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Boundary and medial shape analysis of the hippocampus in schizophrenia

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Abstract

Statistical shape analysis has become of increasing interest to the neuroimaging community due to its potential to precisely locate morphological changes and thus potentially discriminate between healthy and pathological structures. This paper describes a combined boundary and medial shape analysis based on two different shape descriptions applied to a study of the hippocampus shape abnormalities in schizophrenia. The first shape description is the sampled boundary implied by the spherical harmonic SPHARM description. The second one is the medial shape description called M-rep. Both descriptions are sampled descriptions with inherent point correspondence. Their shape analysis is based on computing differences from an average template structure analyzed using standard group mean difference tests. The results of the global and local shape analysis in the presented hippocampus study exhibit the same patterns for the boundary and the medial analysis. The results strongly suggest that the normalized hippocampal shape of the schizophrenic group is different from the control group, most significantly as a deformation difference in the tail region.

Keywords: Medical image analysis; Shape analysis; Schizophrenia; Medial shape description; Brain morphometry

1. Introduction

Quantitative morphologic assessment of individual brain structures is often based on volumetric measurements. Volume changes are intuitive features as they might explain atrophy or dilation due to illness. On the other hand, structural changes at specific locations are not sufficiently reflected in global volume measurements. Shape analysis has thus become of increasing interest to the neuroimaging community due to its potential to precisely locate morphological changes.

One of the first and most influential research in shape analysis was presented by D'Arcy Thomson (1942) in his ground-breaking book *On Growth and Form*. In more recent years, several researchers proposed shape analysis via deformable registration to a template (Davatzikos et al., 1996; Joshi et al., 1997; Csernansky et al., 1998, 2002). Inter-subject comparisons are made by analyzing the individual deformable transformations. This analysis of the transformation fields has to cope with the high dimensionality of the transformation, the template selection problem and the sensitivity to the initial position. Nevertheless, several studies have shown stable shape analysis results. Bookstein (1997) and Dryden and Mardia (1993) presented some of the first mathematical methods for 3D shape analysis based on sampled descriptions. The shape analysis of densely sampled 3D point distribution models (PDM) and their deformations was first investigated by Cootes et al. (1995). Inspired by their experiments, Gerig et al. (2001b) proposed shape analysis based on a parametric boundary description called SPHARM (Brechbühler et al., 1995). The SPHARM shape analysis approach was

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extended by Gerig et al. (2001a) to use the implied PDM, a method recently also used by Shen et al. (2003). Pizer et al. (1999); Styner et al. (2003) and Golland et al. (1999) proposed shape analysis on medial shape descriptions in 3D and 2D, respectively. They used a fixed topology sampled model with implicit correspondence that is fitted to the objects.

In this paper, we present the comparison of a sampled boundary representation (PDM derived from SPHARM) and a sampled medial description (M-rep), which leads to discussions of their strengths and limitations. In the following section, these methods are described and in the result section, a shape study of the hippocampus structure in the setting of schizophrenia is presented.

2. Methods

This section first describes the SPHARM–PDM shape description, followed by the template based shape analysis. Next, the medial M-rep description and its shape analysis methods are described. Alignment and scaling of the objects are two important issues in shape analysis that are not discussed in detail here (see Gerig et al., 2001a). For both SPHARM–PDM and M-rep, the objects are normalized prior to the shape analysis by rigid-body Procrustes alignment (Bookstein, 1991) and by scaling to unit volume. We chose volume scaling since many clinical studies with different anatomical objects provided optimal shape discrimination using this normalization scheme.

2.1. Boundary shape analysis via SPHARM–PDM

In summary, the SPHARM description is a hierarchical, global, multi-scale boundary description that can only represent objects of spherical topology (Brechbühler et al., 1995). The spherical parameterization is computed via optimizing an equal area mapping of the 3D voxel mesh onto the sphere and minimizing angular distortions. The basis functions of the parameterized surface are spherical harmonics. Each individual SPHARM description is composed of a set of coefficients, weighting the basis functions. Kelemen et al. (1999) demonstrated that SPHARM can be used to express shape deformations. Truncating the spherical harmonic series at different degrees results in object representations at different levels of detail. SPHARM is a smooth, accurate fine-scale shape representation, given a sufficiently high representation level. Based on a uniform icosahedron-subdivision of the spherical parameterization, we obtain a PDM.

Correspondence of SPHARM–PDM is determined by normalizing the alignment of the parameterization to an object-specific frame. In the studies presented in this paper, the normalization is achieved by rotation of the parameterization, such that the spherical equator, 0° and 90° longitudes coincide with those of the first order ellipsoid (Gerig et al., 2001a). We are currently also studying other normalization schemes based on anatomical landmarks located on the object-surface. After normalization, corresponding surface points across different objects possess the same parameterization.

The SPHARM–PDM shape analysis is visualized in Fig. 1 using a lateral ventricle structure (more detailed in (Gerig et al., 2001a)). Prior to the shape analysis, the group average object is computed for each subject group, and an overall average object is computed over all group average objects. Each average structure is computed by averaging the 3D coordinates of corresponding surface points across the group. The overall average object is then used in the shape analysis as the template object. At every boundary point for each object, we compute a distance map representing the signed local Euclidean surface distance to the template object. The sign of the local distance is computed using the direction of the template surface normal. In the global shape analysis, the average of the local distances across the whole surface is analyzed with a standard group mean difference test. The local shape analysis is computed by testing the local distances at every boundary point. This results in a significance map that represents the significance of these local statistical tests and thus allows locating significant shape differences between the groups. We corrected the shape analysis for the multiple comparison problem using a uniformly sensitive, nonparametric permutation test approach (Pantazis et al., 2004). The non-corrected significance map is an optimistic estimate of the real significance, whereas the corrected significance map is a pessimistic estimate that is guaranteed to control the rate of false positives at the given level α (commonly $\alpha = 0.05$) across the whole surface.

2.2. Medial shape analysis via M-rep

An M-rep (Pizer et al., 1999) is a linked set of medial primitives called medial atoms, $m = (x, r, \underline{F}, \theta)$. The atoms are formed from two equal length vectors and are composed of: (1) a position x, (2) a radius r, (3) a frame $\underline{F}$ implying the tangent plane to the medial manifold and (4) an object angle θ. The medial atoms are grouped by intra-figural links into figures that are connected by inter-figural links. Via interpolation, a fully connected boundary is implied by the M-rep. The single figure M-rep of a hippocampus object is visualized in Fig. 2 with its implied boundary. The individual M-rep description is determined by fitting a previously computed M-rep model to the object-boundary. Individual M-reps originating from the same model have an inherent atom-by-atom correspondence. The model generation and the

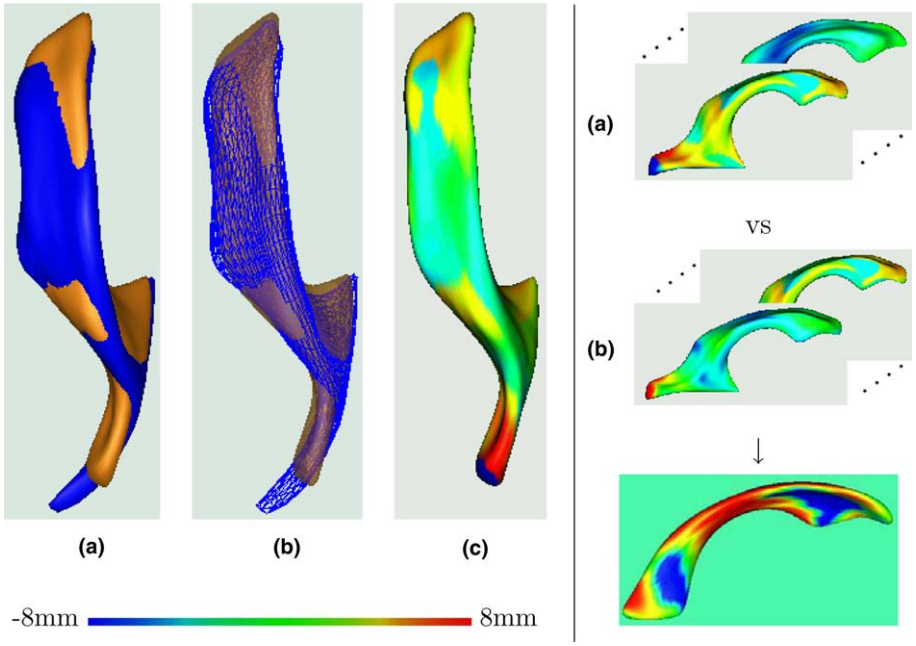

Fig. 1. SPHARM–PDM shape analysis. Left: Signed distance map computation between an individual object (blue) and a template structure (orange). (a) Objects after alignment and scaling. (b) Same as (a), but the template is shown transparent and the object as grid-mesh. (c) Distance map with color-coded distance at each boundary-point. Right: Statistical map computation: For two groups of objects, distance maps are compared in statistical tests yielding a statistical map. The significance map shows the color coded significance (non-significant = blue; significance level = green (low) to red (high)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web of this article.)

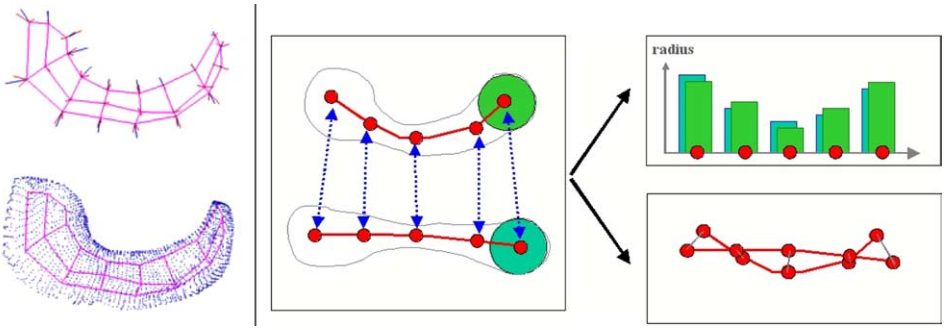

Fig. 2. Left: Single figure M-rep of a hippocampus without (top) and with (bottom) implied boundary from superior view. Right: M-rep shape difference (schematically in 2D) of 2 M-rep objects: Differences in the thickness (top graph) and position (lower graph) are studied separately. The properties express different kinds of underlying processes (growth vs. deformation).

fitting process are described in detail in (Styner and Gerig, 2003). In summary, the model is computed such that it adequately represents the underlying anatomy in a given training population. A fully automatic optimization procedure computes both the set of medial figures and the set of medial atoms of the medial manifolds. The optimization finds the minimal M-rep model that represents the training population with a predefined maximal approximation error.

In contrast to the boundary shape analysis, a medial shape analysis separately studies the two medial shape properties: local position and thickness (Styner et al., 2003). The analysis is performed similarly to the SPHARM–PDM shape analysis. We first compute the overall average object by averaging the position x and radius r for each medial atom across the group. The overall average object serves as the template. Then, the signed position and thickness differences to the template are computed for each M-rep. The sign of the position difference is computed using the direction of the template medial surface normals. In the global shape analysis, the mean of the local differences across the medial manifold is analyzed by standard mean difference tests. The local shape analysis is computed by testing each medial atom independently. The same procedure is applied as in the case of the boundary shape analysis in order to correct for the multiple comparison problem.

2.3. Differences in shape analysis: medial vs. boundary

The computation of the boundary shape changes yields a deformation field with a deformation vector at

each boundary location. The signed magnitude of the deformation field is then analyzed. Alternatively we are also developing methods for the direct analysis of the deformation vector field. In both cases, we represent the shape changes as local deformation processes. The deformation vector at each location captures thus the positional change relative to the template. This analysis detects locations of shape difference, but it does not yield insight into the nature of the difference, i.e., whether it is due to a growth/shrinkage or a bending/shift process.

In the medial shape analysis, we perform a separate analysis for the two medial properties of local position and thickness. Fig. 2 demonstrates how thickness and position capture different forms of shape change, i.e., thickness changes are due to locally uniform growth forces and positional changes are due to local deformation forces. The separation of these 2 processes is a major advantage of the medial over the boundary shape analysis, since shape changes due to uniform growth processes can be determined more intuitively. Non-uniform growth processes are less intuitively handled as such processes partially affect the thickness as well as the position analysis. It has been suggested that thickness properties can also be measured using the boundary analysis. In theory this can be done, but it seems impossible to separate the boundary deformation analysis from the thickness analysis, and thus the deformation analysis would always capture both growth as deformation processes. Additionally, a reasonable definition of thickness should be symmetric, i.e., the thickness of the object associated with a point on the boundary should be equal to the thickness at the corresponding point on the opposite side of the boundary. This condition is guaranteed in medial descriptions and is not met in many boundary based thickness computation methods.

Since our M-rep model is based on a coarse grid of medial atoms, the medial shape analysis captures only large scale shape differences, whereas the SPHARM–PDM boundary shape analysis captures both small and large scale shape differences. The low number of medial atoms, as well as the separation of position and thickness provide additional statistical power to the medial shape analysis.

3. Results of the hippocampus schizophrenia study

We investigated the shape of the hippocampus structure in the left and right brain hemisphere in schizophrenic patients (SZ, 56 cases) and healthy controls (Cnt, 26 cases). The hippocampus is a gray matter structure in the limbic system and is involved in processes of motivation and emotions. It also has a central role in the formation of memory. Hippocampal atrophy has been observed in studies of several neurological diseases, such as schizophrenia, epilepsy, and Alzheimer's disease. The goal of our study was to assess shape changes between schizophrenic patients and the control group.

The subjects in this study have all male gender and same handedness. The two populations are matched for age and ethnicity. The hippocampi were segmented from IRprepped SPGR MRI datasets ($0.9375 \times 0.9375 \times 1.5$ mm) using a manual outlining procedure based on a strict protocol and well-accepted anatomical landmarks (Duvernoy, 1998). The segmentation was performed by a single clinical expert (Schobel et al., 2001) with intra-rater variability of the segmented volume measurements at 0.95.

The SPHARM coefficients were computed from the segmentation. The objects were normalized via a rigid-body Procrustes alignment and a scaling to unit volume. The SPHARM implied PDMs were computed using a sampling of 2252 points along the boundary. The M-rep model was built on the full population including the objects of all subjects on both sides, with the right hippocampi mirrored at the interhemispheric plane prior to the model generation. The resulting M-rep model has a single figure topology and a grid sampling of three by eight medial atoms, in total 24 atoms. The individual M-rep descriptions were then computed by fitting this model into each object's boundary. The range of the average distance error between the fitted M-rep boundary and the original boundary was between 0.14 and 0.27 mm (mean error 0.17 mm). Since this error is less than half of the voxel size of the original MRI we expect the medial shape analysis to capture all relevant coarse and fine scale changes.

The template for both boundary and medial shape analysis was determined by the overall average structure. As the two population are not equal in size, we computed the overall average as the average of the population averages (see also Fig. 3). Due to age-variation in both population, the shape difference values were corrected for age influence (linear least square model). In the shape analysis with and without correction for age influence very similar patterns were observed. In this paper, only the age-corrected analysis is presented.

The global shape analysis in Table 1 shows that only the right hippocampus is significantly differently shaped at the 0.05 significance level in the SPHARM–PDM analysis and the M-rep position analysis. A strong trend in the M-rep position analysis is also visible on the left side. The M-rep thickness analysis is neither significant for the left nor for the right hippocampus. This suggest a deformation shape change in the hippocampus between the schizophrenic and the control group. The results of the M-rep position analysis show a stronger significance than the SPHARM–PDM analysis. Additionally to the mean difference, several quartile measures (median 75%

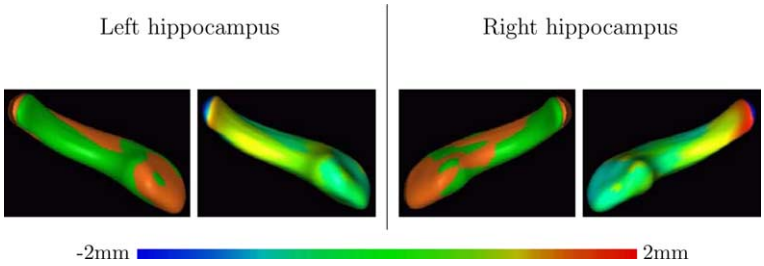

Fig. 3. Population-wise average structure visualization. The left columns show both average structure (green solid: controls, orange transparent: schizophrenics). The right columns show the distance maps between the two averages on the template (= the average of the both averages). The main difference between the averages is clearly located at the tail. (For interpretation of the references to colour in this figure legend, the reader is referred to the web of this article.)

Table 1
Results of global shape analysis (average across the surface/medial manifold)

Global analysis	SPHARM–PDM Dist.	M-rep thickness	M-rep position
Left	$p = 0.154$	$p = 0.722$	$p = 0.0513$
Right	$p = 0.015^*$	$p = 0.751$	$p = 0.0001^*$

Table of group mean difference p-values between the schizophrenic and control group.
* Significant at $\alpha = 0.05$ significance level.

and 95%) were analyzed and produced structurally the same results.

The local analysis is visualized as distance maps of the averages (Fig. 3) and as significance maps of the statistical tests (Fig. 4). The results of the local analysis exhibit a similar pattern of regions of significant difference in the SPHARM–PDM shape analysis as in the M-rep position shape analysis. No significance was found in the M-rep thickness analysis. Similar to the outcome of the global analysis, the local M-rep position analysis shows a stronger significance than the SPHARM–PDM analysis. The local shape differences are mainly located at the hippocampal tail. In the uncorrected analysis both left and right side hippocampi show a shape difference, but these results are overly optimistic. In the corrected shape analysis, the left side hippocampus shows little (PDM) or no (Mrep) significant difference, but these results can be regarded as overly pessimistic.

In summary, the results of our local shape analysis methods suggest the existence of a deformation shape difference between the schizophrenic and control group of our study located at the hippocampal tail. This shape difference is more pronounced on the right side. By inspecting the average structures of the two groups, we further find that the hippocampal tail region of the control group in our study is more bent than the one of the schizophrenic group.

4. Discussion and conclusions

We have presented a comparison of the boundary SPHARM–PDM and medial M-rep shape analysis for both global and local changes. The analysis uses similar statistical methods for both the medial and the boundary description, but the descriptions themselves are fundamentally different. The results show a good concordance between the detected changes in the SPHARM–PDM and the M-rep analysis. This concordance strengthens the validity of the reported results.

In the presented study, the M-rep position shape analysis is statistically more significant for both the global and local statistics than the SPHARM–PDM analysis. This is mainly due to separation of medial properties of thickness and position, since the thickness information seems to contain no relevant information and thus effectively additional noise is present in the SPHARM–PDM shape analysis. Also the low number of medial atoms, 24 atoms in the presented study, allows a more appropriate estimation of the local statistics.

The separation of thickness and position in the M-rep analysis in provides additional information of the presence/absence of deformation change and the presence/absence of *local* growth or atrophy. Since the shape analysis is performed on volume normalized objects, *global* growth or atrophy cannot be detected in the shape analysis. For this population, we observed hippocampal atrophy in schizophrenics in the separate hippocampal volume analysis (Schobel et al., 2001). Based on the shape analysis, we can now conclude that the hippocampal atrophy is not limited to a specific part of the hippocampus, but rather can be regarded as uniformly distributed across the whole structure.

The main results of this shape analysis study is the presence of significant hippocampal abnormalities in the schizophrenia patients. The pattern of shape

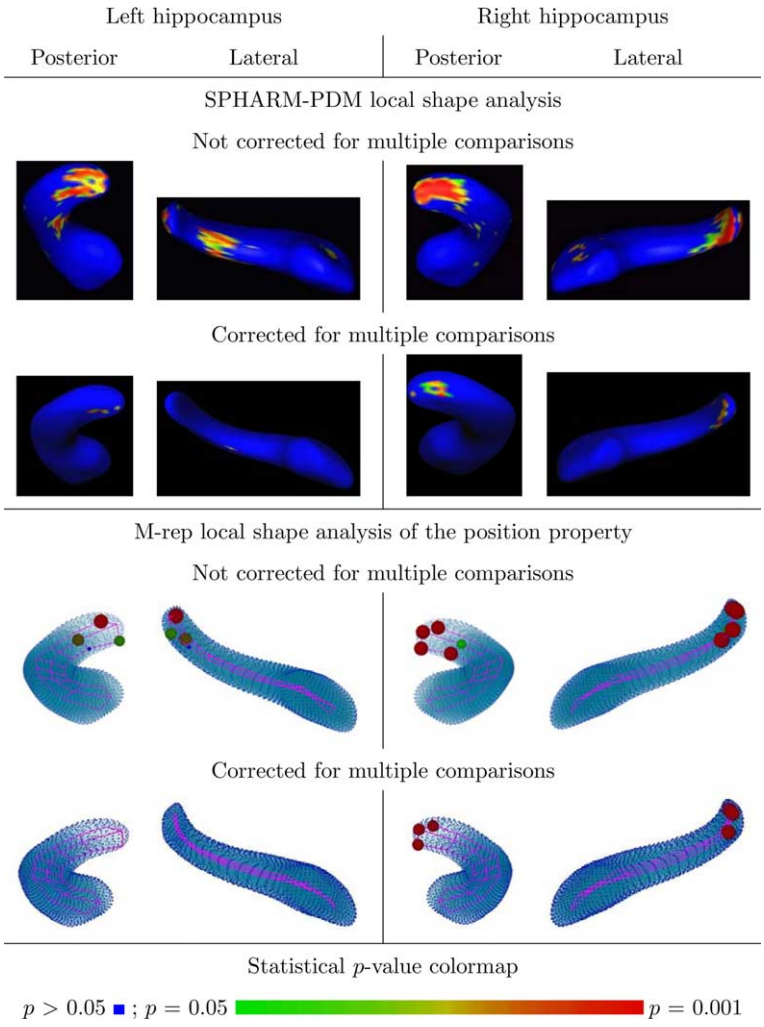

Fig. 4. Statistical maps of the local shape analysis from posterior and lateral views, both uncorrected and corrected for multiple comparisons. Top rows: SPHARM–PDM shape analysis, bottom rows: M-rep shape analysis of the position property. The M-rep shape analysis of thickness property is not shown since no regions of significance are present. The M-rep analysis shows the statistical significance at each medial atom using both the color and the radius of spheres placed at the atom positions. The patterns of the local analysis are similar for both SPHARM–PDM and M-rep analysis. The main area of significance is clearly located at the hippocampal tail. The uncorrected results are overly optimistic. The corrected results are overly pessimistic.

abnormality clearly shows a hippocampal shape change in the tail region due to deformation. This is an interesting result as it suggests deformation of the hippocampal tail at a position where it connects to the fimbria. Future shape analysis of objects in the context of embedded objects will help to explain the reason for such a finding. In contrast to these results, Csernansky et al. (2002), reported local shape analysis results of hippocampal abnormalities in schizophrenia located mainly in the head region, but also, to a minor extent, in the tail. Their shape analysis method is very different from ours and is based on the analysis of a high dimensional brain mapping procedure. It is yet unclear to us whether the source of this divergence is the differences between the methods or the differences between the studied populations. An ongoing study at UNC currently applies the high dimensional warping method to our hippocampus study. At the same time, we plan to apply our analysis method to the datasets analyzed by Csernansky. This will result in a unique sample set that has the potential to decouple a series of methodological differences from the population differences.

The current shape analysis scheme is based on a comparison to a template shape computed by population wise averaging. The selection of the template is to a lesser degree arbitrary and different selections of templates result in different results. To overcome this selection bias we are currently developing novel methods for template free shape analysis based on three-dimensional shape difference metrics.

We presented results for both the uncorrected, optimistic shape analysis, as well as for the corrected, pes-

simistic shape analysis. As a next step, we aim to enhance the correction scheme by introducing geodesic smoothing of the local shape differences. This will lead to more stable maximum statistic and consequently a less pessimistic estimate, while the false-positive rate is still guaranteed to be correct across the whole shape.

The combined SPHARM–PDM and M-rep shape analysis scheme is also applied to other brain structures in schizophrenia and normal brain development studies (Vetsa et al., 2003). These studies show preliminary results with similarly good concordance between SPHARM–PDM and M-rep shape analysis.

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