schizophrenic groups. However, studies of this sort may help in understanding and monitoring schizophrenia. In this study we have combined left and right ventricles of both males and females. We have also removed all overall volume effects by isotropic scaling of the ventricles prior to shape modelling. The differences we observe are residual differences in shape in addition to any volumetric differences. Future work will include investigating age and gender effects as well as comparing left and right asymmetry.

Acknowledgements. We would like to thank the Epidaure group of INRIA, France for Marching Lines code, Professor P. Klienschmidt of Passau University for code for the assignment problem, and Professors Alan Jackson and Bill Deakin of Manchester University for assistance in interpreting the results.

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